Advances in Understanding the Etiologies of ADHD

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Popular Unproven Etiologies[1]

- Excessive TV viewing:
  - TV accounts for just 2-5% of variance in symptoms
  - Studies have not replicated earlier associations of TV viewing and ADHD symptoms
  - ADHD cases may watch more TV but direction of causality not proven and likely to be a consequence of ADHD and of parental use of visual media for babysitting a difficult child
- Food additives (coloring, preservatives):
  - May exacerbate behavioral problems in 5% of fewer of ADHD children in preschool years
  - Associated with small increases in hyperactivity in normal children yet this is not consistently found in ADHD children
  - A recent large study in The Netherlands using a restrictive elimination diet found improvement in ADHD symptoms in 50% of children placed on elimination diets but the study was seriously flawed and the results so dramatically different from all others as to seriously question the methodology

Additional Disproven Causes

- Excess video-gaming:
  - A large longitudinal study from Norway shows that time spent video-gaming is not predictive of subsequent psychiatric problems but initial level of ADHD predicts increasing video-gaming over time.
- Sugar consumption
  - Shown to be the result of parental knowledge that a child was consuming sugar and parental expectations of exacerbation
- Poor child-rearing methods at home:
  - There is more parent-child conflict found in families with ADHD.
  - But research shows this is related to both child and parental ADHD and maternal depression
  - Such conflict improves with medication of child
  - And numerous twin studies show no within-family shared effects
- A breakdown in the traditional family structure
  - Increased divorce rates resulting in father absence from home
- Delayed or disrupted sensory-motor integration (given as a basis for doing Sensory Integration Training)

Advances in Etiology

- ADHD represents the extreme end of a dimensional trait that varies in severity in human populations (comprises 2 highly correlated traits)
- Disorder arises from multiple causes
- All currently recognized causes fall in the realm of biology (neurology, genetics) but interactions with environmental hazards are likely – complex interactive models are needed
- Causes may compound each other
- Final common pathway for disorder appears to be the fronto-striatal-cerebellar executive circuits in the brain
- Variation across cases may come from which circuits are disrupted and gene x environment interactions (epigenetics)
- Social causes lack credibility as main effects (interactive?)

Acquired Cases: Prenatal

- Maternal alcohol drinking in pregnancy (same)
- Prematurity of birth, especially if brain bleeding (45%+ have ADHD)
- Maternal urinary tract infections and pre-clampsia
- Total increased pregnancy & delivery complications
- Maternal hypertensive disorders in pregnancy (odds ratio = 1.29)
- Maternal prenatal opioid exposure*
  - *Research on opioids did not control for maternal ADHD
  - Note – Maternal cocaine/crack exposure during pregnancy is linked to higher ADHD rates in offspring BUT they is not a reliable risk factor after controlling for the above factors and maternal ADHD

Possible Prenatal Factors

- Possible causes but also markers for maternal ADHD instead:
  - Maternal smoking during pregnancy (likely a marker)
  - Maternal pre-pregnancy obesity (?)
  - Gestational diabetes during pregnancy – direct effect on offspring as well as index of maternal ADHD
  - Maternal high phenylalanine levels in blood (?)
  - High maternal anxiety in second trimester (?)
  - Maternal prenatal ingestion of acetaminophen for 22+ days
    - Paternal use also showed a significant association to ADHD
- Maternal methylmercury ingestion (fish diet)(?)
- Maternal inflammation during pregnancy (immune response to increased cytokine levels)
- Maternal exposure to pitocine to induce pregnancy is <u>not</u> a risk factor for ADHD as was once believed

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

- Head trauma, brain hypoxia, tumors, or infection
- Febrile seizures
- Lead poisoning in preschool years (0-3 yrs.)
  - Boys are more sensitive (at risk) than girls if lead burden is elevated
  - But if mothers had adequate HDL and low stress it moderates effects
- Iron Deficiency – more an exacerbating factor than primary
- 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
- Survival from acute lymphoblastic leukemia (ALL)
  - Treatments for ALL causes brain damage resulting in 28%+ of survivors having ADHD (SCT) symptoms

Neuro-Imaging Findings

In ADHD we find smaller (3-10%), less activity (10-25%+), delayed development and variable functional connectivity of EF networks to other posterior regions, especially the Default Mode Network, and delayed cortical development (2-3 yrs.) especially in the frontal brain regions. Reduced volume in:

- Orbital-Prefrontal Cortex (primarily right side)
  - Left frontal, right parietal, and temporal lobes show abnormal sulcal patterns
- Basal Ganglia (mainly striatum & globus pallidus)
- Cerebellum (central vermis area, more on right side)
- Anterior cingulate cortex
- Corpus callosum (primarily anterior splenium)
- Amygdala and Thalamus (??)

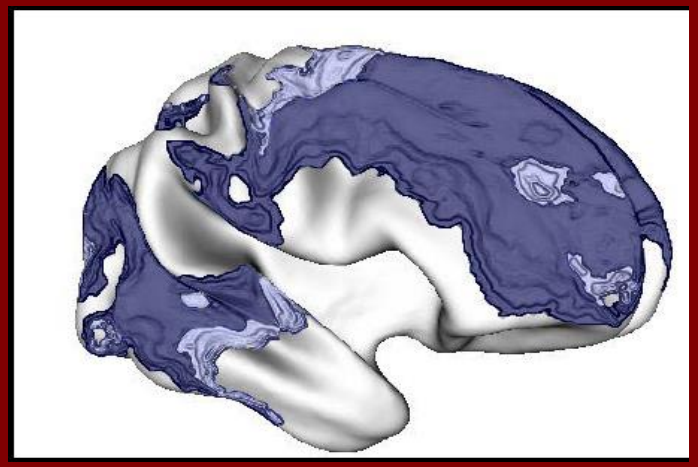
All 7 functional brain networks involve the cortical, basal ganglia, thalamic, and cerebellar regions to varying degrees. BUT the executive network originating in the prefrontal regions is the most involved in ADHD.

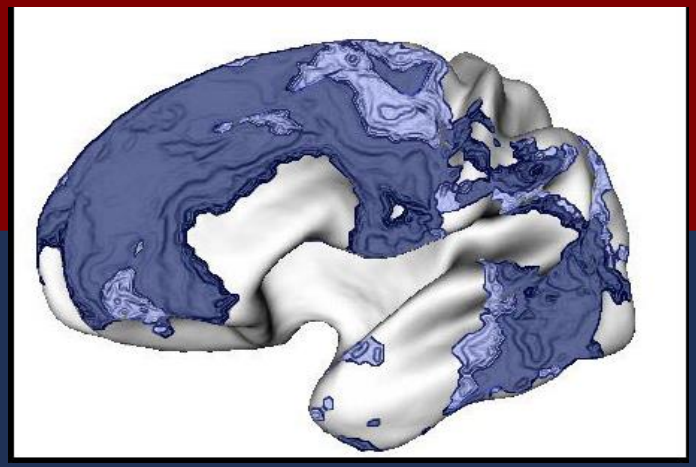
More Neuro-Imaging Results

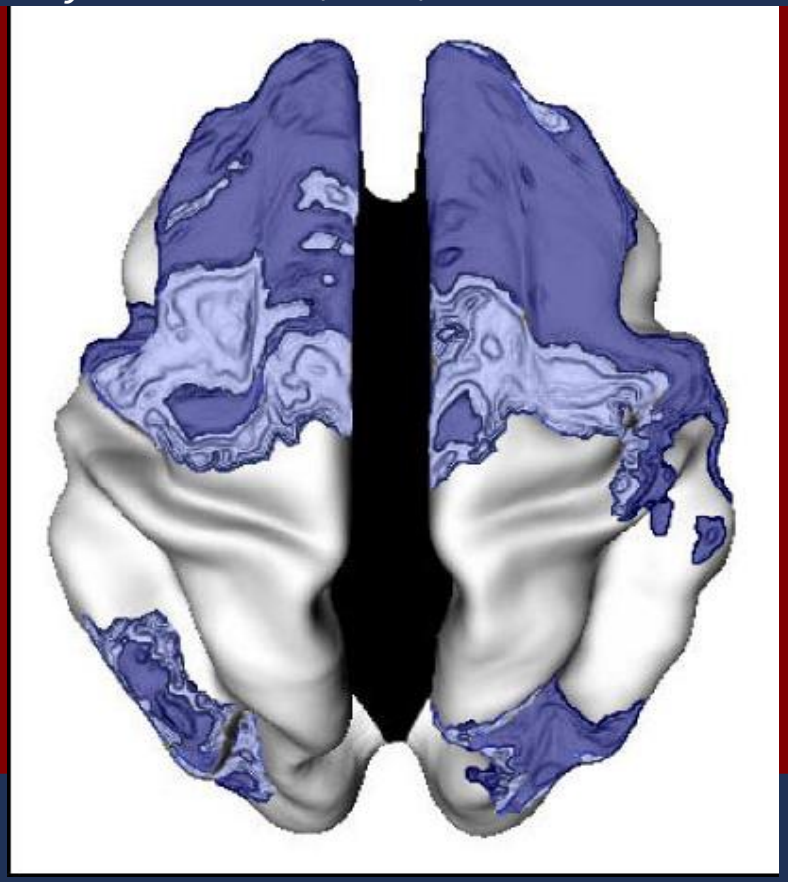
- Size of these regions is correlated with degree of ADHD symptoms, particularly inhibition
- No substantial gender differences
- Structural differences in volume persist to late adolescence then some normalization
- Functional differences may persist into adulthood in most cases, especially in frontal-parietal regions
- It is the variability of functional connectivity that is most prominent in ADHD vs. other disorders
- Longer term use of stimulants has been associated with improved growth in the ADHD regions (neuroprotection)

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.







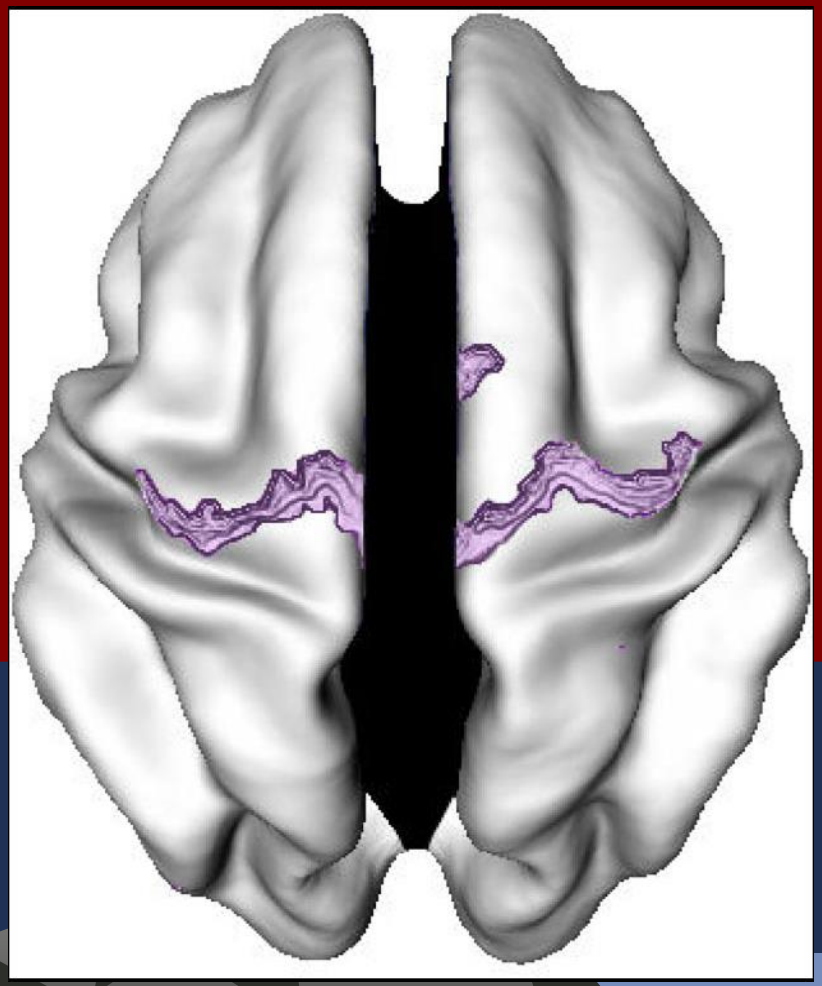
Greater than 2 years' delay
0 to 2 years delay

Ns: ADHD=223; Controls = 223

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.



Basal ganglia abnormalities in ADHD vs Normal

Sobel et al. (2010). *American Journal of Psychiatry, 167,* 977-986

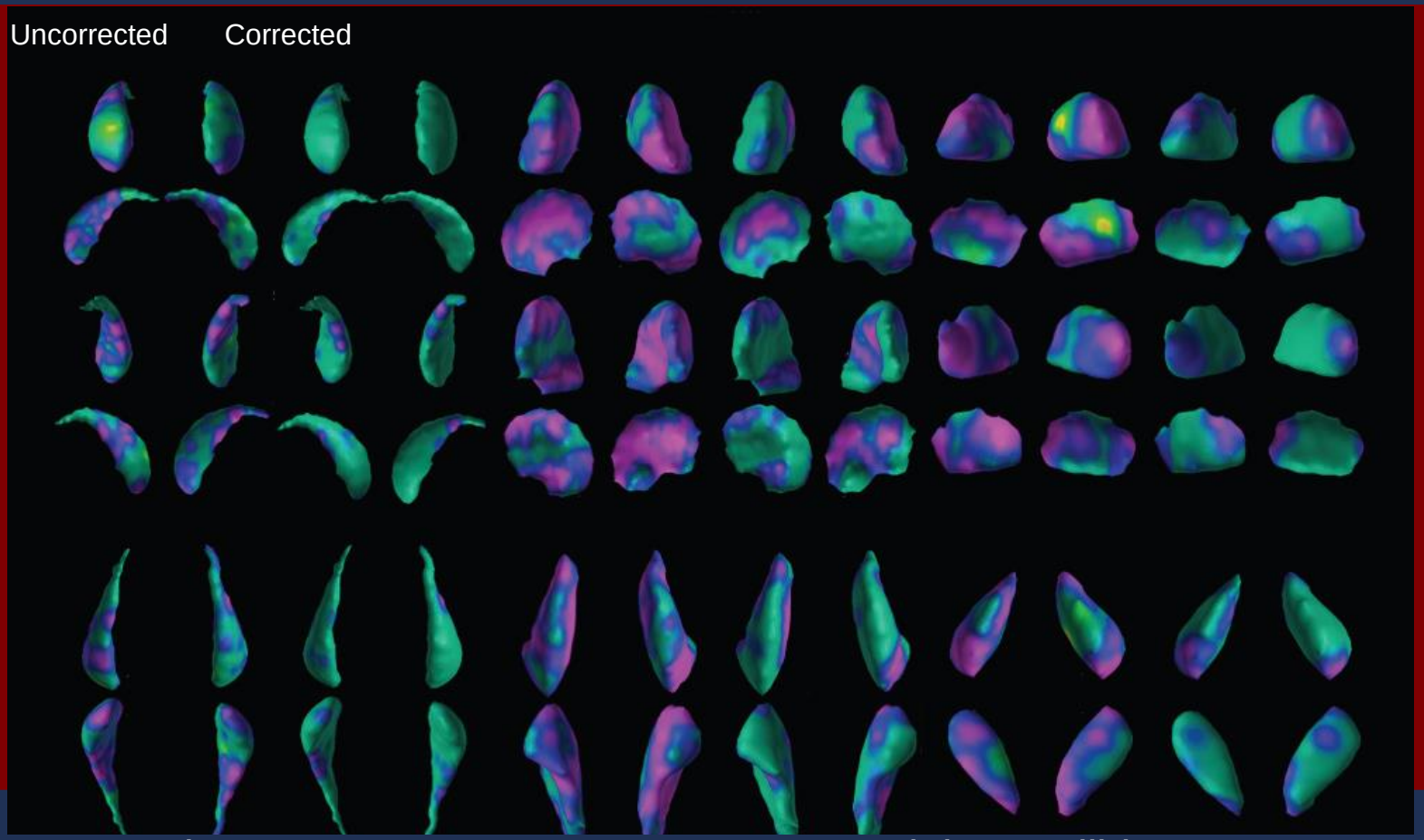
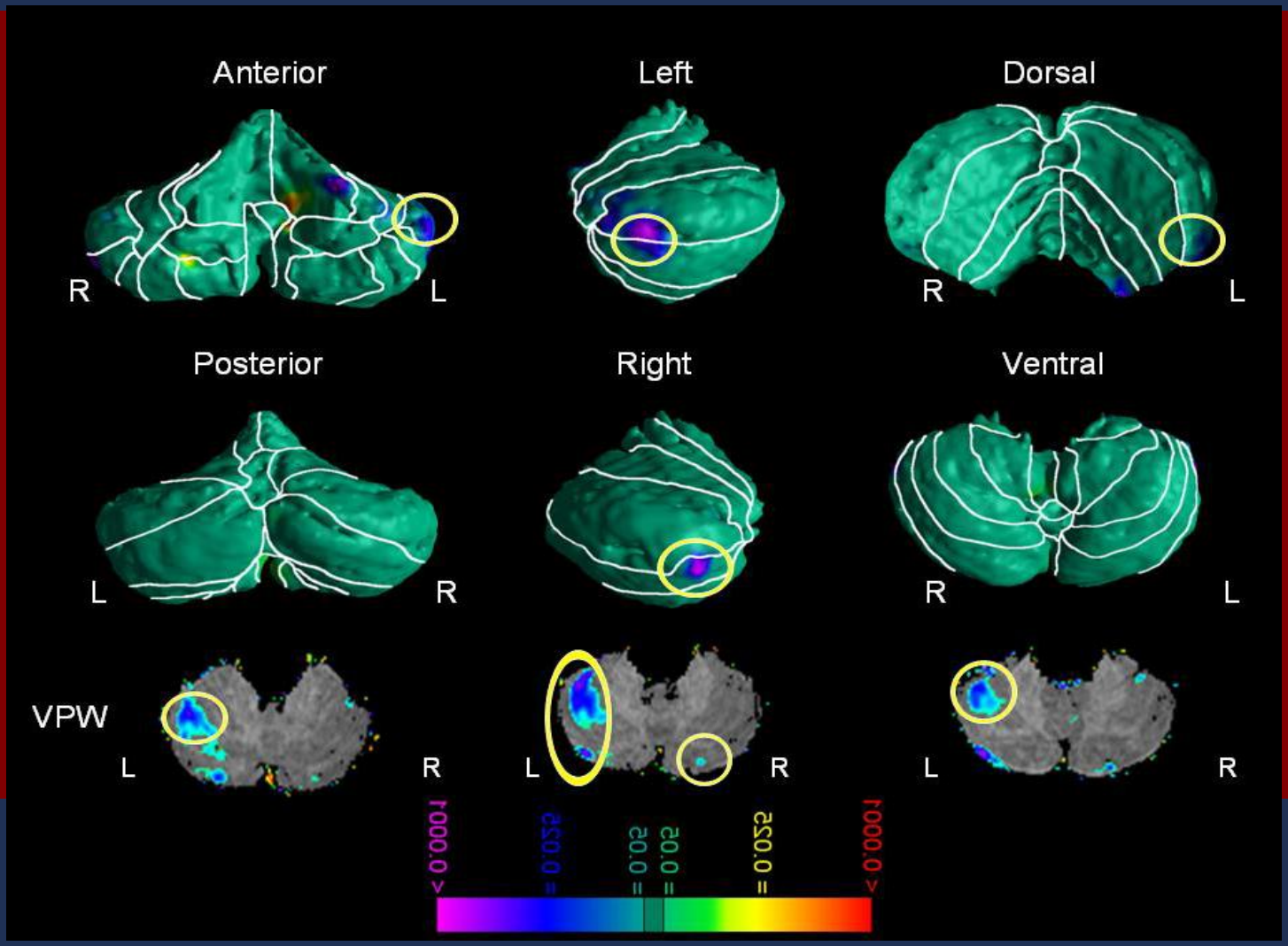


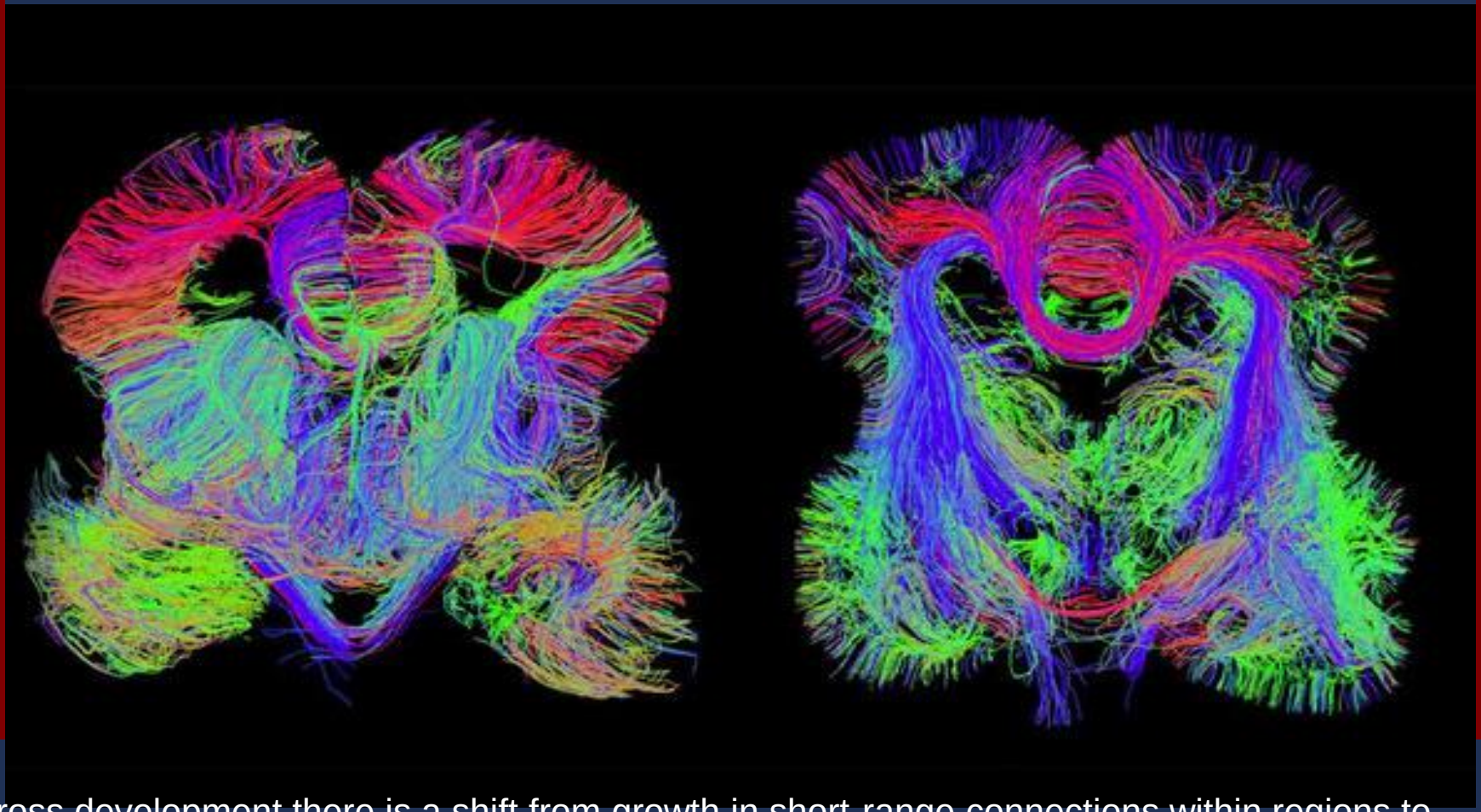
FIGURE 1. Main Effects of Diagnosis on Surface Morphologic Features of Basal Ganglia Nuclei in Youth With ADHD Relative to Healthy Comparison Subjects. The right and left caudate, putamen, and globus pallidus are displayed in rotational views and in their dorsal and ventral perspectives. Anterior (A), posterior (P), lateral (L), and medial (M) views of each nucleus are shown. The color bar indicates the significance value for group comparisons at each point on the surface. Green values represent statistically nonsignificant differences ($p \geq 0.05$) of the surface of the basal ganglia nuclei between groups. Yellow and red values ($p < 0.0001$) represent outward deformations of the surfaces or local volume increases, whereas blue and purple represent inward deformations of the surfaces or local volume reductions ($p < 0.0001$). Ns = 47 ADHD vs 57 controls ages 7-18

Cerebellar Abnormalities in ADHD Diagnosed Children



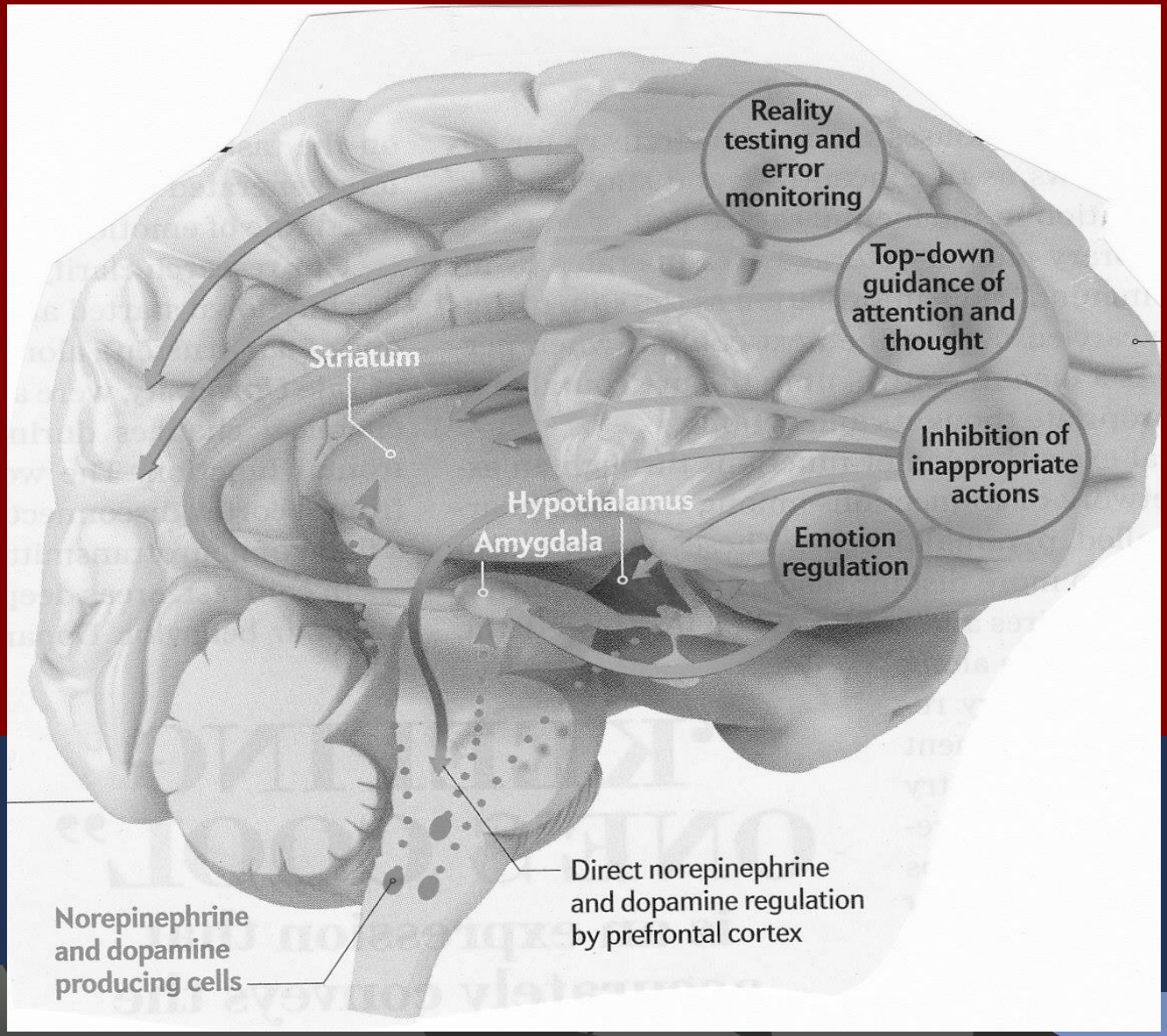
The figure shows statistical maps in different cerebellum views; the color bar indicates the color coding for p values associated with the main effect of ADHD diagnosis, ranging from p<0.0001 in red (i.e. increased regional volumes) and p<0,0001 in purple (i.e. decreased regional volumes). The theory of Gaussian random field was used to correct for multiple comparisons. The maps show significantly smaller regional volumes in cerebellar lobules I-IV and crus I on the left as well as crus II on the right in youths with ADHD compared to healthy controls. L= left; R= right; VPW = Volume preserve warping.

Typical Brain Network Development

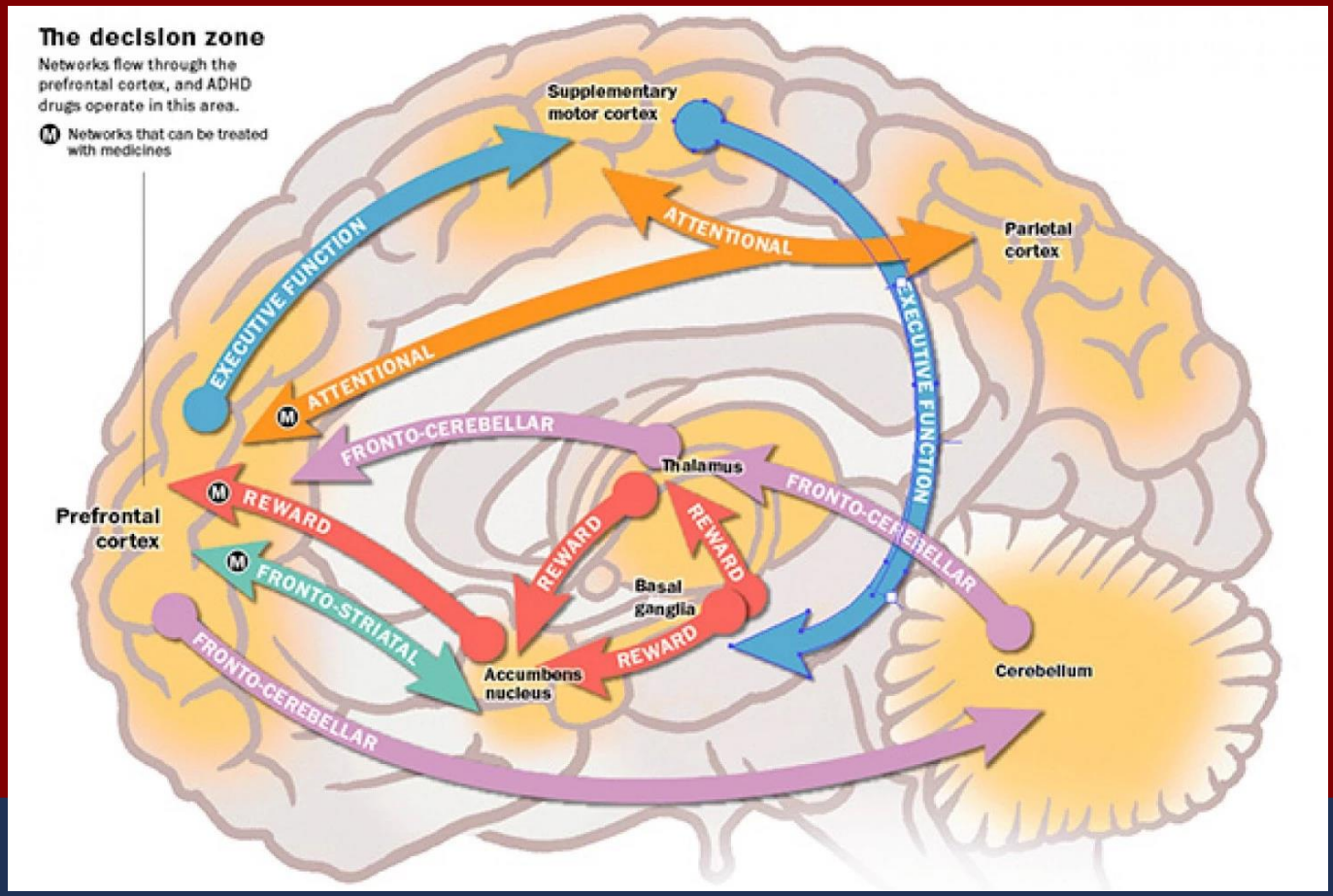


Across development there is a shift from growth in short-range connections within regions to increased long-range connections across regions along with pruning of some connections to form the functional cortical networks – this is delayed and disrupted in many of the networks implicated in ADHD. With maturation, it is mainly the frontal-parietal (executive) network that remains impaired

Executive Networks



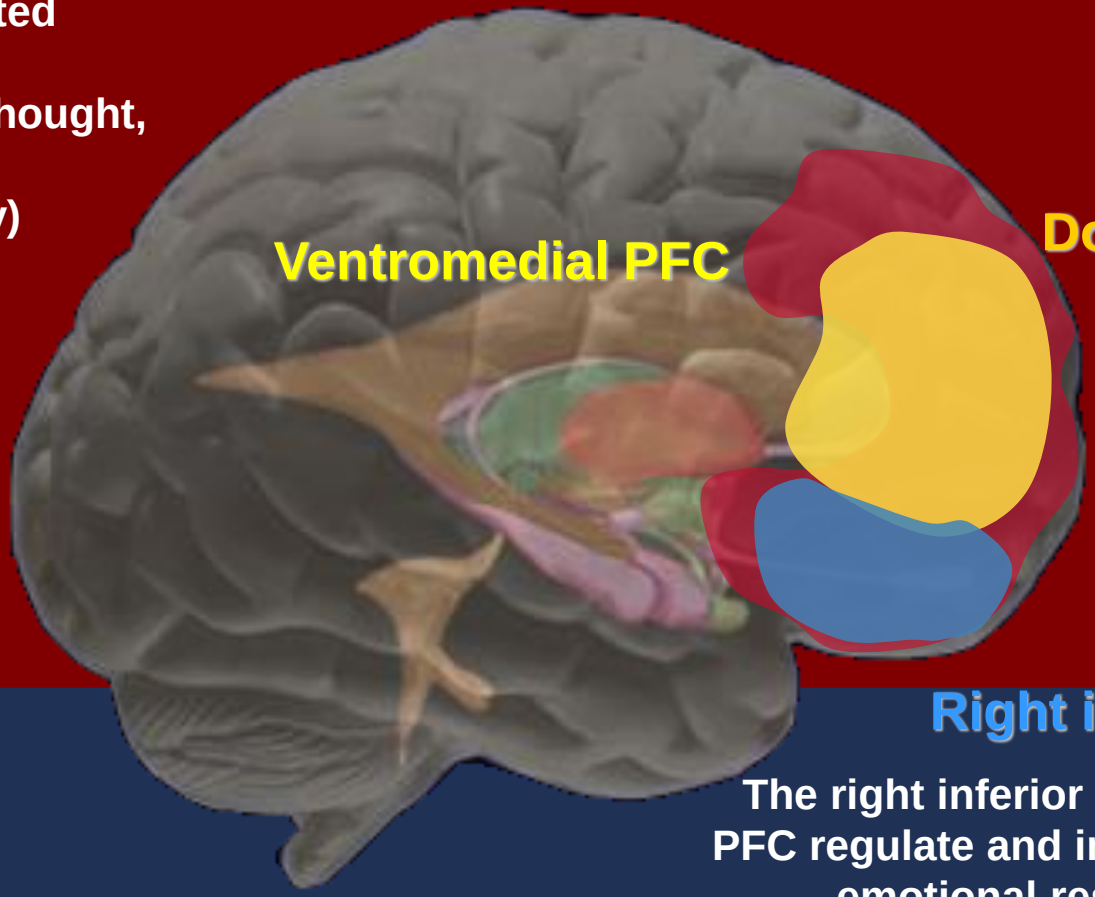
Brain Networks Involved in ADHD



Adapted from the article and illustrations by Bonnie Berkowitz and Patterson Clark, Your Brain on ADHD, *The Washington Post,* June 1, 2015. http://apps.washingtonpost.com/g/page/national/your-brain-on-adhd/1716/. This illustration appeared as part of the larger article by Arlene Karidis entitled Still More Questions Than Answers About How to Treat ADHD. http://www.washingtonpost.com/national/health-science/still-more-questions-than-answers-about-how-to-treat-adhd/2015/06/01/294b0df2-c738-11e4-aa1a-86135599fb0f_story.html

Emotion Regulation in the Prefrontal Cortex – The "Hot" EF Circuits

PFC and associated neuromodulators guide behavior, thought, and affect (working memory)



The right inferior and ventromedial PFC regulate and inhibit appropriate emotional responses, enabling socially appropriate behaviors

Arnsten et al. *J Child Adolesc Psychopharmacol* 2007;17:393.

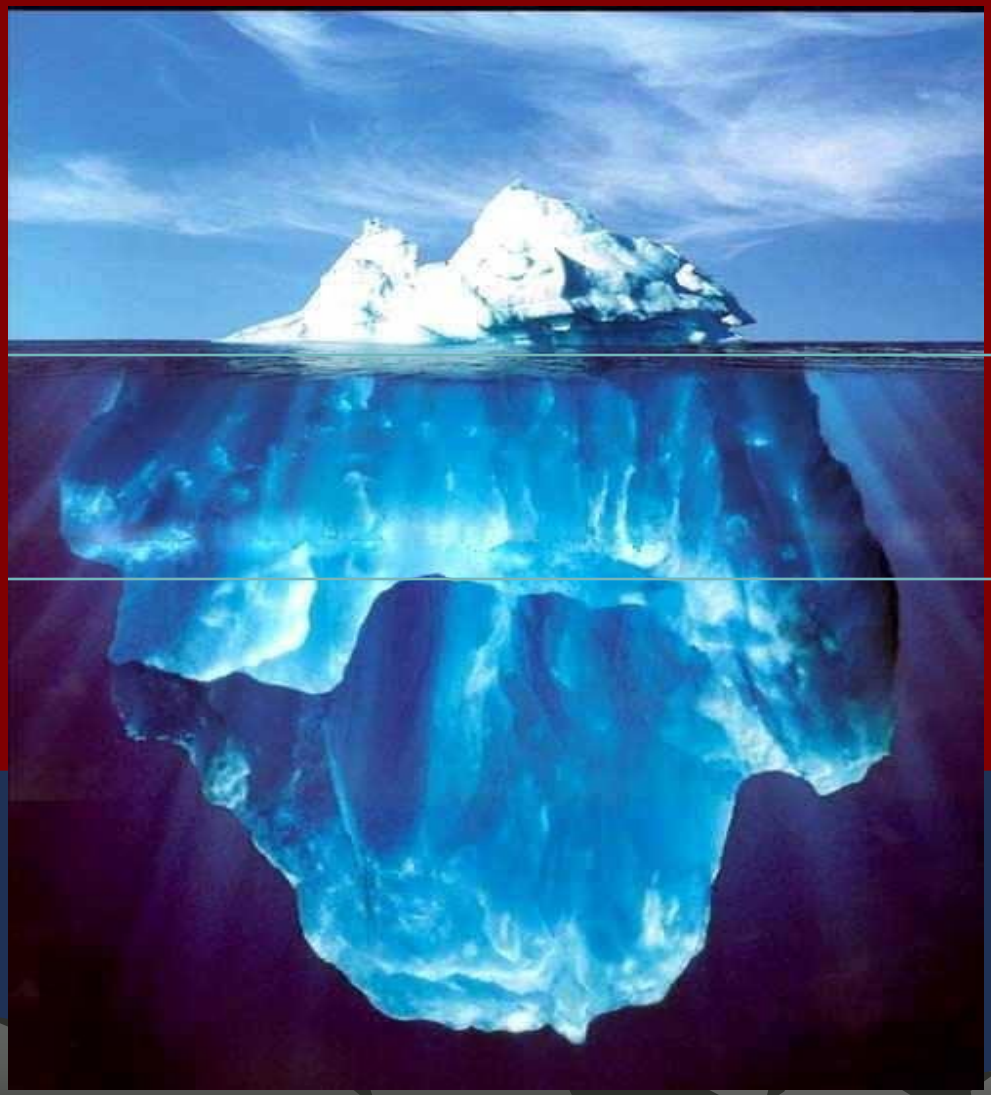
The Frontal Parietal Cortical Network Can Be Usefully Fractionated into Four EF Sub-networks: All are Implicated in Self-Regulation and in ADHD

- The frontal-striatal-thalamic circuit: Associated with deficits in response suppression, freedom from distraction, mental representations that guide behavior (working memory), manipulation of mentally held information (organization, planning, and problem-solving), and responding to novelty known as the "cool" or **"what"** EF network
- The frontal-cerebellar circuit: Associated with motor coordination deficits, but also with problems with anticipation of rewards, and the timing and timeliness of behavior, known as the **"when"** EF network
- The frontal-limbic circuit: Associated with symptoms of emotional self-regulation, motivation deficits, hyperactivity-impulsivity, and proneness to reactive aggression, known as the appraisal, **"hot"** or **"why"** EF network
- The frontal-cingulate-parietal network: Associated with deficits in self-awareness, performance monitoring, and error detection.

Remitters vs. Persisters

- Remitters have different trajectories of brain growth and connectivity in adolescence – especially frontal areas and in the posterior default mode network
- Remitters become closer to typical brain structure than do persisters in cortical and cerebellar areas but not in deep brain areas of the caudate (part of basal ganglia)
- White matter microstructure is similar (larger) in remitters and typical cases than in persistent group
- Connectivity among brain attention, executive, and DMN networks normalizes in remitters
- Results not due to stimulant treatment or comorbidity

Genetic “Iceberg”



Recognized ADHD

Spectrum of ADHD

Unimpaired
(low loading,
high functioning family
members, “ADHD-like”)

Heredity – Family Studies

Evidence of Family Aggregation of the Disorder:

- 25-35% of siblings (hazard ratio [HR] = 8; 8x more likely than control siblings are to have ADHD. Same HR for dizygotic twins. Half-siblings = 2.3-2.8)

- 78-92% of identical twins (HR = 70)

- 15-20% of mothers

- 25-30% of fathers

- If parent is ADHD, 40-54% of offspring (odds = 8+)

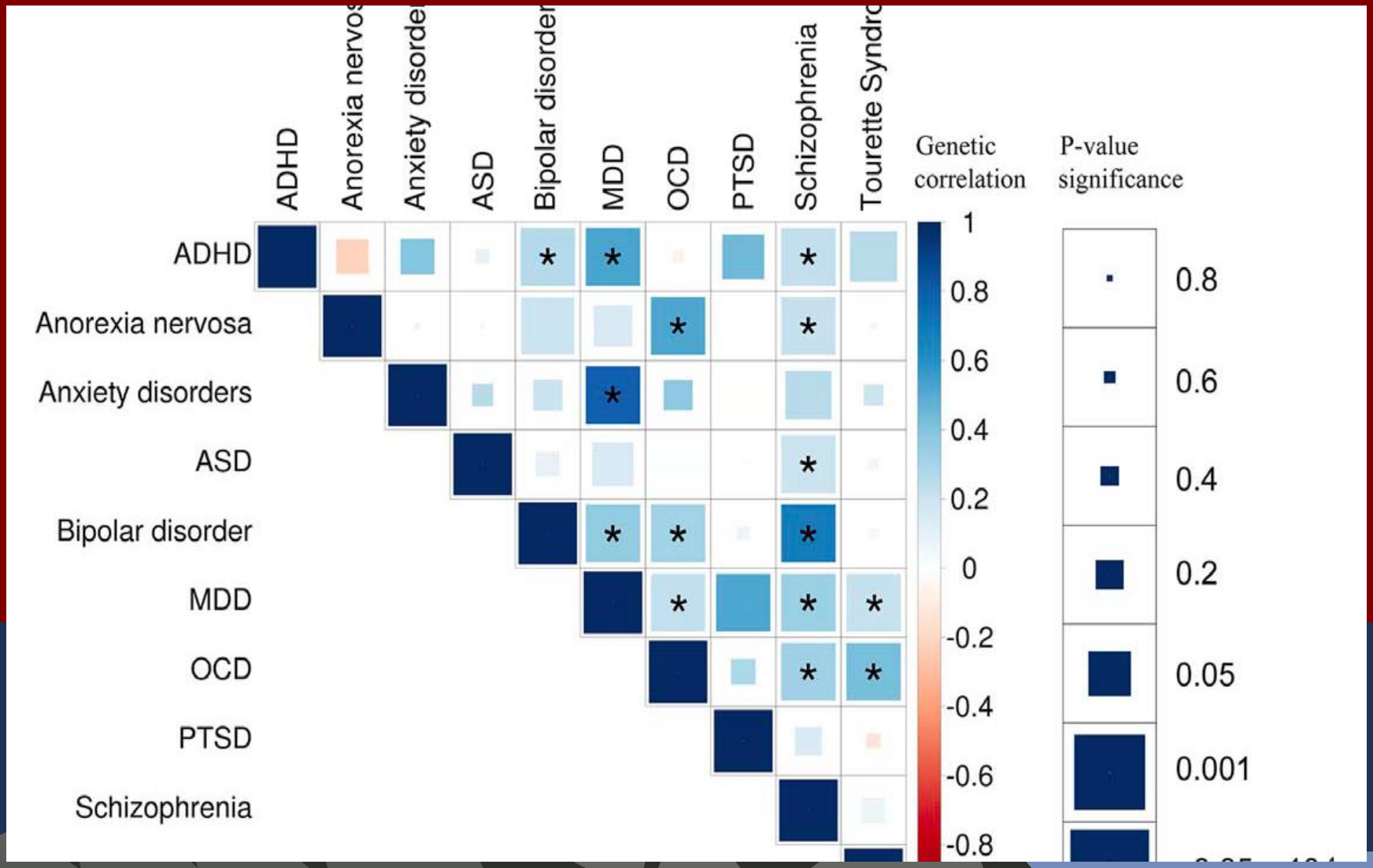
- Parent of origin effects: (Goos et al., *Psychiatry Research, 149, Jan. 2007)*
  - If genes come from the mother, worse ADHD, ODD, & CD; girls have a higher risk of ADHD than if father has the disorder
  - If genes come from the father, worse depression, especially in girls

Heredity – Twin Studies[1,2]

- Heritability (Genetic contribution)
  - 57-97% of individual differences (Mean 80%+)
  - (91-95%+ using DSM criteria)
- 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)

1. Mick, E. & Faraone, S. V. (2008). *Child and Adolescent Psychiatric Clinics of North America, 17* , 261-284.
2. Tuvblad, C. (2009). *Journal of Abnormal Child Psychology, 37*, 153-167.

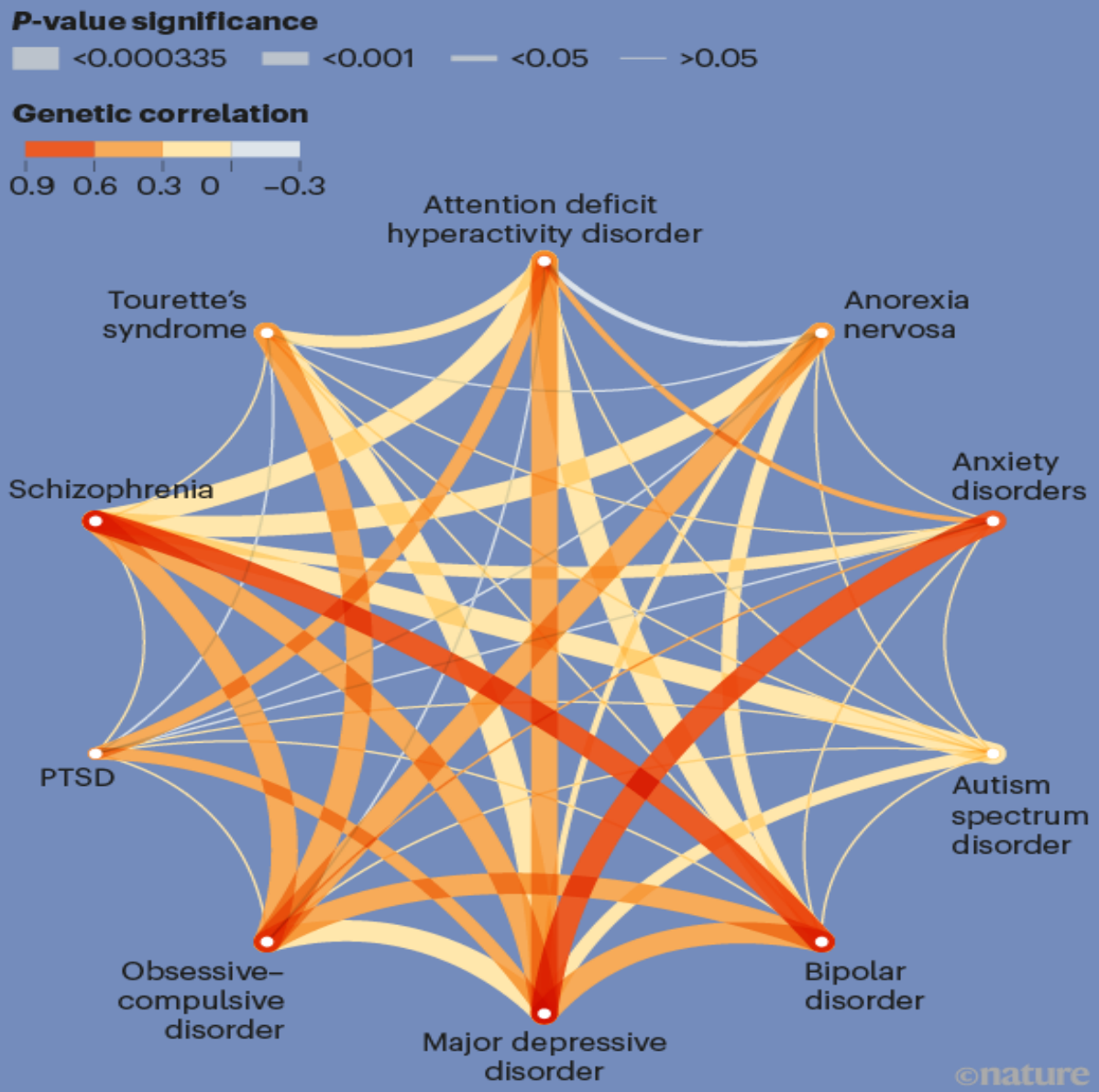
Genetic Correlations Across Psychiatric Disorders



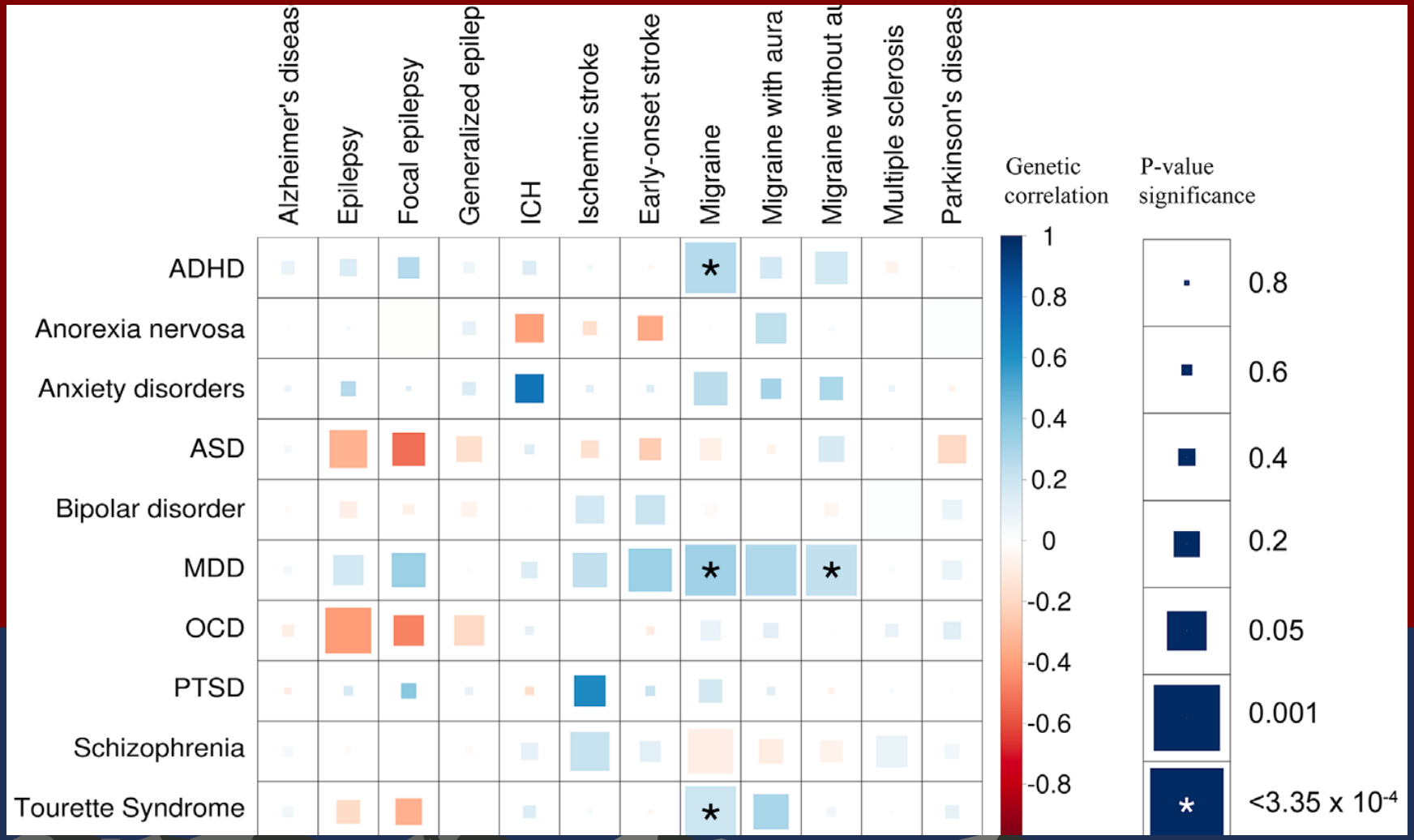
The Brainstorm Consortium (2018). *Science, 360,* eaap8757. Ahead of print.

MENTAL MAP

Similar genetic variants seem to underlie a number of psychiatric disorders. In one study of 200,000 people, schizophrenia was significantly correlated with most other disorders. By contrast, some disorders such as post-traumatic stress disorder (PTSD) showed only weak correlations to other conditions.



Genetic Correlations Between Psychiatric and Neurologic Disorders



The Brainstorm Consortium (2018). *Science, 360,* eaap8757. Ahead of print.

Molecular Genetics

- **Genome wide scans -** suggest that 20-42 chomosome sites that may contain minor genes that are possible candidates[2] The most recent (Demontis et al., 2018) identified 12 reliable loci. Additional research found 4 more genetic loci along with 2 earlier ones that govern whether or not other genes are transcribed (expressed), some of which deal with expression in dorsolateral prefrontal cortex and amygdala.
- Although candidate gene studies find a number of different genes as possibly associated with ADHD, such as those below, genome wide association studies have not supported these gene sites.
  - **DRD4 – 7+ repeat and 4 repeat absent (?):** Related to novelty seeking, exploratory behavior, possibly human migration patterns; Longer genes blunt dopamine sensitivity. Those lacking 4 repeat do better on methylphenidate.[6]
  - **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); Those with single copy 10 variants or with homozygous pairings (10/10) may respond less well to methylphenidate;[6] 10 repeat interacts with maternal alcohol use 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 (DBH) that converts dopamine to norepinephrine
- Instead, sites dealing with cell migration and support during brain development, synpatic connections, and networks relate to language and intelligence (FOX2P) are reliably linked to the disorder, as area genes governing the expression of other genes during development.
- Further research shows that epigenetic methylation markings on ADHD risk genes also govern their activation and expression, which may be where environmental factors act to alter genetic factors and risk for ADHD.

More on Molecular Genetics

- Genes involved in inattention (IN) overlap with those involved in hyperactive-impulsive (HI) symptoms yet some non-overlap (unique genetic effects) exists as well
- Genetic contribution increases with age; new genes contribute to later symptoms besides earlier genes
- Genes in ADHD are also risk genes for Depression, ODD, CD, and Reading and Language Disorders. Possibly Autistic Spectrum as well

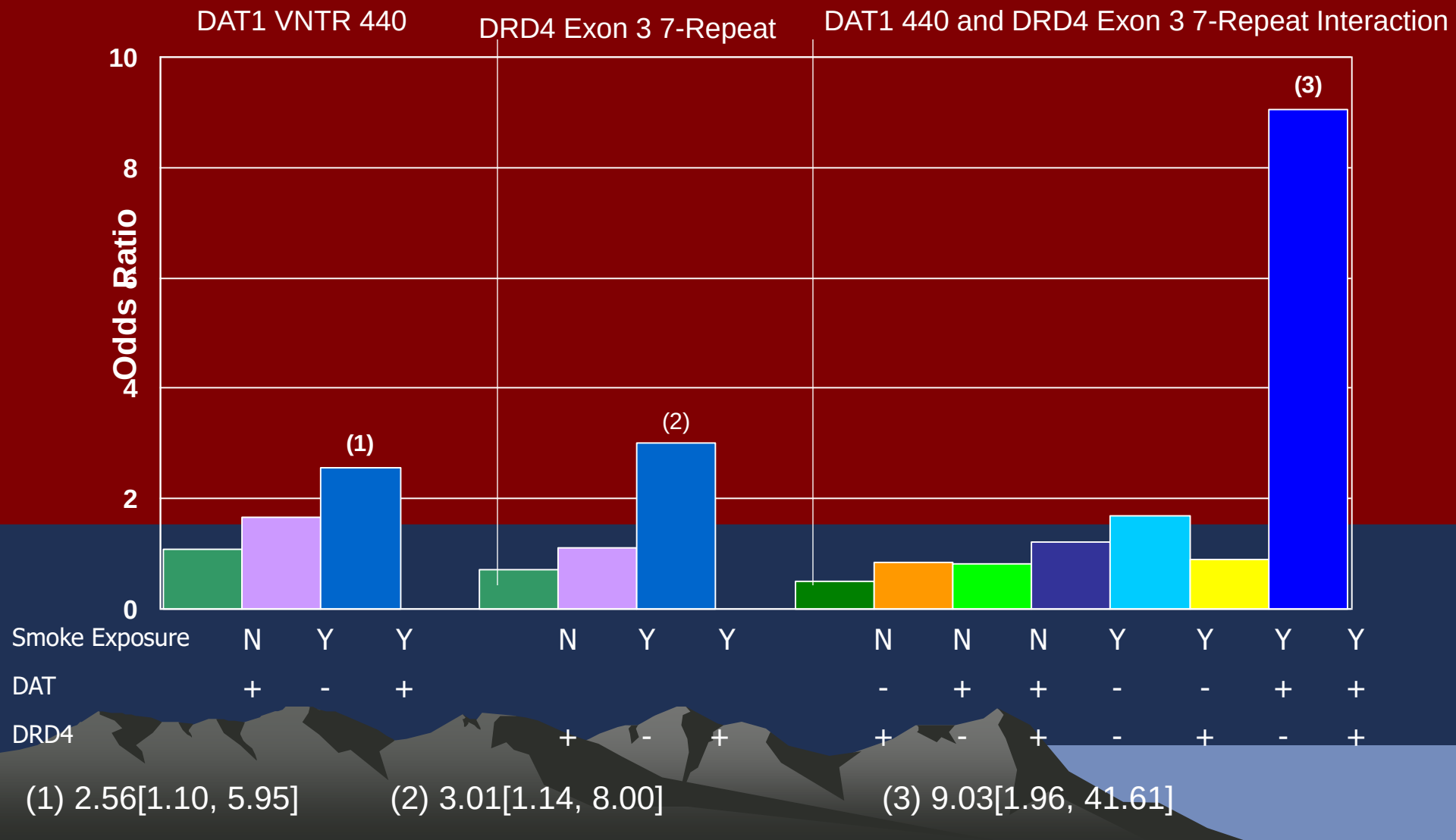
New Findings on Genetics

- Genes involved in ADHD affect not just dopamine and norepinephrine networks but pertain to brain neural cell growth and connections as well as connections of peripheral nerve cells to muscle junctions and feedback from muscles
  - May cause some overlap with Restless Leg Syndrome and possibly with Amyotrophic Lateral Sclerosis (ALS)
- New genetic mutations can arise in a child that contribute to ADHD risk that are not evident in parents (accumulated mutation model)
  - Likely accounts for some of the disparity in identical twins as well as newly genetic cases arising in previously unaffected families
- Gene x Environment interactions
- Some genes may predict drug response. And whether or not the gene has a methylated tag attached to it may further affect drug responding (e.g., DAT1 gene)

Genetic Risk May Interact with Risk From Environmental Toxins

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



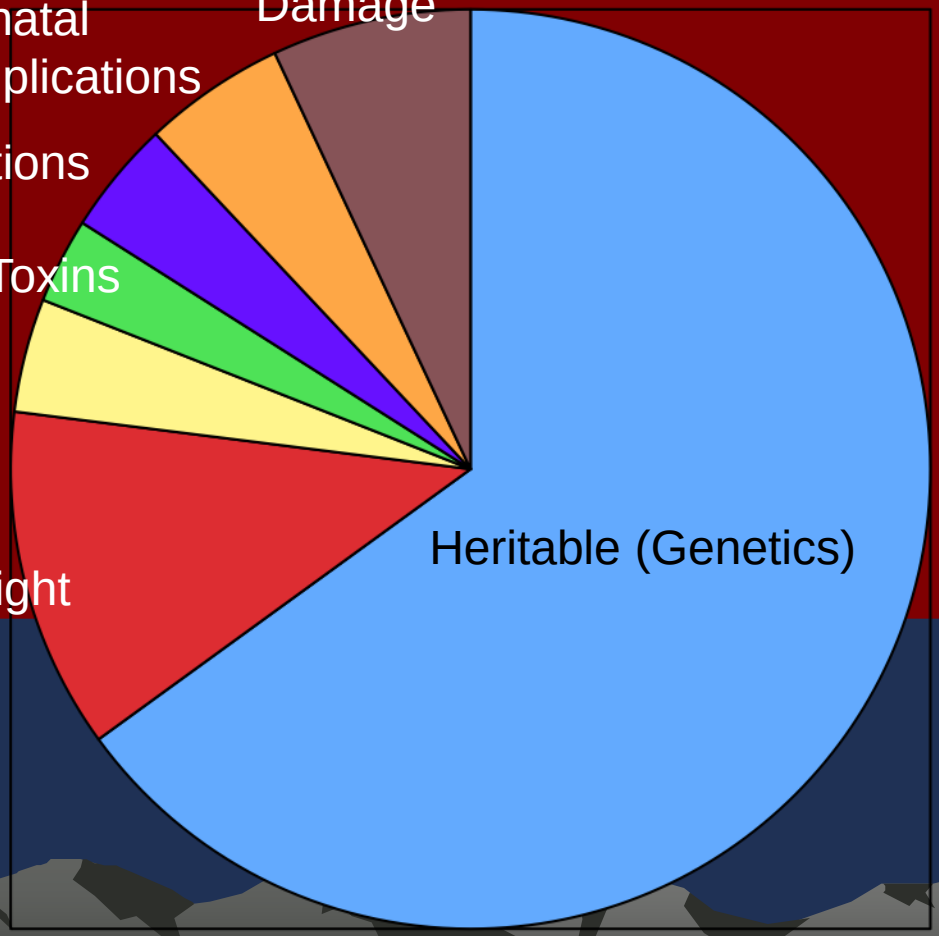
(1) 2.56[1.10, 5.95] (2) 3.01[1.14, 8.00] (3) 9.03[1.96, 41.61]

Expected Advances from Genetics

- Genetic testing to aid diagnosis
- Genetic subtyping of ADHD cases
- Better understanding and prediction of comorbidity
  - Genes already linked to risk for later smoking
- Evaluating gene x gene & gene x environment interactions:
  - In causing risk for the disorder
  - In predicting future risks for impairments and comorbidities
  - In predicting drug responses and side effects
    - DAT1 may predict response to MPH and ATX
  - In predicting response to psychosocial treatments
    - DRD4-7 allele related to response to parent behavior management training
- Developing new drugs targeted to genotypes
- Developing new psychosocial treatments for targeting specific phenotypes

Etiologies of ADHD

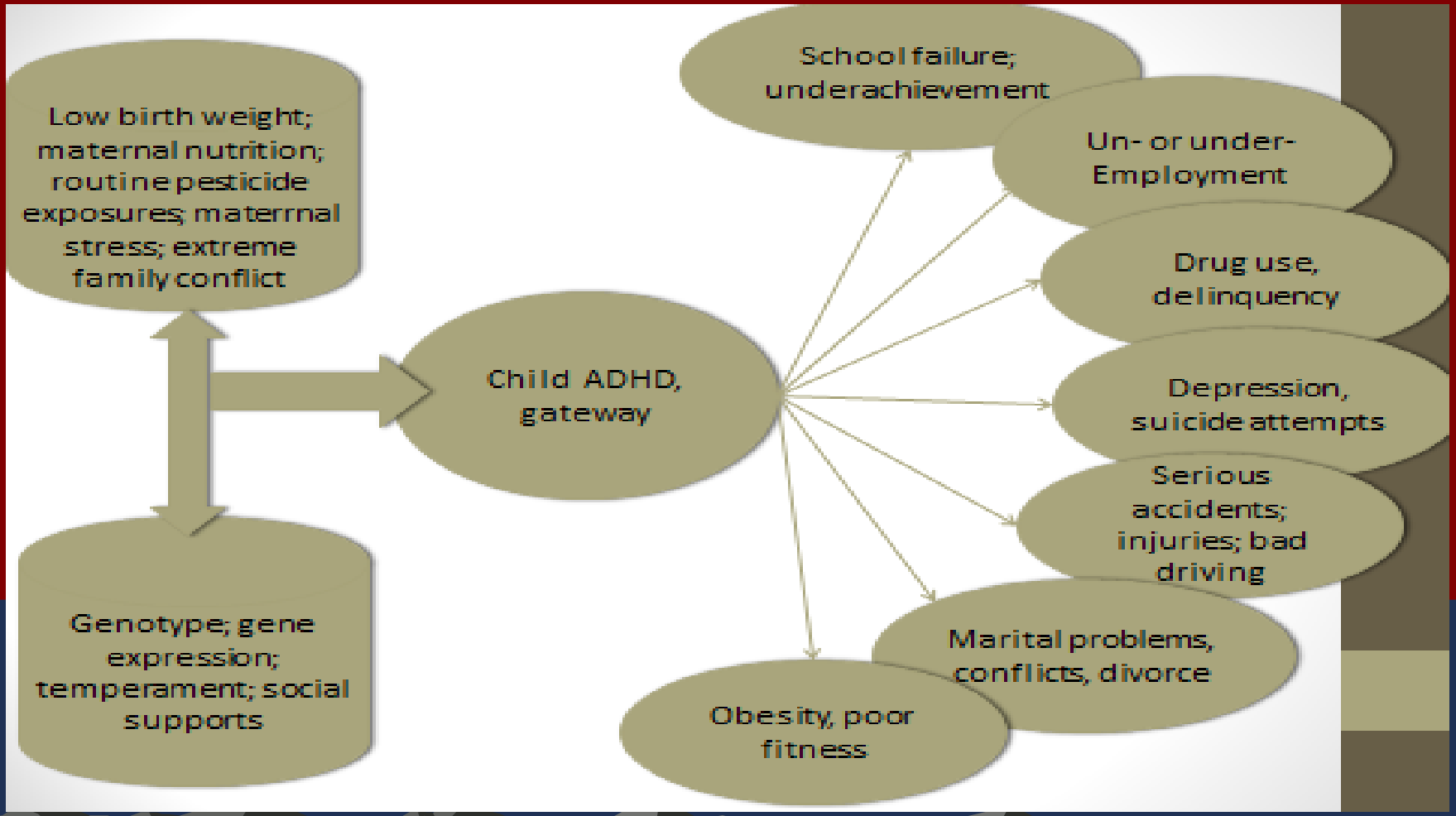
Adapted and updated from Joel Nigg (2006), *What Causes ADHD?* New York: Guilford Publications.



ADHD risk genes can interact with these other causes to further increase risk for the disorder

Some ADHD is due to new genetic mutations occurring in the child but not the parent

Interaction of Causes of ADHD and Association with Outcomes



Nigg, J. T. & Barkley, R. A. (2013). ADHD. In Mash, E. J. & Barkley, R. A. *Child Psychopathology (3rd edition). New York: Guilford Press.*

Conclusions

- ADHD is a neurobiological disorder representing a single spectrum of symptoms in the human population
- Excessive symptoms result in impairment in major life activities resulting in a disorder of adaptive functioning
- Variation in the symptoms among people is largely the result of variation in genes that develop and operate the human brain
- But some variation in ADHD symptoms is the result of unique events, such as environmental biohazards

More Conclusions

- No variation of the symptoms arises from within family factors
- Some cases are due to gene x environment interactions
- The role of the psychosocial environment is not in causing ADHD but in determining:
  - risk for comorbidity,
  - degree of impairments in major life domains,
  - and access to professional resources for treatment