ADHD: Advances in Diagnosis and Etiology

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Sources:

Barkley, R. A., Murphy, K. R., & Fischer, M. (2008) *ADHD in Adults: What the Science Says.* New York: Guilford

Barkley, R. A. (2006) *Attention deficit hyperactivity disorder: A handbook for diagnosis and treatment (3rd ed.)*. New York: Guilford.

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  - DSM-V Work Group on ADHD (APA, NIMH, and WHO co-sponsorship)

What is ADHD?
The Current Clinical View

A disorder of age-inappropriate behavior:

- **Inattention** (Executive Functioning ?)
  - At least 6 types of attention – not all are impaired in ADHD
    - Arousal, alertness, selective, divided, span of apprehension, & persistence
  - Poor persistence toward goals or tasks
  - Impaired resistance to responding to distractions
  - Deficient task re-engagement following disruptions
  - Impaired working memory (remembering so as to do)
- **Hyperactivity-Impulsivity** (Poor inhibition)
  - Impaired verbal and motor inhibition
  - Impulsive decision making; impatient or cannot wait
  - Greater disregard of future (delayed) consequences
  - Excessive task-irrelevant movement and verbal behavior
    - Fidgeting, squirming, running, climbing, touching
  - Restlessness decreases with age, becoming more internal, subjective by adulthood

Inattention Symptoms (DSM-IV)

- fails to give close attention to details
- difficulty sustaining attention
- does not seem to listen
- does not follow through on instructions
- difficulty organizing tasks or activities
- avoids tasks requiring sustained mental effort
- loses things necessary for tasks
- easily distracted
- forgetful in daily activities

Symptoms must occur “Often” or more frequently

Hyperactive-Impulsive Symptoms

- fidgets with hands or feet or squirms in seat
- leaves seat in classroom inappropriately
- runs about or climbs excessively
- has difficulty playing quietly
- is “on the go” or “driven by a motor”
- talks excessively
- blurts out answers before questions are completed
- has difficulty awaiting turn
- interrupts or intrudes on others

Symptoms must occur “Often” or more frequently

DSM-IV Criteria for ADHD

- Manifests 6+ symptoms of either inattention or hyperactive-impulsive behavior
- Symptoms are developmentally inappropriate
- Have existed for at least 6 months
- Occur across settings (2 or more)
- Result in impairment in major life activities
- Developed by age 7 years
- Are not best explained by another disorder, e.g. Severe MR, PDD, Psychosis
- 3 Types: Inattentive, Hyperactive, or Combined

Issues for DSM-V

- Inattention list may be mislabeled
  - Broaden to include poor working memory (and possibly larger domain of executive functions)
- Symptoms and wording are not appropriate past childhood
  - Need more items for adult stage of disorder
- Symptom cutoffs (6 of 9) are also not appropriate past childhood
  - May have to adjust thresholds down to 4 of 9 if > age 17 and higher than 6 if < 4 yrs
- Cutoffs are based mainly on boys (3:1)
  - May be lower for girls; for now use rating scales

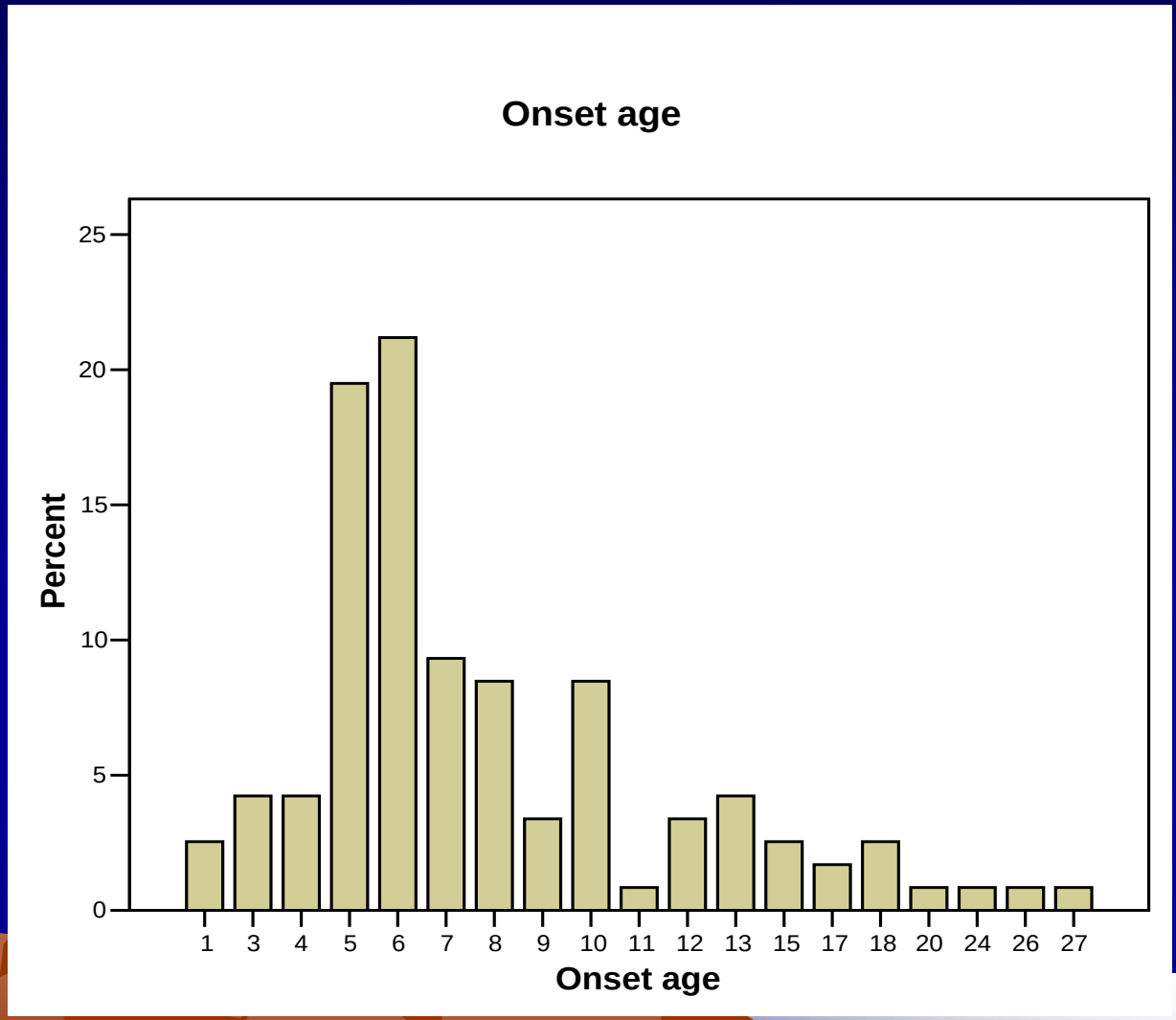
More Issues for DSM-V

- Duration may be too short for preschoolers:
  - try 1 year or more
- Developmental deviance undefined
  - use 93 percentile (+1.5 SDs above normal mean)
- Requires cross-setting occurrence of symptoms that implies need for parent-teacher agreement
  - Instead, blend reports of both and use history of cross setting impairment
- No requirement for corroboration by others
  - Yet that is essential when evaluating teens and young adults up to late 20s-early 30s due to under-reporting of symptoms
- Impairment is undefined (use average person standard)
- Age of onset of 7 years lacks validity
  - use childhood onset – approximately 16 years

Self-reported age of onset in ADHD children as adults (mean age 27)

All had the disorder by age 6 yrs. as reported by their parents at childhood entry into the study

On average, their self-reported age of onset was 4 years or more later than was actually true in childhood
50% reported ≥ age 7



Best New Symptoms for Adults

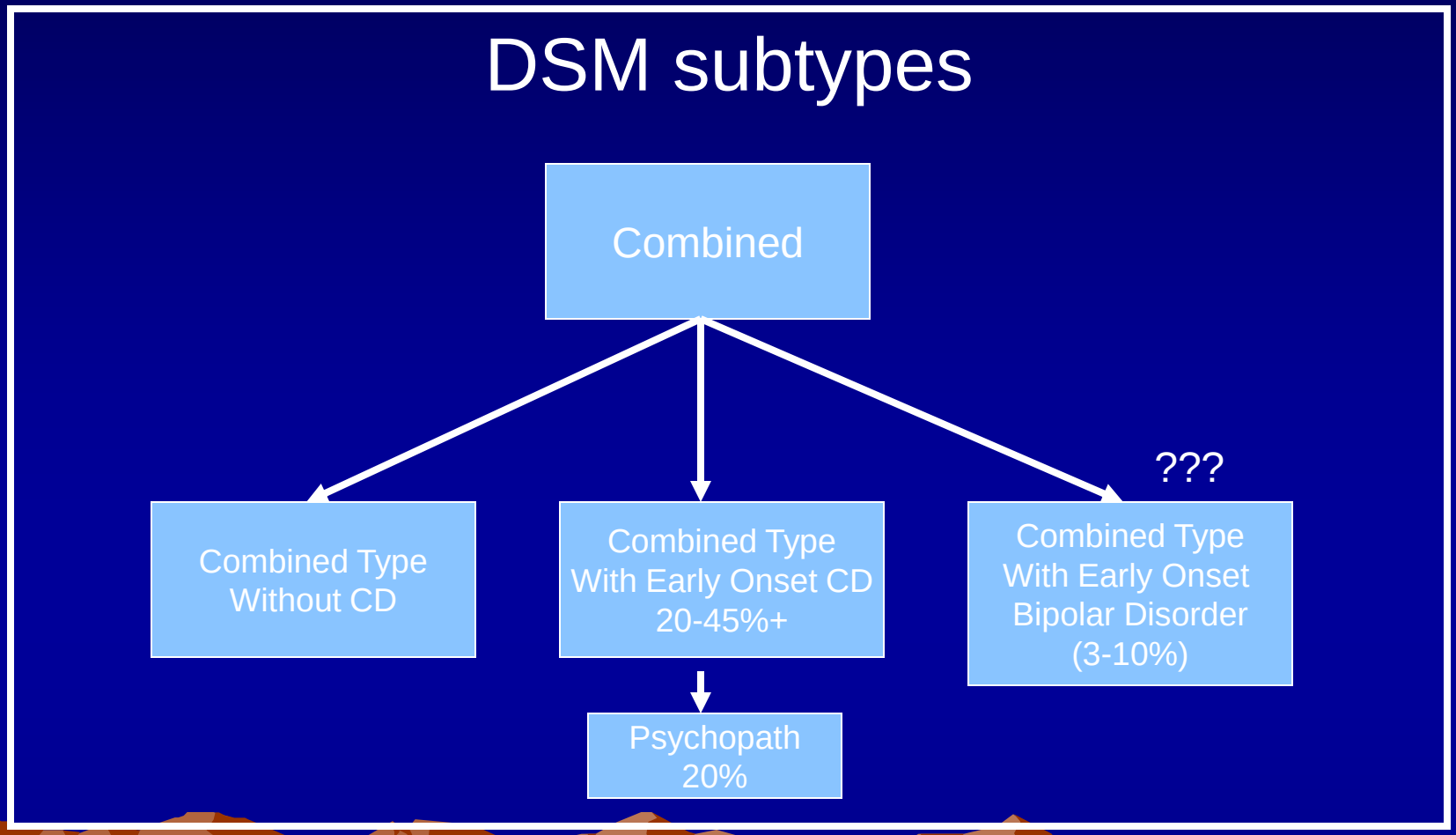
1. Is often easily distracted by extraneous stimuli (DSM-IV)
2. Often make decisions impulsively (EF)
3. Often has difficulty stopping my activities or behavior when I should do so (EF)
4. Often starts a project or task without reading or listening to directions carefully (EF)
5. Often shows poor follow through on promises or commitments I may make to others (EF)
6. Often has trouble doing things in their proper order or sequence (EF)
7. Often more likely to drive a motor vehicle much faster than others (Excessive speeding)(EF) [For non-drivers, substitute this item: "Often have difficulty engaging in leisure activities or doing fun things quietly."
8. Often has difficulty sustaining attention in tasks or play activities (DSM – optional)
9. Often has difficulty organizing tasks and activities (DSM – optional)

Cutoff would be either 4 of first 7 or 6 of all 9 items above

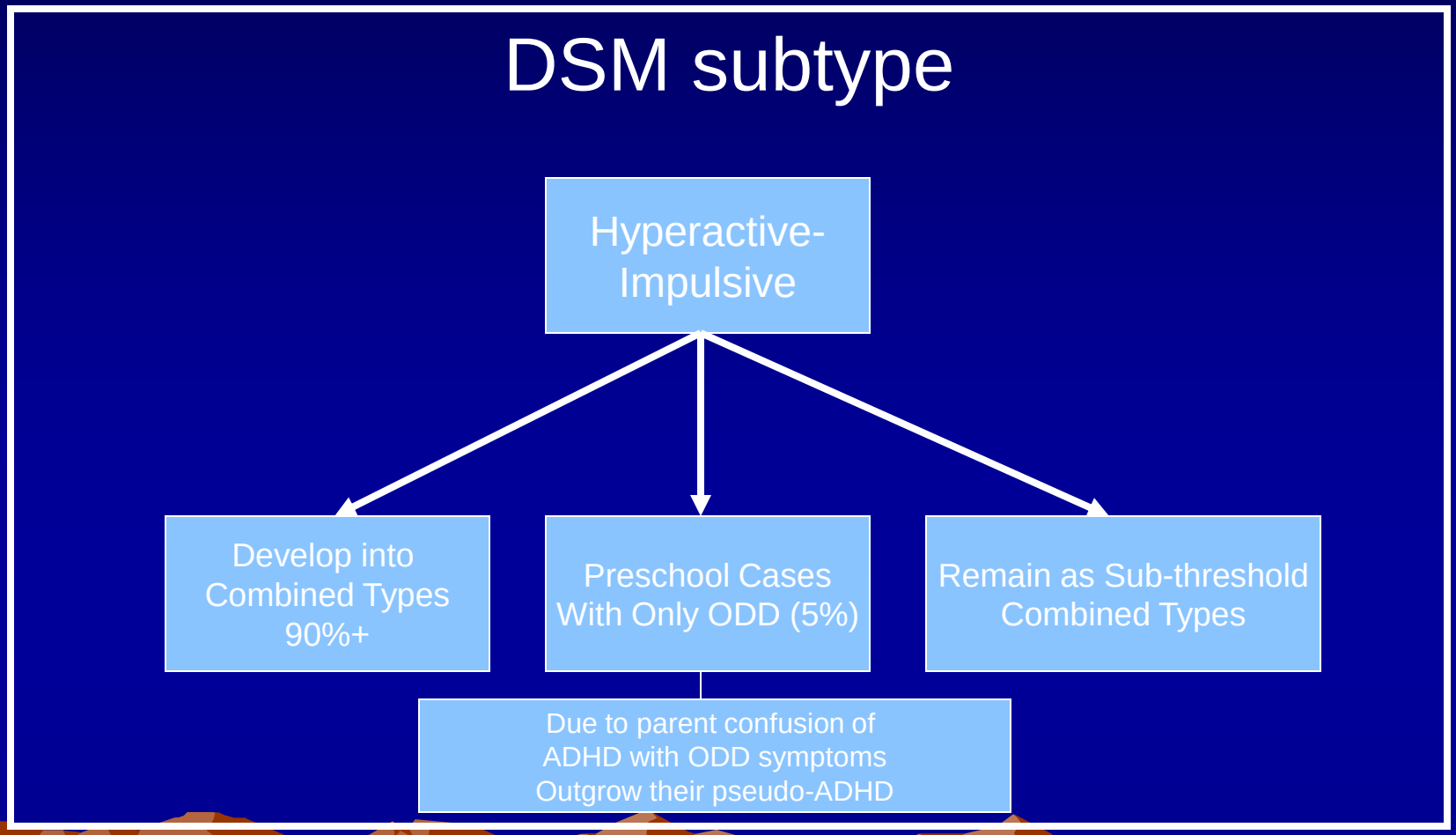
Onset of symptoms producing impairment in childhood to adolescence ($\leq$ 16)

Research to appear in Barkley, R., Murphy, K., & Fischer, M. (2008). *The Science of ADHD in Adults: Clinic Referred Adults vs. Children Grown Up*. New York: Guilford.

DSM Subtypes vs. Research-Based Subtypes



DSM Subtypes vs. Research-Based Subtypes



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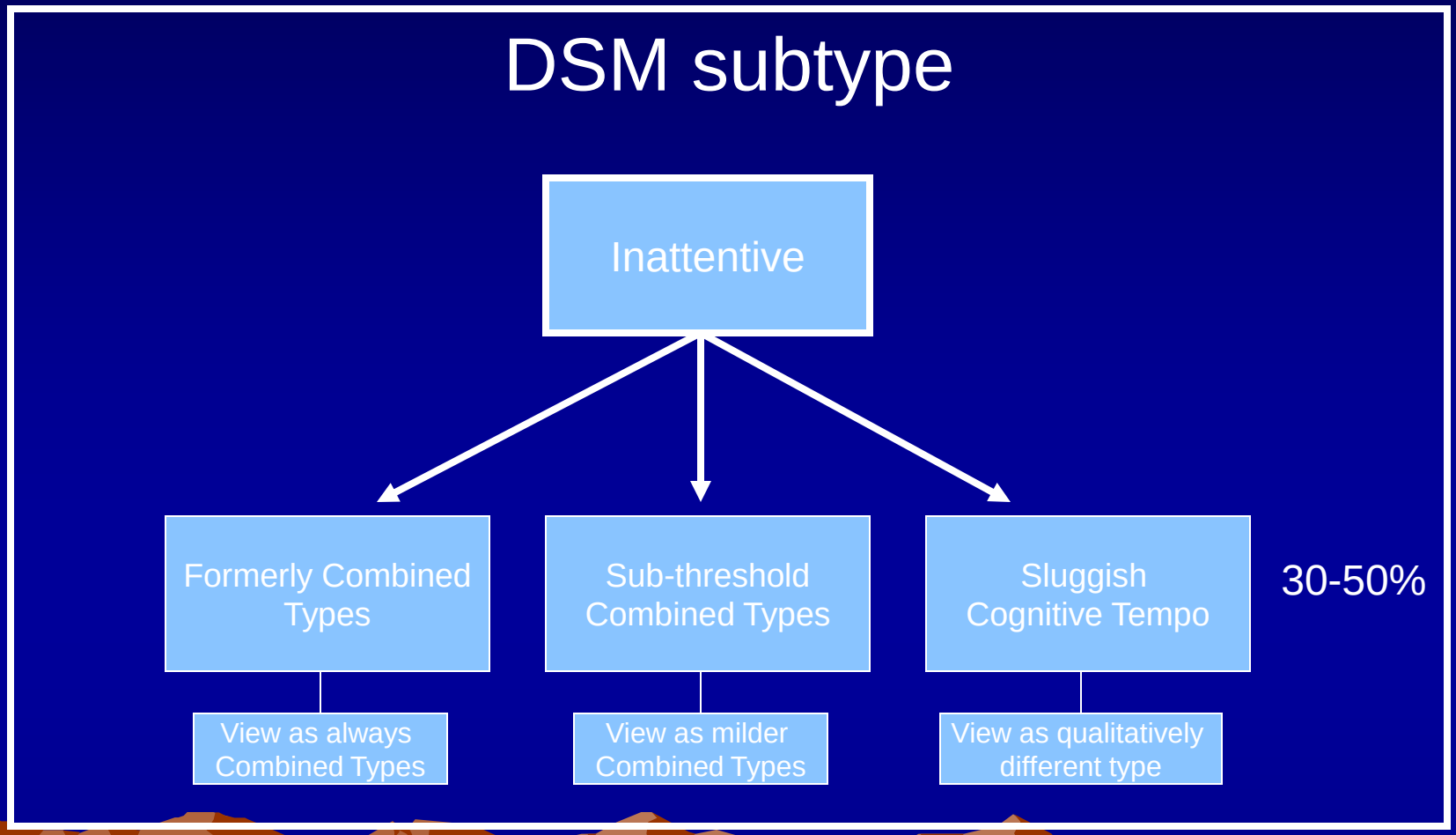


ADHD - Inattentive Type

- Presenting Symptoms not Typical in C-Type:
  - Daydreaming, Spacey, Stares
  - Hypoactive, Slow moving, Lethargic,
  - Motorically and cognitively sluggish
  - Easily Confused, Mentally “Foggy”
- Slow, Error Prone Information Processing*
- Poor Focused or Selective Attention
- Erratic Retrieval - Long-Term Memory (?)
- Socially Reticent or Withdrawn
- No motor inhibition problems or impulsiveness*
- Little evidence for executive function deficits*

*Solanto, M. V. et al. (2007). Neurocognitive functioning in AD/HD, Predominantly Inattentive and Combined subtypes. *Journal of Abnormal Child Psychology, 35*, 729-744.

*Milich, R. et al. (2001). ADHD combined type and ADHD predominantly inattentive type are distinct and unrelated disorders. *Clinical Psychology: Science and Practice, 8*, 463-488.

ADHD Inattentive Type with SCT

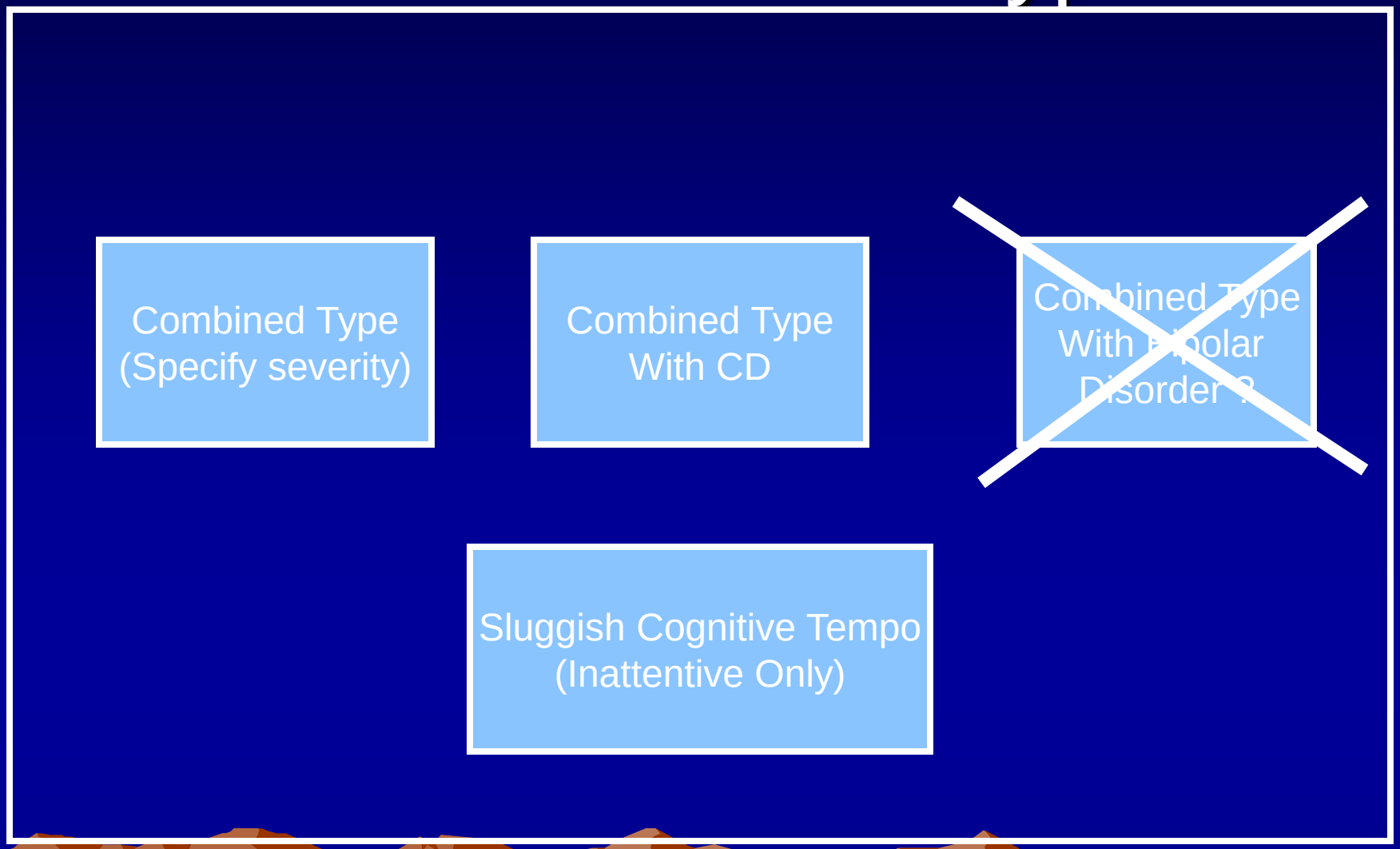
- Comorbidity: Rarely show Aggression or ODD/CD
- Lower levels of parenting stress
- Greater risk of anxiety symptoms
- Possibly greater risk for depression (?)
- Greater parental concerns regarding school failure
- Equally impaired in educational performance
  - But ADHD is a productivity disorder while SCT is an accuracy disorder
  - Greater frequency of math disorders in SCT (?)
- Greater family history of anxiety and LD (?)

Treatment Implications for SCT

- Less Likely to Have a Clinically Impressive Response to Stimulants (based on a few studies; need more research)
  - (UMASS Study 65% improve modestly in symptom ratings but only 20% showed a good clinical response)
- Better response to social skills training than ADHD cases
  - Up to 25% of ADHD cases become more aggressive in social skills groups due to peer deviancy training
  - Training works best for shy, withdrawn, anxious children
- Good (better?) response to joint home-school behavioral treatments
  - MTA study: anxious cases did the best in psychosocial treatment
  - Pfiffner (2007) study shows good response to home-school behavioral training and child training in social and organizational skills that is targeted at ADHD-I specific problems*
- More responsive to cognitive therapy (??)
  - It doesn't work for children with ADHD but is this ADHD?
  - It does work for anxiety disorders and depression
- Consider Strattera (atomoxetine) as it may treat anxiety in ADHD cases – these cases are more likely to have anxiety as a comorbidity**

- *Pfiffner, L. et al. (2007). *Journal of the American Academy of Child and Adolescent Psychiatry, 46*, 1041-1050.
- **Geller, D. et al. (2007). *Journal of the American Academy of Child and Adolescent Psychiatry, 46*, 1119-1127.

Toward DSM-V Subtypes?



ADHD Varies by Setting

Better Here:	***Worse Here:***
Fun	Boring
Immediate	Delayed Consequences
Frequent	Infrequent Feedback
High	Low Salience
Early	Late in the Day
Supervised	Unsupervised
One-to-one	Group Situations
Novelty	Familiarity
Fathers	Mothers
Strangers	Parents
Clinic Exam Room	Waiting Room

Prevalence

- 2-5% of children (using older DSM-III or III-R)
- 7-8% of children in US (using DSM-IV) (~3-4 million)
  - Adding Inattentive Type doubles prevalence over III-R
- 5.5% of children worldwide*
- 4-5% of adults in US (~12 million in US)**
- 3.4% worldwide adult prevalence***
- Varies by sex, age, social class, & urban-rural
  - 3:1 Males to females in children (5:1 in clinical samples)
  - <2:1 males to females in adults
  - More common in children; less so in adults
  - Somewhat more common in middle to lower-middle classes
  - More common in population dense areas
  - More common in certain occupations
    - For instance, 12-15% of U.S. military dependents (DSM-III-R)
  - No evidence for ethnic differences to date that are independent of social class, urban-rural demographics or variable access to care

*Polanczyk et al. (2007). *American Journal of Psychiatry, 164*, 942-948.

**Kessler, R. et al. (2006). *American Journal of Psychiatry,163,* 716-723.

***Fayyad et al. (2007). Cross national prevalence and correlates of adult attention-deficit hyperactivity disorder. *British Journal of Psychiatry, 190*, 402-409.

ADHD Etiologies

- 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 the fronto-striatal-cerebellar brain circuits and anterior cingulate
- Social causes lack compelling evidence
- 25-35% of cases attributable to acquired brain injuries*
- 65-75% of cases due to genetics-heredity*

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

Acquired Cases: Pre- & Peri-natal (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
- Peri-natal 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*

Acquired Cases: Post-Natal (3-7%)

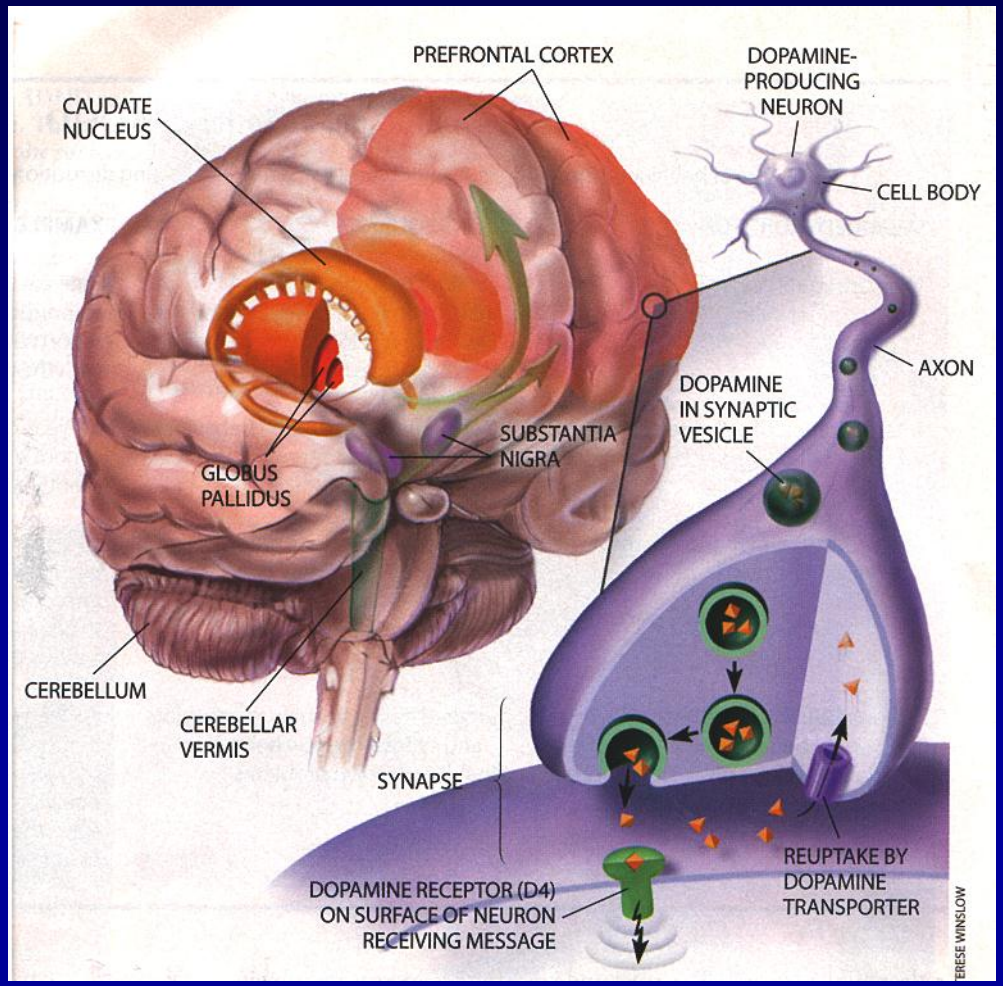
- Head trauma, brain hypoxia, tumors, or infection
- Febrile seizures
- Lead poisoning in preschool years (0-3 yrs.)
- Survival from acute lymphoblastic leukemia (ALL)
  - Treatments for ALL cause brain damage
- Post-natal Streptococcal Bacterial Infection
  - triggers auto-immune antibody attack of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

Neuro-Imaging Findings

Smaller, Less Active, Less Developed Brain Regions

- 3-10% reduced regional volumes in these 3 regions:
  - Orbital-Prefrontal Cortex (primarily right side)
    - Genetics contributes to under-development of this region while acquired ADHD may be related to smaller inferior dorsolateral frontal region
  - Basal Ganglia (mainly striatum & globus pallidus)
  - Cerebellum (central vermis area, more on right side)
- Anterior cingulate (mostly shows underactivity)
- Size of this network is correlated with degree of ADHD symptoms, particularly inhibition
- No gender differences
- 3 year lag in brain development but achieving typical brain volumes by age 16
- Results are not due to taking stimulant medication

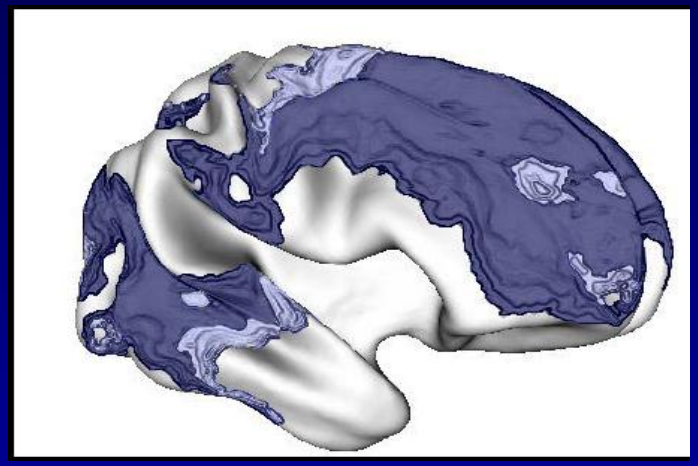
Human Brain

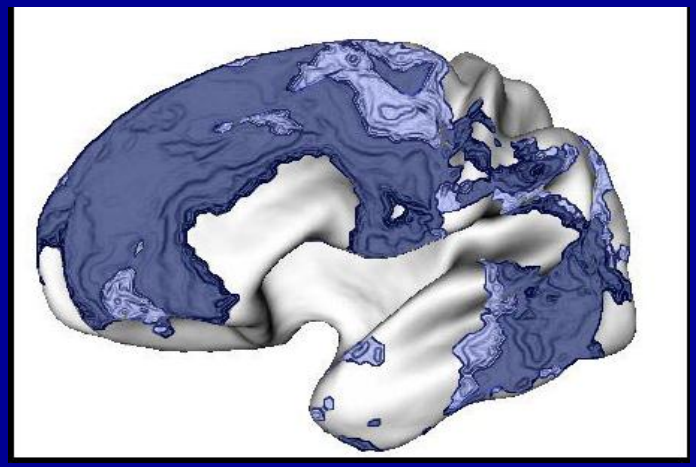


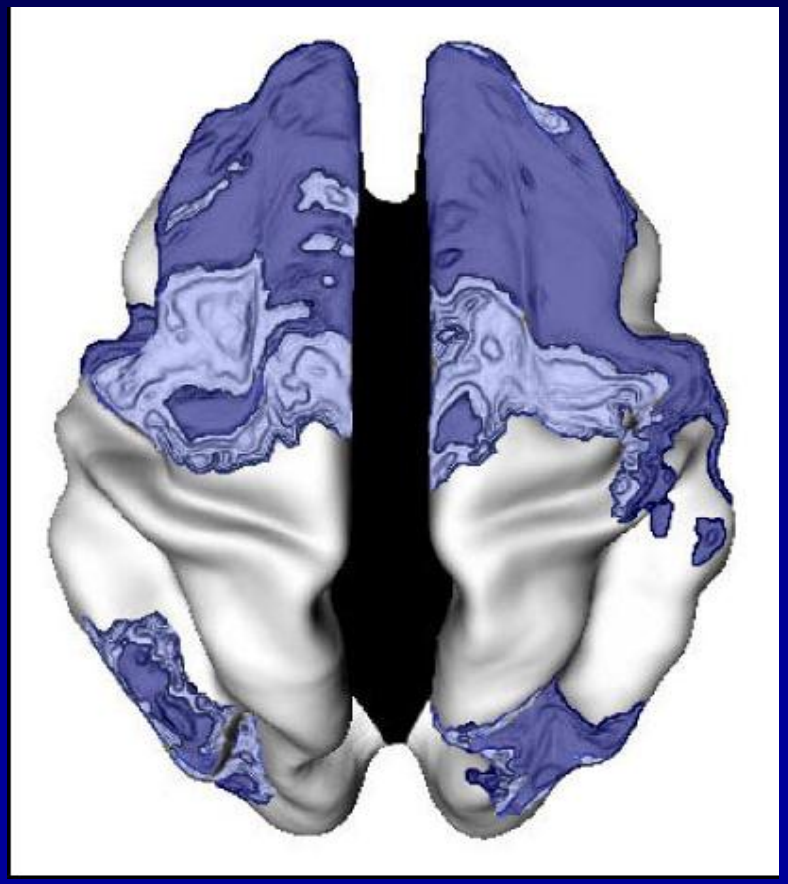
From R. Barkley, *Scientific American*, Sept. 1998, p. 47;
Reprinted with permission of Terese Winslow and *Scientific American*.

Delayed brain growth in ADHD (3 yrs.)

From Shaw, P. et al. (2007). ADHD is characterized by a delay in cortical maturation. *Proceedings of the National Academy of Sciences, 104*, 19649-19654.







Greater than 2 years' delay
0 to 2 years delay

Ns: ADHD=223; Controls = 223

Delayed cortical maturation in ADHD

From Shaw, P. et al. (2007). ADHD is characterized by a delay in cortical maturation. *Proceedings of the National Academy of Sciences, 104*, 19649-19654.

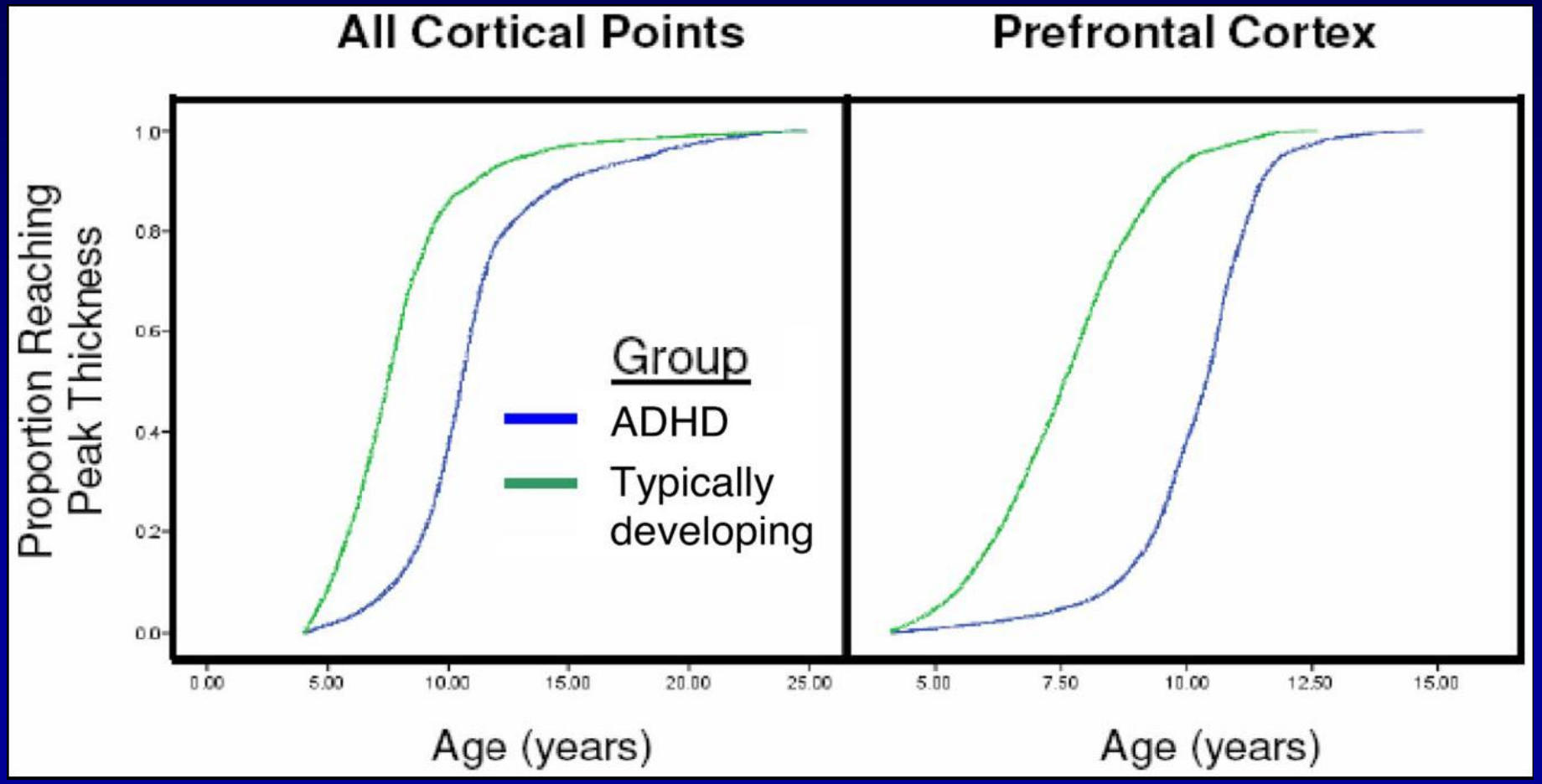
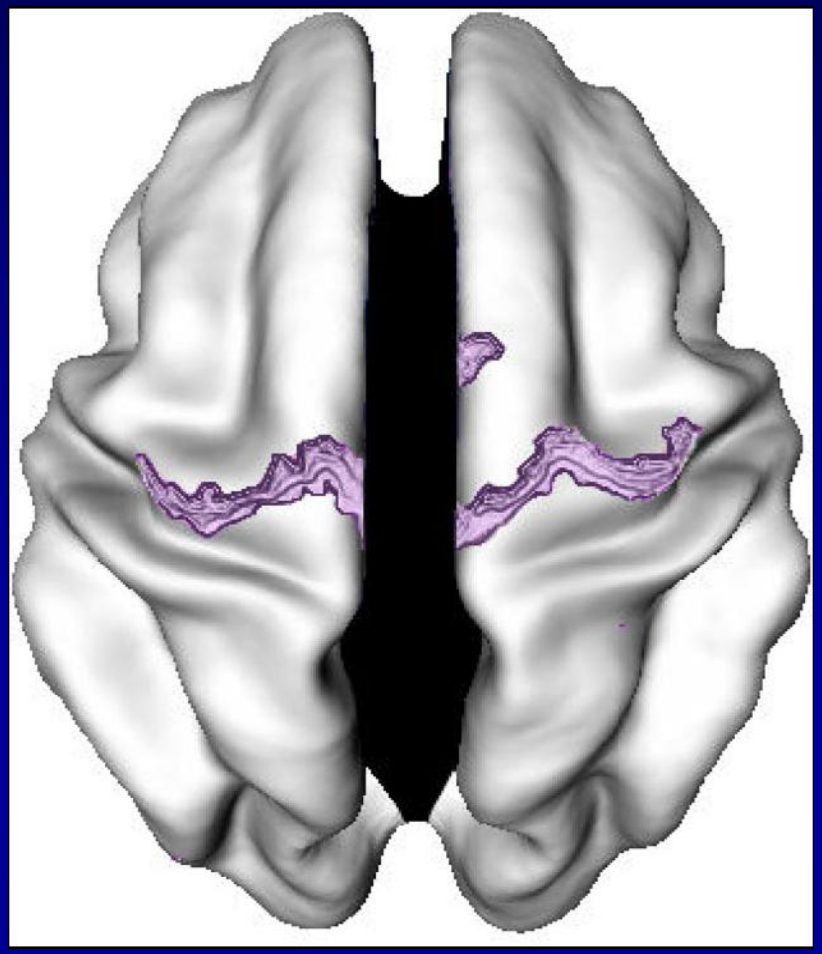


Fig. 3. Kaplan–Meier curves illustrating the proportion of cortical points that had attained peak thickness at each age for all cerebral cortical points (*Left*) and the prefrontal cortex (*Right*). The median age by which 50% of cortical points had attained their peak differed significantly between the groups

Early cortical maturation in ADHD children

From Shaw, P. et al. (2007). ADHD is characterized by a delay in cortical maturation. *Proceedings of the National Academy of Sciences, 104*, 19649-19654.

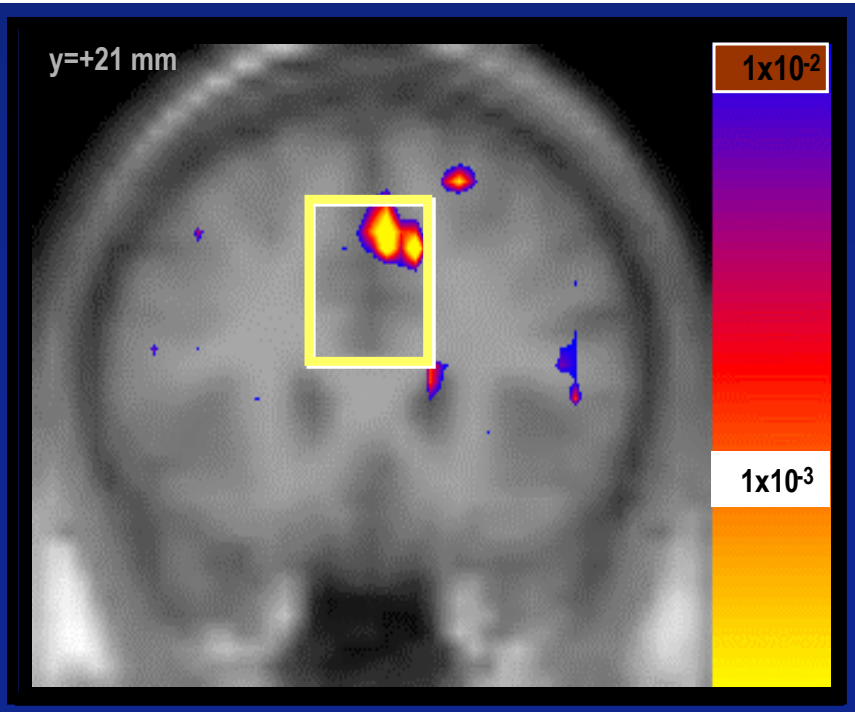
Fig. 4. Regions where the ADHD group had early cortical maturation, as indicated by a younger age of attaining peak cortical thickness.



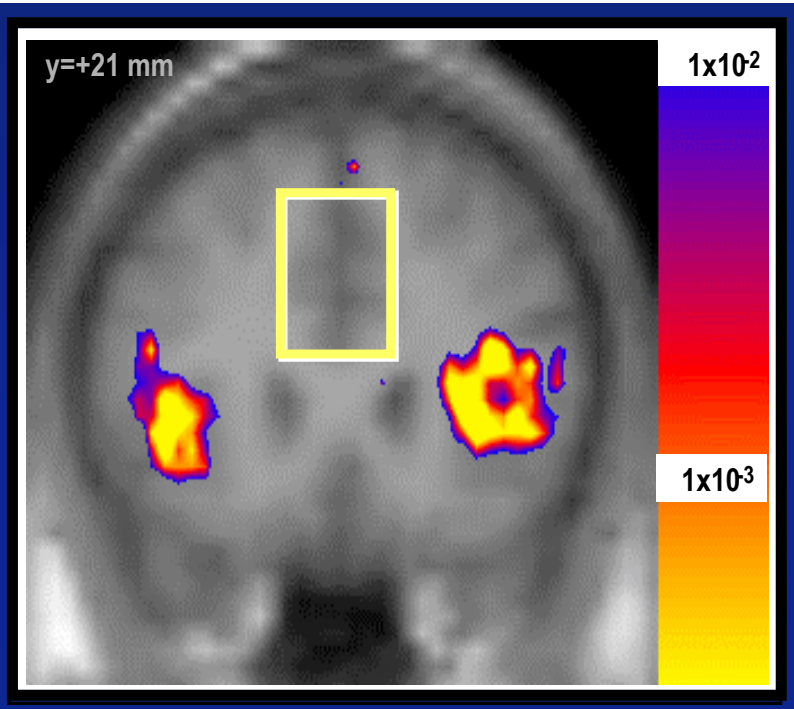
ADHD Is a Serious Neurobiological Disorder With Dysfunctions in Cognitive Processes

- Dorsal anterior cingulate cortex (cognitive division) fails to activate in adults with ADHD using functional MRI

Non-ADHD Controls



Adults With ADHD



Neurochemical Deficits

- Dopamine dysregulation
- Norepinephrine dysregulation
- Evidence from
  - Drug responding:
    - Stimulants increase dopamine outside nerves
    - Methylphenidate by slowing re-uptake
    - Amphetamines by increasing production/release
    - Strattera decreases norepinephrine reuptake
  - Molecular genetics: genes to date are dopamine and norepinephrine regulators
  - Distribution of neurotransmitters in identified brain regions associated with ADHD

Three Neural Networks for ADHD

- The frontal-striatal circuit: Associated with deficits in response suppression, freedom from distraction, working memory, organization, and planning, known as the “cool” EF network
- The frontal-limbic circuit: Associated with symptoms of emotional dyscontrol, motivation deficits, hyperactivity-impulsivity, and proneness to aggression, known as the “hot” EF network
- The frontal-cerebellar circuit: Associated with motor coordination deficits, and problems with the timing and timeliness of behavior, known as the “when EF” network

From:

Nigg, J. T., & Casey, B. (2005). An integrative theory of attention-deficit/hyperactivity disorder based on the cognitive and affective neurosciences. *Development and Psychology, 17*, 785-806.

Castellanos, X., Sonuga-Barke, E., Milham, M., & Tannock, R. (2006). Characterizing cognition in ADHD: Beyond executive dysfunction. *Trends in Cognitive Science, 10,* 117-123.

Sagvolden, T., Johansen, E. B., Aase, H., & Russell, V. A. (2005). A dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD) predominantly hyperactive-impulsive and combined subtypes. *Behavioral and Brain Sciences, 28*, 397-408.

Heredity – Family Studies

- Family Aggregation of Disorder:
  - 25-35% of siblings
  - 78-92% of identical twins
  - 15-20% of mothers
  - 25-30% of fathers
- If parent is ADHD, 40-54% of offspring are also (odds 8+)
- Parent of origin effects – gene imprinting?: (Goos et al., *Psychiatry Research, 149, Jan. 2007)*
  - If from mother, worse ADHD, ODD, & CD; girls have a higher risk of ADHD than if father has the disorder
  - If from father, worse depression, espec. in girls

Heredity – Twin Studies

- Heritability (Genetic contribution)
  - 57-97% of individual differences (Mean 80%+)
  - (88-95%+ using DSM criteria)
  - Both symptom dimensions highly related to each other and have mostly overlapping genetics with some unique genes contributing to each dimension also
- Shared Environment (common to all siblings)
  - 0-6% (Not significant in any study to date)
- Unique Environment (events that happen only to one person in a family)
  - 15-20% of individual differences
  - (but includes unreliability of measure used to assess ADHD)

Molecular Genetics

- **DRD4 – 7+ repeat:**
  - Related to novelty seeking, exploratory behavior, possibly human migration patterns; Longer genes blunt dopamine sensitivity and is related to thinner right frontal cortex but cortical normalization and better outcome
- **DAT1 – 480 bp (9/10 heterozygous differs from 9/9, 10/10)**
  - Function not well known; likely serving as a tag for other nearby functional gene regions; May build the dopamine transporter (reuptake pumps); Homozygous pairings (10/10) may respond less well to methylphenidate;10 repeat interacts with maternal alcohol use and general psychosocial adversity to increase risk for ADHD; 9/10 pairing has marked effect on severity of ADHD across childhood to adulthood.
- **DBH -- TaqI (A2 allele)**
  - May create chemical that converts dopamine to norepinephrine

Human Brain

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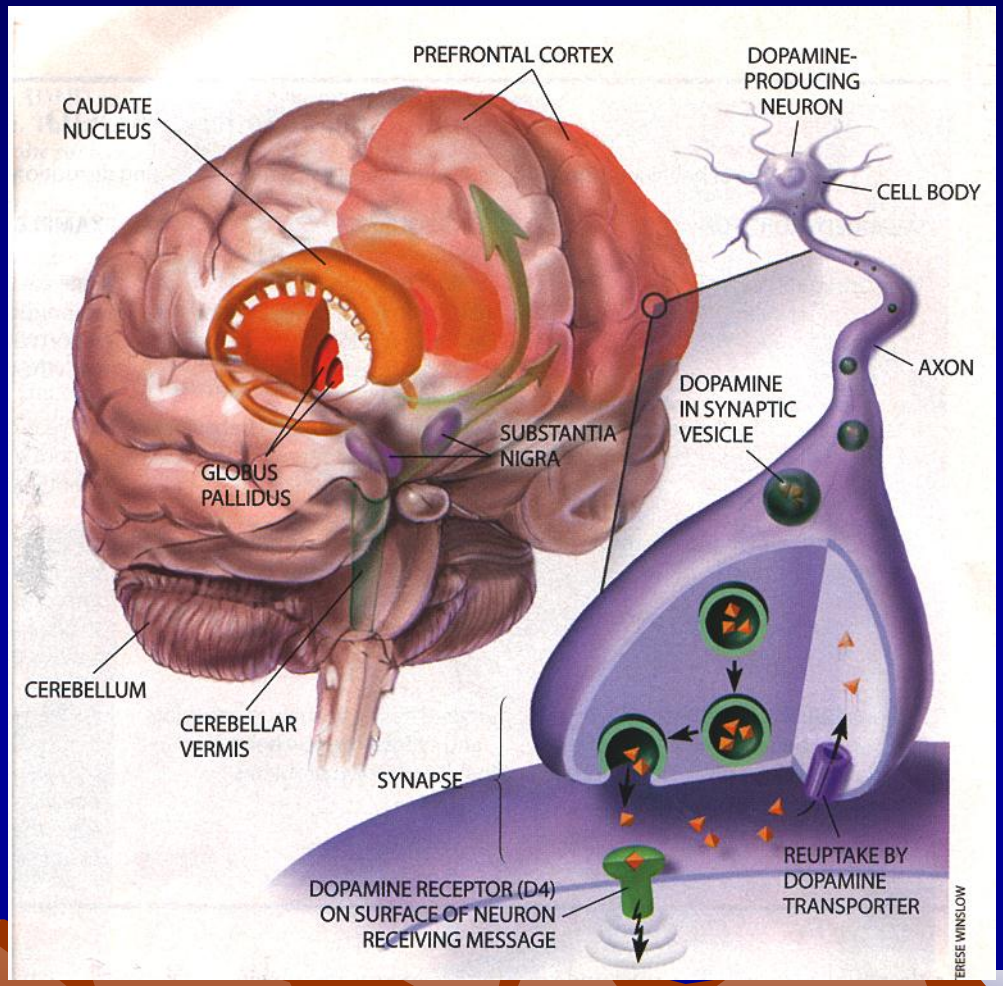


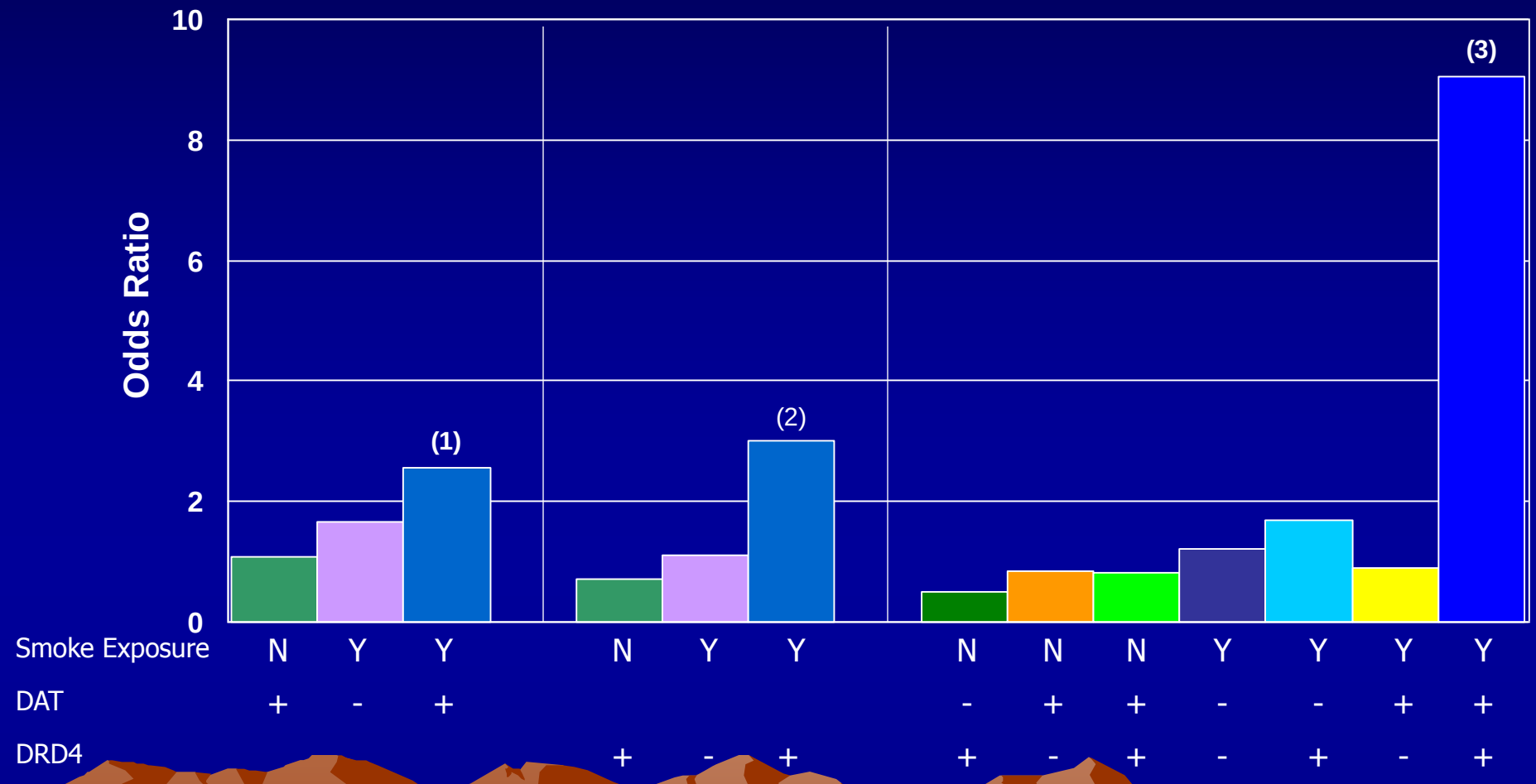
More on Molecular Genetics

- **DRD2:** dopamine receptor density type 2 (only in males)
- **SNAP25:** May be related to methylphenidate response
- **MAO-A:** produces an mitochondrial enzyme that regulates presynaptic dopamine signals and other neurotransmitter systems
- **13 other minor genes are possible candidates**
  - Unknown gene in 16q32 region is preferentially transmitted in ADHD families and in autism
  - Other regions may influence the comorbidity or ADHD with reading disorders
- **Turner's Syndrome:** (missing part or all of an X chromosome) these girls have a risk for ADHD 4-18 times greater than normal (24% vs. 5-7% general population and 1-3% of girls specifically)

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

DAT1 VNTR 440 DRD4 Exon 3 7-Repeat DAT1 440 and DRD4 Exon 3 7-Repeat Interaction



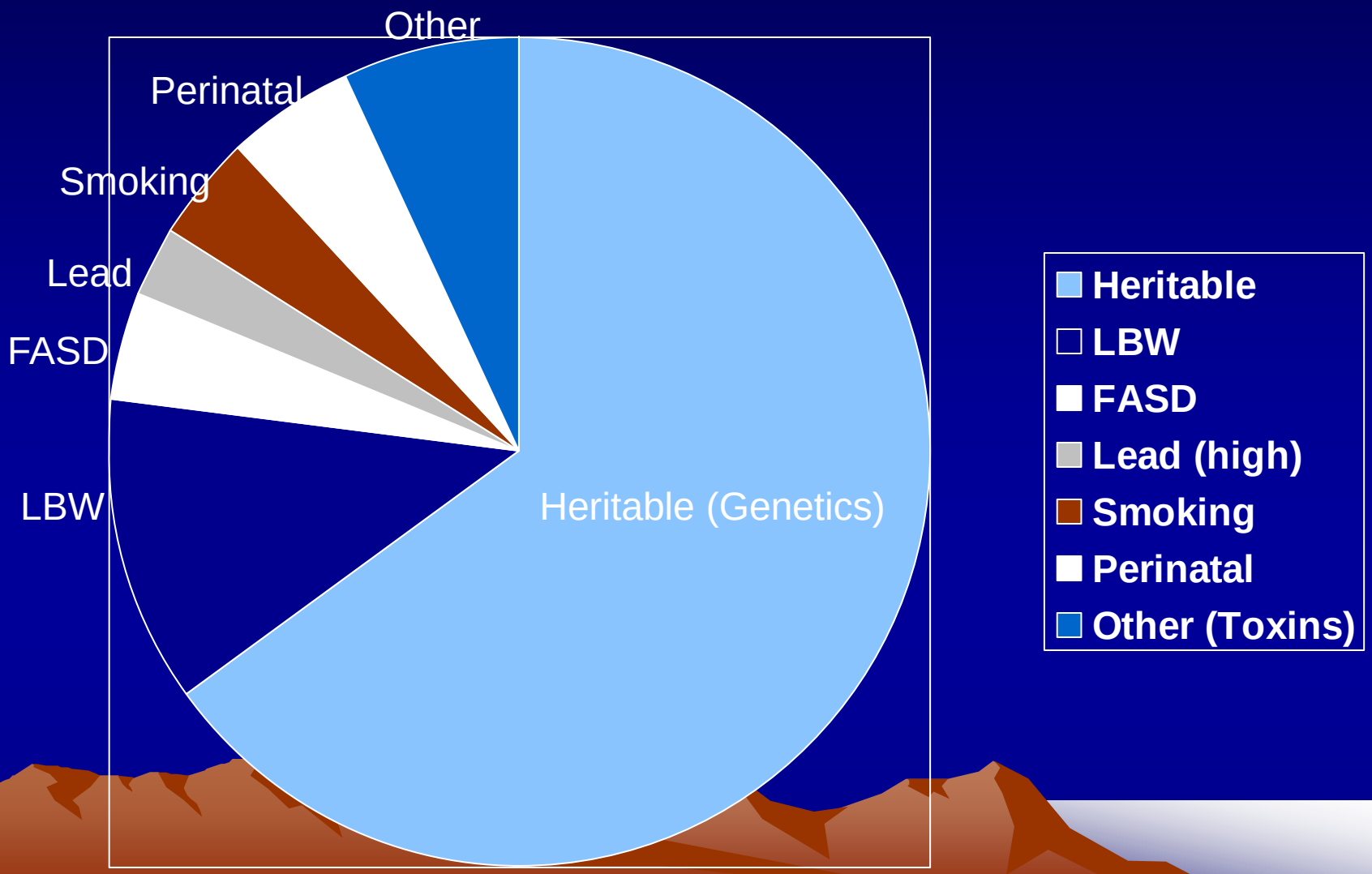
(1) 2.56[1.10, 5.95] (2) 3.01[1.14, 8.00] (3) 9.03[1.96, 41.61]

Expected Advances from Genetics

- Genetic testing to aid diagnosis
- Genetic subtyping of ADHD cases
- Better understanding and even prediction of comorbidity
- Evaluating gene x gene interactions
  - In causing risk for the disorder
  - In predicting drug responses and side effects
  - In predicting response to psychosocial treatments
- Evaluating gene x environment interactions (predicting risks and treatment effects)
- Developing new drugs targeted to genotypes
- Developing new psychosocial treatments for targeting specific phenotypes

Etiologies of ADHD

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



Conclusions

- ADHD is a valid disorder, most likely affecting executive functioning and inhibition
- Adjustments need to be made to DSM-IV to increase the sensitivity and accuracy of criteria
- ADHD is found universally
  - 5-8% of children, 3-5% of adults
- ADHD largely results from biological factors
  - Genetics, neurology, acquired injuries and interactions
  - 25-35% from injuries; 65-75% from genetics
- Social factors likely influence degree of impairment, risk for comorbid disorders, and access to resource