1ST WORLD CONGRESS ON TOURETTE SYNDROME & TIC DISORDERS

New Frontiers in Research, Treatment and Global Collaboration

JUNE 24–26, 2015

LONDON, UK

Tourette Association of America

ESSTS European Society for the Study of Tourette Syndrome

Tourettes action

1st World Congress on Tourette Syndrome and Tic Disorders

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1st World Congress on Tourette Syndrome and Tic Disorders

This volume holds abstracts from the 1st World Congress on Tourette Syndrome and Tic Disorders which took place on June 24-26, 2015, in London UK, hosted by the Tourette Association of America (TAA), the European Society for the Study of Tourette Syndrome (ESSTS), Tourettes Action-UK (TA) and other global partners. This event was the first-ever global summit for Tourette Syndrome, bringing together world experts with the common goals of 1) sharing state of the art knowledge, 2) advancing our understanding of the pathophysiology of Tourette Syndrome, 3) working towards improved management of Tourette Syndrome, and 4) strategizing on increasing advocacy for and on behalf of people living with Tourette Syndrome and related disorders.

Tourette Syndrome (TS) is a common, albeit often misdiagnosed disorder, with a reported prevalence of 0.4-1%. It is part of a spectrum of childhood-onset neurodevelopmental conditions referred to as Tic Disorders. The core features of these conditions, which affect both children and adults, are motor and vocal tics: sudden, uncontrollable repetitive movements and/or sounds (e.g. head bobbing, arm jerking, shoulder shrugging and grunting). Related features, such as Obsessive Compulsive Disorder (OCD), Attention Deficit Hyperactivity Disorder (ADHD) and learning difficulties, are very common in individuals with TS and Tic Disorders and often cause more impairment than the do the tics themselves. Symptoms in Tic Disorders can range from mild to severe and, in some cases can be debilitating, markedly reducing quality of life. The etiology of the disorder remains elusive and is clearly complex, with multiple genes interacting with environmental factors to lead to the onset of symptoms. At the same time, while some treatments are available for people with TS and other Tic Disorders, approaches to care are inconsistent around the world, medications are often ineffective and there is no cure.

Over the past few years, we have witnessed exciting developments not just in the understanding of the neurobiology and treatment of TS, but also in international collaborations for TS research and advocacy, such as the international DBS registry and the European Multicentre Tics in Children Study (EMTICS). Vibrant multi-national research networks for TS have been established and national patient groups have started joining forces to support the mission of outreach and education for TS around the world. These collaborative efforts inspired the 1st World Congress on Tourette Syndrome and Tic Disorders. More than 430 research scientists, physicians, neurosurgeons, psychologists, social workers and other experts from 38 countries and six continents gathered in London and discussed on all facets of TS research, including drug development, genetics, comorbid conditions, surgical therapies and behavioral treatments for children and adults. This unprecedented global assembly marked the first time a collective forum of such size and significance has ever been convened to explore means of improving the lives of people affected by these neurodevelopmental conditions. Leading experts in the field laid the foundation for a new global workforce focused on TS and Tic Disorders research, presenting 185 scientific abstracts and 161 posters with important discoveries and developments that have the potential to change our understanding and ability to treat these conditions. We are grateful to the TS global community of researchers for their enthusiastic response and we are certain that this was the first of many such gatherings. We share with you the aim of improving the lives of families and individuals affected by TS through research, clinical care, and advocacy.

The co-chairs of the Scientific Program Committee

Carol A. Mathews, University of Florida, USA

Jeremy Stern, St George's Hospital, UK

Peristera Paschou, Democritus University of Thrace, Greece

Committees

Award Recipients

The following awards were presented at the 1st World Congress on Tourette Syndrome and Tic Disorders:

Dr. Oliver Sacks Award for Excellence in Tourette Syndrome, presented by the Tourette Association of America:

- Jonathan W. Mink, University of Rochester, USA

  Jonathan W. Mink, MD PhD is the Frederick A. Horner M.D. Endowed Professor of Pediatric Neurology and Professor of Neurology, Neurobiology & Anatomy, Brain & Cognitive Sciences, and Pediatrics at the University of Rochester School of Medicine and Dentistry. He has an active basic research program that focuses on understanding the function of the basal ganglia in the control of movement and mechanisms of movement disorders due to basal ganglia disease. In addition to his basic work on basal ganglia physiology, he is engaged in clinical research on dystonia in children, Tourette syndrome, and Batten disease. Clinically, he specializes in pediatric movement disorders with special interests in dystonia and Tourette Syndrome. Dr. Mink has received teaching awards at both Washington University and the University of Rochester, and from the American Academy of Neurology. In 2002, Dr. Mink received the Derek Denny-Brown award from the American Neurological Association. Dr. Mink is Associate Editor of Neurology. Dr. Mink is co-chair of the scientific advisory board of the Tourette Association of America and serves on a number of medical and scientific advisory boards including the Batten Disease Support and Research Association and the Pediatric Neurotransmitter Disease Association.

2015 Professor Mary Robertson Award for Research Contribution, presented by the European Society for the Study of Tourette Syndrome:

- Christos Ganos, University College London, UK for paper on "Beliefs and facts about tic inhibition in Gilles de la Tourette syndrome"

Award for Best Oral Presentation by an Early Stage Researcher, presented by the European Society for the Study of Tourette Syndrome:

- Caitlin Gauvin, Massachusetts General Hospital, USA for presentation on "Refining the Population Prevalence of Tourette Syndrome and Exploring Sources of Heterogeneity: The Clinical Importance of an Accurate Prevalence Estimate"
- Juan Carlos Baldermann, Uniklinik Köln, Germany for presentation on "Effects of Deep Brain Stimulation in treatment-refractory Tourette Syndrome: A Meta-analysis"

Award for Best Poster Presentation by an Early Stage Researcher, presented by the European Society for the Study of Tourette Syndrome:

- John Alexander, Democritus University of Thrace for presentation on "Network analysis on Tourette Syndrome associated genes using genome wide data"
- Jessica B. Lennington, Yale University School of Medicine for presentation on "Transcriptome Analysis of the Human Striatum in Tourette Syndrome"

Scientific Programme

Wednesday, June 24Th	**Pre-Congress**
7:15 - 9:00am	**Refreshments**
8:00am - 5:30pm	**Registration**
9:00am - 5:30pm	**International Deep Brain Stimulation Meeting** **Chair:** *Michael Okun, M.D.* **Global Advocacy Summit** **Co-Chairs:** *Suzanne Dobson, Jen Davis, Andrea Bonzini, Dr. Huei-Shyong Wang*
9:00am - 3:00pm	**ESSTS & TS-EUROTRAIN Training Workshop: Neurotransmitters in TS** **Co-Chairs:** *Kirsten Mueller-Vahl, M.D. & Andrea Ludolph, M.D.*
10:00am - 5:30pm	**Behavior Therapy Workshop** **Co-Chairs:** *Douglas Woods, Ph.D. & Cara Verdellen, Ph.D.*
12:00 - 1:00pm	**Lunch**
6:30 - 9:00pm	**Welcome Reception**

	CONGRESS SESSIONS
Thursday, June 25Th	**Session 1: Etiology** **Genetics, Environment & Epidemiology** **Co-Chairs:** *Pieter Hoekstra, M.D., Ph.D. & Jay Tischfield, Ph.D.*
8:00 - 8:30am	**Plenary:** *Peristera Paschou, Ph.D.*
8:30 - 9:00am	**Plenary:** *Jeremiah Scharf, M.D., Ph.D.*
9:00 - 9:30am	**Plenary:** *Matthew State, M.D.*
9:30 - 9:50am	*Thomas Fernandez, M.D.*
9:50 - 10:10am	*Caitlin Gauvin, BS*
10:10 - 10:30am	**Break**
	Session 2: Pathophysiology **Neurophysiology, Imaging & Immunology** **Co-Chairs:** *Tamara Hershey, Ph.D. & Kirsten Mueller-Vahl, M.D.*
10:30 - 11:00am	**Plenary:** *Bradley Schlaggar, M.D., Ph.D.*
11:10 - 11:30am	*Susan Swedo, M.D.*
11:30 - 11:50am	*Jessica Church, Ph.D.*
11:50am - 12:10pm	*Marc Lavoie, Ph.D.*
12:10 - 12:30pm	*Deanna Greene, Ph.D.*
12:30 - 1:30pm	**Lunch & Poster Session 1**
1:30 – 2:00pm	*Professor Mary Robertson Awardee Talk* **Speaker:** *Chris Ganos, M.D.*

2:00 - 2:40pm	**Debate Session 1:** *Marijuana and TS* **Co-Chair:** *Joseph Jankovic, M.D.* **PRO:** *Kirsten Mueller-Vahl, M.D.* **CON:** *Paul Sandor, M.D.*
2:40 - 3:10pm	**Break**
	Session 3: Animal Studies **Animal Models & Cellular Physiology** **Co-Chairs:** *Nicole Calakos, M.D., Ph.D. & Andrea Ludolph, M.D.*
3:10 - 3:40pm	**Plenary:** *Izhar Bar-Gad, Ph.D*
3:40 - 4:00pm	*Kevin McCairn, Ph.D.*
4:00 - 4:20pm	*Simone Macri, Ph.D.*
4:20 - 4:40pm	*Christopher Pittenger, M.D., Ph.D.*
4:40 - 5:00pm	*Roberto Frau, Ph.D.*
	Session 4: Clinical **Clinical-Motor and Non-Motor Aspects of TS** **Co-Chairs:** *Alan Apter, M.D. &Noa Benaroya-Milshtein, M.D., Ph.D*
3:10 - 3:40pm	**Plenary:** *Alan Apter, M.D.*
3:40 - 4:00pm	*Kirsten Mueller-Vahl, M.D.*
4:00 - 4:20pm	*Tammi Steinberg, M.D.*
4:20 - 4:40pm	*Ella Gev, M.A.*
4:40 - 5:00pm	*Andrea Ludolph, M.D.*
5:00 - 6:00pm	**Essts General Assembly Meeting**
7:00 - 10:30pm	**Reception & Banquet with Keynote Presentation** **Keynote Speaker:** *Mort Doran, M.D.*

	CONFERENCE SESSIONS
Friday, June 26th	
7:15 - 9:00am	**Refreshments**
	SESSION 5: IMPACT **Comorbid Conditions, Social Impact & QOL** **Co-Chairs:** *Samuel Zinner, M.D., & Yukiko Kano, M.D., Ph.D.*
8:00 - 8:30am	**Plenary:** *Andrea Cavanna, M.D., Ph.D.*
8:30 - 9:00am	**Plenary:** *Valsamma Eapen, FRANZCP, Ph.D.*
9:00 - 9:30am	**Plenary:** *Renata Rizzo, M.D., Ph.D.*
9:30 - 9:50am	*Sabrina Darrow, Ph.D.*
9:50 - 10:10am	*Barbara Coffey, M.D.*
10:10 - 10:30am	**Break**
	Session 6: Emerging Treatments **Medication, Behavior & Surgical Therapies** **Co-Chairs:** *Paul Sandor, M.D., & Tara Murphy, Ph.D.*
10:30 - 11:10am	**Plenary:** *John Walkup, M.D.*

11:10 - 11:30am	*Juan Carlos Baldermann, M.D.*
11:30 - 11:50am	*Julie Leclerc, P.Ps, Ph.D.*
11:50am - 12:10pm	*Elia Abi-Jaoude, M.D., FRCP(C)*
12:10 - 12:30pm	*Katie Edwards, BSc*
12:30 - 2:00pm	**Lunch & Poster Session 2**
2:00 - 2:40pm	**DEBATE SESSION 2: CBIT vs. Pharmacotherapy** **Co-Chair:** *Stanley Fahn, M.D.* **PRO:** *Douglas Woods, Ph.D.* **CON:** *Donald Gilbert, M.D., MA FAAN, FAAP*
	Session 7: Hot Topics **Breakthroughs and Late Breaking News** **Co-Chairs:** *Carol Mathews, M.D. & Jeremy Stern, M.A., FRCP*
2:40 - 3:10pm	*Michael Himle, Ph.D.*
3:10 - 3:30pm	*Aysegul Gunduz, Ph.D.*
3:30 - 3:50pm	*Yoav Ben-Shlomo, M.B.B.S., Ph.D.*
3:50 - 4:10pm	*Fotis Tsetsos, BSc*
4:10 - 4:30pm	*John Walkup, M.D.*
4:30 - 4:50pm	*Beth Hobson, BSc*
4:50 – 5:10pm	*Alden Huang, B.S.*
5:10 - 6:00pm	**Awards Presentation & Post Congress Refreshments**

Decreased activation of prefrontal cortical regions associated with self-regulatory control in Tourette syndrome relative to healthy controls

E. Abi-Jaoude[1*], B. Segura[2] and P. Sandor[3]

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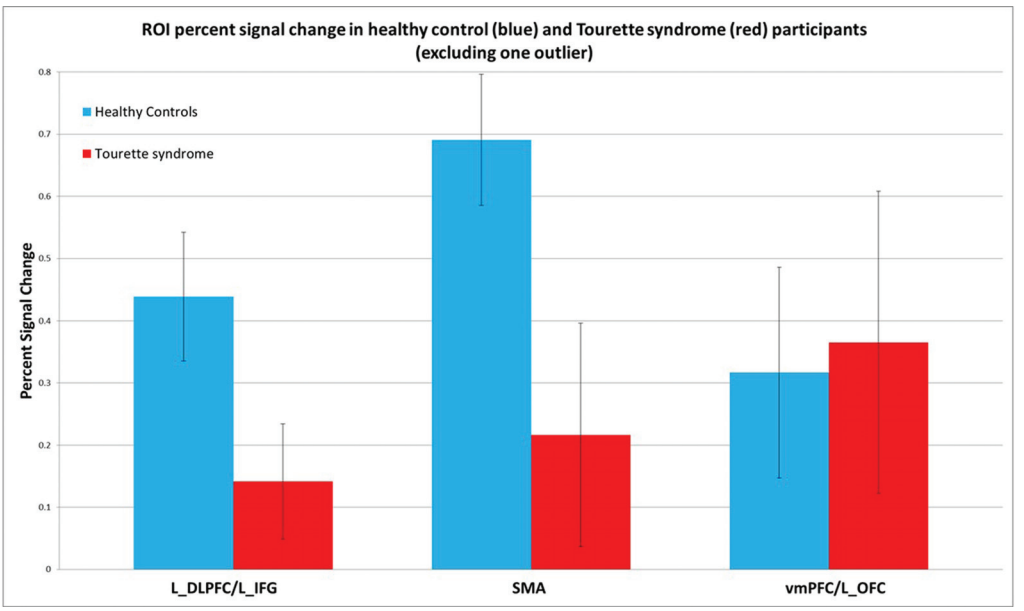
Introduction and objectives: The capacity to regulate urge is associated with a range of academic, financial, legal, physical and mental health outcomes (Mischel et al., 2011). The neural substrates of self-regulation are believed to entail a balance between prefrontal cortical control regions and limbic and affective areas (Heatherton and Wagner, 2011; Goldstein and Volkow, 2011). We have shown that self-regulatory failure in healthy subjects was associated with decreased activation of prefrontal cortical regions associated with self-regulatory control (Abi-Jaoude et al., manuscript in preparation). We set out to investigate differences in activation of these regions in Tourette syndrome (TS) relative to healthy controls (HC) during a motor self-regulatory control task.

Methods: BOLD fMRI was used to detect brain activations in 19 HC subjects during inhibition of eye blinking in a block design. This entailed 1 min blocks of effortful inhibition of eye blinking, alternating with 1 min blocks without such inhibition (2 runs, 6 min each). We identified regions showing activation changes associated with self-regulatory failure, defined as an increased number of blinks during blink inhibition blocks. From these, we selected prefrontal cortical regions known to be involved in self-regulatory control, such that we obtained the following three regions of interest (ROIs): left dorsolateral prefrontal cortex/inferior frontal gyrus (DLPFC/IFG), supplementary motor area (SMA), and ventromedial prefrontal cortex/left orbitofrontal cortex (vmPFC/OFC). Subsequently, percent signal change in these areas was compared between the HC and 12 TS participants carrying out the same blink inhibition task.

Results and discussion: On initial analysis, while there was increased signal change the DLPFC/IFG and SMA ROIs in HC relative to TS, this was not statistically significant. However, one TS participant was a clear outlier, with percent signal change values of at least 3.5 standard deviations in comparison to the rest of the study participants. Upon exclusion of this participant, there emerged a clear difference between the two groups, such that there was substantially less percent signal change in the DLPFC/IFG ($p = 0.041$) and SMA ($p = 0.036$) ROIs in the TS group in comparison to the HC group (see Figure 1). There was no group difference in activation changes in the vmPFC/OFC ROI ($p = 0.87$).



Conclusion: During a motor self-regulatory control task, subjects with TS had significantly lower activation of ROIs encompassing the DLPFC/IFG and SMA, which are prefrontal cortical regions known to be involved in self-regulatory control. On the other hand, there was no difference in activation in vmPFC/OFC, considered hedonic areas given their involvement in immediate reward. This suggests that self-regulatory deficits in TS arise from aberrant control rather than increased hedonic drive.

Acknowledgements

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Disclosures

Dr. Paul Sandor has received unrestricted grants in support of conferences from Purdue, Shire, CME speaker fees from Purdue, clinical trial support from Otsuka, and has been on the data safety monitoring committee for Psyadon. Drs. Elia Abi-Jaoude and Barbara Segura report no financial relationships with commercial interests.

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What do teachers know about Tourette syndrome?

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Introduction and objectives: Teachers receive little education about Tourette Syndrome (TS) (Shady et al., 1988) and most students with TS view teachers as not knowledgeable (White et al., 2011). However, education programs (Nussey et al., 2013) or increased TS severity or impairment may increase teacher awareness and impact knowledge. There are no studies as yet that explore whether improved knowledge about TS translates to teachers' behavior change or better outcomes for students, though enhancing knowledge and attitudes about TS and related conditions may result in greater acceptance (Nussey et al., 2013). We investigated teachers' knowledge of TS and relationships to students' TS severity and impairment.

Methods: Teachers (n = 114) of children with TS and teachers (n = 78) of controls completed the "Teacher Understanding of Tourette Syndrome" questionnaire. We evaluated bivariate associations (Pearson or Spearman correlations) between actual and perceived TS knowledge, and prior TS learning activities. TS and Control groups were compared using independent samples t-tests. Actual knowledge was calculated as the proportion of correct responses to 12 questions about TS. Perceived knowledge was based on teachers' self-assessments of their general understanding about TS.

Results and discussion: Actual TS knowledge was higher among teachers of students with TS (mean = 0.53, SD = 0.09) than control teachers (mean = 0.49, SD = 0.12; t (190) = −2.73, $p < 0.01$ but not YGTSS impairment score (? = 0.18, *ns*). Actual knowledge was not associated with YGTSS total tic (Pearson r = 0.10, *ns)* or impairment scores (r = 0.17, *ns*). The number of teachers' TS learning activities was not associated with actual knowledge, but participation in certain activities was associated with perceived knowledge (Table 1). Perceived knowledge was not associated with actual knowledge in either group (Spearman ? = 0.24, *ns* (Control), ? = 0.08 *ns* (TS).

Tabic: TcaclKts' Perceived Undemanding of TS

	Perceived Understanding[1]					
Participation in learning activity	**Mean NO**	**Mean YES**	**t-value**	**df**	**CI -95%**	**CI +95%**
Support Organization	2.62	3.22	-4.23**	77	-0.88	-0.32
School Inservice	2.81	3.60	-3.66**	76	-1.22	-0.36
Parent Information	2.78	3.03	-1.63 (ns)	77	-0.56	0.06
Personal Learning	2.63	3.13	-3.38*	75	-0.79	-0.20

*p<.01
**p<.001
[1]Teachers' responses to the question: *"Please rate your current understanding of Tourette Syndrome on a scale of 1–5:1 = 'no understanding of TS; 5 = complete understanding of TS'"*

Conclusion: Teachers of students with TS knew slightly more about TS than did teachers of controls, but self-perception of TS knowledge was unrelated to actual knowledge. Severity or impact of tics may not be associated with what teachers actually know about TS.

Acknowledgement

Study Sponsor: CDC Grant U01DD000510.

Disclosures

Dr. Augustine and Dr. Mink serve on the scientific advisory board of the Tourette Syndrome Association (TSA) Dr. Bitsko is a Health Scientist at the Centers for Disease Control and Prevention (CDC) Dr. Lewin (in the past 5 years) has research support from the International OCD Foundation, NARSAD, USF Research Council, travel support from the Tourette Syndrome Association (TSA), Rogers Memorial Hospital, USF Research Council the American Psychological Association, and the National Institute for Mental Health, and honoraria from Springer Publishing, Elsevier, TSA the Children's Tumor Foundation, and the University of Central Oklahoma. He has served as an educational consultant for Prophase, LLC. Dr. Lewin is a member of the scientific and clinical advisory board for the International OCD Foundation and is on the executive board for APA Division 53 – Society for Clinical Child and Adolescent Psychology. Dr. Murphy has received research support from the International OCD Foundation (IOCDF), National Institutes of Health, Florida Mental Health Institute, Otsuka Pharmaceuticals, Pfizer, Inc., F. Hoffmann-La Roche Ltd, Shire Pharmaceuticals, Neurocrine Biosciences, Inc., Psyadon Pharmaceuticals, and Auspex Pharmaceuticals. Dr. Murphy was on the Medical Advisory Board for Tourette Syndrome Association and is on the Scientific Advisory Board for IOCDF. She receives a textbook honorarium from Lawrence Erlbaum.

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Examining partial-interval recording as a treatment outcome measure

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Introduction and objectives: Researchers often rely on indirect measures of tic assessment, rather than direct measures, to evaluate treatment outcomes for Tic Disorders. Studies that do utilize direct assessment measures often use exact tic counts to evaluate treatment effectiveness rather than more pragmatic direct assessment measures, such as partial-interval recording (PIR). Although evidence regarding the utility of PIR is mixed (Himle et al., 2006; Piacentini et al., 2006; Lane and Ledford, 2014), its practicality is irrefutable. The current study examined whether PIR can be used to predict treatment effectiveness as determined by scores on the Clinical Global Impressions- Improvement Scale (CGI-I; Guy, 1976) above and beyond scores on the Yale Global Tic Severity Scale (YGTSS; Leckman et al., 1989).

Methods: Analysis was performed on data from 93 children (M = 11.75 years, SD = 2.40) with Tourette's Syndrome or a chronic Tic Disorder who enrolled in a randomized control treatment study. Forty-one of these participants were received Comprehensive Behavioral Intervention for Tics (CBIT; Woods et al., 2008) group and 52 were received supportive psychotherapy and psychoeducation. As part of their baseline and post-treatment (10-w) clinic visits, participants were assessed with the YGTSS and were videotaped for 10-m. Videotapes were coded subsequently using the partial interval coding technique. For this technique, coders indicate the presence of a motor and/or vocal tic in each 10-s video interval. The percentage of intervals in which tics were observed was used as the PIR measure.

Results and discussion: ANCOVAs were used to examine whether PIR was able to identify CBIT as the effective treatment. An ANCOVA demonstrated that there was a main effect of treatment assignment on post-treatment YGTSS scores when controlling for baseline YGTSS scores, F (1, 90) = 8.12, p = 0.005. However, when controlling for PIR at baseline, (IOA = 98%) there was not a significant main effect of treatment on PIR at post-treatment (IOA = 0.99%), F (1, 90) = 0.56, p = 0.46. To examine whether PIR data was as useful as the YGTSS in predicting treatment outcomes as measured by the CGI-I, a regression was used. Change scores were computed for PIR scores and YGTSS scores by subtracting baseline scores from post-treatment cores and were entered into a multi-linear regression model to predict post-treatment CGI-I scores. YGTSS scores significantly predicted CGI-I scores, ? = 0.75, p < 0.001. However, PIR change scores did not significantly predict post-treatment CGI-I scores, ? = 0.08, p = 0.27. These results suggest that PIR scores may not be useful in measuring treatment outcomes for large scale randomized trials evaluating treatments for Tourette syndrome. Future research efforts should be exerted to identify alternative measures of tic assessment that are both practical and sensitive to change.

Disclosures

Piacentini, Woods, Scahill, Wilhelm, Peterson, Walkup receive royalties from Oxford University Press. Woods, Piacentini, and Walkup receive royalties from Guilford press.

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Network analysis on Tourette syndrome associated genes using genomewide data

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Introduction and objectives: Tourette syndrome (TS) is a neurodevelopmental disorder with a complex genetic background characterized by vocal and motor tics. Analyzing 4220 TS cases of European ancestry and 8994 ancestry-matched controls from the first (Scharf et al., 2013) and second (Yu et al., In preparation) genome-wide association study (GWAS) of TS, we investigate the molecular mechanisms underlying TS by performing protein-protein interaction analysis and constructing networks of genes that harbor the top TS-associated and potentially functional SNPs.

Methods: Using DAPPLE (Rossin et al., 2011), we construct networks of the top TS associated genes, looking for significant physical connectivity among proteins encoded for genes in loci associated to disease according to protein-protein interactions reported in the literature. Using a novel ranking method developed for prioritizing genes and variants according to functional annotations, we rank variants by functional importance, exploiting information from open-source annotation databases. Using Cytoscape and combined information from our protein-protein interaction and prioritization analysis we build networks of genes that are implicated in TS etiology.

Results and discussion: Our ranking method prioritizes various genes and single nucleotide polymorphisms (SNPs) playing a role in neurogenesis (PNMA1, EPHA1) and our network analysis reveals pathways related to nervous system and signaling pathways. Protein interaction networks from DAPPLE reveal genes involved with cell adhesion, neurotransmission, and neuronal cell development (including NRG1, GABRA2, NEUROG1, CSDC2).

Conclusion: Our analysis reveals novel genes operating together in the aetiology of TS.

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Dental approach on neurofunctional disorders

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Introduction and objectives: One point of view on neurofunctional orders and disorders are from dental side. Upcoming effects mostly starting after early childhood.

Embryological reasons are common for TIC and Tourette. The search for the starting point is beginning in "Carnegie 7–8"(day 19–23) when proliferation gives the change from chondrosis to ossification. Before Carnegie 7 it is only soft tissue. That stadium is the part of research to find out the reason for those disfunctions.

http://www.embryology.ch/francais/bvueOrgan/vueorgan.html#anc22

Carnegie 9 gives us the information on 3 coming up somites.

http://www.ehd.org/virtual-human-embryo/stage.php?stage=9

http://www.ehd.org/virtual-human-embryo/intro.php?stage=9

Somites becoming vertebra and all corresponding tissue. Furthermore it becomes the junction to extremities and head. Therefore we have to search for the possibility why Tourette/ TIC and other neurofunctional disorders can start. It is the junction between these somites and brain and extremities. All (mostly) functions of movements have to be coordinated by the brain. Brain is influenced from primary elementary conditions and educated circumstances. We already know human's education may directed into severe fields. Some we call "genetic 'some' habits".

If deviations happen in early time we may see some. Some not. Tourette/TIC only appears after uprighting of a child. Only that time we recognize it.

Methods
Why?

Functions for muscles/movements are brain programmed and streamed by nerve tracks. Along my experience I found that spine and occlusion may show us one reason for neurofunctional disorders. It is known that our brain is the programming part for our functional abilities (except some nerval immediate reactions). More it is located in the head and there is only one way to reach all extended locations. If there is a barrage or deviation from the Atlas to C3 no correct information will be transported. It starts mostly in early childhood or by sudden hits.

Some cases end with Tourette/TIC.

It is visible that long lasting unusual motocerebral effects give wrong order to an estimated aim (especially: arms, legs, speech).

One way to find out whether Tourette/TIC belongs to dental subground is to check spine and occlusion and alignment. I found out that spine disorder gives wrong occlusion and opposite. Together they give non regulative programming or disprogramming. We regularly don´t know which was the first problem but to check both parts does give the chance to correct.

Results and discussion: With simple testing's I found out teeth and spine posture are based on idioms for Tourette/TIC. I want to show and learn you how to assist patients to get free from there disability and to stay with more quality. The changing period after getting the proper teeth positioning and spine posture is from 1 to 18 month. The advantage during the change is the absence of the disorder. Having reached the new posture and occlusion patients are free and no more treatments are necessary.

Conclusion: I want to show and demonstrate a new way of treatment to aligne disorders. It is much more visible and to demonstrate instead of writing. After having seen once the change people may understand the importance of "to be upright".

My abstract is not along what you estimated to get usually. Anyway I try to give you the chance to learn something on Tourette and TIC. My approach is as much different from others and from written words.

God bless you.

Acknowledgement

Atlas therapy Dr. Arlon, France.

References

There is no reference as none has done before. I never heard, read and found anything on this subject.

Medical cannabis for the treatment of Tourette syndrome; a descriptive analysis of 10 patients

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Introduction and objectives: Several single case studies have suggested that marijuana might be effective in suppression of tics and in the treatment of associated behavioral problems in Tourette syndrome. Two small controlled trials have demonstrated beneficial effects of delta-9-tetrahydrocannabinol, the most psychoactive ingredient of cannabis sativa, in the treatment of tics in patients with Tourette syndrome (Müller-Vahl, 2013).

Methods: A descriptive analysis of a "real world" cohort of 10 patients with multiple treatment-resistant Tourette syndrome treated with medical cannabis.

Results and discussion: The cohort consisted of 9 adult male (average age 27, range 20–42) and 1 female (age 26) that did not respond satisfactorily to multiple medication regimens. The patients were treated at the Tourette clinic of the movement disorder unit in a tertiary hospital. The patients received a permit for cannabis from the Israel Medical Cannabis Agency. Doses were between 20 and 40 g/month. Six patients were treated with cannabis oil drops orally, and 4 patients were treated with cannabis by smoking. The duration of treatment varied between 6 and 18 months. None of the patients discontinued treatment. Three patients remained with a steady dose of 20 g/month and 7 patients increased the dose from 20 to 40 g/month.

All the patients were satisfied with their improvement following treatment with medical cannabis and reported a meaningful reduction in the quantity of tics, as well as in tic intensity. They reported a decrease in premonitory urges that resulted in alleviation of stress and also a reduction in tic-associated pain. All patients experienced improvement in their functional abilities; some of them began academic studies, others were able to improve their work capabilities. Eight patients reported an improvement regarding interpersonal relationships. Six patients described attenuation of their obsessive compulsive behavior. No worrisome side effects were noted.

Conclusion: In this small cohort of Tourette patients, treatment with medical cannabis resulted in subjective improvements in symptom severity, functional status and interpersonal and family relationships. Prospective controlled trials of medical cannabis for the treatment of severe, resistant Tourette syndrome are warranted.

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Behavioural therapy via Skype

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Introduction and objectives: Behavioural therapy has been shown to be an effective treatment of tics (Piacentini et al., 2010). In the Tourette Clinic at the paediatric department of Herlev University Hospital, we have offered this treatment since 2013. In December 2014, the Danish translations of the original Dutch treatment manuals were published (Verdellen et al., 2011). Since we have patients with Tourette syndrome from the whole country, some patients need to travel for several hours to come to our clinic. Therefore, it can be difficult for them to participate in behavioural therapy. In this pilot study, we want to examine the effectiveness of behavioural therapy via Skype and we hypothesize that its effectiveness is comparable to behavioural therapy with weekly sessions at the Tourette clinic.

Methods: We started a pilot project with Skype in December 2014. Until now, 10 patients have participated. Before starting behavioural therapy, the family is introduced to the methods during a meeting at the Tourette clinic and if behavioural therapy is indicated and feasible, sessions two to eleven will be offered via Skype. The last session takes place at the Tourette clinic. Both before start and after the 12th session, the following instruments are used to assess the effectiveness of the treatment:

1. Yale Global Tics Severity Scale (YGTSS).
2. Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS).
3. ADHD-Rating Scale (ADHD-RS).
4. PedsQl (Quality of Life).

We will compare these results with the other patients from our clinic receiving behavioural therapy with weekly sessions at the Tourette Clinic.

Results and discussion: We will present the results on tics severity, comorbidity, and quality of life of the patients joining the pilot study. If the effectiveness of behavioural therapy via Skype turns out to be equally effective compared to behavourial therapy with weekly sessions at the Tourette clinic, we will offer Skype-treatment to all the patients who find it difficult to physically meet weekly at the Tourette clinic.

Conclusion: If behavioural therapy via Skype turns out to be as effective as behavioural therapy with weekly sessions at the Tourette clinic, it will be possible to offer behavioural therapy to many more patients with Tourette syndrome in Denmark.

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EQUIPE: A French parent group intervention for children with behavior problems

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Introduction and objectives: Behavior problems (such as aggressiveness, hyperactivity and withdrawal) are frequently associated with Tourette Syndrome (TS). Behavior problems are frequently the main reason for demand of mental health services for children (Wilens et al., 2002) including those with TS, because of their major impact on the development of the child, his/her family, his/her schooling and socialization (Caspi et al., 1996). Parenting attitudes are the most important environmental factor in the onset and evolution of behavior problems in children. Indeed the use of inappropriate interventions by parents influences the emergence and evolution of behavior problems in young children and, to the contrary, a positive parenting intervention may promote better behavioral and social development. It is now well established that children with behavior problems will have better personal development, academic performance and social relationship if effective interventions are implemented, especially at an early age (Daley et al., 2009). That is the reason why many parent psychoeducation programs have been used to reduce behavior problems in children. In particular for preschool children, studies recommend a Canadian program known as the Community Parent Education Program (COPE) (Cunningham et al., 1995), COPE is a brief, cost-effective intervention delivered in community setting. The efficacy of this evidence-based large group interventions had not been explored in French population.

The objective is (1) to evaluate the effects of the French version of COPE program (EQUIPE) in behavior problems and parent stress in Canadian French population and (2) to study the barriers and facilitators of its implementation in a community setting.

Methods: A mixed qualitative/quantitative study have been conducted in Quebec city area, including 9 local community services.

Repeated measures of behavior problems (CBCL) and parenting stress (Parental Stress Index PSI) had been measured pre- post and 6 month after the intervention.

Manova analysis has been conducted for the repeated measures of *T* scores CBCL scores and PSI scores. significant level was set at $p < 0.05$

Results and discussion: Nine intervention groups were held between April 2012 and 2014. A total of 288 parents of preschoolers (101 children, mean age = 4 years) with behavior problems enrolled in the program, Significant improvement had been found for all CBCL subscales *T* scores before and after participation to the program ($p < 0.001$), as well as between pre and 6 months post-program. No significant difference was found between the scores after the participation and 6 month later. Improvements in PSI scores were significant between before and after the program ($p < 0.001$) as well as before and 6 months after the program.

Qualitative data shows a high level of parents satisfaction with program participation.

Conclusion: EQUIPE, the French version of COPE program has a significant effects in improving behavior problems in children and reducing parental stress. This improvement is maintained until 6 month after participation to the program, with a high level of parent satisfaction.

Disclosures

Leila Ben Amor has received honorarium as a speaker and member of advisory committee for pharma compagnies (Shire, Jansen-Orth. Ely-Lilly and Purdue) (2006–2013)

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Aggressive symptoms in children with tic disorders

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Introduction and objectives: Sudden and explosive episodes of anger or aggression are a postulated to be a significant source of psychosocial morbidity in children and adolescents with tic disorders but this is controversial. Sudden and explosive episodes of anger or aggression, occur between 25 and 70% of patients with TS (Budman et al., 2000; Freeman et al., 2000; Cavanna et al., 2008).

Objectives: To study the relationship between tic disorders, their associated comorbidities, and aggressive behavior

Methods: Fifty six children and adolescents (ages 7–17) suffering from Tourette syndrome or other chronic tic disorder were assessed. Thirty two healthy children served as control group. The participants were assessed by the following questionnaires: Yale Global Tic Severity Scale; Yale Brown Obsessive Compulsive Scale; ADHD Rating Scale IV; Screen for Child Anxiety Related Emotional Disorders; Child Depression Inventory; Overt Aggression Scale.

The internal consistency of the OAS was calculated by Cronbach's alpha. *t*-tests were conducted between TD and control children, and one way analysis of variance (ANOVA) was conducted on OAS scores for TS + ADHD children, TS-ADHD children and healthy children. Finally, a multiple regression analysis was conducted between the significant variables, with the OAS total score as dependent variable.

Results and discussion: Results: No significance difference in aggression score was found between tics group and control group. However, boys with tic disorders reported significantly more aggressive behaviors than girls with tic disorders. Verbal aggression was found in 69.6% of the subjects with tic disorders, which was also the most prevalent type of aggression. The level of aggression was not correlated to tic severity. ADHD and OCD enhanced the probability of explosive outbursts in the group with tic disorder. Aggression score was significantly associated with compulsions. Regression analysis showed that the only significant predictor of aggression was ADHD severity score.

Discussion: Many of the comorbid disorders in TS may be associated with aggressive outbursts Our findings suggest, as do some of previous studies quoted above, that the level of aggression in TS is not correlated to tic severity, but to the severity of comorbidities, such as ADHD, OCD, anxiety and depression. Tourette syndrome children with and without ADHD, demonstrate significant differences.

Conclusion: Our study suggests that there is no difference in aggressive behavior between children with uncomplicated tics and a control group. Thus, aggressive behavior in children with tic disorders is not related to having tics, but rather to the associated co morbidities; ADHD and compulsions.

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Dissemination of behavior therapy for tic disorders to occupational therapists: a pilot study

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Introduction and objectives: The efficacy of Comprehensive Behavioral Intervention for Tic Disorders (CBT) as a treatment for pediatric tic disorders is well documented (Piacentini et al., 2010). However, widespread use of CBIT is impaired by lack of access to providers with adequate training in this methodology (Bennett et al., 2013). Occupational Therapists (OTs) are ideally suited for the delivery and dissemination of CBIT because they are often close collaborators of physicians within pediatric specialties, they receive referrals from physicians for young children with common tic co-morbidities (i.e., sensory integration difficulties, attention problems), and they offer a system of treatment that is typically accessible, low in stigma, covered by insurance, and connected to medical referral networks. In addition, many OTs are well trained in functional and behavioral methods of intervention, similar to the model used in Comprehensive Behavioral Intervention for Tic Disorders (CBIT) (Woods et al., 2008). The objectives of this study were to develop a training program and treatment manual for occupational therapists to learn and deliver CBIT to youth across two study sites (Weill Cornell Medical College and Children's Hospital Alabama at Birmingham), and to assess the feasibility, utility, acceptability and efficacy of this treatment model.

Methods

Study Design: The study is a two-site open trial.

Sample: The sample includes 16 youth ages 7–18 with TS or CTD (YGTSS >16). Youth with significant comorbid symptomatology of higher priority than the tic disorder were excluded due to the insufficient training for the OTs to address comorbid symptoms. Medication was stable prior to study participation.

Measures: Primary outcome measures included the Yale Global Tic Severity Scale (YGTSS) and the Clinical Global Impressions Scale, Severity and Improvement (CGI-S/I), as well as OT and patient indicators of satisfaction with the treatment model.

Results and discussion: Following initial training with the CBIT model, the OTs reported high satisfaction with the treatment and the training (see Table 1). They provided important qualitative feedback on how to improve training methods and increase comfort with the treatment model, including the use of video in training and supervision, in-depth case examples, and a focus on the inter-disciplinary approach of integrating how the theoretical model of CBIT relates to traditional OT approaches.

Table 1 |

Training feedback	**Training 1 N = 6**		**Training 2 N = 4**	
	Mean	**(SD)**	**Mean**	**(SD)**
CBIT "goodness of fit" with OT background	5.0	0	4.75	0.5
CBIT acceptability within OT practice & career	4.8	0.45	5.0	0
Usability of CBIT within OT practice & career	4.8	0.45	5.0	0
Feasibility of CBIT within OT practice & career	4.6	0.89	4.5	1.0
Satisfaction with CBIT training	4.8	0.45	4.25	0.5
Preparedness to implement CBIT	3.9	0.74	4.0	0.82

*Scored on 0–5 likert scale, 5 = maximum.

To date, 13 patients have enrolled in the study and 6 of these participants have completed all study procedures to date. Complete data is expected for all enrolled participants, and we plan to enroll the remaining three participants in the coming weeks. The six patients who have completed the CBIT program showed a statistically significant decrease in reported tic symptoms on the YGTSS (see Table 2). Five of these six participants were rated as Very Much Improved on the CGI-I scale at the end of treatment. Post-treatment parent satisfaction ratings were also strong (Mean = 3.65/4).

Table 2 |

TEST (N = 6)	PRE-TX Mean (SD)	POST-TX Mean (SD)	*T*-score	Significance
YGTSS total score	28.5 (7.5)	15.0 (8.3)	4.30	0.008
YGTSS impairment	23.3 (10.32)	5.0 (5.48)	4.57	0.006
CGI-severity	4.17 (0.41)	2.17 (0.75)	5.48	0.003

- 5 of 6 participants rated as Very Much Improved on CGI-Improvement (Considered Treatment Responder).
- Post-treatment parent satisfaction ratings: Mean = 3.65 (Max = 4).
- 6 participants enrolled at WCMC (4 completed) and 5 participants enrolled at CHA (2 completed).

Conclusion: Thus far, the Occupational Therapists and the families they worked with reported high satisfaction with the CBIT approach, as evidenced by high satisfaction scores and no participant drop-outs. The participant report of pre-treatment tic severity and post-treatment outcome data are consistent with larger CBIT trials. There are limitations inherent in a small uncontrolled open trial study, however these data indicate that using this treatment and training model with occupational therapists holds strong promise for inter-disciplinary dissemination.

Acknowledgements

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Characteristics of children with tic disorders by insurance type and race

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Introduction and objectives: Children with tic disorders are at risk for co-occurring conditions and significant healthcare needs (Bitsko et al., 2014). More non-Hispanic white children have diagnosed tic disorders than other racial/ethnic groups; the reason for this is unknown. This study describes patterns of co-occurring conditions and treatment among insured US children with tic disorders, by insurance type and race/ethnicity.

	Insurance		Race/Ethnicity | (Medicaid only)			
	Commercial	**Medicaid**	**Non-Hispanic White**	**Non-Hispanic Black**	**Hispanic**	**Other**
Any tic disorder	0.11% N=9,431	0.12% N=2,211	0.17% N=l,531	0.05% N=321	0.05% N=97	0.13% N=262
Co-occurring conditions						
Any mental disorder (of 11}	51.0%	67.8%	71.3%	63.6%	32.0%	66.0%
Any chronic health condition (of 4)	12.2%	19.0%	16.2%	25.5%	23.7%	25.6%
Treatment						
Medication only	20.7%	36.1%	35.5%	35.5%	29.9%	43.1%
Psychological service only	18.5%	7.2%	8.0%	6.5%	6.2%	4.2%
Both	16.5%	31.5%	33.5%	29.9%	12.4K	29.0%
Neither	44.3%	25.1%	23.1%	28.0%	51.6%	23.7%

Methods: Data from the 2011 MarketScan database on paid medical and prescription drug claims were used to identify children aged 6–17 covered by Medicaid (public insurance; n = 1,884,732) in 11 states and commercial insurance (n = 8,678,355) in the US. Race/ethnicity data were available for Medicaid only. Children with tic disorders were identified by having two tic disorder codes (307.2×). Co-occurrence of 11 mental disorders and four chronic health conditions (asthma, cerebral palsy, diabetes, epilepsy) was calculated. Medication treatment was defined by having at least one claim for a medication that is used to treat tic disorders; psychological treatment required at least one claim for a psychological service (PS). Mutually exclusive treatment groups were created: both medication and PS, medication only, PS only, or neither.

Results and discussion: The presence of tic disorders was similar by insurance type, while co-occurring mental disorders and other chronic health conditions were more common among those with Medicaid than commercial insurance. Treatment varied by insurance type: 75% of children with tic disorders in Medicaid received either treatment compared to 56% of children with commercial insurance. Children with Medicaid were more likely to receive medication only while children with commercial insurance were more likely to receive PS only.

Considering race/ethnicity within the Medicaid sample, non-Hispanic white children were most likely to have a tic disorder and co-occurring mental disorders but less likely to have a chronic health condition compared to the other racial/ethnic groups. Treatment varied less by race/ethnicity; however, Hispanic children were most likely to receive "neither" treatment, and non-Hispanic white children were most likely to receive PS only or both treatments.

Conclusion: The prevalence of identified tic disorders was low (Knight et al., 2012; Bitsko et al., 2014) and varied by race/ethnicity, but not insurance type. Differences in co-occurrence and treatment patterns among children with tic disorders were noted by insurance type and race/ethnicity (among children in Medicaid). Children with tic disorders were more likely to receive medication only regardless of insurance type or race/ethnicity; however, over one-third of children with tic disorders in all groups except for Hispanic children with Medicaid received some PS.

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The association of Tourette syndrome and co-occurring conditions with school measures in US children

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Introduction and objectives: Children with Tourette Syndrome (TS) are at risk for co-occurring conditions and school problems. This study examines the relationship between TS and co-occurring conditions with school measures.

Methods: Data were pooled from the 2007 and 2011–12 National Survey of Children's Health (Blumberg et al., 2012; Blumberg et al., 2013), a nationally representative telephone-based survey of parents of children aged 0–17 in the United States. Parents reported about their child's health and well-being, including whether a healthcare provider had ever told them their child had certain conditions, and if so, whether the child currently had those conditions. The analyses included current TS and co-occurring mental, emotional and behavioral conditions (MEB: attention-deficit/hyperactivity disorder; behavioral or conduct problems; depression; anxiety problems; autism spectrum disorder) and learning and language conditions (LLC: developmental delay; speech and language problems; learning disability; intellectual disability). Parents rated current TS as mild, moderate or severe.

School measures included (past 12 months): type of school attended (public, private, home); whether child had an individual education plan (IEP); number of school days missed for illness or injury; and how many times parents were contacted about school problems. Parents also reported whether the child cared about doing well in school, whether the child does all required homework, and whether the child had repeated a grade.

The pooled sample size was 129,353 children aged 6–17 years. Weighted descriptive and regression analyses accounted for the complex sampling design. Children with current TS and without TS were compared on each school measure using prevalence ratios. Partially adjusted prevalence ratios considered the effect of age, sex, and race/ethnicity, and fully adjusted prevalence ratios additionally considered presence of a co-occurring condition.

Results and discussion: Among children with current TS, 79.9% had a MEB or LLC compared to 17.6% of children without TS. Among children with TS, 75% had a MEB and 52.9% had a LLC, versus 13 and 10.7% of children without TS, respectively. TS was more often described as mild (67.9%) than moderate or severe (32.1%).

After adjusting for demographics, compared to children without TS, children with current TS were more likely to have an IEP, have a parent contacted about school problems, and not complete homework (all $p < 0.05$).

Conclusion: TS severity and co-occurring conditions are associated with school challenges and educational service needs. Healthcare providers, teachers and parents need to be aware of the potential challenges related to both TS and co-occurring conditions in order to best support the child's education.

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The effect of a cognitive -behavioral treatment for the reduction of explosive outburst on anxiety and depressive symptoms in a population of children with Tourette syndrome

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Introduction and objectives: Tourette Syndrome (TS) is a neurodevelopmental disorder according to the DSM-5 (American Psychiatric Association, 2013), which is characterized by the presence of multiple motor tics and at least one sound tic that occurs before the age of eighteen. The opposition and aggressive behavior is generally high in children with Tourette syndrome (TS). Of these, 35–70% have explosive outburst (EO) which are characterized by excessive tantrums that occurs from sudden and recurring basis (Budman et al., 2000). The prevalence of symptoms of concurrent disorders is high among children with EO. Among others we include mood disorders in 28–50% and anxiety disorders in 10–30% of cases (Budman and Feirman, 2001; Brand et al., 2002; Cath et al., 2011; McNaught and Mink, 2011; Rizzo et al., 2012; American Psychiatric Association, 2013; Leclerc and Forget, 2013; Bitsko et al., 2014). The presence of EO in children with TS, is considered, by the parents like the symptom that cause the most disruption in terms of overall functioning (Sukhodolsky et al., 2003). The "Prends ton Tourette par les Cornes!" (PTC) (Leclerc et al, 2011, 2012) has been shown effective in reducing the EO symptoms. Moreover, the EO are influenced by the presence of concurrent disorders and those symptoms can modulate the efficacy of treatments. Our study focuses on whether or not the PTC program has an effect on the symptoms of the associated disorders.

Methods: Thus, participants (n = 6) received therapy and measures of their depression and anxiety symptoms were assessed using the *Achenbach system of empirically based assessment* (ASEBA) (Achenbach and Rescorla, 2001). These measures were collected pre-treatment and post-treatment and will be analyzed to demonstrate the effectiveness of the PTC program in the reduction of depression and anxiety symptoms.

Results and discussion: The test results will be discussed in terms of the acquisition of cognitive skills focus on reducing the EO (e.g., cognitive restructuring), which could also influence the management of associated disorder symptoms.

Conclusion: By gaining cognitive skills, the children will be able to generalize their learning and will be able to reduce their symptoms of anxiety and depression.

Disclosures

There is no conflicts of interest

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Evaluation of meta-cognitions in Tourette syndrome, chronic tics disorders and the co-occurrence of obsessional symptoms in Tourette syndrome in a cognitive behavioral treatment

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Introduction and objectives: Tourette syndrome (TS) and chronic tics disorders (CTD) are neurodevelopmental disorders characterized by multiple motor and/or phonic tics (APA, 2013). The presence of a co-occurrence of another condition, such as obsessive-compulsive disorder (OCD), may have a greater impact on the daily life functioning (APA, 2013). The comorbidity of a CTD with OCD varies between 25 and 63% (Holzer et al., 1994). Several studies have shown that cognitions process and chronic inner tension contributes to the appearance of CTD and also to some characteristics of TS (Swain and Leckman, 2005; O'Connor et al., 2010; Leclerc et al., 2010). According to O'Connor (2002), cognitive factors are implicated in the emergence and the maintenance of tic behavior. The aim of this study is to explore if the self-reported presence of thinking about tics are direct triggers of tic in 3 groups: Tourette syndrome, persistent chronic tics disorders and Tourette syndrome with obsessive-compulsive symptoms.

Methods: Eighty-six participants were recruited by the *Centre d'études sur les troubles obsessionnels-compulsifs et les tics* of the *l'Institut Universitaire en santé mentale de Montréal.* This study is part of an initial study led by O'Connor, Lavoie and Aardema (2003, 2009). To be included in the study, participants must have a primary diagnosis of Tourette syndrome or chronic tics disorders and be aged between 18 and 65 years. The participants had followed a Cognitive and Psychophysiological treatment (Cops) of O'Connor (2005) to reduce the severity of tics. The treatment work on thoughts and meta-cognitions in the appearance of the tics (O'Connor et al., 2009). The Yale Global Tic Severity of Scale (YGTSS) (Leckman et al., 1989) has been used to confirm the primary diagnosis, chronicity and severity of chronic tics and Tourette syndrome. The Thinking about tics inventory (THAT) (O'Connor et al., 2014) has been use to measure if thoughts, anticipation and judgments can trigger a tic. A Pearson correlation will be done between the score on YGTSS in the 3 groups and the score on the THAT questionnaire in pre-treatment and post-treatment. Also, *t*-test analyses will be done for the 3 groups to compared the result on the THAT questionnaire on pre and post-test.

Results and discussion: The research hypotheses are: (a) more severe symptoms of TS and CTD on the YGTSS will predict a higher score on the THAT questionnaire in pre-treatment; (b) a diminution of symptoms of TS and CTD on the YGTSS of the 3 groups on post-treatment will predict a lower score on the THAT questionnaire at the post-treatment and (c) the group with obsessive-compulsive symptoms in comorbidity with TS will have a higher score on the THAT questionnaire, than the TS and CTD group, considering that reasoning process involve in OCD at the pre and post-treatment (APA, 2013). So theses analyses will check if the self-reported presence of thinking about tic are direct triggers of tic in the 3 groups.

Conclusion: This study will have clinical implications for the importance of cognitive reasoning in TS and CTD. Furthermore, this study will validate the importance of cognitive reasoning in the CTD and TS by showing whether the cognitive component of treatment Cops will reduce harmful thoughts on maintaining tics.

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Centre d'études sur les troubles obsessionnels-compulsifs et les tics of the l'Institut Universitaire en santé mentale de Montréal.

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The real-time relationship between tics and urges in adults with Tourette syndrome

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Introduction and objectives: Premonitory urges are subjective sensory phenomena that are frequently associated with tics (Robertson, 2011; Crossley et al., 2014) and have been assumed to build up before a tic is executed and to subside subsequently (Leckman et al., 1993). However, the exact temporal relationship between tics and urges remains largely unclear. The purpose of the study was to clarify whether urges increase prior to tics and decrease after the execution of a tic.

Methods: In this study, patients were asked to report the intensity of their urges (0–100%) continuously for 5 min (a) during a baseline condition and (b) during tic suppression. Tics were captured by video. The continuous real-time urge measure resulted in 3000 data points over 5 min and was down-sampled to 300 data points (see Figure 1). Tics were rated per second resulting in 300 tic data points per 5 min (see Figure 1). Tics were rated by two independent raters, judging whether or not a tic occurred in a given second and if so how intense the tic was on a scale from 0 to 100.

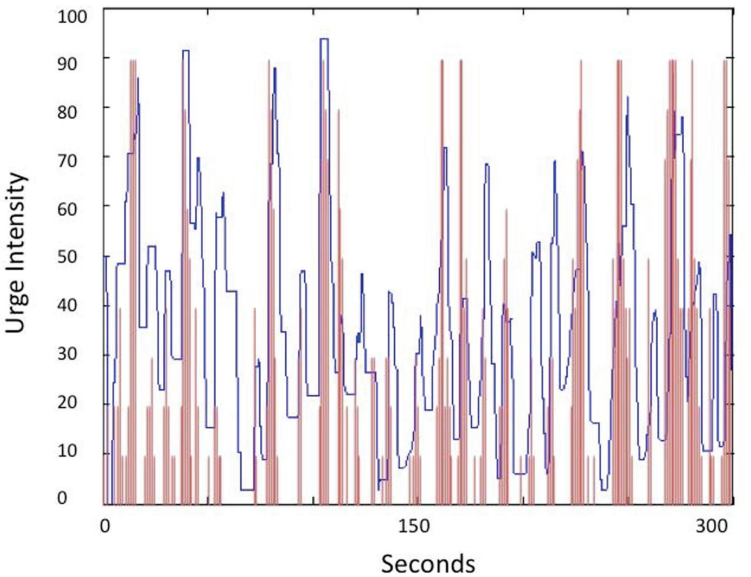

Figure 1 | Displays the data of one patient across 5 min. Real-time fluctuations of the urge are shown in blue, tic events and their intensity are shown in red.

Results and discussion: Data from 17 GTS patients suggests that patients were able to suppress tics in the tic suppression condition and that the mean urge was higher during tic suppression than during baseline. Whether the urge increased or decreased during tic suppression varied across patients. The majority of patients showed only a small temporal relationship between single tics and urges during the baseline condition but a larger relationship between the intensity of tics and urges, indicating an association between the intensity of the urge and the occurrence of bouts of tics. Based on the assumption that urges increase slowly and then return to baseline steeply after a tic or a bout of tics has occurred, a pattern was developed to describe each patient's urge around a tic. The parameters of the pattern were individually optimized and convolved with noted tic-occurrence. Mean, variance and skewness of the patterns will be reported.

Conclusion: The data show that urges co-vary with bouts of tics rather than individual tics. The exact pattern of an urge surrounding a tic varies across patients. Moreover, urges do not subside in all patients under tic suppression.

Disclosures

No conflict of interest

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Twenty-four-year unremitting course of facial tics in progressive catatonia complicating autism spectrum disorder

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Introduction and objectives: Differentiating tics (Brasic et al., 2000), catatonia (Brasic et al., 2000; Neumärker, 2006; Schieveld, 2006; Ross, 2014), autism (Brasic et al., 2000; Neumärker, 2006; Schieveld, 2006; Ross, 2014), and schizophrenia (Schieveld, 2006; Ross, 2014) can be challenging. The occurrence of tics (Brasic et al., 2000; Ohta et al., 2006), catatonia (Brasic et al., 2000; Ohta et al., 2006), and autism (Brasic et al., 2000; Ohta et al., 2006) in young adults suggests possible underlying neuronal mechanisms (Dhossche et al., 2006). We hypothesize that tics in people with progressive catatonia and autism spectrum disorder reflect marked sensitivity to exposure to dopamine-receptor blocking drugs and other environmental influences.

Methods

Subject

Case report (Brasić et al., 1999; Brašic et al., 2000)
A 39-year-old man in childhood demonstrated abnormalities of speech and communication and an unusual range of interests and activities consistent with autism spectrum disorder.
At age 13, after his teacher told him that he would not be promoted from eighth grade, he told his mother that he wanted to go to high school. That was the last time that his mother heard him speak. After making clicking sounds for a few weeks, he made no communicative sounds altogether.
At age 14 years and 8 months his performance intelligence quotient was 63 on the Revised Wechsler Intelligence Scale for Children (WISC-R) (Wechsler, 1974).
At 14 years and 11 months he was administered 1 mg benztropine mesylate twice daily and 1 mg haloperidol each morning and 3 mg at bedtime for a month. Due to lack of improvement, the treatment was then stopped.
At 17 years, his parents noticed weakness of the right arm and leg and dragging the right leg.
At 18 years of age he required assistance for feeding.
At 18 years 5 months he required assistance with toilet activities and dressing.
At 18 years 8 months, a left sural nerve biopsy and a left deltoid biopsy were performed.
At 19 years 8 months, he received a course of 25 electroconvulsive treatments without improvement.
At 39 years, he is unable to perform activities of daily living.

A reliable movement assessment battery (Brasić et al., 1998) was performed sequentially during videotaped sessions to be subsequently rated in a nonblind fashion by the child neuropsychiatrist who performed the initial assessments (Brašic et al., 2000).

Results and discussion: Table 1 summarizes the scores of movement ratings on sequential assessments of a man demonstrating facial tics in progressive catatonia and autism spectrum disorder (Brašic et al., 2000). At 18 years 8 months, a left sural nerve biopsy showed degeneration of large axis cylinders (Figure 1) (Brašic et al., 2000) and a left deltoid biopsy showed perimysial fibrosis and type II fiber predominance (Figure 2) (Brašic et al., 2000). These findings are consistent with a degenerative process of peripheral nerves and muscles.

Table 1 Movement ratings[1, 10] of a man with tics in progressive catatonia and autism spectrum disorder[7,8]

Age									
Years	**16**	**17**	**17**	**17**	**17**	**18**	**18**	**19**	**19**
Months	**8**	**4**	**8**	**8.5**	**10**	**3**	**7**	**1**	**2**
Medications	**None**	**None**	**None**	**None**	**D**	**A, D**	**D**	**D**	**D**
General dyskinesias Abnormal Involuntary Movement Scale[11]									
	1	**17**	**15**	**16**	**8**	**13**	**13**	**19**	**19**
TDRS Face[12]	**20**	**21**	**31**	**28**	**27**	**28**	**31**	**27**	**28**

TDRS Neck and trunk[12]	**8**	**8**	**11**	**11**	**8**	**11**	**14**	**17**	**13**
TDRS Upper extremity[12]	**8**	**8**	**13**	**14**	**8**	**8**	**8**	**8**	**8**
TDRS Lower extremity[12]	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**
TDRS Entire body[12]	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
TDRS Total[12]	**48**	**49**	**67**	**65**	**55**	**59**	**65**	**64**	**61**
Akathisia Hillside Akathisia Scale[13]									
OI[13]	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
CGISA[13]	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**
CGIGI[13]	**3**	**4**	**4**	**5**	**4**	**4**	**4**	**5**	**5**
Parkinsonism									
UPDRS MBM[14]	**3**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
UPDRS Activities of Daily Living[14]	**5**	**6**	**10**	**6**	**16**	**21**	**19**	**17**	**14**
UPDRS Motor Examination[14]	**13**	**11**	**11**	**20**	**21**	**22**	**22**	**21**	**17**
UPDRS Complications of Therapy[14]	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
UPDRS MHYS[14]	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
UPDRS SEADLS[14]	**76%**	**71%**	**71%**	**56%**	**10%**	**11%**	**10%**	**16%**	**19%**
UPDRS Total[14]	**21**	**21**	**25**	**30**	**41**	**47**	**45**	**42**	**35**
Stereotypies Timed Stereotypies Rating Scale[15]									
	31	**20**	**50**	**51**	**40**	**81**	**44**	**60**	**59**
Tics TSCGIS[16]									
	0	**3**	**3**	**3**	**3**	**3**	**3**	**4**	**4**
Yale Global Tic Severity Scale[17]									
	8	**13**	**16**	**13**	**14**	**14**	**14**	**16**	**20**
General psychiatric symptomatology Brief Psychiatric Rating Scale Overall JE. et al., The Brief Psychiatric Rating Scale. Psychol. Rep. 10:799–812, 1962									
	22	**25**	**29**	**27**	**31**	**26**	**27**	**28**	**29**
BPRSC[18]									
	22	**20**	**30**	**33**	**30**	**30**	**33**	**32**	**35**
Children's Psychiatric Rating Scale A[19]									
	32	**41**	**44**	**57**	**47**	**53**	**50**	**50**	**52**
Children's Psychiatric Rating Scale B[19]									
	9	**6**	**12**	**12**	**11**	**9**	**10**	**10**	**18**
Children's Psychiatric Rating Scale Total[19]									
	41	**47**	**56**	**69**	**58**	**62**	**60**	**60**	**70**
Attention deficit disorder ADDCGIS[16]									
	0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Obsessive compulsive disorder OCDCGIS[16]									
	0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**

Overall psychiatric functioning Children's Global Assessment Scale*[20]									
	42	36	31	28	9	9	9	9	14
CGIRGE[21]									
	4	4	5	6	4	4	4	6	6
CGI Severity of Illness[11]									
	6	6	6	6	6	6	6	6	6
CGIGI[11]									
	4	5	5	5	4	4	4	6	6
CGI Efficacy Index[11]									
	13	13	13	13	13	13	13	13	13

A 250 mg amoxicillin by mouth daily
D 240 mg diltiazem by mouth daily
ADDCGIS[16] Attention Deficit Disorder Clinical Global Impression Scale[16]
BPRSC[18] Brief Psychiatric Rating Scale for Children[18]
CGIRGE[21] Clinical Global Improvement Rater Global Evaluation[21]
CGISA[13] Clinical Global Impression Severity of Akathisia[13]
CGI[11] Clinical Global Impressions[11]
CGIGI[11,13] Clinical Global Impression(s), Global Improvement[11,13]
MBM[14] Mentation, Behavior, and Mood[14]
MHYS[14] Modified Hoehn and Yahr Staging[14]
OCDCGIS[16] Obsessive Compulsive Disorder Clinical Global Impression Scale[16]
OI[13] Objective Items[13]
SEADLS[14] Schwab and England Activities of Daily Living Scale[14]
TDRS[12] Tardive Dyskinesia Rating Scale[12]
TSCGIS[16] Tourette Syndrome Clinical Global Impression Scale[16]
UPDRS[14] Unified Parkinson's Disease Rating Scale[14]
*On this scale only a higher score indicates better functioning.

Higher levels of gamma-amino butyric acid (GABA) in children with autism than in typical children (Dhossche et al., 2006) suggest dysfunction of GABA-ergic neurotransmission. Grimaces, a tic-like phenomenon present in the current patient, occurred in many individuals with progressive catatonia in autism spectrum disorders (Wing and Shah, 2006; Mazzone et al., 2014). While people with schizophrenia and catatonia may demonstrate marked remissions with lorazepam and/or electroconvulsive treatment, people with tics, catatonia, and autism may be refractory to those interventions (Shah and Wing, 2006). Nevertheless, lorazepam and electroconvulsive treatments remain the recommended treatments for severe progressive catatonia in autism spectrum disorders (Dhossche et al., 2006; Fink et al., 2006; Mazzone et al., 2014).

The onset of progressive catatonia in our patient with autism spectrum disorder after treatment with haloperidol and environmental stress suggests a marked sensitivity to a dopamine-receptor blocking drug exacerbated by negative life events. Degenerative changes in his peripheral nerve and muscle likely result from the immobility that he exhibits since the onset of his catatonia.

Conclusion: A 39-year-old man with a twenty-four-year history of facial tics in progressive catatonia complicating autism spectrum disorder after treatment with a dopamine-receptor blocking drug and stressful life events demonstrated degenerative changes in nerve and muscle biopsies at age 18 years and 8 months. Individuals with autism spectrum disorder may be vulnerable to develop progressive catatonia with facial tics precipitated by environmental stress and exposure to dopamine-receptor blocking drugs.

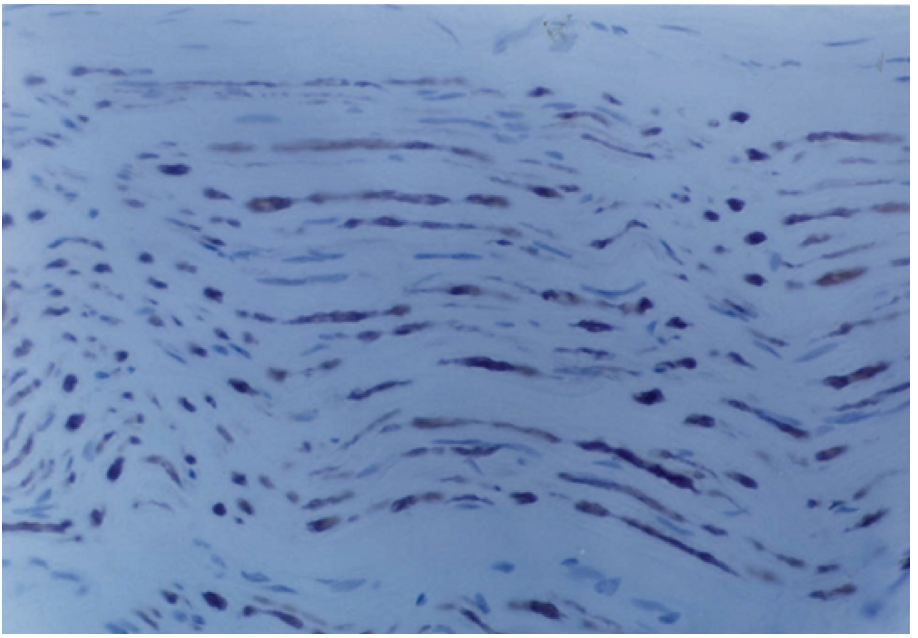

Figure 1 | Immunohistochemistry for neurofilament protein (NFP) of the left sural nerve of a man aged 18 years and 8 months with tics in progressive catatonia complicating autism spectrum disorder. There is loss of axon cylinders (Immunoperoxidase, DAKO 2 F 11 antibody, ABC method, magnification x 100)[8].

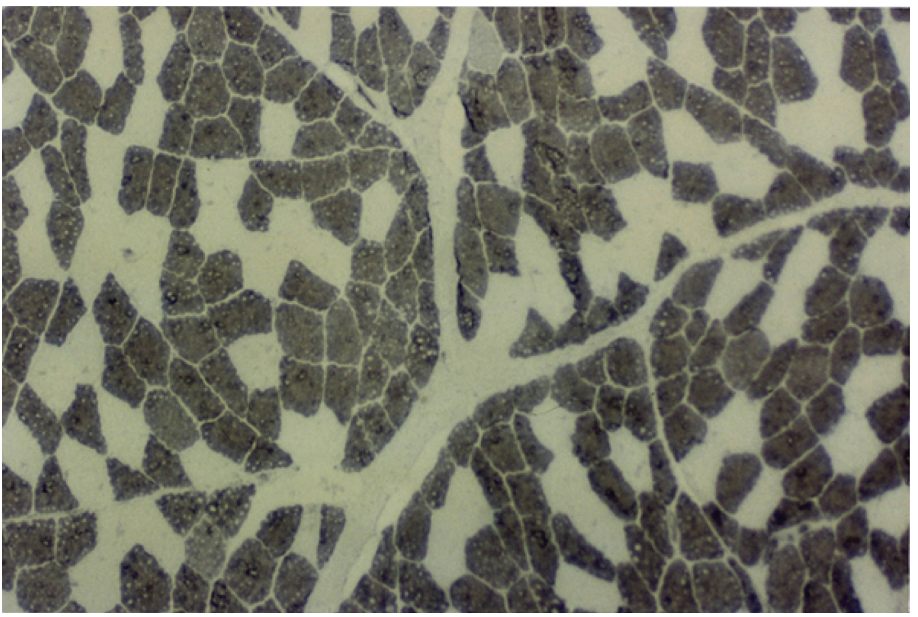

Figure 2 | Muscle biopsy of the left deltoid muscle of a man aged 18 years and 8 months with tics in progressive catatonia complicating autism spectrum disorder. There is a type II myofiber predominance. (ATPase stain, pH 10.4, magnification x 50).[8]

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Disclosures

None

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Almost full remission of Tourette syndrome in a 25-year-old man after heat-induced dehydration

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Introduction and objectives: Anecdotal reports of Tourette syndrome (TS) provide conflicting data about either improvement or worsening with heat (Lombroso et al., 1991). Tourette himself reported that acute fever alleviated tics (Lombroso et al., 1991; Lajonchere et al., 1996). People with autism, another developmental disability, also demonstrate improvement of stereotypies and other movements with high temperature (Brasic, 2014). On the other hand, five of ten adult men with TS demonstrated prominent increments in tics when the ambient temperature was increased from 22°C (71.6°F) to 35°C (95.0°F) (Scahill et al., 2001).

The literature contains contradictory and conflicting reports about the occurrence of remission in TS (Coffey et al., 2000). A remission of TS can be defined as the attainment of a score of <10 for the total (0–50) tics [motor (0–25) and phonic (0–25)] of the Yale Global Tic Severity Scale (Leckman et al., 1989; Coffey et al., 2000). Remission occurs in half of children with TS by age 18 (Leckman et al., 1998; Robertson, 2000). Among 53 children with TS attending a university child neurology clinic, 41.5% experienced a total remission of at least 3 months duration. Failure to attain a remission was associated with an earlier age of onset, a longer duration of the syndrome, and school failure (García-Ribes et al., 2003). Among 53 participants with TS aged 13–31 years attending a university TS clinic, complete remission of tics occurred in a third at a mean age of 17.4 years (Rubenstein et al., 2009). On the other hand, complete remission occurred in 2 of 31 people with TS in another outpatient clinic (Ohta and Kano, 2003).

People with TS typically experience a decrement in tics with dopamine-receptor blocking drugs and an increment in tics from stimulants (Lombroso et al., 1991; Scahill et al., 2001). Release of dopamine in the preoptic area and the anterior hypothalamus plays a role in heat regulation (Scahill et al., 2001). The release of dopamine likely plays a role in mediating the effects of heat on tic intensity in people with TS (Scahill et al., 2001). Mediation of thermoregulation by the dopaminergic pathways from the anterior hypothalamus to the basal ganglia and the substantia nigra may be altered in a subset of people with TS (Scahill et al., 2001).

Retching and vomiting are rarely manifestations of tics in TS (Rickards and Robertson, 1997; Robertson and Stern, 1998; Singer, 2000).

Methods: Since the age of 7 years, a man experienced motor tics, including eye blinking, grimacing, and movements of head, shoulders, and fingers, and phonic tics, including grunting, snorting, and sniffing. Tics were exacerbated by fatigue and anxiety. Tics waxed and waned. Since childhood he experienced multiple tics simultaneously.

Since the age of 10 years, he experienced recurrent episodes of 2–3 months of daily emesis occurring intermittently throughout the year alternating with complete resolution of the emesis for 2–3 months. Each episode of emesis was preceded by an uncontrollable sensation in his throat, a short premonitory awareness of a feeling that the food is going to regurgitate (Rickards and Robertson, 1997). The emesis occurred only when eating solid foods. Emesis fluid never contained bile or stomach contents. He experienced a sore throat when he had emesis. Emesis occurred after one or two bites of food or midway through each meal. He successfully resumed eating after completing the emesis. Antacids did not relieve the emesis. He undertook diets with foods of various textures without beneficial effects. The symptoms occurred only during eating. He had no other swallowing difficulty, no nausea, no abdominal pain, and no odynophagia.

At age 22 trials of clonidine and topiramate produced minimal effect on tics.

At age 23, he began to occasionally smoke marijuana with relief of tics for 3–4 days.

At age 23 years, 5 months, he had his baseline evaluation. For the baseline evaluation please refer to Table 1 for subject assessments and to Table 2 for objective assessments.

Diagnoses. Please refer to Table 3.

Past medical history. At age 13 he was hospitalized for a concussion with loss of consciousness for 90–120 min.

Operations. At age 13 he underwent a tonsillectomy to treat his vomiting without any effect.

Growth and development. He gave a history of untreated attention deficit without hyperactivity as a child. He had problems controlling angry impulses. He has obsessive and compulsive traits.

Table 1. Subjective assessments of a 25-year-old man 7 months before an almost full remission following dehydration in a hot tub at at 103°F (39.4°C) to 104°F (40.0°C) for 3 to 4 hours.

Instrument	Range of scores	Seven months before remission
Compulsion checklist[15]	(0, 111)	10
Dental pain/fear/anxiety[15]	(0, 112)	4
Dental pain/fear/anxiety Mid[15]	(0, 112)	4
Dental pain/fear/anxiety Post[15]	(0, 112)	1
Dental pain/fear/anxiety 1 month follow up[15]	(0, 112)	0
Dental pain/fear/anxiety 3 months follow up[15]	(0, 112)	0
Fear Questionnaire[15]	(0, 192)	8
Social Situations Questionnaire[15]	(0, 192)	13
Questionnaire for tic disorders[16]	(0, 23)	21
Tic Symptom Self Report Motor[17]	(0, 60)	24
Tic Symptom Self Report Vocal[17]	(0, 60)	11
University of Miami Modified Maudsley Obsessive-Compulsive Inventory[18]	(0, 60)	11
Wender Utah Rating Scale (WURS) Behaviors[19]	(0, 168)	46
Wender Utah Rating Scale (WURS) Medical problems[19]	(0, 28)	1
Wender Utah Rating Scale (WURS) School[19]	(0, 48)	11
Wender Utah Rating Scale (WURS) Attention-Deficit/Hyperactivity Disorder (ADHD) items[19]	(0, 100)	39

Table 2. Objective assessments of a 25-year-old man 7 months before and 1 and 11 months after an almost full remission following dehydration in a hot tub at at 103°F (39.4°C) to 104°F (40.0°C) for 3 to 4 hours.

Instrument	**Range of scores**	**Six months before remission**	**One month after remission**	**Eleven months after remission**
Urine drug toxicology for tetrahydrocannabis	Negative or positive	Negative	Positive	Positive
Abnormal Involuntary Movement Scale (AIMS)[20, 21, 22]	(0, 40)	9	0	1
Clinical Global Impression (CGI) Severity Index (SI)[23]	(0, 7)	4 Moderately mentally ill	3 Mildly ill	2 Borderline mentally ill
Clinical Global Impression (CGI) Global Improvement (GI)[23]	(0, 7)	4 No change	2 Much improved	1 Very much improved
Clinical Global Impression (CGI) Efficacy Index (EI)[23]	(0, 16)	13	5	13
Clinical Global Impression (CGI) Therapeutic effect[23]	Not applicable	Unchanged or worse	Moderate	Unchanged or worse
Clinical Global Impression (CGI) Side effects[23]	Not applicable	None	None	None
Clinical Global Impression (CGI) Attention Deficit Disorder (ADD)[24]	(0, 6)	1 Borderline	0	1 Borderline
Clinical Global Impression (CGI) Obsessive-Compulsive Disorder (OCD)[24]	(0, 6)	3 Moderate	2	2 Mild
Clinical Global Impression (CGI) Tourette syndrome (TS)[24]	(0, 6)	3 Moderate	1	1 Borderline

Clinical Global Improvement (CGI) Rater Global Evaluation (RGE)[25]	(1, 7)	4 Unchanged	2 Much improved	1 Very much improved
Hillside Akathisia Scale (HAS) Subjective items[21, 26]	(0, 8)	0	0	0
Hillside Akathisia Scale (HAS) Objective items[21, 26]	(0, 12)	6	0	0
Hillside Akathisia Scale (HAS) Clinical Global Impression (CGI) Severity of Akathisia (SA)[21, 26]	(0, 7)	3 Mildly akathisic	11 Normal, not akathisic	1 Normal, not akathisic
Hillside Akathisia Scale (HAS) Clinical Global Impression (CGI) Global Improvement (GI) [21, 26]	(0, 7)	4 No change	1 Very much improved	1 Very much improved
Brief Psychiatric Rating Scale (BPRS) Anchors[27-31]	(20, 140)	26	21	21
Movement Disorders Checklist[21]	(0, 23)	14	8	0
Myoclonus versus tic checklist[32]	(-2, 6)	6	3	0
National Institutes of Mental Health (NIMH) Obsessive-Compulsive Scale (OCS)[25]	(0, 15)	5	2	1
Rating Scale for Acute Drug-Induced Akathisia (RSADIA) Subjective[33]	(0, 9)	0	0	0
Rating Scale for Acute Drug-Induced Akathisia (RSADIA) Objective[33]	(0, 21)	1	0	0
Rating Scale for Acute Drug-Induced Akathisia (RSADIA) Global Rating[33]	(0, 3)	0	0	0
Rating scale for drug-induced akathisia (RSDIA) Subjective[34]	(0, 6)	0	0	0
Rating scale for drug-induced akathisia (RSDIA) Objective[34]	(0, 3)	1	0	0
Rating scale for drug-induced akathisia (RSDIA) Global Clinical Assessment of Akathisia (GCAA) [34]	(0, 5)	1	0	0
Rating Scale for Tardive Dyskinesia (RSTD) Face[35]	(16, 96)	26	17	18
Rating Scale for Tardive Dyskinesia (RSTD) Neck and trunk[35]	(8, 48)	11	8	8
Rating Scale for Tardive Dyskinesia (RSTD) Extremities (upper) [35]	(8, 48)	11	8	8
Rating Scale for Tardive Dyskinesia (RSTD) Extremities (upper) [35]	(8, 48)	8	8	8
Rating Scale for Tardive Dyskinesia (RSTD) Entire body[35]	(4, 24)	4	4	4
Times Stereotypies Rating Scale[21, 36]	(0, 1000)	27	2	1
Tourette Syndrome Diagnostic Confidence Index (TSDCI)[37]	(0, 100)	61	Missing	82
Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)[38, 39]	(0, 40)	4	10	4
Obsessive-Compulsive Disorder[a] through the application of the current criteria[40] to the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)[38, 39]	(0, 1)	0	1	0

Yale Global Tic Severity Scale (YGTSS) Motor[6]	(0, 25)	19	13	12
Yale Global Tic Severity Scale (YGTSS) Phonic[6]	(0, 25)	9	0	11
Yale Global Tic Severity Scale (YGTSS) Impairment[6]	(0, 50)	27	0	9

[a]Obsessive-Compulsive Disorder (OCD) is diagnosed according to the *Diagnostic and statistical manual of mental disorders, fourth edition, text revision (DSM-IV-TR™)*[40] if on the Y-BOCS a person scores 2, 3, or 4 on any of the following items: 1 time spent on obsessions, or 2 interference from obsessions, or 3 distress of obsessions, or 6 time spent on compulsions, or 7 interference from compulsions, or 8 distress of compulsions.

Table 3. Multiaxial Evaluation at baseline at age 23 years 6 months[40; 41]

Axis I Clinical Disorders	
307.23 Tourette's Disorder	
Axis II Personality Disorders, Mental Retardation	
No diagnosis on Axis II.	
Axis III General Medical Conditions	
Status post concussion	
Status post tonsillectomy	
Axis IV Psychosocial and Environmental Problems	
Occupational problems	
He seeks full-time employment.	
Axis V Global Assessment of Functioning Scale	
Current	81
Highest past year	83

Habits. He has 3 or 4 shots of alcohol monthly. He does not smoke cigarettes. He has occasionally smoked marijuana for a few years for relief of tics.

Family history. His mother has TS. His sister has obsessive-compulsive disorder.

Clinical course. At the age of 24 years and 1 month, he deliberately induced dehydration by entering a hot tub of 103°F for 3 and a half hours. He had read online that dehydration affects dopamine. During the last one and a half hours in the tub, he noticed that his tics had subsided. He reports that his tics have not recurred. After leaving the hot tub, he vomited clear fluid. He drank water because he was thirsty. He then regurgitated the fluid. He did not experience subsequent emesis. After leaving the tub he experienced cramps in his legs, arms, and neck. He then slept overnight. For 2 days after leaving the hot tub, his urine was pinkish orange. He felt weak for a couple of days after leaving the hot tub. Please refer to Table 2 for a record of the multiple assessments to document his improvement. He can now carry a box of wine bottles without dropping any. He is able to work full time as a computer technician. He remains almost completely free of tics for 18 months after heat-induced dehydration.

Results and discussion: At age 25, a young man with TS experienced an almost full remission of symptoms sustained for 18 months after undergoing dehydration in a hot tub at 103°F (39.4°C)–104°F (40.0°C) for 3–4 h. Based on the available literature on spontaneous remission, our patient, with moderately severe, long-standing TS in his mid-twenties, represents an exceedingly low probability for spontaneous remission.

He may have experienced reproductive casualty related to his mother's TS (Pasamanick and Knobloch, 1966). He has inattentive, obsessive, and compulsive traits since childhood. He experienced several traumas in childhood including a hospitalization for a concussion at age 13. These comorbid insults to his brain likely predisposed him to tics through early adulthood. He may be particularly susceptible to the effects of heat and dehydration since he already had an abnormal brain as indicated by his attentional, compulsive, and obsessive traits, and multiple head traumas. People with prenatal, natal, and developmental disabilities likely have cerebral pathology from obstetric and childhood insults.

Their abnormal brains leave them vulnerable to exhibit striking responses to heat, dehydration, and other environmental influences that have negligible effects on healthy people.

Cerebral hyperthermia results in an increased blow flow to the brain (Kiyatkin, 2004). Heat exhaustion is a moderate illness resulting from depletion of water and salt associated with core body temperatures between 37°C and 40°C (Yeo, 2004). Heat produced alterations in excitatory neurotransmitters, aspartate and glutamate, and inhibitory neurotransmitters, gamma-amino-butyric acid (GABA) and glycine (Wetsel, 2011). Since dysfunction of the GABA-ergic system is a major effect of heat on the nervous system, the reduced inhibition resulting from damage to GABA neurotransmission likely results in increased excitatory neurotransmission in response to heat (Wetsel, 2011).

Increased excitatory neurotransmission may stimulate further dopaminergic neurotransmission and may predispose a person to develop seizures (Wetsel, 2011). It is not implausible that sustained excitatory neurotransmission produced a marked phasic increase in dopamine in our patient to effect a lasting effect on thermoregulation by the dopaminergic pathways from the anterior hypothalamus to the basal ganglia and the substantia nigra. The hyperthermia experienced by this man may have reset his thermostat for normal heat-loss mechanisms through dopaminergic pathways from the anterior hypothalamus to the basal ganglia and the substantia nigra. Whether or not that mechanism or some other mechanism relevant to the heat exposure and/or dehydration is at play, the sudden and marked improvement in his tics needs further attention. Prospective testing of the heat and dehydration effect on tics should be pursued. Clinical trials of dehydration and heat on TS may prove beneficial.

Conclusion: A young man with TS experienced a partial remission of symptoms sustained for 12 months after undergoing dehydration in a hot tub at 1038°F (39.48°C)–1048°F (40.08°C) for 3–4 h. The heat exposure may have reset his thermostat for normal heat-loss mechanisms through dopaminergic pathways from the anterior hypothalamus to the basal ganglia and the substantia nigra. Clinical trials of dehydration and heat on TS may prove beneficial.

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Dr. Brasic is a member of the Medical Advisory Board of the Tourette Syndrome Association of Greater Washington.

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The influence of musical engagement on Tourette's syndrome symptoms

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Introduction and objectives: Tourette's syndrome is reported to affect 1 out of every 360 children between the ages of 6 and 17 (Bitsko et al., 2014). Although there have been anecdotal references to music as a therapeutic aid for those who are affected (Leckman, 2005; Sacks, 2010), no empirical research has explored this area as a possible behavioral modifier. This study seeks to identify those who are diagnosed with TS and who regularly engage in musical activities to assess their perceptions of how music influences their symptoms. For purposes of this study, the previous term "engagement" is defined as the active involvement of music making and those being surveyed are self-reported musicians. A review of extant literature suggests some possible connections between the corpus callosum development in TS subjects and musicians (Schlaug et al., 2005; Schlaug et al., 2005; Tallur and Minns, 2010). The exploration into the perceptions of those diagnosed with TS who are musicians is the initial step in validating future research.

Methods: A nine-question survey instrument was created in order to evaluate perceptions regarding the effects of musical engagement has on those diagnosed with TS. Recruitment occurred through advertisements via websites including the TSA-USA.org approved research page and a personally generated research website as well as social media. Internal Review Board protocols included anonymity of survey takers who were of adult age or adults responding for their minor children. Respondents were provided a consent document with an electronic submittal agreement. Participants answered questions regarding demographics, diagnosis and symptoms, musical engagement activities and the perceived effect of those activities on their symptoms. The apex of the questionnaire was a 5-point Likert scale question where 1 = drastic symptoms increase (caused by the musical activity), 3 = no change in symptoms and 5 = drastic symptoms decrease. Responses were saved via a Google spreadsheet document for further analysis.

Results and discussion: The number of survey respondents who reported regularly engaging in a musical activity and having Tourette's was 173 ($N = 173$). Participants included 120 males and 53 females with an average age of 24 years, 6 months. Ninety percent were White/Caucasian. The Likert-scale response to the survey apex was 4.45 (out of 5), suggesting a perception of symptoms decrease while engaged in a musical activity, which warrants future exploration into the reasons for diminution.

Conclusion: Based upon survey responses, further research is merited into music as a possible behavioral modifier. Future studies may also include the introduction of musical engagement activities in order to stimulate the growth of the corpus callosum, which has been found to be smaller in those studied with TS verses control groups (Plessen et al., 2006). Musicians have been found to have altered brain structure (including corpus callosum sizes) especially when prolonged musical training has occurred (Schlaug et al., 2005). Penhune describes the early years of a child's brain development as a "sensitive period" and suggests that early musical training is better for their cognitive growth (Penhune, 2011). Perhaps these studies imply that the early introduction of a musical activity for children with a genetic disposition for Tourette's could alter their brain structure and therefore play a role in the decline or cessation of symptoms onset.

Disclosures

Author reports no conflicts of interest.

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Tourette's disorder in African American youth: rare or rarely diagnosed?

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Introduction and objectives: Little is known about Tourette's Disorder (TD) in African American youth. The reportedly lower frequency of TD diagnosis in non-Hispanic black children does not clarify whether this represents under-recognition, under-diagnosis, or "true" lower prevalence (Robertson, 2008; Scahill et al., 2009; Bitsko et al., 2014).

This pilot study examines characteristics of African American youth evaluated and diagnosed with tic disorders between 2007 and 2012 at outpatient child psychiatry clinic. Hypothesis that TD/other tic disorders are less commonly diagnosed in African American youth was tested.

Methods: Retrospective chart review of youth ages 5–17 years evaluated at metropolitan child psychiatry outpatient clinic from 2007–2012. Identified group diagnosed with DSM-IV-TR tic disorders (i.e., Transient, Chronic motor/vocal tic, Tourette, Tic disorder NOS) and identified sub-group African American youth diagnosed with tic disorders; compared demographic and clinical characteristics for each. Determined frequencies of overall tic disorders and of African American subgroup.

Results and discussion: Overall sample 4,442 youth, mean age 12.5 years, 59.6% male/40.4% female; 22.4% African American, mean age 11.7 years, 63.6% male/36.4% female. Overall 2.1% received tic disorder diagnoses, mean age 11.4 years, 73.1% male (Tables 1 and 2).

Table 1: Demographic characteristics: Youth ages 5-17 years Child Psychiatry Clinic 2007–2012

Demographic Characteristics of Subject Population				
Demographics	**Overall Youth in Sample (4442)**	**African American Youth in Sample (997)**	**All Youth with Tic Diagnoses (93)**	**African American Youth with Tic Diagnoses (5)**
Age (average)	12.5 years	11.7 years	11.4 years	12.7 years
Males	59.6% (2649)	63.6% (634)	73.1% (68)	100% (5)
Females	40.4% (1793)	36.4% (363)	26.9% (25)	0
Current Psychotropic Usage	37.7% (1674)	41.2% (411)	47.3 (44)	40.0% (2)
2 or more Axis I diagnosis	8.8% (390)	7.6% (76)	97.8% (91)	80.0% (4)

Table 2: Frequencies of Tic Disorder Diagnosis in Youths Ages 5-17 years Child Psychiatry Clinic 2007–2012

Tic Disorder Frequencies in American African and Non-African American Youth				
Tic Disorder Diagnosis	**All non-African American Youth with TD**		**African American Youth with TD**	
	Frequency	**Percentage**	**Frequency**	**Percentage**
Chronic Motor/Vocal Tic Disorder	6	6.8%	0	0
Tourette's Disorder	52	59.1%	4	80%
Tic Disorder NOS	23	26.1%	1	20%
Transient Tic Disorder	7	8.0%	0	0

Five African Americans received tic disorder diagnoses, mean age 12.7 years, 100% male, representing 0.1% overall youth and 5.4% all youth diagnosed with tic disorders during study period.

97.8% all youth with tic disorder diagnoses diagnosed with ≥one Axis I co-occurring psychiatric disorder; 47.3% taking ≥one psychotropic medication. 80% African American youth diagnosed with tic disorders had ≥one additional Axis I co-occurring psychiatric disorder; 40% taking ≥one psychotropic medication (Table 3).

Table 3: African American Youth with Tic Disorder Diagnosis Child Psychiatry Clinic 2007-2012

African American Youth Identified With Any Tic Disorders			
Subject	**Age at Diagnosis (years)**	**Tic and Comorbid Psychiatric Diagnoses**	**Psychotropic Medication Status**
1	7.5	TD, OCD, ADHD	aripiprazole
2	7	TD, None	pramiprexole
3	6	TD, None	None
4	13	TD, ADHD-Combined type	None
5	14	Tic Disorder NOS, ADHD, Selective Mutism, Depressive Disorder NOS	None

Conclusion: Impression that tic disorders are less frequently diagnosed in African American youth is supported by lower frequencies of tic disorder diagnoses in this cohort. Our findings may reflect methodology, access, under-recognition, misdiagnoses, cultural and psychological influences on health-seeking behaviors. Whether tic disorders are rare or rarely diagnosed in African American youth remains unclear.

Disclosures

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Exploring the potential utility of eyetracking and cognitive control measures in the diagnosis and treatment of Tourette syndrome

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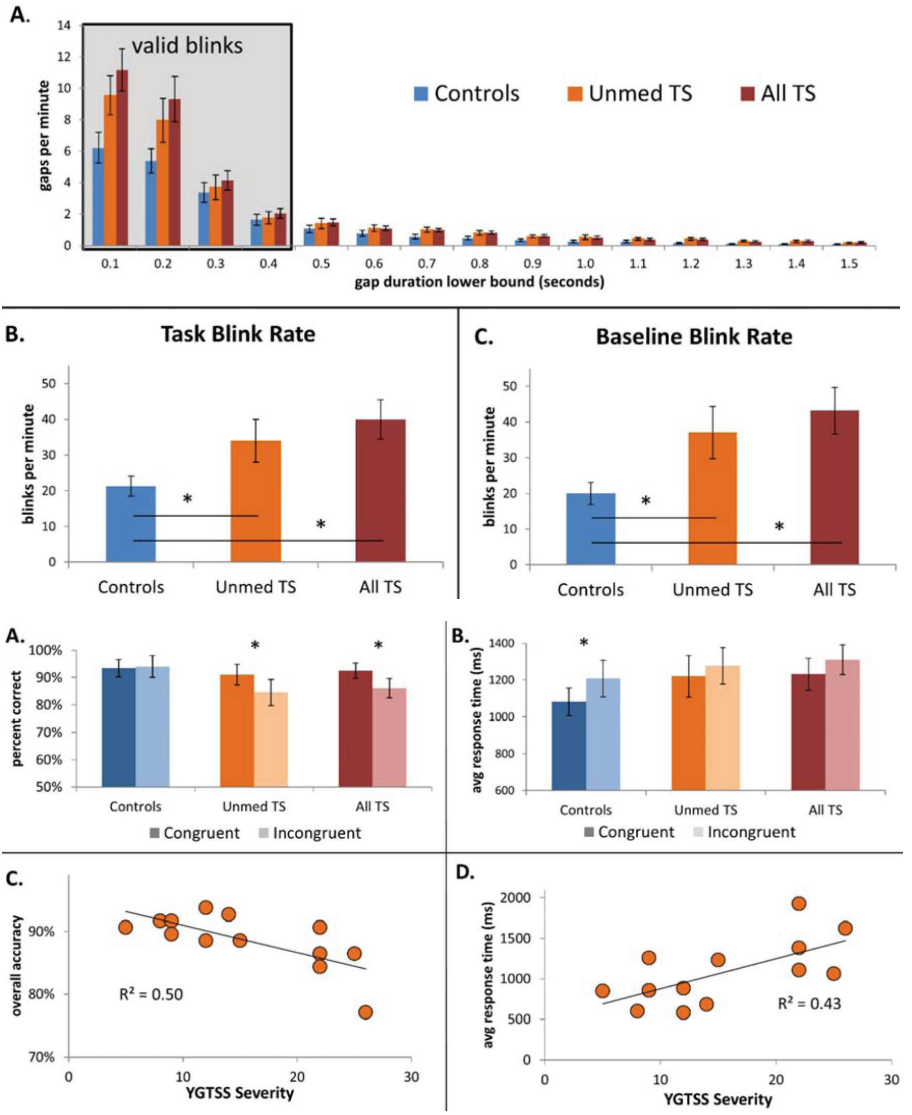
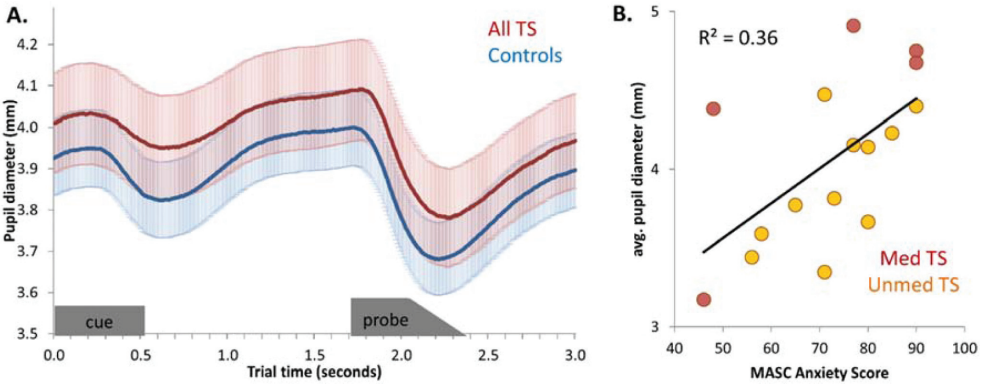
Introduction and objectives: The prognosis of a patient with Tourette Syndrome likely reflects a combination of factors, including the degree to which one or more neurotransmitter systems have been affected (Baym et al., 2008), and the degree to which she/he can exert cognitive control to suppress unwanted tics (Albin et al., 2006). As such, we proposed that measures that reflect neurotransmitter levels, on one hand, and cognitive control on the other, could be clinically useful.





Methods: Here, we used an eyetracker to collect ocular data from 26 children with TS and 26 age-matched controls while they performed a cognitive control task. We measured spontaneous eyeblink rate, which have been linked to DA levels, as well as resting and task-evoked pupil dilation, which depend on NE neurotransmission.

Results and discussion: Our key findings were as follows: (1) Patients with TS exhibited higher spontaneous eyeblink rates than controls, both during task performance and at rest, consistent with elevated tonic DA levels. (2) Contrary to our prediction of a positive relationship between blink rate and tic severity among patients, the correlation was marginally *negative*. (3) Pupil diameter at rest and during task performance was positively correlated with self-reported anxiety, consistent with elevated tonic NE transmission in patients with comorbid anxiety. (4) The strongest predictor of tic severity was performance on the cognitive control task.

Conclusion: In conclusion, measures of cognitive control, blink rate, and pupil diameter provide complementary insights that could prove useful in the diagnosis, treatment, and monitoring of patients with TS and comorbid conditions.

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Quantifying the temporal dynamics of youths'tics under resting and reinforced tic suppression conditions

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Introduction and objectives: It is "common knowledge" among Tourette syndrome (TS) specialists that tics occur in bouts, such that the occurrence of one tic predicts the occurrence of another shortly thereafter. However, only one study by Peterson and Leckman (1998), has systematically and objectively examined the temporal dynamics of tics. In that study, two adults with TS were videorecorded at rest, and their tics were coded. The duration of observed inter-tic intervals (ITIs) formed a positively-skewed frequency distribution that, after a double logarithmic transformation, was characterized by a linear function. The slope of this function indexed the extent to which tics clustered temporally into bouts.

This quantitative model showed preliminary evidence of validity, but no replications or expansions of initial findings have been published. The present study aimed to: (a) systematically replicate Peterson and Leckman's study with a large sample of youth, (b) compare the temporal dynamics of tics under conditions of rest and reinforced tic suppression, and (c) explore relations between tic temporal dynamics and clinical variables.

Methods: 50 youth with chronic tic disorders participated in one of six experiments and contributed data to present analyses. Each study included "resting" conditions (REST; in which subjects were instructed to tic freely) and reinforced tic suppression conditions (SUP; in which children were instructed to suppress tics and received a reward following each 10 s tic-free interval).

ITI data were modelled quantitatively using Peterson and Leckman's approach, with separate functions fitted to REST and SUP data for each subject. Function slope (k) and total variance accounted for (R^2) were variables of interest.

Results and discussion: Tics clustered into bouts, as evidenced by the model accounting for significant variance in REST (mean $R^2 = 0.75$, SD = 0.17, $p^2 = 0.45$, SD = 0.26, p^2 ($r = 0.74$, p^2 values were related to tic or urge severity.

Subjects' tics clearly clustered into bouts during REST, but, during SUP, followed a more chaotic temporal pattern with less bouting. Associations between observed tic suppression and change in model parameters suggest that tic suppression is associated with disruption of typical temporal dynamics of tics.

Conclusion: Tics naturally occur in bouts in youth with TS, and tic suppression is associated with bout disruption. Clinically, results support the use of tic suppression strategies after a bout has begun, rather than only contingent upon pre-tic urges. Further examination of the temporal dynamics of tics may be useful in elucidating mechanisms of tic suppression.

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Disclosures

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The relationship between anxiety and tic severity revisited: beyond DSM classification

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Introduction and objectives: The relationship between anxiety and tic severity has long been documented. TD patients have high rates of anxiety disorders, not limited to OCD, and comorbidity plays a role in tic severity (Kurlan et al., 2002). Findings have been limited to categorically-defined DSM anxiety disorders, thus excluding dimensional analyses of anxiety severity. As DSM disorders are based on symptom clusters, examination of the relationship between tic and anxiety severity independent of the presence of an anxiety disorder is important. We sought to examine the distribution of anxiety severity in a sample of youth with TD, and the relationship between anxiety evaluated both quantitatively and categorically – and tic severity. We hypothesized that (1) anxiety severity among TD youth would manifest a full distribution of symptom severity, which would be higher than in healthy controls (HC); (2) findings would remain significant when subjects with anxiety disorders were excluded; and (3) anxiety severity would be associated with tic severity both dimensionally and categorically.

Methods: Sample was 72 children and adolescents ages 6–17 with TD and 37 HC. Tic and anxiety symptoms were assessed using the Yale Global Tic Severity Scale (YGTSS) and Multidimensional Anxiety Scale for Children (MASC). Analysis of covariance (ANCOVA) was used to compare TD and HC groups, with age and gender as covariates. ANCOVAs were performed, both including and excluding comorbid DSM anxiety diagnoses, for the TD group on measures of anxiety severity. To examine relationships between anxiety and tic severity, Spearman correlations were applied.

Results and discussion: *T*-scores for MASC total anxiety were normally distributed for all TD subjects and HCs. As hypothesized, TD subjects had significantly higher anxiety severity compared to HC. Findings remained significant when subjects with DSM-IV-R anxiety disorders were excluded. MASC Total Anxiety *T*-scores were significantly positively correlated with YGTSS total tic, vocal tic, tic-related impairment, and global severity scores. Two categorically distinct subgroups were created by extracting the quartile of TD subjects with lowest and highest MASC Total Anxiety *T*-scores. ANCOVA controlling for gender revealed high-anxiety TD subjects had significantly greater total tic scores than low anxiety TD subjects.

Conclusion: These findings support our hypotheses regarding the relationship between anxiety and tic severity, and the importance of accounting for anxiety variability among patients with TD. TD subjects had higher anxiety severity compared to HC, even when patients with anxiety disorders were excluded. Since these subjects were seeking treatment for tics and not for anxiety, the higher range of anxiety symptoms suggests a complex presentation of comorbidity. Results also suggest that higher self-reported anxiety symptoms are associated with greater tic severity, emphasizing the importance of quantitative anxiety assessment. Our findings support a role for anxiety as a contributor to tic severity, and use of a dimensional approach to the investigation of anxiety in youth with TD.

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Decreased occipital glutathione levels in Tourette's disorder

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Introduction and objectives: Tourette's Disorder (TD) is an neurodevelopmental disorder characterized by multiple motor and at least one vocal tic (Grados and Mathews, 2009). We recently reported decreased levels of gamma-aminobutyric acid (GABA) in adolescents with TD compared to healthy controls (HC) (Gabbay *et al*., 2011). Here, we extend these findings to examine the role of oxidative stress in TD, indexed via glutathione (GSH), the major antioxidant of the brain. Using proton magnetic resonance spectroscopy (1H MRS), we measured occipital (OCC) levels of GSH in subjects with TD and HC. We hypothesized that patients with TD would have significantly decreased levels of GSH relative to HC.

Methods: Our sample was comprised of 7 TD and 13 HC subjects ages 12–29. TD diagnosis was confirmed by the K-SADS-PL, and tic severity was assessed using the Yale Global Tic Severity Scale (YGTSS). All participants had negative day-of-scan urine toxicology, and the TD group had YGTSS scores > 10.

In Vivo brain GSH measurement by H MRS was obtained using the volume-selective J-editing difference method. Specifically, we used a standard PRESS sequence augmented with frequency-selective Shinar-LeRoux"editing"pulses on alternate scans, with TE = 68 ms, to invert the GSH cysteinyl ? doublet resonance at 2.9 ppm on every other scan; these were then subtracted to yield the GSH resonance. This process is demonstrated in Figure 1. GSH levels were represented as the ratio of the GSH to water (w) signals.

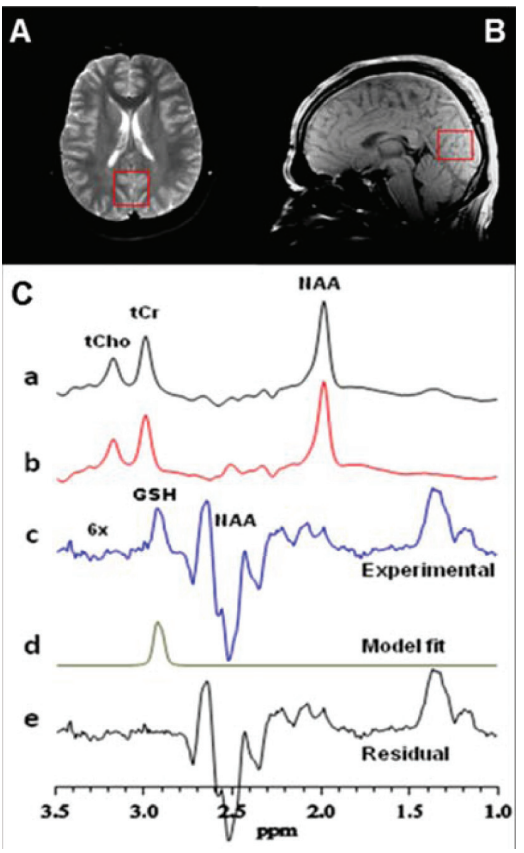

Figure 1 | *In vivo* human brain detection of OCC GSH by [1]H MRS. **[A]** and **[B]** show the voxel position **[C]** shows: **(a)** and **(b)** single-voxel subspectra acquired in 15 min with the editing pulse on and off, respectively, using TE/TR 68/1500 ms, 290×2 interleaved scans; **(c)** difference of **(a)** and **(b)** yielding the edited brain GSH; **(d)** model fit of the GSH peak in **(c)**; **(e)** residual of the difference between **(c)** and **(d).**

Results and discussion: As hypothesized, subjects with TD had significantly decreased OCC GSH compared to HC ($2.18 \pm 0.53 \times 10^{-3}$ vs. $2.83 \pm 0.64 \times 10^{-3}$, $p = 0.03$). Results are shown in Figure 2.

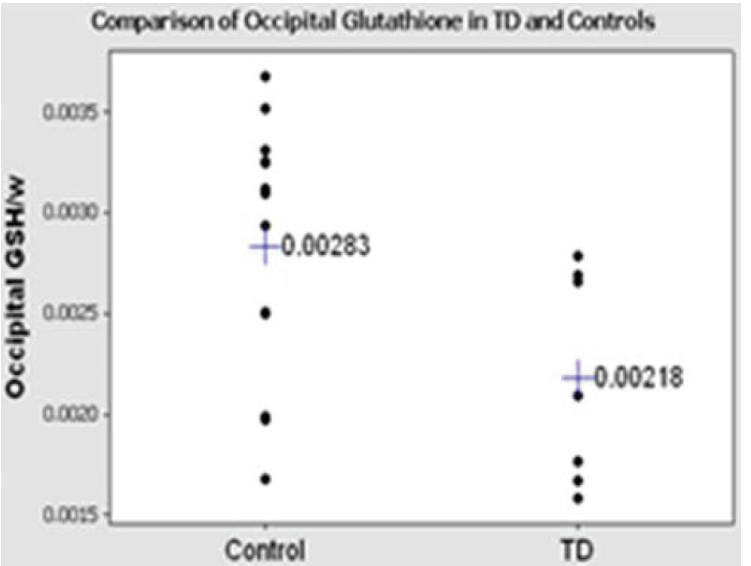

Figure 2 | Comparison of OCC GSH leve s in HC and TD subjects.

Conclusion: These findings support a role for oxidative stress in TD and are consistent with the reported effectiveness of antioxidant treatments such as *N*-Acetylcysteine in the treatment of related disorders. Future studies in larger samples and investigation of specific TD symptoms appear warranted.

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Peer victimization in TD: are there similarities or differences between youth in New York and Buenos Aires?

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Introduction and objectives: Peer victimization is a significant problem in school-age children with Tourette's Disorder (TD) (Storch et al., 2007). Bullying literature is extensive, but studies which address prevalence and risk factors for peer victimization in children with TD are sparse. To explore these issues, this study investigates similarities and differences in prevalence and risk factors (clinical presentation, tic severity, psychiatric symptomatology, and overall functional impairment) in clinically referred TD youth from large metropolitan areas in North and South America.

Study aims are to (1) examine prevalence, demographic characteristics, and tic and non-tic factors associated with peer victimization in well-characterized samples of TD youth from two specialized clinics in New York (NY) and Buenos Aires (BA), and (2) explore differences and similarities in these factors. We hypothesized that prevalence and risk factors are similar in both samples, and differences may result from cultural factors.

Methods: Sample was 72 US and 112 Argentinian TD youth. Through a retrospective cross sectional analysis we used *T*-tests and Chi square analyses to (1) analyze the prevalence of peer victimization, and (2) compare bullied and non-bullied children on risk factors including: age at first evaluation, gender, tic severity, psychiatric comorbid disorders, global assessment of functioning (GAF), and level (mild, moderate, severe) of psychosocial stressors.

Results and discussion: Bullying was significantly more frequent in the BA (27% total, 87% male) vs. NY sample (14% total, 80% male), X^2 (1, N = 184) = 4.285, p = 0.038. In the NY sample, no significant differences were found between bullied and non-bullied youth in age at evaluation, tic severity, or comorbid disorders. However, GAF was significantly lower in the bullied (M = 54.90, SD = 6.855) vs. non-bullied group. (M = 60.11, SD = 5.040), t (69) = −2.877, p = 0.005. Bullied individuals had a significantly higher level of psychosocial stressors than non-bullied individuals, X^2 (6, N = 72) = 14.317, p = 0.026.

In the BA sample, age at evaluation was significantly higher in the bullied (M = 12.20, SD = 3.295) vs. non-bullied group (M = 10.59, SD = 3.107), t (110) = −2.397, p = 0.018. GAF was significantly lower in the bullied (M = 51.77, SD = 10.441) vs. non-bullied group (M = 59.72, SD = 11.781), t (109) = 3.251, p = 0.002. Among psychiatric comorbid disorders, mood disorders were more frequent in the bullied (M = 0.50, SD = 0.509) vs. non-bullied group (M = 0.23, SD = 0.425), t (44.633) = −2.579, p = 0.013; there was a trend toward significance for OCD, t (53.874) = −1.843, p = 0.071 in the bullied vs. non-bullied group. Bullied individuals had a significantly higher level of psychosocial stressors than non-bullied individuals, X2 (6, N = 111) = 20.442, p = 0.002.

Conclusion: Our results indicate that, contrary to our hypothesis, the prevalence of bullying in BA was higher than in NY in these youth. Our findings that bullying was associated with lower global levels of functioning, and higher levels of psychosocial stress in both samples supported our hypothesis. Our finding that older age at evaluation and comorbid mood disorders predicted bullying in the BA sample and not the NY sample is intriguing, and may suggest a role of cultural factors. Study limitations include small sample size and retrospective analysis. Additional investigation is needed.

Disclosures

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Environmental triggers of older adults with Tourette syndrome

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Introduction and objectives: Less research has been published about the health and societal challenges that older adults with TS encounter across their lifespan. Some community samples of adults, reveal that tics and co-morbidities do not entirely go away, yet the frequency, intensity, complexity, and duration of specific tics, sometimes change or lessen. Consequently, a person's school or job functioning, self-esteem, family life, social acceptance, and physical well-being remains affected (Leckman et al., 2006).

This study recognized that little research has focused on older adults who have lived resiliently with TS, for many years. Research questions included: (1) Which environmental triggers might older adults with TS report as being most or least common? (2) How have older adults with TS coped with symptoms (e.g., co-morbidities) and environmental triggers over their life course?

Methods: A non-experimental, cross-sectional mixed methods approach was used. Self-administered surveys, observational techniques, and in-depth interviews were used to collect data. The newly constructed *TS Older Persons Questionnaire* had four components: Indicators of levels of TS severity levels, creativity, social support and others; Checklists of environmental triggers; YGTSS; and Gilles de la Tourette – Quality of Life scale.

Results and discussion: The main unexpected findings were that: (1) subjects reported a higher proportion of less common triggers than most common triggers, and (2) an interesting commonality existed between the top triggers (excitement, stress, noise, lights, clothing fabrics, alcohol and caffeine), in that these identified triggers all affect the nervous system and are sensory-related.

Conclusion: Study participants still experienced environmental triggers, and the results (the proportion who experienced the most and less common triggers), among those selected were a high proportion of less common rather than most common triggers. The commonality between the top triggers (excitement, stress, noise, lights, clothing fabrics, alcohol and caffeine) identified are all sensory related or affect the nervous system. This concurs with Leckman et al. (2006) research that found that many of their respondents reported a variety of sensory and mental states associated with their tics.

Participants typically reported mild to moderate (48%) perceived tic severity. Due to the high correlation between perceived tic severity and the various scales and variables, this study really was measuring tic severity itself. Conflicting research (Pappert et al., 2003) suggests tic severity is not the primary factor related to adult dysfunction because tic severity decreases with age. However, this study indicates that tics do not go away but adults with TS just learn how to cope with TS which is consistent with previous research by Altman et al. (2009). Approximately 50% of the participants reported taking medication. Non medication assistance such as therapy and anger management programs were not frequently used. Approximately one-third of the sample used Yoga as nonpharmacological treatment. Hence, results also reveal that the majority of the participants go into problem solving mode (81%) to cope with TS. These findings suggest they received adequate support, with emotional (76%) being the primary support provided by their family and friends.

Study results reveal that older adults with TS do experience environmental triggers commonly. As well, they have coped rather well with strategies ranging from tic substitution, problem solving, doing yoga, and receiving positive social support.

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Group A *Streptococcus* (GAS) exposure and pediatric tic disorders: preliminary results from the EMTICS project

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Introduction and objectives: The primary aim of the EMTICS (European Multicentre Tics Study) project, funded by the FP7 Program, is to identify the genetic and environmental susceptibility factors of tic disorder (Roessner and Hoekstra, 2013). EMTICS hypothesizes that the onset and/or exacerbation of tic and comorbid obsessive-compulsive disorders in children is associated with increased preceding occurrence of GAS exposure or infection of specific molecular subtypes as well as with host genetic susceptibility factors, mediated by immunological mechanisms. The preliminary results of Workpackage 2, that deals with the microbiological characterization, including serotype distribution and virulence factors analysis, of GAS strains isolated from the throat swabs of tic patients and controls, is reported.

Methods: GAS strains were isolated from the throat of children, swabbed both at the time of recruitment and according to a planned visit schedule by clinical partners. Throat swabs are processed by the microbiology laboratories following a common validated microbiological protocol (Creti et al., 2004; Martino et al., 2011). Children are part of two longitudinal observational studies: the COURSE study, a 16 months study, includes aged 3–16 years tic-affected children; the ONSET study, a 3 years study, includes high-risk group of children aged 3–10 years who have a first degree relative with a diagnosis of Tourette syndrome and at study entry have no tics.

Microbiological characterisation of GAS isolated was performed by using the emm typing "gold standard" method. It consists in the assignment of the emm type by the sequencing of the hypervariable *N*-terminal portion of the M protein coding gene, a fibrillar surface protein of which more than 100 types are recognized.

The presence of superantigen speC gene, a prophagic virulence factor, highly represented in GAS strains isolated from throat (Creti et al., 2005), was assessed by Polymerase Chain Reaction (PCR). Allelic variants of speC gene were assigned by speC amplicon sequencing and comparison with databank.

Results and discussion: GAS strains from non redundant samples of the COURSE study showed a wider range distribution of serotypes compared to the ONSET study isolates. When tic patients were divided in two groups according to tic severity using the Clinical Global Impression (CGI) Severity Scale (score 1: normal, to score 7: extremely ill patient), it was noted that some GAS emm types were more frequently isolated in one group respect to the other.

The superantigen speC gene was equally present in both GAS COURSE and ONSET isolates (68.4 vs. 63.8%) but SpeC1 allele was significantly more present in GAS COURSE isolates (Fisher's exact test: 0.03). Isolates from the tic population showed that an enrichment in speC-positive GAS strains paralleled an higher CGI severity scale.

Conclusion: GAS strains isolated from the children presenting the most severe tics were enriched in particular serotypes and speC alleles. With the available number of isolates, this observation represents a trend more than an evidence. At the end of the study, a more extensive description of the group A *Streptococcus* genetic structure and virulence characteristics on a pan-European scale will give a reliable answer on the possible involvement of GAS and/or specific subpopulations in the pathology of pediatric tic disorders.

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Tic-related versus tic-free obsessive-compulsive disorder: clinical picture and two-year natural course

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Introduction and objectives: The tic-related subtype of obsessive-compulsive disorder (OCD), present in about 29% of the adult patients (Gomes de Alvarengo et al., 2012), has a distinct clinical profile (Leckman et al., 2010). The course of tic-related OCD has previously been investigated in treatment studies, with inconclusive results (McDougle et al., 1993; Rosario-Campos et al., 2001; Shavitt et al., 2006; Husted et al., 2007; Jakubovski et al., 2013). This study aimed to compare clinical profiles between tic-related and tic-free OCD patients, expanding previous knowledge by adding questionnaires on attention-deficit hyperactivity disorder (ADHD) and autism symptoms. A second aim was to establish the influence of tics on the two-year natural course in adult OCD patients.

Methods: Within the Netherlands OCD Association cohort 377 patients with a current DSM-IV diagnosis of OCD were divided in a tic-related group (28%) and a tic-free group, and compared on demographic and clinical variables with *t*-tests or ? (Leckman et al., 2010) tests. Linear mixed-model analyses were used to compare the two-year course between the groups, with the Yale-Brown Obsessive-Compulsive severity scale (Y-BOCS) as primary outcome measure. Variables that differed between the groups at baseline and interacted with change in Y-BOCS over two-years were added as covariates to the linear mixed-model.

Results and discussion: Compared to tic-free OCD, tic-related OCD patients reported earlier disease onset ($p = 0.009$) and more symmetry/ordering symptoms ($p = 0.002$), which is in line with previous reports (Leckman et al., 2010). Overall symptom severity was similar in both groups. Tic-related OCD patients reported increased symptoms of two neurodevelopmental disorders; attention-deficit hyperactivity (*p*

Clinical improvement at two-year follow-up (mean 5.3 points decrease on the Y-BOCS, *p*

Conclusion: Tics do not critically affect the two-year course of adult OCD. Tic-related OCD shows differences from tic-free OCD, such as early onset and increased autism spectrum and ADHD symptoms. This suggests that tic-related OCD may be characterized as a neurodevelopmental subtype of OCD.

Table 2: Demographic and clinical characteristics of tic-related and tic-free OCD and group differences at baseline

	OCD without tics (N=270, 72%)		OCD with tics (N=107, 28%)		Statistical analysis			
	Mean	SD	Mean	SD	t	df	p-value	95% CI of the difference
Demographic measures								
Age (years)	37	10.8	35	11.3	1.2	375	0.24	-1.0 – 3.9
Gender (female:male)	161:109	60%	52:55	49%	3.8[a]	1	0.05	n.a.
Education (number of years)	13	3.1	12	3.4	3.3	374	0.001	0.5 –1.9
Clinical measures								
Late onset diagnosis (>19 years)	101	42%	27	27%	6.9[a]	1	0.009	n.a.
Chronicity (number)	171	63%	61	59%	0.70[a]	1	0.40	n.a.
Family history of OCD[b]					11.7 [a]	3	0.008	n.a.
0	161	60%	57	54%				
1	74	27%	20	19%				
2	28	10%	20	19%				
3 or more	7	3%	8	8%				
Family history of tics[b]					27.9 [a]	3	<0.001	n.a.
0	238	88%	72	69%				
1	27	10%	20	19%				
2	5	2%	9	9%				
3 or more	0	0%	4	4%				
Y-BOCS severity (points)	21.3	6.7	21.1	7.9	0.13	167	0.9	-1.6 – 1.8
BDI (points)	15.6	9.3	17.5	11.7	-1.4	143	0.17	-4.5 – 0.8
BAI (points)	18.4	11.9	18.1	12.5	.21	355	0.84	-2.5 – 3.1
Total ADHD symptoms	4.9	3.7	6.7	3.9	-4.2	372	<0.001	-2.7 – -1.0
attention deficit symptoms	2.8	2.3	3.9	2.4	-3.9	375	0.002	-1.6 – -0.5
hyperactivity symptoms	2.05	2.1	2.8	2.4	-2.6	171	0.009	-1.2 – -0.2
Autism Quotient (points)	113.6	15.5	119.0	17.4	-2.8	356	0.005	-9.1 – -1.6
Probable autism spectrum diagnosis (number of patients)	12	5%	13	13%	8.0 [a]	1	0.005	n.a.
Y-BOCS check/aggression	4.5	3.2	5.1	4.0	-1.5	155	0.15	-1.5 – 0.2
Y-BOCS symmetry/ordering	2.4	2.6	3.4	3.0	-3.1	164	0.002	-1.7 – -0.4
Y-BOCS contamination/ cleaning	2.2	2.4	2.5	2.5	-1.1	367	0.29	-0.8 – 0.3
Y-BOCS hoarding	0.3	0.6	0.4	0.7	-1.5	170	0.15	-0.3 – 0.04

[a] χ^2, [b] number of 1st degree relatives with OC symptoms or tics, Y-BOCS, Yale-Brown Obsessive-Compulsive scale, BDI, Beck Depression Inventory, BAI, Beck Anxiety Inventory, ADHD, attention deficit hyperactivity disorder. SD; standard deviation, df; degrees of freedom, CI; confidence interval

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Research diagnostic criteria for complex Tourette syndrome

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Introduction and objectives: Tourette Syndrome is currently defined as a tic disorder. However the literature and the clinical studies clearly indicates that 85–92% of patients present with an array of others conditions: ADHD, OCD, ODD in children and Explosive Intermittent Disorder in adults being the most common comorbid conditions. Anxiety and Affective disorders are also quite prevalent. Self-mutilation, coprolalia and other socially inappropriate behaviors are also part of this complex picture. Contrary to the principle of Unicity, the clinicians and the researchers are obliged to deal with multiple diagnosis and treatments. This leads to confusion in the literature about complex TS and to a lack of research about the basic brain dysfunction involved in all those other manifestations of this disorder.

We are proposing to redefine Complex TS with an new name and a new set of diagnostic criteria for research purposes. We are suggesting the name of **Pervasive Inhibitory Brain Dysfunction Disorder (PIBDD)** as a more precise and descriptive term for this condition. Most of the symptoms observed in TS could be understood as a manifestation of dysfunctions of the inhibitory systems in the brain of affected people.

Methods: **Diagnostic Criteria's for PIBDD:**

(A) Diagnosis of TS as in DSM-5

(B) At least three of the following conditions or symptoms:

1. ADHD
2. OCD
3. ODD or Intermittent Explosive Disorder
4. Socially Inappropriate Behavior (mainly coprolalia and copropraxia)
5. Self-Mutilatory Behavior
6. Affective Dysregulation
7. Anxiety Disorder

Results and discussion: Such research criteria are needed to encompass the complexity of TS. This integrated view would permit us to study the basic neurophysiological and brain system dysfunctions involved in this condition. Otherwise, we are limitating ourself to study the ears, tail or tusk of the elephant without a clear understanding of the global picture.

Conclusion: We are proposing a new set of diagnostic criteria which could be used in the study of the brain dysfunctions in TS. Instead of a condition with multiples associated diagnosis, we suggest that an integrated view would lead to an improved research and a better understanding of this condition.

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Differential responsiveness of attention, OCD and tics to the atypical neuroleptics risperidone and aripiprazole in Tourette syndrome

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Introduction and objectives: Treating attention disorders associated with Tourette Syndrome (TS) with psychostimulants carries the risk of potential aggravation of tics or OCD (Denckla et al., 1976; Duane, 1977). Atypical neuroleptics often decrease tics in TS however, it is unclear how attention (attn) and OCD, the other two major symptoms of this condition, respond to these medications either concurrently or independently of tic benefit (Singer, 2010). This study attempts to ascertain if atypical neuroleptics, in particular risperidone (risp) and aripiprazole (arip), have positive effects on more than one of the symptom triad and if there is differential benefit between these two medications.

Methods: Retrospective chart analysis of 26 TS patients in which at least two evaluations were conducted, both prior to and after the addition of either risp (10 patients, 6 male/ 4 female, mean age of 10.3), or arip (16 patients, 13 male/ 3 female, mean age of 11.1), in which attention (both cognitive-CPT, TOVA, LCT and behavioral measures-DSMIV Rating Scale, Achenbach CBCL), OCD (Achenbach CBCL; Yale Brown Obsessive Compulsive Rating Scale) and tics (Yale Tic Rating Scale) were simultaneously assessed.

Results and discussion: In both the risp and arip group, tics were generally improved (70, 81%). In the arip group, if attn improved, either cognitively, behaviorally or both, tics also improved (100%). In the risp group if attn improved, tics improved in 63% of patients. Arip outperformed risp 2:1 on benefit to attention irrespective of effect on OCD or tic. OCD improved in 69% of arip patients and in 13% of risp patients. If OCD improved, behavioral attn tended to improve in both groups (100, 78%). While tics, OCD, cognitive attn and behavioral attn were improved simultaneously in 25% of arip patients, these symptoms were never simultaneously benefited in the risp group.

Conclusion: While attention, tics and OCD can simultaneously improve with use of an atypical neuroleptic, the closest correlation is between a positive effect on tics and a positive effect on attention. However, attn improvement is not dependent on tic improvement. It is possible that (1) tics and attention disorders share similar mechanisms of responsiveness to medication (2) that a reduction in tics benefits attn, or (3) that an atypical neuroleptic provides a previously unrecognized benefit to attn in TS irrespective of benefit to tics. The use of arip is associated with a positive outcome on attn and OCD more often than is risp although both medications effectively reduce tics in TS patients.

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Callosal white matter microstructure relates to tic symptoms, cortical excitability, and GABA levels in adolescents with Tourette syndrome

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Introduction and objectives: Tourette Syndrome (TS) is a developmental neurological disorder characterised by vocal and motor tics and is associated with cortical-striatal-thalamic-cortical circuit dysfunction and hyper-excitability within cortical motor areas (Albin and Mink, 2006; Orth and Rothwell, 2009). TS symptoms often become more controlled throughout adolescence until the individual is largely tic-free by early adulthood (Leckman et al., 1998). Diffusion Tensor Imagining (DTI) has indicated that the white matter of the corpus callosum is related to tic symptom severity in adolescents with TS (Jackson et al., 2011). It is possible that plastic changes in white matter development during adolescence helps to reduce excess excitability in areas of the cortex involved in tic-production, which in turn leads to tic remission. To investigate this we used multiple brain-imaging approaches to look at the relationships between cortical excitability, GABA (the main inhibitory neurotransmitter), callosal white matter microstructure and tic severity in a group of adolescents with TS and an age-and gender-matched control group.

Methods: White-matter microstructure was measured using DTI performed on a 3Tesla MRI scanner. The data was analysed using a probabilistic tractography approach. The body of the corpus callosum where fibres project to the primary motor cortex (M1) or supplementary motor area (SMA) were regions of interest (ROIs). GABA levels were measured using Magnetic Resonance Spectroscopy (MRS) performed on a 7Tesla MRI scanner using 2×2×2 cm ROIs placed over SMA or M1. Cortical excitability was measured using Transcranial Magnetic Stimulation (TMS) delivered to the motor hot spot of the right hand. Motor evoked potentials were recorded from the FDI muscle of the right hand at rest (input-output curves), and during a go/no go task.

Results and discussion: A significant positive relationship was found between white matter structural integrity (FA) measured from the body of the corpus callosum and motor tic severity. The TS group had increased levels of GABA in the SMA, as measured by MRS, compared to the control group. SMA- GABA levels had a significant positive relationship with FA from the SMA ROI but a negative relationship with TMS measures of cortical excitability. This suggests that those individuals with the least severe tic symptoms also have reduced callosal white matter from the SMA [an area implicated in the production of tics Bohlhalter et al., (2006)] in adolescents with TS, which relates to a reduction in cortical excitability and a reduction in SMA-GABA compared to those with more severe tics.

Conclusion: The white matter microstructure in the body of the corpus callosum that projects to the SMA has been shown, robustly, to relate to motor tic severity in adolescents with TS. Our current research suggests that local changes in cortical excitability, may in part, be driven by these changes in white-matter microstructure, and are likely to be closely related to the tic reduction over time that occurs in the majority of adolescents with TS (Leckman et al., 1998). Longitudinal data is needed to examine this theory.

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Comprehension of direct and indirect sarcastic remarks in children with Tourette's syndrome (TS)

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Introduction and objectives: Previous research has reported that aspects of social cognition such as nonliteral language comprehension are impaired in adults with Tourette's syndrome (TS) (Eddy et al., 2010, 2011), but little is known about social cognition in children and adolescents with TS. Sarcasm comprehension was selected as an area of interest for the present study since it has been found to be sensitive to differences in social cognition in adults with TS and may have implications for everyday interactions (Eddy et al., 2010, 2011). Mentalising ability (Sullivan et al., 1995; Bosco et al., 2004) and executive functions (Eddy et al., 2010; Grice, 1975) have both been implicated as important processes underpinning sarcasm comprehension. The present study aimed to examine sarcasm comprehension in a sample of children with TS and no comorbidities (TS-alone) and those with TS and comorbid ADHD (TS + ADHD) The main prediction was that children with TS-alone or TS + ADHD would show relative impairment in the comprehension of sarcastic but not sincere materials. The study also explored whether children with TS showed greater difficulties in interpreting indirect than direct sarcastic remarks, and the possible contributions of mentalising and executive function to performance

Methods

Participants: 15 participants diagnosed with TS-alone, 13 participants diagnosed with TS + ADHD, and 25 healthy control participants took part in the study. Participants were all aged between eleven and seventeen. ANOVA showed no significant differences between the three groups in age, $F(2,50) = 0.08$, $p = 0.993$, or WASI matrix reasoning age-scaled scores, $F(2,50) = 0.50$, $p = 0.613$.

Materials: A scenario-based measure was developed based on previous measures used with adults (Channon et al., 2005), with adaptations made to ensure that the stories were age-appropriate and relevant to young people. The task consisted of 15 brief scenarios describing a social context, ending with a single remark by one character. Five scenarios ended with a sincere remark, five with a direct sarcastic remark (which could be understood by reversal of the direct meaning), and five with an indirect sarcastic remark (the meaning of the remark was indirectly related to the literal interpretation of the remark but could not be solved by direct reversal). Examples of the item types are shown in Figure 1. Participants were presented with four alternative interpretations of the final remark: a 'best' or direct interpretation, a more indirect but not incorrect interpretation, an irrelevant interpretation, and a clearly incorrect interpretation that for the sarcastic (but not the sincere) items provided a salient, literal interpretation of the remark. Participants also answered yes/no factual inference questions to check understanding of the social context of the story, one mentalistic in content, and one non-mentalistic. Participants also completed two executive function tasks: the Hayling task (Burgess and Shallice, 1997) to test interference control, and the Verbal Fluency task from the D-KEFS (Delis et al., 2001) to assess generation ability, since these executive functions may be particularly relevant to sarcasm comprehension.

Statistical methods: Mixed model ANOVA was used to examine sarcasm comprehension in both studies. One-way ANOVAs were used to explore interactions. Pearson product moment correlations were used to examine the relationship between sarcasm scores and the mentalistic and non-mentalistic inference questions, and the relationship between sarcasm comprehension and executive function.

Results and discussion

Results: The groups did not differ significantly on the sincere items, $F(2,50) = 0.36$, $p = 0.701$, or on the direct sarcastic items, $F(2,50) = 2.08$, $p = 0.136$. However, the groups did differ significantly for interpretation of the indirect items, $F(2,50) = 5.51$, $p = 0.007$, and post-hoc Scheffé tests showed that both the TS-alone group ($p = 0.032$) and the TS + ADHD group ($p = 0.030$) scored below the control group; the two groups with TS did not differ ($p = 0.990$).Incorrect literal alternatives were chosen more commonly by both TS-alone group (10.67% of choices) and the TS + ADHD group (18.46% of choices) by comparison with the control group (3.20% of choices), and this difference reached significance for the TS + ADHD versus control comparison (Scheffé $p = 0.017$). The groups did not differ significantly on either the mentalistic inference questions, $F(2,50) = 1.42$, $p = 0.251$ or the non-mentalistic questions, $F(2,50) = 2.49$, $p = 0.093$. The groups differed significantly on the Hayling test, and post-hoc Scheffé tests showed that the TS + ADHD group scored below the level of the control group ($p = 0.003$) and the TS-alone group ($p = 0.032$); the TS-alone group did not differ significantly from the control group ($p = 0.826$). On the fluency test the TS + ADHD group scored below the level of the control group ($p = 0.004$); the TS-alone group did not differ significantly from the TS + ADHD group ($p = 0.376$) or the control group ($p = 0.257$).

Mentalistic inference scores were significantly correlated with comprehension of direct and indirect sarcasm for the TS-alone and control groups, but not for the TS ADHD group ($p > 0.1$). Non-mentalistic inference scores were significantly correlated with direct and indirect sarcasm comprehension for all three groups. There were no significant correlations between sarcasm scores and the executive measures for the control or TS-alone groups; for the TS + ADHD only one correlation reached significance: poorer category fluency was associated with less frequent selection of best alternatives for the direct sarcastic items, $r = 0.58$, $p = 0.038$.

Discussion: The finding that those with TS performed better on direct sarcasm compared to indirect sarcasm could potentially indicate that the TS groups used a strategy based on reversing the literal meaning for direct sarcasm rather than a strategy based on salience or contextual cues. Previous developmental studies have found that indirect sarcasm is more difficult for younger children to comprehend compared to direct sarcasm (Dews et al., 1996; Bosco et al., 2004), although these findings were for children somewhat younger than the TS participants in the present study, which may be indicative of a developmental delay in sarcasm comprehension in TS. Literal interpretations of the remarks were the most common type of error, suggesting that individuals did not recognise the non-literal meaning of these remarks.The bias in the present study towards literal interpretations of the remarks could potentially be explained by an executive account (e.g., failure to inhibit the literal meaning of the items or generate an alternative interpretation of the remarks) or by a mentalistic account (e.g., failure to take theory of mind into account). Mentalising skills alone are unlikely to account fully for the pattern of findings in the present study, since there were no group differences for the mentalistic control questions. An executive account may be most parsimonious for the TS + ADHD group, since they performed below the level of control participants on both executive tasks, and there was some evidence of an association between executive performance and selection of best alternatives for the direct sarcasm items. However, an executive account is unlikely to explain the performance of the TS-alone group, since they did not differ from the control group on the executive measures or the non-mentalistic inference questions and there was also no evidence of a link between executive performance and comprehension of direct or indirect sarcasm for the TS-alone group. One possible explanation for the performance of the TS-alone group is that the combination of executive and mentalistic demands in the sarcasm task produced a higher level of task difficulty than either the mentalistic or executive measures alone.

Conclusion: The finding of impaired sarcasm comprehension in children with TS-alone and TS + ADHD is consistent with previous findings of impaired comprehension of sarcasm and other nonliteral language in adults with TS (Eddy et al., 2010, 2011), although there are also reports of intact nonliteral language comprehension in adults with TS-alone (Channon et al., 2004). These adult studies have also reported some evidence of executive dysfunction in those with TS, including impairments in fluency (Eddy et al., 2011) and inference control (Eddy et al., 2010); although only the latter study found any association between executive function and nonliteral language comprehension. Taken together with the findings of the present study, this suggests that some aspects of social cognition such as nonliteral language comprehension may be impaired in children with TS as well as in adults. This may manifest in communication difficulties in everyday language, although the fact that group differences were confined to indirect sarcasm suggests that these may be relatively subtle. Further work is required to better understand the developmental trajectory of social cognition in TS, and the social cognitive profile of children and adolescents with TS.

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Disclosures

The authors have no conflicts of interest to declare.

Example of a sincere item

‘Tariq had gone to his friend’s house after school. He said he would be back by eight o’clock. He was still not home by nine o’clock. His mother began to worry, and rang his friend’s house. They said that they had not seen Tariq. Ten minutes later he walked through the door. His mother said:

“I’m very angry with you, Tariq!”

Question: What did his mother mean when she said that?

Alternatives:

Best alternative: ‘I’m very cross with you.’

Indirect alternative: ‘You are very thoughtless.’

Irrelevant alternative: ‘You should take me to your friend’s house too.’

Incorrect alternative: I’m very pleased with you.

Questions:

Mentalistic question: 'Did his mother feel anxious about Tariq staying out late?'

Non-mentalistic question: 'Was Tariq at his friend's house?'

Example of a direct sarcastic item

'Vicky had bought tickets for a new film at the cinema. One was for herself and the other for her friend Jean. Vicky told Jean the film would be good because her favourite actor was in it. The film turned out to be terrible. They were both disappointed.

Jean said: "That was a fantastic film you took me to see!"

Alternatives:

Best alternative: 'That film was terrible.'

Indirect alternative: 'Next time I'll check what other people say first.'

Irrelevant alternative: 'That was very good popcorn.'

Incorrect literal alternative: 'That was a very good film.'

Questions:

Mentalistic question: 'Did Vicky like the film?'

Non-mentalistic question: 'Had Vicky seen the film before?'

Example of an indirect sarcastic item

Rachel was fifteen and was watching TV with her parents. A horror film started and they told her to change the channel. Rachel was cross. She argued with them, but they would not let her watch the film. Her mother switched off the TV. Rachel said:

"I suppose I should play with my dolls!"

Question: 'What did Rachel mean when she said that?'

Alternatives:

Best alternative: 'I'm not a little girl any more.'

Indirect alternative: 'You shouldn't control everything I do.'

Irrelevant alternative: 'You don't want me to play with my dolls.'

Incorrect literal alternative: 'You want me to play with my dolls.'

Questions:

Mentalistic question: 'Did Rachel agree with her parents?'

Non-mentalistic question: 'Did Rachel switch off the TV?'

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Group habit reversal training for young people with tic disorders

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Introduction and objectives: The prevalence of tic disorders in children and adolescents has been estimated to range from 1 to 29%, (Mason et al., 1998; Lanzi et al., 2004) with onset usually occurring during childhood and peaking in severity following in adolescence (Leckman et al., 2006).

Recent research has demonstrated the effectiveness of behavioural interventions, particularly habit reversal training (HRT), in managing tics (Piacentini et al., 2010). Furthermore, group work has been proposed as a useful intervention for children with Tourette syndrome, in order to facilitate friendship formation and to develop social skills (Murphy and Heyman, 2007). Large numbers of children with tics attend our service; implementation of a group format enabled children to be provided with input in a timelier manner.

As this project was developed as a service evaluation, specific hypotheses were not devised. However, it was hoped that attendance at the group would result in children feeling more confident about managing tics as well as reducing distress associated with their tics.

Methods:

Participants: Four young people aged 11–14 years enrolled in the first group. All participants were male and were experiencing at least two motor or vocal tics. The mean duration since tic onset was 21.75 months. A group for younger children ($N = 4$; aged 8–10 years) is due to commence in April 2015.

Outcome measures: Parents completed the Parent Tic Questionnaire (Chang et al., 2009) and the Yale Global Tic Severity Scale (Leckman et al., 1989). Children completed the Tic Hassles form (Woods et al., 2008) the Paediatric Index of Emotional Distress (O'Connor et al., 2010) and children and parents were asked to provide weekly feedback.

Procedure: Parents of children who were referred to paediatric psychology services for difficulties with tics were contacted via telephone and asked whether they would be interested in attending the group. For the older group, three children declined participation due to other commitments or because tics were no longer causing difficulties.

Group format: Following an assessment session, children and parents were invited to attend the group which comprised of a 6 session weekly intervention with 3 week follow up. The group focused on rapport building, psychoeducation on tics, HRT, progressive muscle relaxation training and relapse prevention. Follow up sessions were arranged for 3 weeks post group completion to evaluate maintenance of strategies in the longer term. A second group running with the younger cohort is due to commence in late April 2015.

Results and discussion: The current study employed a case-series design. By June, there will be more concrete feedback from both the younger and older groups; plans for analysis include individualised pre-post outcome measure comparisons as well as consideration of qualitative feedback. Preliminary feedback suggests the usefulness of the group.

Conclusion: Given the large number of tic-related referrals in our clinic and in the context of increasing evidence on the effectiveness of HRT, the current evaluation aims to provide support for the benefits of group administrated HRT for children with tics in routine clinical practice.

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Disclosures

None identified

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Apophenia and anthropomorphising in Tourette syndrome

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Introduction and objectives: Complex tic-like features of Tourette syndrome (TS) include urges to mirror other people's behaviour and to act in a socially inappropriate way (Kurlan et al., 1996; Eddy and Cavanna 2013a). These symptoms, and the finding of altered performance on tasks involving social cognition (Eddy et al., 2011; Eddy and Cavanna, 2013b), suggest that individuals with TS may show differences to controls in the way they reason about mental states. In this study we aimed to investigate spontaneous mentalizing tendencies in TS in response to ambiguous visual stimuli.

Methods: Twenty individuals with TS and twenty healthy controls matched for age and gender completed the animations task (Abell et al., 2000; Castelli et al., 2000) which involved watching and describing short ambiguous video-clips featuring two triangles. Some clips showed random movements, while others portrayed social interactions that were simple (e.g., fighting) or more complex (e.g., one triangle tricking the other). Participants were simply asked to"describe what is happening"in the video-clips. Executive functions and clinical symptoms (severity of tics and premonitory urges, obsessive compulsive behaviours etc.,) were also assessed.

Results and discussion: Individuals with TS answered very similarly to controls in response to those video-clips involving simple and complex interactions, demonstrating intact mentalizing ability. However, significant group differences were apparent for the random video-clips ($p = 0.001$). Individuals with TS were more likely than controls to attribute mental states including intentions to the triangles in these video-clips. Instead of simply floating or drifting, patients with TS often thought the triangles were looking for something or trying to interact. Sometimes they even interpreted these random movements as flirting or arguing. TS was associated with a mild difference in set-shifting, but intact working memory. No significant associations were found between animations task scores and clinical or executive measures.

Conclusion: Our findings indicate that individuals with TS can show an increased tendency to mentalize when confronted by ambiguous visual stimuli in the form of randomly moving shapes. TS may therefore be associated with a propensity to adopt the intentional stance. A specific cognitive style involving hyper-mentalizing may underlie a range of characteristics commonly associated with TS such as magical thinking, enhanced creativity, and altered social behaviour.

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Development and usability pilot testing of a smartphone application for youth with chronic tic disorders

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Introduction and objectives: Mobile applications are a unique way to deliver health information. An increasing number of youth own smartphones (s et al., 2013) and emerging evidence indicates that mobile devices can be used to effectively track and manage pediatric health conditions (Hanauer et al., 2009; Stinson et al., 2013).

Current guidelines for the treatment of chronic tic disorders (CTDs) recommend behavioural strategies, namely comprehensive behavioural intervention for tics (CBIT) based on habit reversal training, as first-line interventions when tics warrant treatment (i.e., are significantly impairing to the patient) Steeves et al. (2012). Unfortunately, few clinicians are trained in CBIT (Woods et al., 2010) and despite renewed interest, CTDs remain stigmatized conditions (Fat et al., 2012).

In response to difficulties accessing evidence-based information about CTDs, we developed a prototype smartphone application (app) for youth with CTDs, which we called Ticbusters. The prototype provides education about tics, includes interactive features regarding habit reversal strategies, and collects longitudinal data on tic impairment, frequency, antecedents and consequences.

Our objective was to test the usability of and satisfaction with the Ticbusters prototype in patients with CTDs and their parents.

Methods: Thirteen participants (6 youth with CTDs,7 parents), recruited through *Tourette Canada*, took part in qualitative audio-taped interviews. During a single session, we asked participants to navigate the prototype, provide feedback on the design and content, and contribute suggestions for improvement. Participants also completed a satisfaction and ease-of-use questionnaire. We used qualitative thematic analysis of the interviews to capture themes related to usability.

Results and discussion: Thematic analysis indicated that overall, the app was appealing. Most participants highlighted the value of the central tic list and longitudinal symptom tracking features. Youth expressed a desire for more audio and a game component. One youth noted,"It's cool that there is an app being made for kids with tics... Not a lot of people know about TS. I wish all the people in my life could have this app."Questionnaire results indicated that all participants owned a smartphone or device (e.g., iPad) with apps and 85% of the sample indicated that they would use the app for 2 months or longer. When asked to rate how helpful this app could be for them from 1(very unhelpful) to 5(very helpful), the mean score was 4.31.

Conclusion: Overall, participants reported high satisfaction with the prototype and an intent to use the app. Pilot testing prompted prototype improvements and ongoing discussion about including a game component. In future studies, we intend to evaluate clinical utility and feasibility.

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Staphylococcus aureus colonization of the oral cavity, normalization of anti-streptococcal antibody levels and symptom improvement in a Tourette patient: a case report

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Introduction and objectives: High levels of antibodies against group A beta-hemolytic streptococci (GAS) are frequently reported in Tourette's children but the role, if any, of a post-streptococcal autoimmunity in tic exacerbations is still controversial (Martino et al., 2011). The aim of our studies is to explore possible correlations between Tic severity, anti-streptococcal antibody levels and microbiological isolation of *Streptococcus pyogenes*. The results obtained from a longitudinal study on a 12 years old girl with Tourette syndrome are reported.

Methods: Throat swabs were sent in duplicate to the Clinical Laboratory of ASL CN1 and to C.D.C. (Centro Diagnostico Cernaia, Cuneo-Italy) and were tested for presence of microbiological pathogens. Anti-streptococcal antibodies against streptolysin O (ASO) and deoxyribonuclease B (anti-DNase B) were also analysed in the two laboratories. A complete blood cell count and erythrocyte sedimentation rate were evaluated too. Tic disorders were monitored utilizing the Yale Global Tic Severity Scale (YGTSS 0–50).

Results and discussion: The worst-ever tic severity score was 23 in June 2012 when ASO titre reached 472UI/ml. A combined pharmacological treatment with Pimozide and SSRI proved to be effective in controlling eye, head and shoulder movements and a phobic anxiety co-morbidity disorder (ICD 10: F 40.2) both in frequency and severity but less efficient in controlling trunk movements. Abdominal movements with tensing of abdomen and urine incontinence occurred late in 2013 under Pimozide therapy indicating poor control of these symptoms by the drug. In December 2014 an "unusual" long-lasting improvement was recorded and YGTSS score reached the lowest value of 7 in February 2015. Lab test indicated a dramatic drop of ASO titre to normal levels (47 UI/ml) along with a decline of anti-DNase B titre (from 336 UI/ml to 223 UI/ml), in absence of any antibiotic treatment. More interestingly, microbiological analyses of throat swabs revealed for the first time a "heavy" presence of *Staphylococcus aureus*. One month later also anti-DNase B antibodies came back to normal values. Microbial isolation of GAS was always negative.

It has been reported that *Staphylococcus aureus* and GAS rarely coexist in tonsils (Zautner et al., 2010) and that *Staphylococcus aureus* colonization modulates host immune response (Brown et al., 2014), inducing tolerance and suppression of pro-inflammatory reactions. Whether *Staphylococcus aureus* colonization facilitates GAS elimination from any "protected niche" (*i.e.*, tonsillar crypts) or promotes a down-regulation of the immune (and autoimmune) response, remains to be elucidated. Our data indicate that oral colonization by *Staphylococcus aureus* occurred first, before "normalization" of both ASO and anti-DNase B antibody titres. Meanwhile a clinical improvement of the tic disorders was recorded.

Conclusion: A cause-effect relationship between *Staphylococcus aureus* colonization, normalization of anti-streptococcal antibody production and symptom improvement can be hypothesized.

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Cognitive and behavioral control in children with Tourette syndrome

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Introduction and objectives: Tourette Syndrome (TS) is a neurodevelopmental disorder characterized by vocal and motor tics with an onset of tics at the age of around 6 years and a maximum of motor and vocal tics at 10 to 12 years of age. Tics gradually tend to decline in their intensity during or after puberty. Circumstantial evidence from neuropsychological studies and from studies using anatomical Magnetic Resonance Imaging suggests that this decline of symptoms relates to the development of self-regulatory control in adolescents during that age period. We thus hypothesize that cognitive control is an important factor for the clinical impact of tics in children with TS. To this end, we measured brain activity with electrophysiology related to cognitive control in 25 children with TS compared with 35 healthy control children and 40 children with ADHD aged 8–12 years at time of inclusion.

Methods: Participants performed a PC-based modified Eriksen-Flanker task while recording EEG. On compatible trials, arrows pointed to the same direction (<<<<<<>>>>>>). On incompatible trials flanker arrows and target arrow pointed to different directions (<<<><<>><>>>). Participants were instructed to respond to the direction of the central target arrow while ignoring the flanker arrows by pressing the left or right mouse button. Electroencephalogram was simultaneously recorded from 34 scalp channels. Data from each dataset were subjected to temporal ICA using infomax, implemented in EEGLAB, estimated 30 components after PCA compression. We used automated sorting routines to cluster components for further analysis and identify the clusters containing event related components most relevant to attention, conflict, and error processing.

Results and discussion: We found differences in the stimulus-locked P300 potential across clinical groups indicating alterations of attention between children with TS, control children and children with ADHD.

Conclusion: Our results indicate underlying neurophysiological group differences that may be due to adaptive phenomena in TS.

References

None

An international survey of health services delivery for patients with Tourette syndrome

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Introduction and objectives: Tourette syndrome (TS) is a developmental neuropsychiatric disorder characterized by chronic motor and vocal tics. It is strongly associated with several comorbidities, namely attention deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD). Given its complex, multifaceted nature, TS is managed by a wide variety of practitioners in different disciplines, often working in multidisciplinary teams (Abi-Jaoude et al., 2009). Little is known about the different models of care in TS. Thus, this survey aims to elucidate what health services are available to patients with TS in different settings.

Methods: We developed a comprehensive questionnaire to assess clinical care resources and approaches for TS patients in several geographic regions. After piloting, the questionnaire entailed 30, mostly multiple-choice questions. We obtained a list of clinicians that manage TS patients in Canada, the United States of America, Australia, Europe, and the United Kingdom, through the respective TS associations. We contacted clinicians by phone to request e-mail contacts of those interested in participating in our questionnaire. The electronic survey was created and distributed using SurveyMonkey. A pre-determined response rate of at least 20% was set as a condition to include the data from each English speaking geographic region.

Results and discussion: We had 32 responses from USA, 20 from Canada, and 87 from Europe and UK. All regions exceeded the 20% response rate. Forty-six percent of respondents are part of a teaching hospital and 18.2% work in a private clinic. The vast majority of respondents (91.9%) are located in an urban setting, with catchment populations ranging from 150,000 to 7 million. Over half of the respondents (53.3%) allocate their resources primarily for comprehensive and continuing care of TS, whereas only a minority (8.1%) reported prioritizing assessment of new patients. Sixty percent of the respondents use Yale Global Tic Severity Scale as intake questionnaires. Large majority of the respondents (85.6%) manage OCD, ADHD, and anxiety, and just over half (54.1%) manage other co-morbidities that include skin picking, sleep disorders, ASD, and learning disabilities. Only a minority (7.5%) of respondents work almost exclusively with patients with TS. The majority of clinicians serviced only children and adolescents, with just under a third providing care to adult patients. A third of respondents reported wait times that were less than 3 weeks, another third of 1 to 3 months, and almost a quarter of 3 to 6 months. Three quarters of respondents in each region do not utilize a triage system for referred patients.

Conclusion: Most health care delivery for TS occurs in specialized urban centers. These provide a variety of services and focus on optimizing care to current patients. This needs to be balanced with maximizing access to care.

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De novo mutation in Tourette syndrome

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Introduction and objectives: Tourette syndrome (TS) is a developmental neuropsychiatric disorder characterized by chronic motor and vocal tics. Symptoms maximize in their adolescence. Although they often improve or remit in adulthood, some patients are tortured by refractory tics for long time into adulthood.

Genetic risks are suggested by twin studies. Previous studies had focused on common variants, but aside from small effect size, the results were inconsistent, or account for only a small fraction of Tourette syndrome. So recent attention had shifted to rare variants or de novo mutations.

Exome studies have successfully identified causal role of de novo mutations in sporadic autism or schizophrenia cases. We apply this approach to Tourette syndrome unveiling the genetic contributions of rare variants.

Subjects

Methods: Sporadic Tourette cases who meet the DSM-IV criteria, and their parents are recruited in four institutions in Japan. Sporadic Cases are; no parents or siblings manifest tics and no 2nd, 3rd relatives are diagnosed with Chronic tics, Tourette syndrome, or Obsessive Compulsive disorder. To minimize other environmental factors that might cause tics or Tourette syndrome, probands with following conditions are excluded; fewer than 36 weeks of gestation, less than 2000 grams of birth weight, complications in pregnancy or delivery, a history of preceding Streptococcal infections (i.e., PANDAS).

We plan to include twenty trios and at present six families were recruited. Peripheral blood samples of Parent-child trios were collected.

SNP call & annotation

Genomic DNA was enriched through hybridization with biotinylated RNA library baits. Captured DNA was sequenced using an HiSeq 2000. FASTQ files are aligned to hg19. The pipeline was designed according to GATK's best practice, which consists of BWA, SAMTOOLS, Picards, GATK. Variants were annotated against GRCh37.74. Sanger sequencing was performed for all de novo candidates.

Results and discussion: We achieved sufficient coverage (10-fold), on average 98% of the region for target exome. Twenty DNM are validated by Sanger sequencing. These include 3 missense, 3 silent, and 14 modifier mutations.

Conclusion: Three missense mutations could be candidate genes of Tourette syndrome. Further functional analyses are needed.

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Available at: https://www.broadinstitute.org/gatk/guide/best-practices

Decreased fractional anisotropy and diffusivities in un-medicated patients with obsessive-compulsive disorder and their unaffected siblings

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Introduction and objectives: Obsessive-compulsive disorder (OCD) is a common neurobiological disorder with strong genetic influence which has not yet been well understood. In terms of white matter abnormalities in OCD, evidence has been mixed. By using diffusion tensor imaging (DTI) technique, we were able to exam whether there were any white matter abnormalities in these un-medicated OCD patients. Unaffected siblings were also undertaken the study hence the role of white matter endophenotypes in this disorder could be investigated.

Methods: Forty-four un-medicated OCD patients, fifteen of their unaffected siblings and thirty-seven healthy controls were taken part in the study. Voxel-wise group comparisons of white matter fractional anisotropy (FA), axial diffusivity (AD), mean diffusivity (MD) and radial diffusivity (RD) were performed using tract base spatial statistics (TBSS) on the bilateral cingulum, bilateral inferior longitudinal fasciculus/inferior frontal-occipital fasciculus (ILF/IFOF) and bilateral superior longitudinal fasciculus (SLF).

Results and discussion: Un-medicated OCD patients had significantly reduced FA in the left cinglum. They also showed trends of decreased FA in all other regions of interests (ROIs). Significant three-group effects were found in mean FA and diffusivities values in the left cingulum.

Significant decreases in FA and increased in RD were found in OCD patients compared to healthy controls. Unaffected siblings also had significantly increased RD in comparison to healthy controls. All other ROIs (uncorrected for multiple comparisons) showed highly similar patterns of white matter changes to the left cingulum.

Conclusion: Above findings suggest the decreased FA could be driven by decreases in RD, where RD also seems to play a critical role in white matter endophenotypes in OCD

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Oculogyric crisis as a complication from antidopaminergic treatment for Gilles de la Tourette syndrome – presentation of three patients

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Introduction and objectives: Oculogyric crisis (OGC) is characterized by spasmodic deviations of the eyes, most commonly upwards, and is a rare complication from antidopaminergic treatment for tics in patients with Gilles de la Tourette syndrome (GTS) (Robertson, 2000; Mejia and Jankovic, 2010; Rizzo et al., 2012).

The object of this paper is to describe the clinical phenotype of antidopaminergic-induced OGC dyskinesia in patients with GTS.

Methods: We present three patients with GTS who developed OGC after antidopaminergic treatment for tics.

Results and discussion: OGC was characterized by recurrent episodes of upward gaze lasting from 1 to 4 h per day and was found in three males. All patients were previously exposed to other neuroleptics and had tics rated severe in Yale Global Tic Severity scale (mean score- 34.7; SD ± 9.9). Patient 1 developed tardive OGC after therapy with haloperidol 6 mg for 2 years. Recurrent acute OGC in case 2 was caused for the first time by therapy with risperidone 4 mg daily. Acute OGC developed in patient 3 after 8 days of therapy with tetrabenazine 62.5 mg. The age of OGC onset varied from 16 to 18 years. Duration of GTS was 7 years in patient with acute OGC, 4 years in case of recurrent acute OGC and 10 years in case of tardive OGC. Acute OGC resolved after the dose of tetrabenazine was decreased to 37.5 mg daily. Tardive OGC resolved gradually 3 months after discontinuation of haloperidol. Recurrent acute OGC resolved 2 months after risperidone was stopped. However, OGC reappeared when risperidone was introduced again 3 and 5 years later due to major deterioration of tics when using other medications.

Conclusion: OGC may occur as a complication from treatment with antidopaminergic medications in patients with GTS. Long exposure to antidopaminergic drugs predisposes to the development of OGC. Clinical outcome is good in non-adult patients.

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D1 receptors mediate the protective effects of finasteride in animal models of Tourette syndrome

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Introduction and objectives: Cogent epidemiological evidence suggests that Neuroactive steroids (NS), including androgens and neurosteroids, play a critical role in the pathogenesis of Tourette Syndrome (TS). Indeed, TS is markedly predominant in males and exposures to environmental and psychosocial stress exacerbate symptom severity in TS patients (Martino et al., 2013). This framework prompted us to validate the hypothesis that alterations in NS biosynthetic pathways may be directly implicated in TS pathophysiology. Accordingly, our group reported that the inhibition of 5-alpha reductase (5?R), the rate-limiting enzyme in NS synthesis, attenuates a wide array of effects induced by dopaminergic activation in rodent models of TS (Bortolato et al., 2008; Devoto et al., 2012; Frau et al., 2013). In addition, these preclinical findings have been translated into clinical trials, in which the prototypical 5?R inhibitor FIN showed tic-suppressing properties in TS patients (Bortolato et al., 2007; Muroni et al., 2011). In spite of these promising results, the underlying molecular mechanism of 5? R and its related-NS in TS is yet to be elucidated. Here, using animal models with high relevance for TS, namely the prepulse inhibition (PPI) of the startle reflex and the eye blinking assay (Swerdlow and Sutherland 2006), we show that the protective effects of FIN lie on the specific involvement of D_1 dopamine receptor subtype.

Methods: To examine the specific implication of dopamine (DA) receptors in the PPI-ameliorative effects of finasteride, we used several rodent strains with different sensitivities to the effects of dopaminergic agonists. Sprague-Dawley, Long-Evans and C57/BL mice (n = 8–12/group) were injected with selective D_1- and D_2-DA receptor agonists in combination with FIN (100 mg/kg, IP) and then tested in PPI. In addition, to further verify whether FIN may regulate D_1-DA receptors, FIN effects were investigated in the increases of eye blinking rates induced by the selective D_1 receptor agonist SKF 82958 in rats. Statistical analyses were performed by multiple-way ANOVA, as appropriate, followed by Tukey's test as post hoc.

Results and discussion: Overall, we found that FIN was able to counter the PPI deficits induced by the full D_1-like receptor agonist SKF-82958 but not by the D_2 receptor agonists quinpirole or sumanirole. Eye blinking tests confirmed PPI results, showing that the pretreatment with FIN fully counteracted the D_1-mediated increases of eye blinking rates in Sprague-Dawley rats. Interestingly, despite its antidopaminergic properties, FIN failed to exert extrapyramidal symptoms in both PPI and blinking tests, even at highest dose administered. These results collectively indicate that 5?R inhibition elicited its antipsychotic-like effects through negative modulations of D_1 receptor.

Conclusion: These findings lend further evidence to the role of NS in TS pathophysiology. Based on our preclinical and clinical evidence, we hypothesize that perturbances in 5?R activity in critical phases of development and/or ensuing adverse life events, may impair the signaling of dopamine and other neurotransmitters, leading to exacerbation of tics and other behavioural abnormalities in TS. Finally, since pharmacologic antagonism of the dopamine D_1 receptor has been proposed as a novel approach to tic reduction in TS, this study indicates 5?R inhibitors as promising tools for TS, with no remarkable side-effects elicited by common drugs used for the treatment of this disease.

Disclosures

The authors declare that there are no conflicts of interest.

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Ten years experience of the living with Tourette syndrome program; educational and psycho-social intervention model for people with TS and their families created by Andalusian Association of Tourette syndrome Patients and Associated Disorders- ASTTA, Spain

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Introduction and objectives: Launched in 2005 by ASTTA, and on going, "Living with TS" is a pioneer program for psycho-social and educational support to people with TS and their families in Spain.

- Endorsed by Andalusian Health Ministry

Staff:

- Creator and Director: Diana Vasermanas*
- Coordinator, Children and Youngsters Area: Alejandra Frega*

*Clinical psychologists.

- General Coordinator: Salud Jurado. President of ASTTA

Objectives: To improve the health, quality of life and integration of people with TS, and their families, aiming at improving support and resources necessary to fulfill their rights and needs in different contexts (school, home, work, recreation, care), and to reduce the impact of stress on tics and other disorders.

Rationale:

- Inadequate psycho-social support creates stressing situations leading to higher risks of school and work failures, with consequent marginalization, increasing tics and other disorders (ASTTA, 2003; Vasermanas and Cubo, 2004).
- The reports"Creation and Follow-up of Psycho-social Support Circles for the Integrations of Children with TS" (IMSERSO, 2003) and "Incidence of Psycho-social Support in Anxiety and Depression on TS Children and Youngsters and Their Parents" (EFPA, 2005), (Vasermanas et al.), assessed empirically the effects of psycho-social support.

Methods: Developed over 10 consecutive years (2005–2015) in Andalusia, and other Spanish regions, by the Interdisciplinary Team of ASTTA.

Live and on-line activities, free of charge to participants:

- Psychological cognitive-behavioral interventions for children, adolescents and adults with TS
  - Workshops; individual sessions
- Psycho-educational workshops for patients and families.
- Integral Care Service for Students
  - Personalized reports; counseling to schools, high schools and universities.
- Reports and Legal Counseling for Disabilities Declarations.
- Family relief and integrative recreation.
- Awareness and Education on TS.
  - Organization of university events and congresses.
  - Collaboration with studies and research.

- Documentation production.
- Dissemination on the media and social networks.

Coverage

- People with TS of all ages
- Families
- Students, voluntary workers, professionals
- Educational communities; social care services

Evaluation of results

- Specific registries and questionnaires
- Pre/post Psycho-diagnostic Evaluations
- Annual reporting

Results and discussion: *The Evaluations show and increase of the following factors:*

- Abilities and psycho-social resources for *(Image 1):*

Living with Tourette Syndrome Program activities of promotion and trainning about TS and associated disorders

➢ **Organization of 9 university meetings:**

- Five meetings in the School of Psychology, Granada University
- Three meetings in the School of Medicine, Malaga University
- One meeting in the School of Psychology, Cadiz University. UIMED

➢ **Presentation of communications on TS at specialized congresses:**

- Symposium on TS; IX European Psychology Congress; Granada, 2005
- III Spanish Congress on TS and associated disorders; Barcelona 2007
- III International Congress on Orphan Drugs and Rare Diseases, Seville, 2007
- III International Multidisciplinary Congress on ADD and Behavior Disorders, Madrid 2008
- VI & VII International Congress on Forensic & Juridic Psychology, Granada, 2012 Madrid, 2013
- XXVI National meeting on Nursing Care; Ceuta 2015
- II Educational Congress on Rare Diseases; Barcelona, 2015

➢ **Collaboration with research projects:**

- "Incidence of Anxiety and Depression Dissordesrs on TS Children and Youngsters and Their Parents"; Vasermanas D, Frega A. Psicotourette
- "Treatment of TS in children with magnesium and vitamin B6"; Garcla-Lopez et al.
- "Advances in physio-pathological mechanisms of TS" Berthier M, Davila G. Malaga University
- Production of audiovisuals and documentation
- Dissemination on the media and social networks

- Facing stress and conflict resolution in different circumstances
- Decrease Anxiety and Depression in children with TS and their parents (Image 2).

Example of annual psycho-social, educational and empowerment support activities of the Program, organized byASTTA- From Annual Report 2013

- ❑ Five Psychology workshops for childrens and adults with TS
- ❑ Individual on-line psychotherapy session for 16 patients with financial needs
- ❑ Eight Psycho-educational workshops for patients and families
- ❑ Eight meetings with familes of inclusive recreations; week-end in Almeria
- ❑ Fifteen personalized reports for educational purposes
- ❑ 6 for schools, 8 for high schools and 1 for universities
- ❑ Twelve reports for disabilities assesments
- ❑ 120 individual conselings, on different subjects and problems
- ❑ **Directs Beneficiaries**
  - ❑ People with TS of all ages and their families; 250 people
- ❑ **Indirects Beneficiaries**
  - ❑ Students, voluntary workers, professionals of Educational communities and social care services.

Results : Improvements in people with TS and families on
- Communication, coping with symptoms and stress.
- Self esteem, perception of social support.
- Academic achievements and integration of students with TS.
- Granting of benefits and access to community resources.

Evaluation*

93% very satisfied and recommends the Program to obtain resources and support indifferent environments

*Specific registries and questionnaires

- More Participation in activities of integrative recreation
- Obtaining Disability Certificates

- Involvement of the educational community (schools, high schools, universities), to attend the needs of students with TS.

- Spaces for TS awareness and education *(Image 3)*

Evalution of effects of the Program on the health of people with TS and their families

Study on the incidence of Anxiety and Depression disorders in Children and Youngsters with TS and their parents *(Vasermanas D, Frcga A ctal. 2005)*[3]

Annual Psycho-diagnostic Evaluation (PE) of 17 families at the start and end of the Program.

Initial PE Results: presence of Depression in children and youngsters with TS*, correlating with Anxiety and Depression states in their mothers and fathers.*

Final PE Results: improvements in Anxiety and Depression in children and youngsters with TS and in the Anxiety and Depression of their fathers and mothers, clinicaly and statistically significant**

PARENTS: HAD, ***(Zipmond y Snaith)***

Average	Mothers Anxiet	Mothers Depression	Father Anxiety	Father Depression
Initial	12.6	7.8	7.4	4.5
Final	7.24	4.25	5.5	3
Reduction %	42.3**	39.3**	25.6*	33.3*

CHILDREN: CDI ***(Kovacs)*** **&CDCN-1** ***(Bas)***

Average	CDI	CDCN
Initial	14.8	3.5
Final	9	2.4
Variation %	39**	31.4**

Correlation depression-cognitive distrotions: =0.81**
Correlation depression mothers-depression children= 0.74**
Correlation depression fathers- depression children = 0.66**

- *Recognition of the Program results*

- Incorporated into the Health Promotion Programs and the Manuals for Students with Specific Developmental Needs Government of Andalusia (Education Andalusia's Government, 2008).

- Used as a model for programs for children with Rare Diseases (Vasermanas and Frega, 2012). However, it should be verified with other groups of people with TS

Conclusion: Living with TS Program contributes to increase the psycho-social and educational support to improve the health and quality of life, decrease symptoms and limitations, and improve the integration, visibility and empowerment of people with TS and their families (ASTTA, 2010).

Acknowledgements

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Premonitory urge to tic in Tourette's is associated with interoceptive awareness

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Introduction and objectives: A contribution of aberrant interoceptive awareness to the perception of premonitory urges in Tourette's has been hypothesized, but has not been tested directly.

Methods: We assessed interoceptive awareness in 19 adults with Tourette's and 25 age-matched healthy controls using the heartbeat counting task. We also used multiple regressions to explore whether the severity of premonitory urges was predicted by interoceptive awareness or severity of tics and obsessive-compulsive symptoms.

Results and discussion: We observed lower interoceptive awareness in Tourette's compared to controls. Interoceptive awareness was the strongest predictor of premonitory urges in Tourette's, with greater interoceptive awareness being associated with more urges. Greater tic severity was also associated with higher rates of premonitory urges.

Conclusion: The observed relationship between severity of premonitory urges and interoceptive awareness suggests that interoception might be involved in self-reported premonitory urges in Tourette's. High levels of interoceptive awareness might reflect a self-attentive capacity to perceive urges.

Disclosures

None

The somatotopy of tic inhibition: where and how much?

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Introduction and objectives: Tics are the hallmark feature of Tourette syndrome. The basic phenomenological and neurophysiological characteristics of tics have been widely investigated. Interestingly, the spatial distribution of tics across different body parts has received little attention. No previous study has investigated whether the capacity for voluntary tic inhibition also varies across body parts.

Methods: We analysed video sequences of 26 adolescents with Tourette syndrome in a "free ticcing" condition, and in a "voluntary tic inhibition" condition, to obtain absolute tic counts for different body parts. Two measures of the spatial distribution of tics were then analysed. First, tic counts for each body region were pooled across all patients, and expressed as a percentage of the total number of tics in the entire dataset. Second, the number of patients presenting with tics in each body region was calculated. Finally, the capacity to inhibit tics was evaluated for each patient and each ticcing body part. The mean inhibitory capacity for each body part across patients was then calculated. Linear regression analyses were employed to investigate the relationship between the contribution of each body part to overall tic behaviour and the ability to inhibit tics in that body part, averaged over our patient group.

Results and discussion: Tic distribution across patients showed a characteristic somatotopic pattern, with the face most strongly represented. A significant negative relation was found between the ability to inhibit tics and pooled tic frequency across body parts. The body parts that exhibited fewest tics were the ones for which tic inhibition was most effective.

Conclusion: Our data is consistent with the idea that tic recruitment order reflects a "tic generator" spreading across a somatotopic map in the brain. Voluntary tic inhibition did not simply cause a proportional reduction of tics in each body part. Our findings suggest that tic inhibition involves a voluntary shift of physiological signal processing that suppresses motor noise by preferentially transmitting only stronger signals within cortico-striato-thalamo-cortical motor loops.

How are we doing? A survey to assess the current approach to Tourette syndrome in Catalonia

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Introduction: The first European guideline for the diagnosis and treatment of Tourette Syndrome was published in 2011 (Cath et al., 2011; Roessner et al., 2011; Verdellen et al., 2011; Muller-Vahl et al., 2011). To the moment, no data is available to know the extent to which its recommendations are followed in Catalonia.

Objectives: The aim of this study was to assess the current approach to the diagnosis and the treatment of Tourette Syndrome among child and adolescent psychiatrists working in Catalonia.

Methods: An electronic tool was used to disseminate a survey with 28 questions on Tourette Syndrome to child and adolescents psychiatrists in Catalonia. To have a better understanding of the physician's regular practice, questions on the diagnostic and the treatment processes were raised from three clinical cases. All the answers were kept anonymous.

Results and discussion: A total of 40 invitations were sent. After a 3-month period, 18 surveys (45%) were completed. From those who answered, 13 participants (72.2%) were female and 11 (61.1%), were aged below 45 years old. Each psychiatrist was following up a mean of 3, 5 patients with Tourette Syndrome at the time the survey was completed. Regarding the diagnosis, 10 participants (55.5%) stated that they would use standardized instruments to complete the assessment: 9 to evaluate symptoms of Attention Deficit and Hyperactivity Disorder (ADHD), 7 to evaluate symptoms of Obsessive-Compulsive Disorder (OCD) and 5 to evaluate the tics themselves. Only 6 participants (33.4%) reported that they would perform a physical examination and 5 (27.8%), would indicate complementary tests. When it comes to the treatment, all the participants affirmed that they would start a treatment for tics in case of patient's distress. Only 2 psychiatrists (11.1%) would indicate a psychological intervention as the first treatment, referring basically to behavioral therapy. From the pharmacological options, atypical antipsychotics were chosen as the first choice in 17 cases (94.4%). In case of comorbidity with ADHD, 17 participants (94.4%) reported that they would start treating the inattention and hyperactivity symptoms, with a non-stimulant medication in 13 cases (72.2%).

Conclusion: (1) When tics are detected, most psychiatrists use standardized instruments to assess tics and comorbid symptoms. (2) When tics appeared together with ADHD, most psychiatrists start treating the ADHD symptoms first. In that case, non-stimulant are preferred to stimulant medications. (3) When a specific intervention for tics is required, psychological treatments are rarely indicated by psychiatrists as the first option. More training and dissemination of evidence-based psychological therapies for tics are needed to reduce the use of medication in children and adolescents with Tourette Syndrome in Catalonia.

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On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Tourettes Syndrome: case series in Tier 3 CAMHS

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Introduction and objectives: Tourette Syndrome (TS) is an inherited, neurological condition, characterised by multiple motor and vocal tics. It is a complex condition, covering a wide spectrum of symptoms, co-morbidities and severities. TS is often linked to other behaviours, e.g., Obsessive Compulsive Disorder (OCD) and Attention Deficit Hyperactivity Disorder (ADHD). People with TS also often experience a range of associated symptoms such as anger, low mood which can sometimes be the most challenging aspects of the condition. There is no cure for TS, although different drugs and psychological therapies such as Cognitive Behavioural Therapy and Habit reversal training have been used successfully in a small number of TS patients. None of these treatments completely eliminate symptoms and outcomes are variable depending on multiple factors. Here we present a series of Tourettes cases seen in a generic Tier 3 CAMHS clinic which demonstrates the complex interplay of the above issues.

Methods: All the Tourettes Syndrome cases currently open to my Tier 3 CYPS clinic at present were reviewed in this case series.

We have looked at the age of onset of the Tic disorder, co-morbidities and other psychosocial factors, current treatments and treatments received in the past and their current outcomes in terms of symptom severity and functioning socially as well as in Education/ work.

Results and discussion: *Observations from our case series*: When the Tourettes Syndrome had been around for number of years, with symptom severity requiring trial of several different medications, over time, the medications seemed to prove less effective. If reasonable symptom control was to be achieved, this tended to be within first few trials of medication. Recognising and managing co-morbidities such as ADHD and low mood seemed to be crucial. Apart from symptom severity, other factors seemed to play a much bigger role in determining functioning ie warm accepting supportive family, supportive schooling environment, having another focus eg vocational college/ performing arts seemed to be associated with better functioning whereas psychosocial adversity, other challenging behavioural issues were associated with poor functioning. High IQ with an excessive focus on the TS symptoms, was associated with more subjective distress, even when the symptoms were relatively mild.

Conclusion: In Tourettes Syndrome, the focus of assessments right from the beginning, needs to be on the associated psychosocial factors in addition to the symptoms themselves, as they seem to determine the functioning regardless of symptom severity. Finding potential strengths and building on them, developing a focus on purposeful activities that can be handled despite ongoing TS symptoms, can lead to good functioning even with poor symptom control. Also having a warm supportive family seems crucial to good functioning. Efforts need to be put in place to support the whole family so that they develop a shared understanding and acceptance of the TS and work together to manage it.

Gender	Age of onset (yrs)	Current age (yrs)	Co-morbidities	Current treatment	Past treatment	Other factors	Outcome/ functioning
Male	8	17	Ld, ADHD	Clonidine Sulpiride Atomoxetine	Risperidone Haloperidol Aripiprazole Pimozide Quetiapine Concerta XL	One of Twins EBD school Animal care course Warm supportive family	Poor symptom control Frustrated at times Coping well in college Good social network
Male	8	17	ADHD	Clonidine Haloperidol Atomoxetine	Risperidone Aripiprazole Pimozide Quetiapine Concerta XL	One of Twins EBD school Vocational college Warm supportive family	Moderate symptom control Coping well in college Good social network

Male	9	15	ODD, ADHD	Pimozide Concertal XL	Risperidone Haloperidol	Marital discord In care home EBD school Cannabis user	Reasonable symptom control Poor engagement with education Anger/offending/ challenging behaviour Poor social functioning
Male	8	14	ADHD, anxiety	Clonidine	Risperidone Concerta XL	Anxious mom High expectations	Reasonable symptom control Struggled++ at school Coping better since privately tutored Excellent in performing arts
Male	11	16	ASD, Depression	Clonidine Risperidone Fluoxetine	Risperidone Habit reversal training	ASD provision Warm supportive family Anxious mom	Reasonable symptom control Coping at school except when low Good social network
Female	9	13	Dyscalculia, anxiety	Pregabalin	Aripiprazole Risperidone Sertraline	Mainstream school Professional parents High expectations	Mild symptom Coping at school but keeps it all in gets frustrated++ at home Good social network
Female	4	14	None	CBT	Aripiprazole Risperidone	Mainstream school Bright, high achiever	Mild symptoms But distressed++ by symptoms, low Doing very well in school

Disclosures

None

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Parent versus child ratings of tic and non-tic impairment in TS in multiple domains

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Introduction and objectives: For children and adolescents with Tourette Syndrome (TS), collaborative decisions about initiating or modifying behavioral and pharmacological interventions for tics and other symptoms are based in part on assessments of interference and impairment. As children mature, their assessments of symptom-related impairment may mature and diverge from their parents' assessments, and parents generally have less direct knowledge of problems in the school setting. The primary aim of this study was to determine the extent to which children and adolescents with TS and their parents agree in assessments of functional impairment related to tics and co-occurring symptoms in multiple settings, and to compare these parent/child assessments of functional status to those of healthy, non-TS children. Secondarily, the aim was to explore factors that may influence differences in parent/child ratings.

Methods: We examined parent and child perceptions of tic and non-tic related impairment in 85 parent/child dyads in which the child was diagnosed with TS, and 92 control parent/child dyads. The primary assessment tool was the Child Tourette Syndrome Impairment Scale, Parent Report. The same scale, with pronoun modification, was used separately to ascertain directly ratings by children and adolescents. Primary group comparisons were performed with *t* tests and Chi Square, as appropriate. Pearson correlations were used to compare within domains and across parent child groups as well as to evaluate possible effects of other factors such as age on parent/child differences.

Results and discussion: Participants with TS ranged in age from 10 to 17 years (mean 12.0, SD 2.2), 83% were male, 95% were Caucasian. In TS dyads, mean rating scores of non-tic impairment were 27.1 (SD 25.3) by parents and 14.7 (SD 16.4) by children. Mean tic impairment scores were 20.5 (SD 21.0) rated by parents and 18.3 (SD 18.7) by children. For non TS children, mean total impairment ratings were 6.7 (SD 6.4) by parents and 6.1 (SD 5.5) by children. Parent child correlations of impairment ratings in TS dyads were moderate: non-Tic impairment $r = 0.42$, $p < 0.001$; Tic impairment $r = 0.56$; $p < 0.001$. Correlations were similar for ratings by parents and children in the control group: $r = 0.58$; $p < 0.001$. Differences between parent and child ratings for tic impairment increased with age ($p = 0.04$). Parents also rated tic impairment higher in children prescribed medication ($p = 0.03$).

Conclusion: For both tic and non-tic symptoms, parents and their children with TS demonstrated only moderate agreement in ratings of impairment. Overall, parents rated non-tic impairment higher than tic impairment. Parent-child rating differences for tic impairment were greater in older children. This study provides insights into the importance of obtaining perspectives of both parents and children for clinical decision making.

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Disclosures

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Reduced sensory adaptation correlates with tic severity in children with Tourette syndrome

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Introduction and objectives: Persons with Tourette Syndrome (TS) often self-report heightened sensitivity to sensory stimuli, Belluscio et al. (2011) and subjective sensations are a component of premonitory urges for tics (Woods et al., 2005). Neuroimaging studies have shown differences in thickness of sensorimotor cortex in TS (Sowell et al., 2008). To date, however, prior research has not demonstrated clear differences in sensory function (Belluscio et al., 2011). The objective of the present study was to evaluate central sensory processing and adaptation in children with TS, to compare their sensory processing with that of age-matched typically developing (TD) peers, and to correlate sensory measures with tic severity.

Methods: Children ages 9–17 years with TS and TD controls were recruited. All participants underwent a 30 minute vibrotactile testing battery using a CM5 stimulator (Cortical Metrics®, Chapel Hill, NC, USA). Stimuli were applied to the index and middle fingers of the non-dominant hand. Thresholds for amplitude detection, discrimination of vibratory frequencies, and detection of temporal order were performed. Similarly, discrimination of amplitudes (which of two simultaneously delivered stimuli was "stronger") was determined. To evaluate effects of adaptation, the amplitude discrimination was then re-obtained with each trial preceded by a longer sensory stimulus, shown in prior studies of healthy children and adults to reduce ("worsen") amplitude discrimination. Tic severity was assessed independently by clinicians using the Yale Global Tic Severity Score Total Tic Score (TTS). TS and TD groups were compared with non-parametric tests.

Results and discussion: Demographics of the two groups were comparable (TS $n = 21$, mean age = 13 years, 16 male, 17 White, 19 Right-Handed; TD $n = 21$, mean age = 13 years, 12 male, 15 White, 19 RH). Median amplitude thresholds, frequency discrimination, and temporal order judgement did not differ. Median amplitude discrimination was 49 μm (33, 76) in the TS group and 44 μm (29, 66) in the TD group (p = NS). After a preceding stimulus, adaptation occurred in the TD children, reducing discrimination by 173%, to median 120 μm (70, 166). There was significantly less adaptation ($p = 0.03$) in TS, a 14% reduction to median 56 μm (13, 180). Within TS, children with greater (worse) tic scores demonstrated both less absolute adaptation ($r = -0.42$; $p = 0.03$) and less percent change in adaptation ($r = -0.49$; $p = 0.01$).

Conclusion: Children with TS, particularly those with more severe tics, displayed less central sensory adaptation than their age-matched peers. Higher level sensory adaptation may reflect or contribute to the pathophysiology underlying tics in TS.

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Perspectives on the experience of Tourette syndrome in secondary school: a mixed methods study

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Introduction and objectives: Schools can play an important role in promoting health and wellbeing and recent European guidelines have emphasised the importance of educating schools about Tourette Syndrome (TS) (Verdellen et al., 2011). Children with TS have reported that the condition can affect academic performance but school personnel lacked sufficient knowledge about the condition to support them (Shady et al., 1988). The condition also has significant psychosocial impact (Kadesjö and Gillberg, 2000) and bullying has been identified as problem in separate studies with parents and children. This study aims to examine the school experience of the young person from the perspective of parents, teachers and the young person.

Agreement between self- Parent- and Staff-report of school difficulties

School difficulties	Agreement between self-and parent-report Kappa [95% CI]	Agreement between self- and staff-report Kappa [95% CI]	Agreement between patent- and staff-report Kappa [95% CI]
Concentration	.07[-27,.40]	.08 [-.24, .40]	.14[-.18, .45]
Unhelpful staff response to tics	.35[.04, .67]*	.32[.01, .53]*	.18 [-.03, .40]
Difficulties with other students	66[.42, .90]**	.00 [-.24, .24]	.10[-.18, .38]
Homework	.26[-.06, .58]	.32[.03, .61]*	.44[.19.68]**
Examination	.l6[-.17, .48]	.13 [-.17, .42]	.41 [.09, .75]*
Anxiety in school	34 [.01, .67]*	.02 [-29, .32]	.14 [-.18, .45]
writing	64[.35, .93]**	.30[-.06, .66]	.42[.09, .76]*
Managing anger in school	.10 [-24, .45]	.08 [-26, .42]	.25[-.12, .61]

Note: kappa< 0 = no agreement, 0 to 0.20 = slight agreement, 0.21 to 0.04 = fair agreement, 0.41 to 0.60 = moderate agreement, 0.61 to 0.80 = substantial agreement, 0.81 to 1.00 = almost perfect agreement [41].
**p*<.05, ***p*<.01.

Methods: Thirty-five young people with TS, their parents and key members of school staff took part in semi-structured interviews about TS-related difficulties in secondary school. Theme analysis was used to identify school difficulties reported by the young people, before moving on to analysis of the parents' and staff members' transcripts. Themes were then quantified in order to examine the level of agreement between informants and the association with clinical symptom severity as measured by the Yale Global Tic Severity Scale

Results and discussion: A range of TS-related difficulties with academic work, and social and emotional well-being in school were reported by young people, parents and staff. Three super-ordinate themes are described: (1) TS makes school work more difficult, (2) Staff and student's response to TS and (3) TS makes it more difficult to manage emotions in school. The three difficulties most frequently reported by the young people were problems concentrating in class, unhelpful responses by school staff to tics and difficulties with other students such as name-calling and mimicking tics. Additional difficulties reported by more a quarter of young people related to homework, examinations, writing, anxiety and managing anger in school. Motor tic severity was significantly and positively correlated with homework problems ($r_{pb} = 0.39, p = 0.02$) and with writing problems ($r_{pb} = 0.44, p = 0.01$). Phonic tic severity was significantly and positively correlated with reporting unhelpful staff responses ($r_{pb} = 0.46, p = 0.01$). School staff recognised fewer difficulties and there was poor agreement between the young person and teacher about difficulties with other students and anxiety in school. There was moderate agreement between parents and young people in these areas.

Conclusion: Although parents, teachers and young people tended to agree about the impact of TS on school performance, school staffs appear to underestimate the emotional consequences of TS which could impact negatively on the child's school experience.

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Prevalence and predictors of trichotillomania and excoriation disorder in Tourette syndrome

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Introduction and objectives: Trichotillomania (hair-pulling disorder) (HPD) and excoriation (skin-picking) disorder (SPD) are childhood-onset body-focused repetitive behaviors (BRFBs) included in the new DSM-5 Obsessive-Compulsive and Related Disorders (OCRD) category. Both disorders have been proposed to share genetic susceptibility and underlying pathophysiology with obsessive-compulsive disorder (OCD), Tourette Syndrome (TS), and each other (Yu et al., 2015; Monzani et al., 2014; Keuthen et al., 2014). We sought to determine the prevalence of HPD and SPD in a TS cohort with and without OCD, and to identify clinical factors most predictive of HPD and SPD in TS subjects.

Methods: Subjects included 811 TS probands recruited from TS specialty clinics for a multi-center genetic study. Subjects were assessed using standardized, semi-structured interviews. TS clinical investigators, using a best-estimate consensus approach, determined clinical diagnoses of HPD and SPD. HPD and SPD prevalence rates were calculated and clinical predictors of HPD and SPD in TS patients were evaluated using regression modeling in STATA.

Results and discussion: 3.8% of TS subjects met DSM-5 criteria for HPD, and 13.0% met DSM-5 criteria for SPD. In univariable analysis, multiple factors including female gender, OCD, and worse lifetime scores on the Yale Global Tic Severity Score (YGTSS) and Yale-Brown Obsessive-compulsive Scale (YBOCS)) were associated with HPD and/or SPD. In the multivariable analysis, only YGTSS worst-ever motor score remained significantly associated with HPD, while female gender, comorbid OCD, ADHD and YGTSS worst-ever motor score all remained independently associated with increased risk of SPD.

Conclusion: This is the first study to examine HPD and SPD prevalence in a TS population using structured diagnostic instruments. The elevated rates of HPD and SPD in TS patients, along with their association with tic severity and co-occurrence with each other and OCD are consistent with a shared biological and genetic relationship between TS, OCD, HPD and SPD. This study should help to direct future research on HPD and SPD risk factors, pathophysiology, phenomenology, and treatment models.

Acknowledgements

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Disclosures

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Risk factors for tic disorders and obsessive-compulsive disorder in a population-based cohort

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Introduction and objectives: Tic disorders, including Tourette syndrome (TS) and chronic tic disorder (CT), and obsessive-compulsive disorder (OCD) are notable for phenotypic overlap and co-occurrence in individuals and families (do Rosario-Campos et al., 2005). The Danish registry system is a novel resource to prospectively examine risk factors for TS/CT and OCD with high precision and minimal ascertainment bias. We utilized these registries to examine the sibling and parent-offspring recurrence risk and cross-disorder risk for TS/CT and OCD and to assess the role of parental age, a known risk factor for other neuropsychiatric conditions such as autism and schizophrenia (Parner et al., 2012; Frans et al., 2011), in TS/CT and OCD.

Methods: Of 1,741,271 individuals born from 1980 to 2007, 5,596 had a TS/CT diagnosis and 6,191 had an OCD diagnosis. Prevalence and recurrence risk (RR) were estimated using Kaplan-Meier methods and relative RRs were calculated using Cox regression. Parental age was divided into three age groups:

Results and discussion: Prevalence was 0.42% (95% CI, 0.41–0.43%) for TS/CT and 0.84% (95% CI, 0.81–0.87%) for OCD. TS/CT sibling RR was 9.88% (95% CI, 8.02–12.16%) and parent-offspring RR for TS/CT was 19.00% (95% CI, 14.90–25.34%). Individuals with an oldest sibling with TS/CT were 18 times more likely to be diagnosed with TS/CT (adjusted hazard ratio [aHR] 18.63; 95% CI, 15.34–22.63) when compared to individuals without an affected oldest sibling (Figure 1). Individuals whose parent had TS/CT were 61 times more likely to have a TS/CT diagnosis (aHR 61.02; 95% CI, 44.43–83.82) (Figure 2). Sibling and parent-offspring OCD and cross-disorder risk were also significant. Although advancing paternal age was associated with a very small increased risk for OCD when mothers were under age 35 (paternal age 35–39 aHR 1.13, 95% CI 1.04–1.23; paternal age 40+ aHR 1.11, 95% CI 0.96–1.28), this finding was inconsistent through age groupings; thus the risk of TS/CT and OCD was not reliably associated with paternal or maternal age.

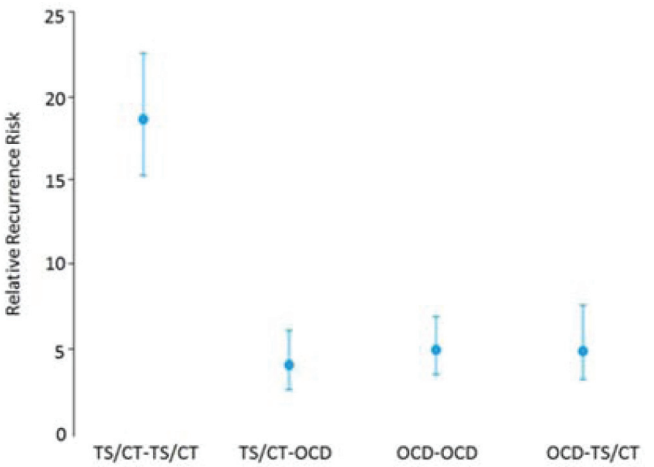

Figure 1 | Adjusted sibling relative recurrence risk and cross-disorder recurrence risk for TS/CT and OCD. TS/CT-TS/CT: relative recurrence risk of TS/CT for individuals with an oldest sibling with TS/CT; TS/CT-OCD: relative recurrence risk of OCD for individuals with an oldest sibling with TS/CT. OCD-OCD: relative recurrence risk of OCD for individuals with an oldest sibling with OCD; OCD-TS/CT: relative recurrence risk of TS/CT for individuals with an oldest sibling with OCD. Data represents mean +/− 95% CI.

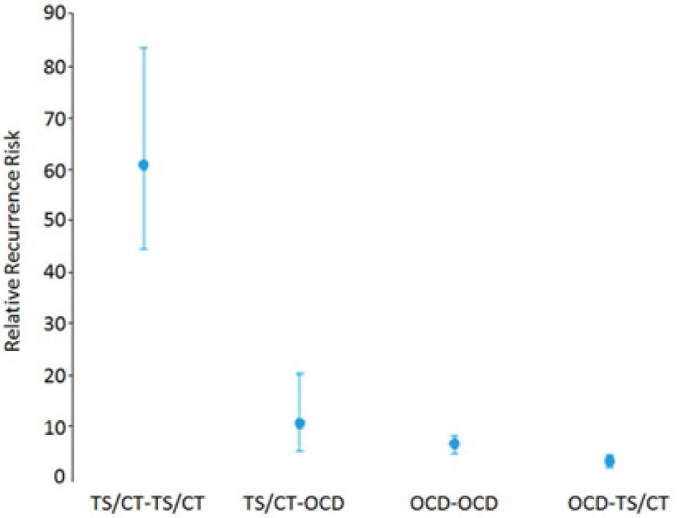

Figure 2 | Adjusted parent-offspring relative recurrence risk and cross-disorder recurrence risk for TS/CT and OCD. TS/CT-TS/CT: relative recurrence risk of TS/CT for offspring of a parent with TS/CT: TS/CT-OCD: relative recurrence risk of OCD for offspring of a parent with TS/CT. OCD-OCD: relative recurrence risk of OCD for offspring of a parent with OCD; OCD-TS/CT: relative recurrence risk of TS/CT for offspring of a parent with OCD. Data represents mean +/− 95% CI.

Conclusion: Our population-based recurrence risk estimates demonstrate high TS/CT and OCD sibling and parent-offspring recurrence risk, particularly for TS/CT. The strong familial clustering of TS/CT and OCD reflects an important role for genetic and/or shared environmental factors. In addition, we were able to exclude a significant role for parental age in risk for these disorders. Thus, factors associated with advanced parental age, such as *de novo* mutations, likely play a smaller role in TS/CT and OCD risk compared to other neuropsychiatric disorders.

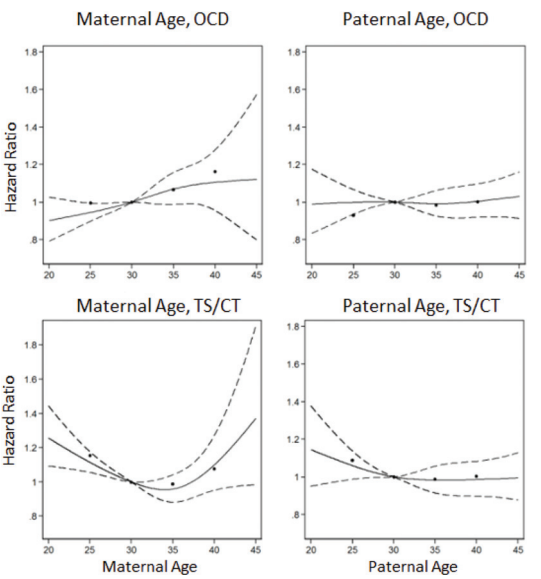

Figure 3 | The hazard ratio for OCD and TS/CT associated with maternal and paternal age. Data are adjusted for age of the opposite parent and relative to age 30 for each parent. Dashed lines represent 95% CI's.

Acknowledgements

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Preliminary data on 6 years follow-up on tics and comorbidity in children and adolescents with Tourette syndrome

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Introduction and objectives: In the literature, there are relatively few clinical longitudinal studies of patients with Tourette syndrome. With the present knowledge of Tourette syndrome, its pathogenesis and clinical course, it is difficult to predict prognosis in the individual patient, both regarding severity of tics and development of comorbid disorders and thus change of phenotype (TS− only, TS+ ADHD, TS+ OCD, TS+ ADHD+ OCD) (Leckman et al., 2001; Bloch and Leckman, 2009; Rizzo et al., 2012). In this study, we hypothesize, that *the severity of tics declines over time* and *the patients without comorbidities (TS-only) at baseline will not develop comorbid disorders over time.*

Methods: We performed a longitudinal clinical study. At baseline, 314 patients with Tourette syndrome (mean age 12.4 years) and 81 healthy controls were included. At follow-up, after average time 5.89 years, 227 patients and 53 healthy controls were reexamined. At both examinations, the participants were examined thoroughly with several diagnostic instruments, among others; Yale Global Tics Severity Scale (YGTSS), Yale-Brown Obsessive Compulsive Scale (CY-BOCS and Y-BOCS) and ADHD-Rating Scale (ADHD-RS and ASRS).

Results and discussion: The phenotype distribution between the baseline cohort (n = 314) and the reexamined cohort (n = 227) at first examination (T1) differs slightly, see Table 1. The phenotype distribution at the re-examination (T2) is also shown in Table 1. The preliminary analyses are made on direct comparison between the 227 patients; aged 11–25 years (mean 18.05). Of the 227 patients 45.9% did not change phenotype between T1 and T2 with the majority (64.7%) in the TS-only group. The change of phenotypes is shown in Figure 1. For the tic severity, the range on the YGTSS global score was similar in T1 and T2 (score 0–83 and 0–84, respectively), but the median decreased from 23 at T1 to 16 at T2. The change of score on YGTSS is shown in Figure 2. Both the average global tic score (total tic + impairment) and the total tic score (motor + vocal tic) declined from T1 to T2. The average total tic score declined more (6.42 points) than the average global score (5.93 points) due to a higher impairment score at T2, although around half of the patients reported none impairment at all, neither at T1 nor at T2. In summary, we see a tendency towards less severe tics but slightly higher impairment score over time. We will further examine this tendency by correlating it with quality of life and presence of comorbidities.

Table 1 | Distribution of phenotypes at baseline (Tl) and at reexamination (T2).

Time of examination	T1 (n=314)	T1 (n=227)	T2 (n=227)
TS-only	38.7%	40.7%	55.2%
TS+ADHD	21.4%	19.5%	19.7%
TS+OCD	18.2%	18.1%	12.1%
TS+ADHD+OCD	21.7%	21.7%	13.0%

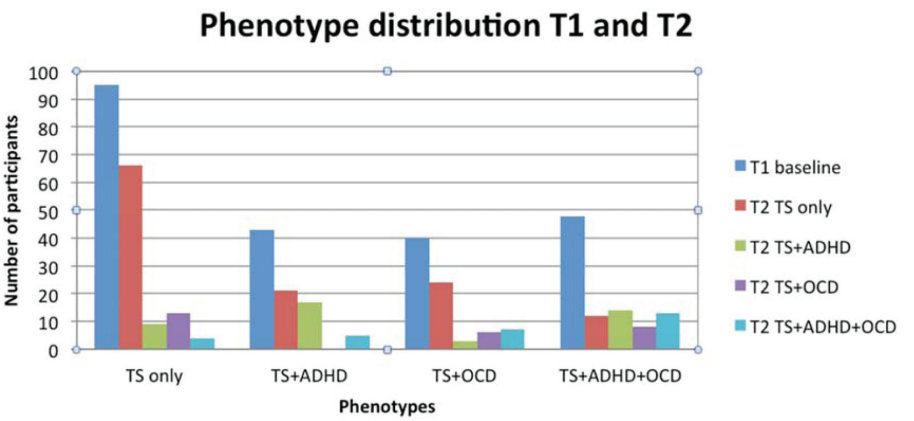

Figure 1 | Change of phenotypes from baseline to reexamination within each baseline-phenotype.

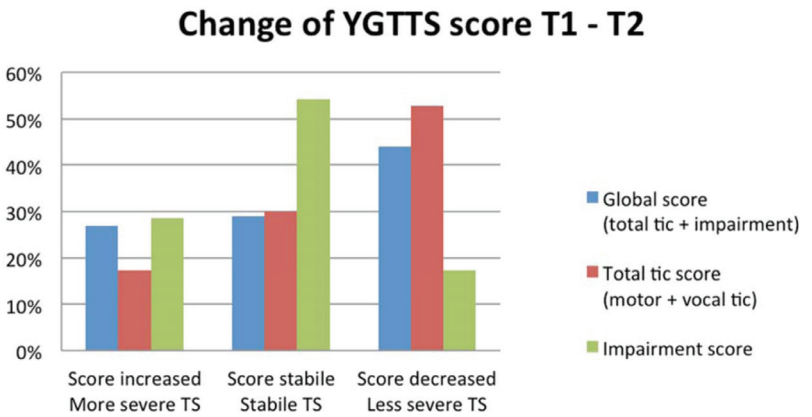

Figure 2 | Change of score on YGTTS from baseline to reexamination.

Score between +5 and −5 is considered as natural fluctuation of tics and noted as stabile.

Conclusion: Longitudinal studies are important in order to better be able to predict the individual course and prognosis in patients with Tourette syndrome. As hypothesized we see a small average tic decline over time and only a third (35.3%) of the patients without comorbidities at baseline develop comorbidities over this six years period.

Disclosures

None

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Cannabinoid SR141716A induces hyperactivity and vocals in mice

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Introduction and objectives: Attention-Deficit Hyperactive Disorder (ADHD) is a common disorder, affecting 3–9% of children and 2–5% of adults around the world. About 50% of the patients with Tourette Syndrome are also diagnosed with ADHD. ADHD is characterised with attention deficit, hyperactivity and impulsivity. Interestingly, recent studies have shown that hyperactivity can be induced by the cannabinoid SR141716A, a selective antagonist of the cannabinoid CB_1 receptor.

Methods: In this study we injected mice with SR141716A and examined their locomotor activity. As alterations in the brain structure of children and adolescents with ADHD have been documented, we performed an MRI study in order to examine whether SR141716A induced changes to the brain structure of the hyperactive mice. We also recorded their Ultra Sonic Voices (USV). In addition, the effect of Ritalin® (methylphenidate), one of the most common drugs for treatment of hyperactivity and ADHD, was tested on SR141716A-induced hyperactivity.

Results and discussion: Our results show that SR141716A increased the number of USV. It also induced a significant increase of locomotor activity in female but not in male mice at age 1 month. A quantitative MRI measurement (T2 analysis) at this age revealed that compared with the brain structure of vehicle-treated mice, the tissue density of several brain areas was significantly higher in the SR141716A-treated mice. The areas that were affected are related to movement (caudate putamen and thalamus), the reward system and addiction (nucleus accumbens and septal nuclei), memory (hippocampus) and impulsivity (nucleus accumbens and amygdala). At age 4 months, the female mice were still hyperactive. Interesting, the SR141716A-induced hyperactivity was not reversed by Ritalin®.

Conclusion: Our results suggest that postnatal inhibition of the CB_1 receptor induces irreversible changes to the brain structure and increases the number of vocals of young mice. The lack of response to methylphenidate suggests that dopamine transporter is not involved in the mechanism of SR141716A-induced hyperactivity. These results further support the emerging view that the endocannabinoid system is involved in hyperactive behaviour and suggest it may also be involved in vocal tic disorder.

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Verbal learning during tic suppression in children with a chronic tic disorder

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Introduction and objectives: One of the more interesting aspects of tics is, though involuntary, they can be temporarily suppressed with active inhibitory effort. Imaging and behavioral studies provide strong evidence that tic suppression is a highly effortful process. Historically, there have been many concerns regarding tic suppression, including a potential exacerbation of symptoms following a period of suppression. While many of these concerns have failed to garner supporting evidence in laboratory and suppression-based treatment studies, concerns have been raised about the potential cognitive effects of tic suppression because of its effortful nature. Studies have suggested that tic suppression requires the activation of frontal-cortical networks to down-regulate abnormally high levels of activity in subcortical structures that are thought to produce tics. These networks appear to overlap with those required for executive and attention-demanding tasks, such as learning of new information (Peterson et al., 1998). Researchers have also found that tic suppression may interfere with performance on an attention-demanding auditory task, suggesting that tic suppression may interfere with concurrent processes requiring active cognitive resources (Conelea and Woods, 2008).

Methods: In this study we examined the effects of tic suppression on learning of new verbal information. Participants were 31 treatment-naïve children ages 7 to 17 with a diagnosis of a chronic tic disorder. Participants were randomized to a tic-freely control group or a reinforced suppression group. The California Verbal Learning Test, Children's Version (CVLT-C) was administered to children (with concurrent suppression for the suppression group). A distraction task, and then short delay recall trials were administered during suppression for the suppression group. Following a release from suppression and appropriate time delay interval, participants were then administered the long delay recall and recognition trials of the CVLT-C. At no time was the control group instructed to suppress their tics.

Results and discussion: Paired samples *t*-tests confirmed that suppression occurred in the suppression group (71.3% reduction, $t(11) = 3.27$, $p = 0.007$), but not the control group. Tic rates then significantly increased following a release from suppression ($t(6) = 2.674$, $p = 0.037$) to near baseline rates. Controlling for age and IQ estimate, there was a significant main effect of condition at short delay free recall with the suppression group correctly recalling fewer words ($F(1, 26) = 4.601$, $p = 0.041$). Due to an administration error, 6 participants from the suppression group were excluded from the post-suppression analyses. There was a significant main effect of condition on the recognition task, again with the suppression group performing more poorly ($F(1, 21) = 6.124$, $p = 0.022$). There were no detected group differences on other CVLT-C free recall variables. Current results indicate that suppression interferes with registration and retrieval. The suppression group performed more poorly, though not significantly, on all free recall variables, which if significant in a larger sample would suggest a broader encoding interference.

Conclusion: Study results suggest that tic suppression may interfere children's ability to learn new verbal information.

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Lifetime prevalence, age of risk, and etiology of comorbid psychiatric disorders in Tourette syndrome

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Introduction and objectives: Psychiatric comorbidity is common in Tourette syndrome (TS); when present, these conditions typically cause more distress and impairment than do tics (Coffey et al., 1989). High rates of attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD) are well documented and thought to be core components of the TS phenotype (Freeman et al., 2000; Denckla et al., 2006; Robertson et al., 2012); however, few studies have fully characterized other comorbidities. The objectives of this study were to characterize the prevalence and impact of psychiatric comorbidity in a large sample of individuals with TS and their family members.

Methods: The lifetime prevalence of comorbid psychiatric disorders, their heritabilities, and ages of risk were determined in participants with TS (N = 1,374).

Results and discussion: The lifetime prevalence of any psychiatric comorbidity was 85.7%; 57.7% of participants had ? 2 psychiatric disorders. The mean number of lifetime comorbid diagnoses was 2.1. Prevalence of mood, anxiety, and disruptive behavior disorders was ~30%. The age of greatest risk for most psychiatric disorders was 4–10 years, except eating and substance use disorders, which begin in adolescence (Figure). TS was associated with increased risk of anxiety and decreased risk of substance use disorders; high rates of mood disorders among participants with TS may be accounted for by comorbid OCD. Parental history of ADHD was associated with a higher burden of non-OCD, non-ADHD psychiatric disorders. Genetic correlations between TS and mood, anxiety, and disruptive behavior disorders were better accounted for by ADHD and, for mood disorders, by OCD.

Conclusion: This study confirms that psychiatric comorbidities begin early in life and are extremely common among individuals with TS, and demonstrates that some may be mediated by the presence of comorbid OCD or ADHD. Genetic analyses suggest that some comorbidities may be more biologically related to OCD and/or ADHD than to TS.

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Disclosures

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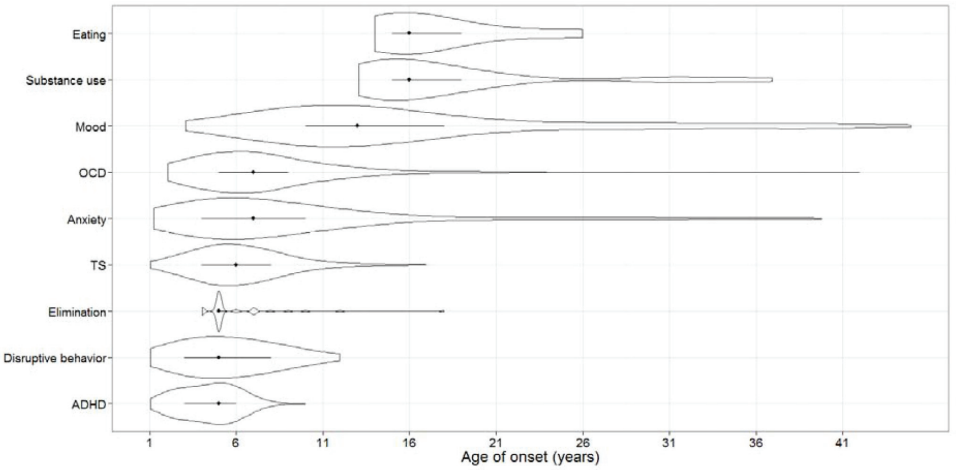

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Latent class analysis of Tourette syndrome and common comorbid disorders: clinical and genetic implications

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Introduction and objectives: Tourette syndrome (TS) is phenotypically complex and etiologically related to obsessive-compulsive disorder and attention-deficit/hyperactivity disorder (ADHD) (Freeman et al., 2000; Worbe et al., 2010). Latent variable modeling can reduce heterogenetity by identifying subgroups of individuals based on patterns of symptom expression. Such symptom subtypes may be heritable and thus appropriate for genetic studies. The objectives of this study were to 1) analyze tic, obsessive-compulsive symptom (OCS), and ADHD symptoms using exploratory factor (EFA) and latent class analyses (LCA) in TS-affected families, 2) clinically characterize the resulting subphenotypes, and 3) examine their utility for genetic studies.

Methods: This study included 3494 individuals recruited for TS genetic studies. EFA and LCA of tic, OCS, and ADHD symptom-level data were conducted. Heritability and TS-associated polygenic burden were also estimated.

Results and discussion: The final EFA model for tics had 6 factors, including 3 organized somatotopically (e.g., body/trunk tics) and 3 by content (e.g., socially disinhibited tics). The final 4-class LCA tic model was notable for 2 classes distinguished by low and high endorsement of disinhibited tics. When tic, OCS and ADHD symptoms were combined, the final EFA solution separated symptoms by type (i.e., tic, OCS, or ADHD symptoms) except for socially disinhibited/aggressive symptoms, which consisted of both tics and OCS. The all-symptom LCA yielded a 5-class best-fit solution, including 1) high endorsement across all symptoms, 2) tics only, 3) symmetry, 4) tics + ADHD, and 5) unaffected. Heritability estimates ranged from 0.19 to 0.47; symmetry/exactness and socially disinhibited symptoms had the highest heritability estimates ($h^2r = 0.53$, $P < 1 \times 10^{-10}$ for both). TS-associated polygenic burden was associated with the symmetry but not the disinhibition phenotype ($P = 0.047$).

Conclusion: We identified two novel TS-related phenotypes with high heritabilities, one of which had a high polygenic load of TS associated genetic variants. These new phenotypes may reflect underlying biological networks more accurately than traditional diagnoses, thus potentially aiding future genetic, imaging and treatment studies.

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Treatments for Tourette syndrome in children and young people: a systematic review and meta-analysis

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Introduction and objectives: Tourette syndrome (TS) and chronic tic disorder (CTD) affect 1–2% of children and young people (CYP) but the most effective treatment strategy is unclear (Verdellen et al., 2011; Roessner et al., 2011). To establish the current evidence-base and to identify areas for further research we conducted a systematic review and meta-analysis.

Methods: Twenty-one databases were searched for placebo-controlled trials of pharmacological, behavioural, physical or alternative interventions in CYP (age

Results and discussion: Thirty-nine trials in children (<18 age) or mixed studies (where pure CYP studies were not available for a particular intervention) met eligibility criteria. Of the 39 included trials, 31 were of pharmacological interventions, 5 of behavioural interventions, 2 of physical interventions and one of a dietary intervention. *Pharmacological interventions***:** Noradrenergic agents (clonidine and guanfacine) had a medium sized benefit on tics (SMD = −0.72; 95% CI −1.04, −0.40). Certainty in the effect estimate was moderate. Antipsychotic drugs (SMD = −0.78; 95% CI −1.13, −0.43), improved tics, but certainty in the effect estimates was low. Stimulants did not appear to worsen tics (SMD = −0.17; 95% CI −0.45, 0.11). *Dietary interventions:* For omega 3 fatty acids, the evidence was inconclusive regarding the effect on tics (SMD = −0.24; 95% CI −0.93, 0.45). Certainty in the effect estimate was low. *Behavioural interventions:* There was evidence of a medium sized effect in improving tics in favour of behavioural therapy (habit reversal training/comprehensive behavioural intervention for tics) (HRT/CBIT) (SMD = −0.64; 95% CI −0.99, −0.29). Certainty in the effect estimate was moderate. *Physical interventions:* Evidence was inconclusive as to the benefit of botulinum toxin (SMD = 0.02; 95% CI −0.63, 0.67) and IV immunoglobulins (SMD = −0.51; 95% CI −1.25, 0.23) on tics. Certainty in the effect estimates was low. There was no evidence for DBS or rTMS in CYP.

Discussion: Considering the small amount of available evidence, continued research and review of the evidence for all types of treatments is needed, in particular, the combination of pharmacological and behavioural interventions and the use of technology to increase access to behavioural interventions.

Conclusion: The balance of clinical benefits to harm favours noradrenergic agents (e.g., clonidine, guanfacine) as first-line drug treatments for tics in children and young people. Antipsychotics (e.g., risperidone or aripiprazole) may be as effective as noradrenergic agents but, considering the low quality of evidence and adverse-effect profile, they should be reserved for treatment of tics when noradrenergic agents are either ineffective or poorly tolerated. There is evidence that HRT/CBIT is an effective treatment for tics in children and young people with TS. However, there is currently no evidence available regarding the relative benefits of HRT/CBIT alone compared to combining medication and HRT/CBIT. There is currently no evidence to suggest that the physical/alternative interventions reviewed are sufficiently effective and safe to be considered as treatments for tics in children and young people with TS.

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Disclosures

None

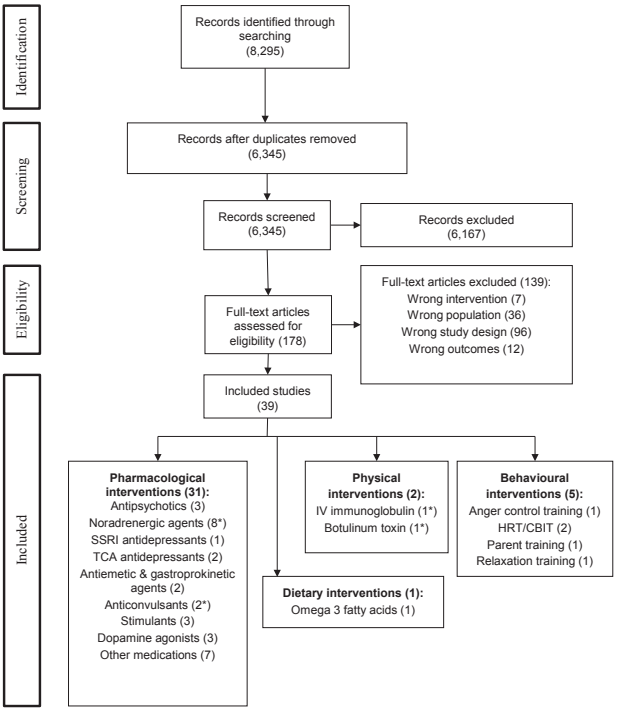
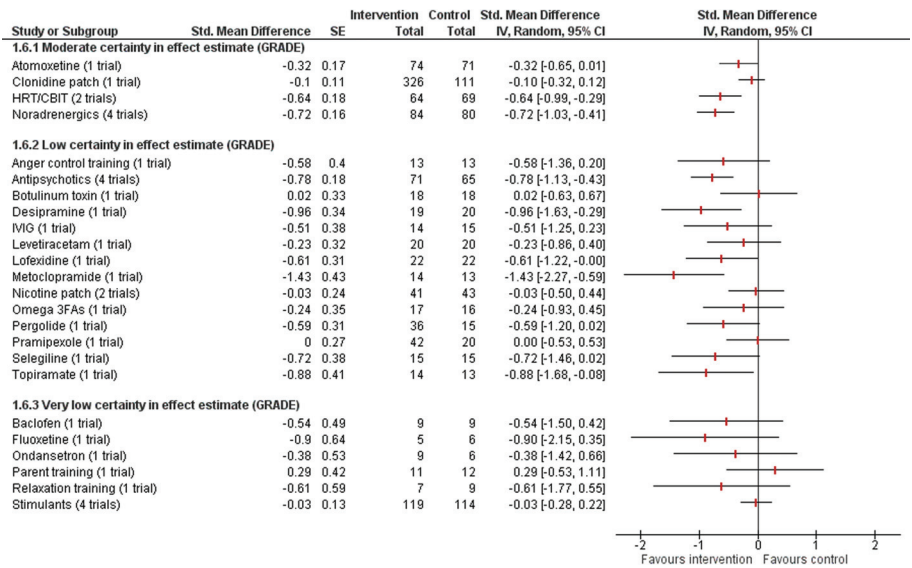


Figure 1 | PRISMA flow diagram (the number of studies are shown in parentheses; numbers marked with an asterisk include at least one mixed study of children/young people and adults)



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International internet-delivered behavior therapy to treat a foreign patient with Tourette syndrome

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Introduction and objectives: Tourette syndrome (TS) is a chronic and typically childhood-onset neurologic disorder, which is characterized by motor and vocal tics. TS is commonly associated behavioral comorbidities. Antipsychotic medications are usually the first-line treatments for moderate to severe tics, but medications may have adverse effects. Behavior therapy has been shown to be effective for reducing tics in children with TS. The patients who lived in remote districts of some countries may not have access to a physician and be unable to receive medication or behavior therapy. Modern communication technology, such as internet and videoconference, may deliver therapeutic or consultation services to the patient living in remote districts. A study compared videoconference versus face-to-face delivery of Comprehensive Behavioral Intervention for Tics (CBIT) (Himle et al., 2012).The results show that both treatment delivery modalities resulted in significant tic reduction, besides, the acceptability and therapist-client alliance ratings were strong for both groups.

Methods: A 16-year-old girl is a Malaysian Chinese. She had motor tics including eye blinking, head jerking, shoulders shrugging, facial grimacing and hands movement. Vocal clearing sound and coprolalia were also noted. Her tics first appeared at the age of 7 years, but diagnosis of TS was confirmed at 16 years of age. She was diagnosed by a psychiatrist in Malaysia and received pharmacologic treatment. She later quit the medication because of severe adverse effects. The patient's mother searched for different therapy from the Internet, and contacted a pediatric neurologist of Taiwan, who had received CBIT training. They used two-way Skype interface to deliver behavior therapy remotely from two different countries, and they both spoke Mandarin for communication. The 8-session CBIT protocol was administered across 10 weeks (Piacentini et al., 2010). Psychoeducation was provided to the patient's family and schoolteacher.

Results and discussion: Baseline Yale Global Tic Severity Scale was 40 points and reduced to 34 at 3-month follow-up. The associated impairment scale reduced from 40 to 20. The Long-term outcome should be followed-up. The severity of tics did not reduce significantly, but the patient has less impairment after CBIT treatment and her school life is much better. Tourette syndrome is not a rare childhood-onset neurologic disease. However, the information about TS is still limited in some countries, and patients who live in remote areas may be unable to visit a specialty doctor and they cannot receive an appropriate treatment. Our reported case had a definite diagnosis about 10 years later since her initial presenting symptoms.

Conclusion: Nowadays, internet and computers or cell phones are very popular nearly all over the world. Internet or videoconference-delivered behavior therapy may be a good treatment modality for TS. We suggest that behavior therapy via internet is a good treatment option for the patients living in remote areas; even the patients and therapists can be in a different country.

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GDNF gene is associated with Tourette syndrome in a family study

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Introduction and objectives: Tourette syndrome (TS) is a disorder characterized by persistent motor and vocal tics, and frequently accompanied by the co-morbidities attention deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD).Several lines of evidence have involved the cortico-striatal-thalamo-cortical (CSTC) circuitry in this disorder. Postmortem studies have found a decreased number of striatal parvalbumin (PV+) and cholinergic (Chat+) interneurons (Kataoka et al., 2010). The dopaminergic and glutamatergic systems play major roles in CSTC pathways and both systems are believed to be involved in TS (Leckman et al., 2010). Neurotrophic factors interact with glutamate and are highly expressed in the striatum. Our aim was to investigate the association of 28 candidate genes, including genes related to dopaminergic and glutamatergic neurotransmission and neurotrophic factors, with TS.

ACKNOWLEDGEMENTS	Gene	Tag-SNPs
11	BDNF	6
22	CACNG2	29
5	CAMK2A	16
6	CNR1	3
22	COMT	10
5	DRD1	3
11	DRD2	8
3	DRD3	7
11	DRD4	1
4	DRD5	12
5	GDNF	10
5	GRIA1	46
4	GRIA2	4
23	GRIA3	6
11	GRIA4	28
9	GRIN1	4
16	GRIN2A	88
12	GRIN2B	93
17	GRIN2C	3
19	GRIN2D	3
9	GRIN3A	21
19	GRIN3B	5
6	GRM1	19
11	GRM5	23

23	MAOA	1
23	MAOB	3
9	NTRK2	40
5	SLC6A3	11
9	TRKB	3

Methods: We genotyped 506 polymorphisms in a discovery cohort from the United States composed of 112 families and 47 unrelated singletons with Tourette syndrome (201 cases and 253 controls). Association analysis was performed using the DFAM test available in PLINK. We also conducted the TDT test to have an estimate of the risk, by odds ratio (OR). Genes containing significant polymorphisms were imputed and the linkage disequilibrium (LD) with the functional variants in the gene identified by Regulome database was examined with Haploview. Allelic analyses in TS cases were performed with Chi-square test to check the role in ADHD and OCD co-morbidities. Target polymorphisms were further studied in a replication cohort from southern Spain composed of 37 families and 3 unrelated singletons (44 cases and 73 controls).

Results and discussion: The polymorphism rs3096140 in glial cell line-derived neurotrophic factor gene (GDNF) was significant in the discovery cohort after correction ($p = 1.5 \times 10^{4}$). This polymorphism showed low LD with neighboring variants and we did not find a link with a functional variant. We selected rs3096140 as target polymorphism and the association was confirmed in the replication cohort ($p = 0.01$). TDT test estimated a risk of OR = 2.4 and OR = 2.7 in the discovery and replication cohorts, respectively. No association with any co-morbidity was found. GDNF is expressed primarily in PV+ and Chat+ interneurons (Pascual et al., 2008), cell subtypes that are affected in TS. Therefore, a defect in the production of GDNF could compromise the survival of these interneurons thus altering the excitatory/inhibitory balance in the CSTC circuitry. This imbalance may underlie TS symptomatology.

Conclusion: A common genetic variant in GDNF is associated with TS. Further research is needed to validate the association in other family-based cohorts and to fine-map the causal variant.

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Direct and indirect effects of anxiety, depression, and OC symptoms on tic severity and quality of life in Tourette's patients

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Introduction and objectives: Anxiety disorders and depression are common co-morbidities in people with Tourette's, yet little research has been done concerning this relationship. This study aims at exploring anxiety, OCD, depressive symptoms, related to tic severity and quality of life in tourettes patients. Expected was that having a comorbid anxiety disorder will cause lower quality of life compared to GTS patients without comorbidity, especially in case of comorbidity with OCD. Also higher tic severity was expected in GTS patients with comorbid anxiety disorders compared to GTS patients without comorbidity. Also it was hypothesized that anxiety, depression and OC-symptom severity was positively correlated on tic severity and negatively correlated with quality of life.

Methods: 187 participants with GTS took part in the study. Participants were assessed on mental disorders using the MINI and the SCID-I; Symptom severity was measured using the YBOCS for OC-symptoms, the YGTSS for tics; BDI and BAI for depression and Anxiety and the EQ-VAS for quality of life. ANCOVA's were used to assess differences in tic severity and quality of life between patients with and without comorbid depression, OCD and anxiety. Bootstrap mediation anayles were used to assess the direct and indirect influence of depression, anxiety and OC-symptom severity on tic severity and quality of life.

Results and discussion: Patients with comorbid Depression, OCD or Anxiety disorder score lower on quality of life GTS patients without comorbidity. GTS members without comorbidity have the highest quality of life, then follows the group with GTS members with non OCS comorbidities and lowest scores are seen in the group with GTS patients with OCD. GTS patients without comorbidity and GTS patients with non OCD comorbid disorders do not differ in tic severity, GTS patients with comorbid OCD differ significantly with the other groups, showing higher tic severity to GTS patients with and without non OCD comorbid disorders. However, the difference between GTS without comorbidity and GTS with OCD is only trend-level significant. Only depression severity has a direct negative influence on quality of life, whereas anxiety and oc symptom severity do not have a significant effect on quality of life. However, indirect results show, that by influencing depression severity, OC-symptoms indirectly influences quality of life. Only OC-symptoms have a direct influence on tic severity. An increase of OC-symptom severity causes more severe tics. Depression and anxiety do not show a direct effect on tic severity. However indirectly both anxiety and depression have an effect on OC-symptom severity, causing an increase in tic severity.

Conclusion: In relation to quality of life as well as to tic severity, OC-symptoms play a crucial role. The influence of depression, anxiety and OC symptoms are complex, where depression work as a mediator of the effect of OC-symptoms on quality of life and vice versa. Also the effect of depression, anxiety and OC-symptoms are best described by a complicated model where oc symptoms is a mediator of the effect of depression on tic severity, making comorbid OCD a complicating factor in the lives of tourette's patients.

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Deep Brain stimulation for Tourette syndrome: clinical outcome of thalamic stimulation in a cohort of treatment-resistant patients

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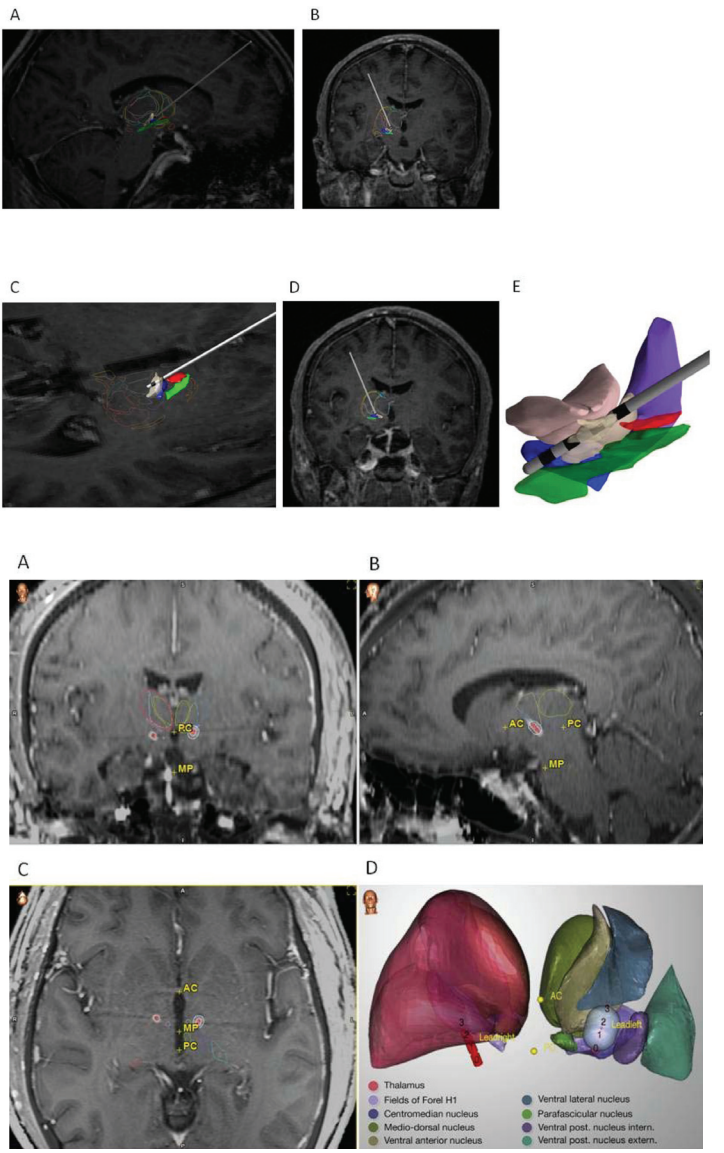
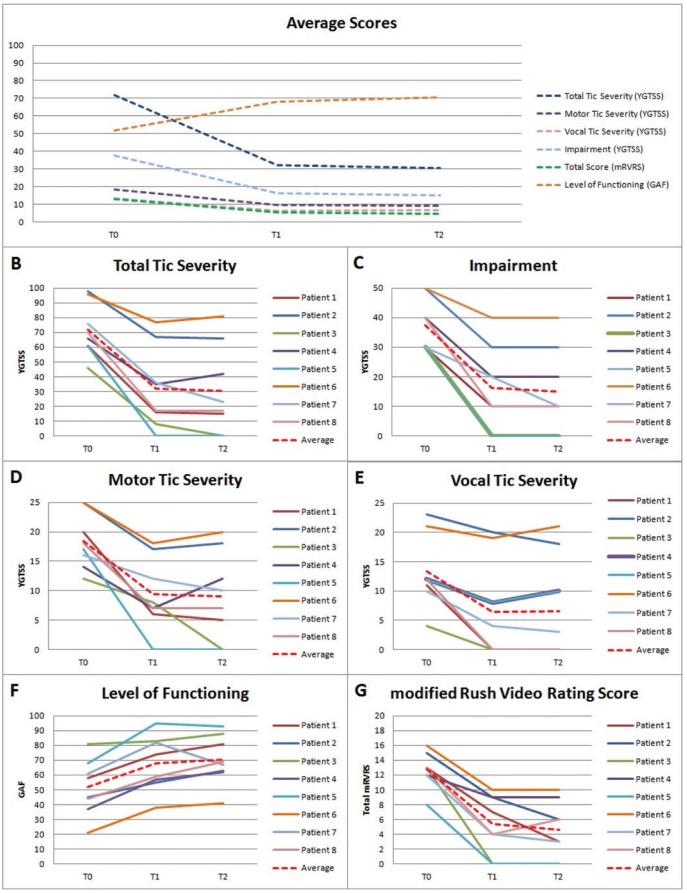
Introduction and objectives: Since its first application in 1999, the potential benefit of DBS in reducing symptoms of otherwise treatment refractory Tourette Syndrome (TS) has been documented in several publications. Yet, uncertainty regarding the ideal neural targets remains while the eventuality of so far undocumented but possible negative long-term effects on patients' personality fuels the debate about the ethical implications of DBS.





(A) Average response of all patients to stimulation preoperative (TO) as well as after 6 month (T1) and 12 month (T2). Individual and average (dotted line) responses of all patients in the subscales of the YGTSS concerning **(B)** total tic severity (motor tic score + vocal tic score), **(C)** impairment, **(D)** motor tics and **(E)** vocal tics **(F)** Individual and average responses concerning the level of functioning of all patients **(G)** Individual and average scares of all patients in modified Rush videobased Tic Rating Scale.

Methods: In this prospective open-label trial, eight patients with severe and medically intractable TS were treated with high-frequency DBS of the ventral anterior and ventrolateral motor part of the thalamus. To assess the course of TS, its clinical comorbidities, personality parameters, and self-perceived quality of life, patients underwent repeated psychiatric assessments at baseline and 6 and 12 months after DBS onset.

Results and discussion: Analysis indicated a strongly significant and beneficial effect of DBS on TS symptoms, trait anxiety, quality of life, and global functioning with an apparently low side-effect profile. In addition, presurgical compulsivity, anxiety, emotional dysregulation, and inhibition appeared to be significant predictors of surgery outcome.

Conclusion: Trading off motor effects and desirable side effects against surgery-related risks and negative implications, stimulation of the ventral anterior and ventrolateral motor part of the thalamus seems to be a valuable option when considering DBS for TS.

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Disclosures

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Temporal properties of tic generation

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Introduction and objectives: Motor tics are repetitive, involuntary brief muscle contractions which interfere with ongoing behavior and appear as a symptom in several disorders, such as Tourette syndrome. Tics have been associated with abnormalities in the cortico-basal ganglia system, and specifically with abnormal inhibition within the striatum. Motor tics can be induced experimentally in rodents and primates by local micro-injection of bicuculline ($GABA_A$ antagonist) into the motor striatum leading to focal disinhibition (McCairn et al., 2009; Bronfeld et al., 2011, 2013). Our previous studies have established the role of the striatal organization in determining the location of the tic (Bronfeld et al., 2013). In the current study we aim to study the effect of cortical input to the basal ganglia on the timing of individual tics and on the associated neuronal activity in the basal ganglia.

Methods: We injected bicuculline to the motor striatum of freely behaving rats and examined the animals'behavior and neuronal activity in the course of on-off phases of cortical excitation. Tic properties were quantified using electromyography (EMG), high-speed video cameras and local field potential (LFP) recordings. Neuronal activity was acquired using chronically implanted multi-electrodes enabling recordings in multiple brain areas (striatum and globus pallidus).

Results and discussion: During the tic expression period cortical excitation changed the timing of individual tics via an accumulation process and led to tic related activity changes in striatal and pallidal neurons. The summation of cortical input and the timing of the previous tic determined the precise time of the next tic expression. Based on our results, we generated a computational model for tic formation enabling the prediction of tic timing based on incoming cortical activity and the tic history.

Conclusion: The current findings establish the key role of the cortico-striatal pathway in determining the timing of individual tics. The combination of striatal disinhibition with a control over cortical excitation enables the generation of an animal model displaying highly-predictable finely timed tics. This novel model enables both basic science studies of the underlying mechanism of tic expression and clinical studies of behavioral, pharmaceutical and medical device based control of the tics.

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How ADHD symptoms can influence adhesion to a treatment for tic management?

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Introduction and objectives: Tourette's syndrome (TS) and chronic tic disorders (CD) are neurodevelopmental disorders characterized by motor and vocal tics (American Psychiatric Association (APA), 2013) affecting an average of 1% of the population (Robertson, 2008). People with tics often present co-morbid conditions and one of the most common is attention deficit hyperactivity disorder (ADHD) (Hirschtritt et al., 2015). When ADHD occurs at the same time as TS or CD, it can have multiple consequences such as increasing cognitive and psychosocial difficulties (Brand et al., 2002) and worsening quality of life (Rizzo et al., 2011). Only a few studies on psychological treatment of tics give details about the impact of comorbidities on the outcomes of the treatment (Döpfner and Rothenberger, 2007). In this study, we will explore the role of ADHD symptoms on the adhesion to a treatment addressing tics called CoPs (O'Connor, 2002, 2005). This ten-step treatment addressed tic management and has been shown to be effective in several studies (O'Connor et al., 2001; O'Connor, 2005).

Methods: Recruitment has been done at the Centre de recherche de l'Institut universitaire de Montréal for a primary study evaluating the effect of the CoPs treatment on tics in adults. They received several questionnaires pre and post treatment such as The Tourette Syndrome Global Scale (TSGS) (Harcheri et al., 1984) and the Conners' Adult ADHD Rating Scales (CAARS) (Conners et al., 1999).

Results and discussion: Results obtained at the TSGS and the CAARS will be analyzed and to this purpose, we will use correlation coefficients and ANOVA tables. This study aimed to clarify how ADHD symptoms can influence adhesion to a treatment addressing tic management.

Conclusion: Results could be used to indicate the need for treating ADHD symptoms before treating tics.

Disclosures

The authors declare that they have no conflict of interest.

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The effects of co-occurring ADHD symptoms on behavioural and electrophysiological correlates of cognitive control in young people with Tourette syndrome

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Introduction and objectives: Cognitive control refers to a set of self-regulatory processes that facilitate voluntary control of thought and action. Efficient cognitive control is implicated in the control of tic symptoms in young people with Tourette syndrome (TS) (Jackson et al., 2007; Baym et al., 2008). Attention-deficit/hyperactivity disorder (ADHD) frequently co-occurs with TS and is associated with impaired cognitive control (Kofler et al., 2013). Young people with TS and ADHD (TS + ADHD) show poorer cognitive control performance than those with TS (Roessner et al., 2007), but how co-occurring ADHD affects underlying neural activity is unknown. We investigated this issue by examining behavioural and event-related potential (ERP) correlates of cognitive control in young people with these conditions.

Methods: Participants aged 9-17 with TS (n = 17), TS + ADHD (n = 17), ADHD (n = 11) and unaffected controls (n = 20) performed a visual Go/Nogo task during EEG recording. Measures of behavioural performance (D-prime, RT, reaction time variability, post-error slowing) and underlying neural activity (the N2, P3, error-related negativity (ERN), error positivity (Pe) ERPs) were derived and analysed in a 2 (TS-yes, TS-no) × 2 (ADHD-yes, ADHD-no) factorial analysis to investigate effects of TS, ADHD and their interaction.

Results and discussion: There were significant main effects of ADHD-present on D-prime (p = 0.002, ? ² = 0.155), Reaction time variability (p < 0.001, ?² = 0.200), and Post error slowing (p = 0.04, ?² = 0.068), with ADHD-yes producing lower D-prime scores, more variable RTs on Go trials, and reduced post-error slowing than ADHD-no. ADHD was associated with reduced amplitude of all ERPs.

TS was associated with slowed RTs (p = 0.05, ?² = 0.078 but there were no other significant main effects of TS-present, or interaction between the TS and ADHD factors, for any behavioural or ERP measure (all p > 0.1).

The lack of a significant interaction between the TS and ADHD factors, indicates that the impairing effects of ADHD on behaviour and electrophysiological markers of cognitive control were present in TS + ADHD group, and that RT slowing associated with TS was unaffected by co-occurring ADHD symptoms (all p > 0.1).

Conclusion: This study identified a profile of largely typical behavioural and ERP markers of cognitive control in young people with TS but significantly impaired cognitive control associated with ADHD. The findings demonstrate the impairing effect of atypical cognitive control in ADHD on those with TS when the two disorders co-occur.

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Users' views on psychoeducation for individuals with Tourette syndrome and tic disorders

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Introduction and objectives: Tourette syndrome (TS) and chronic tic disorder are conditions characterised by motor and phonic tics, typically starting in early childhood. Psychoeducation is recommended as an essential component of any treatment package for TS (Verdellen et al., 2011; Nussey et al., 2014). Studies indicate that educational information enhances knowledge and attitudes towards individuals with TS, and improves how individuals with TS perceive the condition (Nussey et al., 2013, 2014). It is suggested that studies are needed to investigate the optimal method of offering educational information and what themes it should encompass (Nussey et al., 2014). The objective of this study was to identify the views of service users regarding optimal information about TS.

Methods: An online survey (n = 247), facilitated by Tourettes Action, was used to explore the needs of patients and parents regarding psychoeducation on TS and tic disorders. Four focus groups (n = 15) were facilitated with children (and parents), adolescents and adults with TS to obtain direct feedback about information that individuals believe would be of benefit to them. Participants were recruited from survey responses and service users of the Great Ormond Street Tourette Syndrome Clinic. Focus groups were recorded, transcribed and analysed using a thematic approach.

Results and discussion: Feedback from the online survey demonstrates that 61% respondents (n = 166) felt they had not received adequate information on TS from health professionals. Respondents wanted information on alternative treatments for tics, why tics change over time, and the hereditary nature of tics. 71% (n = 123) reported a need for educational support on TS in a format that they could use at home. Qualitative data from the survey highlighted that individuals need more information on comorbid difficulties associated with TS, e.g., anger, low mood and anxiety. A need to enhance the knowledge of educational professionals was highlighted, as was the need to correct public misconceptions. Feedback from focus groups highlighted the need for information for educational and health professionals, and that reliable, accessible information is needed at the point of diagnosis. Findings support existing literature which states that many patients do not receive adequate information (Cath et al., 2011), and that psychoeducation represents an important component in providing support and enhancing knowledge in TS (Cath et al., 2011).

Conclusion: The results support the need for a new educational programme, developed and informed by people with TS and tailored to their needs.

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Deep brain stimulation for intractable tics associated with Tourette syndrome in Japan

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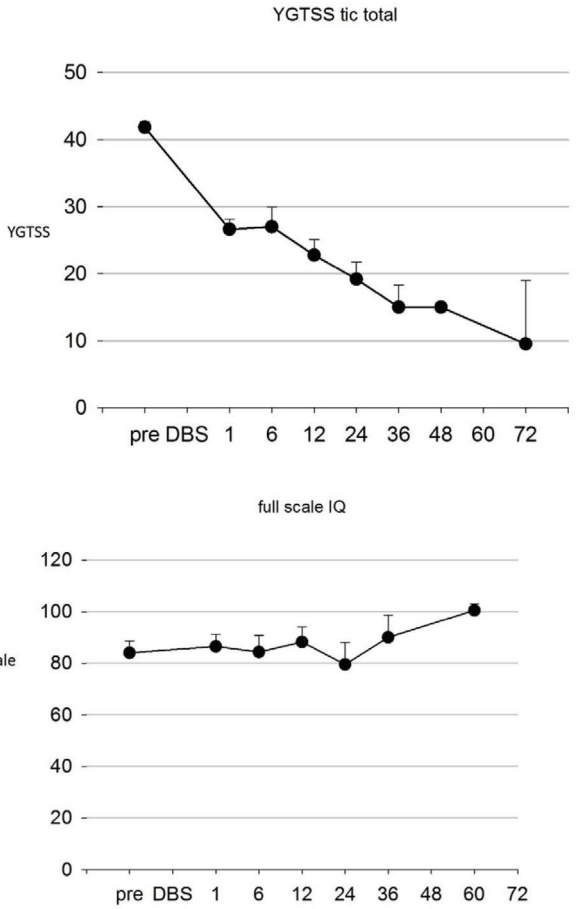
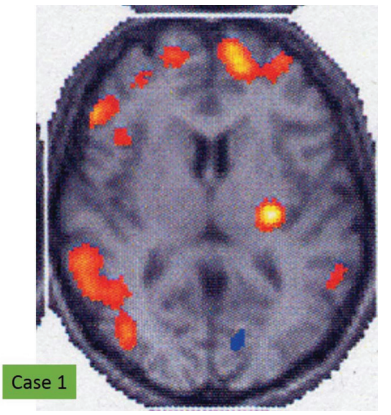
Introduction and objectives: Severe intractable tics associated with Tourette syndrome break down daily life of patients. Deep brain stimulation (DBS) is recently reported as possible alleviative therapy of severe tics. Recently our institute treats intractable severe tics using DBS. Patients with severe tics are diagnosed with having Tourette syndrome which is often recognized as the neuropsychiatry disorder because this disease are often treated by psychiatrists and sometimes has other psychiatric comorbidities such as the obsessive-compulsive disorder (OCD) and attention-deficits/hyperactivity disorder (ADHD). We focus on only the tics of the involuntary movement disorders as the therapeutic target because severe tics break down daily life of patients. Here we reported case series of our experience of DBS for intractable tics.

Methods: This study was permitted by IRB. Target of stimulation was centromedian-parafascicular nucleus (CM-Pf) of bilateral medial thalami. Psychological examination was examined before and after DBS. The cerebral blood flow (CBF) was measured before and after DBS with SPECT.



Results and discussion: Fifteen patients (16–36 years old, 10 men and 4 women, 5–10 years old of onset age) underwent DBS. Follow-up term was 1–84 months. Tic scores dramatically decreased. Scores for depression showed some tendency to decrease after DBS, which would be caused by attenuation of disturbed symptoms. Scores of OCD did not show improvement. Etiology of Tourette syndrome is thought that abnormal excitement of the cortico-striato-thalamo-cortical (CSTC) circuit induces hyperactivity of the thalamocortical network. The CM-Pf complex cooperates with

the striatum to adjust the bias of the voluntary movement. DBS of the CM-Pf would control the activity of the nucleus to modulate reward system. Preoperative SPECT revealed hyperperfusion of the posterior rim in the internal capsule. After DBS, there is a tendency that superficial CBF decreases and medial CBF increases. The results of CBF would indicate that the hyperactivity of the motor, premotor, and associative system are allayed and the limbic system regains the primary function.



Conclusion: After DBS, tics dramatically improved without any psychological changes. DBS for severe intractable tics would be a therapeutic option if indication is carefully managed.

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Affective regulation of motor processing in Tourette's syndrome

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Introduction and objectives: Tourette's syndrome (TS) is a neuropsychiatric disorder characterized by unwanted motor and vocal tics (Association AP, 2013). The symptoms, also marked by a mosaic of emotional, cognitive and motor deficits; usually, first appear between the ages of 5–7 years and decline by late adolescence. The empirical studies on TS have mainly focused on associated structural, functional and genetic deficits. Nevertheless, these studies have neglected a crucial frontier of TS research, which is, the role of affective dysregulations in influencing these internal processes (Robertson, 2012).

The present study is a part of a broader research aimed to examine the impact of affective regulations on motor processing in patients with TS, considering Event Related Potentials (ERP),behavioral responses (e.g., latency and accuracy) while performing a cueing task, and their relationship with anxiety, depression, and Quality of Life (QOL) scores.

Methods: Subjects Sample: Ten children of age 8–12 years with pure TS (with no comorbid condition) and eight matched control group with no psychiatric condition were recruited.

Psychological measures were: State Trait Anxiety Inventory for Children (STAIC), Multidimensional Anxiety Inventory for Children (MASC), and Child Depression Inventory and Gilles De La Tourette Syndrome-Quality of Life scale for children and adolescents (C&A-GTS-QOL).

Study design: A Cueing task designed on E-Prime software using 6 emotional faces (3 male, 3 female) with happy (H), sad (S), angry (A), Neutral (N) expressions from Karolinska Directed Emotional Faces (KDEF) (Lundqvist et al., 1998). These served as a cue for the position of upcoming star shaped target.

ERP recording: Scalp electric activity from 256-channel hd-EEG was recorded using the Geodesic Sensor Net while the subjects performed the designed task.

Preliminary analysis of ERP components that are thought to reflect planning, execution or inhibition of motor activity were carried out using Netstation. Further statistical analysis would be conducted on respective component to study within group and between group differences.

- ERP components are associated to the levels of anxiety and depression as well as QOL.
- Between-groups differences in ERPs, during neutral (N) and emotional cues (S + A + H), indicating the effect of emotions on motor process.
- Within-groups differences of the single emotional (S, A, H) vs (N) cues on ERPs, suggesting their possible role in underlying neurological deficits.
- Within- and Between-groups differences in the reaction time and average accuracy during trials.

Conclusion: This study may provide novel insights into the interplay of neurological and affective deficits in TS that may open interesting therapeutic perspectives for children with TS.

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TS-EUROTRAIN: European wide investigation of the etiology and pathophysiology of Gilles de la Tourette syndrome and related disorders

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Introduction and objectives: The majority of psychiatric disorders fall into the category of complex genetic disorders, which are likely caused by genetic susceptibility factors that interact with the environment to confer the total risk of acquiring complex phenotypes. Such complex traits do not usually exhibit clear-cut boundaries between affected and non-affected states, but exhibit a phenotype that extends over a range of severity and comorbidity. Over the past decade, it has become increasingly evident that a wide range of clinically distinct, developmental and neuropsychiatric disorders exhibit a significant degree of etiological overlap. Gilles de la Tourette syndrome (GTS) provides an excellent model for the exploration of shared etiology across such disorders, as it is a complex developmental disorder that wavers along the fine margin between psychiatry and neurology. GTS is characterized by the presence of multiple motor tics and one or more vocal tics, and presents with comorbid conditions that frequently include Attention Deficit Hyperactivity Disorder (ADHD) and Obsessive Compulsive Disorder (OCD). TS-EUROTRAIN is a Marie Curie Initial Training Network (http://ts-eurotrain.eu) that aims to build on current knowledge in the field. The majority of psychiatric disorders fall into the category of complex genetic disorders, which are likely caused by genetic susceptibility factors that interact with the environment to confer the total risk of acquiring complex phenotypes. Such complex traits do not usually exhibit clear-cut boundaries between affected and non-affected states, but exhibit a phenotype that extends over a range of severity and comorbidity. Over the past decade, it has become increasingly evident that a wide range of clinically distinct, developmental and neuropsychiatric disorders exhibit a significant degree of etiological overlap. Gilles de la Tourette syndrome (GTS) provides an excellent model for the exploration of shared etiology across such disorders, as it is a complex developmental disorder that wavers along the fine margin between psychiatry and neurology. GTS is characterized by the presence of multiple motor tics and one or more vocal tics, and presents with comorbid conditions that frequently include Attention Deficit Hyperactivity Disorder (ADHD) and Obsessive Compulsive Disorder (OCD). TS-EUROTRAIN is a Marie Curie Initial Training Network (http://ts-eurotrain.eu) that aims to build on current knowledge in the field.

Methods: Our consortium tackles several major challenges that include (i) assembling a large genetic database for the evaluation of the complex etiology of GTS and related disorders with high statistical power; (ii) exploring the role of gene-environment interaction as the role of epigenetic phenomena in GTS have not even begun to be evaluated; (iii) employing endophenotypic based approaches to dissect the basis of shared etiology between GTS, OCD and ADHD; (iv) establishing new developmental animal models for GTS as such models are important and severely lacking; and (v)

gaining new insights into the neurobiological mechanisms of GTS via transverse and longitudinal imaging based studies to pave the way for new treatment strategies.

Results and discussion: NA.

Conclusion: The project is pursued by ten partners, from academia and industry and 12 PhD students. Our ultimate aims are to elucidate the complex etiology of the onset and clinical course of GTS, investigate the neurobiological underpinnings of GTS and related disorders, translate research findings into clinical applications, and establish a Pan-European infrastructure for the study of GTS and associated disorders.

Acknowledgements

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Test-retest quantitation of absolute metabolite concentrations with partial-volume correction: implications for longitudinal studies in psychiatric disorders

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Introduction and objectives: Magnetic Resonance Spectroscopy (MRS) is a powerful method that allows the in-vivo quantitation of metabolite concentrations in health and disease. In longitudinal study designs, the accurate quantitation of absolute metabolite concentrations requires the precise re-localiziation of the voxel to the region that was initially targeted. In this study, we implement an automatic re-localization procedure and test the effects of this strategy on the test-retest reliability of absolute quantitation of metabolite concentrations with partial-volume correction. Previous work has shown that different segmentation approaches yield different partial-volume corrected estimates of metabolite levels (Gasparovic et al., 2006). Here, we implement two segmentation algorithms for correcting absolute metabolite concentrations. This work has implications for investigators seeking to undertake longitudinal MRS studies in psychiatric disorders.

Methods: Anatomical and MRS data from 12 controls were acquired at 3-T from two regions of interest (Anterior Cingulate Cortex, ACC and thalamus, THA). An auto-alignment sequence was used to re-localize the same region of interest on the re-test scan. The voxel was then mapped onto anatomical space and tissue fractions (grey matter (GM), white matter (WM) and corticospinal fluid (CSF)) within the voxel were calculated based on two different segmentation algorithms (SPM12 and Freesurfer). Frequency domain spectra were analyzed with LCModel (Provencher, 1993) and compartmentation within the MRS voxel was considered for the quantitation of absolute concentrations.

Results and discussion: The reliability of the automatic MRS voxel re-localization method was assessed using the Sørensen–Dice metric, which yielded mean ± SD values of 0.78 ± 0.10 for the ACC voxel and 0.71 ± 0.28 for the THA voxel. Anatomical image segmentation using SPM and Freesurfer yielded results that were significantly different between the two algorithms (Table 1). Within the same package, the segmentation algorithms exhibited high reliability across scanning time-points as the tissue class estimates did not reach significance using a paired t-test. However, between segmentation algorithms, results exhibited discrepancies of more than 20% depending on the ROI. Given that a criterion for localizing the THA voxel was to maximize the amount of GM, Freesurfer's results demonstrate better estimates based on visual inspection (Figure 1). Overall, Freesurfer yielded higher estimates of absolute metabolite concentrations when compared to SPM. The averaged SDs of absolute percentage difference were consistently lower for SPM-corrected concentrations for the ACC voxel (Table 2). No general trend was observed for the THA voxel.

Table 1 | Test/re-test tissue fraction estimates of SPM and Freesurfer.

Fraction	Scan A: SPM (%)	Scan B: SPM2 (%)	Scan A: FS (%)	Scan B: FS (%)
ACC_{gm}	74.5 ± 3.0	72.9 ± 3.1	47.3 ± 4.4	47.3 ± 4.2
ACC_{wm}	11.9 ± 2.5	11.9 ± 2.6	19.5 ± 2.9	19.5 ± 2.9
ACC_{csf}	13.6 ± 4.0	15.2 ±4.0	33.1 ± 5.0	33.1 ± 5.0
THA_{gm}	54.2 ± 3.4	48.0 ± 1.3	85.8 ± 4.2	80.3 ± 2.1
THA_{wm}	38.5 ± 4.2	39.3 ± 15.3	3.9 ± 1.8	3.9 ± 4.2
THA_{clf}	7.3 ± 2.9	12.7 ± 15.3	10.3 ± 3.3	15.3 ± 15.6

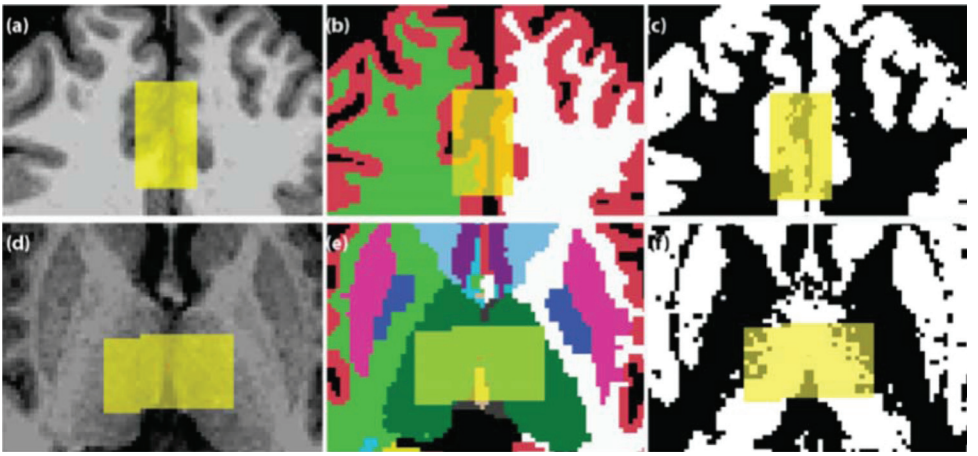

Figure 1 | Masks illustrating voxel positioning superimposed over (a/d) T1w images, (b/e) Freesufrer and (c/f) SPM GM segmentations.

Table 2 | Means and SD's of the percentage difference of metabolite concentrations (corrected and uncorrected) between the test and rest scans.

Metabolite	Uncorrected	SPM	Freesurfer
ACC-tCre	0.13 ± 0.11	0.16 ± 0.07	0.22 ± 0.14
ACC-tNAA	0.43 ± 0.31	0.56 ± 0.52	0.85 ± 0.88
ACC-ml	0.29 ± 0.27	0.28 ± 0.36	0.47 ± 0.65
ACC-Glu+Gln	0.40 ± 0.36	0.55 ± 0.41	0.77 ± 0.99
ACC-Glu	0.35 ± 0.24	0.48 ± 0.26	0.64 ± 0.30
ACC-Gin	0.39 ± 0.17	0.79 ± 0.46	1.17 ± 1.07
THA-GPC+PCh	0.08 ± 0.06	0.31 ± 0.27	0.37 ± 0.77
THA-NAA+NAAG	0.60 ± 0.35	1.21 ± 1.06	1.46 ± 2.91
THA-ml	0.15 ± 0.08	0.64 ± 0.53	0.81 ± 1.68
THA-Glu+Gln	0.08 ± 0.06	1.42 ± 1.20	1.71 ± 2.53
THA-Glu	0.55 ± 0.61	0.82 ± 0.75	0.94 ± 1.03
THA-Gln	0.40 ± 0.27	1.83 ± 1.69	2.22 ± 3.55

Conclusion: In psychiatric disorders, the use of MRS for the interrogation of treatment effects on metabolic activity serves as a powerful approach for understanding pathophysiology. Here, we show that commonly used segmentation methods yield different corrected estimates of absolute metabolite concentrations in cortical and subcortical regions. To interrogate changes of relevant metabolites (e.g., ACC glutamate) in the longitudinal setting, our results indicate that the percentage change between the baseline and treatment stages should be greater than 24% with SPM correction and above 38% using Freesurfer correction. Therefore, we recommend investigators to carefully consider which package to use for estimating compartmentation within different spectroscopic regions of interest for absolute metabolite quantitation correction.

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Significant tic reduction in a treatment resistant Gilles de la Tourette syndrome patient following treatment with nabiximols (Sativex®)

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Introduction and objectives: Despite the fact that the range of treatments available for the management of the symptomatology of Gilles de la Tourette syndrome (GTS) have been expanding over the last decade, treatments are either ineffective or cause significant adverse effects in some patients. As a result, there is an urgent need for uncovering novel treatment strategies that are more effective in treatment resistant patients, cause less adverse effects and could potentially ameliorate both tic and behavioural symptoms. Early anecdotal reports provided evidence that patients with GTS choose cannabinoids as a form of self-medication either legally or illegally. Along this line, preliminary studies suggested that cannabinoid based medicine's (CBMs) such as delta-9-tetrahydrocannabinol (THC) are effective in the treatment of GTS. Here we report the first case of an effective treatment of a patient with treatment resistant GTS using nabiximols (*Sativex®*) - a plant extract from Cannabis sativa L. containing THC and cannabidiol (CBD) at a 1:1 ratio.

Methods: The 22 years old male patient suffered from severe treatment resistant GTS starting at age 17. The patient exhibited extreme simple and complex motor and vocal tics in addition to the presence of comorbid attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), pathological gambling, and sleep problems. Most pronounced of his symptoms were extreme vocal tics including coprolalia which pushed him to seek different pharmacological treatment strategies such as haloperidol, risperidone, aripiprazole, and clonidine, but also methylphenidate, atomoxetine, fluphenazine, and pramipexole (alone or in combination). All treatments were either ineffective or caused severe adverse effects. Therefore, treatment with nabiximols (*Sativex®*) was initiated. Several clinical measures were acquired before and after the treatment was commenced. These included the Yale Global Severity TS scale (YGTSS); Global Clinical Impairment (GCI); GCI for premonitory urges; Premonitory Urge for Tics Scale (PUTS); GTS-Quality of Life (GTS-QOL); GCI for GTS QOL and the Tourette Syndrome Symptom List (TSSL).

Results and discussion: Treatment with nabiximols commenced at a dose of 1 puff/day (= 100 µl containing 2.7 mg THC and 2.5 mg CBD) and slowly increased up to a dosage of 3 × 3 puffs/day (24.3 mg THC and 22.5 mg CBD). Clinical assessments were performed twice, once before treatment with nabiximols and once after 2 weeks of a stable dose of 3 × 3 puffs/days. As shown in Table 1, treatment resulted in major improvement of both tics, premonitory urges, global impairment, and health related quality of life without causing relevant adverse effects.

Conclusion: This is the first case study suggesting that treatment with nabiximols may be effective in the treatment of patients with severe and treatment resistant GTS. Anecdotal reports as well as preclinical data have provided some evidence that nabiximols may be more effective and better tolerated than pure THC. Nabiximols is formulated as an oromucosal spray and is partly absorbed sublingually, resulting in reduced first pass effects, faster absorption, accelerated onset, and stronger effect compared to orally administered pharmaceutical products such as pure THC. Given the positive response exhibited by the patient highlighted in this report, further investigation of the effects of nabiximols is proposed on a larger group of patients in a clinical trial setting.

Acknowledgements

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Retrospective control for motion-artifacts in functional neuroimaging datasets using Wavelet and ICA based methods

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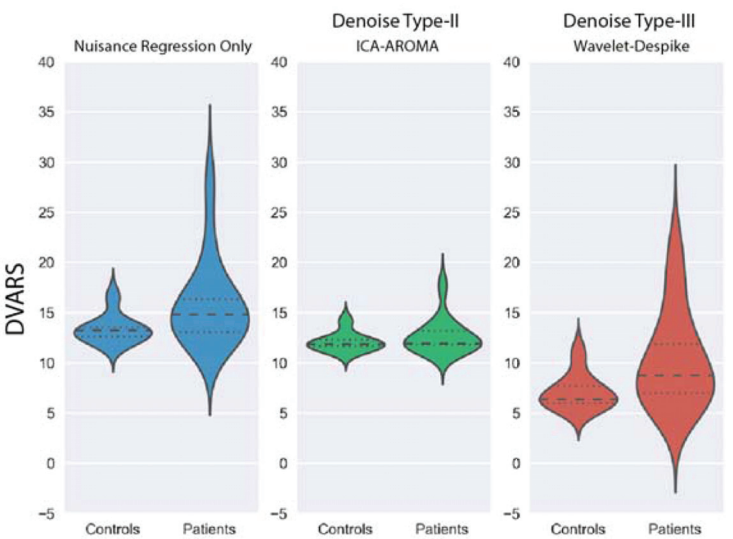
Introduction and objectives: It has recently been well established that head motion during fMRI data acquisition introduces undesirable and artifactual effects that can significantly bias group comparisons of functional connectivity (Power et al., 2012). As a result, several groups have put forth different retrospective denoising strategies, such as nuisance regression, aCompCor, Scrubbing and Global Signal Regression. Nonetheless, these strategies have their drawbacks as their implementation might lead to the alteration of the temporal structure of the data, the loss of temporal degrees of freedom, the inadvertent removal of the signal of interest or the increase of the likelihood of anti-correlations (Power et al., 2014). In this work, we investigate the utility of two recently published methods – (i) the discrete wavelet transform and (ii) automated independent-component analysis (ICA) feature classification – for the identification and removal of non-stationary events in resting-state fMRI time-series, while potentially circumventing common drawbacks (Patel et al., 2014; Pruim et al., 2014).

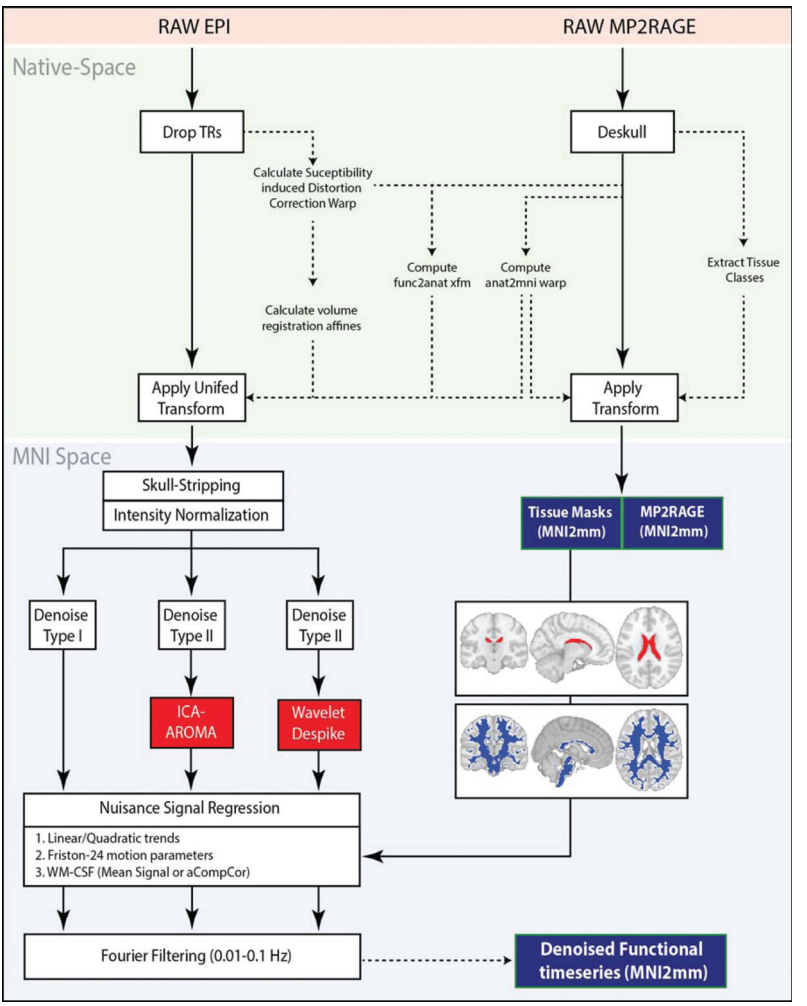
Methods: Anatomical and resting-state fMRI data from 10 healthy controls and 10 Gilles de la Tourette patients (GTS) was pre-processed with a custom-built processing pipeline as outlined in Figure 1. Three denoising strategies were utilized in the processing stream. Strategy Type-I included the regression of nuisance variables from linear/quadratic trends, 24 motion parameters, and WM/CSF signals via aCompCor. Type-II and Type-III strategies included the regression of nuisance variables of Type-I, with the addition of ICA-AROMA (ICA Automated Removal Of Motion Artifacts) (Pruim et al., 2015) and Wavelet Despike (Patel et al., 2014), respectively. The Derivative of the VAriance of the Root mean Square of the BOLD signal (DVARS) was used as a metric of motion as it indexes the variance in the fMRI signal between successive frames.

Figure 1 |



Results and discussion: Our results indicate that Type-I and Type-III denoising strategies do not completely remove group differences of BOLD signal variance as illustrated in Figure 2. On the other hand, data processed with ICA-AROMA (Type-2 stream) resulted in a significant reduction in the mean and standard deviation of the high-motion GTS group, and more importantly, a matching of DVARS group means. To interrogate the effects of the denoising strategy on removing distance-dependent connectivity artifacts (which increase locally and decrease globally), we used the delta-R plot (Power et al., 2012) on the GTS sample to inspect the change of correlation between Type-I/Type-II and Type-I/Type III with respect to Euclidian distance. A trend for a decrease in short-distance correlations was observed for Type-II ICA-AROMA denoising.

Figure 2 |



Conclusion: Our results indicate that the ICA-AROMA denoising strategy performs well at decreasing group differences of the DVARS motion metric between a high motion clinical population and control population. Additionally, ICA-AROMA results in a decrease in short-distance correlations, which might affect group comparisons. On other hand, Wavelet Despike is a promising strategy for the removal of non-stationary events in fMRI time-series, however, its implementation on our data did not result in the matching of DVARS means between the groups. It is possible that the performance of the discrete wavelet transform is dependent on the acquisition strategy. In this case, it is difficult to comment on the performance of the algorithm since the discrete wavelet filter parameters may need to be optimized for the specific sequence parameters. In sum, with sequence specific optimization, ICA and wavelet-based denoising methods perform well at removing non-stationary events in the fMRI time-series, while circumventing the drawbacks

of the alteration of the temporal structure of the data or the loss of temporal degrees of freedom, which are associated with scrubbing.

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Impulsivity and compulsivity in Japanese patients with refractory Tourette syndrome before and after deep brain stimulation

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Introduction and objectives: In Japan, Department of Neurosurgery, National Center of Neurology and Psychiatry (NCNP) has performed deep brain stimulation (DBS) for refractory patients with Tourette syndrome (TS) (Kaido et al., 2011).

Sensory phenomena (SP) including premonitory urges for tics and "just right" perception are recognized as crucial symptoms of TS (Martino et al., 2013).

We assessed clinical features related to impulsivity and compulsivity including SP and obsessive-compulsive symptoms (OCS), in two patients once before and twice after DBS, and compared their changes toward useful information for DBS.

Methods: Both cases were 29-year-old men. The worst ever period of tics was 11–12 years old in Case 1 and 22–24 years old in Case 2. They underwent DBS at 24 years old in Case 1 and at 25 years old in Case 2.

Assessment scales included Yale Global Tic Severity Scale (YGTSS) for tics, Premonitory Urge for Tics Scale (PUTS) (Rosario et al., 2009) for premonitory urges, University of São Paulo Sensory Phenomena Scale (USP-SPS) (Woods et al., 2005) for broader SP, Dimensional Yale-Brown Obsessive-Compulsive Scale (DY-BOCS) (Rosario-Campos et al., 2006) for OCS, and Global Assessment of Functioning (GAF) scale for global functioning.

Results and discussion: After DBS, YGTSS global severity scores and PUTS total scores decreased consistently in both cases. USP-SPS total scores and DY-BOCS global severity scores decreased consistently in Case 1, but fluctuated in Case 2. "Just right" perception wasn't identified at any assessments in Case 1, but identified at all assessments in Case 2. Although GAF scores increased after DBS in both cases, their improvement was less in Case 2 than in Case 1.

Comparison between the cases showed that OCS and broader SP including "just right" perception were different and that improvement of impairment by tics and global functioning was less in Case 2 than in Case 1. This difference may be partly influenced by experience of the most severe tics in late childhood of Case 2.

Conclusion: It is suggested that systemic assessment of impulsivity and compulsivity including SP and OCS is necessary for investigation of usefulness of DBS.

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Disclosures

Authors have no conflict of interest.

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Genetic association and targeted gene expression profiling help explore the role of histamine's metabolic and signaling pathways in Gilles de la Tourette syndrome

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Introduction and objectives: Abnormalities of cortico-striatal-thalamic-cortical pathways and dysfunction of both dopamine and serotonin neurotransmitter systems are associated with Gilles de la Tourette Syndrome (GTS). However, the implication of the *L-histidine decarboxylase* (*HDC*) gene recently raised the intriguing hypothesis of the involvement of the histaminergic pathway in disease onset (Ercan-Sencicek et al., 2010). In the past, we showed that common *HDC* variants and haplotypes are significantly associated with GTS in Caucasians (Karagiannidis et al., 2013). Following up on our previous work, we explore potential associations of genetic variation and gene expression profiles of genes encoding for proteins involved in histamine's metabolic and signaling pathways, in GTS cases and unaffected individuals.

Methods: *Genetic association:* A genetic association study of polymorphic markers, representing the genetic variation of seven genes involved in histamine's metabolic (*HDC*, *HNMT*, *DAO*) and upstream signaling pathway (*HRH1*, *HRH2*, *HRH3*, and *HRH4*), was performed in a total of 355 GTS cases of European origin (107 French, 71 Hungarian, 17 Greek, 48 Italian, and 112 German) and origin-matched controls: Genotypes for the loci of interest, represented by 206 markers, were extracted from Illumina OmniExpressExome-8 arrays on which the samples had been previously genotyped (Paschou et al., 2014). Genetic associations and statistical analyses were conducted using Haploview 4.2/ PLINK 1.07/1.9 and correction for population stratification using EIGENSOFT 6.00.

Gene expression: In order to examine the expression patterns of the above-mentioned genes, peripheral blood was collected from ~50 GTS cases and ~50 controls. Total mRNA was purified, followed by cDNA synthesis and real-time qPCR on a customized array, after having optimized the most stably-expressed housekeeping genes (HKGs). Transcript levels will be compared between cases and age-matched controls, as well as between subgroups of GTS patients, based on particular clinical characteristics, such as tic severity and/or comorbidities, including ADHD and/or OCD.

Results and discussion: Histamine is an important mediator of inflammation; however, its importance in neurotransmission and in neuropsychiatric disorders has only recently started to become appreciated. We believe that given the lack of cure, currently, for GTS, as well as the limited availability of therapeutic options for this disorder, defining genetic susceptibility factors of GTS will provide new insights in disease etiology. For our genetic association analysis we corrected for population stratification using the ADNI control dataset and also additional datasets of southern-European origin. *GAPDH* and *B2M* proved to be the most stably-expressed HKGs, among 12 HKGs analyzed across four cases and four controls. Preliminary data for the seven genes of interest show that expression levels do not differ between TS cases and controls. On-going studies will reveal whether this holds true for subgroups of TS cases.

Conclusion: We set off to explore the role of histamine in GTS predisposition in an effort to unravel whether the histaminergic pathway may contribute to the etiology of GTS thus potentially providing novel ground for future drug therapies.

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Once-daily oral aripiprazole for treatment of tics in children and adolescents with Tourette's disorder: a randomized, double-blind, placebo-controlled trial

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Introduction and objectives: The precise cause of Tourette's disorder is unknown, but disturbances in dopaminergic and/or serotonergic pathways may play a role (Steeves and Fox, 2008). Aripiprazole can modulate the dopamine and serotonin systems as a partial agonist at dopamine D_2 and serotonin 5-hydroxytryptamine $(5\text{-HT})_{1A}$ receptors and as an antagonist at serotonin 5-HT_{2A} receptors. Results of a previous exploratory controlled study suggested that treatment with oral aripiprazole may provide benefit in children and adolescents with Tourette's disorder (Yoo et al., 2013). The primary objective of the present study was to further evaluate the efficacy, safety and tolerability of oral aripiprazole, compared to placebo, in the suppression of tics in patients with Tourette's disorder.

Methods: This was a phase 3, multicenter, randomized, double-blind, placebo-controlled clinical trial in children and adolescents aged 7–17 years with a diagnosis of Tourette's disorder (*DSM-IV-TR*), documented by the Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime Version including the Diagnostic Supplement 5 (Substance Abuse and Other Diseases, i.e., Tic Disorders). Patients also had a total tic score of ? 20 on the Yale Global Tic Severity Scale (YGTSS) at screening and baseline (randomization), and the tic symptoms had to cause impairment of each patient's normal routine. Eligible patients were randomized (1:1:1) to receive oral treatment with low-dose aripiprazole (5 mg/day) if.

Results and discussion: The randomized population included 133 patients (44 low-dose aripiprazole, 45 high-dose aripiprazole, 44 placebo); most were boys (78.2%) and white (87.2%). Mean age was 11.5 years. At baseline, the mean YGTSS total tic score was 29.3–31.5 across the 3 treatment groups. There was a significant improvement in symptoms with both low-dose aripiprazole (LSM change −13.4 ± 1) and high-dose aripiprazole (LSM change −16.9 ± 1.6) versus placebo (LSM change −7.1 ± 1.6); low dose treatment effect: −6.3 [95% CI, −10.2 to −2.3]; $P = 0.002$; high dose treatment effect: −9.9 (95% CI, −13.8 to –5.9); $P = 0.0001$) and between the high-dose aripiprazole and placebo groups (−1.0 [95% CI, −1.5 to −0.5]; $P = 0.0002$). These between-group differences were significant by week 1. The three most common AEs were sedation (18.2% low-dose, 8.9% high-dose, and 2.3% placebo), somnolence (11.4, 15.6, and 2.3%, respectively), and fatigue (6.8, 15.6, and 0%, respectively).

Conclusion: Both high- and low-dose aripiprazole showed efficacy in the treatment of tics in patients with Tourette's disorder. AEs were in line with other studies of aripiprazole in children and adolescents. With approval of the US Food and Drug Administration in December 2014, aripiprazole represents a new option for treatment of tics in patients with Tourette's disorder.

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Disclosures

Full time employee of Otsuka.

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Social functioning of children and adolescents with tic disorders

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Introduction and objectives: Improving social functioning and quality of life of children and adolescents is in the heart of modern rehabilitation approaches in child psychiatry (Peterson, 2007). Comprehensive assessment of social functioning allows practitioners to systematically evaluate actual psychosocial needs of children and adolescents with tic disorders involving consideration of such an important issue as family burden. That may be essential for selection of psychosocial interventions targets and evaluation of short-and long-term efficiency of treatment and rehabilitation programmes (Woods et al., 2011). *Objective*: assessment of social functioning of children and adolescents with tic disorders and related family burden.

Methods: Examination of 38 children (23 – boys, 15 – girls), aged 8–14 years (average: 10 ± 3.8) with tic disorders (based on ICD-10 criteria) and their parents has been carried out using CGSQ (Caregiver strain questionnaire), CGAS (Children's Global Assessment Scale) and children and their parents (mainly mothers) were also asked to fill in H. Remschmidt's ILK questionnaire (Inventory of Quality of Life in Children and Adolescents) that addresses preoccupations concerning the existing mental disorder and diagnostic and therapeutic measures "overload." Sample consisted of 20 children with simple motor tics (blinking, winking, shrugging, etc.), 18 – multiple (jumping, bouncing, etc.), in some cases accompanied by vocalisms.

Results and discussion: Overall level of family burden in families with children and adolescents with tic disorders was quite high – 11.34 points – indicating a high degree of parents' anxieties about their children problems. Higher burden was observed in families of children with multiple tic disorders with vocalisms. Studying together the results of family burden evaluation and social functioning assessment based on CGAS and with a predominance of moderate degrees of social disadaptation (41–48 points, average: 44.7 ± 2.5) has shown a negative correlation ($r = -0.463$, $P = 0.005$), meaning that an increase in family burden would be associated with a decrease in social functioning of children with tic disorders. Children ILK score equaled 22.9 ± 2.2 points, parents' score – 30.9 ± 1.8. This difference between children and parents scores proved to be a general trend. Parents tended to be less positive when evaluating all aspects of children social functioning, including overall assessment of quality of life and treatment related issues. The largest discrepancies between children and parents assessments were noted in social contacts, school, concerns about disorder, mental health and therapeutic measures overload subscales. However, in children aged 12–14 years a marked tendency of an increase in assessment of social contacts, school and diagnostic and therapeutic measures overload subscales was observed.

Conclusion: High level of family burden in families with children and adolescents with tic disorders has a negative impact on social functioning of these children. This dynamic parameter is to be considered when developing individualized psychosocial rehabilitation programmes and psychosocial support measures for the family.

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Modified GIM - Modified Guided Imaginary Music Therapy for Tourette

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Introduction and objectives: Hippocrates described the positive influence of music in people 2500 years ago (music is medicine).

There is scientific proof that exposure to musical training shapes the brain, and that musician's brains in some areas are larger than non-musician's brains.

It has been proved that music especially beyond stimulation the primary acustic center also stimulates many other areas, primarily the prefrontal area, the limbic system, especially hippocampus, and brain stem as well as cerebellum. Music is a strong activator for several neurotransmittors, especially dopamine, oxytocin, serotonin, endorphines, endocannabinoids, immunoglobulin A, opioid receptors. Also, it reduces the stress hormone cortisol.

Music especially stimulates the prefrontal area. This is involving creation and suppression of tics.

It is proved that the prefrontal activity can suppress tics.

My hypothesis was that tics must be able to be reduced by music therapy.

Even if there – until now – is no scientific material, which confirm music therapy acting in tics, there are a lot of case stories referring to suppressing tics by playing an instrument or by singing/dancing or listening to music.

Also, there is a previous documentation that music can improve arousal and thereby concentration as well as social adaptation.

Methods: Method 1 (2013) In our clinic we have performed 1 project in 2013 with professional music therapy for 19 Tourette patients aged 8–16 years. They received different types of individual music therapy, depending on the interest of the person.

They were informed to practise for 20 min at home and count their tics. The result from this project is presented earlier at ESSTS in Athens.

Method 2 (2014–2015) Almost all, except from 1, could suppress their tics, as long as they listened to the music, an as long as they were in close contact with the music therapist. But the end result was very dependent on the person's ability to practise at a daily basis.

The project shows that age and maturity had a large influence on the end point.

The patients who fulfilled the project and were very active with practising at home experienced 50–60% reduction of their tics. An improvement which continued for several months.

The project inspired us to perform 2 other projects, of which the last is not yet finished.

The first project with 9 Tourette patients aged 12–30 years. All received professional music therapy (Modified GIM therapy – Guided Imaginary Music therapy).

Results and discussion: All patients but one suppressed their tic in relation to the music therapy seance. All 9 could suppress their tic when practising at home. The end result was that 5 of the 9 patients demonstrated reduction of their tic by 50–60% from the start until finishing the project. The result was very dependant on the amount of practising.

The second project included 9 patients aged 12–25 years in Modified GIM therapy.

The preliminary results are the same – that all patients can suppress their tic in relation to the music therapy seance, but also when being active at their practising at home.

The project is not yet finished (We already see some very positive results). We expect that it will be finished before the congress in London and will be presented there.

Conclusion: I hope that the preliminary positive results will inspire neurologists/child psychiatrist and music therapist to a cooperation for a larger Ph.D. project where it will be possible to compare music therapy to "Exposure and Response" and "Habit reversal." I hope that future projects could be larger and include control groups.

Acknowledgements

The project in 2013 was performed by bachelor in music therapy Karen Marie Thoby and neurologist Anne Gersdorff Korsgaard. The projects in 2014/15 were performed by GIM music therapist, cand.phil. Annette Møller Larsen and neurologist Anne Gersdorff Korsgaard.

Disclosures

None.

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Longitudinal study of intelligence in Tourette syndrome

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Introduction and objectives: There have been diverging conclusions about the general IQ level in Tourette Syndrome (TS). However, many earlier studies have failed to control for possible effects of the high comorbidity of ADHD and OCD (Debes et al., 2010). Furthermore, it is not known whether individual IQ levels may change with age as the overt symptoms of TS change. Thus, we set out to study variation in intelligence over time in a cohort of children and adolescents diagnosed with TS. To our knowledge this is the first longitudinal study on intelligence in TS. The large sample size enables us to divide the participants by their comorbidities of ADHD and OCD. This gives us the opportunity to investigate both stability of IQ in TS and the effect of comorbidity.

Methods: 266 children and adolescents diagnosed with TS and 81 controls completed a WISC-III or WAIS-III intelligence test from 2006-2008 (Debes et al., 2010). 176 of the TS patients and 51 healthy controls were retested after an average of 5.6 years. At both baseline (T1) and retest (T2) all participants had a clinical interview and filled out ADHD-RS/ADRS and Y-BOCS/CY-BOCS depending on age, to determine the degree of comorbid ADHD and/or OCD, along with YGTSS to determine severity of tics (Mol Debes et al., 2008; Debes et al., 2010). At T1 the TS group was divided into four subgroups: TS-only (41.5%), TS + ADHD (17.6%), TS + OCD (17.6%) and TS + ADHD + OCD (23.3%). Before the analyses we implemented a conversion procedure to make data from WISC and WAIS compatible.

Results and discussion: At T2 both TS groups and controls had a slightly but significantly higher full scale IQ (FIQ) ($t(226) = -2.15$, $p = 0.03$) (see Table 1). This was also reflected by strong correlations between T1 and T2 for both the TS group ($r = 0.86$, $p < 0.01$) and the controls ($r = 0.75$, $p < 0.01$; see Figure 1). The controls had a 12.03 point higher mean FIQ than the TS group at T2 ($t(226) = -4.96$, $p < 0.01$; see Figure 2). This is consistent with the findings from T1. We also found differences at the subgroup level; the largest being 8.53 FIQ between TS + ADHD + OCD and TS + OCD, ($t(70) = 2.22$, $p = 0.03$). However, the TS + OCD FIQ is still significantly below that of the controls ($t(80) = -2.19$, $p = 0.03$).

Table 1 | Mean scores on full scale IQ, verbal IQ, performance IQ at T1 and T2 divided by subgroups.

	N (%)	Full IQ T1	Full IQ T2	Verbal IQ T1	Verbal IQ T2	Performance IQ T1	Performance IQ T2
TS only	73 (41.5%)	92.03	93.82	96.64	96.24	89.33	91.92
TS+ADHD	31 (17.6%)	88.06	87.46	92.13	90.63	86.68	85.95
TS+OCD	31 (17.6%)	94.29	97.18	98.19	100.89	90.39	93.27
TS+ADHD+OCD	41 (23.3%)	87.4	88.65	93.38	95.46	84.5	82.93
Full TS group	176	90.58	92.07	95.23	95.81	87.93	89.09
Controls	51	103.22	104.1	106.92	106.96	97.84	99.69

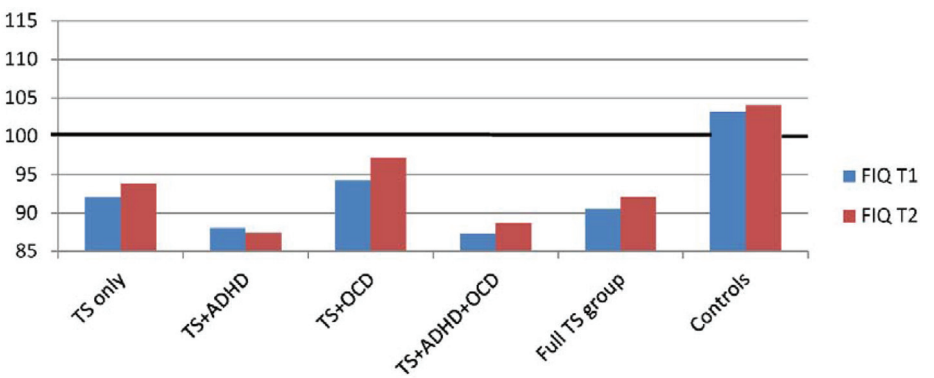

Figure 1 | Full IQ at T1 and T2 divided by subgroups.

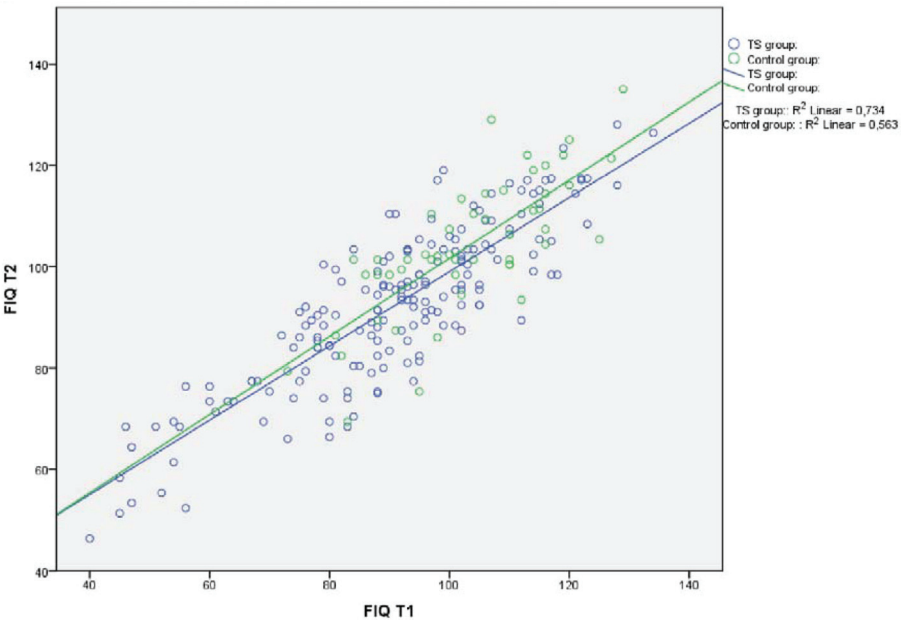

Figure 2 | The correlation between T1 and T2 for full scale IQ.

Conclusion: Consistent with the findings from T1, the TS group has significantly lower FIQ than the healthy controls. Furthermore there are significant within-group differences when comorbidity is taken into account. Our next step is to investigate these group differences further by taking tic remission and current comorbidity into account.

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Randomized sham controlled double-blind trial of repetitive transcranial magnetic stimulation for adults with severe Tourette syndrome

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Introduction and objectives: A small proportion of individuals with Tourette syndrome (TS) have a lifelong course of illness that fails to respond to conventional treatments. Open label studies have suggested that low frequency (1-Hz) repetitive transcranial magnetic stimulation (rTMS) targeting the supplementary motor area (SMA) may be effective in reducing tic severity. The Objective of this study was to examine the efficacy of rTMS over the SMA for TS in a randomized double-blind sham-controlled trial (RCT).

Methods: We conducted a two-site RCT-rTMS with 20 adults with severe TS for 3 weeks. Treatment consisted of 15 sessions (1-Hz; 30 min; 1800 pulses per day) of active or sham rTMS at 110% of the motor threshold over the SMA. A subsequent 3 week course of active rTMS treatment was offered.

Resting motor thresholds across 3-week active and sham rTMS in patients with Tourette syndrome.[a]

Motor Threshold (MT)	Active rTMS (n = 8)		Sham rTMS (n = 10)	
	Baseline	Week 3	Baseline	Week 3
Right MT[b]Mean(SD)	68.0(11.5)	63.5(10.3)	61.0(11.2)	61.6(12.0)
Left MT Mean (SD)	63.5(10.9)	61.8(10.4)	66.4(12.0)	65.0(13.1)

rTMS, Repetitive transcranial magnetic stimulation; Resting motor threshold (MT) was defined as the minimum magnetic flux needed to elicit a threshold EMG response (50 μ\N in peak-to-peak amplitude) in a resting right or left target muscle (abductor poliicis brevis).

Clinical Measures across 3-week active and sham rTMS in 20 patients with Tourette syndrome.

Dependent measures	Active rTMS (n = 9)				Sham rTMS (n = 11)				MMRMA
	Baseline	Week l	Week 2	Week 3	Baseline	Week 1	Week 2	Week 3	
YGTSS	3 5.8 (9.2)	28.1(10.4)	30.3 (9.0)	29.6(11.9)	36.3(8.2)	34.5(8.7)	33.2 (9.0)	31.5(8.1)	NS
PUTS	25.5 (6.5)	23.1 (7.3)	24.9 (6.9)	24.6(6.0)	29.0(5.6)	27.2 (5.3)	28.5 (4.7)	28.7 (5.3)	NS
CGI - Severity	4.9 (0.8)	4.7(0.9)	4.6(1.3)	4.6(1.1)	5.4(0.8)	5.1 (0.9)	4.8(1.0)	4.4(1.0)	NS
Y-BOCS	12.1 (9.5)	6.3 (6.5)	8.4 (8.3)	7.0 (7.9)	8.2(10.2)	6.1 (10.2)	5.4(9.9)	4.8 (7.8)	NS
ASRS	27.5(12.8)	23.6(13.2)	29.4(16.9)	25.1(12.3)	21.5(10.5)	20.8(15.2)	20.5(14.1)	19.1 (13.0)	NS

rTMS, Repetitive transcranial magnetic stimulation; OCD, Obsessive-compulsive disorder; ADHD, Attention Deficit Hyperactivity Disorder; YGTSS, Yale Global Tic Severity Scale; PUTS, Premonitory Urge Tic Scale; CGI, Clinical Global Impression Severity scale; YBOCS, Yale-Brown Obsessive Compulsive Scale; ASRS, ADHD Sell Rating Scale; MMRMA, Mixed model repeated measures analysis with baseline scores as a covariate; NS: $P > 0.05$.

Results and discussion: Of the 20 patients (16 males; mean age of 33.7 ± 12.2 years), 9 received active and 11 received sham rTMS. After 3 weeks, patients receiving active rTMS showed on average a 17.3% reduction in the YGTSS total tic score compared to a 13.2% reduction in those receiving sham rTMS, resulting in no statistically significant reduction in tic severity ($P = 0.27$). An additional 3-week open label active treatment for those patients ($n = 7$) initially randomized to active rTMS resulted in a significant overall 29.7% reduction in tic severity compared to baseline ($P = 0.04$).

Conclusion: This RCT did not demonstrate efficacy of 3-week SMA-targeted low frequency rTMS in the treatment of severe adult TS. Further studies using longer or alternative stimulation protocols are warranted.

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Transcriptome analysis of the human striatum in Tourette syndrome

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Introduction and objectives: Thus far, genome-wide association studies have not revealed any risk-conferring common genetic variants in Tourette syndrome (TS), requiring the adoption of alternative approaches to investigate the pathophysiology of this disorder. Prior post-mortem studies have documented a decreased number of parvalbumin and cholinergic interneurons in the striatum (caudate and putamen) of individuals with Tourette syndrome.

The objective of this study was to characterize transcriptional differences in the striatum of individuals with severe, persistent TS compared to matched controls.

Methods: We obtained the basal ganglia transcriptome by RNA sequencing tissue from the caudate and putamen of nine individuals with severe persistent TS and nine matched normal control subjects. Weighted gene coexpression network and gene set enrichment analyses were performed on the up-regulated and down-regulated genes.

Results and discussion: Differential gene expression analysis revealed 309 down-regulated genes related primarily to neuronal signaling and 822 up-regulated genes. Weighted gene coexpression network and gene set enrichment analyses revealed 17 gene co-expression modules associated with TS. The top-scoring down-regulated modules were enriched for genes expressed in striatal interneurons. In contrast, the top-scoring up-regulated module was enriched in immune-related genes, consistent with activation of microglia in patients'striatum.

We found a lack of correlation between the expression of interneuron-related and immune system-related classes of transcripts, suggesting that these two signatures may independently contribute to TS pathophysiology.

Immunohistochemical studies of fixed tissue series further confirmed that three classes of striatal interneurons are significantly reduced in TS: (1) cholinergic and (2) parvalbumin$^+$-GABAergic interneurons, which had been previously reported; as well as (3) nitric oxide synthase1(NOS)$^+$/neuropeptide Y(NPY)$^+$/somatostatin(SST)$^+$-GABAergic interneurons. Reductions in these classes of interneurons were also indicated by significant decreased striatal expression of CHAT, CHRM2, SLC5A7 and several other cholinergic-related genes, and several GABAergic-related genes including GAD1, NOS1, NPY, and SST.

Genes implicated by copy number variants in TS were also enriched in the interneuron module, as well as in a protocadherin module. We also evaluated the intersection of the network modules with genomic variants. Intersection of our network modules with genes implicated in a recent study of TS-associated copy number variants revealed enrichment in interneuron- and protocadherin-related gene modules. Analysis of rare single nucleotide variants (SNVs) from the RNA seq data revealed significant association of UTR SNVs within the immune-related gene module with TS, and marginal association of nonsynonymous SNVs within the protocadherin-related gene module.

Conclusion: Convergence of differential expression, network analyses, and module clustering, together with copy number variants implicated in TS, strongly implicates disrupted interneuron signaling in the pathophysiology of severe TS and suggests that metabolic alterations may be linked to their death or dysfunction. Concomitantly, but decoupled from the neuronal changes, we found a significant increase in immune and inflammatory transcripts that appear to be endogenous to the central nervous system. Developmentally relevant modeling may help to untangle the cause-effect mechanisms underlying these phenomena.

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Beyond tics; managing underlined processes in the treatment of Tourette syndrome

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Introduction and objectives: This 3 h presents a cognitive behaviour therapy package suitable for managing tics and Tourette syndrome (TS). Although the program draws on existing techniques such as habit reversal and relaxation, it is based on a cognitive-psychophysiological model which emphasizes regulation of sensorimotor activation, management of emotions linked with frustrated action, and cognitive restructuring of perfectionist style of planning action in high risk tic situations (O'Connor, 2005). Two treatments have been adapted for children with TS targeting tics and explosive outbursts as an emotional tic. Different issues related with intervention in children will be addressed as well as the main steps of the therapy.

Methods: The *principal objective* of this skills based workshop is to become familiar with the treatment for TS in children and adults. *Learning objectives* are: to understand the psychological characteristics of TS and their impact on tic onset; employing functional analysis to reveal psychological profiles for evaluating triggers in tic disorders, and high/low risk situations; awareness of how negative/positive thoughts and reinforcement processes maintain the tic cycle; establishing forces and personal strengths to treat tics.

Results and discussion: Participants will be sensitized to tics *assessment strategies*, and the main steps of *treatment*: awareness training, constructing high/low risk profiles, planning action, sensorimotor regulation, cognitive behavioural restructuring, and relapse prevention. The presenters will offer a formulated therapy model that focuses on an individualized situational assessment that the clinician uses during the intervention.

Conclusion: The workshop will have a didactic part to ensure the understanding of the theoretical model. In parallel, examples of exercises, videos and case studies illustrate the application of the program with findings from recent clinical studies.

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Tourette syndrome is associated with insecure attachment and higher aggression

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Introduction and objectives: The aim of this study was to explore the degree to which individuals with Tourette syndrome (TS) exhibit particular attachment styles and the possible association between underlying attachment dimensions and various forms of aggression.

Methods: Fifty-three TS patients (ages 17–72 years) and 54 matched healthy controls completed the Experiences in Close Relationships-Revised Scale (ECR-R) (Ehrenthal et al., 2009) and the Aggression Questionnaire (AQ) (Buss and Perry, 1992). The data were analysed with ANOVA *F*-tests, *t*-tests, and Pearson's correlation coefficient.

Results and discussion: TS patients showed significantly higher scores in relationship anxiety (? $p < 0.001$) and relationship avoidance (?p –0.001) in the ECR-R and significantly higher aggression scores in the AQ (?$p < 0.001$). The total AQ score correlated significantly with the ECR-R dimension anxiety (?$p < 0.001$).

Conclusion: In this first study on attachment and anger in TS patients we found higher levels of anxiety and avoidance in intimate relationships in TS patients, and pronounced anger and hostility. The first clinical implication is to have a closer look at patient's relationships and self-management.

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Parental psychopathology and Tourette syndrome: A nationwide register study

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Introduction and objectives: The etiology of Tourette syndrome (TS) remains unclear, but it is likely to involve complex and multifactorial genetic basis (Deng et al., 2012) and contribution of environmental factors (Hoekstra et al., 2013). TS and obsessive compulsive disorder aggregate in families (Browne et al., 2015). It has also been suggested that different neurodevelopmental disorders may share common genetic etiology (Lichtenstein et al., 2010) and parental psychiatric disorders have been associated with neurodevelopmental disorders, e.g., autism (Jokiranta et al., 2013). However, the associations between a wider spectrum of parental psychiatric disorders and TS remain unexplored. This study aimed to elucidate the relationship between parental psychiatric history and Tourette syndrome.

Methods: This was a nationwide register-study based on a nested case-control study design. All children born and diagnosed with TS 1991-2010 in Finnish Hospital Discharge Register (FHDR) were identified. Each case was matched to four controls on sex, date of birth and birth place. The parents of the participants were identified from the Central Population Register and parents' psychiatric diagnoses based on International Classification of Diseases (revisions 8–10) were derived from the FHDR. The psychiatric diagnoses were categorized as presented in the table. Group 1 was at the highest in the hierarchy and group 4 at the lowest. Each parent having a psychiatric disorder was assigned to only one diagnostic category and if the parent had several of group 1–4 diagnoses group standing highest in the hierarchy was chosen. In addition to groups 1–4, the disorders with onset in childhood (autism, hyperkinetic disorders, tic disorders, intellectual disability, developmental disorder of scholastic skills, language or motor function) were considered as group 5 and this group was outside the hierarchy meaning that one parent could be in group 5 and one of the groups 1–4. Conditional logistic regression was used for analysis.

Results and discussion: Associations between parental psychiatric diagnoses and Tourette syndrome.

Conclusion: This is the first study to report that all maternal psychiatric disorders, except addictions, and paternal affective disorders and neurotic and personality disorders are, in addition to childhood onset disorders, associated with TS in the offspring. The observed familial aggregation between these disorders suggests shared genetic susceptibility and/or familial environmental factors.

Parental psychiatric history	**Distribution cases and controls by diagnosis category**		OR (95% CI)	*P*
	Cases *n* (%)	**Controls *n* (%)**		
Maternal psychiatric history				<0.0001
1. Schizophrenia and other psychosis	24 (3.2)	35 (1.2)	3.0 (1.8–5.1)	
2. Affective disorders	102 (13.8)	159 (5.6)	2.9 (2.2–3.8)	
3. Neurotic and personality disorders	66 (8.9)	114 (4.0)	2.6 (1.9–3.5)	
4. Alcohol and drug addiction	9 (1.2)	24 (0,8)	1.8 (0.8–3.8)	
No	541 (72.9)	2522 (88.4)	Reference	
Maternal childhood onset disorder				
Yes	15 (2.0)	16 (0.6)	3.5 (1.7–7.1)	0.0005
No	727 (98.0)	2838 (99.4)	Reference	
Paternal psychiatric history				0.0054
1. Schizophrenia and other psychosis	10 (1.4)	25 (0.9)	1.7 (0.8–3.5)	
2. Affective disorders	55 (7.6)	139 (4.9)	1.6 (1.2–2.2)	
3. Neurotic and personality disorders	40 (5.5)	106 (3.8)	1.6 (1.1–2.3)	
4. Alcohol and drug addiction	17 (2.3)	76 (2.7)	0.9 (0.5–1.6)	
No	606 (83.2)	2483 (87.8)	Reference	
Paternal childhood onset disorder				
Yes	17 (2.3)	23 (0.8)	2.9 (1.6–5.6)	0.0008
No	711 (97.7)	2806 (99.2)	Reference	

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The authors have no conflicts of interests to report.

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The impact of motivation on self-regulatory control in children with Tourette syndrome

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Introduction and objectives: This study investigates the effects of motivation on the inhibition of prepotent motor responses in children with Tourette Syndrome (TS) and those with TS and Attention-Deficit/Hyperactivity Disorder (ADHD) compared with controls. TS involves anatomic and functional disturbances in the cortico-striatal circuitry, which connect the prefrontal cortex to the basal ganglia. These circuits are involved in reinforcement learning. Previous studies have shown that adults with TS are sensitive to positive reinforcement, and that treatment with dopamine receptor antagonists bluntens this sensitivity (Maia and Frank, 2011; Worbe et al., 2011). This hints to a bias in the cortico-striatal circuits, which in turn could facilitate tic formation due to excessive reinforcement of motor sequences. Based on earlier evidence, we thus hypothesise that children with TS will show shorter reaction times without an increase in error rate relative to the other diagnostic groups in the presence of reward.

Methods: Medicine naive 8 – 12 year old children (TS, TS + ADHD, ADHD and typically developing), were included. After clinical characterisation and cognitive profile estimation, we use a modified Simon task, contrasting conditions of prospect of reward (POR) and no POR. Participants had to press the right or left button depending on the color of the stimulus, which was presented on either the left or right side of the screen. Thus, the cue had a relevant dimension (colour) and an irrelevant dimension (spatial position), creating an incongruency effect. In 50% of all trials (POR trials), red and blue coins were presented instead of circles to indicate the reward given. We investigated differences in accuracy and in reaction time (RT), using SPSS v.15, using a general linear model to implement repeated measure ANOVA with within-subject factors (POR, congruency) and between subject factors (group).

Results and discussion: Preliminary behavioural data (data collection in progress) from 18 control children, 27 TS children, 10 TS + ADHD children and 13 ADHD children will be updated for presentation. *Accuracy*: We found main effects of congruency ($p = 0.032$) and POR (pRT: There were significant main effects of congruency (p

Conclusion: Improving our knowledge of motivational processes in fronto-striatal circuits in TS children, with and without comorbid ADHD, will allow us to better understand how disturbances in the development of those circuits contribute to difficulties associated with childhood neuropsychiatric disorders. Hopefully they will inform and improve treatment options, especially those involving active changes in habit formation, for these different diagnostic groups.

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Stigma in youth with Tourette's syndrome: a systematic review and synthesis

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Introduction and objectives: Tourette's syndrome (TS) is a childhood onset neurodevelopmental disorder, characterised by tics. Although the nature of the disorder and its symptomology encompass the most important dimensions that result in a person being stigmatised (Jones et al., 1984), to our knowledge, there have been no systematic reviews that focus on examining the body of literature on stigma in association with youths with TS. It is therefore the objective of the current article to review the existing research on a) social stigma in relation to children and adolescents with TS, b) self-stigma and c) courtesy stigma in family members of youth with TS.

More analytically, the aims of this review are as follows:

- To identify publications which explore the public's stereotypical knowledge about TS, unfavourable attitudes and discriminating behaviour towards children and adolescents with TS.
- To understand the reasons behind the perpetrators behaviour in excluding and marginalising individuals with TS.
- To identify if stigma is associated with age or gender in children and adolescents with TS and to ascertain if gender and age could be identified as characteristics that could predict the perpetrators behaviour towards individuals with TS.
- To provide an overview on how stigma is experienced and managed by children and adolescents with TS and to point out the overt and subtle forms of discrimination they endure.
- To evaluate the self-stigma in individuals with TS and identify managing mechanisms.
- To access courtesy and affiliate stigma in family members.
- Lastly, this review aims to summarize, evaluate and provide a comprehensive overview of the current knowledge and evidence and to indicate future research directions.

Methods: For the purpose of this review three electronic databases were searched: PsycINFO, PubMed and Web of Science. Search terms focused on two areas: Tourette and stigma. This systematic review was restricted to empirically based studies that used explanatory, observational, experimental or survey study design and were published in peer review journals after 1994 and before 2015.

Results and discussion: The research from the three database searches yielded 3635 results of which 19 peer reviewed articles that were based on 17 empirical studies met all the criteria of inclusion of the systematic review. The results suggest that in rating their own beliefs and behavioural intentions, youth who did not have TS showed an unfavourable attitude towards individuals with TS in comparison to typically developed peers. In their narratives about their lives, people with TS described some form of devaluation as a response to their disorder. Self- degrading comments were denoted in a number of studies in which the children pointed out stereotypical views that they had adopted about themselves. Lastly, parents expressed guilt in relation to their children's condition and social alienation as a result of the disorder.

Conclusion: Notably there is not a single study that focuses primarily on stigma in relation to TS and further studies that examine the subject from the perspective of both the perpetrator and the recipient of stigma are warranted. Relative data could provide a basis for developing effective and tailor -made interventions aimed at reducing the misconceptions and the social stigma associated with the condition.

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Modifications in brain functioning after cognitive-psychophysiological therapy in Tourette syndrome patients

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Introduction and objectives: For years, Tourette syndrome has been solely treated with pharmacotherapy, producing various undesirable side effects (Wile and Pringsheim, 2013). Now, cognitive-behavioural therapies have evolved in a way that they can reduce symptoms as much as pharmacotherapy does (McGuire et al., 2014). A specific type of therapy, with a special aim on regulating the chronically heightened sensorimotor activation and elevated muscle tension, can improve motor function and general condition in TS patients (O'Connor et al., 2008). Nevertheless, the effects of this therapy on motor processing are not fully understood. Therefore, the goal of this project is to study the effects of a cognitive-psychophysiological therapy on brain functioning during a motor task.

Methods: Twenty participants with motor tics were matched on age, sex and intelligence with 20 healthy controls. EEG activity was recorded at 500 Hz during a Stimulus-Response Compatibility task. EEG data was averaged into event-related potentials. Lateralized readiness potentials (LRP) were then obtained through a double subtraction, to eliminate any electrical activity unrelated to motor processes. LRP were recorded with a topographical design, at electrodes F1′, FC1′, FC3′, C1′, C3′, CP1′ and CP3′. The stimulus-locked LRP (sLRP) was measured from the stimulus onset, while the response-locked LRP (rLRP) was measured from the onset of the motor response. TS symptoms intensity was measured with the Yale Global Tic Severity Scale (YGTSS). Measures were taken before and after the therapy for the TS group, while the control group was only tested once. Two LRP measures were studied: the maximum peak of the LRP, reflecting activation of the correct response, and the Gratton dip, a measure of the activation of the incorrect response.

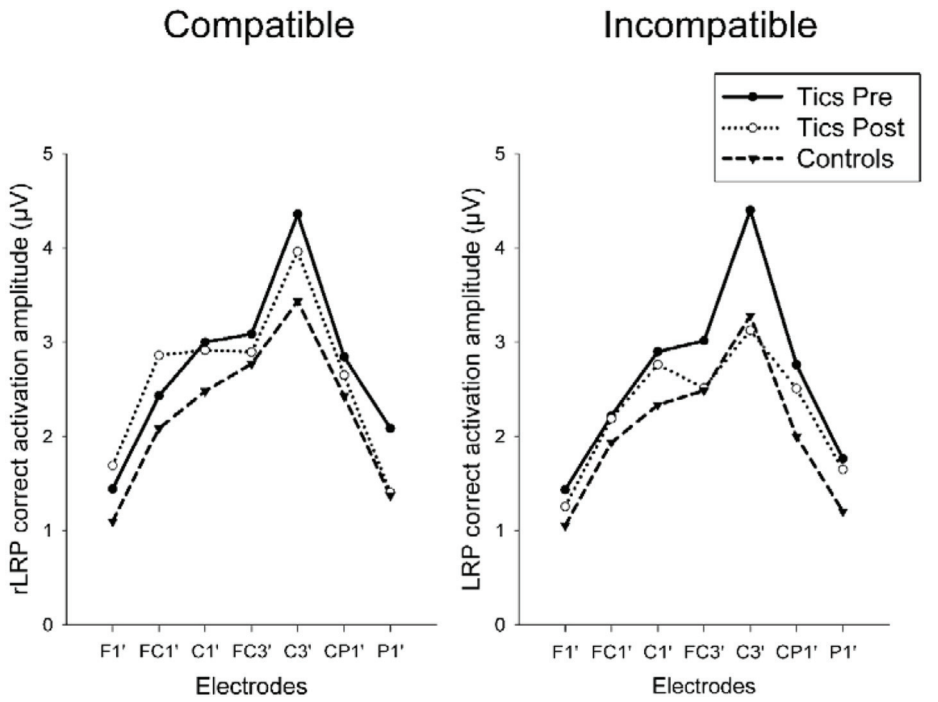
Results and discussion: Before cognitive-psychophysiological therapy, TS patients showed larger rLRP peak at electrode C3′ [$F(1,38) = 4.81$, $p < 0.05$], as well as larger Gratton dip (incorrect activation of the LRP) [$F(1,38) = 4.56$, $p < 0.05$]. After therapy, both the rLRP peak (at electrode C3′) [$F(1,19) = 11.61$, $p < 0.005$] and the Gratton dip (at electrode C1′) [$t(19) = 2.88$, $p < 0.05$] normalized. The therapy also induced a 40% decrease in symptoms intensity. These results show that before cognitive-psychophysiological therapy, TS patients had higher cortical activity in motor regions than controls. This could be an indication that they have impairments in controlling their voluntary movements. Therefore, the normalization of the cortical activity following cognitive-psychophysiological therapy suggests modifications of motor processes.

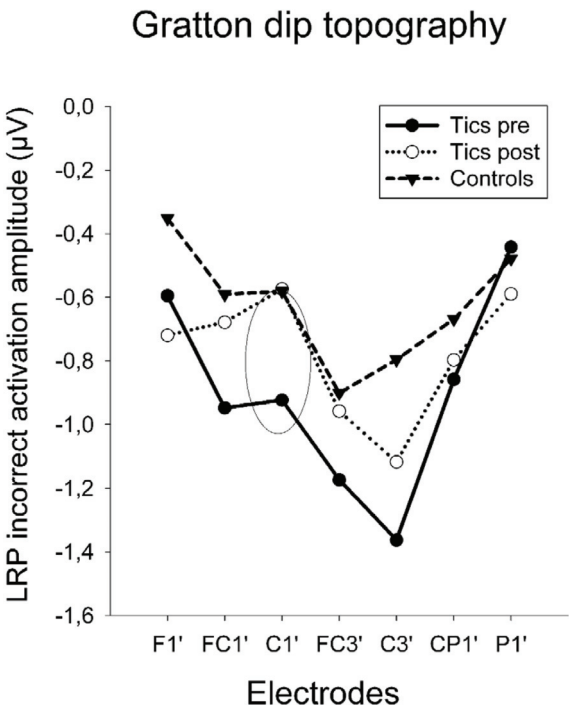
Conclusion: LRPs are partly generated by the supplementary motor area, and this region is also involved in tic production. Therefore, the LRP normalization, combined with a tic severity reduction, could indicate a modification of the cerebral activity in the supplementary motor area.

Table 2 | Pre-post comparison of clinical scales

			TD group						
			Pre		Post				
			Mean	SD	Mean	SD	*t*	p	d
Depression (BD1)			10	9.5	7	7.1	2.05	.055	.36
Anxiety (BAI)			7	4.4	3	3.3	1.85	.081	1.03
Tic severity	TSGS total score		19	10.9	10	9.2	4.40**	.000	.89
	YGTSS	Total	42	15.1	28	10.9	7.10**	.000	1.06
		Tics impairment	21	9.8	11	5.0	6.02**	.000	1.29
		Motor tics severity	13	4.8	11	4.2	3.03*	.007	.44
		Phonic tics severity	8	5.8	6	4.8	3.36*	.003	.38
Obsessive-compulsive symptoms (VOCI)			28	16.9	30	17.5	-0.77	ns	.12
Impulsiveness (Barratt)			61	8.6	60	8.2	1.01	ns	.12

Note: SD: Standard deviation, BDI: Beck Depression Inventory, BAI: Beck Anxiety Inventory, TSGS: Tourette's Syndrome Global Scale, YGTSS: Yale Global Tic Severity Scale, *: p<.01, **: p<.001, d: Cohen's d.





Disclosures

The authors report no conflict of interest.

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Neuropshychological profile in an Argentinian sample of children and adolescents with Tourette Syndrome

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Introduction and objectives

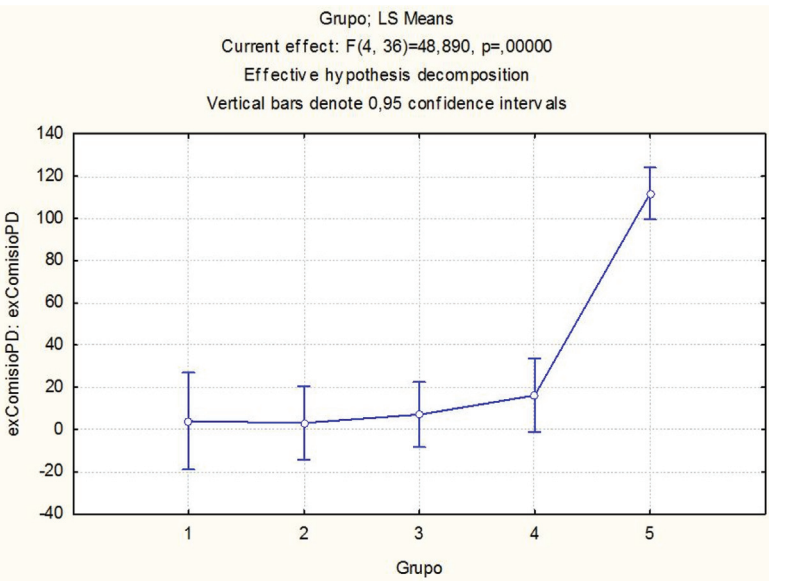
Introduction: Tourette syndrome (TS) is a neurodevelopmental disorder characterized by motor and vocal tics of childhood onset that persist more than a year. More than 90% of patients have associated psychopathology,specially OCD and ADHD (Leckman, 2002). A variety of neuropsychological deficits have been described in subjects with TS depending on the severity and type of comorbidities, conditioning academic underachievement, and lack of social skills abilities in a considerable amount of patients. None or only mild cognitive deficits are present in pure TS involving visual processing and psychomotor difficulties, attention and executive deficits (Ossmon and Smerz, 2005). Executive disfunction in TS is more typically associated with comorbid disorders, specially with ADHD, and also with OCD but with a different pattern (Moyano, 2013). Several recent studies have also demonstrated inhibitory control's deficits (Stern et al., 2008) and social cognition deficit in TS's patients (Eddy and Cavanna, 2013)

Objectives: to describe the cognitive profile and to analyze executive function in a clinical sample of Children and Adolescents with pure TD, and TD in comorbidity with ADHD, OCD or both.

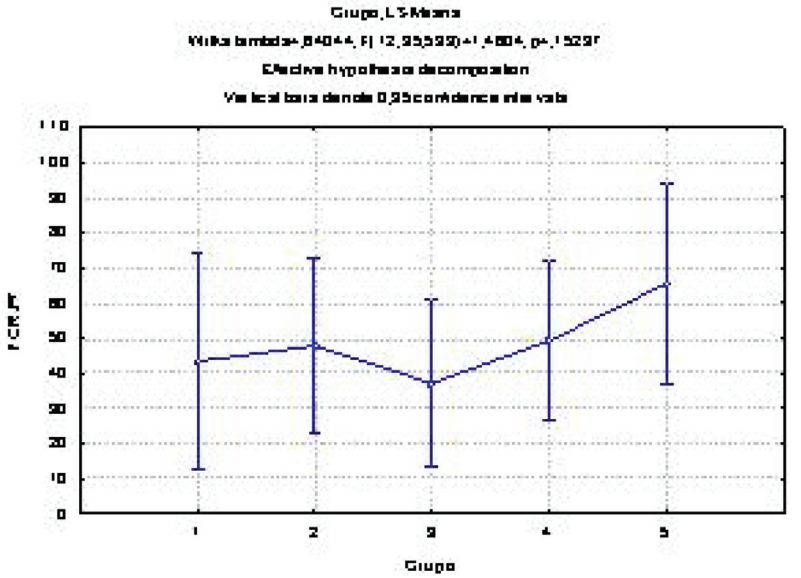
Methods: A clinical sample of 77 children & adolescents with TD aged 6–16 years (64 males (83.1%) years 13 females (16,9%) was randomized selected from the CITA database by chart review. We grouped them at follows: (G1) 10 patients with TS (pure TS), (G2) 17 patients with OCD comorbidity (TS/OCD), (G3) 30 children with ADHD comorbidity (TS/ADHD), (G4) 20 patients with TS, OCD and ADHD (TS/OCD /ADHD), and (G5) 20 typically developing children (TDC). Psychiatric assessment of subjects had been diagnosed by a psychiatrist expert in TS (BM) throughout the KSADS – PL.

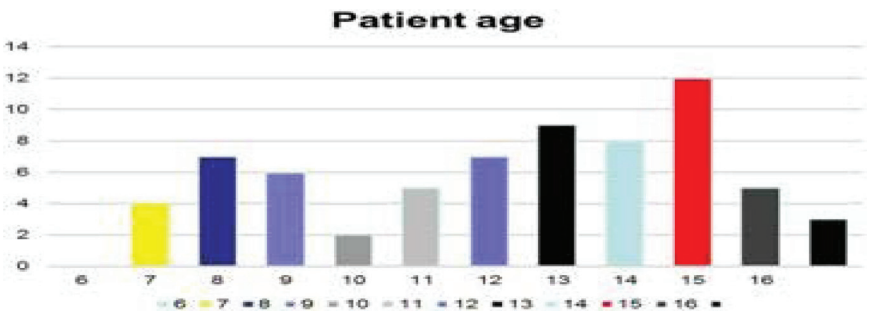
Data analysis: groups were compared using an ANOVA test. The *p* value for significant differences was set as >0.05.

Results and discussion: Wechsler Intelligence Scale for children: The total sample showed a Media or Superior Total Intelectual Capacity (IQ de 98.74 (typical deviation of 14.65) in 70% of subjects, and a predominant Verbal/Executive discrepancy (favoring Verbal) in the majority of them. Speed Processing Scale was the most impacted In all the groups, with a media CI of 87.45, being the most impacted group the ST + TDAH &OCD (low visual processing, visomotor deficits). Comprehension subtest of the WISC was the most impacted in all subgroups showing preliminar evidence of social judgement deficits in clinical populations with TD (Moyano, 2013).



Rey Complex Figure: Decreased performance relative to the TDC was observed in the copy stage in all groups, showing impact of viso-constructive processes. The most impacted group was 3 (TS + ADHD),





TOMAL (Visual memory) Obtained mean scores were still descended in all groups (g1 $z = 0.66$, z g2 = 0.33, g3 $z = -1.66$; g4 $z = 0.40$) compared to the TDC (g5 $z = 1.66$). Group 3 was the most affected ($z = -1.66$). Results show deficits in visual memory in the global sample of TD and specially in G 3, even when controlling graphomotor function.

D2 Attentional test: No significant differences were observed between clinic groups, but all them were all lower respect to TDC in comission errors indicating control inhibitory impairment in TS.

Social Cognition: Mind in the Eyes Test (Baron-Cohen et al., 2001) showed significative deficits for patients with TD in the reading of complex emotions when compared with control subjects, confirming social cognition deficits in subjects with TD. ST total de aciertos 353 (Media = 17.65, DS = 4.030). TDC ($n = 20$) 409 aciertos (Media = 20.45, DS = 2.856). Faux Paus test didnot show to be impaired in any group.

Conclusion

- Clinical populations with TD show to be highly comorbid with ADHD, OCD or both, which condition the level and profile of present cognitive deficits.
- Patients with Pure TD showed mild or no neuropsychological deficits.
- Patients with pure TD and comorbid with ADHD and/or OCD showed normal IQ (70%) and specific cognitive profiles, predominating a verbal/executive discrepance typical of Right Hemisphere pathology.
- Mayority of patients show comprehension and social judgement deficits.
- Visual memory was impaired in pure ST, TS/ADHD and TS/OCD.

- Visual constructive processes are impaired in TS specially when the graphomotor variable and planning strategies are involved.
- Inhibitory control deficits were evident specially in pen and paper tasks (visual channel)
- Subtle social cognition deficits were detected in subjects with TD (reading of complex emotions)

Acknowledgements

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Disclosures

We have no conflict of interest for this presentation.

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Impact of obsessive-compulsive disorder comorbidity in children and adolescents with tic disorders

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Introduction and objectives: Tic disorders, including Tourette syndrome (TS), are neuropsychiatric disorders characterized by the childhood onset of motor tics and vocal tics. Tic disorders are frequently associated with a wide range of behavioral and psychological difficulties, including highly disruptive behavior, interpersonal difficulties, and anxiety and mood disturbances. Consequently, there is a high rate of co-occurring conditions between tic disorders and other psychiatric disorders, such as obsessive-compulsive disorder (OCD) (Coffey et al., 2000) and attention-deficit/hyperactivity disorder (ADHD) (Robertson et al., 2009). Previous research has identified greater tic severity, increased levels of depressive and anxious symptoms, elevated psychosocial stress, and poorer global functioning among youth with comorbid OCD and TS (Lebowitz et al., 2012). We aimed to examine the impact of comorbid OCD on tic severity, social functioning, self-concept, and global functioning in a sample of youth with a diagnosed tic disorder.

Methods: Participants were 115 youth, aged 6–17 years (mean = 11.1 years ± 3.03; 77% male), with expert clinician-diagnosed tic disorder (including TS, Chronic Motor or Vocal Tic Disorder, or Tic Disorder – Not Otherwise Specified) recruited from the normal patient flow of the University of South Florida (USF) Rothman Center for Pediatric Neuropsychiatry. Subjects were administered a battery of self-report or clinician-administered measures assessing the presence and severity of psychiatric comorbidities and psychosocial impairment.

Results and discussion: Of the 115 youth with a diagnosed tic disorder, 44.3% ($n = 51$) had comorbid OCD. Compared to youth without comorbid OCD, those with OCD exhibited significantly higher tic severity ($t(110) = -3.65$, $pt(107) = 3.39$, $pp = 0.04$) or tic disorder, OCD, and ADHD combined ($p = 0.009$). Medium-to-large-sized associations were observed between youth's self-concept and the severity of OCD.

Conclusion: Findings suggest that among youth with tic disorders, the presence of comorbid OCD may have a significant impact on tic severity, global functioning, social deficits, and overall self-concept. Future research is needed to develop interventions to address the role of comorbid OCD symptomology among youth with tic disorders in order to improve overall functioning.

Acknowledgements

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Dr. Tanya Murphy has received research support from the International OCD Foundation (IOCDF), National Institutes of Health, Florida Mental Health Institute, Otsuka Pharmaceuticals, Pfizer, Inc., F. Hoffmann-La Roche Ltd, Shire Pharmaceuticals, Neurocrine Biosciences, Inc., Psyadon Pharmaceuticals, and Auspex Pharmaceuticals. Dr. Murphy was on the Medical Advisory Board for Tourette Syndrome Association and is on the Scientific Advisory Board for IOCDF. She receives a textbook honorarium from Lawrence Erlbaum. Dr. Adam Lewin (in the past 5 years) has research support from the International OCD Foundation, NARSAD, USF Research Council, All Children's Hospital Research Foundation, travel support from the Tourette Syndrome Association (TSA), Rogers Memorial Hospital, USF Research Council, the American Psychological Association, and the National Institute for Mental Health, and honoraria from Springer Publishing, Elsevier, TSA, the Children's Tumor Foundation, and the University of Central Oklahoma. He has served as an educational consultant for Prophase, LLC. Dr. Lewin is a member of the scientific and clinical advisory board for the International OCD Foundation and is on the executive board for APA Division 53 – Society for Clinical Child and Adolescent Psychology. Dr. Eric Storch has received grant funding in the last 3 years from, All Children's Hospital Research Foundation, Centers for Disease Control, the National Institutes of Health. He receives a textbook honorarium from American Psychological Association, Lawrence Erlbaum, and Springer publishers. Dr. Storch has been an educational consultant for Rogers Memorial Hospital. He is a consultant for CroNos, Inc. and Prophase, Inc., and is on the Speaker's Bureau and Scientific Advisory Board for IOCDF. Dr. Rahman, Camille Hanks, and Joseph McGuire do not have any financial disclosures to report.

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Antibiotic treatment outcomes in youth with PANS

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Introduction and objectives: Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS) is a subtype of acute-onset obsessive compulsive disorder (OCD) marked by an abrupt onset or exacerbation of neuropsychiatric symptoms (e.g., reduced and restricted food intake, sensory symptoms, handwriting deterioration, separation anxiety, frequent urination, tics, and/or emotional lability) (Swedo et al., 2012; Murphy et al., 2015). Although inadequately examined, the current treatment for youth meeting PANS criteria include immune therapies, prophylactic antibiotic therapy, and the same standard of care practices for pediatric OCD. In this pilot study, we examined the safety and efficacy of azithromycin in reducing symptom severity in children with PANS.

Methods: Thirty-two youth (aged 4–14 years, $M = 7.93 \pm 2.70$, males $n = 20$) were randomized to receive placebo ($N = 14$) or azithromycin ($N = 18$) for 4 weeks (10 mg/kg up to 500 mg per day). The primary outcome measure was the change from baseline in scores on the CYBOCS and the CGI-S OCD ratings at 4 weeks with secondary outcomes of changes in YGTSS and CGI-S tic. Considering that characteristics of PANS differed whether tics were present or not 2, a sub analysis was performed on those with PANS + tics.

Results and discussion: Subjects receiving azithromycin had a mean decrease in OCD CGI-S of 26% versus 0% change in placebo group. Overall, many domains (mood, tic, cognition, general health) improved in both groups with the active group showing the largest improvement. The placebo group showed worsening in inattention and self-esteem. In the tic subset analysis, subjects receiving azithromycin ($n = 12$) versus placebo ($n = 12$), though not statistically significant, showed notable improvements of a moderate effect size ($d = 0.70$) across groups on the CYBOCS ($F) = 3.53$, $p = 0.074$). At the end of week 4, youth in the placebo arm had a mean CYBOCS score decrease of 19.9%, and youth in the active arm had a mean decrease of 40.5%. CGI-S OCD scores at end of week 4 indicated little functional impairment in subjects in the active arm, differing significantly from scores for youth in the placebo group ($p = 0.001$), whom presented with moderate-severe functioning. No significant differences were observed across conditions at end of week 4 on the YGTSS or CGI-S tic. Adverse effects were minor and primarily gastrointestinal symptoms with no study drop outs due to side effects. A 10 point increase in QTc was noted in the active group with no change in placebo group but no clinically significant QTc prolongation was observed.

Conclusion: In the present study, azithromycin was well tolerated and may be an effective treatment for youth with PANS whose symptoms include tics. Although this study is limited by its small sample size, findings suggest that those with OCD and comorbid tics may respond differently to azithromycin therapy compared to youth without tics.

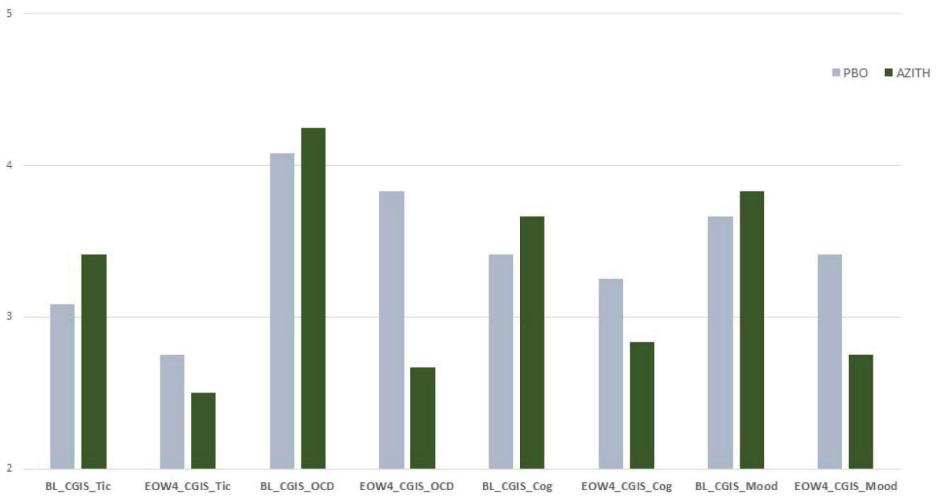

Figure 1 | Tic subgroup analysis.

Acknowledgements

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Disclosures

Dr. Tanya Murphy has received research support from the International OCD Foundation (IOCDF), National Institutes of Health, Florida Mental Health Institute, Otsuka Pharmaceuticals, Pfizer, Inc., F. Hoffmann-La Roche Ltd, Shire Pharmaceuticals, Neurocrine Biosciences, Inc., Auspex Pharmaceuticals, and Psyadon Pharmaceuticals. Dr. Murphy was on the Medical Advisory Board for Tourette Syndrome Association and is on the Scientific Advisory Board for IOCDF. She receives a textbook honorarium from Lawrence Erlbaum. Dr. Adam Lewin (in the past 5 years) has research support from the International OCD Foundation, NARSAD, USF Research Council, All Children's Hospital Research Foundation, travel support from the Tourette Syndrome Association (TSA), Rogers Memorial Hospital, USF Research Council, the American Psychological Association, and the National Institute for Mental Health, and honoraria from Springer Publishing, Elsevier, TSA, the Children's Tumor Foundation, and the University of Central Oklahoma. He has served as an educational consultant for Prophase, LLC. Dr. Lewin is a member of the scientific and clinical advisory board for the International OCD Foundation and is on the executive board for APA Division 53 – Society for Clinical Child and Adolescent Psychology. Dr. Eric Storch has received grant funding in the last 3 years from Agency for Healthcare Research and Quality, All Children's Hospital Research Foundation, Centers for Disease Control, IOCDF, National Alliance for Research on Schizophrenia and Affective Disorders, the National Institutes of Health, Ortho McNeil Scientific Affairs, and Tourette Syndrome Association. He receives a textbook honorarium from American Psychological Association, Lawrence Erlbaum, and Springer publishers. Dr. Storch has been an educational consultant for Rogers Memorial Hospital. He is a consultant for CroNos, Inc. and Prophase, Inc., and is on the Speaker's Bureau and Scientific Advisory Board for IOCDF. Dr. Parker-Athill, Dr. Mutch, Erin Brennan, and Camille Hanks do not have any financial disclosures to report.

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Prevalence estimates of tics in pre-school children in the Republic of Moldova

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Introduction and objectives: Gilles de la Tourette syndrome (GTS) occurs in 0.3–1% of all children, while the tic disorder (TD) prevalence is of about 3–4% for chronic TD and even higher for provisional TD (Robertson, 2008; Knight et al., 2012; Scharf et al., 2012; Scahill et al., 2014; Scharf et al., 2015).

In the Republic of Moldova (RM) tics are commonly considered to be rare, but the exact prevalence of TD and GTS in this geographic area is not known yet. In RM, 83.8% of children are included in pre-school education (National Bureau of Statistics of the Republic of Moldova, 2014). The pre-school teachers' (pST) 7-h working day allows them a close monitoring of children's behaviour as well as an easy noticing of any unusual movement pattern.

Aims: To assess the frequency of tics in pre-school children.

Methods: We created a comprehensive presentation on TD and GTS, which was presented to the pST by the previously trained medical student. A structured questionnaire was fulfilled by the pST before and after presentation. Children with tics currently frequenting the institution were noted.

Results and discussion: Were tested 60 pST from 9 pre-school institutions enrolling 1559 children with age range 2–7 years. Overall they reported that 32 (2.05%) children had tics (22 boys and 10 girls, ratio 2.2:1). Of them, 26 (81.25%) had only motor tics and 6 (18.75%) had possible GTS (4 boys and 2 girls). The highest prevalence of tics was observed in the age groups of 5–6 and 6–7 years, and represented 10 (2.75%) of 364 children and 8 (2.52%) of 317 children, respectively.

Conclusion: The prevalence of tics in the tested group of pre-school children was of 2.05% (GTS – 0,38%, TD – 1,67%) being somewhat lesser than the worldwide data. This difference is probably due to the particular design of this study. However, the results confirm the relative frequency of tics in pre-school children in RM.

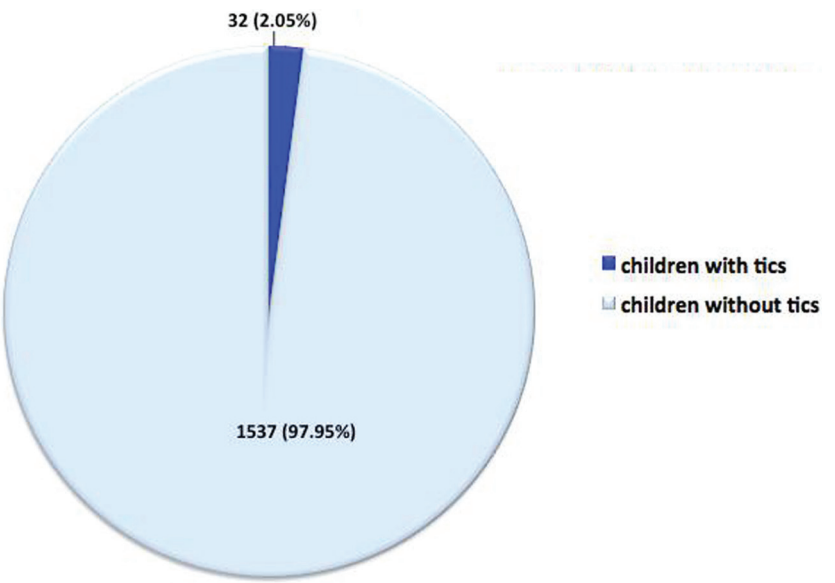

Fig. 1. | Prevalence of tics in pre-school children in the Republic of Moldova

Disclosures

No conflict of interests.

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Exploring developmental aspects of tics in a neurodevelopmental rat model of repetitive behavior

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Introduction and objectives: Tourette Syndrome (TS) is a neurodevelopmental disorder which affects 0.4–1% of the population (Robertson et al., 2009). It is defined by the presence of multiple motor and at least one vocal tic, typically starting during childhood (XXXX, 0000).

The exact cause of TS remains elusive, but dopamine (DA) appears to have a central role (Buse et al., 2013), through its regulation of the direct and indirect striatal pathways controlling movement.

Unilateral 6-hydroxidopamine (6-OHDA) lesion in adult rats is a well-established model used in Parkinson´s Disease research. In this model, selective degeneration of nigrostriatal dopaminergic neurons is chemically induced through the administration of 6-OHDA. Subsequent chronic application of levodopa leads to the development of repetitive involuntary movements, mainly involving the forepaw, neck and mouth (Lee et al., 2000). This is a consequence of striatal super sensitivity to DA, which is also a putative pathological mechanism of TS, and is induced in this model via previous DA deprivation.

We propose to translate this model to juvenile rats, and monitor its neurodevelopmental consequences in order to address the lack of juvenile animal models featuring a tic-like phenotype. This could allow evaluating the consequences of DA super sensitivity during development, and could represent a new tool for investigating new therapeutic options for tic disorders.

This work was supported by the Marie Curie ITN TS-EUROTRAIN (FP7-PEOPLE-2012-ITN, under the REA grant agreement n°316978).

Methods: Male Wistar rats (PD21) received double stereotaxic injections of 4.4 µg 6-OHDA ($n = 16$) or vehicle ($n = 8$) in the mFB[4]. Injection coordinates had been adjusted from an adult rat brain (3 months old, 600 g).

Repetitive behavior was induced through chronic administration of levodopa/benserazide (P.O. 6/15 mg/kg). The abnormal involuntary movements observed were scored according to previously published protocols (Lee et al., 2000). The phenotype was challenged using different dopaminergic and glutamatergic agents.

Post-mortem analysis of brain tissue included tyrosine hydroxylase staining, and DA quantification in the denervated striatum with HPLC.

Results and discussion: The model of repetitive behaviors was successfully reproduced in juvenile animals, and the correct positioning of the lesion was verified through IHC and DA quantification. The tic-like phenotype appears comparable to the adult model regarding body localization, intensity and time duration. Preliminary results indicate that different dopaminergic and glutamatergic agents are able to modulate intensity and duration of the phenotype.

Conclusion: Further characterization of the model is still needed; however, to our knowledge, this is the first model representing a tic-like behavior in juvenile rodents. Further experiments will focus on elucidating the interplay of the dopaminergic and glutamatergic systems and the dissociable roles of indirect and direct pathway phenotype occurrence.

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What makes kids "tic"? A child's-eye view of Tourette syndrome

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Introduction and objectives: I will review results from decades of basic research about what children of various ages and from various cultures think causes physical, psychological, and/or neurobehavioral disorders. Such information may serve the practical aim of guiding parents, teachers, and health care professionals in providing "developmentally-appropriate" explanations about Tourette's for the diagnosed child and for their siblings and peers.

If the diagnosed child's understanding of TS could be enhanced by appropriate scaffolding of information, they may be more amenable to treatment, be able to better educate others and/or better advocate for themselves. Siblings and peers may fear the disorder less upon understanding its aetiology and therefore be more accepting of the TS child.

Methods: This review will include the early cognitive-developmental literature and studies that assume cognitive development plus experience with the illness is essential for understanding illness causality or that experience alone is the relevant issue. Then I will mention studies within the theory-theory constraint framework which argue either that an understanding of biological illness emerges in early childhood, or the late-emerging view that a biological theory follows a psychological framework for understanding illness.

There is also a group of studies that are somewhat atheoretical, dating as far back as the 1970s, that assess children's understanding and acceptance of various types of mental illness or behavioral disorders such as depression, conduct disorder, or ADHD. Young children think such disorders are the result of psychological/ environmental causes like "doing it to be cool", imitating others, bad parenting, or trauma of a psychological or physical kind. Older children or children *with* the behavioral disorder can point to biological causes as well (e.g., birth complications, genetics, contagion).

Results and discussion: Since the basis for this review is the assumption that knowledge about a disorder may lead to changes in attitude towards persons with the disorder and therefore more positive behavioral interactions between the typical and atypical child, I will also summarize results from some of my own work and published peer intervention studies that have attempted to effect a change in knowledge about TS and interactions with a hypothetical peer with TS.

Since these peer intervention studies do not actually assess their research participants' knowledge about Tourette's before or after the intervention, we don't yet really know whether an increase in *knowledge or understanding* is the mediating variable that affects attitudes towards or changes in willingness to interact with someone with the disorder. Not all studies even show an effect of having more information on attitudes or behavioral intentions. We also do not know whether such changes in knowledge would affect attitudes or behavior towards a *real* classmate with the disorder, as compared to the hypothetical peer or filmed actor that is central to most studies.

Conclusion: After summarizing decades of research on children's understanding of what causes illness (which is remarkably similar to the history of medicine over centuries), I will conclude with implications for health care providers, parents, teachers, and even the authors of children's storybooks who wish to provide developmentally-appropriate explanations of behavioral disorders like Tourette's.

References

A handout of dozens of article citations (1970s- present) will be provided at the presentation.

Habit reversal training (HRT) and exposure and prevention (ERP) therapy: a group-based treatment manual for youth with Tourette syndrome or chronic tic disorder

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Introduction and objectives: Tourette syndrome and chronic tic disorders are characterized by often disabling sudden twitches, movements or sounds that are done over and over again. Habit Reversal Training (HRT) and Exposure and Prevention (ERP) therapy are well-established treatments with main focus on helping the sufferers to manage their tics better so that the impact, tics may have on their daily function, is reduced. Two well-established manuals describe the individual treatment of Tourette syndrome (Woods et al., 2008; Verdellen et al., 2011). Several studies have shown that treatments in groups might be beneficial for young people with different psychiatric disorders. The present study focuses on a group manual based on the experience from individual treatments of Tourette syndrome.

The aim of the study is 1. to develop a group manual for treating children and adolescents with Tourette syndrome and chronic tic disorder, 2. to evaluate the efficacy of the manual in a clinical trial.

Methods: The manual comprises eight structured sessions in groups of six (11–15 years of age) focusing on a. psychoeducation, b. HRT, c. ERP, d. functional analysis and intervention and e. prevention of relapses. The training for the youth is preceded by a group psychoeducational session for the parents. The group manual is still under clinical testing as to implement final corrections before a randomized controlled trial is carried out. All sessions are videotaped and evaluated. The outcome of the therapy is evaluated by the Yale Global Tic Severity Scale including an evaluation of the general functioning.

Results and discussion: In two clinical trials of group treatment, eleven males and females participated. Seven of the participants experienced a reduction in the average total YGTSS score of 7.3 (38.9%) and four experienced an increase in YGTSS scores of 5.25 (38%). Seven of the participants experienced a better general function whereas one participant reported an increase in the daily impairment and three experienced an unchanged function.

Conclusion: Although scarce, several of the participants experienced a better general function and reported to have gained important strategies for working with their tic disorder. As such, the group approach seems to provide the same experience as an individual approach. In addition, working together with other young people with resembling difficulties was reported as very motivating.

A randomized controlled trial is under preparation, where the goal is to evaluate the efficacy of the group manual in treating Tourette syndrome and chronic tic disorder in the youth.

Disclosures

No conflicts to report.

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Impact of physical activity on cognitive control performance in Tourette syndrome

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Introduction and objectives: In our recently published work (Nixon et al., 2014), we demonstrated significant tic attenuation in young people with Tourette Syndrome (TS) after an acute aerobic exercise session. These findings provided empirical support for the previously reported beneficial impact of aerobic exercise on tic regulation and the impetus for further exploring the potential exercise-induced effects on self-regulatory control mechanisms in TS. In light of experimental evidence suggesting that moderately vigorous aerobic exercise may not only facilitate executive control in healthy children but also in children with Attention Deficit Hyperactivity Disorder (ADHD) (Gapin et al., 2011), we carried out the present study to investigate whether similar exercise-induced improvements in cognitive control can be observed in TS.

Methods: Employing the previously reported paradigm[1] which involved the delivery of two 5-min aerobic exercise sessions via the X-Box 360 Kinect videogame station, young people (n = 17; aged 10–20) with TS performed a moderately vigorous kickboxing task and a mild-intensity tai chi task on two separate occasions, following the same experimental protocol. On both occasions, participants performed a saccadic cognitive control task before exercise (baseline) and post-exercise while their eye movement reaction time and accuracy were measured using a saccadometer (Ober-consulting, Poland). Baseline and post-exercise task performance was compared using repeated measures ANOVAs and *post-hoc t*-tests in order to determine whether a single bout of exercise would lead to improvements in inhibitory control, particularly on trials requiring an antisaccade (eye movement in the opposite direction of the target) or a switch from an antisaccade to a prosaccade (eye movement towards the target) and vice versa. Participants' changes in post-exercise task performance were also correlated with their scores on the Yale Global Tic Severity Scale (YGTSS) to explore any associations between exercise-induced cognitive control improvement and TS severity.

Results and discussion: Results suggest a global improvement in task performance after both exercise sessions, i.e., kickboxing and tai chi, but a specific enhancement in inhibitory control performance following the kickboxing session only (Jackson et al., 2011; Jung et al., 2015).

Conclusion: The present findings provide novel data for the beneficial effects of moderately vigorous exercise on inhibitory control performance in young people with TS, bearing important implications for self-regulatory control management approaches in research and clinical settings.

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Marijuana use by teens and young adults with Tourette's syndrome, a self-medication behavior?

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Introduction and objectives: This poster provides a literature review of studies which suggest that teens and young adults with Tourette's syndrome (TS) could use marijuana to self-medicate. Self-medication is considered to be an appropriation and consumption of substances not prescribed by a health care professional in order to reduce specific physical or psychological symptoms (Khantzian, 1985). The substance use is made because of its psychopharmacological specificity (Fasseur and Delafosse Santiago, 2012). Many teens and young adults with diagnoses of disorders associated with TS, report using marijuana to improve their symptomatic condition (Bolton et al., 2009). Consumption allows them to improve their physical, physiological, and psychological condition, and helps them better adapt to the surrounding environment when the available treatments do not allow them a complete remission of symptoms (Weiss et al., 2004). In parallel, there is no cure that allows complete reduction of the symptoms of tics (Singer, 2005). As per Leckman (2002), the symptoms in people with TS usually reach its maximum severity during the preteen and then decreases or stabilizes in adulthood. The worsening of tics during this period of life can be particularly difficult for teens with TS since adolescence is often characterized by the search for approval and compliance with the peer group (Juvonen and Cadigan, 2002). The beginning of adulthood can also be a difficult time for people suffering from TS due to the acquisition of new social roles that are often associated with professional and family level (Gaudet, 2007). Psychosocial, physical and occupational impacts associated with symptoms of tics can therefore encourage teens and young adults with TS looking to implement specific strategies to reduce the symptoms of tics and better adapt and perform in the surrounding environment (Storch et al., 2007). In parallel, a number of studies and anecdotal reports suggest that marijuana may have beneficial effects in reducing the symptoms of tics (Müller-Vahl et al., 1998, 2002, 2003). Although the results of several studies suggest that teens and young adults with TS may be at risk for marijuana use for reducing the symptoms of tics and related disorders, no studies confirm this. The consequences associated with marijuana use, and the complexity and nature that underlie the use of it requires further attention. Anecdotal reports and studies focusing on marijuana's use in people with TS will be presented as well as their limitations. It is important to note that a doctoral essay is underway at Université du Québec à Montréal to explore the use of marijuana as self-medication in people with TS.

Methods: *Literature review.

Results and discussion: *Literature review.

Conclusion: *Literature review.

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Genome-wide association of SNPs in Danish cohort for Gilles de la Tourette syndrome (GTS)

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Introduction and objectives: Gilles de la Tourette Syndrome (GTS) is a neuropsychiatric disorder characterized by multiple motor and phonic tics (Paschou, 2013). The aetiology of TS involves complex interaction of different genetic variants and environmental factors. The first Genome-wide Association Study (GWAS), investigated the role of genetic variant Single Nucleotide Polymorphisms (SNPs) in GTS (O'Rourke et al., 2009), identified SNPs that did not meet the genome-wide significance level, but they serve as indicators of possible association with GTS. Here we explore the role of SNPs in aetiology of GTS using well characterised cohort of individuals with GTS from Denmark. 261 Danish individuals with GTS were genotyped in four different batches for around ~750,000 SNPs from Affymetrix CytoScan High-Density (HD) array and 800 Healthy Controls with European ancestry (Uddin et al., 2014) were used to find significant SNPs associated with Tourette Syndrome (TS) in the Danish cohort.

Methods: Quality Control (QC) was applied at SNP level to remove SNPs with lower genotyping rate, ambiguous strand orientation, deviations from Hardy-Weinberg Equilibrium and batch effects. Quality control at sample level checked for genotype call rate, heterozygosity, discordance in sex, removal of closely related samples and population stratification. European ancestry check of both cases and controls is performed using the 500 European samples from 1000 genomes. Multiple models of association tests were performed on QC passed samples. The whole analysis was performed using software PLINK and GCTA software. The scripts for whole analysis were written in R and Python scripting languages.

Results and discussion: Results from quality control at SNP level left with 654717 SNPs and at sample level left with 968 samples of which 228 cases and 740 controls. Association analysis was performed using logistic regression on 967 samples on PLINK and GCTA.

Conclusion: Our study sheds further light into possible role of SNPs in aetiology of Gilles de la Tourette Syndrome.

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Disclosures

None declared.

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Studies on epigenetic mechanisms in Tourette syndrome

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Introduction and objectives: Tourette Syndrome (TS) is a neurodevelopmental disorder characterized by motor and vocal tics. It presents high comorbidity rates with other disorders such as attention deficit hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD). Epigenetics represents all the phenotype alterations which are not due to changes in DNA sequence.

It is known that many developmental disorders are characterized by alterations in genes linked to epigenetic mechanisms. Moreover, environmental factors may represent a risk for TS and they might act via epigenetic alterations. However, very few studies on epigenetics of TS have been done so far.

The aim of this project, within the TS-EUROTRAIN network, is to investigate all the main epigenetic mechanisms (such as miRNA regulation, DNA methylation and histone modifications) and their possible involvement in the pathogenesis of TS.

Methods

MiRNA: Starting from a list of all candidate genes (n = 74) for TS available from the literature, we screened for presence of SNPs in the 3'UTR regulatory regions in our susceptibility gene list. This analysis [data retrieved by mirSNP (http://202.38.126.151/hmdd/mirsnp/search/) and polymiRTS (http://compbio.uthsc.edu/miRSNP/) led to the identification of those SNPs (n = 32) which are predicted to change the seed sequence of *in silico* proposed miRNAs. Genotyping of a sample of n = 564 TS patients and controls was performed by TaqMan method on an OpenArray platform. Furthermore, other polymorphisms in TS candidate genes (GDNF and WFS1) were investigated by real-time PCR.

DNA methylation: Different techniques were used to analyze DNA methylation patterns (such as targeted bisulfite sequencing, RRBS, HRM) both on human TS and control samples as well as on a rodent model of TS where the striatal dopaminergic neurons were lesioned unilaterally by 6-OHDA (see poster by Nespoli et al. WorkPackage 3 in TS-EUROTRAIN).

Histone modifications: chromatin immunoprecipitation from striatum of the rodent model was set up using H3K27ac, H3K27me3, H3K4me3 and H3K36me3 antibodies. Chip-Seq from these samples is underway.

Results and discussion: We identified SNPs in 3'UTR of TS candidate genes, which might affect the binding of some miRNAs and thus have an impact on the gene expression. Some of these were followed up by functional validation studies using luciferase assay (see poster by Vereczkei et al. for more details). Analyses of methylation and chromatin structure also identified differences in a number of gene regions.

Conclusion: This project is a combined epigenetic investigation on Tourette Syndrome. Further analyses such as genome-wide Illumina-450K methylation array, targeted bisulfite sequencing and ChIP-Seq will provide more information about the role of epigenetic mechanisms in the pathophysiology of TS.

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European multicentre tics in children studies (EMTICs): the profile of group A beta-haemolytic *Streptococci* (GAS) associated with EMTICs cases and carriage in the UK

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Introduction and objectives: EMTICS is a pan-European project to explore mechanisms that may underpin tic disorders which remain poorly understood (Roessner et al., 2013). The study hypothesis that onset and/or exacerbation of tic and comorbid obsessive-compulsive disorders is associated with the interaction of genetic and environmental factors including throat carriage or infection from GAS (Schrag et al., 0000).

Methods: EMTICS comprises two multicentre longitudinal cohort studies (COURSE and ONSET). Individuals aged 3–16 years with a known tic disorder are followed up for 16 months in the COURSE study assessing fluctuation and exacerbation of symptoms. First-degree unaffected relatives of COURSE participants aged 3–10 years are followed up for 3 years in the ONSET study to explore all factors when a child presents acutely with a new tic disorder. Data on genetic factors, neuro-psychiatric disorders, immune and environmental factors are obtained via diaries, questionnaires, interviews and biological samples (blood, throat swab and hair). Identification of GAS from throat swabs is performed using highly sensitive and specific standard methods. The accuracy of these methods was confirmed across centres from 11 European countries using an external quality assessment study. Microbiological characterisation of GAS isolates is performed using methods such as *emm* typing.

Results and discussion: In the UK, amongst 33 ONSET participants, 14 (42%) tested GAS positive and nine (20%) of 44 COURSE participants were GAS positive. This indicated a high level of GAS carriage amongst these cohorts and a higher level of carriage in the ONSET cohort. GAS isolates from the ONSET study belonged to six *emm* types whilst GAS isolates from the COURSE study were assigned to five *emm* types, four of which were found in both cohorts. Therefore, a subset of GAS isolates from ONSET or COURSE participants are genetically diverse compared to GAS isolates among the other cohort. All *emm* types exhibited between the cohorts are among the top 10 prevalent *emm* types from invasive GAS (iGAS) disease. Seventeen percent of isolates from both cohorts were assigned to *emm* 1 and 3, the two most prevalent iGAS *emm* types. The most prevalent type in the cohorts (? 43%) was *emm* 28, which is the third most frequent type among iGAS cases. This indicates distinct differences in the prevalence of these *emm* types between the cohorts and iGAS cases.

Conclusion: Distinct differences in the level of GAS positivity and diversity of the strains between the ONSET and COURSE cohorts was identified. Further investigation of the genetic diversity within GAS isolates using whole-genome sequencing is underway and could identify specific virulence markers or other genetic factors that are associated with the onset or exacerbation of tics. Furthermore, this could also identify differences in the prevalence of *emm* types amongst carriage and invasive isolates.

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An empirical examination of symptom substitution associated with behavior therapy for Tourette syndrome

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Introduction and objectives: Over the past six decades, behavior therapy has been a major contributor to the development of evidence-based psychotherapy treatments for Tourette Syndrome and tic disorders. However, a longstanding concern with behavior therapy among many non-behavioral clinicians has been the potential risk for symptom substitution. Unfortunately, few studies have been conducted to empirically evaluate any symptom substitution that may occur as a result of behavioral treatments. The multiple motor and vocal tics associated with Tourette's disorder provide an excellent opportunity to empirically evaluate the potential risk for symptom substitution associated with behavior therapy.

Methods: Data were analyzed from the combined data set of two previously published randomized clinical trials comparing behavior therapy to supportive therapy (Piacentini et al., 2010; Wilhelm et al., 2012) including 228 adult and youth participants with Tourette's disorder or chronic tic disorder. In the present study, four methods were used to examine possible symptom substitution: (1) changes in tics associated with behavior therapy and supportive therapy treatments, (2) the occurrence of adverse events, (3) changes in tic medications, and (4) changes in comorbid or co-occurring symptoms.

Results and discussion: The results indicated that participants treated with behavior therapy were not more likely to develop new tics, report adverse events, change their medications, or have an exacerbation in comorbid/co-occurring symptoms as compared to participants treated with supportive therapy. These findings are particularly noteworthy considering that the participants receiving the behavior therapy treatment had significantly greater overall reductions in tics (45.3% classified as responders) as compared to supportive therapy (12.5% responders).

Conclusion: These findings provide strong empirical support to refute the longstanding concern of symptom substitution in response to behavior therapy. Behavior therapy treatments such as habit reversal and comprehensive behavioral treatment for tics (CBIT) are safe and effective treatments for Tourette Syndrome and tic disorders.

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Drs. Peterson, Wilhelm, Piacentini, Woods, Walkup, and Scahill report receiving royalties from Oxford University Press for treatment manuals on tic disorders.

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Intensive outpatient comprehensive behavioral intervention for tics: a pilot investigation

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Introduction and objectives: Two large randomized clinical trials have found that Comprehensive Behavioral Intervention for Tics (CBIT) (Woods et al., 2008) is superior to supportive counseling in reducing tics in children and adults with Tourette Syndrome (TS) at post-treatment and 6-month follow-up (Piacentini et al., 2010; Wilhelm et al., 2012). In response to mounting evidence, CBIT is now considered a first-line treatment for tic disorders in Europe (Verdellen et al., 2011) and Canada (Steeves et al., 2012). The efficacy of CBIT has been established using a standard outpatient format (8 sessions over 10 weeks). However, weekly sessions may be impractical for patients with limited access to care. Instead, these patients may benefit from an intensive outpatient program (IOP) that compresses CBIT into a week-long protocol. To date, no open studies or clinical trials have been published evaluating the effectiveness of IOP CBIT, although the outcomes of our clinical cases have been favorable (Blount et al., 2014).

Methods

Study aim: To conduct a pilot study to evaluate potential pre- to post-treatment changes in tic severity following participation in IOP CBIT.

Hypothesis: Participation in IOP CBIT will result in significant tic reduction as measured the Yale Global Tic Severity Scale (YGTSS) (Leckman et al., 1989).

*Design***:** This clinical replication series includes 5 participants (10.5–26.9 years) with TS.

*Procedures***:** Participants completed a baseline assessment, 8 CBIT sessions in 4 days, and post-treatment and 4-week follow-up assessments (see Table 1 for schedule).

*Analysis plan***:** Examine changes in YGTSS total scores before and after treatment.

Results and discussion: Participants endorsed clinically significant tics (YGTSS score >13) at baseline ($M = 31.4$, Range: 20–44). Participants reported clinically meaningful tic reduction (>4 decrease on YGTSS) (Piacentini et al., 2010; Wilhelm et al., 2012) at post-treatment, with an average decrease of 10.4 points. Two-thirds of the participants who completed the 1-month follow-up maintained treatment gains. More than half of our participants traveled substantial distances to receive care, and the majority expressed high treatment satisfaction at post-treatment. The results indicate that IOP CBIT can produce meaningful tic reductions in individuals with persistent tics.

Conclusion: Initial results indicate that IOP CBIT maybe a viable options for individuals unable to attend standard outpatient CBIT. Further examination of the efficacy of IOP CBIT is warranted.

Disclosures

Dr. Peterson reports receiving royalties from Oxford University Press for treatment manuals on tic disorders.

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Table 1 | Treatment Schedule.

	Monday	**Tuesday**	**Wednesday**	**Thursday**	**Friday**
Morning Session	Baseline Assessments	Comprehensive Behavioral Intervention for Tics (CBIT) Session 1 (90 min)	CBIT 3 (60 min)	CBIT 5 (60 min)	CBIT 7 (60 min)
Lunch Break (2 + h)		Monitor Tic 1	Monitor Tics Practice CRs 1, 2	Monitor Tics Practice CRs 1–4	Monitor Tics Practice CRs 1–6
Afternoon Session	Introduction and Overview	CBIT 2 (90 min)	CBIT 4 (60 min)	CBIT 6 (60 min)	CBIT 8 (60 min)
Homework		Practice Competing Response (CR) 1 Monitor tics	Practice CRs 1–3 Monitor Tics Relaxed Breathing	Monitor Tics Practice CRs 1–5 Relaxation	Post-treatment Follow-Up Assessment

Table 2 | Change from Baseline on Yale Global Tic Severty Scale (YGTSS).

YGTSS Total	**Patient 1**	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**
Baseline	22	20	29	42	44
Post-treatment	14	14	23	22	32
Change	−8	−6	−6	−20	−12
1-Month	4	15	–	–	46
Change	−18	−5	–	–	+2

Relaxation training for Tourette syndrome: a pilot investigation

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Introduction and objectives: Relaxation training is a behavioral treatment approach that has consistently been found to help improve symptoms for a wide variety of psychological and physiological conditions (Russo et al., 1980; Lichstein, 1988; Peterson et al., 2011). Current behavioral treatments for persistent tic disorders, such as Comprehensive Behavioral Intervention for Tics (CBIT) (Woods et al., 2008), contains a relaxation component, and there is some evidence that relaxation training alone has promise as a treatment for persistent tic disorders such as Tourette Syndrome (TS). However, the research on the efficacy of relaxation trainings for TS has been mixed. For example, Peterson and Azrin found relaxation training reduced TS tics by 32% in a small laboratory-based study ($N = 6$) (Peterson and Azrin, 1992), whereas Bergin and colleagues found no significant differences between relaxation training and a relaxation comparison condition (Bergin et al., 1998). However, a close examination of the results of the Bergin study indicates that the primary reason for failure to detect differences between groups is that both groups improved. Importantly, the majority of participants treated with relaxation training in the Bergin study had clinical improvements and 100% had decreased tics at the 6-week point as measured by the Hopkins Motor and Vocal Tic Scale. The purpose of the present study is conduct a pilot study to evaluate the potential benefit for Relaxation Training as a treatment for Tourette Syndrome.

Methods

Design: A-B-C-D Study Design: Participants completed a baseline assessment (A), 4 weekly sessions of relaxation training followed by a post-relaxation training assessment (B), 8 weekly sessions of CBIT followed by a post-CBIT assessment (C), and a 1 month post-CBIT follow up assessment (D).

Participants: Six participants (Male = 5, Female = 1) ages 10–18 ($M = 12.5$) completed the entire study from baseline to 1 month post-CBIT.

Hypothesis: Participants will see a significant decrease in tic symptoms following relaxation training followed by a further significant decrease in tic symptoms following CBIT.

Analysis plan: Examine changes in YGTSS total scores at all assessment points: baseline, post-relaxation training, post-CBIT and 1 month post-CBIT.

Results and discussion: A statistically significant difference in mean YGTSS scores was found using a repeated measures ANOVA ($F(1.514, 7.571) = 10.460$, $p < 0.01$). *Post hoc* testing indicate that relaxation training alone did not significantly reduce tic symptoms from baseline to post-relaxation treatment (27.167 ± 2.4 vs. 25.000 ± 3.435, $p = ns$). Mean YGTSS scores at post-CBITs (14.167 ± 4.339) were significantly lower than baseline ($p < .05$). See Figure 1.

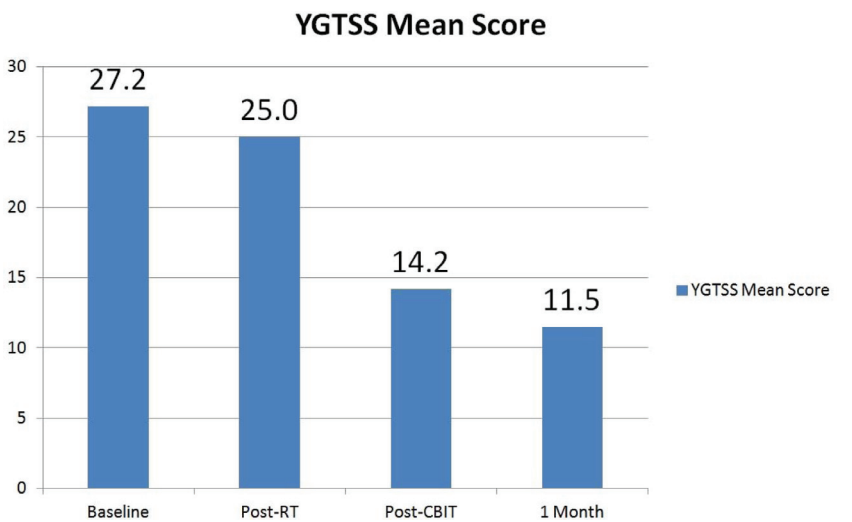

Figure 1 | YGTSS mean source.

Conclusion: Results suggest that relaxation training alone is not effective as a standalone treatment for reducing tic symptoms. However, results indicate that relaxation training in combination with CBIT is effective in significantly reducing tic symptoms. The results of this study provide continued empirical support for CBIT as an effective behavioral treatment for Tourette Syndrome.

Disclosures

Dr. Peterson reports receiving royalties from Oxford University Press for treatment manuals on tic disorders.

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CBIT-Jr: behavior therapy for chronic tics in 5–8 year olds

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Introduction and objectives: Up to half of affected youth have tic onset before age 5 with 40% experiencing worst tics ever by age 8 (Gadow et al., 2002; Leckman et al., 2006). Early negative social reactions to tics may increase the risk for chronic disorder and the development of comorbid problems (Woods et al., 2005). There is significant need for effective intervention efforts for youth younger than those targeted in existing behavioral trials (Piacentini et al., 2010) especially given concerns over chronic medication use in this age group. This study examined the feasibility, acceptability and preliminary efficacy of a downard extension of CBIT (Piacentini et al., 2010) designed to provide parents psychoeducation and eliminate environmental factors shown to shape and maintain tics. CBIT-Jr also assessed readiness for habit reversal through an age-appropriate game and taught HRT to those evidencing sufficient cognitive development, including tic awareness, to potentially benefit from this procedure.

Methods: Eligibility entailed: age 4–8, motor and/or vocal tics > =6 months duration, tic severity <=4 on the CGI-S scale (tics clearly noticeable to others and associated with minimal or greater distress/interference). Pre-existing stable medication was allowed. Standardized battery completed at baseline, post-treatment and 3-month and 1-year followup, including YGTSS, CYBOCS, PTQ, CGI-Improvement and Achenbach CBCL. Interviewers were not blind but kept unaware of any treatment details. Parents received targeted psychoeducation about tics and completed a functional analytic protocol to address tic triggers/consequences. Child readiness for habit reversal training (HRT) was assessed using an opposite simon sez procedure, and most children received some HRT.

Results and discussion: Fifteen children (67% male, mean tic onset 3.9 years, mean tic duration 2.8 years) entered the study from three sites (UCLA, University of Wisconsin-Milwaukee, Weill Cornell Medical College) and 14 completed the study. Mean entry YGTSS Total Score of 23.7 was simliar to that for the older CBIT sample (24.7). Response rate was 50% with a 39% decrease in tic severity post-tx and 43% at 3 months (p

Conclusion: Environmental factors can significantly impact the severity and course of tic disorder. Early intervention to address these factors may reduce future morbidity and possibly provide preventative benefit for youth at increased risk of chronic tic disorder.

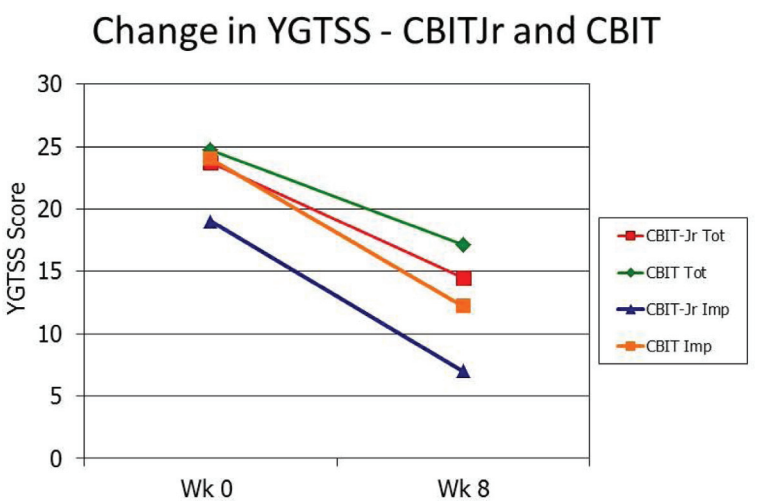

Figure 1 | Change in YGTSS – CBITJr and CBIT

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Disclosures

None

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Developing a novel, picture-based tool to assess interpretation bias in adolescents

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Introduction and objectives: Anxiety is common in Tourette's syndrome and chronic tic disorders (TS/CTD) (Lewin et al., 2011). During adolescence, social anxiety in particular emerges as the most common co-occurring psychiatric condition in young people with TS/CTD (Specht et al., 2011). As anxiety in social situations contributes to quality of life and can trigger tics (O'Connor et al., 2003; Cutler et al., 2009), people with TS/CTD could benefit from transdiagnostic treatments that target social anxiety. Interpretation biases are central in the maintenance of social anxiety (Clark and Wells, 1995; Rapee and Heimberg, 1997). Yet, few measures are available to assess these biases in adolescence, a time when they begin to mature and stabilise.

Here, we present self-report and physiological data from two studies investigating a new, developmentally-appropriate, picture-based tool that extends previous measures of interpretation bias towards a more ecologically valid assessment. Our primary aim was to establish reliability and validity of the measure. A secondary aim was to examine the relationship between social anxiety and interpretation bias. Once validated in the general population, this measure can be applied to adolescents with TS/CTD to identify the extent to which biased interpretations explain social fears and worries in these individuals.

Methods: Pictures of an agent (from behind) interacting with one or more peers were created. *Study 1*: 20 female adolescents (aged 16–19) rated the likelihood of three interpretations (positive, neutral and negative) for each picture. *Study 2*: 53 female adolescents (aged 14–19) completed the measure whilst eye-gaze and pupil dilation were recorded. Additionally, the value of personalising pictures was assessed by replacing the agent with a picture of the participant. All participants completed a measure of social anxiety.

Data was analysed using Pearson's product-moment correlation coefficient and repeated-measures ANOVAs with *post hoc* independent *t*-tests.

Results and discussion

Study 1: adolescents with higher social anxiety rated negative interpretations as more likely compared to their less socially anxious peers ($t(18) = -2.79$, pr = 0.55; see figure 1). The measure significantly correlated with existing measures of interpretation bias (negative scale, $r = 0.71$, p. *Study 2*: personalized stimuli generated increased bias ratings and increased pupil dilation compared to the agent being an unknown peer. Adolescents with increased bias ratings exhibited increased pupil dilation.

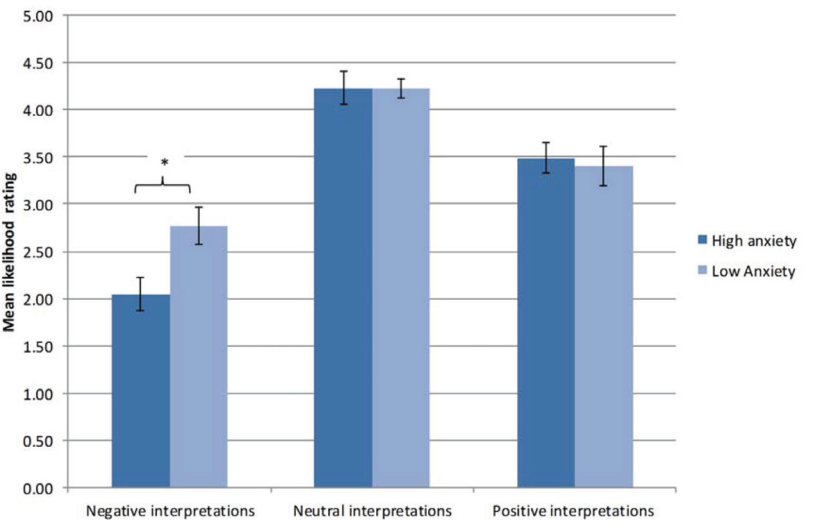

Figure 1 | Likelihood ratings for inietpretalions of picture stimuli in high and low socially anxious groups (*p<0.05).

This novel picture-based tool adds value to existing measures of interpretation bias, can be used in conjunction with physiological measures of cognitive processing and has potential as a tool to train benign interpretations. This work lays the groundwork for investigating the presence of interpretation biases in adolescents with TS/CTD. Whilst all participants were female and TS/CTD predominates in males, no gender differences have been identified in the presentation of anxiety in adolescents with TS/CTD (Specht et al., 2011). If TS/CTD shares these same interpretation biases as anxiety disorders, then applying anxiety treatment protocols to target these in TS/CTD could ameliorate a major source of disability and a triggering factor for the tics.

Conclusion: This novel picture-based tool can be used as a measure for assessing interpretation bias and demonstrates an association between social anxiety and negatively interpreting social scenes.

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Monitoring antipsychotic safety in Tourette syndrome: a prospective longitudinal study

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Introduction and objectives: For children with severe symptoms of Tourette Syndrome and/or co-morbid disorders, antipsychotics may provide symptom relief. Treatment of children with second generation antipsychotics is associated with extrapyramidal, metabolic and hormonal side effects. The CAMESA (Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children) (Pringsheim et al., 2011) Guidelines provide evidence based recommendations for monitoring antipsychotic medication safety in children, and on how to manage and mitigate these complications. The objective of this study is to prospectively monitor children with Tourette Syndrome treated with antipsychotics for extrapyramidal, metabolic and hormonal side effects using an evidence based monitoring protocol.

Methods: All children seen at the Calgary Tourette Syndrome Clinic at the University of Calgary who were started on an antipsychotic and whose guardian consented were prospectively monitored using the CAMESA monitoring protocol. The monitoring protocol includes measurement of body mass index, waist circumference, the Extrapyramidal Symptom Rating Scale examination, and laboratory tests. Children are monitored at baseline, month 1, 2, 3, 6, 9 and 12 and 6 monthly thereafter. We prospectively recorded the rate of metabolic, extrapyramidal and hormonal side effects.

Results and discussion: 45 children were started on an antipsychotic medication between December 2012 and March 2015 and were prospectively monitored for adverse effects, representing complete ascertainment of all children started on antipsychotic medications at the clinic. 23 children were started on risperidone and 22 on aripiprazole. Children ranged in age from 6 to 17 years. 40 males and 5 females were monitored for a range of 1–24 months. Monitoring continued until drug discontinuation.

16 children developed extrapyramidal symptoms over the course of therapy; 11 developed parkinsonism, 2 akathisia, 2 parkinsonism and akathisia, 1 dyskinesia and 1 parkinsonism and dyskinesia. 4 children required a dosage change and 2 had to discontinue treatment because of extrapyramidal symptoms.

At baseline examination, 4 children were overweight (BMI >85th percentile) and 11 children had laboratory metabolic abnormalities (decreased HDL, increased triglycerides, or increased LDL). Over the course of therapy, 11 children went from lean to overweight or obese, 2 children went from overweight to obese, and 6 children became abdominally obese (waist circumference >90th percentile). 6 children developed new metabolic laboratory abnormalities. 5 children had persistently elevated prolactin levels. 1 child required a dosage change and 5 children had to discontinue therapy because of metabolic or hormonal adverse effects.

Conclusion: Metabolic, hormonal and extrapyramidal side effects are common in children treated with second generation antipsychotics. 12 of 45 children in our sample had to discontinue or adjust their antipsychotic medication treatment due to metabolic, hormonal or extrapyramidal side effects. Discontinuation of antipsychotic treatment was more commonly due to metabolic than extrapyramidal or hormonal adverse effects. Extrapyramidal symptoms, while frequent, were usually mild. Clinicians need to monitor children systematically and provide anticipatory guidance if antipsychotics are prescribed.

Acknowledgements

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The structure of co-morbid disorders in the polish population of patients with Gilles de la Tourette's syndrome – pre follow up study

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Introduction and objectives: Attention Deficit/Hyperactivity Disorder (ADHD), obsessive compulsive disorder, depressive disorder, sleep disorders (nightmares, somnambulism) and rage attacks are most often observed comorbidities in patients with Gilles de la Tourette's (GTS). Clinical observations also suggest the possibility of empathy and social deficits in patients with GTS which may stem from difficulties in emotion recognition and formulation of mental representations, similar to patients with autism spectrum disorders. The goal of the study is to assess the functioning of patients with GTS within Tourette Syndrome Genetics – the Southern and Eastern Europe Initiative as well as the presentation of progress of the follow up study. The project was launched in 2008 in 17 European countries. The project is designed to identify comorbidities as well as genetic and family factors contributing to the onset of tic disorders.

The main goal of the study is the identification of possible relationships between comorbid disorders, family factors and the intensity of tics as well as the structure of comorbid disorders. The second goal is to assess the presence of possible mental states formulation and complex emotion understanding deficits in children and adolescents with GTS as well as identification of possible relationships between Theory of mind Deficits (ToM) and the intensity of motor and/or vocal tics.

Methods: The following methods will be used in the study: structured family interview, Yale Global Tic Severity Scale, The Children Yale-Brown Obsessive-Compulsive Scale, ToM tests, The Childhood Asperger Syndrome Test and Autism Spectrum Quotient. The study group will consist of children and adolescents aged 9 to 18 with the diagnosis of GTS or tic disorders who participated in the pre-follow up study in 2008.

Results and discussion: At least one psychiatric disorder was diagnosed in 50% of participants. (ADHD, OCD and Asperger's Syndrome). The presence of comorbid disorders correlated with the existence of psychiatric disorders in family members.

Conclusion: The structure of comorbid disorders in the Polish follow up group who qualified for the study is similar to the structure presented in other studies.

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Premonitory urge fluctuation during reinforced tic suppression and habit reversal therapy in children with chronic tic disorders

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Introduction and objectives: Although tics are the hallmark feature of chronic tic disorders (CTD), a growing body of research has suggested that premonitory urges may play a central role in shaping the expression of tics over time. It has been hypothesized that some tics may become more frequent and forceful because they function to remove the aversive premonitory urges, a view that has been referred to as the negative reinforcement hypothesis (Evers and van de Wetering, 1994; Himle et al., 2006). Evidence for the negative reinforcement hypothesis comes from phenomenological studies showing that many individuals with tics report relief from urges after performing a tic (Kwak et al., 2003); however, laboratory studies on this phenomenon are mixed. Contemporary behavioral models have suggested that nonpharmacological treatments might be effective because they alter the functional relationship between urges and tics (Himle et al., 2006). The current study aims to better understand the urge-tic relationship in the context of reinforced tic suppression and habit reversal therapy (HRT).

Methods: In the first study, an ABAB reversal design was used to examine fluctuations in tic frequency and urge severity during periods of (a) free-to-tic and (b) reinforced suppression, where 7 individuals with CTD were asked to suppress a single, urge-driven tic. Across all phases, urge ratings were collected every 5 s. In the second study, a multiple-baseline across participants design was used to examine the impact of HRT on urge ratings and tic frequency across time in the same 7 subjects. For both studies, experimental sessions were recorded and two trained research assistants coded videotapes for the presence of tics. Interrater reliability was 84% and 93% for the first and second study, respectively. For both studies, visual analysis was used to see if there was a systematic change in tic frequencies and urge ratings across conditions.

Results and discussion: The results of these two studies provide mixed support for the negative reinforcement model. During both reinforced suppression and HRT, participants were able to successfully suppress their tics. However, reinforced suppression and HRT had a differential effect on premonitory urges. Contrary to the negative reinforcement model, none of the participants demonstrated an increase in urge ratings during reinforced suppression or when the competing response was initially utilized. The competing response did, however, lead to decreases in urge severity, which is consistent with the urge habituation assumption of the negative reinforcement model.

Conclusion: To conclude, our results demonstrate that the type of suppression strategy utilized (reinforced suppression versus HRT) may impact urges differently. This may influence what treatment method health-care providers use to treat urge-driven tics.

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Analysis of rare non-coding variation in the Tourette syndrome chr2p linkage region

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Introduction and objectives: A significant fraction of phenotypically important DNA elements are located in the non-coding regions of the human genome (Schaub et al., 2012). This emerging understanding is based on the unprecedented growth of data on human genome regulation (ENCODE Project Consortium, 2012; Roadmap Epigenomics Consortium et al., 2015). Earlier studies in large TS pedigrees have found evidence for the genome-wide significant linkage signal on chromosome 2p (The Tourette Syndrome Association International Consortium for Genetics, 2007). Existing methods accounting for coding (exome) variants only did not suggest any explanation for the observed disease phenotypes. The goal of this work was to identify potentially functional regulatory variants under the chromosome 2p linkage peak with global aim to explain the linkage signal observed in TS large families by means of accounting for both coding and non-coding variation with potential regulatory function.

Methods: We designed a custom capture array containing 5.7 Mbp of target sequence from the entire short arm of chromosome 2 (1–91 Mbp). CIDR used this array and Agilent HumanExon 50 Mb Kit for targeted sequencing of the set of 115 TSAICG individuals from large TS pedigrees. Single-nucleotide variants (SNVs) were identified and annotated using in-house UCLA ICNN pipeline (UCLA ICNN, 0000) that aggregates more than 50 annotations, including SNV databases (dbSNP, HGMD), functional predictions for coding and genome-wide variants (dbNSFP, CADD, DANN, fatHMM-mkl), nucleotide conservation estimates for primate and mammalian lineages (GERP RS, PhyloP), predicted binding sites for human transcription factors (TFBS), gene regulatory elements and chromatin state data in multiple cell lines and tissues (ENCODE, Roadmap Epigenomics, FANTOM5). The multiple independent annotations along with phenotypic information are used for variant filtering and ranking that suggest potentially functional sequence variants.

Results and discussion: The exome-wide and targeted resequencing discovered extensive amount of genetic variation including 21,905 high-quality single-nucleotide variants located in non-coding regions under the chromosome 2 linkage peak, with 5,477 of SNVs being rare (dbSNP138 MAF

Conclusion: The discovered top candidate variants will be genotyped in individuals from 213 affected sib pair TS families with subsequent association tests based on potentially functional coding and non-coding variants.

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Prevalence of tics, tics-severity and quality of life in Tourette syndrome in the middle-aged and elderly: an observational study

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Introduction and objectives: It is well known that tics can persist into adulthood in 33–50% of patients (Bloch et al., 2006). Recent studies that studied the impact of Tourette syndrome in adult patients showed a decreased perceived quality of life and higher levels of self-reported depression (Jalenques et al., 2012; Conelea et al., 2013). The mean age of patients studied in these studies was 30–35 years. One study on tics in middle-aged (>50 years of age) patients reported that the vast majority of tics presenting during adulthood represented recurrences of childhood-onset tics (Jankovic et al., 2010). This study does not provide any prevalence numbers, since the patients studied constituted a selected group already referred to the clinic because of troublesome tics. Recently 48 older adults (>40 years of age), of which 8 patients are 50 years of age or more, attending a Tourette syndrome specialist were described (Man et al., 2014). In this clinical cohort, older adults have more severe tics and are often in poor psychological health, with a history of past and current social impairment, but also in this study there is a referral bias.

To our knowledge, there are no studies describing prevalence of tics, tic-severity and quality of life in middle-aged and elderly patients with Tourette syndrome that were not already referred to a Tourette syndrome specialist.

The prevalence of tics, tic-severity and quality of life in 50 patients with GTS aged >50 years will be assessed in a cross-sectional observational study.

Methods: All patients that have visited our outpatient clinic for tic disorders in the last 20 years will be approached by mail by the main investigator (JR). In addition, a call for study participants will be placed at the website of the Dutch Tourette patient association (www.tourette.nl). Patients have to meet DSM-IV criteria for GTS and have to be born before January 1965. Patients with diagnosis of dementia, severe psychiatric disorders (e.g., psychosis) or aphasia will be excluded. Patients not able to read and/or speak the Dutch language will be excluded.

The primary outcome measure is the total tic severity score on the Dutch version of the Yale Global Tic Severity Scale (YGTSS). Secondary outcome measurements include general assessment of quality of life, severity of premonitory urges and severity of comorbidity.

Results and discussion: Inclusion will start first of March 2015, so there are no results available yet.

Conclusion:

Not applicable

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Antipsychotic-induced hyperprolactinemia in Tourette syndrome

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Introduction and objectives: Tourette syndrome (TS) is a common neuropsychiatric disorder characterized by motor and vocal tics with a prevalence of 6 cases per 1000 school-aged children in the United States (Martino and Leckman, 2013). The mainstay of pharmacological management of tics has been the use of antipsychotic drugs (Roessner et al., 2013). Children and adolescents with TS are frequently treated with antipsychotics, whether or not in combination with psychostimulants, melatonin and SSRI's.

Antipsychotics are most often used in schizophrenia and related psychotic disorders. In these conditions, hyperprolactinemia is one of the most common side effects associated with antipsychotics and occurs in 40–50% of patients (Cookson et al., 2012). Symptoms of hyperprolactinemia include gynecomastia, galactorrhoea, sexual dysfunction, infertility, oligomenorrhoea and amenorrhoea (Haddad and Wieck, 2004). To our knowledge, prevalence of symptomatic hyperprolactinemia in TS is unknown. However, clinical trials in early psychosis report symptomatic hyperprolactinemia in 2.2–9.8% of patients treated with olanzapine, quetiapine and risperidone (McEvoy et al., 2007), at doses that are also used in TS.

Methods: We report two TS patients with antipsychotic-induced hyperprolactinemia.

Results and discussion: Treatment options generally consist of dose reduction or switching from classic to atypical antipsychotics. However, diminishing dosages can lead to exacerbations of tics. Also, not all atypical antipsychotics have the pharmacological properties that are required to normalize prolactin levels. The choice of treatment may also be affected by the patient's age and sex.

Conclusion: These factors are discussed in relation to these cases, and illustrated by the results of therapeutic interventions over the years.

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Disclosures

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An investigation of workplace experiences and job discrimination in Canadian adults with Tourette syndrome

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Introduction and objectives: Previous studies have shown that adults with Tourette Syndrome face challenges in the workplace including difficulties in hiring and promotion, social alienation and occupational interference /discrimination (Stefl, 1983; Myers, 1988; Shady, 1995; Conelea et al., 2013). This study expands our knowledge by examining the workplace experience of Canadian adults with Tourette Syndrome. For the first time, research with the TS population examines specific types of discrimination defined by the Equal Employment Opportunity Commission. The research findings will be useful for clinicians, policy decision makers and employers.

Methods: A sample of 103 Canadian adults with Tourette Syndrome were recruited to complete an online survey. The instrument included 13 Likert scale items, 24 dichotomous questions, one open-end question and 12 classification/ demographic questions. A modified form of the Yale Global Tic Severity Scale was used to determine the frequency, intensity, complexity, interference and overall impairment of the respondent's symptoms.(Leckman et al., 1989; Conelea et al., 2013) Standard means, frequencies and ANOVA were utilized to analyse the data.

Results and discussion: Respondents faced difficulties in performance evaluation and promotion opportunities at work (Table 1). For example, a total of 43% of the respondents agreed that, at times, their capabilities had been misjudged by their supervisors. One third of respondents indicated that TS had been a negative factor in their performance appraisals.

Table 1 | Experiences in the workplace.

	Agree (%) (Agree / Strongly Agree)
Performance Evaluation	
1. I believe my capabilities, at times, have been misjudged by my supervisors because of my Tourette Syndrome.	43%
2. Tourette Syndrome has, at times, been a negative factor in my performance appraisals at work.	33%
Promotion Opportunities	
1. Due to Tourette Syndrome, I have, at times not been asked to perform certain tasks which are typically required of someone in my position.	23%
2. I have turned down a new job or promotion because I have Tourette Syndrome.	18%
3. At times, I have not received a job promotion due to my Tourette Syndrome.	17%
4. I have, at times, not been asked to perform supervisory duties because of my Tourette Syndrome.	11%

Table 2 shows that a significant number of respondents believe that employers treat them differently than other employees. Many respondents felt that they needed to be "better" than someone without Tourettes in order to get a job or have the same opportunities. Social alienation is also a problem with 27% of respondents indicating that they felt that their co-workers left them out of social and work related activities. ANOVA indicated a significant relationship between symptom severity and level of workplace challenges.

Table 2 | Experiences in the workplace.

		(Agree (%) (Agree / Strongly Agree)
Treatment by Employers		
1.	If two equally qualified individuals, one who has Tourette Syndrome and one who does not have Tourette's apply for a job, the employer will view the person without Tourette Syndrome more favorably.	50%
2.	I feel I need to be 'better' than someone without Tourette Syndrome in order to have the same opportunities for employment.	44%
3.	Employers treat employees with Tourette Syndrome the same as any other employee.	29%

4.	Employers meet their legal obligations to employees with Tourette Syndrome.	27%
5.	Employers are receptive to hiring people with Tourette Syndrome	17%
6.	Employers help people with Tourette Syndrome stay on the job.	11%
Social Inclusion/Alienation		
1.	I feel my co-workers have left me out of social and work related activities because of my Tourette Syndrome.	27%

A total of 39% of respondents indicated that they had experienced some type of discrimination in the workplace. Table 3 shows the specific types of discrimination that the respondents experienced according to Equal Employment Opportunity Commission guidelines. The most common type of discrimination was inappropriate jokes or insults in work or break settings (75% incidence rate). This was followed by failure by employer to provide reasonable accommodation on the job (54%), unfair rules related to working conditions, job environment or employment privileges (54%), receiving excessive supervision or oversight on the job (49%), restriction to a certain type of job (49%), and excessive or inappropriate discipline (46%). In addition, 40% of respondents reported unlawful firing or termination due to their Tourettes.

Table 3 | Types of discrimination encountered in the workplace.

	Applies to Me (%)
Inappropriate jokes or insults in work or break settings	75%
Failure by employer to provide reasonable accommodation on the job	54%
Unfair rules related to working conditions, job environment or employment privileges	54%
Receiving excessive supervision or oversight on the job	49%
Restriction to a certain type of job	49%
Excessive or inappropriate discipline	46%
Assignment to inappropriate job tasks or duties	44%
Unlawful firing or termination	40%
Threats or verbal abuse in work or break settings	37%
Denial or delay of promotion	37%
Refusal to hire due to Tourette Syndrome	36%
Different or harsher standards of performance	33%
Discriminatory (i.e., unfair and illegal) questions during the job interview	31%
Physical intimidation or abuse in work or break settings	26%
Unfair use of written or oral tests for employment screening purposes	26%
Unfair compensation and wages	25%
Restricted access to general use or recreational areas	23%
Unfair layoff practices	21%
Denial of seniority rights and privileges	18%
Unfair pre-employment medical screening	8%

Conclusion: This study shows that Canadian adults with Tourette Syndrome face challenges and discrimination in the workplace. Clinicians, policy decision makers and employers can use this information to better structure workplace environments and create programs to help those with TS succeed on the job.

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A randomized pilot waitlist-controlled trial of voice over internet protocol-delivered behavior therapy for youth with chronic tic disorders

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Introduction and objectives: Comprehensive behavioral intervention for tics (CBIT) is efficacious for youth with chronic tic disorders (CTDs) (Piacentini et al., 2010). However, treatment access is limited due to insufficient trained treatment providers, and perceived financial and time burdens associated with commuting to providers (Woods et al., 2010). Traditional videoconferencing is an efficacious means of connecting children with CTDs directly with treatment providers (Himle et al., 2012), but may be limited due to a lack of portability, and restricted accessibility. A promising alternative is voice over internet protocol (VoIP) or web-based videoconferencing, allowing for remote, real-time delivery of treatment to patients' homes. However, little is known about the effectiveness of VoIP treatment for CTDs. Therefore the present study examined the preliminary efficacy, feasibility and acceptability of VoIP-delivered CBIT (CBIT-VoIP).

Methods: Twenty children (ages 8–17) with CTDs participated in a randomized, waitlist-controlled trial of CBIT-VoIP. A screening evaluation, including an initial home visit, and a VoIP assessment by an independent evaluator was conducted. A baseline assessment was performed 7–10 days later to confirm ratings. Participants were then randomized to CBIT-VoIP or waitlist for a 10-week period, with a post-treatment VoIP assessment following. The primary outcome measure was pre- to post-treatment change in clinician-rated tic severity (Yale Global Tic Severity Scale). The secondary outcome measure was rate of clinical responder status, assessed using the Clinical Global Impressions – Improvement Scale, with ratings of "very much improved" or "much improved" indicating positive response to treatment. Parent-reported tic severity (Parent Tic Questionnaire), parent- and child-report satisfaction, and child-report therapeutic alliance ratings were also obtained. Intention-to-treat analyses with the last observation carried forward were performed.

Results and discussion: At post-treatment, significantly greater reductions in clinician-rated tic severity, [$F(1, 18) = 3.05$, $p < 0.05$, partial $?^2 = 0.15$], were found in CBIT-VoIP relative to the waitlist-control group, with a percent reduction similar to that found in the original pediatric CBIT trial (Piacentini et al., 2010). Significantly greater reductions in parent-reported tic severity, [$F(1, 18) = 6.37$, $p < 0.05$, partial $?^2 = 0.26$] were found in CBIT-VoIP relative to waitlist. One-third ($N = 4$) of those in CBIT-VoIP were considered treatment responders, which is a lower response rate relative to that (53%) reported in the original trial (Piacentini et al., 2010). Treatment satisfaction and therapeutic alliance ratings were high, and the attrition rate was low, at 5%. Technological difficulties occurred during 38% of treatment sessions.

Conclusion: CBIT can be delivered via VoIP with high patient satisfaction, using readily available, low-cost equipment. CBIT-VoIP was generally feasible to implement, with some challenges due to audio and visual disruptions. Modifications are suggested to enhance CBIT-VoIP delivery.

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Investigation of the effect of aripiprazole and riluzole on the behavioural and neurochemical profile of Tourette syndrome juvenile rat model and control animals – an MR spectroscopy study

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Introduction and objectives: Pharmacologic intervention in Tourette syndrome (TS) is suggested when tics are distressing and/or interfere with function. According to the different guidelines available (Roessner et al., 2011; Pringsheim et al., 2012) neuroleptics and alpha-2 agonists are mainly used as first-choice drugs. Beside their efficacy on tics, such interventions show severe side effects. New treatments are required. Aripiprazole has been found to be effective on tic-management and to have a well tolerated side effect profile (Davies et al., 2006; Kawohl et al., 2009). Dopamine (DA) metabolism dysfunctions are well documented in TS, but imaging research data and genetic studies give definite hints that other neurotransmitters take part to tic generation: histamine, serotonin, norepinephrine, glutamate and GABA (Buse et al., 2013; Udvardi et 2013). The glutamate and DA metabolism are closely connected. The glutamatergic modulator Riluzole exerts neuroprotection from glutamate excito-toxicity both *in vitro* and *in vivo* and clinical trials are ongoing (Risterucci et al., 2006). We want to compare the effect of neuroleptics (Aripiprazole) and glutamatergic drugs (Riluzole) on the behaviour and cerebral glutamate metabolism during development using MR spectroscopy (MRS) on control rats and a TS rat model (Bronfeld et al., 2013). The recently published model clearly satisfies the *face validity* criterion in modelling TS. This study will also provide information regarding its *predictive validity*.

Methods: WKY rats and spontaneous hypertensive rats (SHR), an ADHD animal model, undergo instrastriatal bicuculline (GABA antagonist) microinjection that induce an acute tic-session. Control animals are sham-operated. MRS scan are acquired in each group (ARI 1.5 mg/kg; RILU 6 mg/kg and vehicle) from PND 35 to 50, covering the evolving period from childhood to sexual maturation in rats.

Results and discussion: Preliminary spectra acquisition and glutamate, GABA, glutamine and lactate absolute quantification in the left dorsal striatum and prefrontal cortex are on-going. Preliminary behavioural data treated groups compared to vehicle and sham operated are presented. No differences in the body weight in any of the treated groups compared to the vehicle are observed after 15 days of sub-chronic treatment with both drugs.

Conclusion: Differences in the spectra acquired on the treated groups give hints on the mechanism in which drug classical treatments, such as neuroleptics (Aripiprazole) compared to new treatments, such as glutamatergic drugs (Riluzole) induce changes in the brain metabolism during its developmental stages.

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Magnetic resonance spectroscopy (MRS) in Tourette syndrome patients

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Introduction and objectives: Tourette syndrome (TS) is a childhood-onset neuropsychiatric disorder characterized by the presence of multiple motor and vocal tics, commonly associated with ADHD (Attention Deficit and Hyperactivity Disease) and OCD (Obsessive Compulsive Disorders) (XXXX, 0000). TS pathophysiology involves disrupted neuronal circuits and neurotransmitter dysfunction involving the frontostriatal circuit but also limbic and associative circuits that are likely to arise during the brain connection reshape during neurodevelopment. Neuroimaging techniques are applied in TS to assess anatomical, functional and neurochemical aspect of the disorder. Non-invasive techniques like MRS can detect differences in metabolic patterns between grey and white matter. In 2005 the first study using proton magnetic resonance spectroscopy was conducted on TS patients and matched control and since then only a few publications followed (DeVito et al., 2005). They point their attention on GABA and glutamate metabolism, but also choline, creatine, *N*-acetylaspartate and myoinositol (Draper et al., 2014; Tinaz et al., 2014). The investigated brain regions involve frontal cortex, caudate nucleus, putamen, and thalamus. Results are insufficient and contraversive. The absolute quantification of metabolite at low concentration provides information about cell membrane turnover during myelination and cell proliferation, brain energy level, antioxidative defense and osmoregulation. Longitudinal studies are needed in order to correlate neurochemical profile and clinical aspects of the disease such as tic severity and drug resistance.

Methods: We performed a narrative review since meta-analysis and systematic reviews are not possible due to the insufficient published data. Key words searched in the MEDLINE and EMBASE database are: "Tourette + spectroscopy," "Tourette + MRS," "tic + disorder + spectroscopy."

Results and discussion: Over eight neuroimaging clinical trials now on going in TS, only two performed MRS to define differences in metabolites level in TS children and adult patients compared to control. The most recent was concluded in February 2015, but results are not yet available (www.clinicaltrials.gov).

Conclusion: The brain undergoes several structural and metabolic changes during the transition from childhood to adolescence and adulthood. MR spectroscopy provides an *in vivo* snapshot of those neurochemical alterations and represents a non-invasive tool able to track neurologic and/or neuropsychiatric disorders progression over time.

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Tic attacks: panic disorder in Tourette syndrome?

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Introduction and objectives: Tic attacks in Tourette syndrome (TS) have been retrospectively described as distinct bouts of severe, continuous, non-suppressible and disabling tics lasting from 15 min to several hours (Collicott et al., 2013). Tic attacks are referred to in on-line TS communities (http://www.touretteshero.com/2013/11/13/a-step-forward-whatever-you-call-it/). However, there are no reports in the literature that consider the clinical management of these episodes, or whether typical behavioural treatments that increase internal attentional focus to premonitory urges would be effective. The current study sought to contribute to these discussions by reporting the clinical profiles of six children with tic attacks and the treatment of one of these cases.

Methods: Six children presented to a specialist movement disorder clinic (TANDeM) with tic-like movements lasting from 1 to 3 h (mean age tic attack onset = 12 years 5 months, SD = 2.5). Videos are available. All presented with tics and anxiety, four met diagnostic criteria for OCD, four for social anxiety, one for pica and two for depression.

JT was a 15-year-old male. The onset of tic attack episodes was at 13 years, with episodes occurring in school and managed by attending A&E. JT had experienced 14 episodes. Previous medical investigations were normal (EEG, CT, MRI, toxicology, gastroenterology) and pharmacological management was unsuccessful (Aripiprazole). JT was referred for cognitive behavioural therapy (CBT). Questionnaires were administered to assess tics, mood and anxiety.

Results and discussion: JT attended 13 sessions of CBT. Therapy components included external attention training, thought challenging, behavioural experiments, image restructuring and relapse prevention. The clinical formulation is presented in Figure 1. JT reported a relationship between physiological sensations/tic urges, thoughts/worries about having tic attacks and behavioural responses (e.g., body scanning for tics, planning escape route from social situations). A strong internal focus of attention was reported (80%), with the misinterpretation of anxiety symptoms (e.g., elevated heart rate, sweating) triggering tic attacks.

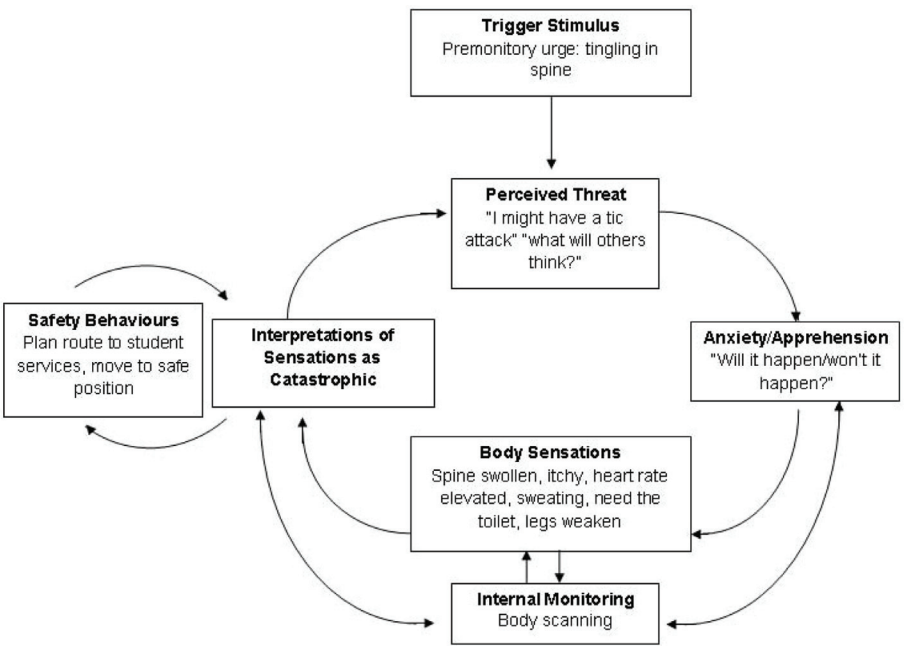

Figure 1 : Clinical formulation of tic attacks

JT experienced two tic attacks during treatment. They were said to be "out of the blue," but associated with increased attention to tics, intrusive images of being filmed and negative thoughts about tics being "uncontrollable." JT's Head of Year described the movements in these attacks as "less severe," lasting a shorter duration (20 min) and with JT

remaining more externally engaged (e.g., eyes open, talking, walking unaided). No attacks were reported after session 8. Pre- and post-treatment questionnaire scores are presented in Table 1.

Table 1: Pre- and post-treatment questionnaire scores

Measure	Pre-treatment Score	Post-treatment Score
MOVES		
Total score	22	12
GTSQ-oL		
Impairment in Quality of Life	43	9
PHQ9		
Depression (clinical cut-off 10)	9	4
GAD-7		
Anxiehy(clinical cut-off 10)	15	8
CHOCI		
Total OCD score	34	24

The current case indicates that tic attacks may be triggered and maintained by psychological factors, especially an internal focus of attention, the misinterpretation of anxiety symptoms as premonitory urges and engagement in safety behaviours to avoid social embarrassment. Tic attacks responded to the types of CBT strategies used to manage panic and social phobia, with typical tic treatments that increase internal attentional focus likely to exacerbate attacks.

Conclusion: This case challenges the view that tic attacks reflect extended bouts of tics. Instead, it is proposed that the tic-like movements experienced during tic attacks may be functional, with tic attacks reflecting episodes of panic for individuals with TS.

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Mindfulness group for children with Tourette syndrome – a pilot study

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Introduction and objectives: Behavioural therapies for children and adults with Tourette syndrome/chronic tic disorders (TS/CTD) focus on tic reduction though awareness and competing response training. Recently, Reese et al. (2014) reported beneficial effects of mindfulness-based stress reduction on tics for adults with TS/CTD. This third wave behavioural therapy has been gaining empirical support across a range of conditions (Chiesa and Serretti, 2011), with mindful parenting interventions being increasingly used in paediatrics (Duncan et al., 2009). No studies have reported on the use of mindfulness approaches in children with CTD/TS. In this pilot study we sought to develop and evaluate the delivery of mindfulness program for children with TS/CTD and their parents.

Methods: Families attending the TANDeM clinic were invited to take part in the (b) mindfulness programme for children and a parallel mindful parenting group. The intervention consisted of 8 weekly 1 h sessions, with content modified to address tics.

Nine children with TS/CTD enrolled in the group (6 boys, 3 girls; mean age = 11 years, range = 8–14 years). Children and parents completed questionnaires within 1 month pre- and post-treatment to assess tics (MOVES), anxiety and mood (RCADS, RCADS-P), quality of life (GTS-QoL) and mindfulness (IMPQ, CAM).

Results and discussion: Four children completed the course (>7 sessions attended). Non-completers were excluded from analysis. Group averages and standard deviations are reported.

Anxiety and depression: On the RCADS-P, parental anxiety and depression scores were clinically significant pre-treatment (*T*-score = 75, SD = 12.73; *T*-score = 80, SD = 34.64 respectively) and normal post-treatment (*T*-score = 55, SD = 4.24; *T*-score = 63, SD = 6.36, respectively). Children's pre- and post-treatment scores on the RCADS were normal.

Tics and QoL: On the MOVES, children's pre-treatment tic scores were at clinical cut-off (score = 10, SD = 2.12), with post-treatment scores in the normal range (score = 7, SD = 0). On the GTS-QoL, children's scores indicated improvements in QoL following treatment (pre-treatment score = 29, SD = 1.41; post-treatment score = 17, SD = 2.82, respectively).

Mindfulness: On the CAM, children reported reduced mindfulness following treatment (pre-treatment score = 57.5, SD = 7.78; post-treatment score = 49, SD = 2.83). On the IMP, scores indicate no change in parenting mindfulness (pre-treatment score = 37, SD = 4.16; post-treatment score = 38, SD = 3.51).

Overall, children reported clinically meaningful improvements in tics and QoL following the 8-week mindfulness group, whilst parents reported clinically meaningful improvements in their child's anxiety and mood. The data are consistent with Reece et al. (2014), who reported improvements in tic severity and impairment for adults with TS/CTD following a mindfulness-based intervention.

Conclusion: To date, little consideration has been given to the application of third wave behavioural interventions for individuals with TS/CTD. The current findings provide preliminary support that mindfulness techniques may have a positive effect on tics and co-morbid anxiety and depression for children with TS/CTD. Larger controlled trials exploring the efficacy of mindfulness approaches for children and adults with tic disorders are required.

Acknowledgement

Roald Dahl's Marvellous Children's Charity.

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Intense imagery movements: is there more to motor stereotypies than meets the eye?

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Introduction and objectives: There is growing interest in stereotyped movement disorders, however, little consideration has been given to underlying cognitive mechanisms. Robinson et al. (2014) have recently identified a subgroup of children who present with stereotyped movements in the context of conscious engagement in acts of imagery or imagination, termed intense imagery movements (IIM). The defining feature is that all children report conscious engagement in acts of imagery or imagination, with stereotyped movements occurring as a secondary response over which they had limited control. The objectives of this study are to report preliminary neuropsychological findings for children with IIMs, to inform clinical management and theoretical understanding.

Methods: Detailed neuropsychological assessments were conducted for four children with IIM (3 boys, 1 girl; mean age 9 years 4 months). Children were referred for these assessments due to parental concerns regarding the impact of IIM on learning and social functioning.

Children were tested individually and administered standardized tests of intellectual functioning (WISC-IV), memory (CMS stories, NEPSY-II Memory for Designs), attention (NEPSY-II Auditory Attention and Response Set), executive functioning (TEA-Ch Creature Counting, NEPSY-II Concept Formation) and expressive language (WIAT-II Oral Expression). Parents completed questionnaires to assess mood (SDQ), behaviour (Conners-3), social-communication (SCQ), sensory profiles (SSP) and motor functioning (DCDQ). Clinicians completed a measure to assess stereotypies (SSS).

Results and discussion: Neuropsychological test scores are in Table 1. Three children (cases 1, 2 and 3) had verbal and perceptual intellectual abilities above average, whilst one (case 4) had verbal intellectual abilities below average, but normal perceptual reasoning. All children exhibited weaknesses in processing speed and sustained attention, whilst memory, concept formation and oral expression abilities were in line (or better) than IQ.

Parental questionnaire scores are in Table 2. Sensory processing difficulties were reported for three of the children, two had features of developmental co-ordination disorder and one (case 4) was identified as presenting with features of ASD. Stereotypes were identified as having a variable impact of day to day functioning.

Overall, across all cases discrepant intellectual profiles were reported, with good perceptual reasoning and memory abilities, but weaknesses in sustained attention and processing speed. The children's good memory and perceptual reasoning skills appear likely to support their ability to recall or imagine real life objects or pictures, with verbal abilities contributing to the complexity of stories or scripts around the images. Attention and executive functioning skills are likely to orchestrate these complex imagery processes, with weaker attention and inhibition skills inline with parental reports of children becoming more easily distracted by their own thoughts to have difficulties disengaging from episodes of IIM.

Conclusion: We tentatively propose that for children with IIM, engagement in episodes of intense imagination may serve the purpose of increasing cognitive stimulation, whilst stereotyped movements may provide a secondary sensory gain that facilitates or enhances the imagery events.

Table 1 | Standardised tests scores (scaled scores and error percentiles)

Domain (Test)	Case 1	Case 2	Case 3	Case 4
	Female	Male	Male	Male
	7 years 5 mths	8 years 7 mths	9 years 11 mths	11 years 6 mths
Verbal Memory Stories				
Immediate Recall	10	12	12	9
Delayed Recall	10	13	12	10
Delayed Recognition	14	9	14	12
Visuo-spatial Memory (Memory for Designs)				
Immediate: Content	12	11	14	9
Immediate: Design	11	9	14	13
Delayed Content	11	10	14	9
Delayed: Design	13	11	13	13
Sustained Attention (Auditory Attention)				
Total Correct	10	8	9	7
Commission Errors	2-5 percentile	2-5 percentile	2-5 percentile	51-75 percentile
Switching and Inhibition (Response Set)				
Total Correct	13	11	8	7
Commission Errors	51-15 percentile	57-75 percentile	6-10 percentile	>75 percentile
Attentional Control (Creature Counting)				
Total Correct	12	12	13	8
Timing Score (seconds)	8	7	12	4
Concept Formation (Category Sorting)				
Total Correct	13	9	11	4
Expressive Language (Oral Expression)				
Total Correct*	18	14	14	5

Scaled scores: band from 1 to 19, the average is 10 and 68 % of people score between 7 and 13
Percentiles: the percentage of scores in the frequency distribution that are the same or lower
*Standard scores have been concerted to scaled scores for ease of comparison

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The experiences of diagnosis for adults with Tourette syndrome

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Introduction and objectives: Tourette syndrome (TS) is a clinical diagnosis, meaning that there is not a specific test for the disorder, it has been noted to be difficult to diagnose with research showing delays in the diagnosis of TS (Wand et al., 1992; Freeman et al., 2000; Shilon et al., 2008). Cultural factors may also play a role in the social perceptions of TS (Mathews et al., 2001; Zinner et al., 2012).

Very little research has looked at the subjective experience of having TS and as far as the author is aware there are no studies which have investigated the reasons for obtaining a diagnosis. The aim of this research was to find out the experiences of those with Tourette syndrome (TS), specifically what having a diagnosis means and whether it this is useful for patients with TS.

Methods: Nine adult participants with TS were recruited through Tourettes action. Semi-structured interviews were completed either face to face or via telephone and the resulting transcripts were analysed using thematic analysis.

Results and discussion: There were three main themes resulting from the data: diagnosis helps with coping, dissatisfaction with the diagnostic process and feelings about TS and diagnosis. Participants felt that diagnosis was useful for self-understanding, accessing support and having an explanation for the behaviour, but expressed disappointment with many stages of the diagnosis. Most felt that clinicians lacked proper knowledge of TS and that there was minimal support after diagnosis. Many had experienced stigma as a result of their TS, and felt that TS was misunderstood and misrepresented by the media. Participants felt that TS played a role in their character or identity.

Conclusion: The findings suggest that a diagnosis of TS is useful for those with the disorder but indicate a gap in services for those with TS post diagnosis. Results indicate that increased knowledge of TS for clinicians and improved support post-diagnosis will be useful in continuing to help those with TS to cope with the disorder.

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Disclosures

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Fewer than 2 h of daily centromedian thalamic stimulation produces significant tic reduction in Tourette syndrome

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Introduction and objectives: Based on the paroxysmal nature of tics in TS, we hypothesized that treatment via a scheduled, as opposed to a continuous DBS approach, might be better suited for TS. Scheduled stimulation is a form of open loop DBS, whereby stimulation is delivered in an a priori determined manner rather than from a responsive, or closed-loop approach (Okun et al., 2013). Still, it may be viewed on the continuum as moving closer to a responsive approach in that (1) it delivers less cumulative stimulation than continuous DBS and (2) it temporally limits the stimulation provided to more pathological states (i.e., periods of greater tic activity) and reduces duty cycles (e.g., turning off the device at night). One advantage to scheduled therapy is that the duty cycle can be personalized to an individual patient's needs. Other advantages are a potential decrease in stimulation-related side effects and an increased battery life.

Objective: To evaluate outcomes at 2-year follow-up for personalized, scheduled deep brain stimulation (DBS) applied to Tourette syndrome (TS).

Methods: A small NIH-sponsored clinical trials planning study of bilateral centromedian thalamic (CM) DBS was performed. The study utilized a scheduled duty cycle strategy for DBS as opposed to the standard continuous DBS paradigm. Five TS patients with implanted DBS were enrolled. One patient was lost to follow-up after month 18. Baseline vs. 24-month outcomes were collected and analyzed. Active participants at 24-month follow-up were categorized into full responders (>40% improvement in YGTSS or MRTRS total score from baseline), partial responders (25–40% improvement in YGTSS or MRTRS total score) or non-responders (

Results and discussion: 3 of the 4-patients (75%) reached full responder criteria and had a mean stimulation time of 1.85 h per day. The YGTSS total scores for the 4-patients improved by 10, 46, 58, and 17% at 24-month evaluation; MRTRS total scores improved by 21, 79, 81, and 44%. Combining the patients into a single cohort revealed significant improvements in the YGTSS impairment [mean (SD) change, −10 (7.37); P = 0.034]; MRTRS total [−7.6 (5.64); P = 0.02], MRTRS phonic tics per minute [−1.4 (1.25); P = 0.0046], MRTRS phonic tic severity s[−2 (1.57); P = 0.047], Quality of Life Assessment Schedule total score [−15.25 (9.22); P = 0.045], and General Health domain of the Short Form 36 [17.8 (9.2); P = 0.012].

Conclusion: DBS of the CM thalamus in a scheduled paradigm was effective in reducing tics. Full responders achieved the positive effect with fewer than 2 h of DBS per day. There were important differences noted between the YGTSS and MRTRS which may impact future study designs, with the MRTRS potentially providing a better objective measure for scheduled stimulation.

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Disclosures

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Parenthood and Tourette syndrome: the interface between attachment, stress, emotion regulation and the child's experience of self

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Introduction and objectives: Tourette syndrome (TS) and its common comorbidities can be a major impediment to normal childhood development. Previous research demonstrated that TS is associated with significantly compromised quality of life, in part due to the decrease in ability to deal with stress (Robertson, 2012; Cavanna et al., 2013). However, the mechanisms through which these pathological developments occur have so far remained unidentified.

Our work focuses on the parents' substantial influence on their child's childhood onset chronic syndrome. We identify two interrelated areas that have not been addressed yet regarding TS: the characteristics of parent-child relationship and the significance of self-representation and emotion-regulation abilities. In the study of these areas we employ insights from Attachment Theory (Bowlby, 1988), which proved a useful framework for understanding parent-child relationships under conditions of stress in other life settings (Mikulincer and Shaver, 2007; Berant et al., 2008).

Methods: Assessing certain psychological characteristics of the parents as well as the child, using semi structured interview, self report questionnaires and mother child interaction. We illustrate the relations between parental attachment styles, care giving, experience of parental functioning, emotion-regulation abilities, the ability to confront the syndrome and the child's psychological functioning.

Results and discussion: Our results illustrate significant relations between parental attachment styles, care giving, experience of parental functioning, emotion-regulation abilities and the ability to confront the syndrome. We show the connections of these characteristics with the child's self-experience, emotion regulation functioning and TS and comorbidities indexes.

Conclusion: Our findings pave the way for designing new psychological interventions for the parents as well as the child. We will demonstrate key aspects of suggested new interventions and discuss the potential of these interventions for handling common comorbidities, promoting benefits from existing "tic target" treatments (Verdellen et al., 2011; Murphy et al., 2013) and securing the healthy mental development of the child with TS (Cohen and Leckman, 2006).

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Hypnagogic dreams in patients with Gilles de la Tourette syndrome: three case reports

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Introduction and objectives: Sleep problems in Gilles de la Tourette syndrome (GTS) patients have been described, e.g., frequent awakenings, sleep stage changes, increased sleep latency (Drake et al., 1992; Maquet et al., 1996; Cohrs et al., 2001; Kostanecka-Endress et al., 2003). Dopamine, histamine, serotonin are involved role in sleep and awakeness states as well as in GTS etiopathology (Nir and Tononi, 2010; Blum et al., 2014; Shan et al., 2015).

In healthy people, dreams occur predominantly but not exclusively during the rapid eye movement sleep (Nir and Tononi, 2010). The dreams are probably related to the limbic system's activity changes (Schwartz and Maquet, 2002).

Hypnagogic state includes mostly visual and sensory events that can sometimes accompany the physiologic sleep. The exact cause of hypnagogic dreams is not known. It is thought, that they occur during the stage I or beginning of stage II of the sleep. During the normal slow sleep a strong deactivation of basal ganglia is seen, probably due to the frontal and thalamic influence on the neuronal synchronous oscillations (Maquet et al., 2000; Peigneux, 2014), which could be changed in GTS.

Up to now, hypnagogic dreams have never been mentioned in relation with GTS.

Methods: Case presentation: a 12-years-old female patient with confirmed GTS described very frequent dreams while falling asleep. Dreams included figures, people, complex actions, and logical sequences, being undistinguishable of any other dreams occurring during the night time. We specifically interrogated another 3 patients with GTS about their dreams and 2 of them (22-year-old male and 29-year-old female) reported frequent hypnagogic dreams.

Results and discussion: The 12-year-old patient had a mild Attention Deficit/Hyperactivity Disorder. She was medicated with valproic acid for her tics (subsequently switched to sultiam). Her Multiple Sleep Latency Test showed no abnormalities (sleep latency 16 min).

The other 2 patients had no neurological comorbidities and were not medicated.

The Epworth Sleepiness Scale score was normal in all the patients. None of them reported confusional arousals, sleep walking or other sleep disorders. Particularly, their hypnagogic symptoms did not fit the criteria for narcolepsy or sleep hallucinations. The patients had no depression, anxiety, and no caffeine abuse.

Conclusion: The prevalence of hypnagogic dreams in GTS is not clear, but their common occurrence in some patients underlines the existent changes in sleep structure of persons with tics. The deeper exploration of the sleep particularities in GTS and their neural correlates could contribute to the better understanding of GTS pathophysiology.

Patient, nr		Age (yo)	Dreams while falling asleep*	Treatment	Comorbidities	Multiple Sleep Latency Test
1.	Female	12	Frequent	Valproic acid, subsequently switched to sultiam	Mild Attention Deficit/Hyperactivity Disorder	Normal (16min)
2.	Male	22	Frequent	-	-	-
3.	Female	29	Frequent	-	-	-

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OCD alone versus tic related OCD in children and adolescents. Comparison of OC symptoms' content and comorbidities

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Introduction and objectives: DSM V has introduced in the diagnostic criteria for Obsessive-Compulsive Disorder (OCD) the specifier "tic related" (American Psychiatric Association, 2013). This identifies a large group of individuals – with OCD onset in childhood – which have a Tic Disorder (TD) and tend to show different themes of OC symptoms, comorbidity and course (Gomes de Alvarenga et al., 2012).

Our aim was to characterize the content of OC symptoms and psychiatric comorbidities in a large group of children and adolescents showing OCD and/or TD.

Methods: We evaluated subjects presenting to the Department of Child and Adolescent Neuropsychiatry of University of Rome La Sapienza in the last 2 years requiring their first psychiatric consultation for the presence of OC and/or tic symptoms.

Clinical diagnosis was assessed by the K-SADS-PL; clinical symptoms were evaluated by the CY-BOCS and the YGTSS; cognitive profiles were assessed by the WISC-III; moreover, self-report (CDI, MASC, STAI-C, PSS-10) and proxy-report questionnaires (CBCL, CPRS-R, *P*-PSS-10) were administered.

For this report we have excluded subjects with a low cognitive profile (IQ < 70) or an ongoing pharmacological treatment.

Results and discussion: We examined 82 subjects (65 males, 17 females), aged between 6.6 and 17.6 years (mean: 12). Twenty-three subjects showed OCD alone, three OCD + ADHD, thirteen TD + OCD, two OCD + TD + ADHD, twenty-five TD alone and fifteen TD + ADHD. In this group, other comorbid diagnosis were uncommon and scattered, including Separation Anxiety Disorder (12), Oppositional Defiant Disorder (6), Generalized Anxiety Disorder (5), Specific Phobia (5) and Mood Disorder (5).

Patients with OCD alone in comparison with those with OCD + TS showed a broader variety of OC symptoms, even if any specific content of obsessions or compulsions couldn't be identified. Moreover, they obtain significantly higher scores at the CDI questionnaire.

In the whole sample however, patients showing only OC symptoms have significantly lower problems of attention and hyperactivity in comparison with both OCD + TD and TD alone subjects.

Finally, beyond the clinical diagnosis, in 72% of our sample tic and OC symptoms coexist.

Conclusion: With the caution due to the limited number of subjects and the possible referral bias, our data shows that in children and adolescents there is a large overlapping between tic, OC and ADHD symptoms. Patients with tic related OCD seem to have more externalizing symptoms, whereas internalizing symptoms are prevalent in patients with OCD alone. There is not a clear-cut difference between the two subgroups in the content of obsessions and compulsions.

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Disclosures

No conflicts of interest to disclosure.

The motor complexity of symptoms influences the event-related brain potentials of patients with persistent tic disorder

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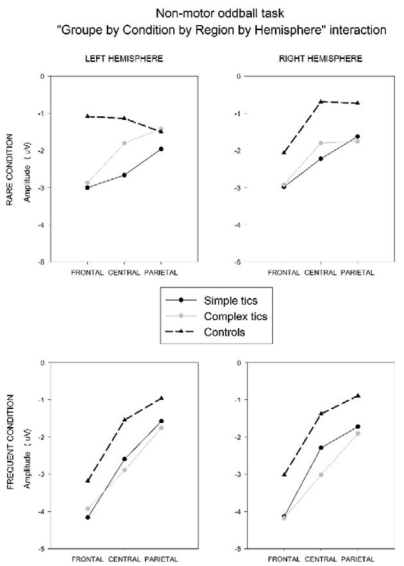
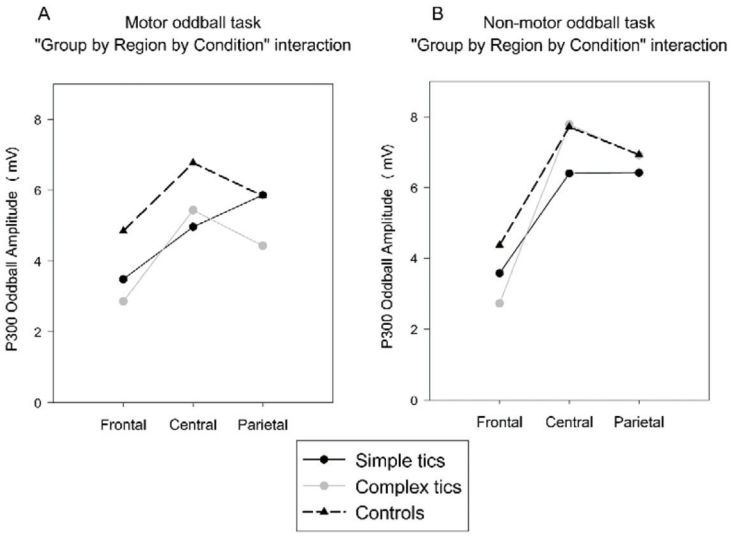
Introduction and objectives: Tic disorders, like Tourette syndrome, are neurodevelopmental conditions afflicting up to 3% (Knight et al., 2012) of children worldwide. Moreover, about 50% (Leckman et al., 1998) of patients will continue to experience symptoms through adulthood, hence lowering their quality of life and increasing the social stigma. In both children and adults, tic disorders' evaluation and treatment are still hindered by the large amount of conflicting neurobiological data. In fact, motor functions and cognitive processes (especially inhibition and memory) might be strongly affected in tic patients. The inclusion of patients presenting distinct phenotypes might explain this large heterogeneity in studies. Four main phenotypes were identified by factor analyses (Grados and Mathews, 2009): (i) tics with attention deficit disorder, (ii) tics with obsessive-compulsive disorder, (iii) simple tics (e.g., eye twitches), and (iv) complex tics (e.g., knee jerks). Several studies have shown functional brain differences between patients from the first two groups. However, very few have investigated the possible brain dissimilarities between patients predominantly exhibiting simple versus complex tics. Hence, we aimed to evaluate the impact of tic complexity on cognitive processes, more precisely inhibition and memory's context updating, using Event-Related Potentials (ERP) techniques.

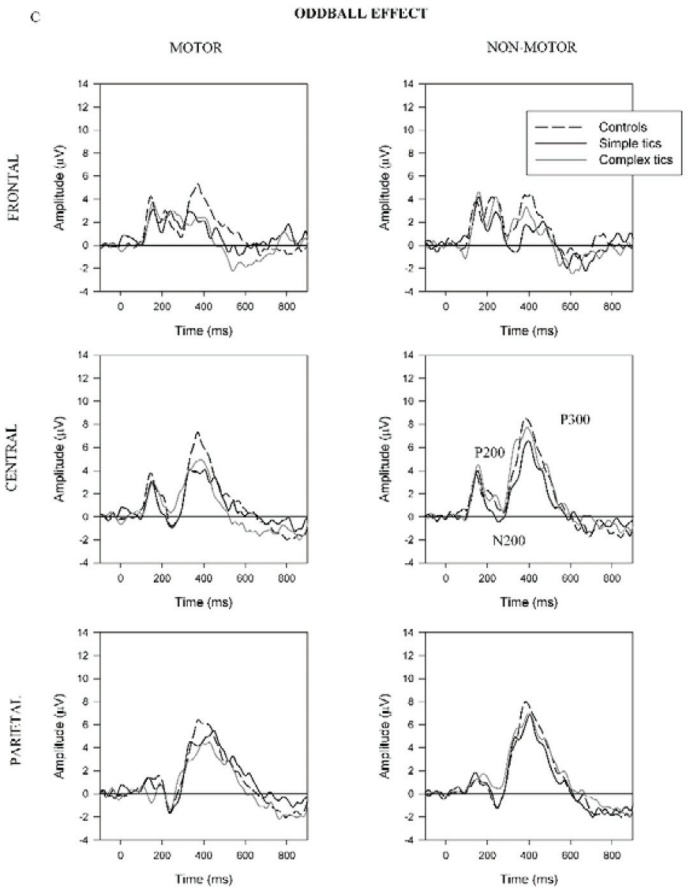


Methods: ERPs were recorded and compared (MANOVAs) in 12 patients exhibiting simple tics, 12 patients showing complex tics and a control group of 15 healthy adults matched to patients on age, sex and intelligence. Tic complexity was assessed using the YGTSS. To measure inhibition (N200) and context updating (P300) processes, participants completed two classical oddball tasks. Tasks were identical, except for the type of response, in order to further investigate the role of cognitive load on inhibition and memory. The motor task required participants to press different buttons when they perceived frequent ("O") and rare ("X") stimuli (i.e., with 80 and 20% probabilities of occurrence, respectively). In the non-motor task, participants had to mentally count the number of rare stimuli.

Results and discussion: Both groups of tic patients showed an enhanced N200 in the frontal region during the non-motor task [$F(2.36) = 5.7$, p

Conclusion: Our results suggest that tic complexity and tasks' cognitive load can modulate tic patients' neural mechanisms. Conflicting results found in previous studies with children and adults might have been confounded by these variables. Our study underlines the impact of clinical symptoms on cognitive assessment.


A
Motor oddball task
"Group by Region by Condition" interaction
B
Non-motor oddball task
"Group by Region by Condition" interaction
P300 Oddball Amplitude (mV)
Frontal
Central
Parietal
Simple tics
Complex tics
Controls


C
ODDBALL EFFECT
MOTOR
NON-MOTOR
FRONTAL
CENTRAL
PARIETAL
Amplitude (μV)
Time (ms)
Controls
Simple tics
Complex tics
P200
P300
N200

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Disclosures

The authors report no conflict of interest.

Psychometric properties of the Yale Global Tic Severity Scales

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Introduction and objectives: The clinician-rated Yale Global Tic Severity Scale (YGTSS) is considered the best available measure for evaluating the treatment effects on tics in children and adults with Tourette syndrome (TS) (Leckman et al., 1989). Prior studies indicate that the YGTSS is reliable, valid and sensitive to change. Few studies have evaluated the psychometric properties in a large sample. We used data from two randomized clinical trials of Comprehensive Behavioral Intervention for Tics (CBIT) to examine the psychometric properties of the YGTSS (Piacentini et al., 2010; Wilhelm et al., 2013).

Methods: The first study included 126 children (age 9–17 years). The second study included 122 subjects (age 16–69 years). These trials used the same study design and outcome measures. YGTSS raters were trained to reliability in the same manner by the same experts. The YGTSS includes: Motor Tic score (range 0–25), Phonic Tic score (range 0–25), Total Tic score (sum of Motor and Phonic scores) and an Impairment score (0–50). The Motor and Phonic subscales each have five dimensions: Number, Frequency, Intensity, Complexity, and Interference, each is scored from 0 to 5. The Impairment score reflects the overall impact of TS on the subject. In clinical trials, the Total Tic score is most commonly employed as the primary outcome measure. This analysis focused on the Total Tic score and the component Motor and Phonic subscales. First, we examined the distribution of the Motor and Phonic subscales and the Total Tic score. Next we examined internal consistency. Six raters have scored 40 randomly selected video recordings from various time points in the CBIT trials. Inter-rater reliability will be calculated from these ratings using intraclass correlation.

Results and discussion: The combined sample (177 males, 71 females) had a mean age of 21.5 ± 13.9. Based on parent or self-report, 77 subjects were on stable tic medication at baseline: antipsychotics (n = 32), alpha-2 agonists (n = 44); anticonvulsants (n = 5), benzodiazepine (n = 4). The mean scores on the YGTSS were 23.8 ± 6.40) for the Total Tic score; 14.9 ± 3.52 and 8.9 ± 5.02 for Motor and Phonic Tic scores, respectively. The Motor and Phonic Frequency scores were skewed to the higher scores (4 and 5). By contrast, Motor Intensity, Complexity and Interference showed normal distributions. The Phonic Complexity dimension was skewed to lower scores. The internal consistency for the Total Tic score was 0.78. In keeping with rightward skewing, the Motor Frequency score showed the lowest correlation with the Motor Total.

Conclusion: The YGTSS has established reliability and validity. The Frequency dimension in the Motor and Phonic subscales need refinement to use the full range of the scale.

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Quality of life and pharmacotherapy in adult and young patients with Tourette syndrome

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Introduction and objectives: Few studies have used standardized and specific instruments to assess the health-related quality of life (HR-QOL) in Tourette Syndrome (TS). Moreover, there are no studies focusing on pharmacotherapy and HR-QOL.

We compared the clinical characteristics and the HR-QOL in youth and adult TS patients with and without pharmacological treatment.

Methods: We recruited 114 TS patients (94 males; age range 7–64 years). All patients were evaluated by a trained neuropsychiatrist in TS and completed the Gilles de la Tourette Syndrome-Quality of Life scale (GTS-QoL). Clinical features of TS and severity of tics were assessed by specific clinical rating such as the Yale Global Tic Severity Scale (YGTSS) and Tourette's Syndrome Diagnostic Confidence Index (TS-DCI). Results were compared between patients with and without pharmacological treatment. We also divided the sample in two groups (<18 years and >18 years), and the same comparison was performed both between groups (young patients vs. adult patients) and within each group.

Results and discussion: Forty-four TS patients (38.6%) were on pharmacotherapy (30 = monotherapy; 16 = dualtherapy). The scores on TS-DCI were significantly higher for patients on pharmacotherapy ($p = 0.04$). No significant differences were found in HR-QOL between youth and adult TS patients with pharmacotherapy. However, young patients on pharmacotherapy showed lower scores on HR-QOL scale compared with peers without treatment ($p = 0.04$).

Conclusion: The treatment for patients with TS is based on a broad diagnostic process. The use of drugs for treatment of TS, especially in children, must be done only when tic interfere with daily life, cause subjective discomfort and cause sustained social/emotional problems. Indeed, our results showed that young TS patients for whom it was necessary a pharmacotherapy are those who had worse HR-QOL. Moreover, patients with pharmachoterapy showed higher severity of TS' symptoms.

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Somatosensory sensitivity discrimination in Tourette syndrome

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Introduction and objectives: Sensory hypersensitivity to external stimuli is commonly described among patients with neurodevelopmental disorders such as autism (Kern et al., 2006) and Gilles de la Tourette syndrome (TS) (Cohen and Leckman, 1992; Belluscio et al., 2011). Hypersensitivity in TS is reported for all sensory modalities, including touch. Belluscio et al. (2011) report that 80% of their TS sample experienced heightened sensory sensitivity and yet their tactile threshold at the site of an active tic was not different to that exhibited by healthy volunteers. Further investigation into sensory thresholds among TS patients is needed and the underlying pathophysiological cause for tactile hypersensitivity is relatively unknown.

Methods: Thirty children and adolescents [16 TS; 14 controls (CS)] participated in our study. Somatosensory stimulation was applied to both the palm of the hand and the cheek using Jamar monofilaments in a 2AFC paradigm by the method of limits. Sensory thresholds [maximum likelihood estimates (75% threshold)] were determined for each participant, in addition to D′ (signal detectability), Beta (response style) and C (criterion location). Patients also completed the PUTS questionnaire and Yale Global Tic Severity Scale. Comparison between groups was done using a one-tailed independent-samples *t*-test.

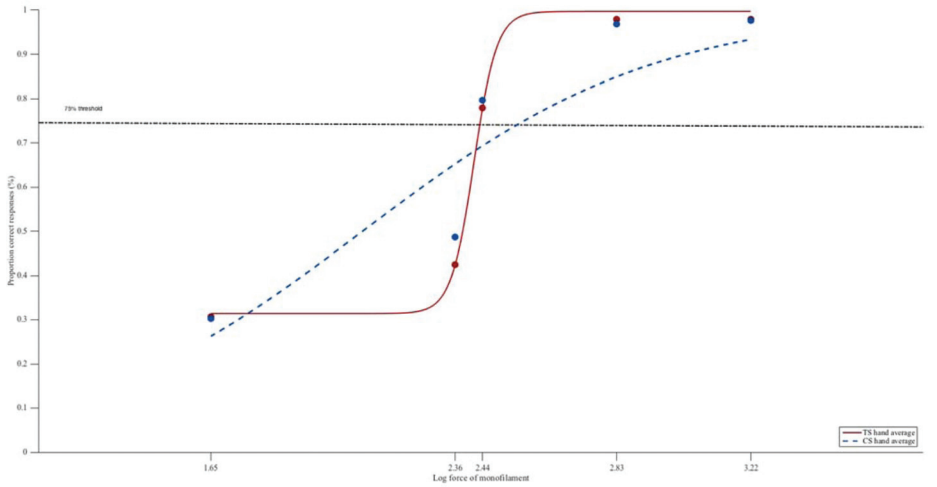
Results and discussion: Participant demographics are shown in Table 1. Groups did not differ with regard to age ($p > 0.05$) nor IQ measured using the Wechsler's Abbreviated Scale of Intelligence ($p > 0.05$). Our TS sample was considered to be mildly to moderately impaired with respect to tics (Yale Impairment Rating mean: 14.4). Sensitivity thresholds did not differ between groups in the cheek condition ($M_{TS} = 2.2$, $M_{CS} = 2.0$, $p > 0.05$). There was a non-significant trend for TS patients to have higher Beta values compared with controls ($M_{TS} = 1.6$, $M_{CS} = 1.1$, $p = 0.06$). On the hand however, TS patients showed marginally higher sensory threshold compared to controls ($M_{TS} = 2.5$, $M_{CS} = 2.4$, $p = 0.07$). TS patients also displayed significantly higher Beta values than controls ($M_{TS} = 2.5$, $M_{CS} = 1.8$, p

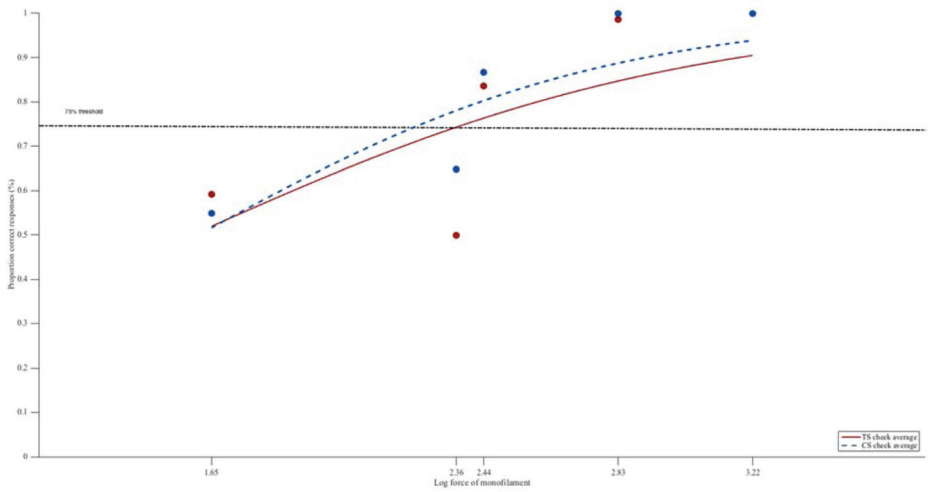
Table 1 | Group characteristics

	TS (n = 16)		CS (n = 14)	*p*-value
Age ± SD (range)	14.3 ± 2.3	(10.3 – 19.1)	14.6 ± 2.9 (10.2 – 19.6)	0.732
WASI scores ± SD (range)	113.3 ± 12.4	(89.0 – 135.0)	115.1 ± 8.5 (97.0 – 129.0)	0.659
PUTS scores ± SD (range)	19.4 ± 5.5	(10.0 – 28.0)		
Yale Global Severity score ± SD (range)	41.6 ± 19.4	(13.0 – 71.0)		
Yale Impairment seale	14.4 ± 10.6	(0.0 – 30.0)		
Yale motor tics seale	15,4 ± 4,7	(9.0 – 23.0)		
Yale phonic tics scale	11.8 ± 5.9	(0.0 – 21.0)		

TS - Tourette syndrome; CS - Control subjects. WASI - Wechsler Abbreviated Scale of Intelligence. PUTS - Premonitory Urge for Tics Scale

Conclusion: Results show that TS patients do not display hypersensitivity to detect a faint stimuli compared to healthy controls on two distinct locations, contrary to their self-reported hypersensitivity to external stimuli (Belluscio et al., 2011). We do however show that TS patients are more inclined to respond "no" when a signal is presented. This is confirmed in our study by evaluating participants response style. It is noteworthy that in both conditions, TS patients have higher signal detectability values, indicative of higher sensitivity to detect a target. Nonetheless, no statistical significance was found. At current, data collection is still on going. Results presented here are part of a larger investigation into the neural basis of TS. The relationship between behavioural and self-report data will be related to structural (VBM, DTI) and functional connectivity measures of regions implicated in sensorimotor processing including sensorimotor cortices, the insular cortex and striatum.





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Impact of tic symptoms persistence on quality of life and self-esteem in teens with Tourette syndrome

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Introduction and objectives: Two out of three patients with Tourette syndrome (TS) achieve remission of tic symptoms within late adolescence (Gorman et al., 2010; Ludolph et al., 2012).

In young adulthood, patients with persistent symptoms give up this hope and become aware of the never-ending course of their disorder. This study aims to evaluate the impact of tic symptoms and psychiatric comorbidities on Health-Related Quality of Life and self-esteem in teens who do not experience remission of TS.

Methods: 24 TS patients, aged 16–19 (7 females), who do not experience remission of tic symptoms, have been recruited in the Department of Pediatrics and Child Neuropsychiatry at Sapienza-University of Rome, between October 2013 and February 2015.

Each patient has been assessed clinically and was asked to fill in questionnaires about perceived Health-Related Quality of Life (GTS-QOL, a questionnaire tailored on Tourette patients; Cavanna et al., 2013), self-esteem (TMA-Test Multidimensionale dell'Autostima) and major comorbid psychiatric disorders (BDI-II, MASC, STAI-Y, YSR 11–18, PUTS, STAXI-2). Tic severity was assessed through YGTSS. Obsessions and compulsions were assessed through Y-BOCS.

STATA Statistical Software (Release 8.1) was used for statistical analyses; non parametric variance analysis (Kruskal-Wallis Test) was performed.

Results and discussion: Highest scores on GTS-QOL, index of a reduced Quality of Life, were found in the Psychological and Cognitive domains of the scale. High scores were found to be associated both to State and to Trait anxiety symptoms. Moreover, the severity of the premonitory urges seems to impair patients' perceived Quality of Life.

Highest scores on TMA, index of a better self-esteem, were found in the Familiar domain of the scale. Lower scores were found in the School and Emotional domains. Low scores on TMA were associated to the presence of comorbid disorders (OCD, ADHD) and to anxious/depressed symptoms. Neither high scores on GTS-QOL nor low scores on TMA were associated to tic symptoms severity.

Conclusion: The presence of comorbid anxiety and/or depression impairs Health-Related Quality of Life and Self-Esteem even more than the well-known comorbidities (OCD, ADHD). A greater attention needs to be paid to highlight and manage the presence of these symptoms in TS teens.

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Disclosures

No conflict of interest.

Tourette's syndrome: a pilot study for the discontinuance of a movement disorder

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Introduction and objectives: Correct growth of the face, head, and neck require that 4 factors must occur simultaneously. The (Enlow and Hans, 1996) base of the cranium must grow properly (Noback and Demarest, 2004) the maxillo-naso complex must develop downward and forward in conjunction with the cranium (Brodal, 2004) the maxilla must grow to its fullest potential vertically, sagittally, and transversely and (Walkup et al., 2006) the airway must develop unobstructed. If there is a mal-relationship between any of these areas of development complications from the temporomandibular joint may result as an attempt to compensate for developmental discrepancies. When the maxilla and mandible do not achieve their genetic potential in length, width, or vertical position, the effects are seen in mal-relationships and dysfunctions in the patient's tissues. The TMJ relationship may then become compromised when this occurs as it compensates for the discrepancies in normal growth and development.

Methods: Six patients with movement disorders are presented ages 7, 25, 36, 36, 40 and 52: 5 patients where given a diagnosis of tic disorder and/or Tourette's syndrome by their neurologist. Each patient was then given a comprehensive temporomandibular joint examination and a history taken. In all cases there where no medicines given, no medicines were being taken for any length of time, minimum of 1 month, and all patients except one were video taped and that one patient gave a statement to their condition and results. Follow up was at 3, 6, and 12 month intervals.

Results and discussion: The retrodiscal tissues originate from the distal portion of the glenoid fossa. This tissue contains nerve fibers of the auriculotemporal nerve, cranial nerve V, an afferent branch of the trigeminal nerve. Constant stimulation of CN V may then result in the stimulation of CN's V, VII, IX, X, via crossover interneurons and other neural elements in the reticular formation. All of these nerves are intimately involved with movement disorders. We find that chronic noxious input via the auriculotemporal nerve causes reflex reactions with CN's V, VII, IX, and X via the crossover pathways at various segmental levels within the spinal cord. Eliminating chronic noxious input into the central nervous system, the procedure utilizing the Neurocranio Vertical Distractor relieves movement disorders associated with T.S. With the procedure, we artificially remove the neuritis by placing the mandible into its proper anatomical position, downward and forward in relation to the patient's cranial base. Consequently, there is no constant conduction of noxious impulses into the subnucleus caudalis and therefore no constant irritation of CN's V, VII, IX, and X including the reticular formation which are some of the nerves implicated in the movement disorder associated with TS. All patients showed a total discontinuance of their movement disorders immediately. All patients stated that their breathing was improved and better. All patients stated they did not have the *urge* to tic or make their involuntary movements.

Conclusion: This procedure eliminates the chronic noxious stimuli into the CNS via the auriculotemporal nerve, by decreasing and/or eliminating the movement disorder involving tics and the associated co-morbid conditions. With this procedure, we remove the neuritis (constant stimulation and irritation of the auriculotemporal nerve which produces the premonitory urge and place the mandible into its proper anatomical position downward and forward in relation to the patient's cranial base). Therefore, there will not be a constant impulse into the subnucleus caudalis and therefore no constant irritation of CN V, VII, IX, and X, with the associated RF neurons which are the nerves implicated in the movement disorder.

Disclosures

There are no conflicts of interest for the authors.

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Rapid response behavioral triage for tics (RR-BTT): a quality improvement clinical case series

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Introduction and objectives: The Comprehensive Behavioral Intervention for Tics (CBIT) is front-line, well-established behavioral treatment for Tourette syndrome (TS) (Piacentini et al., 2010; Wilhelm et al., 2012). CBIT is traditionally conducted in 8 sessions over 10 weeks. The 10-week time-commitment to achieve efficacy when compared to medication effects remains a significant limitation. Condensed cognitive-behavioral treatments for childhood anxiety disorders have been evaluated (Angelosante et al., 2009; Santucci et al., 2009; Crawley et al., 2013). A 1-week Intensive Outpatient (IOP) CBIT treatment showed promise in two youth (Angelosante et al., 2009). However, there is a need for a treatment option that can be delivered across the TS severity spectrum considering the context of the managed health care environment. The primary purpose of this quality improvement study was to preliminarily evaluate the effectiveness and durability of an accelerated Rapid Response Behavioral Triage for Tics (RR-BTT) adaptation of CBIT, which consisted of 8 (~60 min) sessions delivered over 2 consecutive weeks.

Methods: A retrospective chart review was conducted of consecutive, clinically referred patients (n = 6) ages 11–17 years with TS who chose to complete RR-BTT during a summer holiday from school. Session content was adapted from the CBIT treatment manual. Tic severity was evaluated via the Yale Global Tic Severity Scale (YGTSS). Treatment response was determined via the Clinical Global Impression – Improvement (CGI-I) scale. Assessments were completed at pre-treatment baseline, 1-week mid-treatment (session 5), 2-week post-treatment (session 8), and 1-month following acute treatment.

Table 1 | YGTSS Total Scores, Severity Scores, Change Ratios, CGI-S, and CGI-I Scores by Session

	YGTSS Total Score (Severity Score)				YGTSS Total Change Ratio[a] (Severity Change Ratio[c])			CGI-S Scores[b] (CGI-I Scores[c])			CGI-I follow-up descriptor
	Baseline (Session 1)	Mid-treatment (Session 5)	Post-treatment (Session 8)	1-month follow-up	Mid-treatment (Session 5)	Post-treatment (Session 8)	1-month follow-up	Baseline (Session 1)	Post-treatment (Session 8)	1-month follow-up	1-month follow-up
Patient 1	78 (38)	65 (35)	64 (34)	52 (27)	-17% (-8%)	-18% (-11%)	-33% (-29%)	6	5 (4)	5 (4)	No change
Patient 2	30 (10)	17 (7)	17 (9)	19 (9)	-43% (-30%)	-43% (-10%)	-37% (-10%)	4	2 (2)	1 (1)	Very much improved
Patient 3	29 (19)	8 (8)	1 (1)	13 (8)	-72% (58%)	-100% (-95%)	-55% (-58%)	3	1 (1)	2 (2)	Much improved
Patient 4	60 (30)	58 (29)	44 (24)	45 (25)	-3% (-5%)	-27% (-20%)	-25% (-17%)	6	4 (3)	4 (3)	Minimally improved
Patient 5	34 (19)	23 (13)	11 (11)	7 (7)	-32% (-32%)	-68% (-42%)	-79% (-63%)	3	2 (1)	1 (1)	Very much improved
Patient 6	61 (31)	43 (28)	21 (16)	24 (14)	-30% (-10%)	-66% (-48%)	-61% (-55%)	4	3 (2)	2 (1)	Much improved
Total Mean (Severity Mean)	48.7 (24.5)	35.8** (19.9*)	26.3** (15.8*)	26.7** (15.0**)	-27% (-24%)	-54% (-38%)	-48% (-39%)	4.3	2.8 (2.2)	2.5 (2.0)	
Total SD (Severity SD)	20.5 (10.3)	23.3 (12.0)	24.0 (12.2)	18.0 (12.6)	24.0 (26.9)	30.3 (43.1)	20.3 (40.5)	1.4	1.5 (1.2)	1.6 (1.3)	

[a]Rate of decline from baseline (Session 1).

*Significantly different from baseline (Session 1) at $p < .05$.

**Significantly different from baseline (Session 1) at $p < .01$.

[b]1 = Normal, not at all ill; 2 = Borderline mentally ill; 3 = Mildly ill; 4 = Moderately ill; 5 = Markedly ill; 6 = Severely ill; 7 = Among the most extremely ill patients

[c]Functional improvement since baseline assessment; 1 = Very much improved; 2 = Much improved; 3 = Minimally improved; 4 = No change; 5 = Minimally worse; 6 = Much worse; 7 = Very much worse.

Results and discussion: A mean 19% reduction in tic severity a 1-week mid-treatment [$t(5) = 3.25$, $p < 0.05$] with a 35% decrease in tic severity at 2-week post-treatment [$t(5) = 3.23$, $p < 0.05$], which was maintained (39%) at the 1-month post-treatment follow-up [$t(5) = 4.12$, $p < 0.01$] (see Table 1). Individual patient outcomes are displayed (see Table 2). At both post-treatment and 1-month follow-up, 4 participants (67%) were considered much or very much improved (CGI-I ? 2), 1 (17%) was minimally improved (CGI-I = 3), and 1 (17%) experienced no improvement (CGI-I = 4).

Conclusion: Quality improvement results preliminary demonstrated that the RR-BTT adaptation of CBIT yielded similar reductions in tic severity and response rate in just 20% of the time required for traditional CBIT. RR-BTT can be delivered during in-patient or partial hospitalizations for acute patients, during school breaks for less acute to limit risks to academic functioning.

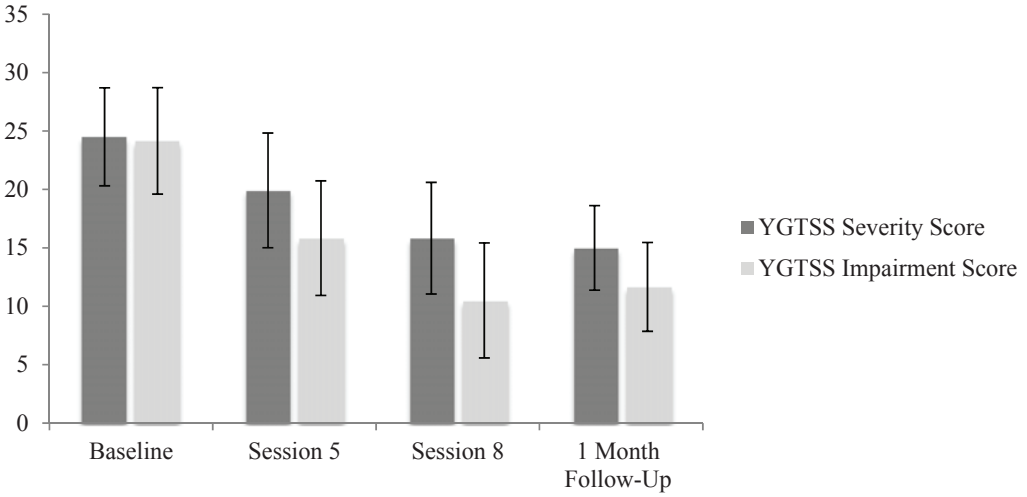

Figure 1 | Mean YGTSS scores by session.

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Patterned changes in urge ratings with tic suppression in youth with chronic tic disorders

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Introduction and objectives: Emerging behavioral models of chronic tic disorder (CTD) suggest that tics result from basal ganglia dysfunction and may be exacerbated as tics serve to alleviate unpleasant premonitory urges (Himle et al., 2007; Specht et al., 2013). These "urge reduction" or "negative reinforcement" models also hypothesize that initial tic suppression produces more intense urges, while prolonged tic suppression results in habituation to urges (Himle et al., 2007; Verdellen et al., 2008; Specht et al., 2013). Prior investigations have yielded inconsistent findings regarding the relationship between urge severity and tic suppression, despite common methodologies (Himle et al., 2007; Specht et al., 2013; Capriotti et al., 2014). The current study examined patterns of urge ratings across periods of tic completion and tic suppression for individual participants (Specht et al., 2013). Based on a review of previous studies (Himle et al., 2007; Capriotti et al., 2012) in which participants demonstrated varied patterns in urge ratings, we hypothesized that data aggregation obscures distinct and meaningful patterns of change in urge ratings and may account for inconsistencies in the literature.

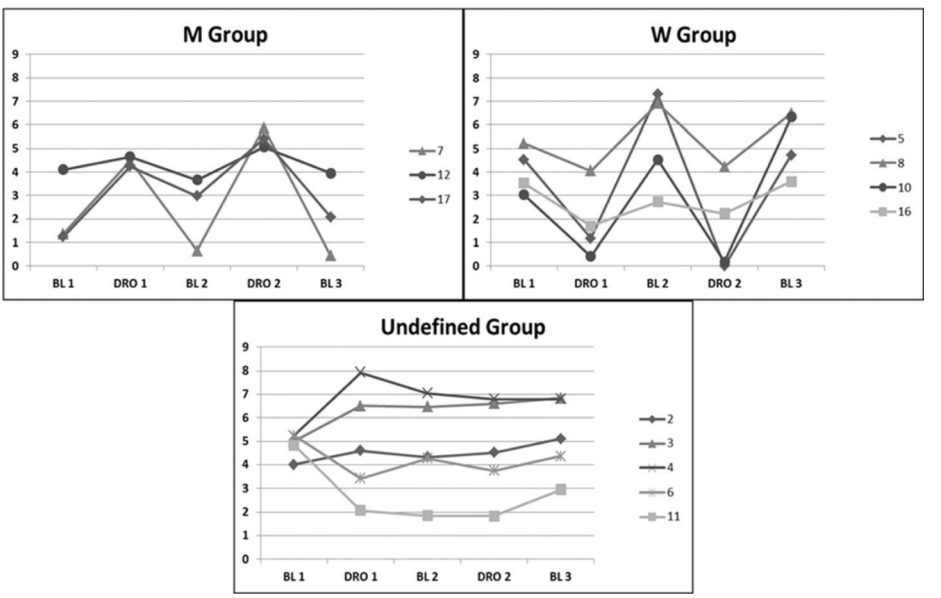
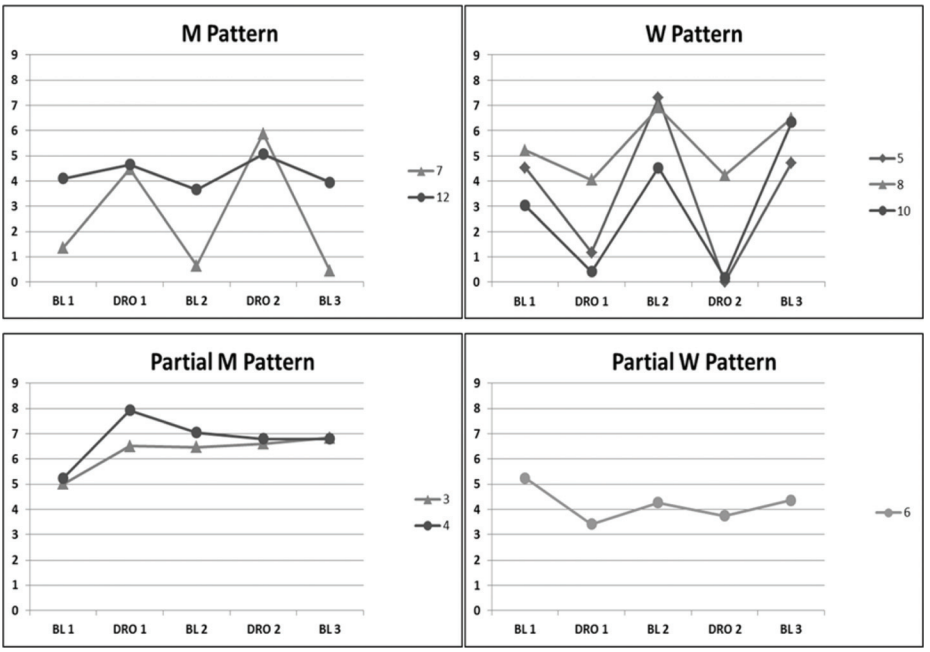
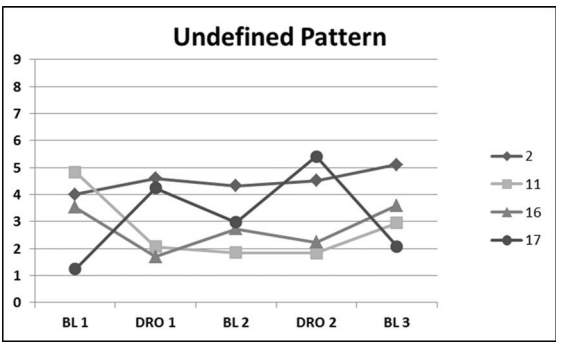


Figure 1 | Each participant's line graph, grouped by patterrs as determined by visual inspection.





Methods: Participants ($n = 12$) included children with moderate-to-marked tic severity and noticeable premonitory urges. Tic frequencies and urge ratings were obtained at 15 and 10-s intervals, respectively, across an alternating sequence of three 10 min tic-freely and two 40 min tic-suppression conditions. Patterns were established using a two-step approach. First, participants were grouped based on similar patterns established through visual inspection of their urge ratings averaged across condition segments. Then, the conservative dual criterion (CDC; Fisher et al., 2006) method was used to more objectively analyze observed patterns.

Results and discussion: Five distinct patterns of urge rating change emerged, suggesting data aggregation may obscure meaningful patterns in the urge-tic relationship when tics are completed versus suppressed. We hypothesize that developmental factors may underlie these individual differences. However, additional research with less stringent eligibility criteria and larger sample sizes is needed to validate our results and to further investigate the possibility of underlying developmental considerations.

Conclusion: The relationship between urges and tics is much more complex than previously theorized. Investigations that rely on global assessments of urge and tic severity and/or assume uniformity when aggregating participant data may obscure meaningful differences in the urge-tic relationship.

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The impact of OCD and ADHD symptomatology on parenting stress in children with Tourette syndrome and in typically developing children

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Introduction and objectives: An overwhelming majority (~90%) of children with Tourette syndrome (TS) have at least one comorbid neuropsychiatric diagnosis, most commonly attention deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD) (Freeman et al., 2002). ADHD and OCD symptoms may have a greater impact on quality of life for patients as they are highly negatively correlated with pediatric quality of life, while tic severity is not (Eddy et al., 2011). Beyond impacting the child, neurodevelopmental disorders are known to negatively affect parents (Cooper et al., 2003). While there is increased caregiver burden in TS (Wilkinson et al., 2002), to our knowledge no prior studies have investigated the impact of TS and its comorbid conditions on parenting stress. We sought to determine the impact of tic severity in children with TS on parenting stress and the impact of comorbid ADHD and OCD symptomatology on parenting stress in both children with TS and typically developing children.

Methods: Seventy-four children (mean age 11.8 years, 13 female) with a clinical diagnosis of TS or Chronic Tic Disorder, together the TS group, and 48 unaffected children (mean age 11.6, 17 female) were included. Standardized measures of parenting stress, tics severity, and OCD and ADHD symptomatology were administered.

Group differences between TS and typically developing participants were examined using chi-square and one-way analysis of variance. Pearson correlations for pairwise relationships between parent stress, tic severity, OCD and ADHD symptomatology were conducted separately in the TS and typically developing groups. Multivariate linear regression models were used for hypothesis testing with the parenting stress variable as the outcome variable.

Results and discussion: The TS group had higher levels of parenting stress compared to typically developing controls. Parenting stress and ADHD measures in both groups were correlated, while OCD symptoms correlated with only the TS group's parenting stress. In the TS group, parenting stress was not significantly correlated with tic severity (Table 1), suggesting that comorbid symptomatology, but not tic severity per se, is associated with parenting stress. This point was confirmed in multivariate regression models in the TS group, as higher severity of ADHD and OCD independently contributed to higher levels of parenting stress, but not tic severity (Table 2). In the typically developing controls, subthreshold ADHD symptoms were also significantly and independently associated with higher levels of parenting stress (Table 2), further suggesting some generalizability of parenting stress with childhood neurodevelopmental symptomatology.

Table 1 | Correlation Coefficients between Parenting Stress and ADHD, OCD, Tic Severities Measures in TS and Typically Developing Participants.

	TS participants (n = 74)		**Typically developing participants (n = 48)**	
Correlation between	**Pearson *r***	**p Value**	**Pearson *r***	**p Value**
ADHD-PSI	0.571	<0.001	0.489	<0.001
OCD-PSI	0.358	0.002	0.314	0.029
Tics-PSI	0.176	0.133	N/A	N/A
ADHD-OCD	0.292	0.012	0.044	0.769
ADHD-Tics	0.324	0.005	N/A	N/A
OCD-Tics	0.316	0.006	N/A	N/A

Table 2 | Association of Clinical and Demographic Variables with Parenting Stress in TS and Typically Developing Participants.

	TS participants (n = 74)			Typically developing participants (n = 48)		
Independent Variable	**Coefficients**	***t***	**p Value**	**Coefficients**	***t***	**p Value**
ADHD	0.718	5.13	<0.001	0.958	2.69	0.011
OCD	5.595	2.00	0.049	15.54	1.18	0.246
Tics	0.037	0.15	0.882	N/A	N/A	N/A
Medication	-3.615	-1.11	0.270	N/A	N/A	N/A
Age	1.057	1.65	0.104	-0.339	-0.57	0.573
IQ	0.201	1.43	0.158	0.263	2.15	0.039
Sex	0.684	0.20	0.844	0.428	0.14	0.891
Ethnicity	-3.196	-0.49	0.623	9.254	1.53	0.134
Household income	-1.252	-0.64	0.521	-1.072	-0.86	0.398

Conclusion: The results indicate two possible clinical conclusions: first, treating tics in isolation will likely not address the elevated parenting stress reported by parents of children with TS. Second, the negative impact of ADHD symptoms on parenting stress extends to a typically developing pediatric population. Clinicians may want to address comorbid ADHD and OCD symptoms in addition to tic severity, even in children without formal comorbid diagnoses.

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Disclosures

The authors declare no conflicts of interest.

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Moderators of response to comprehensive behavioral intervention for tics

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Introduction and objectives: Data from two randomized controlled trials of Comprehensive Behavioral Intervention for Tics (CBIT) were combined to examine baseline characteristics of treatment response (Piacentini et al., 2010; Wilhelm et al., 2012). Presence of tic-suppressing medication, co-occurring psychiatric disorders, demographic (age, gender, family functioning) and clinical characteristics (age of tic onset, current tic severity, tic complexity, premonitory urges, and treatment expectancy) were tested as possible moderators.

Methods: The child and adult studies of CBIT were conducted by a 6-site consortium in the United States and utilized the same design, treatments, and outcomes to enable analysis in a combined sample. Subjects received 8 sessions of CBIT (Woods et al., 2008) or 8 sessions of education about tics and supportive therapy over 10 weeks. Primary outcomes were the Yale Global Tic Severity Scale and the Clinical Global Impression-Improvement Scale score assigned by an independent evaluator. Co-occurring psychiatric disorders were assessed by structured interviews conducted by experienced clinicians. Parents of child subjects provided information about the types and purposes of past and current psychiatric medication. Adult subjects provided similar information. An experienced clinician at each site reviewed this information to confirm the presence and stability of tic suppressing medications. Data analyses were conducted using the mixed-model repeated measures analysis adjusted for baseline tic scores.

Results and discussion: The combined sample included 248 subjects (177 males and 71 females), mean age (SD) = 21.5 (13.9) years, range 9–69 years. 67 subjects met criteria for co-occurring ADHD; 46 for OCD and 73 for anxiety disorder. There were 77 subjects on any tic medication and of these, 32 were on antipsychotics, 44 on alpha-2 agonists for tics, 5 on mood stabilizers for tics, and 4 on benzodiazepine for tics. Because separate drug categories were two small to be included in moderator analysis, we created a dichotomous variable to code the presence of any concomitant tic suppressing medication. There was a significant treatment by tic medication interaction $F(1, 222) = 7.07$, $p = 0.008$. The Cohen's d effect size on the YGTSS total tic severity score was 1.02 for subjects not receiving tic medication and 0.27 for subjects receiving medication. Presence of co-occurring psychiatric disorders, age, gender, family functioning and treatment expectancy did not moderate response to CBIT.

Treatment group randomization was stratified by tic medication status for both the child and adult treatment studies because we reasoned that the presence of concomitant medication might affect response to behavior therapy for tics. However, we were agnostic to the positive or negative direction of this effect. It is possible that being on a tic medication is an indicator of greater tic severity. It is also possible that there might be a certain amount of improvement after which further reduction is unlikely. This could be thought of as a floor effect where those on medication have reached the limit to which their tics can be improved and additional treatment with CBIT did not have room to move tic reduction further.

Conclusion: CBIT is an effective treatment for tics in children and adults with TS. Presence of co-occurring disorders did not moderate response to CBIT. Subjects receiving medication for tics showed a lower level of tic reduction with CBIT.

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Disclosures

None.

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Does OCD symptoms have an impact on tics, depressive and anxiety symptoms in a cognitive behavioural treatment for Tourette's syndrome?

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Introduction and objectives: *Tourette's syndrome (TS)* is a tic disorder characterized by multiple motor tics and at least one vocal tic, which lasted for over a year (American Psychiatric Association, 2003). Obsessive-compulsive disorder (OCD) is a common disorder that's often affect people with TS and is concomitant in about 20–60% of cases (Leckman et al., 1989; Piacentini et al., 2007; Scharf et al., 2012; Mol Debes, 2013; XXXX, 0000a,b). This comorbidity increases social dysfunction, behavioural, academic and decreases the quality of life of sufferers (Scharf et al., 2012, XXXX, 0000a). Also, Mol Debes (2013) reports that when OCD is present in persons with TS, tics, depressive and anxiety symptoms are more severe. The purpose of this study is to compare two groups of participants with TS, one with obsessive-compulsive symptoms and one without in the evolution of tics, depressive symptoms and anxiety symptoms during treatment. These research questions will be raised: Does the severity of obsessive-compulsive, depressive and anxiety symptoms could have an impact on the reduction of tics during a cognitive-behavioural treatment for Tourette syndrome in pre-test and post-test?

Methods: Participants were recruited at the Centre de recherche de l'Institut Universitaire en Santé Mentale de Montréal in a data base of the Centre d'étude sur les troubles obsessionnels-compulsifs et les tics directed by Kieron O'Connor, Marc Lavoie and Frederic Aardema. The research project aimed was to reduce tics in people with chronic tics, Tourette's syndrome and habits disorder. The award of the Yale Global Tic Severity of Scale (YGTSS) (Piacentini et al., 2007) confirmed the primary diagnosis, chronicity and severity of Tourette's syndrome.

To meet the objective of this study, two groups of participants were formed. The first group of participants presents a primary diagnosis of Tourette syndrome without obsessive-compulsive symptoms. The second group of participants presents a primary diagnosis of Tourette's syndrome with obsessive-compulsive symptoms. The YGTSS are administered at the beginning of therapy (pre-test) and at the end of therapy (post-test) to evaluate the reduction in the symptoms of tic disorders. Questionnaires measuring obsessive-compulsive, depressive and anxiety symptoms were administered to participants in the pre-test and post-test. We will compare the results of the two groups on these measures throughout the therapy.

Results and discussion: Using pre-test and post-test results, an Anova was done with both groups on the results of these questionnaires to know if the severity of obsessive-compulsive symptoms had an impact on tics, depressive and anxiety symptoms. The results in pre-test showed that group of Tourette's syndrome with obsessive-compulsive symptoms had more depressive and anxiety symptoms. However, there was no difference between the two groups on the tics severity. At the post-test, results showed a significant diminution of tics symptoms for the two groups of participants. The group of Tourette's syndrome with obsessive-compulsive symptoms had a smaller decrease in tics symptoms in comparison with the group of Tourette's syndrome only.

Conclusion: This study aims is to evaluate whether obsessive-compulsive, depressive and anxiety symptoms can influence the reduction of tics during treatment in people with TS. So, it should be considered in the development of potential treatments for Tourette's syndrome these three moderating variables and if there is a therapeutic component specifically addressing obsessive-compulsive, depressive and anxiety symptoms.

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Non-pharmacological treatment of tics in children with Tourette syndrome

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Introduction and objectives: Behavioural therapy has been shown to be an effective treatment of tics (Piacentini et al., 2010). In this study, we plan to examine several non-pharmacological treatments of tics in patients with Tourette syndrome, namely exposure and response prevention (ER), habit reversal (HR), and ketogenic diet. Ketogenic diet is a well-known non-pharmacological treatment for drug-resistant epilepsy in childhood and it is described to have an influence on the dopamine metabolism (Dahlin et al., 2012). We will develop a new instrument to measure urge, which will be easier to use than the existing instrument and can be helpful in predicting treatment response.

We hypothesize that the non-pharmacological treatments:

1. Will reduce tic severity, measured by Yale Global Tics Severity Scale (YGTSS)
2. Will reduces comorbid symptoms, measured by Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) and ADHD-Rating Scale (ADHD-RS)
3. Will improve Quality of Life, measured by PedsQl
4. Are equally effective compared to pharmacological treatment and more effective than psychoeducation

Furthermore, we hypothesize, that:

5. MRI scans show diminished striatal activity after exposure response prevention compared to healthy controls
6. The new instrument to measure urge can be used to predict the treatment response

Methods: All patients with Tourette syndrome and tics that require treatment will be included in the project from March 2015. The patients receiving behavioural therapy (either ER or HR) will be examined with YGTSS, PedsQl, urge, ADHD-RS and CY-BOCS before treatment and thereafter monthly. We will randomize 20 patients to be examined with cerebral MRI scans (volumetric analyses, functional MRI, and diffusion tensor imaging) and compare them with 20 healthy controls. The patients receiving ketogenic diet will, after an observation period of 2 months, be randomized in a group that starts diet immediately and a group that starts diet after 3 months.

From September 2015 we plan to randomize 20 patients to exposure response prevention, 20 patients to pharmacological treatment, 20 patients to psychoeducation. All the included patients in this study will undergo MRI scans.

International and national questionnaires will be used to develop the new instrument to measure urge.

Results and discussion: With this study we want to examine several non-pharmalogical treatments for Tourette syndrome and assess the effect on tics severity, comorbid disorders and quality of life. We will examine the effect non-pharmacological treatments have on the cortico-striato-thalamo-cortical pathways and thereby reveal neural correlates of these treatments. With the new instrument to measure urge, we hope to be able to predict treatment response and thereby optimize treatment choice for the individual patient.

Conclusion: If the non-pharmacological treatment of tics turns out to be clinically effective, we will offer this treatment option to all the patients with Tourette syndrome in our Tourette clinic.

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Modified Atkins diet might be a new treatment option for patients with severe tics

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Introduction and objectives: The Modified Atkins Diet (MAD) is a variant of the classic ketogenic diet (KD). The diet consists of high fat, adequate protein and minimal carbohydrates, which forces the body (and brain) to use ketone bodies as energy source instead of glucose. KD is an effective non-pharmacological treatment for pharmacoresistant childhood epilepsy.

KD might be neuroprotective and has shown to affect several systems in the brain, as the dopamine system (Dahlin et al., 2012). Since a disturbance in dopamine is a pathophysiological factor in Tourette syndrome (TS), MAD might be effective in reducing tics.

Methods: A prospective study with intention-to-treat design. We include a clinical cohort of children, aged five to seventeen years, with TS and severe tics. After an observation period of two months, the patients are randomized blindly into two groups. The first group will start MAD immediately and the other group will start after three-six months. Tic severity, comorbidities, and QL are assessed by validated diagnostic instruments.

We hypothesize that MAD will

- Reduce frequency and severity of tics assessed by YGTSS (Yale global tics severity scale) and tic counts.
- Reduce severity of Attention Deficit Hyperactivity Disorder (ADHD) and obsessive-compulsive disorder (OCD) severity assessed by ADHD rating scale and CYBOCS respectively.
- Improve the children's quality of life, assessed by PedsQl.
- Reduce the presence of rage attacks, depressive symptoms, and sleeping disturbances.

Results and discussion: Until now, we have included 17 patients of whom ten have started the diet. It has been difficult for some patients to keep the diet. Two patients have been on the diet for three months and show a reduction in global severity score from 61 to 0 and from 54 to 9, respectively. We continue including patients ongoing and will present the newest data at the meeting.

Conclusion: We still need more results to conclude on the effect but we expect that the MAD in the future can be a treatment option for a special selected group of TS patients.

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A teenage boy with sudden onset of tics treated with intravenous immunoglobulins

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Introduction and objectives: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) describe children with abrupt onset of tics and/or obsessive compulsive disorder secondary to a recent group A streptococcal infection (Swedo et al., 1998). PANDAS is still a controversial diagnosis and until now, there is no evidence-based treatment. Both treatment with antibiotics, tonsillectomy, intravenous immunoglobulins, and plasma exchange are reported in the literature (Macerollo and Martino, 2013; XXX, 0000). We report a case of a teenage boy with abrupt onset of severe tics, positive antistreptococcal antibody titers and good effect of intravenous immunoglobulin therapy.

Methods: 15 years old teenage boy was admitted to the hospital because of sudden onset of motor and vocal tics.

The boy had had symptoms of attention deficit hyperactivity disorder (ADHD) for some time and was referred to the department of child and adolescence psychiatry some weeks before onset of tics. He previously had some simple oral motor tics when he was nervous.

There had not been any infection or other disease before onset of tics. There were no obsessions or compulsions.

He was examined thoroughly with among others throat culture, lumbal puncture, blood samples, and Yale Global Tic Severity Score (YGTSS).

Results and discussion: Because of positive Streptolysin O antibody, he was treated with antibiotics without any effect on the severity of tics. He was treated with risperidon and clonidine with some effect on tics.

Positive streptococcal antibody titers in the serum were found (positive CaM kinase II, positive lyso GM1, positive anti-beta-tubulin antibody), and therefore, there were signs of post-streptococcal neurological spectrum disease. He was treated with intravenous immunoglobulins during five days. On the fifth day, both urge and severity of tics declined. Six weeks after intravenous immunoglobulin treatment, the patient decided to stop clonidine and risperidon treatment. YGTSS declined from 81 before treatment with immunoglobulins to 0 after treatment.

Conclusion: We have described a patient with sudden onset of tics, who was treated with intravenous immunoglobulins because of paraclinical signs of post-streptrococcal neurological spectrum disease, although he did not fulfill all criteria for PANDAS. This treatment had a good effect on severity of tics and therefore, professionals might consider treatment with intravenous immunoglobulins in patients with post-streptrococcal neurological spectrum disease. Further studies are needed in order to further examinate treatment options in PANDAS/post-streptococcal neurological diseases.

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Abnormal primary motor cortex LTP/LTD-like plasticity and BDNF polymorphism in Gilles de la Tourette syndrome

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Introduction and objectives: In healthy humans, M1 long-term potentiation (LTP) and depression (LTD)-like plasticity can be examined by testing long-term changes in motor evoked potentials (MEPs) after applying intermittent and continuous theta-burst stimulation (iTBS/cTBS). In two recent studies, we have demonstrated abnormal M1 LTP/LTD-like plasticity, as tested by iTBS and cTBS, in patients with Gilles de la Tourette Syndrome (GTS) (Suppa et al., 2011, 2014). Given that in healthy subjects, brain-derived neurotrophic factor (BDNF) Val66/Met polymorphism significantly influence TBS-induced LTP/LTD-like plasticity in M1 (Cheeran et al., 2008; Suppa and Cheeran, 2014), in the present study, we investigated whether BDNF Val66/Met polymorphism influence TBS-induced LTP/LTD-like plasticity in M1 in patients with GTS.

Methods: The study group comprised 30 patients with GTS and 30 age-matched healthy subjects. All patients were clinically evaluated using the Yale Global Tic Severity Scale (YGTSS). We tested LTP/LTD-like plasticity in M1 by conditioning left M1 with iTBS and cTBS in two separate sessions. Test stimulation consisted of 20 MEPs recorded from right first interosseous muscle before and after TBS. All participants underwent blood sampling for BDNF genotyping (Val/Val, Val/Met and Met/Met).

Results and discussion: Eight out of 30 healthy subjects and 7 out of 30 patients with GTS were Met carriers. Unlike healthy subjects, in the whole group of patients with GTS, TBS left MEP amplitudes unchanged confirming abnormal LTP/LTD-like plasticity in M1 in GTS. When we compared TBS-induced responses in Val/Val and Met carrier individuals in the two study groups, differently from healthy subjects in whom TBS elicited lower responses in Met carrier than in Val/Val individuals, in patients with GTS, TBS elicited comparable responses.

Conclusion: Our findings suggest that differently from healthy subjects, in patients with GTS, BDNF polymorphism does not influence M1 LTP/LTD-like plasticity.

Disclosures

No conflicts of interest to disclosure.

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Profiles of co-morbidity and tic severity in children and adult patients with Gilles de la Tourette syndrome

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Background: Gilles de la Tourette syndrome (GTS) is diagnosed on the basis of presence multiple motor tics and one or more vocal tics (Leckman et al., 1998). GTS starts before 18 years old and may persist to adulthood (Bloch et al., 2006).

Introduction and objectives: The aim of our study was to analyze the differences of tic severity, co-morbid mental disorders and medications used in children and adults.

Methods: 303 GTS patients were retrospectively reviewed: 158 children (136 males), aged 4–17 years (mean: 11.7 ± 3.2) and 145 adults (107 males), aged 18–54 years (mean: 25.3 ± 6.8). Mean duration of GTS was 5.2 ± 3.1 years (range: 1–14) in children and 16.3 ± 7.6 years (range: 1–44) in adult patients. Diagnosis of GTS and psychiatric disorders were made on DSM-IV-TR criteria. Tic severity was calculated by clinician as mild, moderate and severe.

Results and discussion: There were no differences between children and adults in the number of patients with moderate and severe tics. Mild tics were reported more frequently by children (20.3% vs. 11.7%, p

Conclusion: Clinical phenotype of GTS may be related to natural course, decline or increase in severity, of tics and co-morbid disorders. Pharmacological treatment is more often used in adult patients. Limitations include recall bias, different methodology of collecting data in children and adults, and descriptive, not quantitative, way of tic severity calculation.

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'The feeling distracts me and I forget the question': a qualitative study of premonitory urges in children with tic disorders

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Introduction: Premonitory urges are somatosensory events that tend to occur before a tic. These urges are private to the individual and tend to result in a wide range of experiences which include feelings of distress and discomfort which temporarily improve after the tic has been performed. The currently held opinion is that children less than age 10 are unable to report premonitory urges, however review of the literature has highlighted limitations in these studies. Majority of the existing studies have been conducted in a mixed population of adults and children and have been largely based on the use of precoded questionnaires.

Objective: To explore whether children affected by tic disorders experience, recognise and are able to describe premonitory urges.

Methods: Semi-structured interviews were caried out with children to unearth their experiences of living with a tic disorder, alongside exploration of how tics are experienced and whether or not children recognise and are able to describe associated premonitory urges. Participants included 10 children (4 Females, 6 Males, Mean age 8, SD-1.9.) referred to the Paediatrics department at the Queen Elizabeth Hospital, Hertfordshire. All children presented with motor/ and or vocal tics that had been present for at least one year at the time of the study. NHS Research Ethics approval was obtained for the study, alongside written consent from the children involved and their parents. Interviews were digitally recorded, transcribed verbatim and analysed using thematic analysis. Children also completed the PUTS (Premonitory urge in Tic scale to allow further exploration of self-reported urges. Child data was supplemented by parents completing the YGTSS scale.

Results and discussion: Parents report from the YGTSS showed that 50% of the study sample experienced a combination of motor and vocal tics with 30% having vocal tics and 20% predominantly motor tics. Parents reported that 60% of participants had moderate impairment from their tics. Two overaching themes relating to (1) awareness and description of tics and (2) lived experience of premonitory urges. Majority of the children experienced discomfort and annoyance as a result of the premonitory urge. Most participants described the sensory urges as being more troublesome than the tics with some of the participants reporting difficulty with concentration, fidgetiness and poor focussing on activities in order to suppress the urge. The child's age did not influence ability to report the frustration and annoyance felt from the sensory urges.

Conclusion: The presence of premonitory urges can result in children feeling significant discomfort and frustration. Poor concentration and fidgetiness can be an expression of children trying to suppress these urges. Children with tic disorders are at risk of developing ADHD however not all fidgeting and poor concentration is due to ADHD. There is need to consider age appriopriate methods of obtaining information on premonitory urges in children. Using a qualitative methodology, the current study demonstrates that children younger than 10 years with tic disorders have the ability to describe, in detail, the feelings they express as a result of premonitory urges.

Acknowledgement

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Disclosures

I have no conflict of interest.

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Implicit learning and working memory in Tourette-syndrome

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Introduction and objectives: Tourette Syndrome (TS) is a fronto-striatal network related developmental disorder. The functional mapping and cognitive functions of this disorder are not fully characterized. The aim of our study was to investigate two different cognitive functions which are based on fronto-striatal networks: implicit learning and working memory.

Methods: 19 children with TS and 19 age-matched control participated in our study. Implicit learning was measured by the Alternating Serial Reaction Time Task (ASRT), making it possible to measure general skill learning and sequence-specific learning separately. The ASRT task was performed in two sessions with a 16 h delay. Working memory was assessed by counting span and story recall tasks. We conducted repeated measures and mixed design analyses of variance (ANOVAs) with LSD post hoc tests.

Results and discussion: Our results showed intact working memory performance in the TS group, moreover, this group showed a significantly higher performance in digit span task. In implicit learning task measured by the accuracy data, TS group significantly outperformed the controls. In contrast, after the 16 h delay the TS group showed forgetting of the earlier learnt sequence. However, looking at reaction times the TS group showed typical learning and consolidation process. Thus, along with others, we support the theory that different neural processes account for the accuracy and reaction time.

Conclusion: To sum up, our findings indicates intact online but impaired consolidation in TS. The intact online processes are in line with the working memory results. Our study can help not only in deeper understanding of the neurocognitive background of TS, but also the fronto-striatal functions in general. Using these results, therapists can design more effective educational and rehabilitation programs.

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The impact of family communication on parent-child agreement in youth with Tourette syndrome

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Introduction and objectives: Research cites discrepancies between parent and child report of neuropsychiatric symptomology in children. Although multiple factors related to low agreement have been identified (Grills and Ollendick, 2002), very little is known about the potential impact of family communication on agreement. Furthermore, evidence suggests that children with Tourette Syndrome (TS) may exhibit lower parent-child agreement when compared to control children (Termine et al., 2014). We investigated the level of parent-child neuropsychiatric diagnostic agreement in TS and control children and the relationship between parent-child neuropsychiatric diagnostic agreement and parent-reported quality of communication.

Methods: As part of a larger study, children with TS (n = 78), control children (n = 77), and their parents completed the Diagnostic Interview Schedule for Children IV (DISC-IV). Parents also completed the Family Assessment Device (FAD), which contains a Communication subscale. A parent-child dyad was considered to be in agreement if both parent and child endorsed the presence or absence of a diagnosis on the DISC-IV. The proportion of parent-child dyads in agreement were compared across groups and by diagnosis using a test of the difference between two proportions. Because subjects in the control group reported few diagnoses, further analyses to examine the relationship between communication and agreement across groups could not be conducted. The relationship between communication and parent-child agreement in the TS group was examined using a one-way, between-subjects analysis of variance (ANOVA).

Results and discussion: Parent-child agreement was higher for the Control group than the TS group for General Anxiety Disorder (GAD), Major Depressive Episode (MDE), Obsessive-Compulsive Disorder (OCD), Attention Deficit Hyperactivity Disorder (ADHD), and Oppositional Defiant Disorder (ODD) diagnoses (Table 1). There was a significant main effect of agreement upon communication at the p

Table 1 | Proportion of agreement between parent/child dyads for individually-completed D1SC-IV diagnostic interviews.

	Percent agreement		
DISC-IV Diagnosis	**Control N = 77**	**TS N = 78**	**Test of proportions**
GAD	0.97	0.88	p = 0.03
MDE	1.00	0.94	p= 0.03
OCD	0.85	0.71	p = 0.04
ADHD	0.90	0.59	p < 0.0001
ODD	0.84	0.64	p = 0.005
CD	0.94	0.97	p = 0.37 (ns)

Conclusion: Children with TS and their parents exhibited lower levels of agreement than controls for GAD, MDE, OCD, ADHD, and ODD diagnoses. TS parent-child dyads in agreement about the presence or absence of GAD and ODD diagnoses reported healthier family communication; however, those in agreement about a diagnosis of MDE reported less healthy family communication. Findings suggest that the quality of family communication may impact level of parent-child neuropsychiatric diagnostic agreement.

Acknowledgement

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Disclosures

Dr. Augustine and Dr. Mink serve on the scientific advisory board of the Tourette Syndrome Association (TSA).

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Working mechanisms in exposure and response prevention for tics: habituation of premonitory urges?

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Introduction and objectives: Exposure to premonitory sensations and response prevention of tics (ERP) has been shown to be a promising treatment for Tourette's syndrome (TS). A suggested working mechanism is so-called habituation. Verdellen et al. (2008) found a linear reduction of the severity of sensations both within and between sessions (using 15-min ratings), indicating habituation. On the other hand, Specht et al. (2013) found no habituation but a stable pattern of premonitory urges during prolonged tic suppression. The main hypothesis of the current study is, in line with reports from patients, that there is a quadratic habituation trend to premonitory urges with an initial increase of sensory sensations with tic suppression, followed by a decrease of severity of premonitory sensations (see Figure 1).

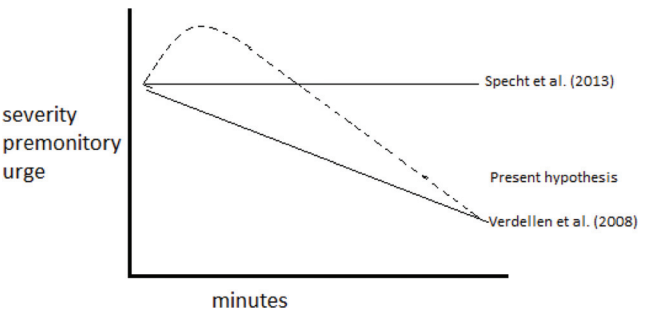

Figure 1 | Different habituation curves: quadratic trend, linear trend and a stable pattern.

Methods: 29 patients (20 men, 9 women; mean (SD) age 17.97 (12.15) years; age range, 7 to 59 years) diagnosed with Tourette Syndrome (TS) or Chronic Tic Disorder (CTD) participated. Treatment consisted of two training sessions and ten actual ERP sessions, with a duration of one hour. In this study, the 10 ERP sessions were measured. Patients were asked to suppress all tics, while focussing on the premonitory urges. At 0, 5, 10, 15, 30 and 60 min, urges were rated at a five-point Likert scale for at most seven different tics (SUD-scores). To enhance treatment integrity, treatment manuals were used.

A Repeated Measures ANOVA and a Latent Growth Model (LGM) were performed to answer the habituation question. The LGM uses a quadratic, a linear and a piece-wise regression function to describe the relationship between time and SUD-score for each combination of patient and session number.

Results and discussion: The results of the Repeated Measures Analysis within session habituation show that the mean SUD-scores significantly change during sessions ($F(1.49, 41.63) = 5.81$, $p < 0.01$). The quadratic model has better fit with the data. The Latent Growth Model shows the same trend; the quadratic model has an almost equal fit as the linear model, as can be seen in Figure 3. Besides Linear and Quadratic curves, also a Piecewise model was tested. This Piecewise Latent Growth Model has the best fit with the data, and shows that the significant change takes place in the first 15 min, and afterwards stays stable.

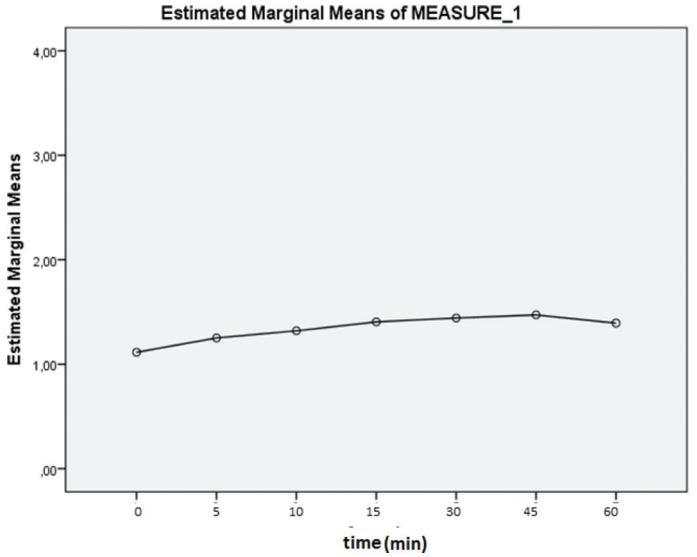

Figure 2 | Graphic representation of the within-session habituation. Mean sensation severity scores (SUD-scores) within sessions, averaged over patients (n = 29) and sessions (n = 10).

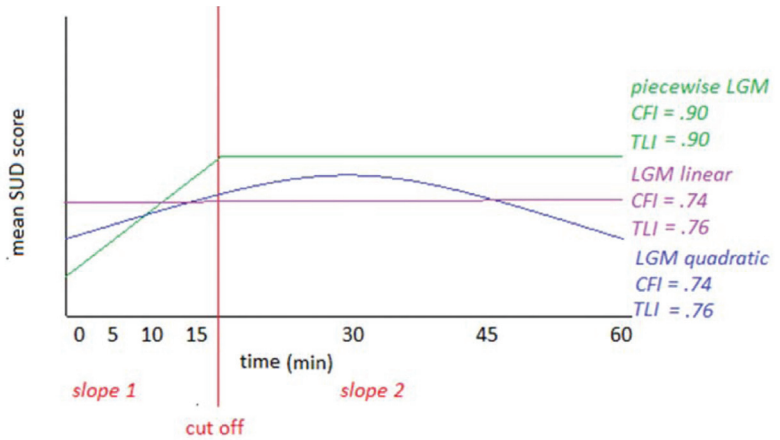

Figure 3 | Graphic representation of LGM linear model, LGM quadratic model and Piecewise LGM.

Conclusion: The results of both Repeated Measure Analysis and Latent Growth Model show that the SUD-scores significantly differ during sessions, with the most evidence for a significant change in the first 15 min, stabilizing afterwards. These results raise the question whether habituation is the working mechanism in ERP. Recent theories for anxiety disorders and obsessive compulsive disorder follows the falsification model instead of the habituation model. This model states that during exposure treatment, patients learn that the feared consequences will not happen. ERP in TS would lead to a decrease of the expectations that the patients cannot control the tics and create alternative expectations and cognitions that they can influence the tics. Future research is needed to test this new hypothesis.

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Improving homework in behavior therapy for TS and tic disorders – development of an application

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Introduction and objectives: Exposure and response prevention (ERP) has shown to be an effective strategy and is considered a first-line intervention in the treatment of tic disorders (Verdellen et al., 2011). In this behavioural treatment, patients learn to systematically suppress tics for increasing periods of time, while focusing on premonitory sensations and urges that precede tics (Verdellen et al., 2004). In this way, the patient may get used to the urge to tic, leading to tic reduction. The therapist acts like a coach in helping the patient to accomplish this task. He encourages the patient to improve his/her achievements, and optimizes exposure by asking the patient to concentrate on the sensory experiences. Homework assignments are given on a daily basis. To aid patients doing the ERP exercises at home, a mobile app has been developed.

Methods: The app was developed to facilitate and optimize the effect of ERP homework. The tool provides positive reinforcement for successful tic suppression. During exposure the patient records urge severity ratings. The app takes into account tic suppression times, urges to tic and the number of tics that are not suppressed. It has the option of both visual and auditive feedback. The app simulates the coaching role of the therapist; whenever a tic occurs, it encourages the patient to extend his/her capacity to suppress the tics and to set new time records. When the urge to tic increases, it encourages the patient to keep suppressing every tic and when the urge to tic declines or is absent, it encourages exposure to the sensory experiences. The app can be used by both children and adults.

Results and discussion: The app is not yet tested in a clinical population. In the near future, a study will start in the Netherlands testing the feasibility and efficacy of the application. The app is prepared to be easily translated in different languages.

Conclusion: The app seems to be a useful tool to aid and facilitate practicing behavior therapy at home.

Acknowledgement

We like to acknowledge the Technical University Eindhoven, the Netherlands, for developing the app.

Disclosures

There are no conflicts of interest.

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Dissemination of behaviour therapy for tics – overcoming barriers

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Introduction and objectives: European clinical guidelines recommend behaviour therapy as a first-line intervention for tic disorders (Roessner et al., 2011; Verdellen et al., 2011). However, despite evidence and availability of treatment manuals, few patients receive a behavioural treatment for tics (Woods et al, 2007; van de Griendt et al., 2013). What are the barriers for dissemination? And how can these barriers be overcome?

Methods: Two surveys were performed into the application of behaviour therapy for tics. The first survey was applied in 2011 among European Tourette syndrome professionals (members of the ESSTS; $n = 49$).The other survey was applied in 2014 among Dutch TS patients and their parents (mostly members of the Dutch TS association; $n = 143$).

Results and discussion: Results of the survey among ESSTS professionals indicated that most responders recommended psychological treatment as first-line intervention for tics. The main reason to advise or initiate psychological treatment instead of medication for tics was the preference of the patient and the main barrier was difficulty finding a knowledgeable treatment provider. The survey among Dutch patients and their parents showed a clear preference for behaviour therapy above medication, although there were some concerns as well, such as the belief that focusing on tics and suppressing tics makes them worse. However, there is no support from scientific research for symptom substitution or rebound following a behavioural treatment for tics.

Conclusion: In line with clinical guidelines (Roessner et al., 2011; Verdellen et al., 2011), these two surveys among European TS professionals and Dutch TS patients indicate a preference for behavioural treatments above medication. However, there are several barriers to the dissemination of behaviour therapy for tics that need to be overcome, such as misconceptions about the consequences of a behavioural treatment and a lack of trained therapists. Education, translating treatment manuals, training therapists, e-health and e-learning can facilitate the distribution of behavioural treatments for tics.

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Disclosures

There are no conflicts of interest.

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Functional validation of proposed epigenetic mechanisms involved in Tourette syndrome

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Introduction and objectives: *Tourette syndrome* (TS) is a neurodevelopmental disorder with one of the highest familial recurrence rates among neuropsychiatric diseases. The complex inheritance and manifestation makes it challenging to identify truly causal genetic factors in the pathophysiology of the disease. Although a wide range of genetic studies have investigated the genetic background of TS, to date only a few findings have been replicated. Among these the nicotinic acetylcholine receptor alpha 7 subunit (CHRNA7) gene and glial cell-derived neurotrophic factor (GDNF) gene has been recently suggested as candidate susceptibility genes in TS. CHRNA7 is known to regulate a wide variety of developmental and secretory functions, however the mechanism of its transcriptional regulation is still unclear. GDNF promotes the survival of dopaminergic neurons and its polymorphisms have been studied in various psychiatric disorders. MicroRNAs are implicated in the regulation of expression of these genes along with epigenetic mechanisms, such as DNA methylation. Correlation between promoter methylation of CHRNA7 and its mRNA transcription has already been shown (Canastar et al., 2012).

Our goal was to investigate the role of epigenetic mechanisms (such as miRNA regulation, DNA methylation) and their possible involvement in the pathogenesis of TS through functional and epigenetic analysis of promoter and 3'UTR regions.

Methods: Plasmids containing the 3'UTR regions of CHRNA7 and GDNF genes were used in transfection assays. MiRNAs were identified using databases as possible factors for regulation of expression (e.g., miR-106b in case of CHRNA7 and miR-194, miR-511, miR-203 and miR-204 in case of GDNF). SKNF1 and HEK human cell lines were co-transfected with the reporter-3'UTR constructs and the corresponding putative miRNAs in the functional validation studies using luciferase assays.

To investigate the possible methylation-based epigenetic mechanisms we conducted high-resolution melting (HRM) analysis using in-house designed primer pairs on case-control TS samples, which were further validated by targeted bisulfite sequencing.

Results and discussion: In the luciferase assays we characterized the regulatory effect of the predicted miRNAs on the expression of the studied candidate genes. Differential methylation patterns were also identified within the promoter region of GDNF using the HRM method and analysis of CHRNA7 is still in progress.

Conclusion: Although several genetic markers have been implicated in the pathogenesis of Tourette Syndrome, the underlying genetic mechanisms are still mostly unknown. Therefore, we aimed to study the epigenetic processes in the background of gene expression regulation of TS-related genes, which would help not only to better understand the full genetic architecture of this disorder but also to determine how miRNA regulation and promoter methylation contributes to the complexity of gene regulation in the development of disease.

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Development of a self- and parent-report questionnaire assessing the quality of life and functional impairment of children and adolescents suffering from tics or Tourette syndrome (QuaLiFITiC) – an interim analysis

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Introduction and objectives: Objective of this study is the development of a German questionnaire on the health-related quality of life (HRQOL) and functional impairment in children and adolescents with tic or tourette disorders, which can be rated by patients and their parents. The rating scale should distinguish between functional impairment /reduced quality of life caused by tic symptoms and caused by comorbid symptoms.

Methods: Based on an operational definition of HRQOL and the questionnaires CTIM-P (Storch et al., 2007) and GTS-QOL (Cavanna et al., 2008) 61 items were created in order to assess 5 a-priori domains of HRQOL: (1) physical problems, (2) feelings, (3) school activities, (4) family, (5) social activities. The items are to be rated on a four-point Likert-scale (from 0 = not at all to 3 = especially) twice: first for difficulties due to tics and second difficulties caused by other problems. After assessing the items for each domain, the respondent evaluates for each domain the overall subjective burden due to tics and other problems. Finally, the general life satisfaction is assessed on a visual analogue scale (from 0 to 100). The items of the self- and parent-report are identical.

We intend to include 100 Tic- and Tourette patients (8–19 years) referred at the Department of Child and Adolescent Psychiatry at the University Hospital Cologne.

Results and discussion: The results of an interim-analysis with ratings of 26 patients aged 8 to 16 years with Chronic Tic Disorder (11.5%) or Tourette Disorder (88.5%) and their parents are reported. On the overall rating scale (ranging from 0 to 100) a high general life satisfaction is reported by children (M = 82.5, SD = 18.87) and their parents (M = 72.31, SD = 22.37).

Based on this preliminary analysis items with a low item-total correlation (r_{it}?.20) were deleted in both questionnaires separately for problems due to tics and other problems. The final item selection will be carried out on the basis of the full dataset of 100 patients.

As shown in Table 1 internal consistency (Cronbach's alpha) for parent-rated and self-rated total scores were good to excellent after item-selection. Impairment ratings due to tics rated by parents and patients did not correlate, while impairment ratings of parents and patients due to other problems showed a moderate correlation. Parent-rated impairment due to tics were substantially correlated with clinician rated motor tics and impairment on the YGTSS, while self-reports are not correlated with YGTSS ratings.

Table 1 | Internal consistency (Cronbach's alpha) of the QuaLiFITiC (parent-/self-report), correlations between parent- and self-report and correlations with YGTSS-symptoms and impairment ratings.

Impairment Scales			Internal consisteny		Pearson Product Moment Correlations				
			Number of items	Cronbach's alpha	92	3	4	YGTSS MotorTic	YGTSS Impairment
Impairment due to tics	self-report	1	33	.89	-.09	.15	.15	-.24	-.11
	parent-report	2	48	.95	1	.47*	.6**	.72**	.71**
Impairment due to other problems	self-report	3	51	.92	.47*	1	.61**	.15	.14
	parent-report	4	49	.96	.6**	.61**	1	.22	.36

Note: YGTSS= Yale Global Tic Severity Scale, *p < 0.05, **p < 0.001.

Conclusion: This interim analysis in small sample of children and adolescents with Tic/Tourette disorders shows that internally consistent parent- and patient-ratings of impairment due to tics and due to other problems can be obtained and that at least the parent-ratings show good convergent validity with tic severity and impairment rated by clinician.

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Tourette syndrome and the hyperreagibility of the immune system

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Introduction and objectives: The etiology of Tourette syndrome is still unknown. Infections resulting in immune activation have been proposed to be a trigger for tic onset and tic exacerbation in a subset of Tourette patients (Leckman et al., 2005; Krause et al., 2010). A hyperreagibility of the immune system or predisposition for it – as seen in autoimmune diseases and allergic reactions – is assumed (Kawikova et al., 2007). In the context of the "hyperreagibility hypothesis" the protein "ezrin" is very interesting. Ezrin is involved in neuron growth and communication in early development (Grönholm et al., 2005). Furthermore it was identified as a potential autoantigen in streptococci induced autoimmune diseases (Besgen et al., 2010) and could therefore play a role in the pathophysiology of tic disorders, which can be triggered by streptococcal infections (Swedo et al., 1998). As data examining the hyperreagibility of the immune system are very fragmentary we planned following study. We expect to find a higher number of patients with elevated IgE levels compared to controls due to a higher prevalence of allergies in patients. Furthermore we expect to find a proinflammatory immune state in patients compared to controls.

Methods: 50 Tourette patients and 50 healthy controls will be recruited and examined twice in an interval of three months. Besides a clinical characterisation by questionnaires (MINI International Neuropsychiatric Interview, Yale Global Tic Severity Scale, Yale Brown Obsessive Compulsive Scale, Hamilton Depression Scale, Beck Depression Inventory, Perceived Stress Scale, Gille de la Tourette Syndrome-Quality Of Life) blood samples, throat swabs (for streptococci) and a stool sample (parasitological screening) will be collected. In doing so the differential diagnosis of expected elevated IgE levels will be examined. Furthermore a differentiated inspection of the immune state in connection with the severity of the disease and psychiatric as well as somatic comorbidities will be conducted. For this purpose immunoglobulines and their subgroups (by turbidimetric method), an allergen panel (by Western Blot), cytokines (by Enzyme-linked Immunosorbent Assay), kynurenine metabolites (by Ultra Performance Liquid Chromatography), antibodies against streptococci and ezrin (Western Blot) will be measured.

Results and discussion: **Perspective:** By examining a differentiated spectrum of laboratory parameters relevant for the characterisation of the immune state as well as an extensive documentation of clinical symptoms we hope to get a better insight regarding the pathophysiology of Tourette syndrome, which might build the ground for new therapeutical interventions. (Recruitment is ongoing)

Conclusion: Recruitment is ongoing.

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Disclosures

No conflicts of interest to declare.

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An integrated molecular landscape for Tourette's syndrome yields novel clues for diagnosis and treatment

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Introduction and objectives: Tourette's syndrome (TS) is a childhood-onset neurodevelopmental disorder characterized by multiple and involuntarily motor tics and at least one vocal tic that persist for more than one year. TS has a prevalence of ~0.3–0.8% and occurs more frequently in boys than girls. In addition, the disorder is often accompanied by other, comorbid neurodevelopmental disorders, especially obsessive-compulsive disorder (OCD) and attention deficit hyperactivity disorder (ADHD). TS is caused by a complex interplay between genetic and environmental factors and although it is highly heritable, a thorough understanding of the biological processes underlying its etiology is essentially lacking. Therefore, we built a molecular landscape for TS, through applying an approach that we have used before for other neurodevelopmental disorders such as ADHD (Poelmans et al., 2011) and autism (Poelmans et al., 2013) and based on all available genetic data (Poelmans, 2013).

Methods: To build a molecular landscape of the (dysregulated) biological processes underlying TS, we combined a genetic network analysis of the top-ranked genes from the only thus far published genome-wide association study (GWAS) of TS (Scharf et al., 2013) with systematic literature searches for these GWAS genes. We also integrated genes implicated in TS through other evidence, including functional and animal studies, into the landscape. In addition, we corroborated our findings and refined the landscape through an upstream regulator analysis of the published genome-wide expression data from (postmortem) brain (Lennington et al., 2014) and blood of TS patients (Tian et al., 2011, 2012).

Results and discussion: The molecular TS landscape is mainly located in neuronal cells and regulates a number of distinct biological processes and signaling cascades that contribute to key neuronal functions such as neuronal growth and myelination. Moreover, cascades within the landscape are directly linked to some of the etiological hypotheses about TS, such as disturbances in GABA and histamine metabolism. Lastly and importantly, the landscape contains putative biomarkers and drug targets for TS that could be ´leads´ for the further development of novel diagnostic and therapeutic strategies.

Conclusion: This approach provides novel insights into the genetic and molecular underpinnings of TS, and highlights putative biomarkers and drug targets as worthy of further investigation as putative diagnostic and therapeutic tools.

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A pilot multicenter study of brain structure in pediatric Tourette syndrome

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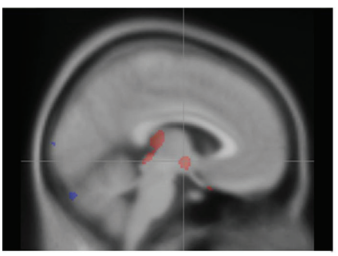
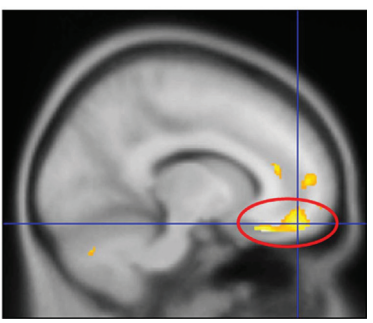
Introduction and objectives: Several previous structural MRI studies have found evidence for abnormalities of brain structure in Tourette syndrome (TS). However, results differed, and most such studies enrolled a limited number of subjects.

Methods: Existing and newly-acquired T1-weighted MP-RAGE images were collected from over 400 children age 7–17 at 4 U.S. sites. The children included 230 with a chronic tic disorder. Scans were excluded for visible artifact by an investigator blind to diagnosis. Control subjects were matched 1:1 to TS subjects by age, sex and handedness, for a final sample of 103 TS and 103 control children. Standard voxel-based morphometry techniques were used to create images gray matter (GM) and white matter (WM) volume for each subject. The GM and WM volume images were smoothed to ~11mm (FWHM). General linear models with GM and WM volume as dependent variables were computed at each in-brain voxel in atlas space, using diagnostic group, MRI sequence and sex as factors, age as a covariate, and group × sex and sex × age interactions. Proportional scaling was used to account for each subject's total brain volume (GM + WM). T images were thresholded at |t|?3 and the significance of suprathreshold clusters was computed, limiting the false discovery rate to 0.05.

Results and discussion: The TS group had greater GM volume in posterior thalamus (4.4 ml, corrected $p = 0.001$) and in hypothalamus-midbrain (2.7ml, corrected $p = 0.011$). The TS group had lower WM volume bilaterally in orbital prefrontal cortex and anterior cingulate (left, 5.2ml, corrected $p = 0.001$; right, 4.6ml, corrected $p = 0.001$). Similar results are seen after removing data from all but the largest site.

Conclusion: In this large study of brain structure in TS, the significant results cannot easily be attributed to differences in populations or methods at different centers, or to artifactual GM reduction due to small-amplitude head movements during the scan in TS subjects. The decreased WM volume in orbital prefrontal cortex is consistent with a finding of 5% lower orbital cortex volume in boys with TS using earlier methods (Peterson et al., 2001). This finding may relate to the increased GM volume in hypothalamus, which shares reciprocal connections with the orbital prefrontal cortex.





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Disclosures

None

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Violent risk in Tourette syndrome? A systematic review and meta-analysis

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Introduction and objectives: Tourette syndrome (TS) is one of the commonest childhood neurodevelopment disorders which carries significant psychosocial morbidities. Studies have been looking into its association with violence but results varied. The aim of this systematic review and meta-analysis was to look for a link between TS and violence and to formulate postulations for reasons behind.

Methods: A systematic review and meta-analysis was conducted according to the PRISMA statement (Figure 1).

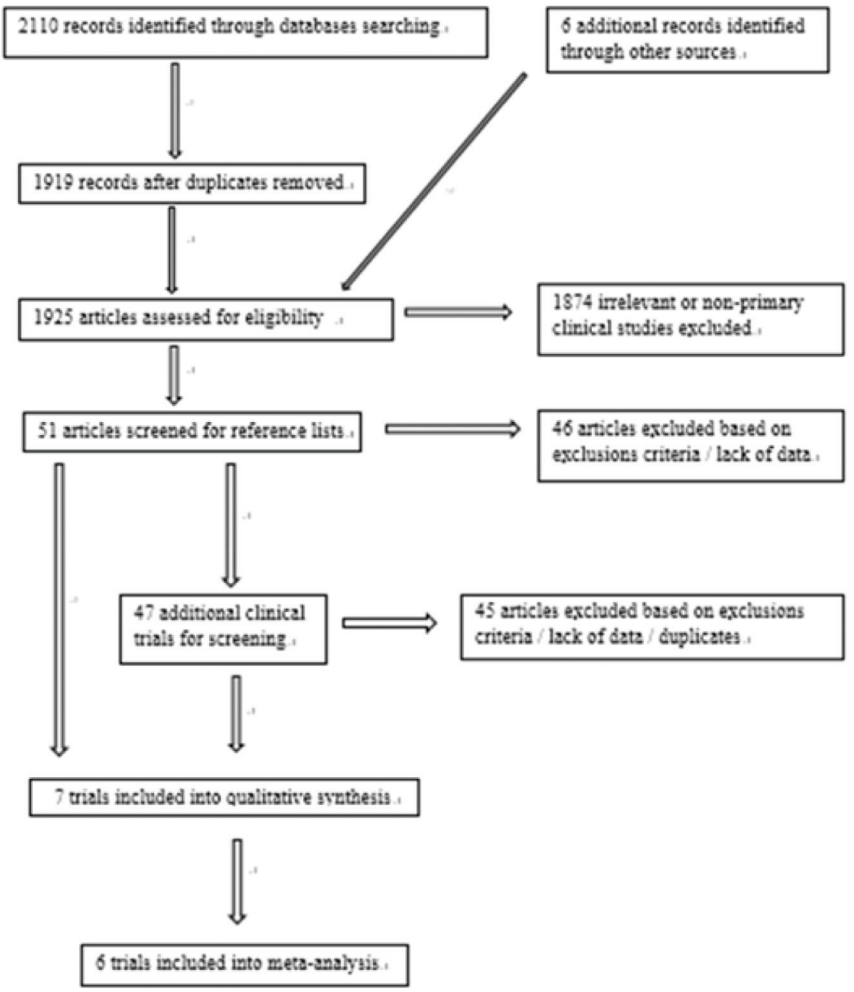

Figure 1 | Study flow diagram.

Studies were selected from three electronic databases based on inclusion an exclusion criteria, the reference lists of which were searched for additional articles. Unpublished studies were located. Methodology quality assessment was performed by the aid of an appraisal checklist (HEB [Wales], 2004).

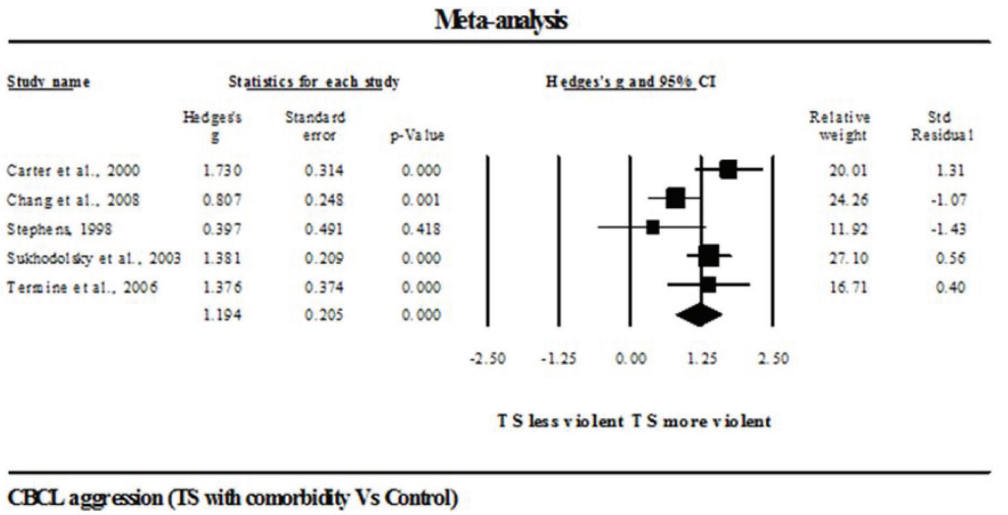

Figure 2 | Violence in TS with comorbidity compared with controls.

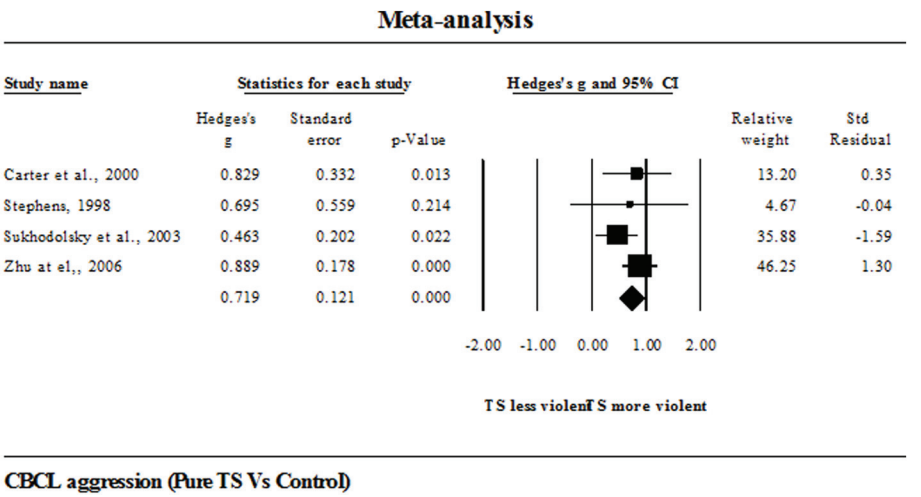

Figure 3 | Violence in pure TS compared with controls

A meta-analysis using the random effects model was conducted. Separate analyses were performed for (1) comparing TS (with comorbidity) and control, (2) comparing pure TS (defined by absence of ADHD and OCD) and controls. Heterogeneity across the studies, moderators and publications bias were studied.

Results and discussion

Systematic review

Seven studies were included for qualitative analysis. Child Behavior Checklist (CBCL) was used as a measure of violence. All the studies showed a positive association between TS and violence.

Methodology assessment identified several potential biases. Clinical sampling was not representative of the general diseased population. The lack of a clear definition of violence might lead to inconsistent interpretation of violence phenomena in the subjects. Retrospective third party rating carried recall bias, and the ratings were subjective estimates instead of reflections of actual violent attempts. Some of the items in the aggression subscale in CBCL were violent triggers instead of actual violent behavior. The presence of confounders, including medications and other psychiatric comorbidities, might also bias the results.

Meta-analysis

After excluding a study looking at actual criminal offences, six studies were recruited into the meta-analysis, pooling the results of 294 TS patients and 203 healthy controls. Mean age of the patients was 10.72 years. The subjects were predominantly male (78.91%).

Compared to controls, both TS groups exhibited more violence, with larger effect size in the group with comorbidity (g'= 1.194, p^2 = 54.622, p = 0.066).

No publications bias was noted. Meta-regression failed to show any no moderating effect by age or intelligence. Effect by tics severity was not explored due to inadequate data.

Discussion

Interpretations of the results of violence studies have to be cautious, as only associations but not causative effects could be deduced from violence studies (Walsh et al., 2002). Confounders, selection bias and measurement bias could also affect the results' validity. Concerning the aetiology of violence in TS, deficient impulse control (Mathews et al., 2004), tics severity (Nolan et al., 1996) and associations with comorbidities (Budman et al., 2000) have been postulated. Social incompetence and emotional dysregulation might as well contribute to the violent risk in TS subjects.

Conclusion: There was an association between violence and TS. Future studies should investigate the moderators of violence in TS. More resources should be invested in reducing the personal and societal impact of the disorder.

Acknowledgement

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Disclosures

No conflicts of interests.

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Attention deficit and hyperactivity as comorbidities of Tourette's syndrome – behavioral and neuronal evidences in the disinhibition rat model

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Introduction and objectives: Attention deficit and hyperactivity are common comorbidities of Tourette's syndrome (TS), affecting roughly 50% of the patients. The high comorbidity hints that the disorders share some aspects of the underlying pathophysiology. In our previous studies we established an animal model of tic expression using disinhibition of the dorsolateral striatum of freely behaving rats (Bronfeld et al., 2013). In this study, we present a rodent model in which hyperactivity and attention deficit are elicited using the same manipulation on the nucleus accumbens (NAc). The striatum and NAc serve as the main input stations of the basal ganglia for the motor and limbic pathways respectively. We sought to explore the involvement of each of these pathways in the pathophysiology common to TS and attention deficit/hyperactivity, their common properties and differences. In order to do so, we manipulated the neuronal state within these pathways and analyzed the emerging behaviors and the corresponding neuronal activity.

Methods: We preformed chronic multi-electrode extracellular recording of the neuronal activity from the basal ganglia of freely-moving rats in both the naïve state and following local microinjections of the $GABA_A$ antagonist bicuculline to the NAc. The animals were placed in a custom built large-scale cage which combines both open space and a maze, and their behavior was continuously monitored by a video camera. The behavior and the neurophysiological signals were offline synchronized and analyzed.

Results and discussion: Following the injection of bicuculline the animals developed hyperkinetic symptoms within 8–12 min lasting for 30 min. Hyperactivity symptoms were expressed as an ongoing increased exploration, phases of excessive running, rapid movements and continuous sniffing. Attention deficit symptoms were observed as multiple beginnings of actions from which the animals were distracted, and multiple returns in the path. The behavior of the animals was offline analyzed, and their traces were automatically tracked. Kinematic properties such as velocity and length of pathways, turnings and grooming were extracted from the data and synchronized with the recorded neuronal activity. The neuronal correlates of these behaviors were calculated for the naïve and attention deficit/ hyperactive state. Comparison between these states reveals qualitative and quantitative changes in behavior which are evident in the neuronal activity. In addition, injections on the border of the striatum and NAc resulted in a display of comorbid symptoms, motor tics and attention deficit/hyperactivity simultaneously.

Conclusion: In this study we characterize a new model for attention deficit and hyperactivity using the same manipulation used in our animal model of motor tics. We have observed a variety of behaviors which express alongside tics, resembling the comorbidities apparent during TS. Our data provides new insights of the interaction between tic expression and attention deficit/ hyperactivity pointing at a common underlying mechanism during TS.

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Parental and child experiences from a service evaluation of the TANDeM MDT clinic

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Introduction and objectives: Parental and child views of services are essential to service provision development and it has been found that multidisciplinary Team (MDT) clinics are sometimes seen as too time-consuming with little efficacy (Raine et al., 2014). The aim was to evaluate parental and child satisfaction of our multidisciplinary clinic (Tics and Neurodevelopmental Movements, TANDeM) to gather information of relevance to (1) inform future referral pathways (2) assess multidisciplinary service provision and (3) enhance service user satisfaction.

Methods: Twenty children and their parents completed general and service-specific questionnaires over a 12 month period. The questionnaires comprised of 80 forced choice questions and 9 open-ended questions that covered accessibility, communication and overall satisfaction with the MDT clinic. All data was analysed using SPSS.

Results and discussion: Most patients were referred by community paediatricians and GPs (42%; 26% respectively). The majority of parents were satisfied with the service they received (88%), but limitations to service provision included waiting 6 months or more for an appointment (50%) and distance to travel (25%). In terms of service provision, most parents and children were satisfied with the MDT setup that included 4–5 professionals in the room, (95%; 84% respectively), however some parents found it difficult to say things with their child present (65%). In relation to tic treatments, parents expressed a preference for psychological therapies (e.g., individual therapy, groups) rather than pharmacological management (55% vs. 33%).

Conclusion: Encouragingly, families reported positive experiences of the MDT clinics and contrary to expectations the large number of professionals did not influence parental and child satisfaction. However, the evaluation demonstrates a need to develop services so that parents can meet clinicians separately from their child, having increased opportunities to engage in talking therapies and more geographically accessible services. The preference for local service provision highlights the demand for a hub and spoke partnership, with specialist and local services forming a collaborative dialogue in delivering evidence-based services for the management of tic disorders.

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Handwriting in Tourette syndrome

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Introduction and objectives: Tourette Syndrome is a neurodevelopmental disorder characterized by multiple motor tics and at least a sound tic (American Psychiatric Association, 2013). Tics often interfere with subjects' activities (Robertson, 2012). Regarding handwriting, patients with Tourette Syndrome may have handwriting tics, including rewriting the same letters or words, or outlining each letter multiple times (Challas et al., 1967; Mitchell and Cavanna, 2013). Moreover, the patient can pull the pen back while writing (Leckman and Cohen, 1999). Milan Tourette Centre study is going to verify if patients with Tourette Syndrome suffer from agraphia more than controls. Clinicians expected that school-age patients suffer from agraphia in 20% of cases more than controls.

Methods: The study is based on the assessment of handwriting in 80 patients with Tourette Syndrome having 10 to 40 years old, compared with controls. During the first visit -no drug use- patients have to complete the handwriting assessment test. It is composed by a spontaneous writing subtest of 10 lines, and a more structured subtest, both in order to analyse handwriting (graphics signs, pen handhold, page setting, and timing).

Results and discussion: Clinicians are still collecting data. In the pilot study, 40% of school-age patients showed reiterative agraphia i.e., echography. The prevalence seems to be masculine more than feminine. Clinicians will repeat the study once patients start drugs use for tics.

Conclusion: The study is going to verify the presence of handwriting tics in patients with Tourette Syndrome and how drugs are efficient in treating handwriting tics. More studies are needed about handwriting tics, and other specific tics, around the world.

Acknowledgement

No funding was received by Milan Tourette Centre for the study.

Disclosures

Nobody of the authors have a conflict of interests.

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Work-life in Tourette syndrome

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Introduction and objectives: Tourette Syndrome is a neurodevelopmental disorder characterized by multiple motor tics and at least a sound tic (American Psychiatric Association, 2013). Tics often interfere with subjects' social activities (Eddy et al., 2011). Regarding work, patients with Tourette Syndrome may have difficulties in finding or holding down a job (Verdellen et al., 2011).

Objective of the poster is the analysis of Italian Law applied to Tourette Syndrome subjects at work.

Methods: Method is a meta-analysis of the existing literature about working for patients with Tourette Syndrome (Jankovic et al., 2006); focus is on Italian Law.

Results and discussion: Simple motor and sound tics may interfere in sense of being discriminated by the office head, and colleagues. E.g., the office head could decide for a not-social task to attribute to the subject with Tourette Syndrome.

Co-existing and comorbid psychopathologies, i.e., anxiety disorders, obsessive compulsive behaviours, self-injury behaviours and non-obscene social inappropriate behaviours may be even more disabling than tics in social contexts, cfr workplace (Channon et al., 2012). Moreover, patients sometimes cannot truly manage many tasks because of their own physical risks –see driving for a patient with hand tics (Cavanna and Nani, 2013).

Despite Italian invalidity employment law no. 68/99, in Italy Tourette Syndrome patients don't have the right to be assigned a job.

For these reasons, each patient with Tourette Syndrome need to be assessed by clinicians and social services to be assigned to an adequate workplace. Consequently, the subject should have the possibility to benefit from social working environment and to be employed in a fitting job with no physical risks.

Conclusion: Tourette Syndrome clinical aspects should be considered by Italian employment law, patients need a right integration in the workplace. Further studies are needed worldwide on local employment law applied to Tourette Syndrome subjects.

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No funding was received by Milan Tourette Centre for the study.

Disclosures

Nobody of the authors have a conflict of interests.

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A push-pull cortico-subcortical effective connectivity pattern in Gilles de la Tourette syndrome: DCM evidence on fMRI data

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Introduction and objectives: Analysis of brain connectivity in Gilles de la Tourette Syndrome (GTS) has only recently gained importance. Previous studies have focused mainly on investigation of anatomical connections using Diffusion Tensor Imaging [see for example Neuner et al. (2010), Cheng et al. (2013)] or on the correlation between activity in different brain areas by means of resting state fMRI [see for example Worbe et al. (2012)].

No study has yet explored the impact of the interaction of cortical and subcortical motor areas by taking into account both endogenous and exogenous features of neural system dynamics in GTS.

Methods: We used fMRI and Dynamic Causal Modelling in 24 adult GTS patients and 24 age and sex matched healthy controls to investigate the effective connectivity of key motor areas during the execution of a self-paced simple finger-opposition motor task.

For each subject we extracted the first eigenvariate of the BOLD time-series from 11 Regions of Interest (bilateral M1, SMA, dPMC, Putamen, Thalamus and rSFG), defined as 4mm spheres centred on individual activation local maxima identified from general linear model (GLM) analyses of regional task specific activation. We used DCM12 within SPM12 software to model endogenous inter-regional effective connectivity interactions, based on previous evidence (Pool et al., 2013) and their respective modulatory changes under exogenous influence of the motor task, based on a proposed network model of GTS pathology (Heise et al., 2010).

Results and discussion: We found an altered pattern of endogenous connectivity in GTS at the level of the premotor network, with stronger connections from premotor areas (dorsal PM and SMA) and subcortical structures (bilateral putamen) to the rSFG (area 6), an area where GTS show over-activation in the GLM analysis.

We also found a significant positive correlation between connections from subcortical regions (Putamen and Thalamus) to M1 and disease severity as measured with the YGTSS. This pattern was mirrored by a negative correlation for connections between premotor regions (SMA) and M1, and it was significant for both endogenous and exogenous task dependent modulatory connectivity.

Conclusion: Our results show the existence of an altered connectivity pattern in the premotor network in GTS. Moreover, our findings partially support the model proposed by Heise et al. (2010), of two competing push-pull mechanisms at the level of the motor circuitry: aberrant subcortical afferents to primary motor cortex compensated by inputs from premotor cortex. Strong effective connectivity effects from premotor cortices to M1 result in a lower disease severity, while strong effective connectivity effects from subcortical regions to M1 are associated with greater tic severity. Interestingly, these contrasting mechanisms seem to be in action independently from the presence of voluntary motor behaviour.

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Cross disorder genetic analysis of Tourette's syndrome, obsessive compulsive disorder and hoarding

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Introduction and objectives: Hoarding, Obsessive-Compulsive Disorder and Tourette Syndrome are common psychiatric disorders that share symptom overlap, which might partly be a result of shared genetic variation. Population-based twin studies have found significant genetic correlations between hoarding and OCD symptoms, with correlations varying between 0.1 and 0.45 (Mathews et al., 2014). Other lines of research including clinical samples and GWAS or CNV data to explore relationships between tics and OCD have failed to detect shared variation (Davis et al., 2013; Yu et al., 2014).

Here our aim was to extend current knowledge on the genetic structure underlying hoarding, OC symptoms and tics and, in a trivariate analysis, assess the degree of common and unique genetic factors contributing to the etiology of these disorders.

Methods: Data have been gathered from participants in the Netherlands Twin Register (Geels et al., 2013) comprising a total of 5293 individuals from a sample of adult monozygotic (n = 2460) and dizygotic (n = 2833) twin pairs (mean age 33.61 years). The data on Hoarding, Obsessive-Compulsive Disorder and Tourrette were simultaneously analyzed in Mplus. A genetic a liability threshold model was fitted to the twin data, analyzing heritability of phenotypes and of their co-morbidity.

Results and discussion: Following the criteria for clinical diagnosis in all phenotypes, 6.8% of participants had a diagnose for Hoarding, 6.3% for OCD, and 12.8% for TS. p {margin-bottom: 0.1in; direction: ltr; line-height: 120%; text-align: left; widows: 2; orphans: 2} Genetic factors explained 52.7%, 69.8% and 74.2% of the phenotypic covariance between Hoarding-OCS, Hoarding-TS and OCS-TS, respectively. Substantial genetic correlations were observed between Hoarding and OCS (0.46), Hoarding and TS (0.39) and between OCS and TS (0.53).

Conclusion: These results support the contribution of genetic factors in the development of these disorders, as well as for their co-morbidity. Furthermore, the values for the genetic correlations indicate that there are shared components in the genetic architecture of these disorders.

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Electromyographic patterns of tic hyperkinesis in children

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Introduction and objectives: Bioelectrical activity of muscles during tic hyperkinesis in children has been studied by several authors (Shanko, 1990; Zykov, 2002). However, to date no electromyographic criteria are formulated specific to tic hyperkinesis in children and adolescents.

Methods: 12 patients were examined aged 6–12 years. Tourette's syndrome was diagnosed in 3 patients, motor and vocal tics in 3 patients, and vocal ones in 3 patients. The control group consisted of 8 healthy children. Potentials were from the following muscles: frontal, circular of the eye, circular of the mouth, trapezius, supraspinatus, m. flexor digitorum superficialis, which corresponded to the localization of hyperkinesis. Interference curve was registered at rest and during stimulated hyperkinesis: test with 10 winkings and 10 fingers clenchings.

Results and discussion: The initial electromyograms showed no difference of the amplitude of the muscles at rest from normal values. Upon stimulation of hyperkinesis high-amplitude curves were recorded in the investigated muscles. In patients with Tourette's syndrome the maximum amplitude was observed on the interference curve from m. flexor digitorum superficialis – 2015.5 ± 89 mkV, duration 73 ± 0.6 ms (compared to normal 652.7 ± 77.82 mkV; p ± 119 mkV, duration 79.3 ± 4.4 ms, with vocal tics – 1431 ± 43.2 mkV, duration 88 ± 2.6 ms. The maximum intensity of "fires"of bioelectric activity was observed in the Tourette syndrome group (p ± 37.6 mkV) and in 2 patients with Tourette's syndrome (1138.7 ± 44.1 mkV); the tests conducted showed significant (p)

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