

Gen-Umweltinteraktion und Infektionen beim Tourette- Syndrom

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18. Tourette Tagung

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Themen für heute

- Wo durch hat jemand Tourette?
 - Genetik
 - Nicht-genetische Einflüsse
- Gen*Umwelt Interaktionen
- Rolle von Autoimmunität
- Europäische Pläne: EMTICS

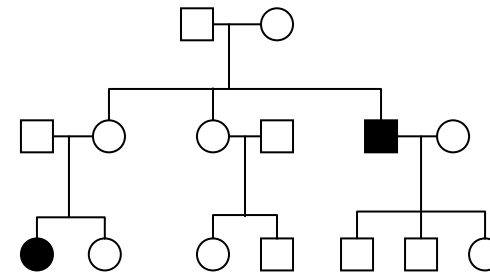
How do we know if a disorder might be genetic?

- Family studies: it runs in families
- Adoption studies
- Studies in monozygotic and dizygotic twins

First Step: demonstrate Familiality

Family studies

- Analysis of multiple families
- Comparing family prevalence with population prevalence



IF : Family prevalence > Population prevalence

➔ Genetic Component

it runs in the family

Adoption studies

Adopted children:

- share genes with biological parents
- share environment with adoptive parents

Adoption studies:

- comparison of phenotype of children with that of biological and adoptive parents

IF: Similarity of phenotype with biological parents $>$ adoptive parents

➔ Genetic Component

Genetic Component in Disease

Twin studies

- MZ and DZ twins share similar (prenatal) environment.
- MZ twins have identical genotypes
- DZ twins share 50% of their genes



Evaluation of large cohorts of MZ and DZ twins

Definition

$$\text{Concordance Rate} = \frac{\text{Both Affected}}{(\text{One Affected} + \text{Both Affected})} \times 100 \%$$

IF: Concordance rate MZ > DZ twins

➔ Genetic Component

Heritability estimates

- Family studies
- Comparison of concordance rates of monozygotic and dizygotic twins
- Adoption studies

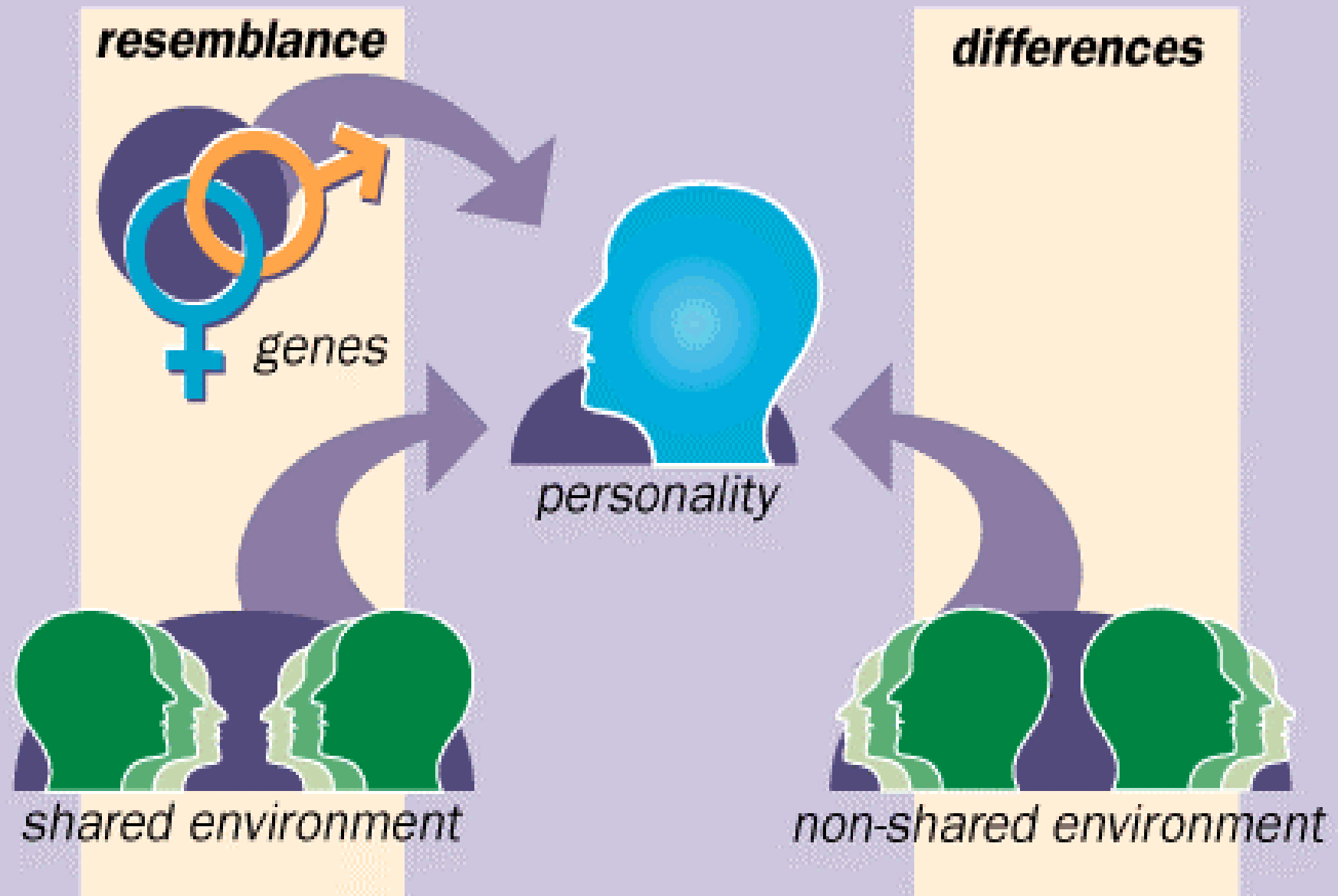
➔ Size of genetic component

Definition

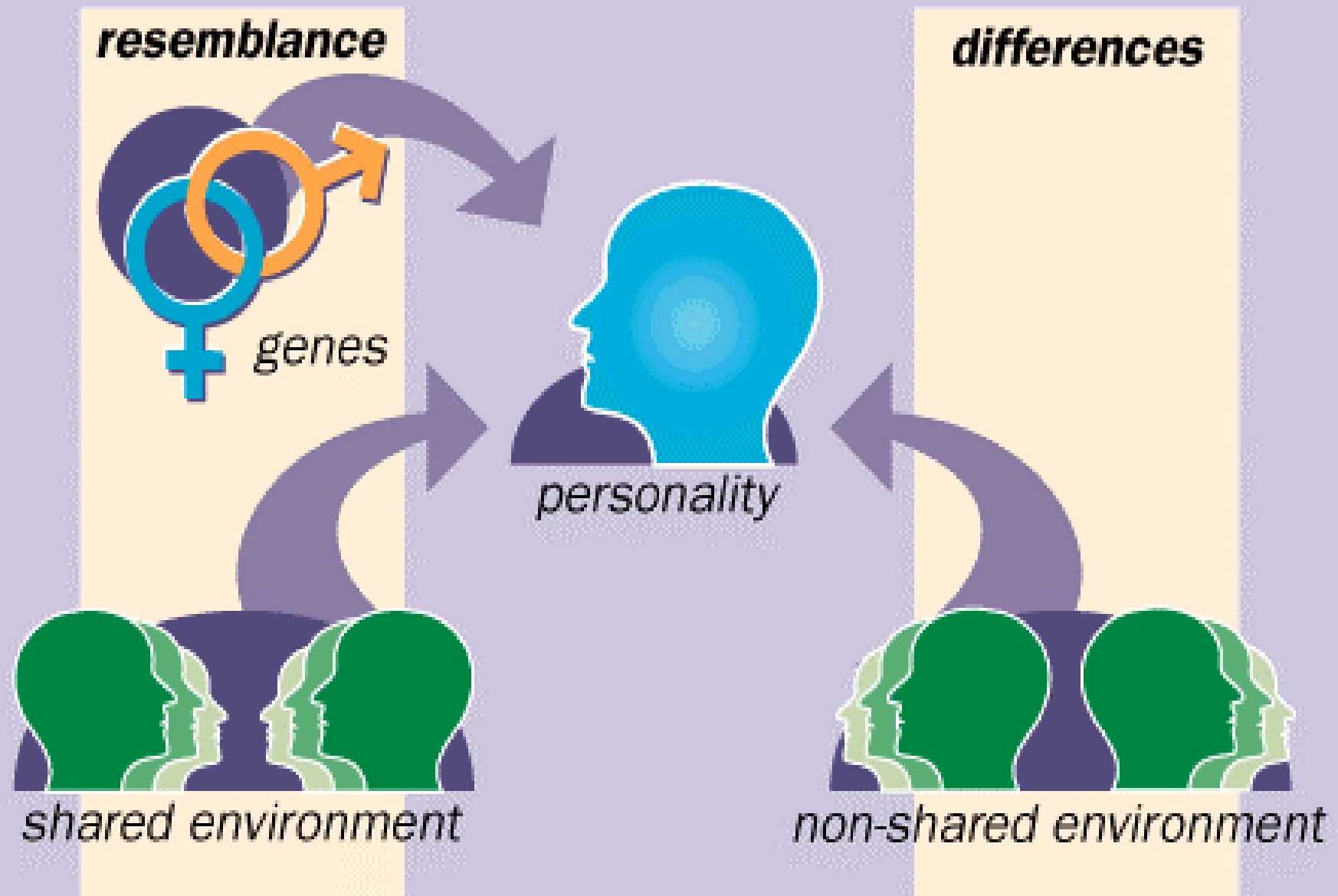
Heritability:

Part of the phenotypic variance explained by (additive) genetic factors

Sources of family resemblance and differences



Sources of family resemblance and differences



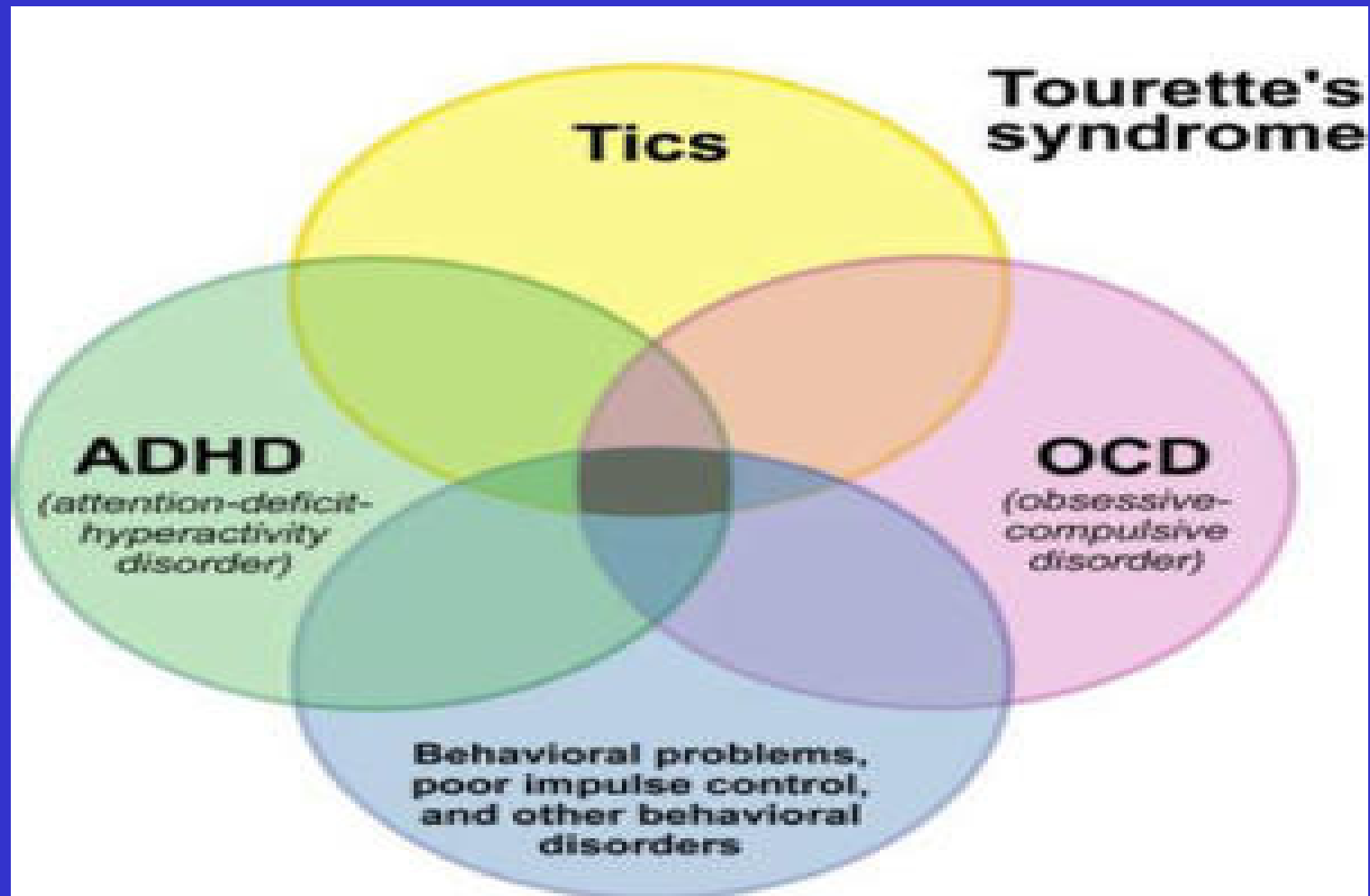
How heritable is Tourette syndrome?

- First degree recurrence risk 30-50%
Much higher than population!
- Concordance in identical twins 90%: much higher than in dizygotic twins
- Heritability app. 70-80%

Warum hat man dann noch kein Tourette Gen gefunden?

- Multiple genes of small main effects
- The relevant phenotype is unknown
- Clinical heterogeneity
- Genetic heterogeneity
- Gene-environment correlation
- Gene-environment interaction
- Importance of endophenotypes
- Importance of developmental factors

What is the relevant phenotype?



Common-Disease Common Variant?

- Or.....Common Disease Rare variant?

New England Journal of Medicine, May 2010

I-Histidine Decarboxylase and Tourette's
Syndrome

Umfeltfaktoren spielen auch eine Rolle

- Perinatale Faktoren
- Psycho-social stress
- Infektionen

Perinatale Faktoren

- Crucial role for **birth weight**
 - Hyde et al (1992) 16 pairs of monozygotic twinsLower birth weight strongly associated with tic severity
- **Associations regarding ADHD comorbidity**
 - Delivery complications
 - Intra-uterine Smoking
 - Pregnancy complications

Perinatal adversities of TS versus controls

Pasamanick et al (1956): 17/51 (33.3%) children with tics had one or more pregnancy complications versus 9/51 controls (17.6%)

Leckman et al (1987): in seven pairs of monozygotic twins, the co-twins with Tourette's disorder (TD) had lower birth weights than the unaffected co-twins

Burd et al (1999): Lower Apgar scores recorded five minutes after birth compared to controls

Relation of perinatal adversities and tic severity

- Leckman et al (1990) Severity of maternal life stress during pregnancy, and severe nausea and/or vomiting during the first trimester were significantly associated with current tic severity (N=31)

Maternal Smoking and Increased Symptom Severity in TS (Mathews et al 2006)

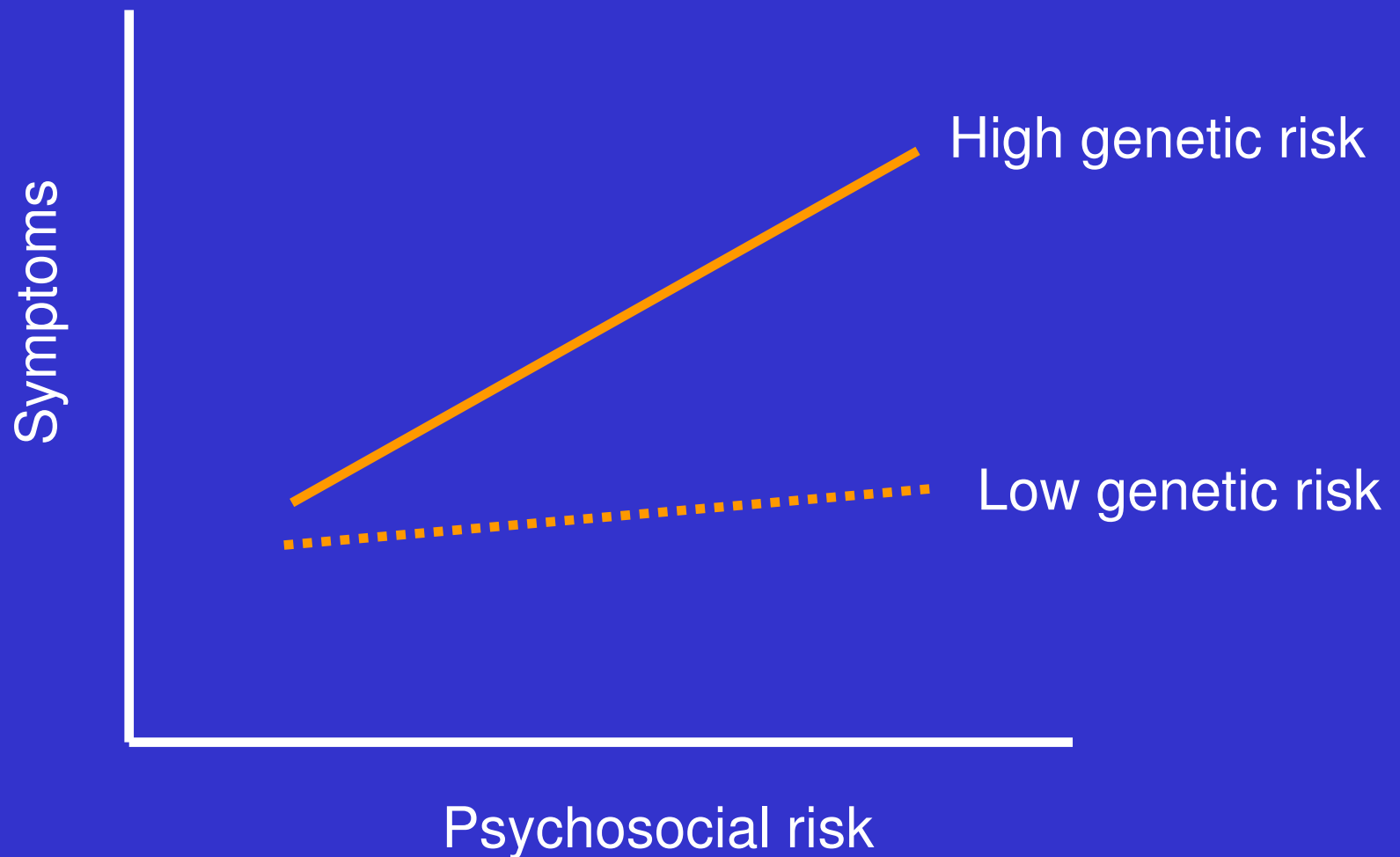
- N=180;
 - Prenatal maternal smoking strongly correlated with increased tic severity.
 - Other variables, such as paternal age and subject's birth weight, less strongly associated with increased symptom severity.
 - No association between symptom severity and hypoxia, forceps delivery, or hyperemesis during pregnancy

Role of psychosocial Stress

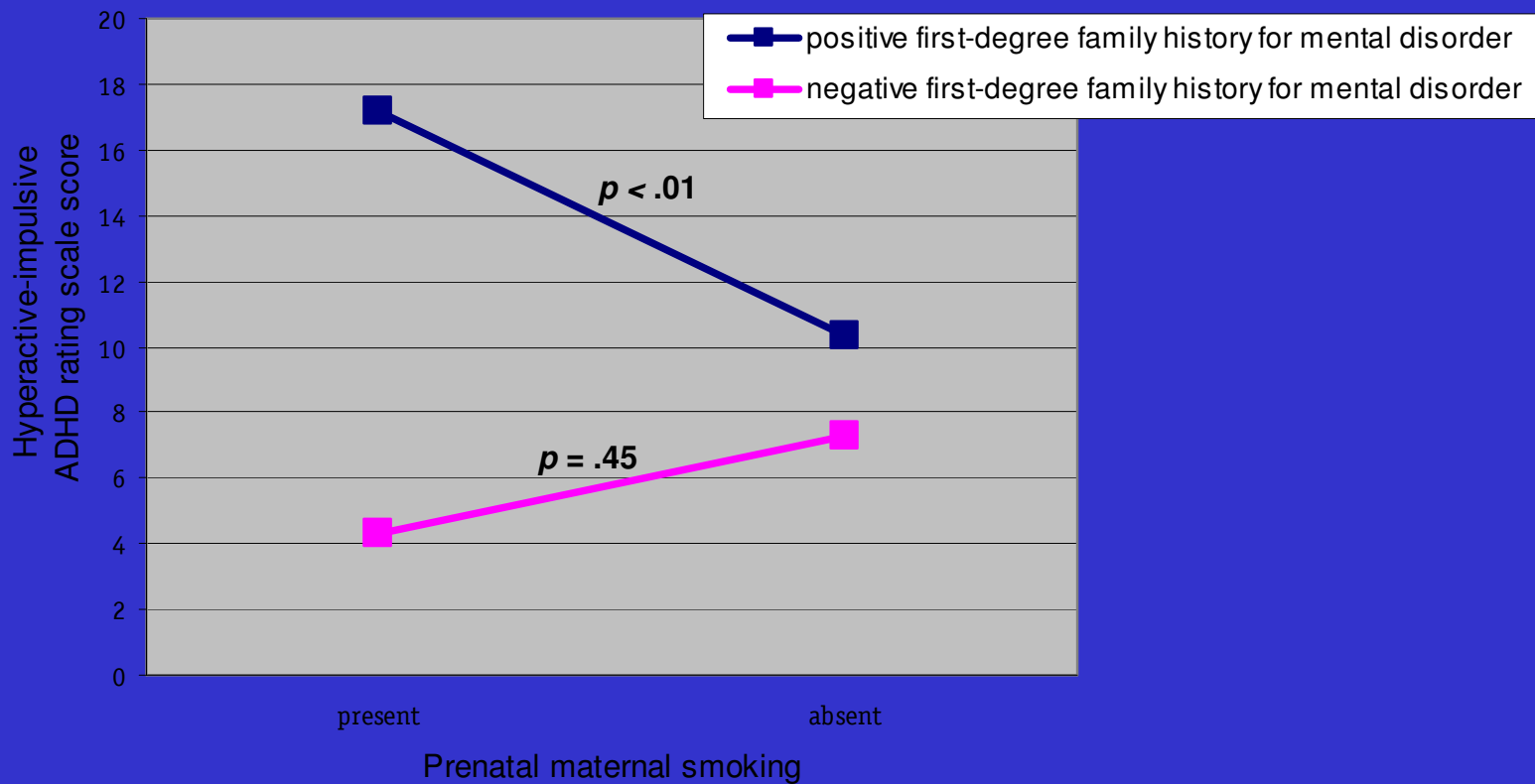
- Higher stress reactivity (salivary secretion of cortisol in response to MRI or puncture)
- Association stress & tic exacerbations

Concept of Gene / environment interactions:

Genes determine sensitivity to environment



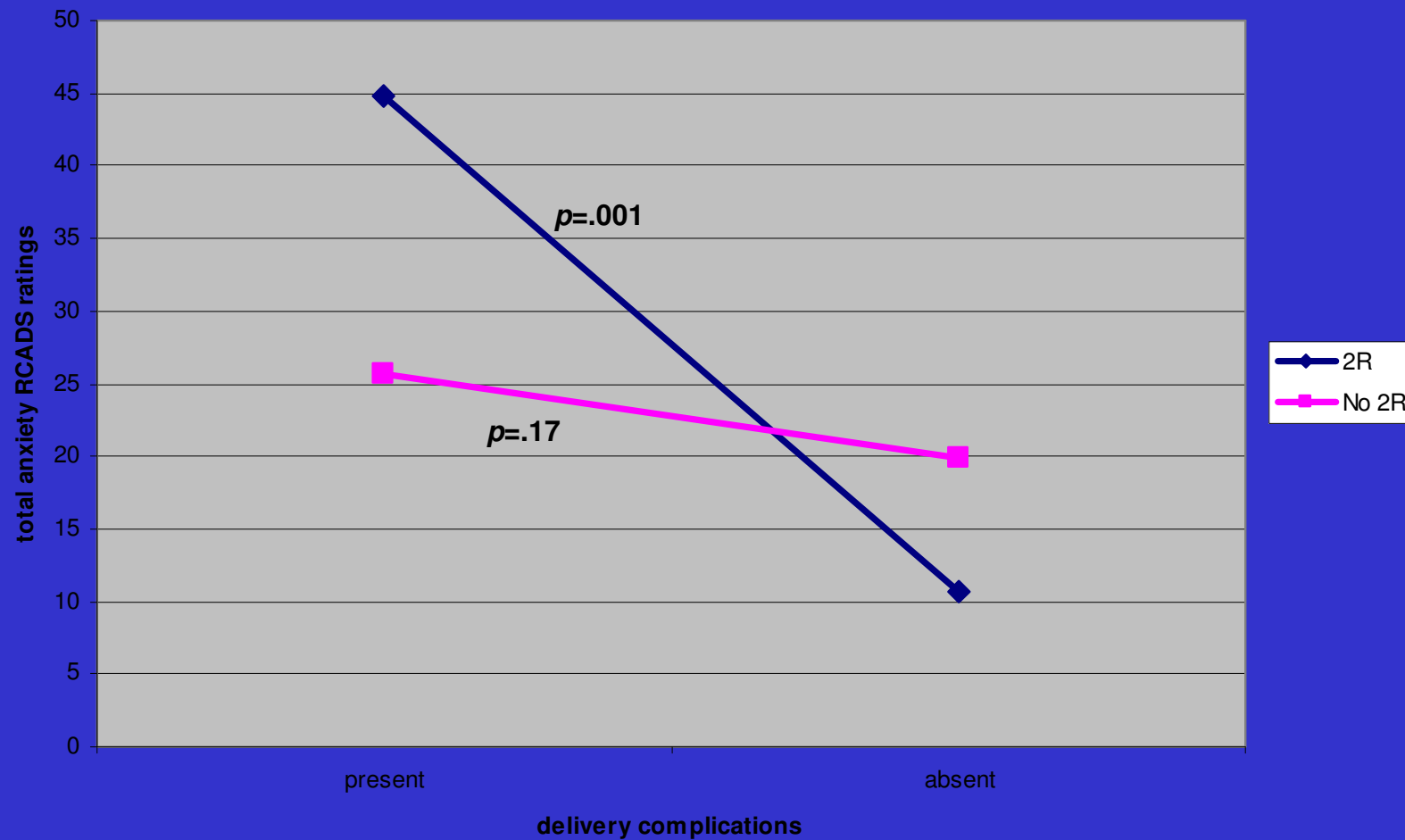
Interaction between pregnancy smoking and family history



MAO-A & delivery complications



DRD4 2R & delivery complications



Spielen Infektionen eine Rolle?

- Model: Sydenham's chorea
- Auto-Antikörper durch molekuläre Gleichheit zwischen Streptokokken und Hirngebiete
- Later infections can lead to subsequent symptom exacerbations

Three pillars of relevance of Autoimmunity

- Antineuronal antibodies
- Association between strep infections and Tourette
- Alterations in humoral immunity (immunoglobulins)

Antineuronal autoantibodies

- Different techniques
 - Indirect immunofluorescence
 - ELISA
 - Western immunoblots
- Different substrates
 - Neuronal cell lines
 - Human post-mortem brain
 - Rodent brains
- Identified targets: pyruvate kinase, lysoganglioside

Association between tics and infections

- Cross-sectional single time point design: markedly increased serum levels of antistreptococcal antibodies

(Muller et al., 2000; Muller et al. , 2001; Cardona et al., 2001; Church et al. 2003; Creti, 2004; Morer et al., 2005)

- Levels of antistreptococcal antibodies correlate with tic severity

(Cardona et al., 2001)

- Treatment with antibiotics may decrease neuropsychiatric symptoms

Association between tics and infections

- Longitudinal study: average annual rate of new streptococcal infections 0.42 infections per subject per year among unselected pediatric patients with Tourette's syndrome or OCD
- 0.28 infections per subject per year for control subjects

(Luo et al., 2004)

Association between tics and infections

- Patients with OCD, TS, or tic disorder more likely than controls to have had prior streptococcal infection in the 3 months before onset date (OR: 2.22).
- Having had multiple infections within 12 months also more likely (OR: 3.10)
- Having multiple infections associated with an increased risk for TS (OR: 13.6)

Mell et al., 2005

Association between tics and infections

- Systematic, longitudinal study with 693 children (ages 3 to 12 years)
- Data were collected monthly for 8 months (October–May) to determine point prevalence of Group A Streptococcal (GAS) infections, tics, behavior, and choreiform movements.
- Simultaneous throat cultures were obtained, and relational analyses were made between GAS and movement/observation ratings.

Association between tics and infections

- ADHD-like behavioral strongly associated with concurrent or prior streptococcal throat cultures ($P < 0.001$)
- Children with repeated positive streptococcal throat cultures show higher rates of behavior problems and distal choreiform observations ($p = 0.005$)
- Motor/behavior changes were noted to occur in relationship to positive GAS culture with support that repeated GAS increases risk.

Decreased Numbers of Regulatory T Cells Suggest Impaired Immune Tolerance in Children with Tourette Syndrome

- Regulatory T (T reg) cells play a major role in preventing autoimmunity, a defect in T reg cells may be present in children with TS
- Significant decrease in T reg cells in patients with moderate to severe TS symptoms compared with control children
- Decrease in T reg cell number also noted during symptom exacerbations in five out of six patients

Kawikova et al., 2007

What main points do we have in hands?

- Strong link (both epidemiological and clinical) between streptococcal infections/carrier states and tics
- Candidate autoantigens have been identified (pyruvate kinase and lysoganglioside) with links to pathogenesis plus mimicry and cross-reactivity with streptococci
- Decreased Treg cells known to prevent autoimmunity possibly decreased

How should we proceed?

- Large scale studies:
 - How prevalent are post-streptococcal sequelae?
 - How broad are post-streptococcal sequelae?
 - Does it include ADHD?
 - Depression?
 - Anxiety?
- Standardization of antibody assays

EMTICS

European Multicentre Tics in Children Studies

- WP01 Longitudinal clinical studies (COURSE & ONSET)
- WP02 Microbiology
- WP03 Antistreptococcal immune response
- WP04 Immune measurements (Norbert Müller)
- WP05 Animal model
- WP06 Genetics & Gene expression

EMTICS-continued

- WP07 Antibiotics prophylaxis clinical trial
- WP08 Stress measures/cortisol (Veit Roessner)
- WP09 Data Management
- WP10 Training and dissemination
- WP11 Project Management
- WP12 Ethics

Deutsche EMTICS-Zentren: Göttingen, Dresden,
Ulm, Hamburg, Hannover, München

Was kan EMTICS uns lernen?

- Neue Gen-gebiete
- Rolle von Stress
- Gen-Umwelt interaktionen
- Relevanz von Strep-infektionen
- Bessere Behandlungen

Zusammenfassung

- Genetik spielt eine Hauptrolle
- Es gibt komplexe Interaktionen mit Umweltfaktoren
- Diese sind zum sehr weiten Teil noch unerforscht

Vielen Dank für Ihre
Aufmerksamkeit?

Fragen?