



Tourette Syndrome and Related Disorders

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Disclosure of Potential Conflicts

| Source | Consultant | Advisory Board | Stock Equity >\$10,000 | Speakers Bureau | Research Support | Honorarium | Travel Support |
|---|------------|----------------|------------------------|-----------------|------------------|------------|----------------|
| Tourette Association of America | | X | | | X | | X |
| National Institute of Mental Health | | | | | X | | |
| National Institute of Neurological Disorders & Stroke | | | | | X | | |
| Abide Pharmaceuticals | X | | | | | | |

- *Off label indications will be discussed.*



Learning Objectives

At the conclusion of this activity, the participant should be able to:

- Explain the current diagnostic criteria for various tic disorders and their limitations
- Describe the epidemiology, natural history and presumed pathophysiology of tic disorders
- Describe the common co-morbidities associated with Tourette Syndrome
- Discuss pharmacological and non-pharmacological treatment options for tic disorders



What are tics?

- Rapid, arrhythmic, stereotyped movements
- Most commonly involve head, neck and arms
- Occur in bouts
- Tend to wax and wane over time
- Usually are partially suppressible
- Often preceded by a premonitory urge/itch/tension
- Separated clinically into different types:
 - motor vs. vocal
 - simple vs. complex

Tics



“I Have Tourette’s But Tourette’s Doesn’t Have Me”, HBO, courtesy of TSA



Simple Tics

- Brief contractions of isolated muscle groups

Motor

- Eye blinks
- Nose twitches
- Grimaces
- Shoulder shrugs
- Head, arm or leg jerks

Vocal

- Sniffing
- Coughing
- Throat clearing
- Grunting
- Barking/animal sounds

- Simple vocal tics are **just contractions of pharyngeal, laryngeal or respiratory muscles** resulting in sounds



Complex Tics

Motor

- Coordinated movements of multiple muscle groups
- May appear slower and “purposeful”
- Complex Gestures/Postures
- Echopraxia (mimicking others)
- Poking/pinching/punching (aggressive, self-injurious)
- Touching/tapping/picking (compulsive)

Vocal

- Complex utterances
- Syllables
- Words
- Phrases
- Echolalia (repeating others)
- Palilalia (repeating oneself)
- Coprolalia (socially inappropriate)
 - Present in **ONLY 10-20%** of TS patients

Spectrum of Developmental Tic Disorders

- Transient Tic Disorder (TTD)
 - Single or multiple tics lasting > 4 weeks, < 1 year
 - Now “Provisional Tic Disorder” in DSM-5

? Part of normal child development
- Chronic (Persistent) Tic Disorder (CTD/PTD)
 - Multiple motor OR vocal tics lasting > 1 year
- Gilles de la Tourette Syndrome (GTS/TS)
 - Multiple motor AND one vocal tic lasting > 1 year
 - Onset before age 18
 - DSM-5 removed “no 3 month period w/o tics”

Continuous biological spectrum





Epidemiology of Tic Disorders

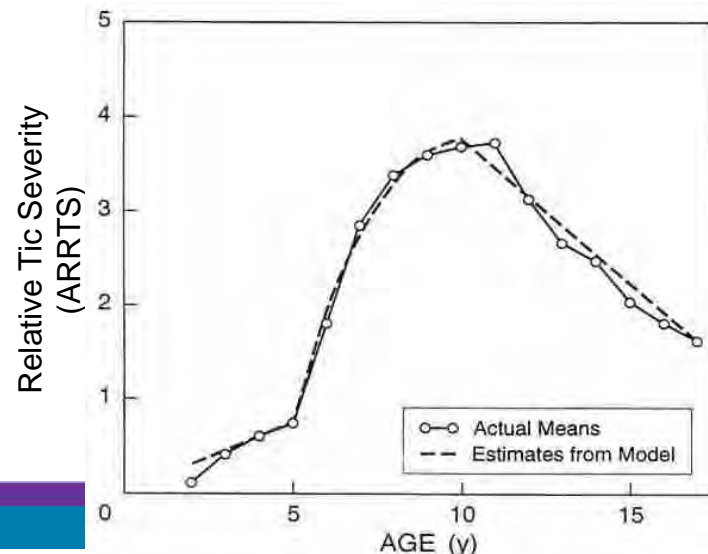
- Population prevalence estimates vary widely
- Recent community based estimates:
- Transient Tics: **25%**
- TS: 0.5-1% (higher in special education population)
- CMT: 1-2%

- 4:1 male:female ratio for TS; 2:1 for CMT



Epidemiology of TS/CTD

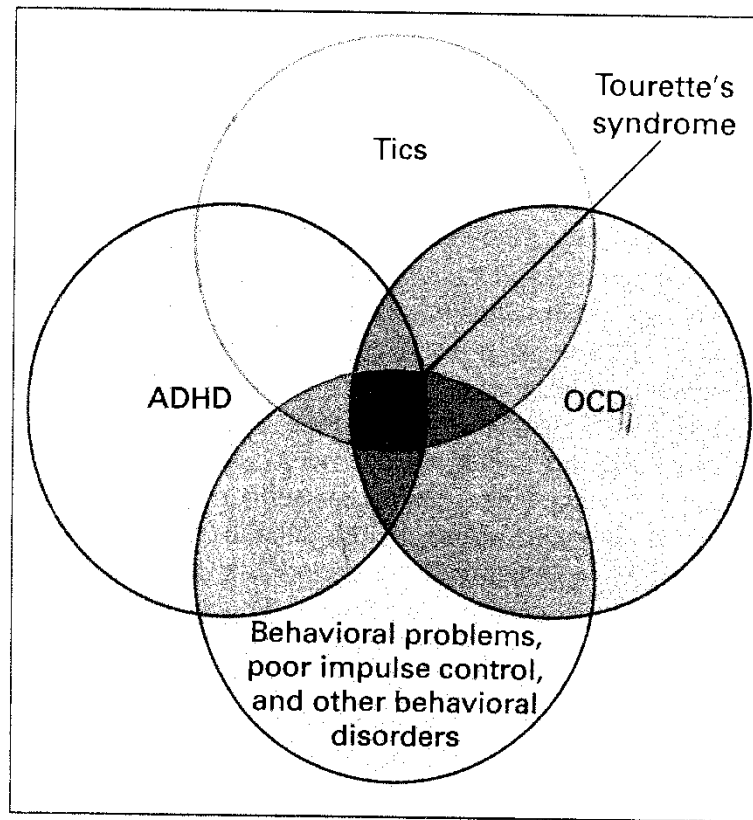
- Mean age of onset is age 5 to 7
- Maximum severity typically in early adolescence
- Most improve in late adolescence/early adulthood
 - Rule of Thirds: 1/3 resolve, 1/3 improve, 1/3 stay the same
- Recent follow-up study of 227 patients from TS clinic
 - 20% of pts >age 16 had no tics
 - 60% had minimal or mild tics
 - 20% had moderate-to-severe tics
 - may be biased toward persistent disease due to differential dropout





TS Comorbid Disorders

- Vast majority of TS clinic patients (~85%) have additional neuropsychiatric disorders
- Often comorbid condition is more disabling than tics!!!





OCD

- Obsessions: recurrent, intrusive thoughts/images
 - Thoughts produce intense distress and anxiety
 - Examples: Contamination, ordering/ arranging, symmetry, aggressive/sexual/religious thoughts, etc.
- Compulsions: Rituals used to neutralize obsessions
 - “Repetitive behaviors” or mental acts that must be performed in response to obsession or with rigid rules
 - Performance causes temporary relief of anxiety
 - Examples: Cleaning/washing, checking, ordering, counting, repeating, praying, evening up, etc.
- Symptoms waste time or cause distress/impairment



Epidemiology of OCD

- Two peaks of onset
- Adult onset form: Age 20s-30s, female predominant
- Childhood onset form: Age 6-18, male predominant
 - Childhood-onset with tic disorder
 - Childhood-onset without tic disorder
- Symptoms thought to persist throughout adulthood**
 - BUT: In follow-up, ~40% of TS pts w/ OCD ~age 12 had OCD >age 16
- Waxing-waning course
- Exacerbated by stress, fatigue, illness



TS and OCD

- 30-60% of TS pts meet DSM-5 criteria for OCD
 - Even more have subclinical OC behaviors
- Most TS patients report a premonitory sensory “urge”/ tension relieved by performance of tic
 - Sensorimotor equivalent of OC urge/response?
- Many complex tics have compulsive features (“evening up”, “just right” phenomena)
 - Treatment implications: Compulsive tics often require “tic” and “OCD” treatments to improve



TS and ADHD

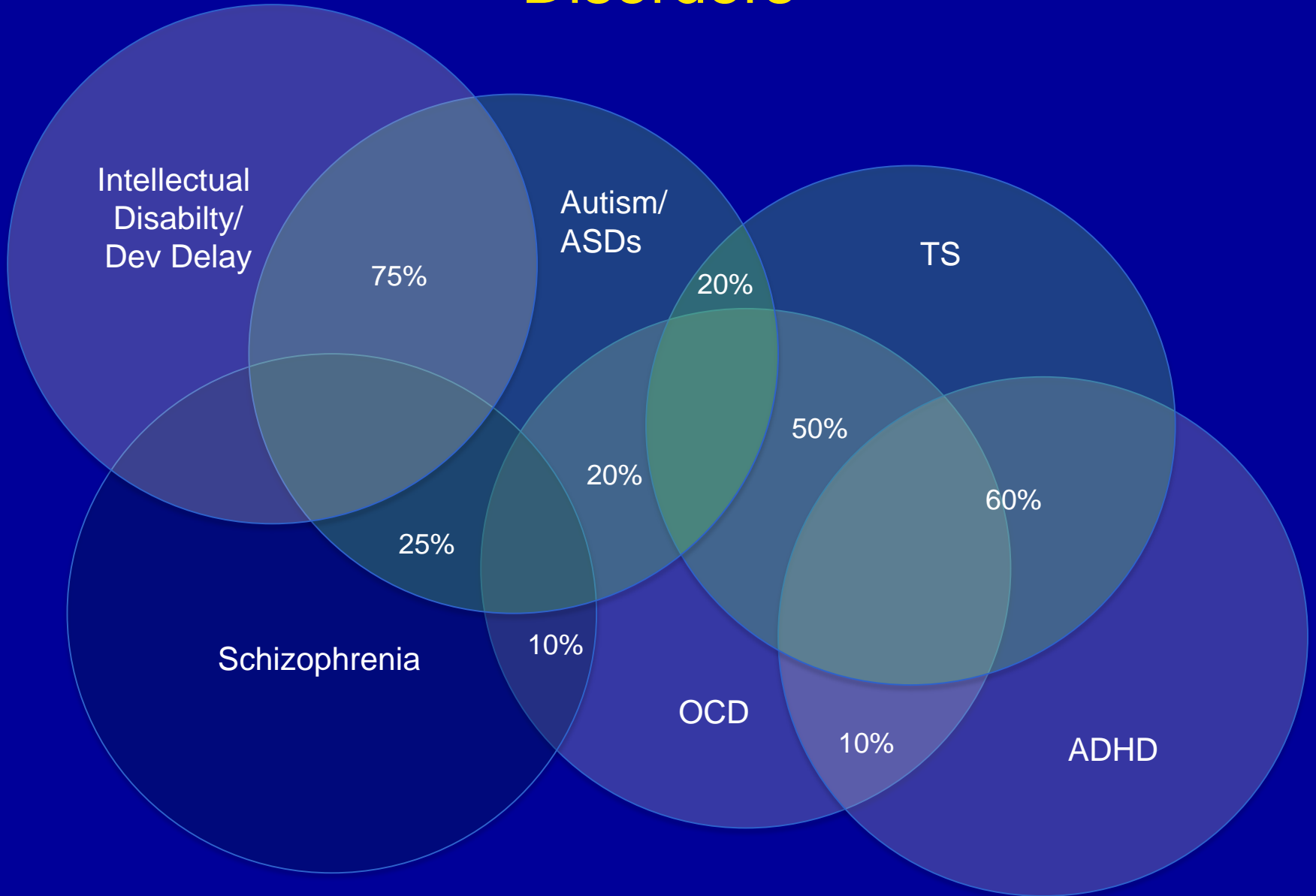
- 60-90% of TS pts have comorbid ADHD
- TS+ADHD is associated with:
 - Increased tic severity
 - Increased impairment
 - Additional co-morbid disorders
 - oppositional defiant disorder
 - intermittent explosive disorder (“rage”)
- **TS/OCD/ADHD tri-morbidity: ~30-50% of TS pts**

Additional Co-morbidities in TS Patients

- Impulse dyscontrol/"rage" attacks: 15-30% of pts
- Anxiety and mood disorders: ~40%
- Self-injurious behavior: ~15%
- Sleep disorders: 25-50%
- Learning disabilities: ~25%
- Autism spectrum disorders: 10-20%

- When seeing a TS patient, screening for co-occurring conditions is often more important than treating the tics!

Phenotypic Overlap in Neurodevelopmental Disorders

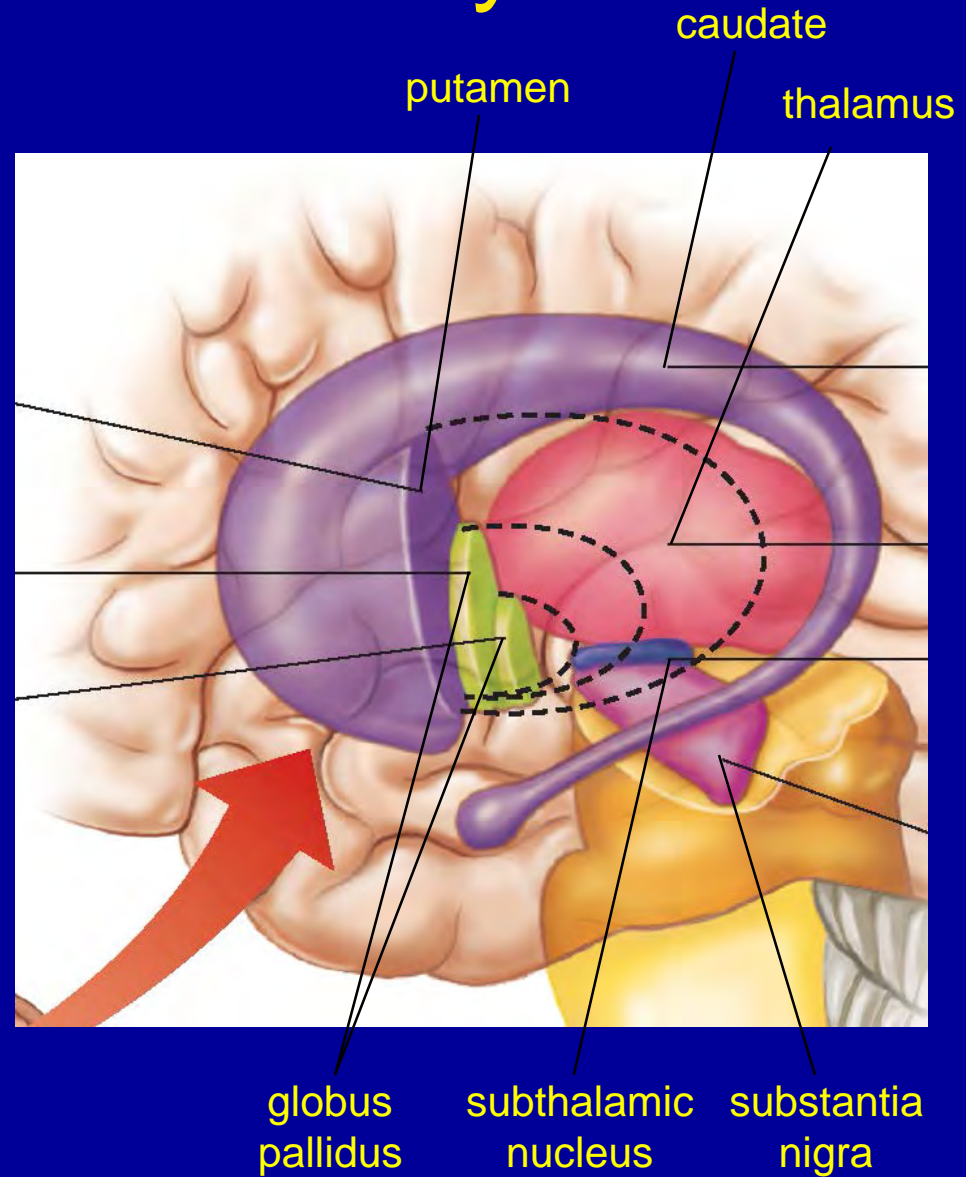
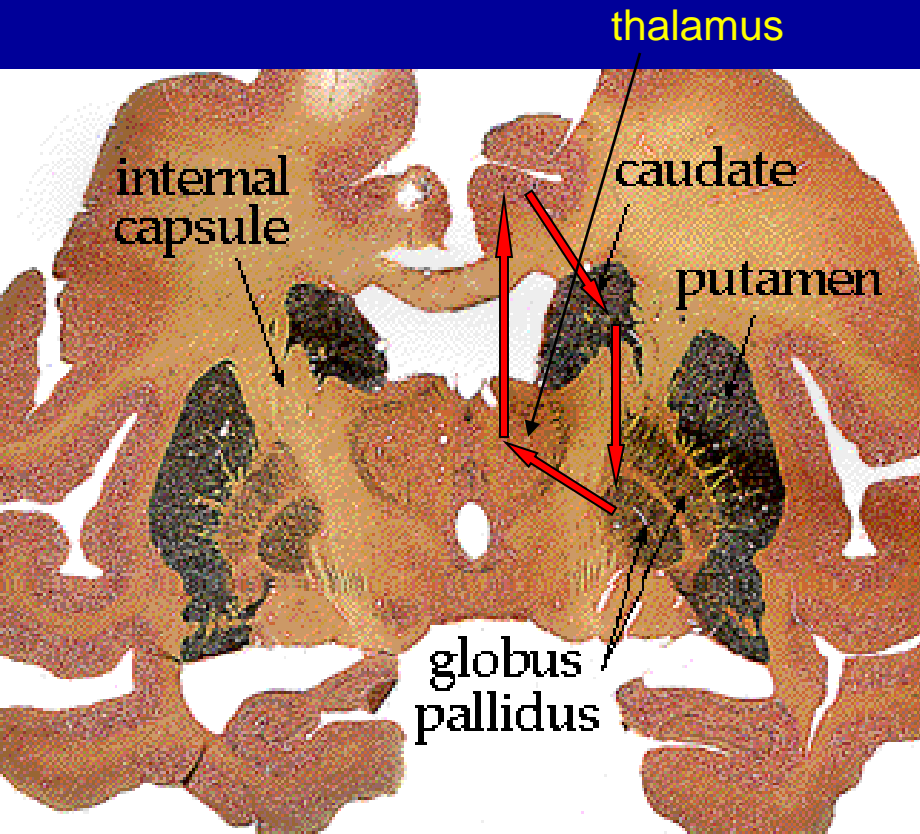




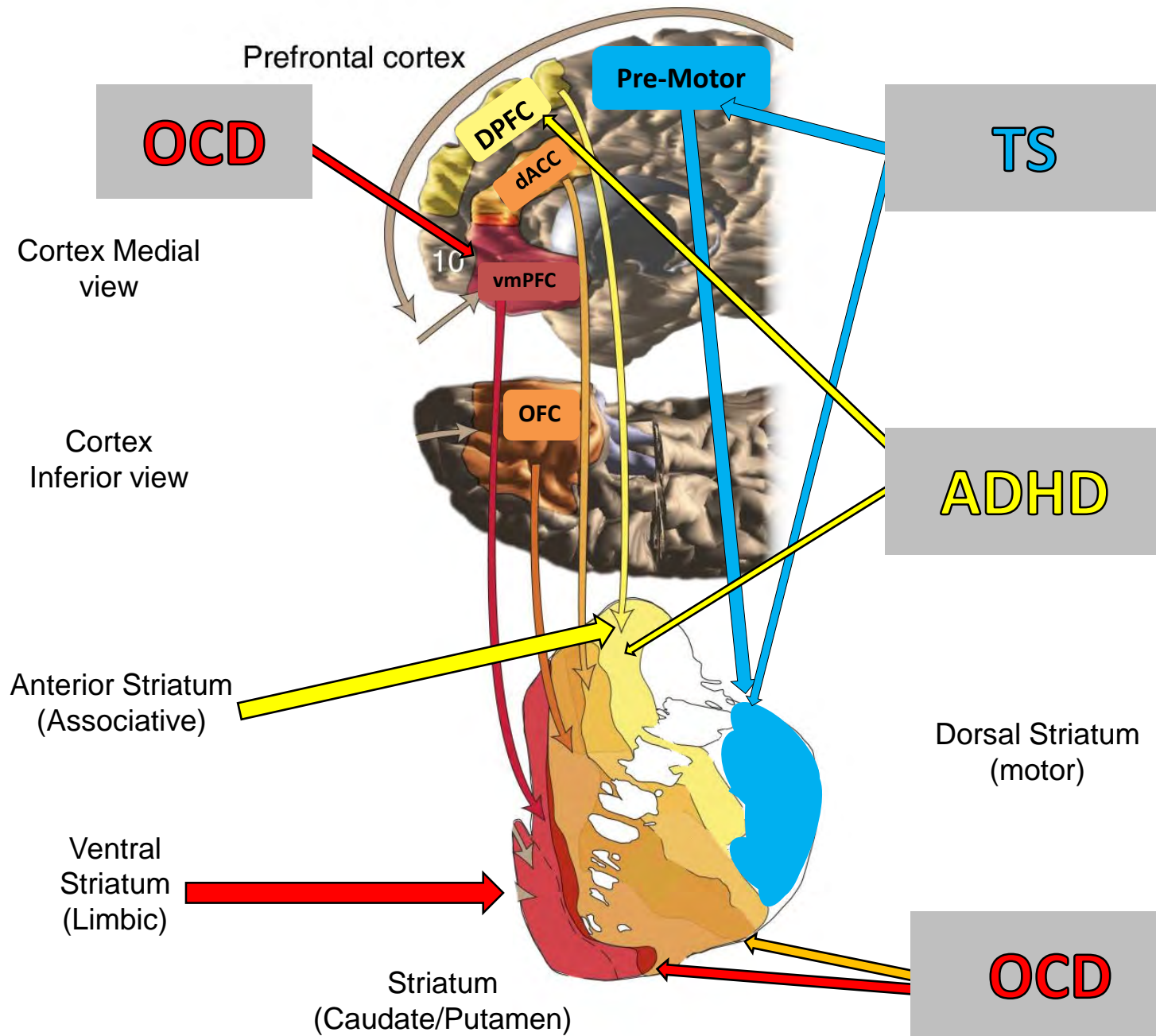
Tourette Syndrome: Pathophysiology

- TS is a biological, neuropsychiatric disorder under the influence of the external environment
- Studies implicate abnormal development of circuits between the ***basal ganglia , thalamus and cerebral [frontal] cortex***
- *Pharmacology:*
 - Altered dopamine (DA) function *in vivo*, though inconsistent
 - DA transport/release/binding abnormalities all reported
- *Imaging*
 - Decreased basal ganglia volumes on CT/MRI (~2-3% Δ)
 - *Altered functional activity in frontal-striatal-thalamic circuits*
 - Impaired **top-down control** of motor circuits
- *Autopsy studies*
 - altered density & number of GABA+, parvalbumin+ inhibitory inter-neurons and cholinergic neurons in the basal ganglia

Basal Ganglia Anatomy



“Cortico-striatal-(pallidal)-
thalamo-cortical loop”





TS has a strong genetic component

- Relatives of TS patients have increased risk of:
 - TS: 10-20%
 - Chronic Tics (CT): additional 10-20%
 - OCD: 10-20%
- Twin studies support TS genetic component
 - Heritability estimates ~80-90%
 - Suggest both genetic and non-genetic risk factors
- Data indicate TS is highly polygenic (i.e., like height)
- Definitive TS genes are starting to be identified
 - *NRXN1* deletions and *CNTN6* duplications in ~1% of TS pts

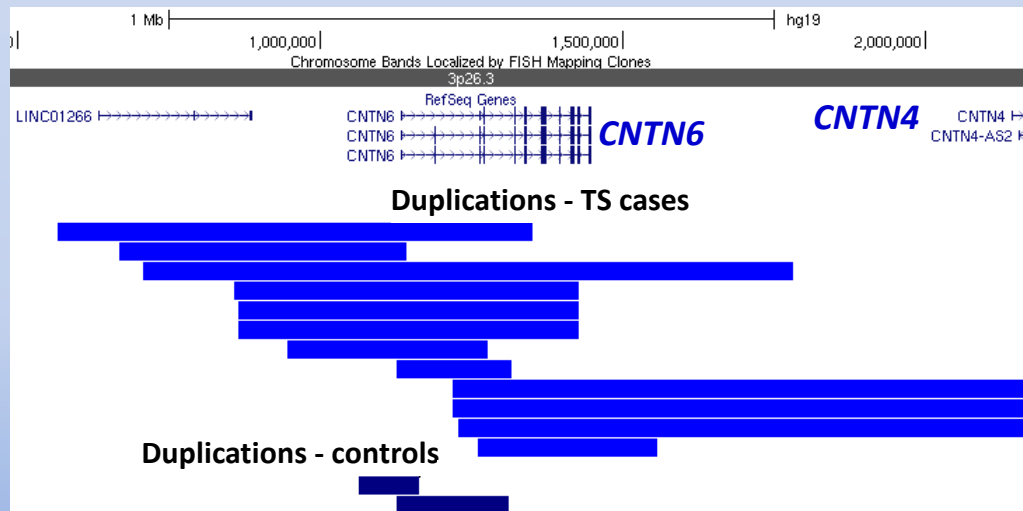
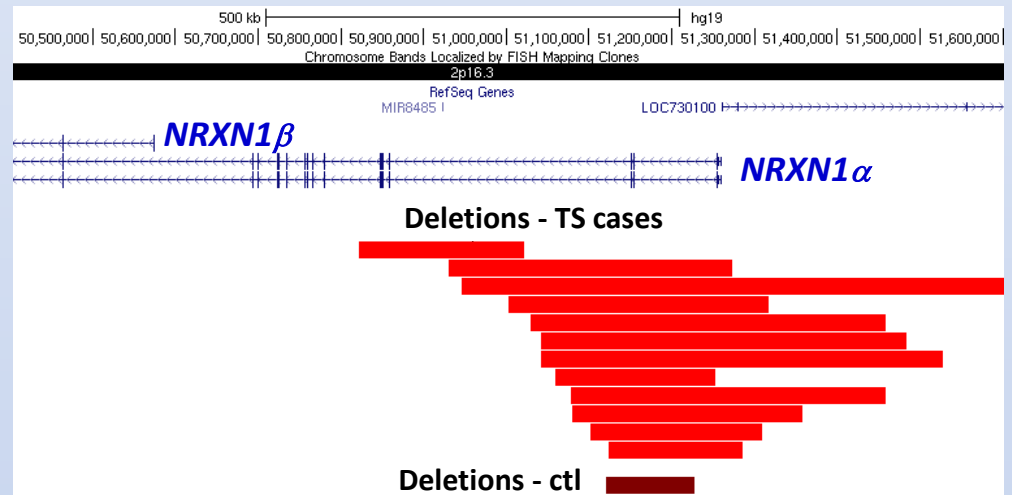
1% of TS cases carry one of these two CNVs

NRXN1 Deletions:

0.49% of TS cases

OR=20.3 (2.6-156.2)

$p_{\text{locus}} = 6 \times 10^{-6}$



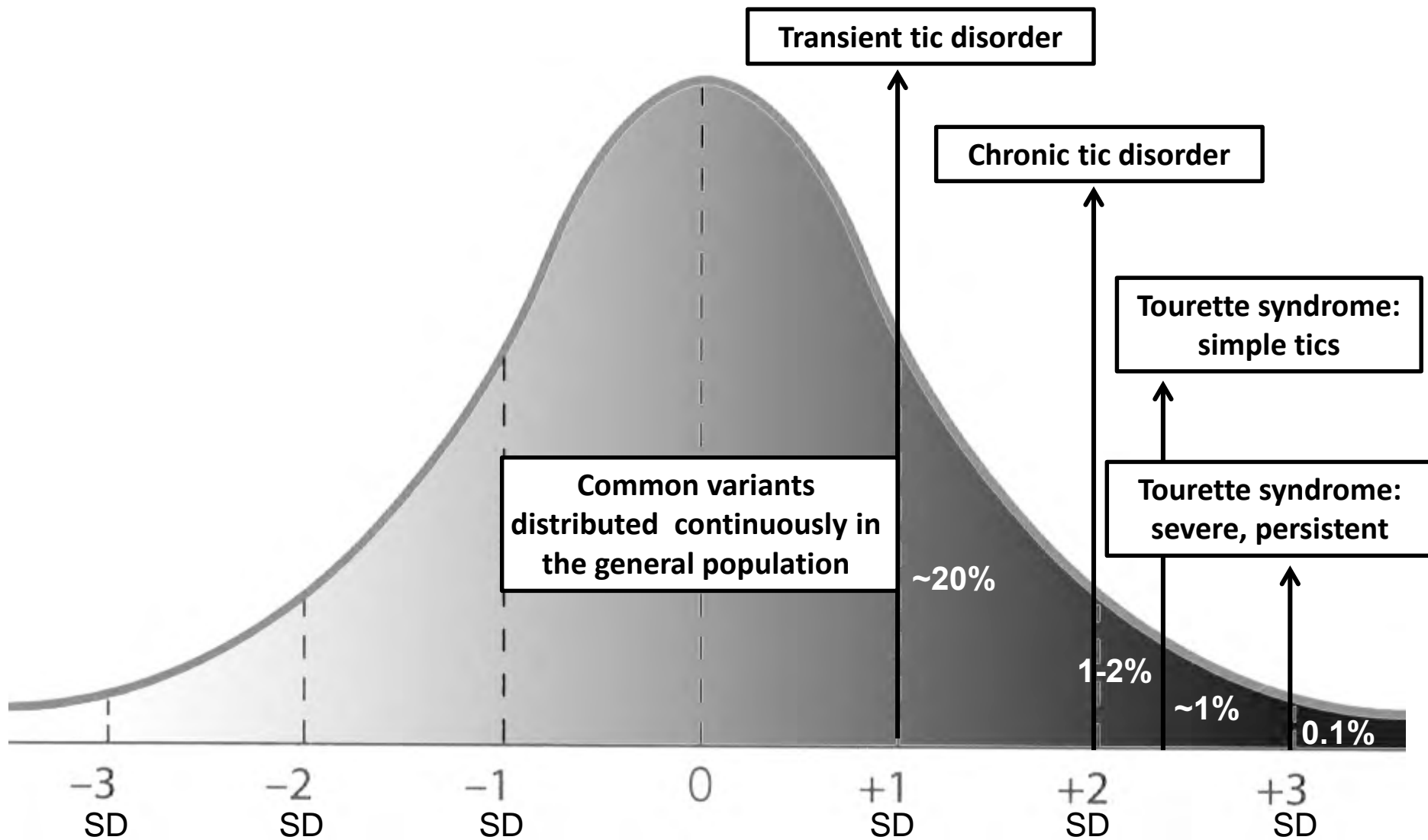
CNTN6 Duplications:

0.49% of TS cases

OR=10.1 (2.3-45.4)

$p_{\text{locus}} = 4 \times 10^{-5}$

Genetic model for heritability of developmental tic disorders





Differential Diagnosis of Tics

- Tic “mimickers”
 - Allergies
 - Stereotypy
 - typically bilateral hand movements; onset <age 3
 - Persistent, rhythmic, non-goal directed movement repeated continuously at the expense of other intended movements
- Tic disorders
 - Primary developmental tic disorder (i.e., TS/CMT)
 - Secondary tic disorder due to basal ganglia injury
 - **Drug-induced movement disorders**
 - Trauma
 - Vascular (stroke/hemorrhage)
 - Toxins
 - Infections (encephalitis)
 - Autoimmune disorders (lupus, antiphospholipid syndrome)
 - Rare inherited basal ganglia disorders (Wilson, Huntington)

Stereotypies



Stereotypies





TS: Diagnostic Evaluation

- Diagnosis made primarily on history
 - Key is observations from multiple historians
- Screen for neuropsychiatric co-morbidities
- Assessment of impairment/distress
 - family, friends, school, work
- Neurological examination usually normal
 - Examine smooth pursuit, voluntary saccades
- No routine labs or imaging necessary unless history is atypical or exam is abnormal



TS Treatment Overview

- Most patients (children) don't need tic treatment
- Treatment should only be considered if tics cause *significant distress and/or impairment*
- Identify/treat most problematic target symptoms first
- Treatments include pharmacological, behavioral or combined interventions.



TS Pharmacotherapy Overview

- Three “tiers” of tic medications
 - Tier 1: Alpha-2 agonists (clonidine, guanfacine)
 - Fewest side effects; generally small effects
 - Good for mild tics
 - Tier 2: Atypical neuroleptics w/ high D2 receptor potency (risperidone, ziprasidone, aripiprazole, etc.)
 - Aripiprazole is now FDA approved for TS
 - Moderate side effects – but can cause tardive dyskinesia!
 - Tier 3: Typical neuroleptics w/ high D2R potency (haloperidol, pimozide, fluphenazine)
 - Haloperidol and pimozide are FDA-approved for TS
 - Often needed for severe tics
 - Generally 3rd line agents due to side effect risk profile



TS Pharmacotherapy: Mild-moderate tics

Alpha-2 agonists

- Clonidine (Catapres) and guanfacine (Tenex, Intuniv)
- Clonidine has been used for >20 years to treat TS
 - reduces both motor and vocal tics
 - reduces ADHD symptoms (disinhibition, impulsivity, hyperarousal, and motoric overactivity)
- Neither as effective for inattention as stimulants
- Guanfacine is usually less sedating and longer acting
 - Clonidine dosed **tid-qid** in children; **bid** in adolescents/adults
 - Consider clonidine patch (less sedating; local skin reaction in ~25%)
 - Guanfacine (Tenex) is dosed **bid** in adolescents & adults
 - Guanfacine XR formulation (Intuniv) more expensive and may not work as well



Additional Tic Reduction Medications

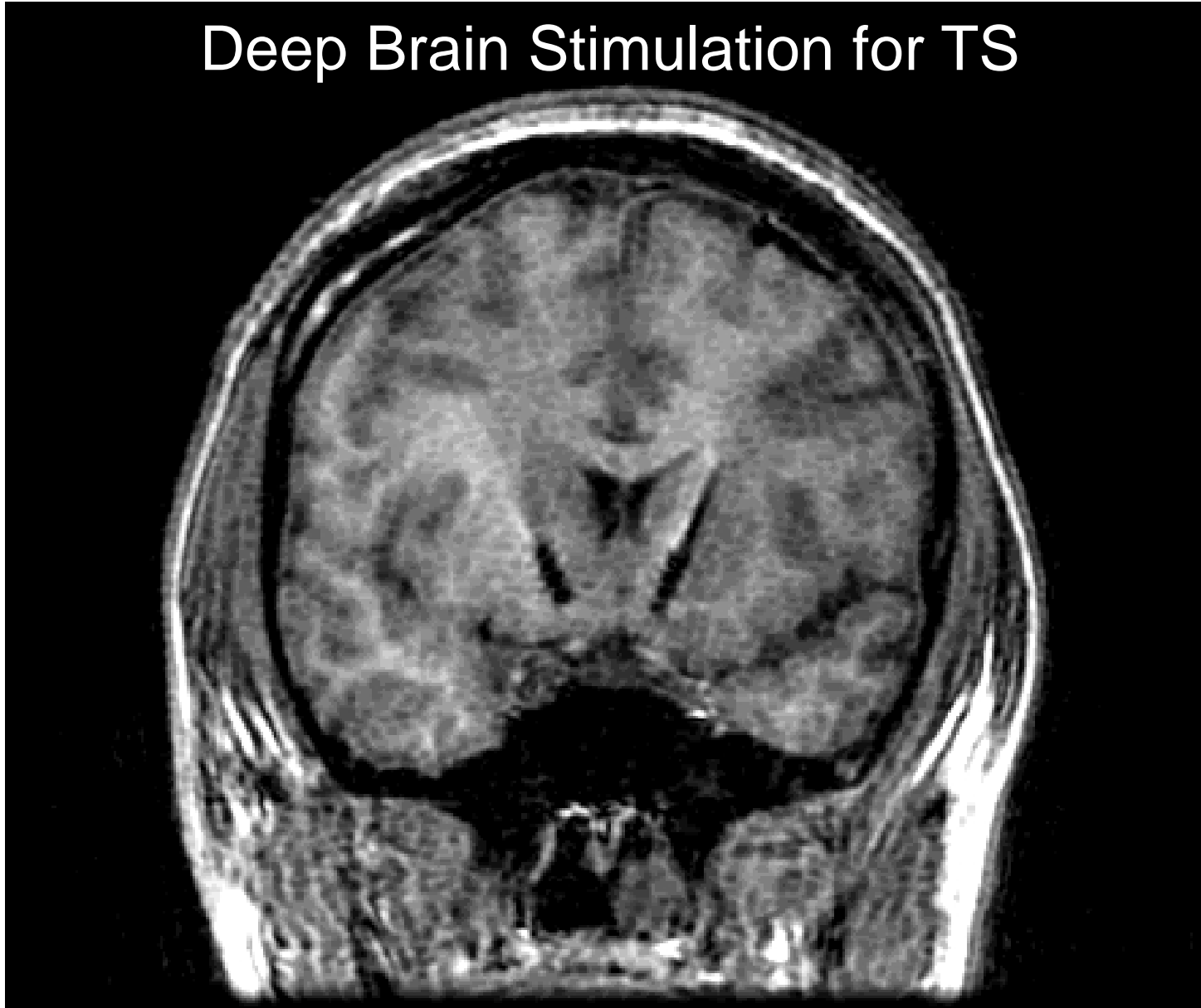
- Benzodiazepines: Clonazepam
- Topiramate (Topamax) (+/-)
- Baclofen (GABA modulator) (+/-)
- Tetrabenazine (Xenazine): effective, but expensive and causes depression in 25%
- ****Botulinum toxin injections**** (eyes, neck, vocal)

Currently in trials

- Ecopipam – D₁R antagonist
- Tetrabenazine analogs (valbenazine; deutetabenazine)
- Histamine H₃R Inverse Agonists
- Extended release acamprosate



Deep Brain Stimulation for TS





Deep Brain Stimulation in TS

- Many different sites explored
 - GPi, STN, centromedian thalamus, internal capsule
- Largest cohort (open label) is 36 pts with bilateral centromedian-parafascicular thalamic stimulation
 - 15 w/ sustained improvement at 2 years, still symptomatic
 - 3 with “less satisfactory” responses; dropped out prior to 2y
 - Higher rates of complications in TS pts vs other disorders
- Unclear how DBS affects TS co-morbidities
 - Mixed results in different studies
- Controlled trials are needed (1 Class III study of 8 pts)



TS: Non-pharmacological Treatments

- **CBIT (Comprehensive Behavioral Intervention - Tics)**
 - **FA (Functional Analysis)**
 - » Identify patient-specific antecedent events (triggers) of tics and potentially reinforcing consequences
 - » Identify social situations that influence behaviors
 - **Function-based Intervention of External Factors**
 - » Intervene to remove or minimize triggers or consequences
 - **HRT (Habit Reversal Training)**
 - » Awareness Training
 - » Competing Response
 - » Social Support
 - HRT demonstrated in RCT to be more effective than supportive therapy



Goals of CBIT/HRT

- Harness brain systems to mitigate symptoms
 - Not about “voluntary control”
 - Learning a management strategy
- Empower patients to do something about their tics
- Help patients feel more in control
- Stress management reduction



CBIT/HRT – Competing Response

- Opposite to or incompatible with the tic movement
 - Motor: Isometric muscle tensing
 - Vocal: Slow rhythmic deep breathing through nose with mouth closed
- Capable of being maintained for a brief period of time (about 1 minute)
- Socially inconspicuous
- Compatible with normal ongoing activities



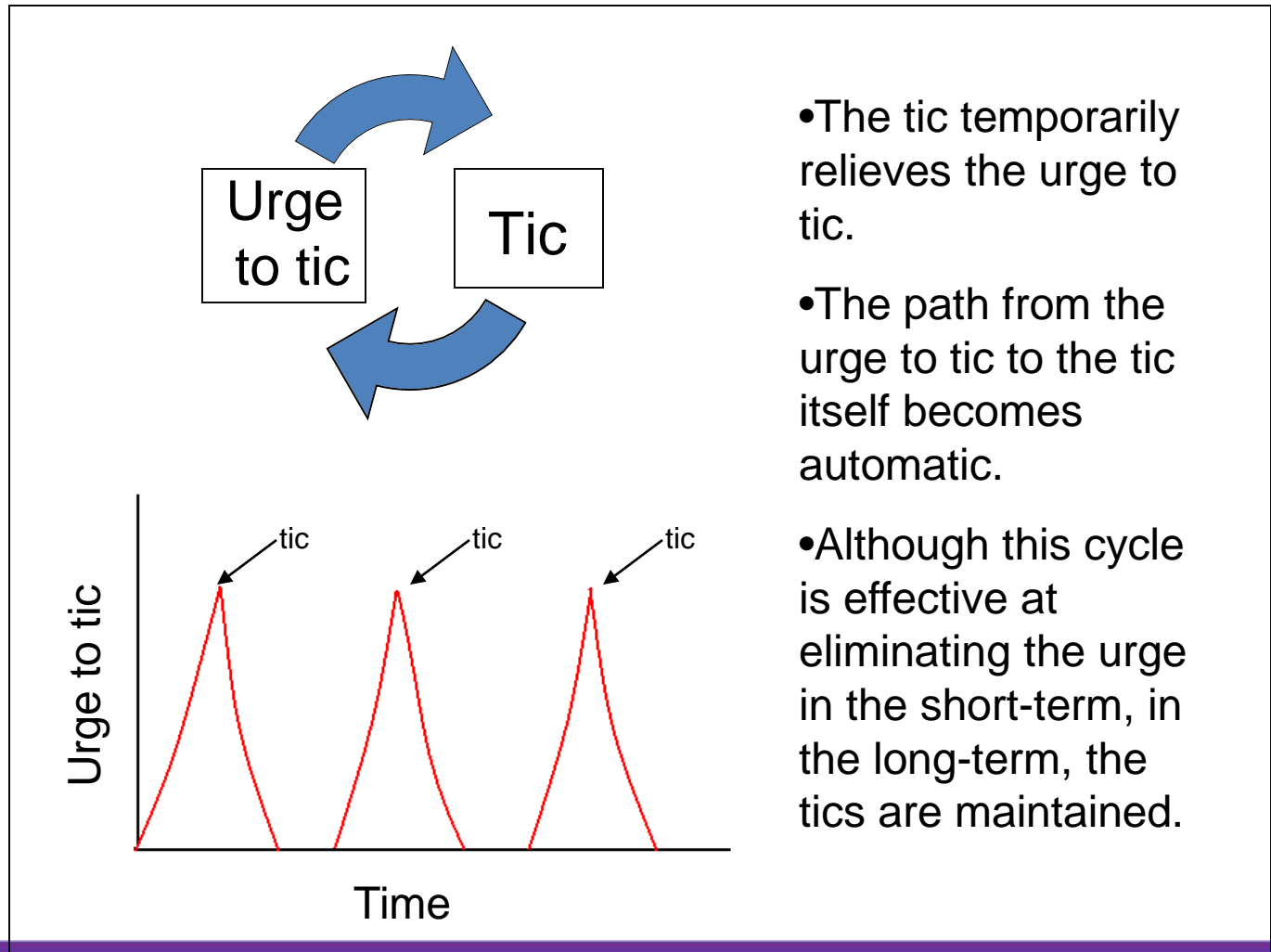
Behavioral Model of Tic Reinforcement

External factors

Certain situations, social attention, activities

Internal factors

Muscle tension, emotions (anxiety, frustration), stress



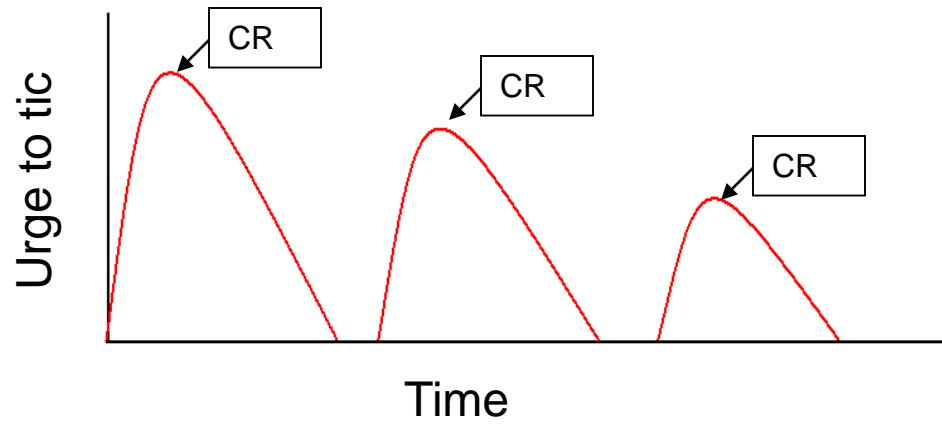
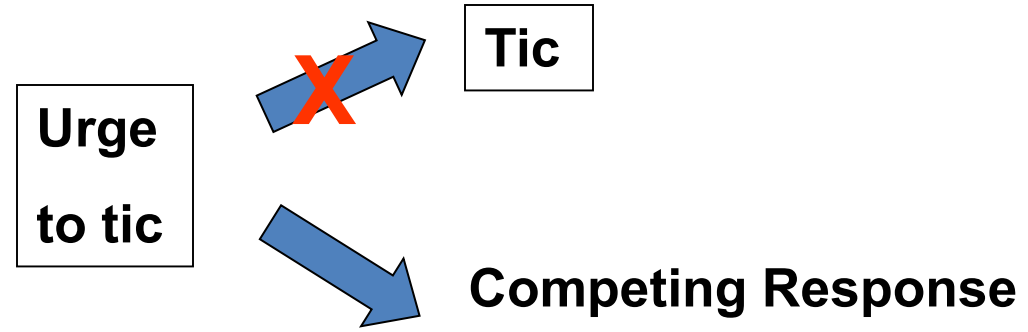


Exploiting Basal Ganglia Function to Reduce Tic Reinforcement

External factors
Functional Interventions →

Internal factors
Relaxation, Deep breathing →

Awareness Training and Competing Response Training





HRT: Habituation to premonitory urges

- Initially competing response prevents tic
- Over time, patients report a reduction in the premonitory urge
 - Short term: rebound effects
 - Long term: no rebound
- Similar to reduction of OC symptoms with Exposure & Ritual Prevention (ERP)

OCD Treatment in TS: Serotonin Reuptake Inhibitors

- Higher doses of SSRIs are needed to treat OCD compared to depression
 - Caution: FDA warning when using citalopram at doses >40 mg/d (↑QTc)
- OCD with tics is generally harder to treat than OCD without tics
- Sometimes augmentation with atypical neuroleptics are needed
- Tics may transiently worsen with initiation of SSRI
- Cognitive Behavioral Therapy (CBT) is very effective



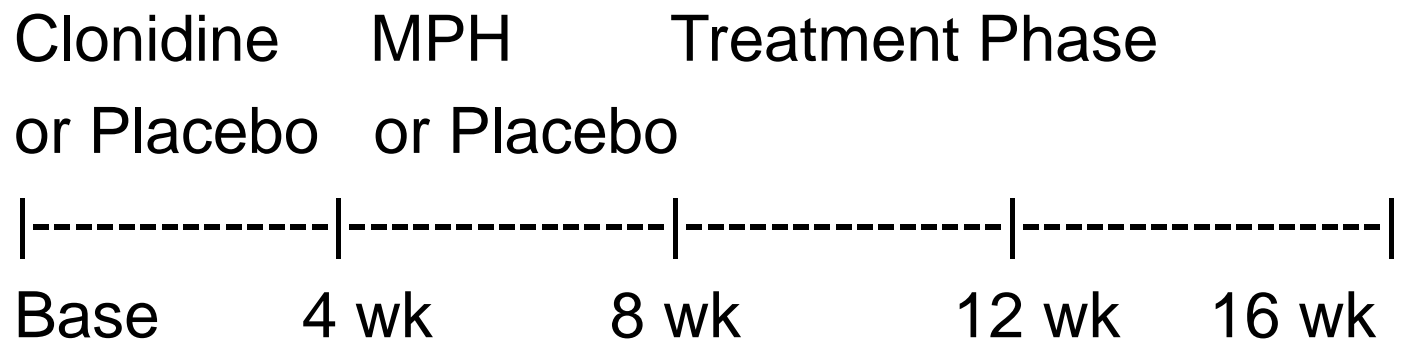
TS and ADHD Pharmacotherapy

- Clonidine or guanfacine can be helpful if ADHD is mild and tics are problematic
 - Good for hyperactivity/impulsivity
 - Less good for inattention
- Atomoxetine has been demonstrated not to increase tics when used to treat ADHD
- Stimulant use in patients with tics traditionally avoided due to concerns about tic worsening, but ...



Treatment of ADHD and Tics (TACT): Targeted Combined Pharmacotherapy Study

- NINDS sponsored multi-center study of clonidine and methylphenidate in children w/ ADHD & TD/CT
- Design: 136 children (ages 7-14) treated in 16 week double blind placebo controlled protocol





TACT Study: ADHD results

- ADHD (Teacher Conners):
- Compared to placebo
 - Significant improvement in CLON ($p < 0.002$) and MPH ($p < 0.003$) groups vs. placebo
 - Greatest benefit for CLON + MPH ($p < 0.0001$).
- Clonidine better for hyperactivity and impulsivity; Methylphenidate better for inattention



TACT Study: Tic symptom results

- Tic Severity *reduced in all treatment groups vs. PBO*
 - Clonidine + MPH > clonidine > MPH alone > placebo
- Mean doses of each drug were low
 - 0.25 mg clonidine
 - 25 mg methylphenidate
- Adverse Events:
 - **No difference in % pts with worsening of tics**
 - MPH (20%), CLON (26%), placebo (22%) groups
- There were **no safety issues**, particularly cardiovascular.



TD and ADHD Pharmacotherapy

- Stimulants are NOT contraindicated in TS patients
- Goal is to START LOW, GO SLOW
- Transient tic worsening may occur but often abates if wait it out
- Generally keep MPH dose less than 1 mg/kg/d
- Combination of clonidine and MPH may provide best outcome



TS Summary

- TS is a common biological disorder with both neurologic and psychiatric features
- TS rarely is an isolated tic disorder
 - “Hidden” comorbidities often more impairing than overt tics
- Many patients need no pharmacological treatment
- For mild tics that need treatment, clonidine or guanfacine is a recommended first line approach.
- Atypical or typical neuroleptics should be reserved for severe cases, used cautiously & monitored closely.



TS Summary

- Co-morbid disorders should be aggressively sought out and treated
- For TS+ ADHD, stimulants are NOT contraindicated, and may be first line treatment if ADHD symptoms are causing impairment
- Non-pharmacological management can be extremely helpful
- CBIT/HRT has demonstrated efficacy in a multi-center RCT and is an excellent option
- Ultimate goal is to help patient develop and maintain appropriate self-esteem and coping skills



Acknowledgments

- Tourette Association of America (TAA)
<http://www.tourette.org>

Patient page for enrolling in TS genetic studies:
<http://www.findtsgenes.org>

Questions? Email: jscharf@partners.org



Extras



TS Pharmacotherapy: Moderate-severe tics

Atypical neuroleptics

- Atypical Neuroleptics studied in Tourette Syndrome
 - risperidone (Risperdal)
 - aripiprazole (Abilify) – now FDA approved for TS in adults & children
 - ziprasidone (Geodon)
 - olanzapine (Zyprexa)
- Anti-tic Efficacy correlates directly with dopamine D2 receptor blocking activity (risperidone>ziprasidone>olanzapine)
- Doses are relatively low compared to those used in other psychiatric disorders
- Due to potential side effects, careful medical evaluation prior to treatment and ongoing monitoring is essential
- For risperidone, start 0.125-0.25 mg daily
- Target dose: Total daily dose 0.5-3 mg daily in divided doses.



Atypical Neuroleptics: Monitoring

- Serum chemistries, Liver Function Tests, Complete Blood Count (CBC) prior to initiation
- EKG prior to initiation (particularly ziprasidone)
- Weight, waist circumference, BMI: outset & followups
- Fasting glucose and lipid profiles: outset & q3-6 mos.
- Neurologic monitoring for motor side effects
- *Take home point: Use if necessary, but serial monitoring is required for longer term use.*



TS Pharmacotherapy: Severe tics

Typical neuroleptics

- FDA approved medications for TS
 - Haloperidol (Haldol)
 - Pimozide (Orap): NOT clearly better than Haldol/Prolixin & has many drug-drug interactions plus QTc prolongation
 - Fluphenazine (Prolixin) commonly used; not FDA approved
- Most effective of all tic medications
- Side effect profile is NOT favorable:
 - Tardive dyskinesia
 - Extrapiramidal (motor) side effects:
 - Parkinsonism, motor restlessness, stiffness, tremors
 - Weight gain
 - Sedation and cognitive dulling



Pediatric

A

Autoimmune

N

Neuropsychiatric

D

Disorders

A

Associated with

S

Streptococcal infection



Pediatric **A**cute-onset **N**europsychiatric **S**ymptoms

Childhood **A**cute **N**europsychiatric **S**ymptoms



PANDAS: Proposed Criteria

- Presence of OCD and/or a tic disorder
- Abrupt symptom onset
- Pre-pubertal onset (age 3-12)
- Episodic course
- Temporal association of onset or exacerbation with Group A β -hemolytic streptococcal infection
- Choreiform movements present
- Presumed auto-immune disorder similar to Sydenham's chorea



Evidence For PANDAS

- 50 cases formally reported
- Positive throat cultures, rising ASO/anti-DNAse B titers documented in association with onset and/or exacerbation of tics/OCD
- Increased serum anti-neuronal antibodies in pts
- Therapeutic response to plasma exchange, IVIG and antibiotics
 - Though recent double-blind placebo-controlled IVIG trial was negative (Williams et al, 2016)
- Animal model



Evidence Against PANDAS

- Most non-PANDAS TS patients have onset before puberty
- Clinical course: 53% of 80 consecutively referred TS patients had sudden, explosive worsening or onset of tics
- **All neurologic disorders worsen with infections**
- Multiple methodological problems with treatment studies
- Studies of anti-neuronal antibodies and inflammatory markers do not correlate with tic exacerbations
- Case-control study did find more exacerbations in presumed PANDAS cases vs. TS/OCD controls, but only 5 of 64 exacerbations were associated w/ GABHS infection
- PANDAS cases had MORE STREP than “non-PANDAS”
 - Is PANDAS an increased susceptibility to strep, but not tic-related?



PANDAS: Current Clinical Implications

- Antibiotic treatment of acute strep infection is indicated by positive throat culture or rapid strep test
- Conventional treatment of tics and/or OCD is indicated if causing significant distress or impairment
- Low threshold for culture and acute/convalescent titers with fever and/or acute exacerbation of tics/OCD
- Immunomodulatory therapy not recommended outside of clinical trials
- Antibiotic prophylaxis not generally recommended, but may be appropriate in some children



PANS/CANS: A useful revision?

- **PANS: Pediatric Acute-Onset Neuropsychiatric Syndrome**
 - Removes streptococcal infection as causal
 - Focuses on acute clinical presentation requiring further study
 - Recommends broad workup for neurologic causes, though in practice emphasizes infection/inflammation as central
 - Expands triggers to include Mycoplasma and Lyme infections
- **CANS: Childhood Acute Neuropsychiatric Symptoms**
 - Focuses on acute, fulminant clinical presentation
 - Does not emphasize infection/inflammation per se
 - Provides broad differential diagnosis for further evaluation
 - Differential diagnosis and workup outlined in Singer et al., 2012
- In general, recommend caution before prescribing IVIG or plasmapheresis outside of formal clinical trials