Brain Research on ADHD

Set aside specific known causes (genetic, perinatal, injury, infection)
Focus on the large "cause unknown" group
Evidence for "delay" in maturation of brain

Delay: Good News, Bad News

Yes, probably "catch up" (outgrown, mature)
BUT many, many years (audience try to guess)
AND environment, or experience, "for better or for worse" sculpts the brain











Neurology—Revealed by aMRI and fMRI—Underlying ADHD

Frontal (and all subdivision!)
Striatal (emphasis on caudate)
Cerebellar (most distinctive)
Underactivated caudate and MPH response of caudate most consistent findings

"Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation."

This is the title of the publication by Shaw P, Eckstrand K, Sharp W, Blumenthal J, Lerch JP, Greenstein D, Clasen L, Evans A, Giedd J, Rapoport JL, 2007 PNAS, 104:19649-19654
Cortical growth-to-max trajectories measured on aMRIs ADHD Involves Dysfunction in Frontal-Striatal-Cerebellar Brain Systems

Neural Structures Related to EF

 Cerebellum has reciprocal connections with the frontal brain systems, including prefrontal regions



http://thalamus.wustl.edu/course/cerebell.html

Motor Function is Often Deficient in ADHD (if you look) See Mostofsky Shapes of caudate and anteroventral putamen are compressed such that volume is diminished in 8-12 year old boys with ADHD

Mostofsky/Denckla group

fMRI shows normal sensitivity to rewards in children with ADHD, although conduct disorder (not ADHD) is associated with diminished activation of the reward circuitry of the orbitofrontal cortex

Rubia et al

Between 12 and 16 years, children with ADHD Rx with stimulants show cortical thickness (for age) closer to typically developing peers than did those not treated

Shaw et al

Human Suffering Rationale

ADHD outcomes
 remain poor despite
 short term benefits
 of stimulant
 medications



MTA study at year 8 Molina et al 2009

Barriers to progress

- ADHD rating scales are subjective, ordinal not quantitative, and capture a heterogeneous group of children
 - Quantitative neurobiological measures are difficult to anchor in DSM-IV's complex, ambiguously described behavior

"Fails to remain seated when remaining seated is expected..."

Relevant Clinical Insight

Children with ADHD often have clumsy fine motor skills

ADHD highly co-morbid with DCD

Impulsivity

Hyperactivity

"The essential impairment in ADHD is a deficit involving *response inhibition*." (Barkley, 1997)

Inattention

ADHD: Dysfunction Across Frontal Circuits





Cognitive/Socioemotional Disinhibition



Motor Disinhibition

The Brain Matures Later in ADHD



Shaw et al. (2008). PNAS

Scientific Opportunity

Motor examination offers ease and precision not achievable in examination of complex behavior.

- Movements can be more precisely defined and reproducibly and quantitatively evaluated than behavioral measures
- The anatomic and physiologic basis of motor control is well delineated (better than that of more complex behavior).
- Motor signs can serve as markers for deficits in parallel brain systems important for control of higher-order behaviors.
- EXAMINATION OF BASIC MOTOR CONTROL MAY BE A WINDOW INTO ADHD NEUROBIOLOGY!

Motor Overflow

- Unintentional motor movements that mimic intentional movements being executed:
 - In more distal body parts (proximal and feet-to-hand overflow)
 - On the opposite side of the body (mirror overflow)
- Present in young children; disappear by adolescence



Excessive Motor Overflow in ADHD

- ADHD is associated not only with impaired "conscious" selection of motor responses, but also with impairments in "unconscious" selection of motor responses.
- Facile motor execution requires the selection of individualized movements (activation of those specific muscle groups necessary to accomplish a task and inhibition of other muscle groups that contribute to unnecessary "overflow" movements).

Goniometer Setup



-goniometers attached with tape and Velcro strap

-goniometer angle measurement of the metacarpophalangeal (MCP) joint during finger tapping

Simultaneous goniometer and video recordings



AAAAAAAA

Left Ring

Left Index

Right Index

Right Ring

Conclusion

Mirror overflow is increased in ADHD (particularly in boys during left (nondominant) hand execution

MacNeil et al, Neurology 2011

Conclusions: Mirror Overflow in ADHD

- Mirror overflow is increased in children with ADHD
 - For children ages 8-12 years, significant differences seen during left (non-dominant) finger tapping, but not right (dominant) tapping
 - Is this an age-related effect? (Would dominant differences be observed in younger children?)
- Mirror overflow is more prominent in boys with ADHD
 - Is this an age-related effect? (Would dominant differences in girls be observed at younger ages?)





Is motor cortex SICI different in ADHD children?



Less SICI in many ADHD children

Gilbert et al, Neurology 2011

Is motor cortex SICI correlated to parent ratings of behavior in ADHD children?

Conclusion

SICI may be a relevant biomarker of ADHD in childhood

Gilbert et al, Neurology 2011

Findings of Impaired Motor Cortex Inhibition in ADHD Offers Potential for Quantitative Evaluation of Children

> Kurt Samson Neurology Today February 17, 2011

More Brain Findings Using DTI (diffusion tensor imaging)

Our KKI group and 3 others find, unexpectedly...
More straight-thru connectivity in ADHD
This "increased F.A." could mean LESS CROSSING paths

Frontiers of Brain Research on ADHD: RS-fmri

- Mapping intrinsic brain connectivity networks
- Resting states/default network/dorsal attentional network
- Visual cortex abnormal? Or its regulation by attentional processes

Project III: The Effects of ADHD (Beyond Decoding Accuracy) on Reading Fluency and Comprehension

E. Mark Mahone, Ph.D.
Martha Denckla, M.D.
Stewart Mostofsky, M.D.
Joshua Ewen, M.D.
Nathan Crone, M.D.
Howard Egeth, Ph.D.

Rapid Naming is Slower

- Children with ADHD show deficits in rapid color naming (*Wodka et al., 2008; Tannock et al., 2000*)
- Treatment with stimulants improves naming speed (*Bedard et al.*, 2002)
- Elements of naming appear separable
 - Articulation time, pause time, <u>variability</u> (*Neuhaus et al.*, 2001)



Visual-Verbal Connection ("see-it/say-it") involving arcuate and/or inferior longitudinal fasciculus

Rapid Automatized Naming (RAN)



Variability Predicts Reading Comprehension



Predictor	β	ΔR^2	р	
Age	275	.075	.100	
Group	.078	.006	.638	
Articulation Time	.071	.004	.722	
Pause Time	242	.039	.240	
Articulation ∨ariability [#]	203	.035	.266	
Pause ∀ariability	447	.136	.022	
				1

Naming variability is a stronger predictor of comprehension than pause time

Li, Cutting, Ryan, Zilioli, Denckla, & Mahone (2009). JCEN