Advances in Diagnosis, Etiology, Theory, and Management of ADHD

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Objectives

Review the major advances in four areas of knowledge of ADHD:

- Understanding the symptoms
- Diagnostic criteria
- Etiologies
- Management

Advances in Understanding the Symptoms of ADHD

The two dimensions of neuropsychological deficits are in:

1. **Hyperactivity-Impulsivity** (Executive Inhibition)

- Deficient motor inhibition (restless, hyperactive)
- Impaired verbal inhibition (excessing talking, interrupting)
- Impulsive cognition (difficulty suppressing task irrelevant thoughts, rapid decision making;
- Impulsive motivation (prefer immediate gratification, greater discounting of delayed consequences)
- Emotion dysregulation (impulsive affect; poor "top down" emotional self-regulation)
- Restlessness decreases with age, becoming more internal, subjective by adulthood

More on ADHD

Inattention: But 6 types of attention exist – not all are impaired in ADHD. What is?

<u>Executive Attention (& Functioning)</u>

- Poor persistence toward goals, tasks, and the future (can't sustain attention/action over time)
- Distractible (impaired resistance to responding to goal-irrelevant external and internal events)
- Deficient task re-engagement following disruptions (skips across uncompleted tasks)
- Impaired working memory (forgetful in daily activities, cannot remember what is to be done)
- Diminished self-monitoring

Changes in DSM5

- Symptom list remains the same (18) but with parenthetical clarifications for teens and adults
- Symptom threshold for children and teens remains the same (#6) but is reduced for adults (#5)
- Age of onset adjusted to age 12 years
- Requires corroboration of self-reports
- Replaces subtypes with “presentations”
- Permits overlap with autistic spectrum

Other Issues DSM5 Failed to Address

- Inattention list is mislabeled
  - Include executive functioning (working memory)
- Symptoms of impulsiveness or poor inhibition are chiefly verbal
  - needed to add poor impulse control generally and motor, cognitive, and affective/motivation specifically
- Symptoms of poor executive emotion self-regulation are important central features but receive no mention
- Symptoms and wording are not appropriate past childhood – parenthetical clarifications may help but not enough
  - Need more items for adult stage of disorder

More Issues

- Symptom threshold (6) not appropriate past childhood – adjustment to 5 for adults helpful but not enough
  - May have to adjust thresholds down to 4 of 9 if > age 17 and higher than 6 if < 4 yrs
- Threshold for children based mainly on boys (3:1)
  - May need to be lower for girls; use rating scales
- Duration may be too short for preschoolers:
  - try 1 year or more
- 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

Advances in Etiology

- ADHD symptoms represent a single dimension that varies in severity in human populations
- Disorder arises from multiple causes
- All currently recognized causes fall in the realm of biology (neurology, genetics)
- Causes may compound each other
- Final common pathway for disorder appears to be the fronto-striatal-cerebellar circuits in the brain
- Variation across cases in which circuits are disrupted likely produces symptom variation
- Social causes lack evidence

Acquired Cases: Prenatal

- Maternal smoking in pregnancy (odds 2.5)
- Maternal alcohol drinking in pregnancy (same)
- Prematurity, especially if brain bleeding (45%+ have ADHD)
- Maternal urinary tract infections and pre-clampsia
- Total increased pregnancy & delivery complications
- Maternal pre-pregnancy obesity (?)
- Maternal high phenylalanine levels in blood (?)
- High maternal anxiety in second trimester (?)
- Perinatal Pitocin exposure (increased risk 2x)(?)
- Maternal methylmercury ingestion (fish in diet)(?)
- Cocaine/crack exposure not a reliable risk factor after controlling for the above factors

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

- Head trauma, brain hypoxia, tumors, or infection
- Febrile seizures
- Lead poisoning in preschool years (0-3 yrs.)
- 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
- Survival from acute lymphoblastic leukemia (ALL)
  - Treatments for ALL cause brain damage resulting in most survivors having ADHD (SCT) symptoms*
- * Reeves, C. et al. (2007). *Journal of Pediatric Psychology, 32*, 1040-1049.

Neuro-Imaging Findings

Smaller (3-10%), Less Active (10-25%+), Less Developed (2-3 yr. delay) in these brain regions:

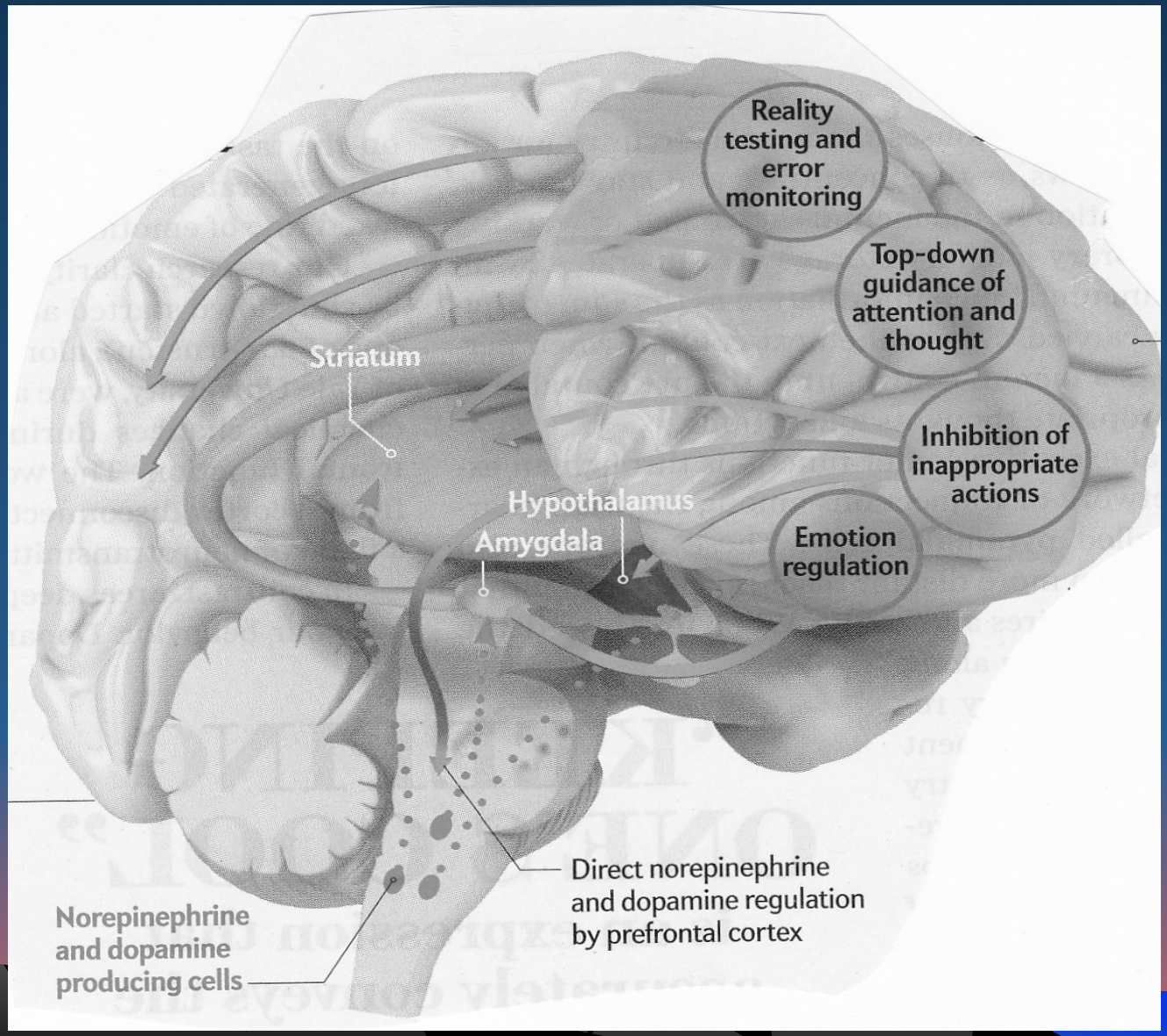
- Orbital-Prefrontal Cortex (primarily right side)[1,2,3]
- Basal Ganglia (striatum & globus pallidus) [1,2,3]
- Cerebellum (central vermis area, right side) [1,2, 3]
- Anterior cingulate cortex[1,2,3]
- Corpus callosum (primarily anterior splenium) [1,2,3,4]
- Thalamus (??)[5]

1. Paloyelis, Y. et al. (2007). *Expert Reviews in Neurotherapeutics, 7*, 1337-1356.
2. Valera, E. M., et al. (2007). *Biological Psychiatry, 61, 1361-1369.*
3. Bush, G. et al. (2005). *Biological Psychiatry, 57*, 1273-1296.
4. Hutchinson, A. D., et al. (2008). *Neuropsychology, 22*, 341-349.
5. Ivanov, I. et al. (2010). *American Journal of Psychiatry, 167(4)*, 397-408.
6. Shaw, P. et al. (2007). *Proceedings of the National Academy of Sciences, 104*, 19649-19654.

More Neuro-Imaging Results

- Lower IQ linked to reduced brain volume whereas higher IQ linked to reduced grey matter.
- Size of this network is correlated with degree of ADHD symptoms, particularly inhibition[1,2,3]
- No substantial gender differences
- Structural differences in volume persist to late adolescence then some normalization
- Functional differences may persist into adulthood in most cases[6]
- Results are not due to taking stimulant medication

Executive Networks



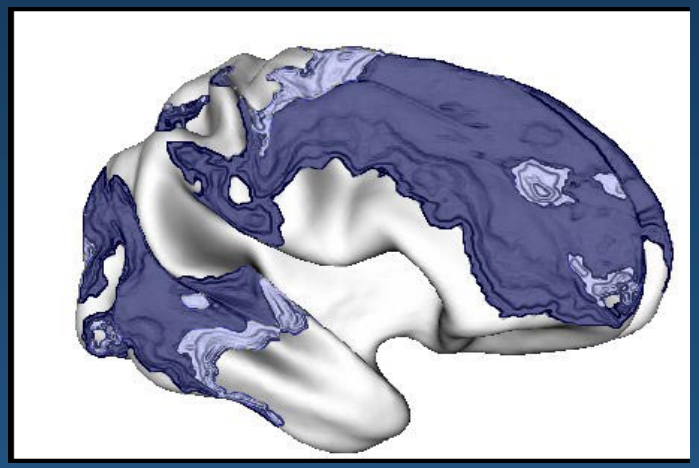
Three Neural Networks for ADHD[1,2,3]

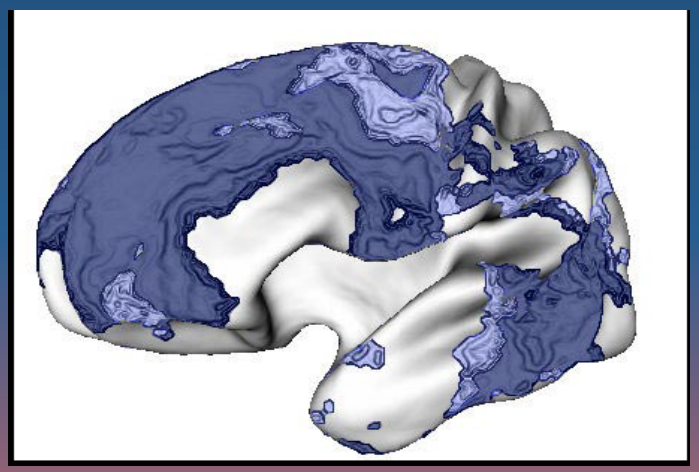
- The "WHAT" network (frontal-striatal circuit): Associated with deficits in response suppression, freedom from distraction, working memory, organization, and planning, also known as the "cool" EF network
- The "WHEN" network (frontal-cerebellar circuit): Associated with motor coordination deficits,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

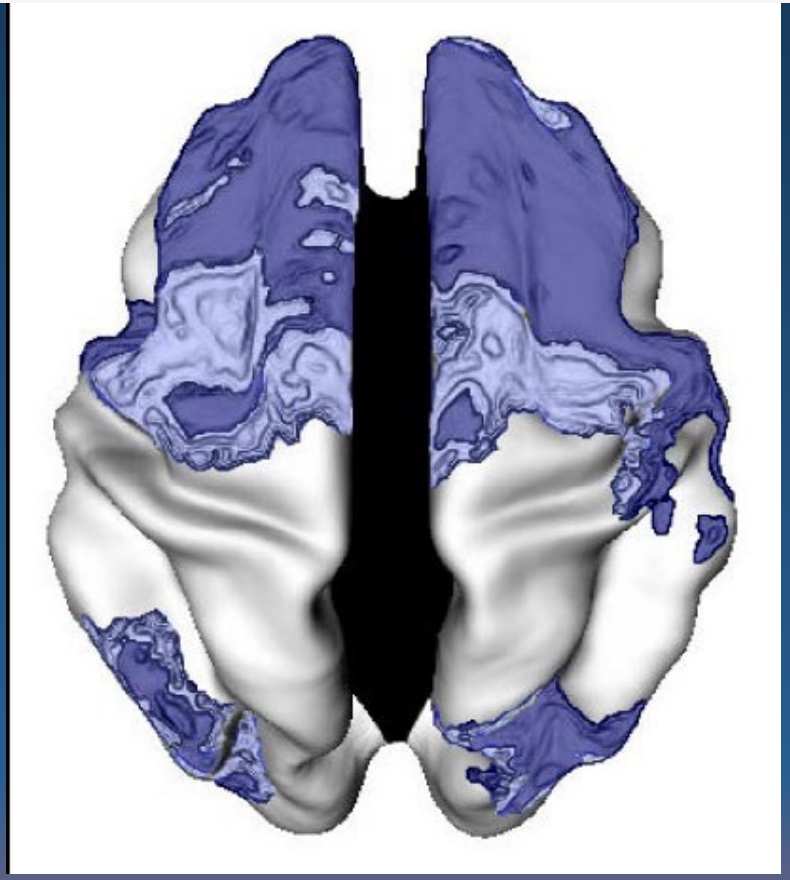
1. Nigg, J. T., & Casey, B. (2005). An integrative theory of attention-deficit/hyperactivity disorder based on the cognitive and affective neurosciences. *Development and Psychology, 17*, 785-806.
2. Castellanos, X., Sonuga-Barke, E., Milham, M., & Tannock, R. (2006). Characterizing cognition in ADHD: Beyond executive dysfunction. *Trends in Cognitive Science, 10,* 117-123.
3. 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.

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.







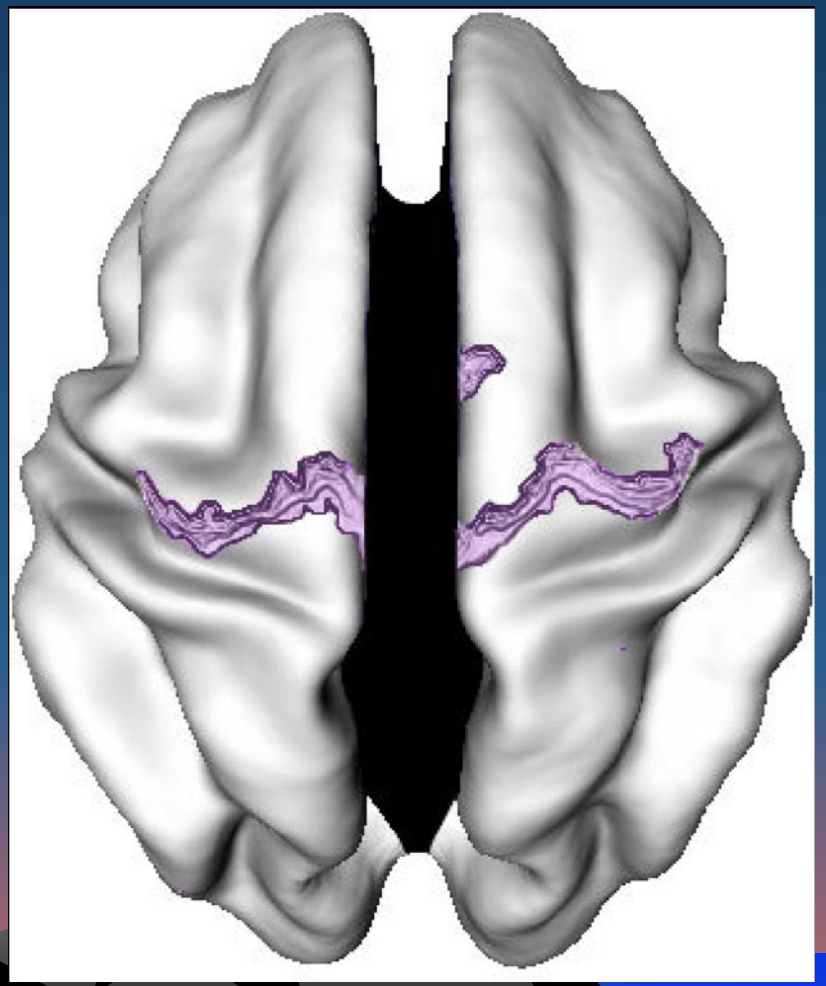
Greater than 2 years' delay
0 to 2 years delay

Ns: ADHD=223; Controls = 223

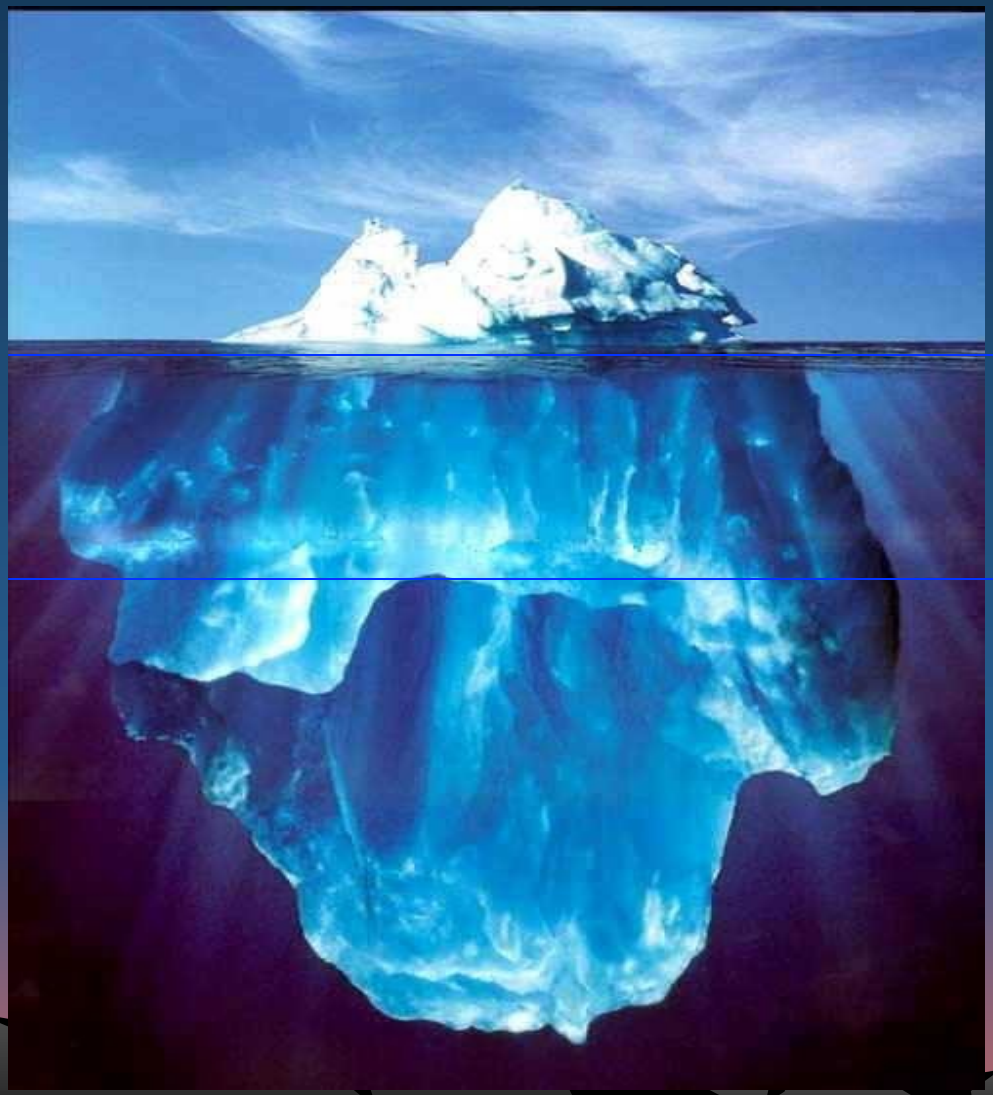
Early cortical maturation in ADHD children

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.



Genetic "Iceberg"



Recognized ADHD

Spectrum of ADHD

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

Heredity – Family Studies[1]

Evidence of Family Aggregation of the Disorder:

- 25-35% of siblings
- 78-92% of identical twins
- 15-20% of mothers
- 25-30% of fathers
- If parent is ADHD, 20-54% of offspring (odds 8+)

- Parent of origin effects: [2](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

1. Mick, E. & Faraone, S. V. (2008). *Child and Adolescent Psychiatric Clinics of North America, 17* , 261-284.
2. Goos et al., *Psychiatry Research, 149, Jan. 2007.*

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.

Molecular Genetics[1,2,3]

- **Genome wide scans -** suggest that 20-42 chomosome sites that may contain minor genes that are possible candidates[2]
- **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
- **MAO-A:** produces an mitochondrial enzyme that regulates presynaptic dopamine signals and other neurotransmitter systems
- **LPHN3 (latrophilin) gene:** linked to G-protein-coupled receptors in amygdala, caudate, cerebellum, and cortex. Controls GABA release presynaptically; GABA is an inhibitory transmitter[4,5]
- **CHRNA7**: duplication in this gene at chromosome location 15q13.3 is involved the alpha-7 nicotinic acetylcoholine receptor modulation that mediates calcium ion channel signaling that further affects dopamine release.[7]

1. Mick, E. & Faraone, S. V. (2008). *Child and Adolescent Psychiatric Clinics of North America, 17,* 261-284.
2. Franke, B. et al. (2009). *Human Genetics, published online April 2009.*
3. *Banaschewski, T. et al. (2010). European Child and Adolescent Psychiatry, 19*, 237-257.
4. Ribases et al. (2010). *Genes, brain, and behavior, online first, doi:10.1111/j.1601-183X.2010.00649.x*
5. Arcos-Burgos, M. (2010). *Attention deficit hyperactivity disorder, 2,* 139-147.
6. Froehlich, T. (2011). *Journal of the American Academy of Child and Adolescent Psychiatry, 50*, 1129-1139
7. Williams, N. et al. (2012). *American Journal of Psychiatry, 169,* 195-204.

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 ODD, CD, Autistic Spectrum and Reading Disorders

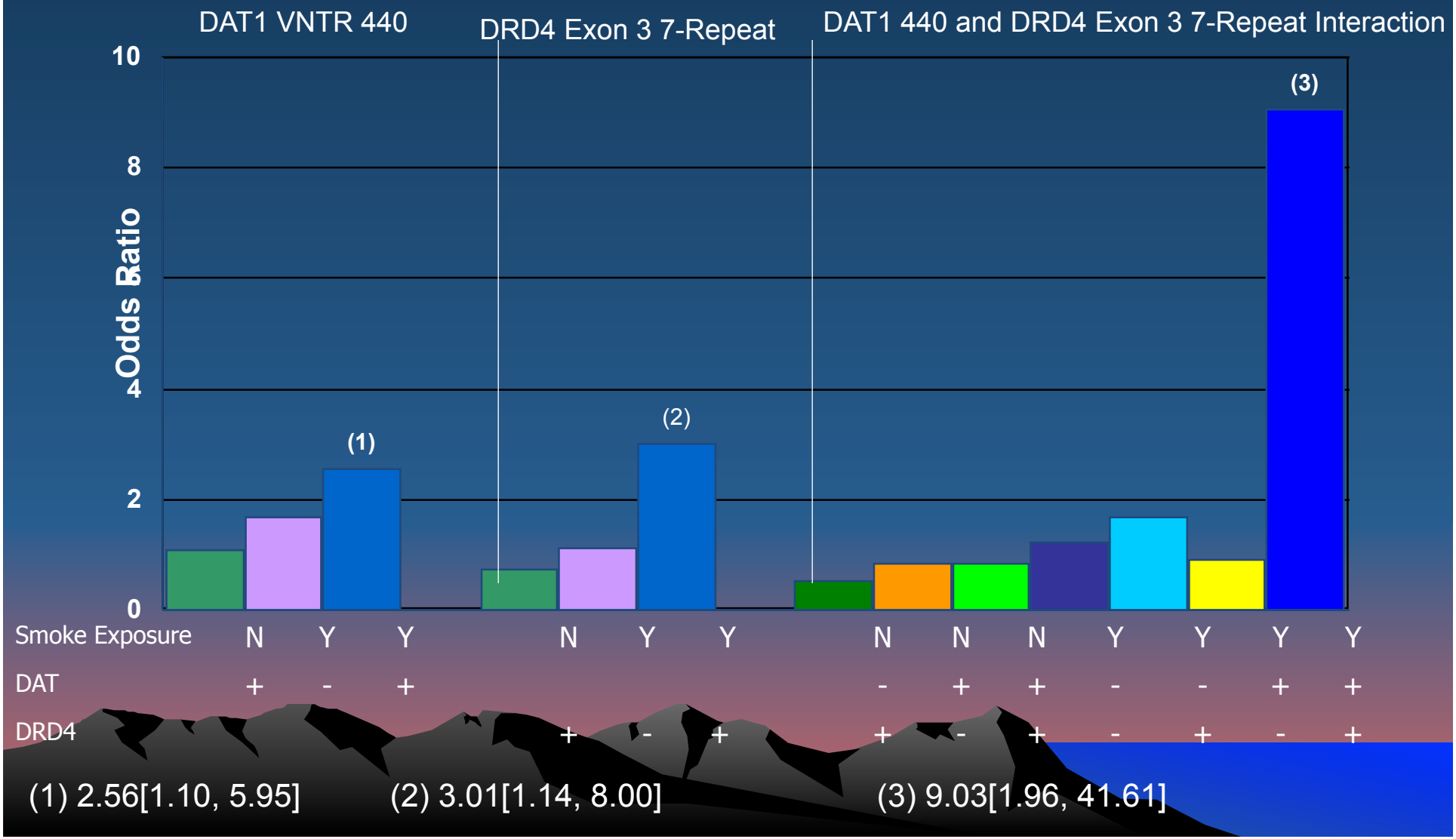
New Findings on Genetics

- Genes involved in ADHD affect not just dopamine and norepinephrine networks but 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

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



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

Advances in Medications

- New stimulant delivery systems
  - Pills, pump, pellets, patch and pro-drug
  - Better understanding of preschooler stimulant response
- Atomoxetine (2003) – highly selective NE reuptake inhibitor; first FDA approved non-stimulant for ADHD in children, teens, and adults
- New even more selective NE reuptake inhibitor due out in next few years
- Guanfacine XR (2009) An alpha-2 agonist (formerly an anti-hypertensive)
- Efforts to develop nicotinic receptor molecules – not yet successful

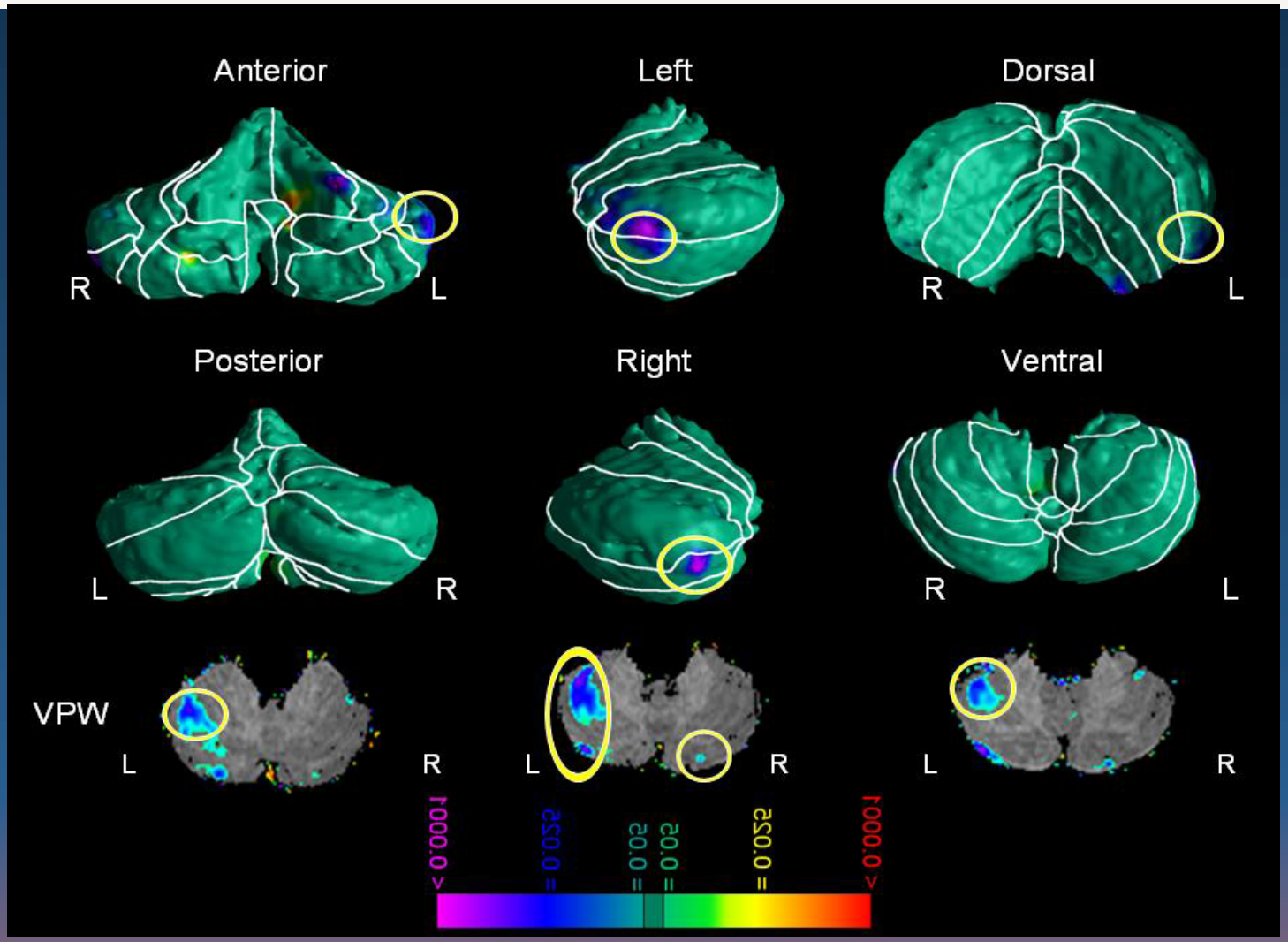
7 Reasons for Early Intervention

- Reduction of symptom severity and associated executive/self-regulatory deficits
- Reduce family stress, parent-child conflict,
- Reduce risks for of impairments in major life activities (home, school, peers, community)
- Reduce risks for health-related problems
- Reduce risks for comorbid disorders, both externalizing (oppositional, conduct) and internalizing (anxiety, depression
- Reduce economic burden to family & society
- Neuro-protection: accelerated brain growth?

Neuro-Protection of Cerebellar Morphology

- Ivanov, I. et al. (in press) compared cerebellar morphology in 46 children with ADHD and 59 comparisons as 8-18 years using a cross-sectional case-control design with MRI of cerebellar surface morphology
- "Results: Relative to comparison participants, youths with ADHD exhibited smaller regional volumes corresponding to the lateral surface of the left anterior and the right posterior cerebellar hemispheres. Stimulant medication was associated with larger regional volumes over the left cerebellar surface, whereas more severe ADHD symptoms were associated with smaller regional volumes in the vermis."
- "Discussion: . . . Duration of treatment correlated positively with volumes of specific cerebellar subregions, supporting a model whereby compensatory morphological changes support the effects of stimulant treatment."
- Ivanov, I. et al. (2013, in press) Cerebellar morphology and the effects of stimulant medications in youths with attention deficit-hyperactivity disorder. *Neuropsychopharmcology.* Epub ahead of print. doi: 10.1038/npp.2013.257.

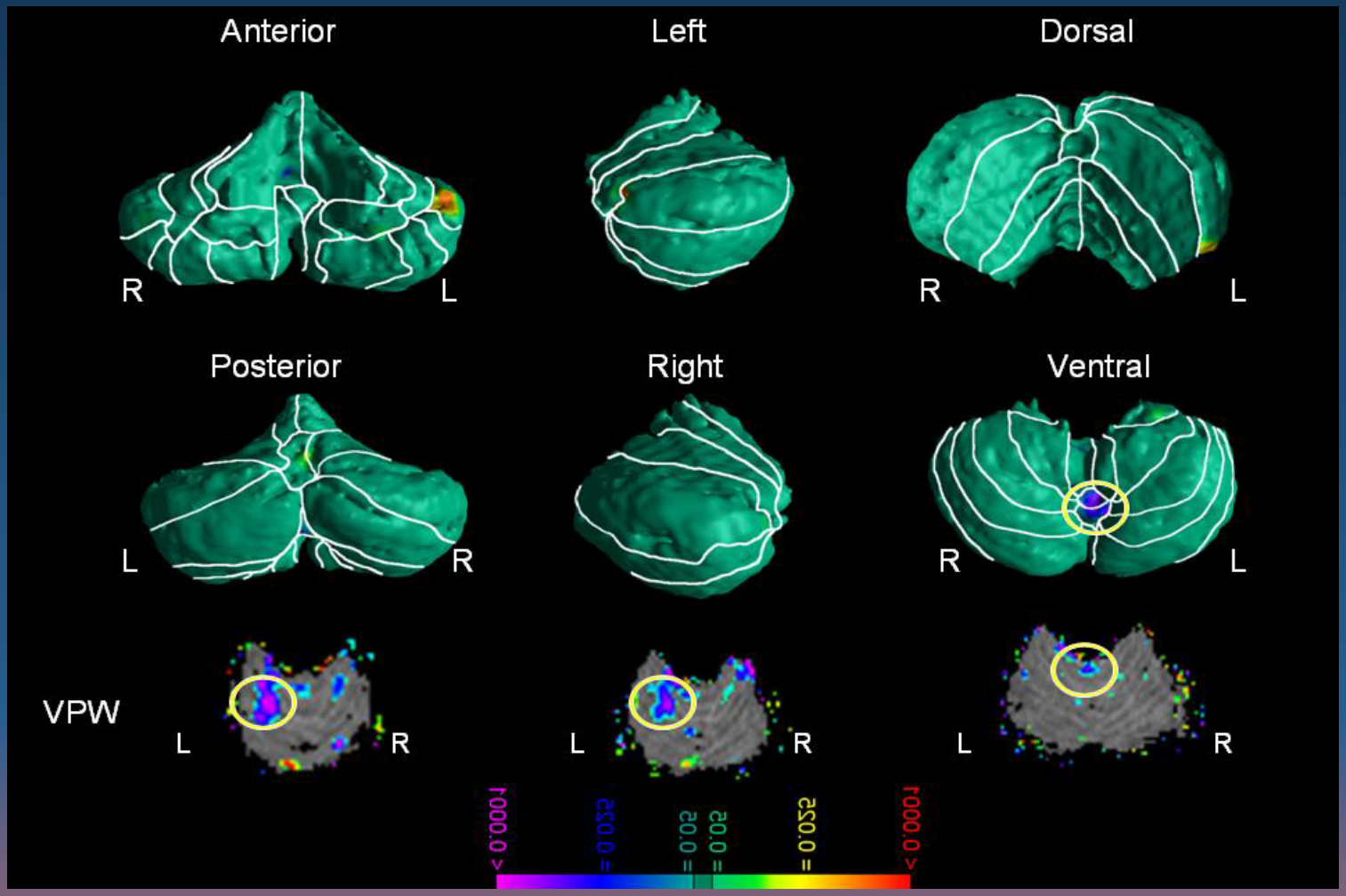
Cerebellar Abnormalities in ADHD Diagnosed Children



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.

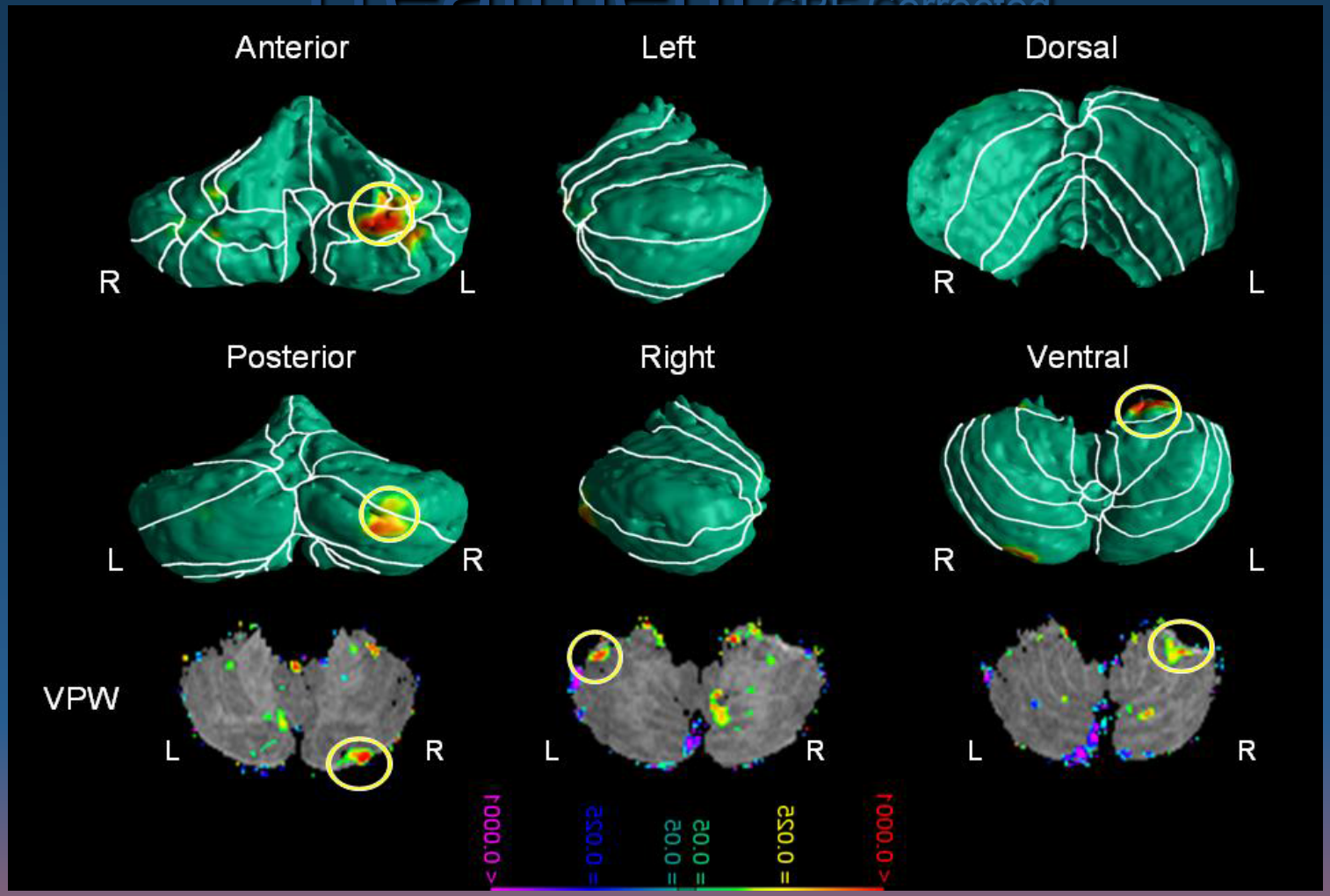
Correlations with symptom severity

GRF Corrected



The figure shows statistical maps in different cerebellum views; the color bar indicates the color coding for p values correlated with the severity scores of ADHD symptoms in all subjects diagnosed with ADHD, 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 the vermis VIII a and VIII b were accompanied by higher ADHD severity scores. L= left; R= right; VPW = Volume preserve warping.

Impact of Stimulant Treatment



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 stimulant treatment in subjects with ADHD diagnosis (n=31), 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 larger regional volumes in cerebellum lobule X on the left and crus II on the right in subjects with ADHD who were receiving stimulant treatment at the time of the scan compared to untreated subjects. L= left; R= right; VPW = Volume preserve warping.

Neuroprotection of Basal Ganglia Morphology

- Sobel et al. (2010) compared 47 ADHD cases against 57 healthy controls ages 7-18 years using corss-sectional case-control methods and anatomical magnetic resonance imaging of conventional volumes and surface morphology.
- “Conclusions: These findings potentially represent evidence of anatomical dysregulation in the circuitry of the basal ganglia in children with ADHD and suggest that stimulants may normalize morphological features of the basal ganglia in children with the disorder. “ (p. 977)

Neuroprotection: medication effects on basal ganglia Sobel et al. (2010).

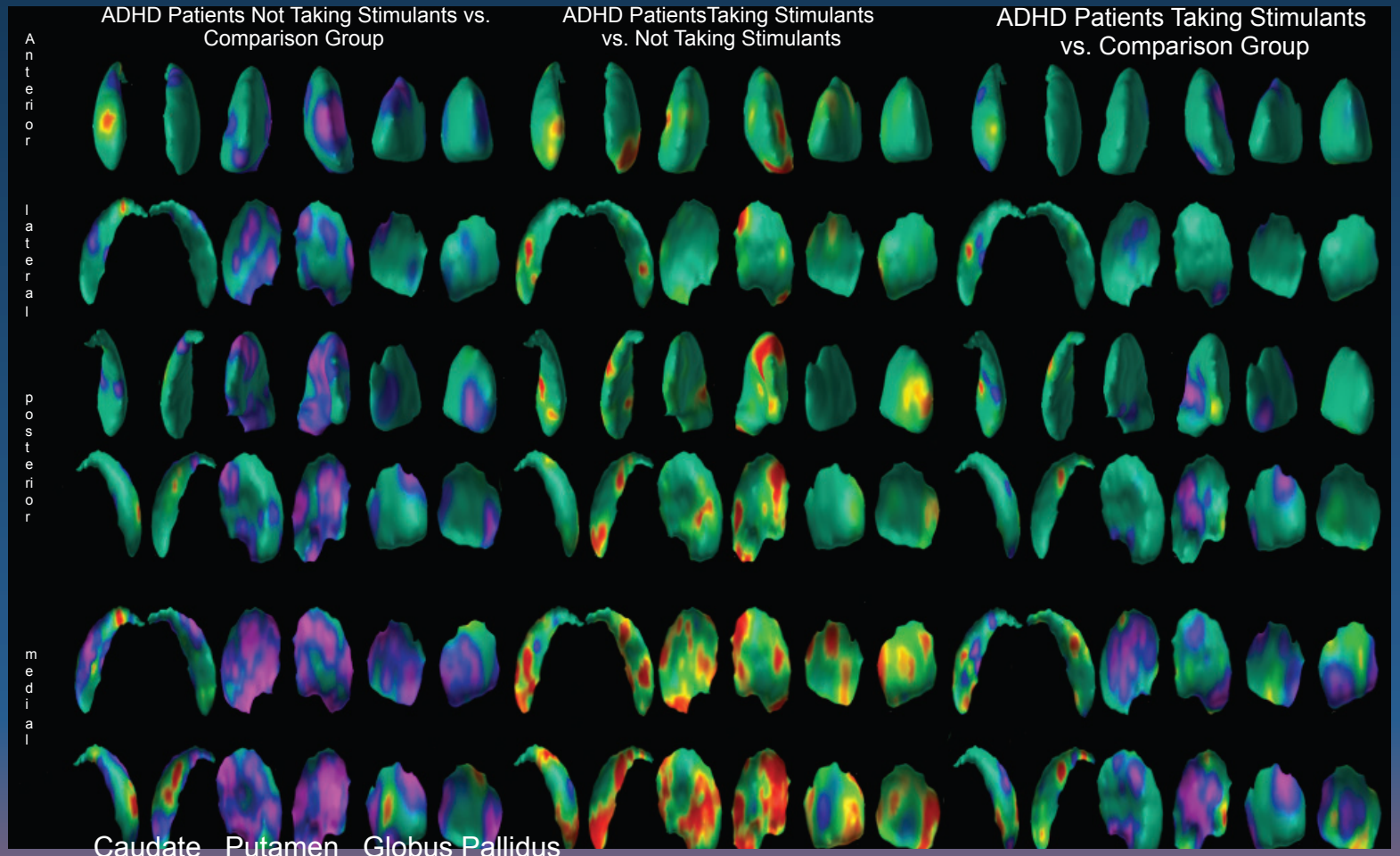


FIGURE 2. Main Effects of Stimulant Use on Surface Morphologic Features of Basal Ganglia Nuclei in Youth With ADHD Relative to Healthy Comparison Subjects. Gaussian random field-corrected images are displayed in anterior (A), posterior (P), lateral (L), and medial (M) views, whereas uncorrected images are displayed in lateral and medial views only. The color bar indicates the p values associated with either the diagnosis term (left, right) or the stimulant term (center). The outward deformations in the basal ganglia of youth treated with stimulants compared with those untreated approximately align with the inward deformations detected in the overall main effects of diagnosis (see Figure 1). The statistical attenuation of the main effects of diagnosis, indicated by a less significant inward deformation on the surface of the basal ganglia in youth taking stimulants versus those not taking stimulants relative to comparison subjects suggests that a major component of the overall main effects of diagnosis (see Figure 1) was attenuated by the effects of stimulant medication on the morphological features of the basal ganglia.

Neuro-Protection Effect

- Review of 11 structural studies - “Here, we show evidence that a higher number of treated patients in studies are associated with smaller structural change in the basal ganglia, ACC, or amygdala region. Thus, treatment might have a positive effect on long-term changes in the brain, but follow-up studies are required to confirm this hypothesis.” (p. 123) Frodl, F. T. & Skokauskas (2012). Meta-analysis of structural MRI studies in children and adults with attention deficit hyperactivity disorder indicates treatment effects. *Acta Psychiatrica Scandinavica, 125,* 114-126.
- Review of 29 Studies - “Conclusions: Despite the inherent limitations and heterogeneity of the extant MRI literature, our review suggests that therapeutic oral doses of stimulants decrease alterations in brain structure and function in subjects with ADHD relative to unmedicated subjects and controls. These medication-associated brain effects parallel, and may underlie, the well-established clinical benefits” (p. 902) Spencer, T. J. et al. (2013). Effect of psychostimulants on brain structure and function in ADHD: A qualitative review of magnetic resonance imaging-based neuroimaging studies. *Journal of Clinical Psychiatry, 74*, 902-917.
- Given that atomoxetine and stimulants share 70-80% of brain regions in the effects they produce (Shulz et al., 2012), it is reasonable to hypothesize that ATX may have similar effects on brain development. Shulz, K. P. et al. (2012). Common and unique therapeutic mechanisms of stimulant and nonstimulant treatments for attention deficit hyperactivity disorder. *Archives of Psychiatry, 69(9),* 952-961.

Advances in Psychosocial Treatment

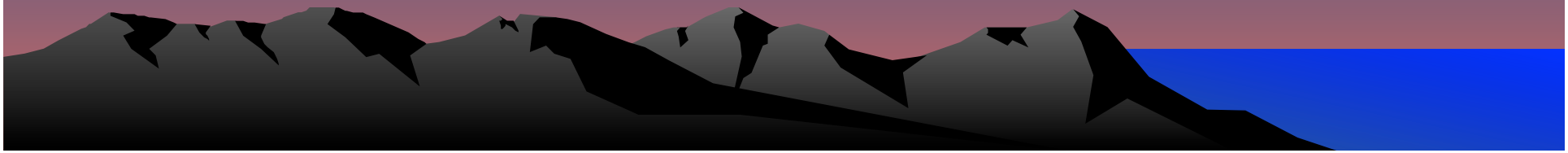
- Parent education about ADHD changes families
- Learning the value and limitations of parent training
  - Changes defiance and parent-child conflict, not ADHD
  - Works best in younger children
    - (<11 yrs., 65-75% respond; falls to 25-35% for teens)
- Effectiveness of classroom behavior management is now solidly established but is time, setting, and person limited
- The value of physical exercise (coping not curing)
- Effectiveness of cognitive behavioral training of adults with ADHD
  - Safren (Harvard Medical School), Ramsay & Rostain (Univ. of Pennsylvania), Solanto (Mt. Sinai Medical Center, NYC)

Experimental Psychosocial Treatments

- Omega 3 Fatty Acids (Fish Oil) – studies show mixed results (effects at home on parent ratings, no effect at school on teacher ratings); Cochrane 2012 meta-analysis finds no effects. Effects found are small in magnitude and mainly on inattention
- Time Management and Organization Training for School (Abikoff, NYU Medical School)
- Friendship Coaching – training parents as social skills therapists for their ADHD children
- Challenging Horizons Program
  - after school supplemental training for teens focusing on social, recreational, and academic remediation (Molina, B. et al. (2008). *Journal of Attention Disorders, 12, 207-217.)*

Unproven/Disproven Therapies

- Elimination Diets – removal of sugar, additives, etc. (Weak evidence for food colorings – effect sizes of .23)
- Megavitamins, Anti-oxidants, Minerals (No compelling proof or have been disproved)
- Sensory Integration Training (disproved)
- Chiropractic Skull Manipulation (no proof)
- Play Therapy, Psycho-therapy (disproved)
- Self-Control (Cognitive) Therapies for Children (disproved)
- Social Skills Therapies for Children (in clinic)
  - Better for Inattentive (SCT) Type and Anxious Cases
- Biofeedback (EEG)*
  - Numerous positive clinical studies but all suffer serious flaws in their methods; 4 randomized placebo-controlled trials find no benefit
- Training of executive functions (espec. working memory)
  - CogMed, Nintendo with Brain Age game, Lumosity.com, mybraintrainer.com, e-mindfitness.com, happyneuron.com, positscience.com

Conclusions

- ADHD is a disorder of self-regulation and executive functioning
- A new attention disorder (SCT/CDD) has been identified that is distinct from ADHD
  - Probably requires a distinct set of treatments than those for ADHD
- Significant advances in etiology have occurred showing that ADHD largely results from neuro-genetic factors
  - But these can interact with environmental factors to increase risk
- Several advances in medication delivery systems and in new medication options occurred in the past decade
  - The most remarkable advance may be in discovering a neuroprotective effect of long-term medication use that facilitates brain development and functioning
- Some advances have been made in modifying previous psychosocial treatments and in developing new ones
- ADHD is among the most treatable psychiatric disorders