Tourette highlights from 2021

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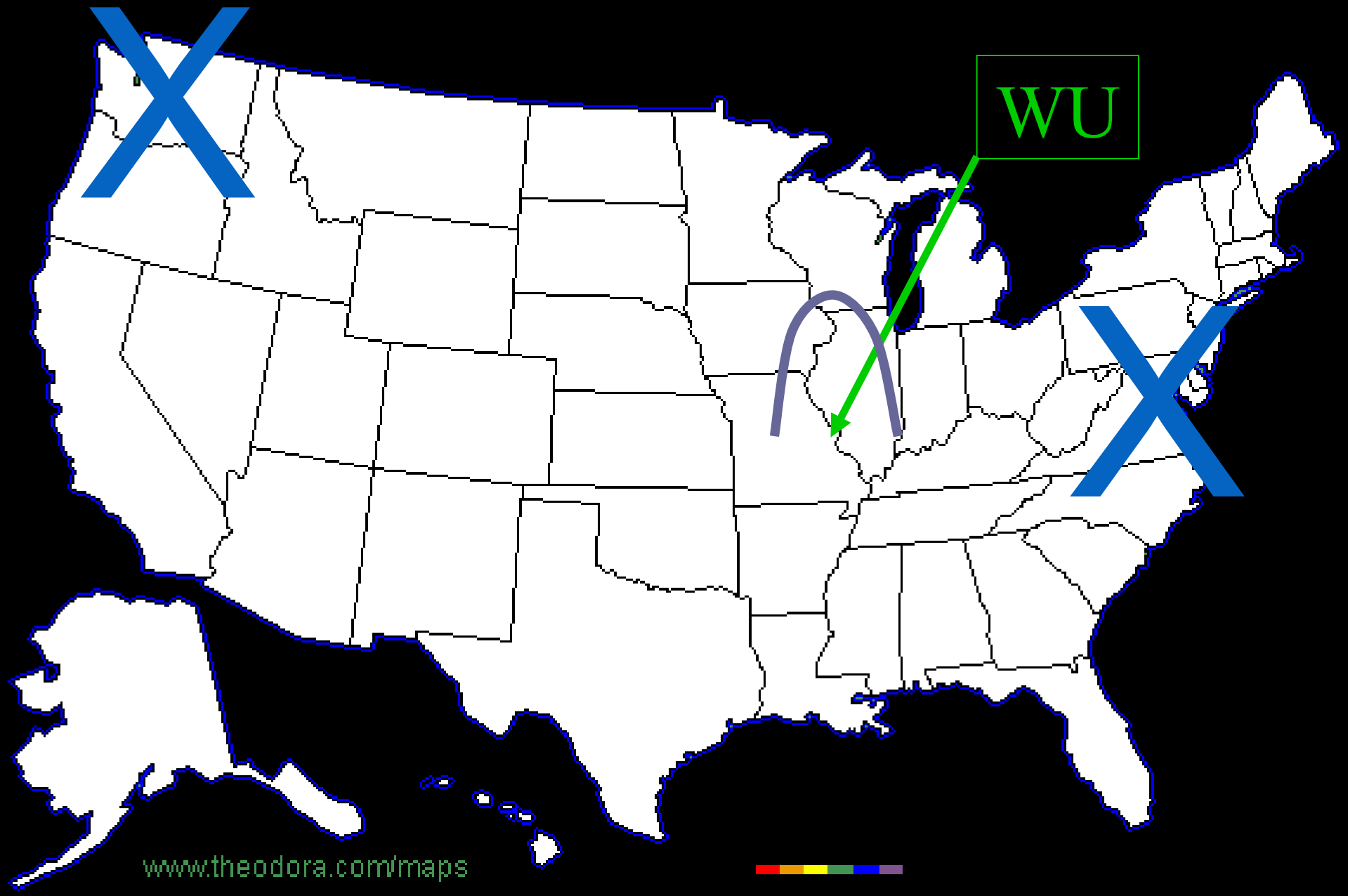
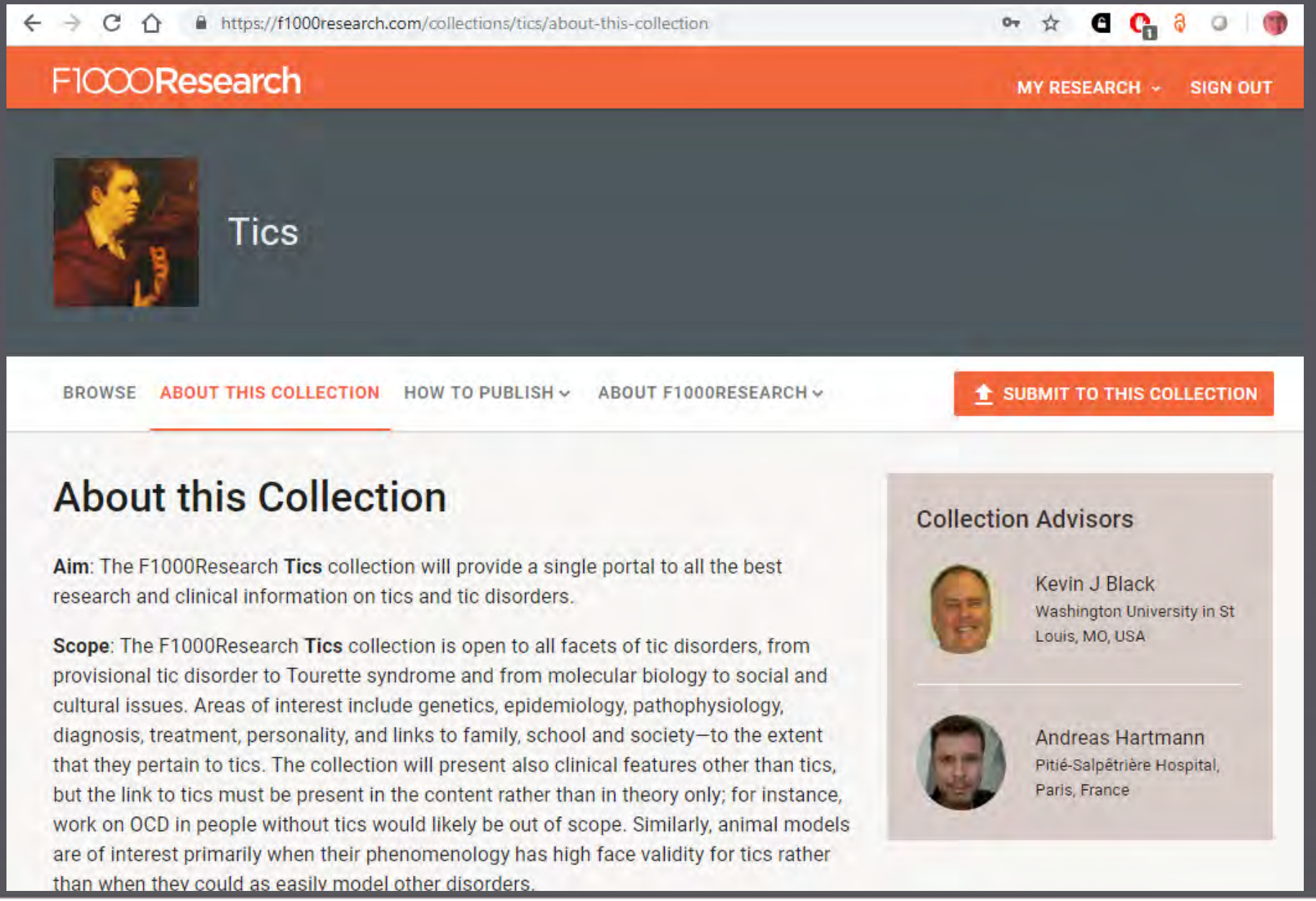

WU
www.theodora.com/maps

Disclosures

- Sources of research support:
  - NIMH, Tourette Association of America
  - Emalex
- Consulting relationships
  - SK Life Science Inc.
- Other
  - Medscape (CME program), MedEdicus (CME program)
  - Huntington Study Group (blinded rater for a study by Neurocrine Biosciences)
- Speaker's bureaus, Stock equity
  - none
- Off-label meds/devices … almost all

Highlights

- **Tics** collection, **F1000Research** platform
- Subjective selection of publications we think are important (or cool)
- Preprints, early online, paper



Thank you

- Andreas Hartmann, M.D.
  - Department of Neurology, Hôpital de la Pitié-Salpêtrière

- Per Andrén
- Cyril Atkinson-Clement
- Virginie Czernecki
- Cécile Delorme
- Nanette M. M. Debes
- Natalia Szejko
- Keisuke Ueda

This is not easy

- Telling you about your own work :/
- Skipping reviews, null results, and other important work
- I don’t understand some areas as well as others
- So … I may miss your important paper
  - But: I have a solution! Stay tuned ...

Phenomenology and natural history

Prognosis in PANS

- Pediatric Acute-onset Neuropsychiatric Syndrome
- Median 3.3 years follow-up after the diagnosis
- Most symptoms improved substantially
- Only 35% of children had a chronic, non-remitting course
- => These results suggest a generally positive outcome for children diagnosed with PANS, and interestingly may not differ substantially from the outcome in recent studies in non-PANS children, including the population of Provisional Tic Disorder

Gromark et al

Other tics / related phenomena

- Tonic tics
  - Abdomen > neck > upper extremities
  - Common, early; with more, ↑ severe, ↑ complex tics
- Blocking tics
  - 37% of 195 consecutive TS patients
  - Occurred early; with more severe symptoms
- "Cognitive tics" *i.e.* brief, sudden involuntary thoughts
  - 15% of 227 patients
  - Older age, more severe tics, anxiety

Kaczyńska and Janik; Janik et al

Cervical spine injuries in TS

- National database study
- 38% to 57% higher in TS *vs.* controls
- Similar risk in male & female
- Fortunately relatively rare, but some injuries can be serious and persistent

Isung et al
DOI: 10.1001/jamaneurol.2021.2798

Insomnia in TS

- National registry study, *N* = 10 million
- Insomnia 6.7 times more common in the 5,877 with a chart diagnosis of TS/CTD
  - adjusting for demographics and non-psychiatric illness
- Odds ratio somewhat lower after excluding
  - ADHD
  - ASD
  - a sibling with TS/CTD
  - or medication for ADHD

Isomura et al

Other movement disorders in patients with TS

- 201 patients with TS
- 1/3 had other abnormal movements
  - Subtle chorea (piano-playing movements), 11%
  - Stereotypies, 8%
- Not associated with tic severity
- Drug-induced 6%, but often no cause identified

Baizabal-Carvallo and Jankovic

Moral reasoning in TS

- This is a complex topic
- One study compared moral reasoning task performance in 21 adolescents with TS and 21 tic-free controls
- → Greater tolerance of unethical behaviors in adolescents with TS

Vicario et al

Food sensitivity

- Adults with TS (n=53, compared to 53 tic-free controls)
- Higher levels of food sensitivity and avoidance in TS
- Food neophobia was predicted by greater sensitivity to taste (gustatory hypersensitivity)

Smith et al

Tics *per se* aren't usually the problem

- Adults with TS at a subspecialty neurology movement disorders center
- Disease-related quality of life (QOL) did significantly correlate with current tic severity.
- However, QOL was explained primarily by current **non-tic** symptom severity (in decreasing order of correlation strength: anxiety, ADHD and OCD, followed by YGTSS total tic score [TTS]).
- In a hierarchical regression analysis, the association of TTS with QOL was statistically significant only after removing the other variables.

Isaacs et al

Phenomenology and natural history

Tic assessment and nosology

Nosology via machine

- Video in 101 patients with TS and 109 healthy controls
- Modified Rush Video Tic Rating Scale (mRVTRS)
- Best predictor of TS diagnosis was severity of motor tics
- (*not*) phonic tics

Paulus et al
DOI: 10.1093/braincomms/fcab282

Human (?) tic detector

- 17 patients with TS
- Surface EMG, accelerometer during voluntary movements and tics
- Modified Rush Video Tic Rating Scale (mRVTRS)
- Evaluated spectral properties of voluntary and tic movements with a sensor capturing the dominant tic
- Support vector machine (SVM) to detect and classify movements
- → Output comparable to expert consensus

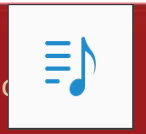
Cernera et al

Competition

- Videos of tic patients
- Unsupervised and supervised machine deep learning method to detect and classify movement
- Overall satisfactory distinction between tics and non-tic movements

Wu et al

Epidemiology



Sex differences?

- EMTICS group
- Males tend to have more severe symptoms than females, except mood and anxiety symptoms.
- Male symptoms seem more predominant at a younger age
  - Therefore their diagnosis might be facilitated compared to females

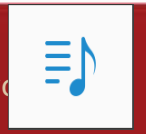
Garcia-Delgar et al,

Show me the future: kids *before* they get TS

- EMTICS group
- 61 children who developed tics in a 7-year follow-up *vs.* 126 children who did not
- Precursors to tics:
  - Male sex
  - Severity of conduct problems
  - Autism spectrum disorder
  - Compulsions
  - Emotional symptoms

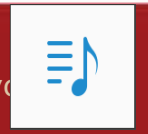
Openneer et al,

Etiology



Etiology

Genetics



Functional groups of genes

- TS/OCD Working Group of the Psychiatric Genomics Consortium
- 1285 cases with TS and 4964 ancestry-matched controls
- Three sets of genes differed in TS
  - ligand-gated ion channel signaling,
  - lymphocytic (driven by variants in FLT3), and
  - cell adhesion and trans-synaptic signaling sets

Tsetsos et al

Cross-disorder approach

- GWAS on 93 294 individuals
- Genes that contribute shared genetic risk for TS, ADHD, ASD, and OCD
- TS-ADHD-ASD:
  - hypothalamus-pituitary-adrenal gland axis

Yang et al

Single large multiply-affected pedigree

- *N* = 122
- DNA from 66
- This family had a high load of common risk alleles for TS
  - multiple common variants probably contribute more to risk than a few variants of strong effect

Halvorsen et al

Genes associated with maternal autoimmunity

- Approach
  - 200 sequential children with TS or OCD
  - 100 controls with autoimmune neurological disease
  - 100 age-matched healthy controls
  - Structured history of maternal & family autoimmune conditions
  - Maternal blood
  - Published transcriptomes from TS
- Results suggest maternal inflammation may contribute to TS/OCD

Jones et al

DNA methylation in identical twins

- Monozygotic twins
  - 8 pairs concordant for +TS
  - 6 pairs discordant for TS
  - 2 pairs with no TS
- No methylation site statistically significantly different
- But possible association with mTOR pathway

Hildonen et al

Connective tissue association?

- Joint hypermobility (as in Ehlers-Danlos) is more common in TS

Baeza-Velasco

Etiology

Environmental

PANDAS is an endangered species

- EMTICS group
- Prospective study for 16 months (mean) in 715 children with TS/CTD
- Regular monitoring of tic severity and regular surveillance for GABHS
- 308 children had 405 tic exacerbations …
- … but these were unrelated temporally to GAS exposure
- The authors conclude that their "study does not support GAS exposures as contributing factors for tic exacerbations in children with CTD. Specific work-up or active management of GAS infections is unlikely to help modifying the course of tics in CTD and is therefore not recommended."

Martino et al

“Tourette” videos on TikTok

- Popular videos on TikTok labeled as “Tourette”
- Showed features unusual for TS
  - aggression (19%), self-injurious behaviors (28%), coprophenomena (over half), long phrases (>3 words, 46%), throwing objects (22%), and very strong influence by the environment (over half)
- Senior clinicians viewing these videos rated them on a 1-5 scale → median was 5 (= “none of the tics are typical of TS”), IQR 4-5
  - *i.e.*, almost none of these patients’ presentations even slightly resembled TS to these clinicians

Vera et al

Specificity of unusual features in post-social media cases

- 13 cases dramatic start after social media, *vs.* 13 TS cases
- Features 100% specific for not-TS included
  - abrupt symptom onset, first symptom was complex, primarily slow and tonic movements, mostly trunk or extremities, a rapidly varying repertoire of symptoms, symptom deterioration in the presence of others, lack of spontaneous symptom fluctuations over the course of weeks to months, goal-directed movement (e.g., aimed at another person), and dramatic context dependence
- Symptoms unabated throughout the exam in 13/13, *vs.* 1 of 13 TS
- Onset 10.1 years later; copropraxia & echolalia in > half

Paulus et al

Prospective study, not circular

- Prospective cohort of children with tic-like phenomenology @ Calgary
  - 20 rapid-onset, 270 primary tic disorder.

Clinical feature	*p*		Clinical feature	Specificity
Older at onset (mean difference 7.5 years)	<.0001		ADHD	56%
Older at first MD visit (mean 3.8 yr)	<.0001		Female	84%
More severe anxiety	<.0001		Anxiety disorder	81%
More severe depression	<.0001		Depression diagnosis	96%
More severe motor sx (ΔTTS 14.9, Δimprt. 12.8)	<.0001			

Also summarize clinical experience at 8 centers across the world

Pringsheim et al

Pathophysiology

Pathophysiology

Animal models

Selective $GABA_A$ receptor agent

- $GABA_A$ receptors are multi-molecule assemblies with complex pharmacology
- Benzodiazepines and ethanol are positive allosteric modulators (PAMs) of $GABA_A$ receptors
- A PAM selective for $GABA_A$ receptors with α_6 subunits showed efficacy in the D1CT-7 transgenic mouse model of tics
- This PAM did not induced catalepsy, while dopamine antagonists did

Cadeddu et al

Pathophysiology

Electrophysiology

Functional connectivity EEG during cognitive inhibition

- EEG functional connectivity study
- Children with tics exhibited abnormal activation and communication patterns within the frontal-parietal lobe network during cognitive inhibition

Jurgiel et al

EEG functional connectivity in tic suppression

- High-density EEG at rest and during intentional tic suppression
- Alpha-band connectivity network differed during suppression
- Increased connectivity during suppression in a subnetwork that included right superior frontal gyrus and the left precuneus
- The pattern depended on age, consistent with maturation of brain circuits involved in tic suppression

Morand-Beaulieu et al

Brain activity preceding movement in TS

- μ- and β-band EEG signal preceding voluntary movements or tics
- μ and β oscillations not seen before tics
- Apparently amore network of brain regions including insula, cingulate cortex, basal ganglia, and cerebellum is involved in tic generation.
- β-band desynchronization when initiating voluntary movement in TS patients
- μ-band desynchronization during voluntary movement: (+) in tic-free healthy controls, (−) in TS
  - Suggests impaired physiological inhibition in TS

Morera Maiquez et al

Are tics "motor noise"?

- Test hypothesis that tics are behavioral surplus, or "motor noise"
- Calculated scale-free EEG activity (1/*f* neural noise)
- Task-related 1/*f* noise and high-frequency band aperiodic activity ↑ in TS during sensorimotor processing
- But apparently not related to tics
- Authors suggested that increased 1/*f* noise and aperiodic activity are not directly related to tics, but more likely reflect a new aspect of TS

Adelhöfer et al

Pathophysiology

Neuroimaging

Structural connectivity of the anterior cingulate cortex

- VBM found decreased volume of the ACC in TS
- In TS, increased structural covariance of ACC volume with motor parts of the cerebellum, inferior frontal cortex and posterior cingulate cortex

Jackson S et al

rs-fcMRI contains diagnosis-specific information

- SVM analysis of resting-state fMRI data could distinguish TS and control volunteers with an overall accuracy of 67% (*vs.* 50% by chance)
- Notable contributions from striatum, fronto-parietal cortex and cerebellum
- In addition, the authors distinguished medicated and unmedicated patients with an accuracy of 69% based on the activity of the striatum, the insular and cerebellar networks.
- Supports and extends previous work

XX et al

Network analysis of urge inhibition

- TS patients with O-C symptoms
- fMRI during a task involving blink suppression while viewing emotional (angry and neutral) faces
- compared to healthy controls, patients had higher activity in the superior temporal gyrus and the middle cingulate cortex
- tic severity ∝ activity during angry faces trials "?in comparison to neutral faces; (2) premonitory urge severity ∝ higher activity in the hippocampus, middle temporal gyrus, thalamus and caudate nucleus and (3) blink inhibition ∝ decreased activity in thalamus & insula

Bhikram" et al

Cognitive impulsivity, tics and regional brain activity

- Delay discounting (choose smaller reward now or bigger reward later)
- Overall discounting normal in TS group
- But subgroup with more impulse control disorders, more impulsivity
- Reward discounting $\propto$ brain activity in a network of orbito-frontal, cingulate, pre-supplementary motor area, temporal and insular cortices, as well as ventral striatum and hippocampus.
- Greater connectivity of pre-SMA with anterior insula predicted both steeper reward discounting and more severe tics.

Atkinson-Clement et al

GABA, MRS, premonitory urges

- MRS in right SM1, SMA and insula
- [GABA+], [glutamine]: no association with tic diagnosis or severity
- But in children with TS, PU severity and frequency $\propto \downarrow$ SMA [GABA+]

He et al

Inhibitory pathways

- Dual-site TMS and diffusion tensor imaging showed reduced prefrontal (pre-SMA) inhibition in children with TS/CTD compared to controls
- The decreased inhibition correlated with impairment of tic suppressibility
- Increased fractional anisotropy was observed in several white matter pathways in patients with TS/CTD
- Supports a plausible pathophysiological mechanism associated with tic persistence.

Bruce et al

Pathophysiology

Clinical and neuropsychological studies

To go or not to go …

- Sturm and colleagues
- 24 TS, 139 ADHD, 19 TD+ADHD, 59 healthy controls aged 9-14 years
- Inhibitory control measured with Attentional Network Task (ANT), Stop Signal Task (SST), Delis-Kaplan Stroop task, Go-Nogo task
- Tic suppression: PUTS item 10, and tic suppression paradigm
- Did not find inhibitory control deficit previously seen in TS ± ADHD
- The only predictor of objective tic suppression was subjective tic suppressibility; inhibitory control deficit, tics and ADHD severity had no effect

Storm et al

Tic timing is fractal in PTD and TS and reflects severity

- Peterson & Leckman 1998
- 535 five-minute videos ~4 months after tic onset (PTD), 358 videos at follow-up 12 months after tic onset (TS/CTD)
- Novel method to quantify fractality, borrowed from engineering
- Results: tic timing is fractal in TS; also in PTD; $D_f \propto$ TTS; D_f sensitive to intentional tic suppression and clinical improvement over time
- Confirmed in data from independent video rater
- We speculate that D_f may differ in FND-tic *vs.* TS

Beeler et al
medRxiv → J R Soc Interface

Treatment

Treatment

Psychological interventions

Behavior therapy for the masses: 1–2

- 224 youth with TS/CTD, therapist-supported, internet-delivered tx
- ERP (BIP TIC ERP) or psychoeducation
- 1° outcome: Δ YGTSS TTS from baseline to end of treatment
  - ERP: mean −4.5 (16%)
  - Comparator: −1.6 (6%); significant interaction of group and time
- Largest yet behavior therapy study for TS/CTD;
- First study to show ERP > active control intervention
- An ongoing similar Swedish RCT will also evaluate BIP TIC ERP

Hollis, Lancet Psychiatry
Andrén et al, Trials

Behavior therapy for the masses: 3

- 161 adult TS/CTD individuals were randomized to unsupported internet-delivered CBIT (n=67), unsupported internet-delivered psychoeducation (n=70), or face-to-face CBIT (n=24).
- Trend towards superiority of internet-delivered CBIT in reducing tic severity (YGTSS-TTS) at the primary endpoint (post-treatment)
- Statistically significant superiority 3 and 6 months post-treatment
- Tic severity improvements were lower than in RCTs of face-to-face CBIT, and dropout rates were relatively high; however, since no therapist is involved, internet-delivered CBIT should be a cost-effective and widely available treatment option

Haas et al
DOI: 77

Behavior therapy for the masses: 4–5

- online therapist support via videoconferencing was added to a regular face-to-face HRT intervention. The aim was two-fold: to provide therapist support for homework directly and to reduce the need for travel to the clinic. The format was shown feasible in a case series of children and adolescents (N=5). Viefhaus et al
- Peterson and colleagues [81] investigated the specific effect of relaxation training as part of the CBIT package (alongside HRT and function-based interventions). The study concluded that relaxation training alone was not effective in reducing tic severity

(Very) long-term follow-up of CBIT RCT

- Followed up young participants 11 years after receiving CBIT or supportive therapy vs education (comparator)
- Tic severity improved across the sample
- Treatment responders to both interventions in the original study achieved at least partial tic remission during the follow-up period (a YGTSS-TTSS score <14)
  - Treatment responders in the CBIT group were significantly more likely to achieve remission than treatment responders in the comparator group

Espil et al

Treatment

Medication

VMAT2 inhibitors for treating tics

- Sadly, both deutetrabenazine and valbenazine failed to meet primary endpoints in their respective studies in TS.

Cannabinoid system 1

- Lu AG06466 (formerly ABX-1431), a monoacylglycerol lipase inhibitor to increase 2-AG (2-arachidonoylglycerol), an endocannabinoid
- 12-week, multicenter, randomized, placebo-controlled, double-blind, phase II clinical trial
- Adults with TS
- No significant group differences on YGTSS, nor for other endpoints (tic severity, premonitory urges, quality of life, common psychiatric comorbidities).
- Further development for TS abandoned

Müller-Vahl et al
DOI: 92

Cannabinoid system 2

- 12-week open trial of a combination of Δ9-tetrahydracannabinol (Δ9-THC) and palmitoylethanolamide (PEA), THX-110
- Mean decrease YGTSS TTS = 7 (> 20%)
- 12 of the 16 participants elected to continue to the extension phase
- Some tolerability issues

Bloch et al

Treatment

Neurosurgery

DBS RCT 1

- DBS at the CM-Voi nuclei of the thalamus
- 8 patients
- Open label plus brief randomized, sham-controlled assessments
- Tics improved with stimulation ON vs. sham stimulation
- Improved quality of life

Baldermann et al

DBS RCT 2

- 10 patients randomized to sham, GPi or thalamic stimulation
- Tics improved with GPi DBS
- GPi > thalamic, sham
- No meaningful improvement in quality of life
- Highly variable response across patients
- 4/10 patients had to be re-operated due to cable dysfunctions
- 6 years after surgery, 5 out of 10 patients stopped stimulation due to infections, technical problems or lack of efficacy

Müller-Vahl et al

DBS: effect of small changes in lead location

- DBS registry study, modeled region of activation
- Tic improvement ∝ predicted activation in the associative pallido-subthalamic pathway, the ansa lenticularis, and the internal capsule tracts projecting to the prefrontal cortex
- Conclusion: anterior GPi DBS may act via associative and limbic pathways; posterior GPi DBS may act via sensorimotor networks

Johnson et al

Treatment

Other

Fluctuating magnetic fields for treatment

- Low-frequency repetitive transcranial stimulation (rTMS) of bilateral parietal cortex
- 30 adults with TS
- Positive results on all measures (YGTSS, mRVBTS, PUTS)
- Beneficial effects lasted for up to a month after the last rTMS session

Fu et al

Tics, family and society

Self-esteem matters (*and so do you* ☻)

- Adolescents with TS
- Psychosocial stress – self-esteem – social adjustment ?
- Self-esteem fully mediated the relationship between psychosocial stress and social adjustment
- Comorbidities moderated the relationship

Lee et al

Where can Johnny go for treatment?

- Health service delivery and care practices by clinicians in Canada, US, Europe and the United Kingdom
  - Conclusion: scarcity of specialized TS clinical care in all regions
- Tourette OCD Alberta Network
  - 10 parents interviewed in person; 140 parents surveyed
  - Often no clear pathway to access healthcare for people with TS and OCD
  - Identified several potential solutions: school-based training webinars, educational outreach in schools, and peer support

Bhikram et al
Fletcher et al

Guidelines

- The European clinical guidelines for Tourette syndrome were updated
  - Summary statement
  - Assessment
  - Treatment (psychological, pharmacological, surgical)
  - Patients' perspectives

Conclusions

Exciting work: maturing research community

- Larger and collaborative studies produced ever more frequent, important contributions.
- On the other hand, the flexibility of the TS clinical and research community was demonstrated by its response to the explosion of rapid-onset Tourette-like cases, beginning with rapid publication of case series but progressing quickly over the past 1-2 years to include international collaborations, controlled investigations, and prospective follow-up studies.
- All this despite severely problematic working conditions during the COVID-19 pandemic

Exciting work: novel or improved treatments

- Of perhaps greatest interest to our patients, new and actionable information appeared regarding numerous approaches to treatment of TS.
- These included the full range from psychological interventions to pharmaceuticals to non-invasive and invasive brain stimulation, and several clinical trials examined approaches that increased the availability of care at lower cost and to patients for whom frequent visits to a specialty center are difficult or impossible.

Subjective try to really pick high future impact on field

- Andrén, ORBIT
- Martino, PANDAS
- Cernera, Human Tic Detector
- Openneer, EMTICS, prospective study before tics start
- Espil, 11-year follow-up of child CBIT RCT
- Tsetsos, Psychiatric Genomics Consortium, functional gene groups
- Baldermann, DBS CM/Voi thalamus, brief sham RCT

Summary

- The literature is increasing fast enough that it's hard to keep up
- Studies are increasingly larger, more collaborative, and prospective
- European centers are outpacing other areas of the world
- A variety of novel treatments are being studied
- There's still a lot we don't know, including basic questions:
  - Why start at ages 5-10? Why boys? Why improved in sleep? Why do tics usually improve in adulthood? Does secondary prevention work?
  - Is there a natural non-human animal model?
  - Do neurosteroids work? Larger studies of cannabinoids. What's the minimum effective component of behavior therapy?
  - **How accurately can we predict outcome for an individual patient?**
  - **Which patients need which treatments?**

Predictions **2018**

Those who have knowledge, don't predict.
Those who predict, don't have knowledge.
—Lao Tzu

- Larger-scale studies will continue to increase
- AI will start to make video or wearables feasible for tic detection
- Newer genetic methods and larger samples will start to produce more frequent and more powerful results
- *Ex vivo* organoids from iPSCs will provide new insights ✗
- Cannabis-related molecules , noninvasive neurostimulation ✗ methods , TMS and CAM ✗ treatments will be tested further

Please help!

- I’m sure I missed something important, or overstated the relevance of a study I included.
- To improve next year’s talk, I warmly invite your cooperation:
  - Comment on the 2022 Highlights article’s first published version
  - Nominate important articles from 2022: Suggest a new publication of your own best work and/or one from someone else, at **https://authorea.com/554771** (or email me or Andreas Hartmann)

Tourette syndrome research highlights from 2022

+6 Andreas Hartmann, k.ueda, natalia.szejko, nanette.marinette.monique.debes, cecile.delorme, virginie.czernecki, cyril.atkinsonclement, Per Andrén, Kevin J. Black

Abstract

We summarize a few research reports from 2022 relevant to Tourette syndrome that the authors consider most important or interesting. This working draft aims towards submitting for publication around the beginning of 2023. The authors welcome article suggestions and thoughtful **feedback from readers**, who can add a comment by clicking on the rectangular comment box icon just to the left of the `BROWSE` link at the top of this page. For private comments you can reach us by email (andreas {dot} hartmann {at} aphp {dot} fr, or kevin {at} wustl {dot} edu).

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