ESSTS

Attention Deficit Hyperactivity Disorder and Tourette syndrome

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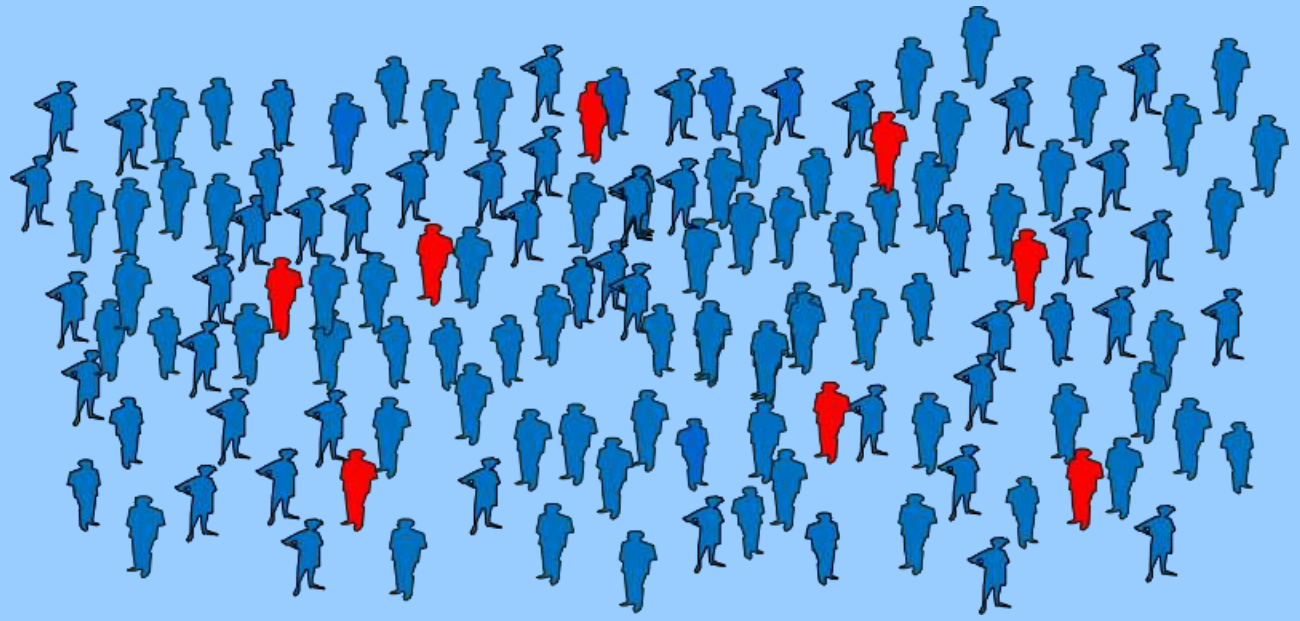
ADHD

- Childhood onset before age 12
- Prevalence 5%
- 3 subtype
  - Inattentive
  - Hyperactive-impulsive
  - Combined

ADHD and TS prevalence

- Population study: minimum 20% of TS has ADHD (Scharf et al, 2012)
- Clinical studies: approx 55% (Freeman et al. 2000, Hirschtritt et al., 2015)

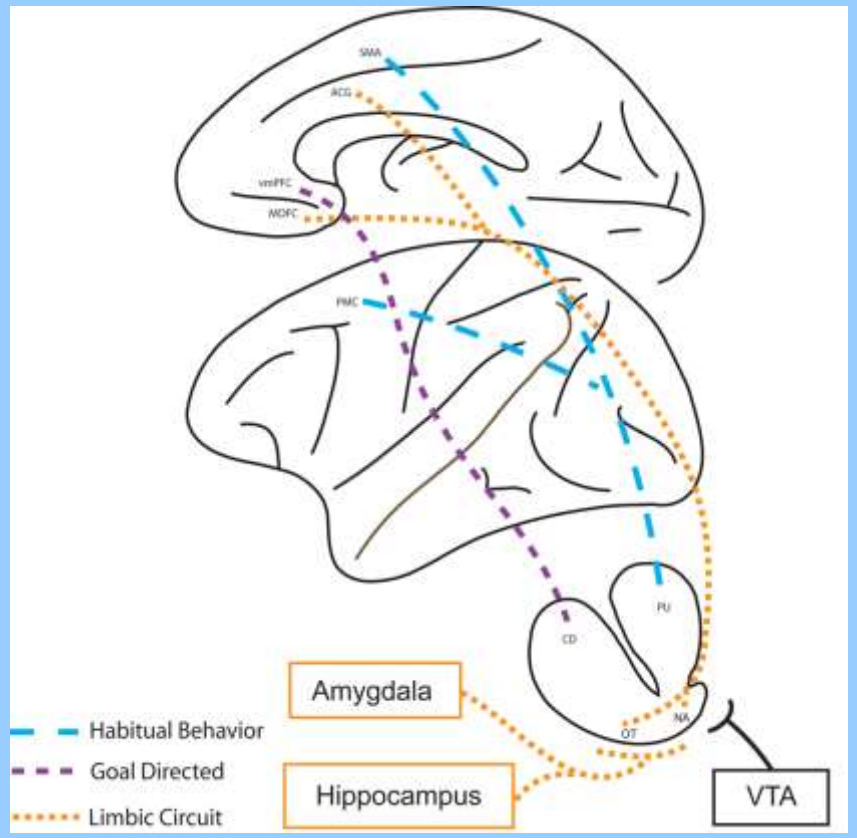


What if ADHD is also present in TS?

- ADHD is linked with various **impulsive behaviors** in TS patients (Palumbo and Kurlan, 2007; Yamamuro et al., 2015)
- ADHD is most associated with **anger problems** in TS (Freeman, 2000)
- **Distruptive behavior** :low frustration tolerance, outbursts, noncompliance and aggression (Roessner et al., 2007)
- **peer relationships**, internalising/externalising behaviors and **academic achi**evement (Poh et al., 2018)
- **Sleep** problems (Freeman, 2007)
- Comorbid ADHD is associated with a **lower ability to suppress tics** (Sambrani et al. 2016)

Common neurobiology?

Large number of studies investigating the question



- the responsible complex pathways are not clear

- ADHD-TS vs TS-OCD abnormalities in glutamatergic neurochemistry in the fronto-striatal circuitry

Naaijen et al, 2016

Shared genetic basis?

Archival Report

Biological Psychiatry

Investigating Shared Genetic Basis Across Tourette Syndrome and Comorbid Neurodevelopmental Disorders Along the Impulsivity-Compulsivity Spectrum

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ABSTRACT

BACKGROUND: Tourette syndrome (TS) is often found comorbid with other neurodevelopmental disorders across the impulsivity-compulsivity spectrum, with attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and obsessive-compulsive disorder (OCD) as most prevalent. This points to the possibility of a common etiological thread along an impulsivity-compulsivity continuum.

METHODS: Investigating the shared genetic basis across TS, ADHD, ASD, and OCD, we undertook an evaluation of cross-disorder genetic architecture and systematic meta-analysis, integrating summary statistics from the latest genome-wide association studies (93,294 individuals, 6,788,510 markers).

RESULTS: As previously identified, a common unifying factor connects TS, ADHD, and ASD, while TS and OCD show the highest genetic correlation in pairwise testing among these disorders. Thanks to a more homogeneous set of disorders and a targeted approach that is guided by genetic correlations, we were able to identify multiple novel hits and regions that seem to play a pleiotropic role for the specific disorders analyzed here and could not be identified through previous studies. In the TS-ADHD-ASD genome-wide association study single nucleotide polymorphism–based and gene-based meta-analysis, we uncovered 13 genome-wide significant regions that host single nucleotide polymorphisms with a high posterior probability for association with all three studied disorders (m-value $>$ 0.9), 11 of which were not identified in previous cross-disorder analysis. In contrast, we also identified two additional pleiotropic regions in the TS-OCD meta-analysis. Through conditional analysis, we highlighted genes and genetic regions that play a specific role in a TS-ADHD-ASD genetic factor versus TS-OCD. Cross-disorder tissue specificity analysis implicated the hypothalamus-pituitary-adrenal gland axis in TS-ADHD-ASD.

CONCLUSIONS: Our work underlines the value of redefining the framework for research across traditional diagnostic categories.

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Tourette syndrome (TS) is a common childhood-onset neuropsychiatric disorder that is often comorbid with other neurodevelopmental disorders along the impulsivity-compulsivity spectrum. In fact, only 10% of cases of TS appear as pure TS, while up to 54.3% of patients are also diagnosed with attention-deficit/hyperactivity disorder (ADHD), 50% with obsessive-compulsive disorder (OCD), and up to 20% with comorbid autism spectrum disorder (ASD) (1–3). The high comorbidity rates among these disorders have led to the hypothesis that TS, OCD, ADHD, and ASD might actually lie on an impulsivity-compulsivity continuum, sharing overlapping etiologies that converge in dysfunctional brain circuitries (4). Here, pursuing a transdiagnostic approach, we seek to identify the common genetic factors and neural underpinnings across this spectrum of phenotypes.

TS, ADHD, ASD, and OCD all have a complex and highly heterogeneous genetic architecture, with both common and rare genetic variants contributing to their etiology (5–9). Over the past few years, 12 genome-wide significant loci have been identified for ADHD (10), and five genome-wide significant loci were described for ASD (11,12). For OCD, no genome-wide significant loci have been detected to date (13), while one genome-wide significant locus was recently reported for TS (14).

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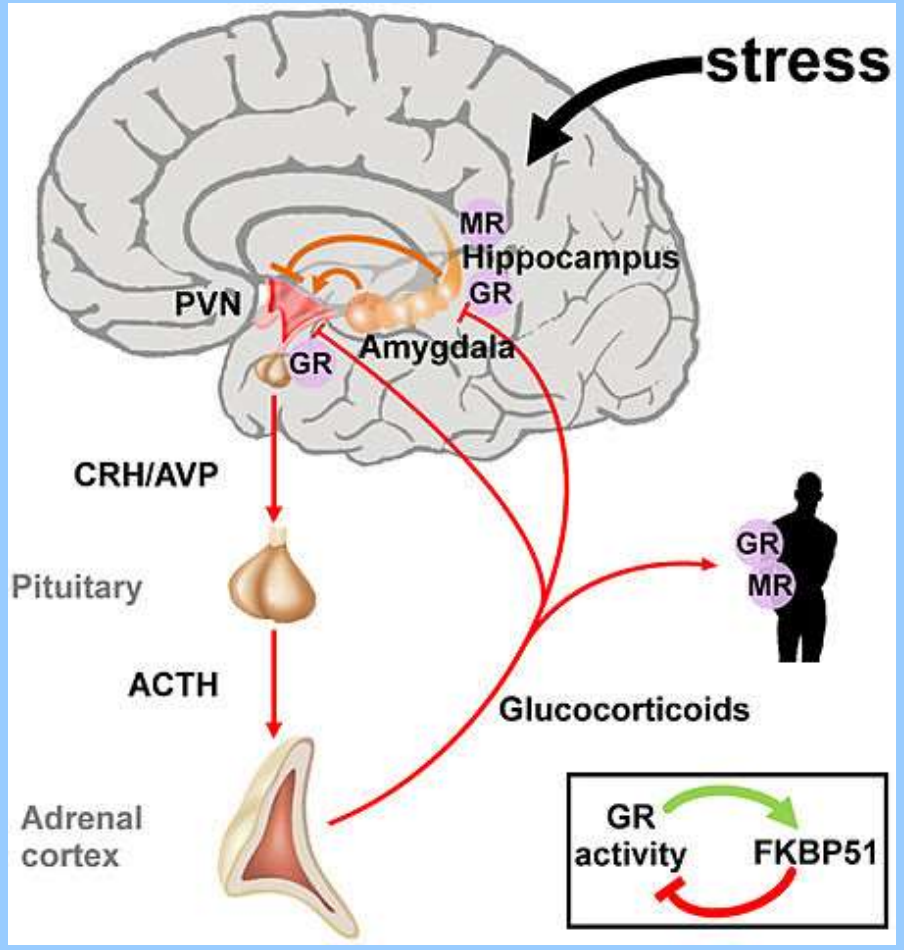
Shared genetic basis?

- the existence of a unifying genetic factor across TS, ADHD, and ASD is confirmed
- the high genetic correlation of TS and OCD appears to be separate from the TS-ADHD-ASD factor
- Cross-disorder tissue specificity analysis implicated the hypothalamus-pituitary-adrenal gland axis in TS-ADHD-ASD



Neuropsychology in ADHD-TS

- May be weaknesses in motor skills, cognitive flexibility, working memory and attention when ADHD is also present (Termine et al., 2016)

- Response inhibition abilities may be predictive of the success of behavioural therapy for tic management (Deckersbach et al., 2006).

inhibitory deficit

- Inhibition of a prepotent, automatic or ongoing response

Inhibitory control improve with age

Inhibitory deficits were associated with tic severity (YGTSS total tic score)

ADHD exacerbate inthibitory deficits

- TS alone vs Control
  - TS has a small effect on inhibitory control
- TS + ADHD vs. healthy controls:
  - Medium effect on inhibitory control
- TS+OCD vs healthy controls:
  - Not enough studies

Morand-Beaulieu et al. 2017 review

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Impaired response inhibition during a stop-signal task in children with Tourette syndrome is related to ADHD symptoms: A functional magnetic resonance imaging study

Thaïra J.C. Openneer, Dennis van der Meer, Jan-Bernard C. Marsman, Natalie J. Forde, Sophie E.A. Akkermans, Jilly Naaijen, Jan K. Buitelaar, Pieter J. Hoekstra & Andrea Dietrich

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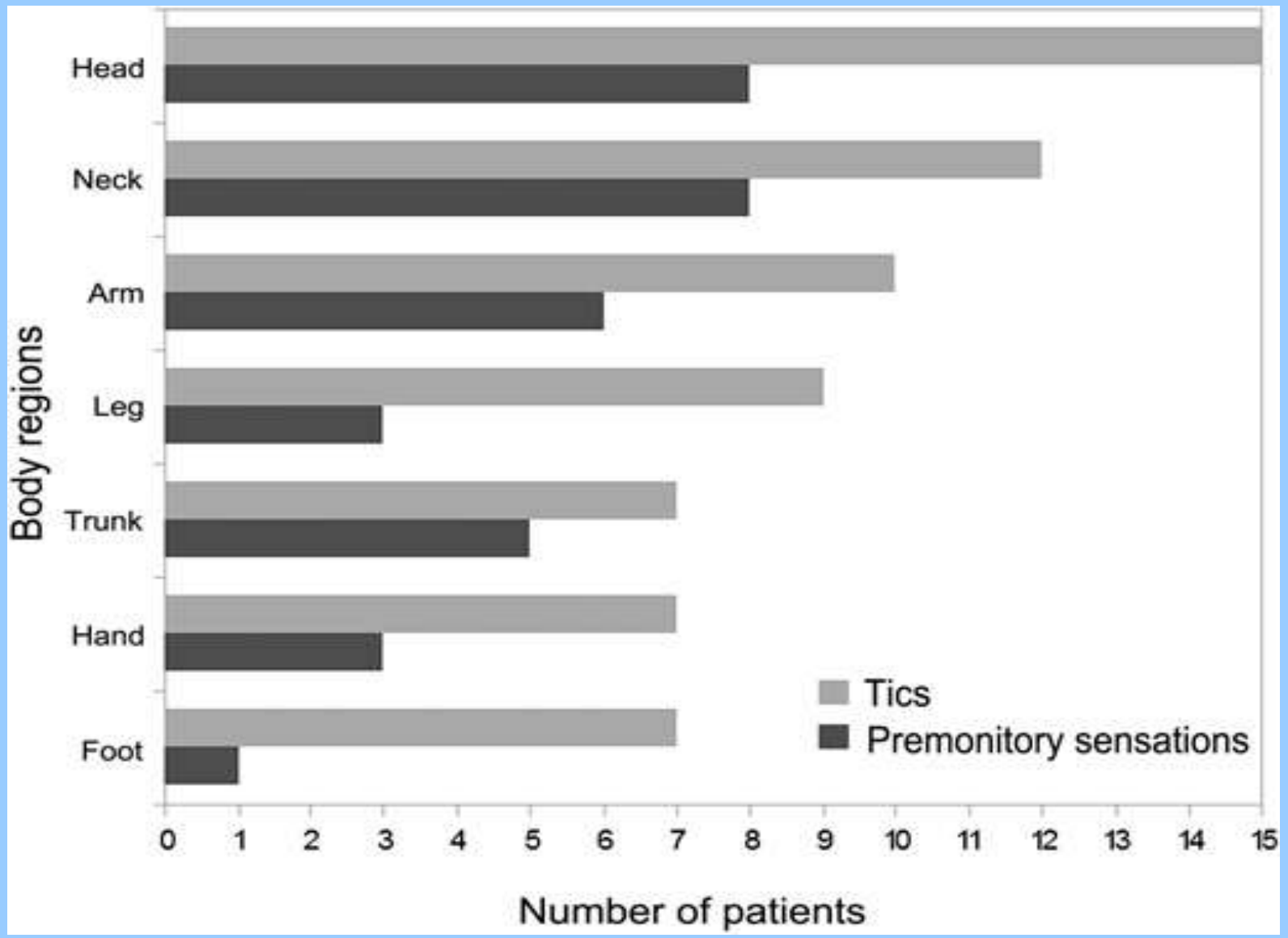


(Ganos et al, 2012)

Tic supression ability and the urge are independent

Clinical implications

- some features of TS might look like ADHD-like symptoms!!
  - the ability to maintain attention could be impaired
    - by the tics themselves,
    - by efforts to inhibit the tics,
    - or by distractions from comorbid anxiety or OCD

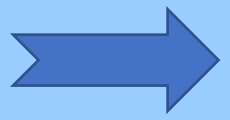
(Erenberg, 2005).

Behavioral therapy in ADHD-TS

- Attentional problems may predict poor tic treatment outcome (Himle and Woods, 2005)
- Preference to treat ADHD first (Döpfner and Rothenberger, 2007),
- When ADHD is stable positive treatment effects are observed (Piacentini et al., 2010)
- ADHD/anxiety does not impact on outcome following CBIT, suggesting that CBIT is effective for tics in patients with co- occurring conditions(Sukhodolsky, Woods ea., 2017)
- TS patients with ADHD are able to suppress tics (Lyon et al 2010, Conelea et al., 2018)

Behavioral therapy in ADHD-TS
Solutions for the problems

- Distracted
- wanting to talk, run around
- Sessions take too long/ boredom
- Not doing homework
- Parental ADHD
- Executive dysfunction



- Parental support
- Involve parents/partners/co-therapist
- Practice in an environment free of distractions
- HRT is more practical
- For ERP, good results have been reported changing the therapist halfway the session (Verdellen et al., 2008a)
- Practice in small pieces of time
- Short sessions- practice little and often
- Physical activity breaks
- Immadiate reward and praise (Fosco et al., 2015)
- Clear visual aids, schedules
- Promote recommendations for school

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Thank you!