

Pay Attention: ADHD Through the Lifespan

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Week 2: Causes of ADHD

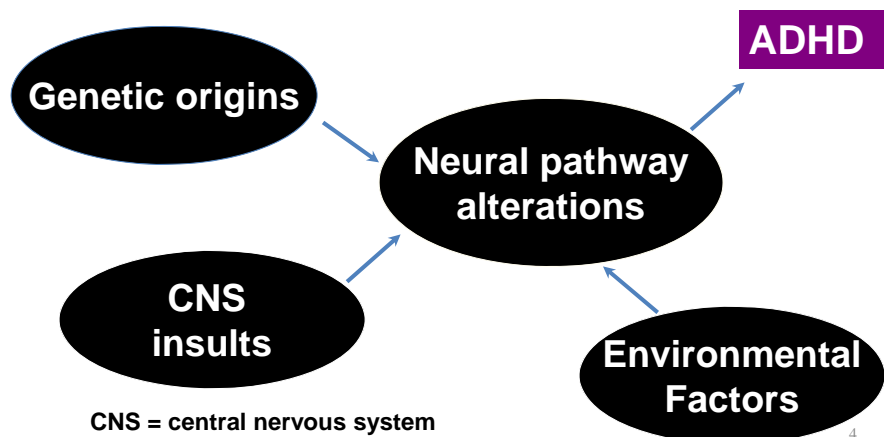
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Homework Review

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ADHD: Causal Factors??

ADHD is a **heterogeneous** behavioral disorder
with multiple possible causes



Brain – Environment Interactions

- Many factors have been identified that affect the development of the Brain and CNS
 - Prenatal environment (exposures during pregnancy)
 - Birth process (stress, anoxia)
 - Postnatal environment (e.g. infections, immunity, nutrition, physical conditions)
 - Psychosocial variables (SES, parenting style, family relationships)
 - Experience, learning, education, recreation

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ADHD: Causal Factors

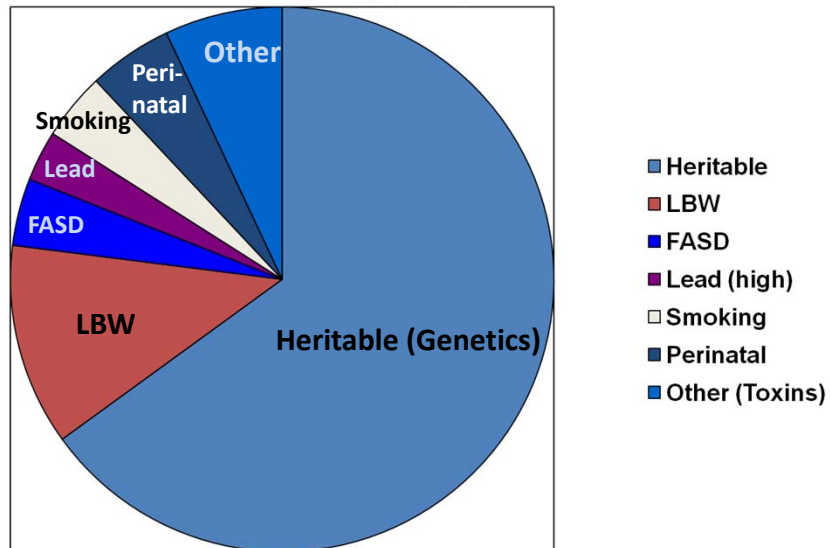
- Disorder arises from multiple causes
- All reliably supported causes fall in realm of biology (neurology, genetics)
- Causes may interact and compound each other
- Final common pathway for disorder appears to be in fronto-striatal-cerebellar brain circuits
- Social causes lack compelling evidence
- **65-75%** of cases due to genetics-heredity*
- **25-35%** of cases attributable to acquired CNS injuries*

*Nigg, J. T. (2006). *What Causes ADHD?* New York: Guilford Publications

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Causes of ADHD

From Joel Nigg (2006), *What Causes ADHD?*

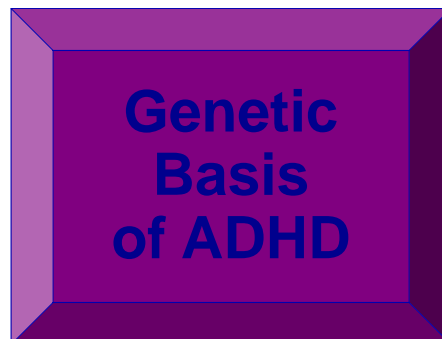


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Genetics of ADHD

Twin Studies

Family Studies



Adoption Studies

Molecular Genetics
Studies

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ADHD is a Complex Genetic Disorder

- Indistinct boundaries between affected and unaffected status (i.e. ADHD and non-ADHD)
- Preferential familial clustering that cannot be explained by exclusively cultural or environmental effects
- Traits don't fit patterns of clear-cut inheritance (Mendelian)

(Max Muenke, MD, NHGRI)

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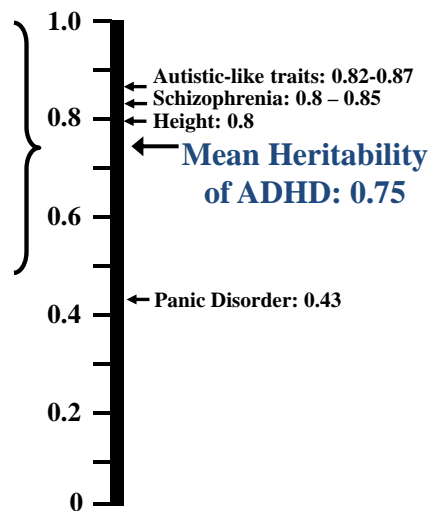
Heritability of ADHD

Heritability of ADHD between 0.9 and 1.0
Willcutt, 2000; Levy, 1997; Gillis, 1992

Heritability of ADHD between 0.8 and 0.9
Coolidge, 2000; Thapar, 2000; Thapar 1995

Heritability of ADHD between 0.7 and 0.8
Rietveld, 2003; Martin, 2002; Sherman, 1997; Gjone, 1996; Stevenson, 1992; Willerman, 1973; Matheny, 1971

Heritability of ADHD between 0.6 and 0.7
Kuntsi, 2001; Hudziak, 2000; Nadder, 1998; Silberg, 1996; Schmitz, 1995; Edelbrock, 1992; Goodman, 1989



Faraone et al. *Biol Psychiatry*. 2005;57:1313-1323. Hettema et al. *Am J Psychiatry*. 2001;158:1568-1578. Visscher et al. *PLoS Genet*. 2006;2:e41. Cardno AG, Gottesman II. *Am J Med Genet*. 2000;97:12-17. Ronald et al. *Eur Child Adolesc Psychiatry*. 2008 Apr 21 [Epub]

Family Studies of ADHD Adults

- If a parent has ADHD, 40-54% chance child will have ADHD (8+ odds)
- Sibling of a child with ADHD has 25-35% risk
- Identical twin sibling has 78-92% risk
- Child with ADHD
 - 15-20% of mothers
 - 25-30% of fathers
- Genetics explain 88-95% variance of ADHD traits using DSM
- Shared environmental factors explain 0-6% of variance (non-shared = 10-20%)

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Mid-Lecture Questions

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Candidate Genes in ADHD

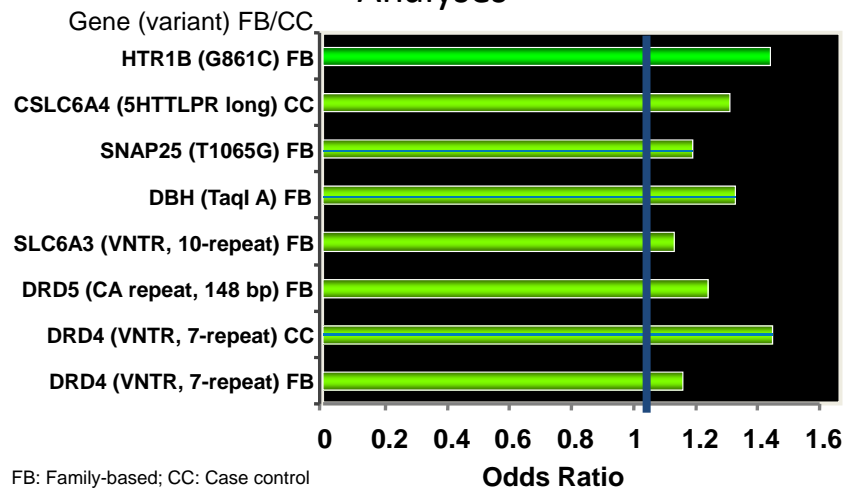
Case-control or family-based studies have shown a statistically significant correlation between ADHD and variants of 7 genes:

- Serotonin HTR1B Receptor
- Serotonin Transporter
- Synaptosomal-Associated Protein 25
- Dopamine β -Hydroxylase
- Dopamine Transporter
- Dopamine D5 Receptor
- Dopamine D4 Receptor

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Candidate Genes in ADHD

Pooled Odds Ratios From Positive Meta-Analyses



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Quiz Questions

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Acquired Cases: Pre- & Perinatal (15-25%)

- Maternal smoking in pregnancy (odds **2.5**)*
 - 10 cigarettes per day or more elevates risk
 - Pregnant women who smoke also have more ADHD (9%+)
 - But even controlling for mother's ADHD shows tobacco use still elevates risk 2.5 times over base rate prevalence
- Maternal alcohol drinking in pregnancy (odds **2.5**)*
- Premature birth, especially if brain bleeding (**>45%**)*
- Maternal respiratory infections
- Increased total pregnancy complications
- Maternal high phenylalanine levels in blood (?)
- High maternal anxiety in second trimester (?)**
- Cocaine/crack exposure not a risk factor after controlling for the above factors
- Perinatal asphyxia/anoxia

*Nigg, J. T. (2006). *What Causes ADHD?* New York: Guilford Publications

** Gutteling, B. M. et al. (2006). *Journal of Abnormal Child Psychology*, 34, 789-798

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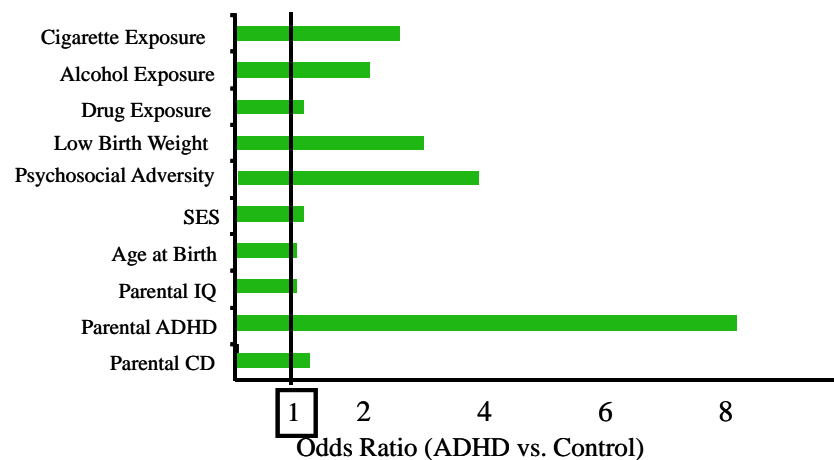
Acquired Cases: Postnatal (3-7%)

- Head trauma, brain hypoxia, tumors, or infection
- Febrile seizures
- Lead poisoning in preschool years (0-3 yrs.)
 - Relates more to hyperactivity-impulsivity than inattention
- Survival from acute lymphoblastic leukemia (ALL)
 - Treatments for ALL cause brain damage
- Postnatal Streptococcal Bacterial Infection
 - triggers auto-immune antibody attack of basal ganglia
- Postnatal elevated phenylalanine (dietary amino acid related to PKU)
 - Prenatal – hyperactivity
 - Postnatal – inattention

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Prenatal & Perinatal Risk Factors for ADHD

Results from Logistic Regression Model

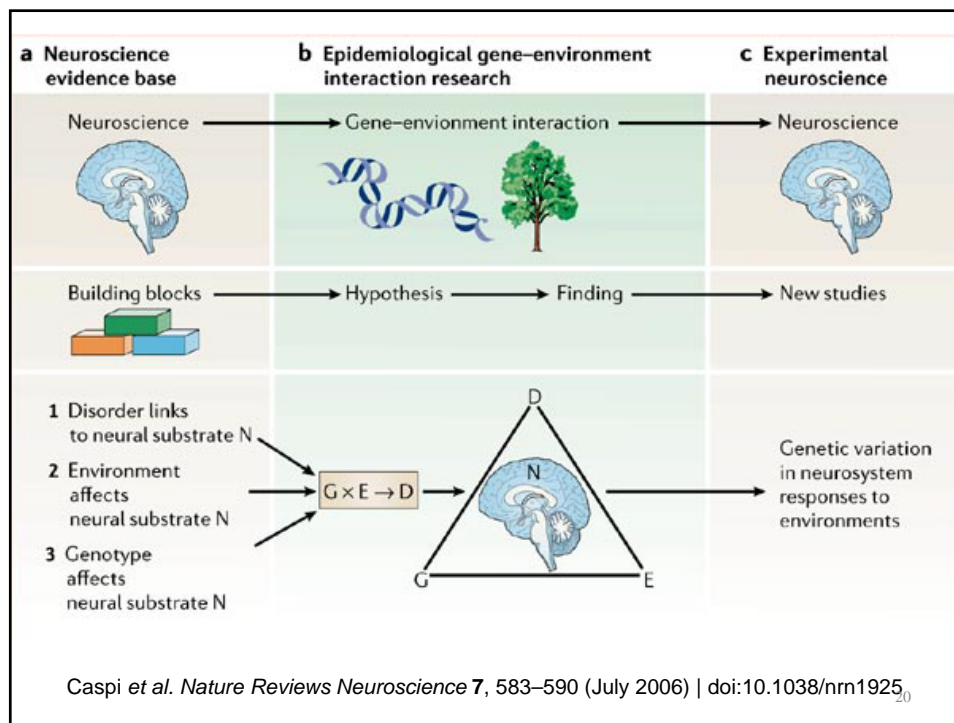


Mick, et al. *J Am Acad Child Adolesc Psychiatry*. 2002 Apr;41(4):378-85.

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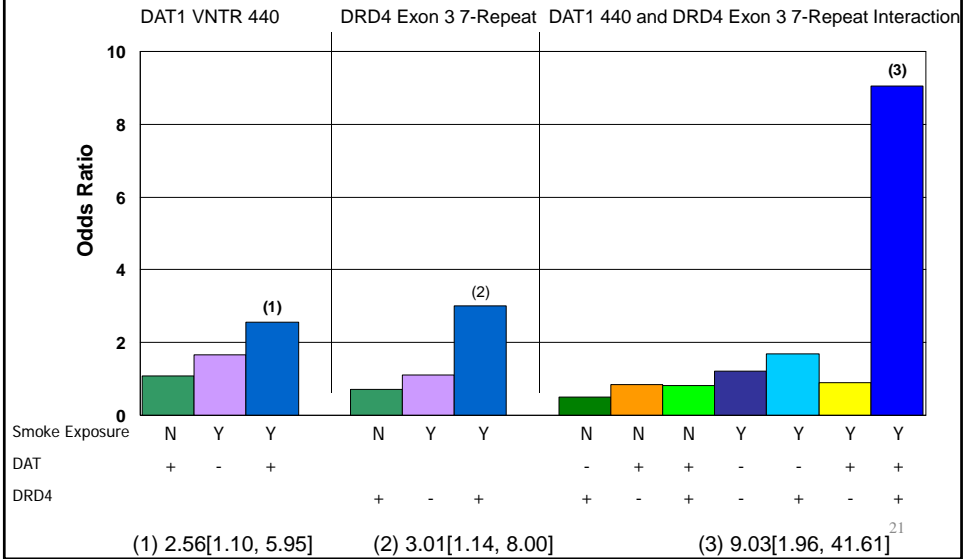
Mid-Lecture Questions

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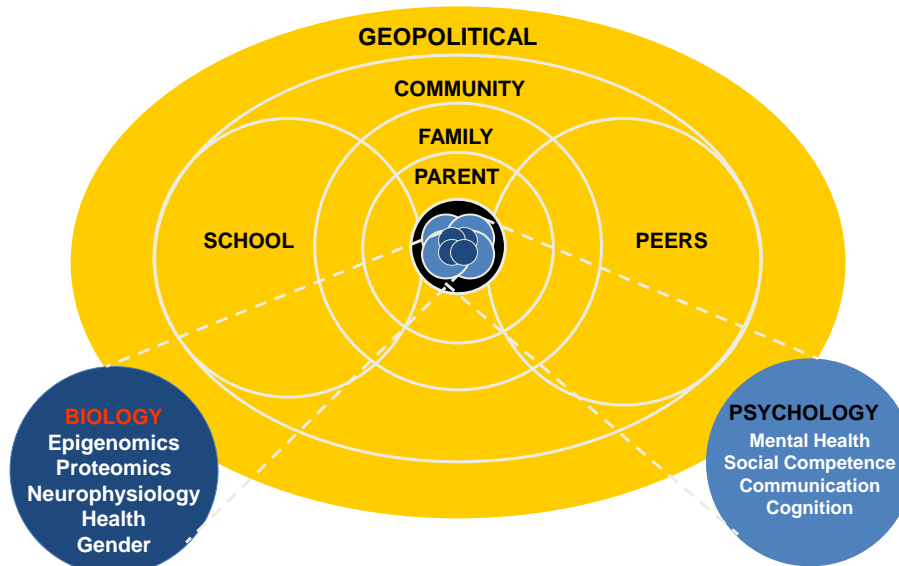


Gene x Environment Interactions

Adjusted Odds Ratios for the Association Between Population Defined ADHD Combined Subtype and *In Utero* Maternal Smoking Exposure and Dopamine Pathway Genotypes (Todd, 2007). Reference Group: No Smoking Exposure and genotype without risk allele



Biopsychosocial Ecological System



Looking Ahead

- Topic for next week: Neuroanatomy
- Reading for next week:

BrainFacts.org free publication

(All of Part 1 and Chap 10 of Part 5)

<http://www.brainfacts.org/about-neuroscience/brain-facts-book/>

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Quiz Questions

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