Attention Deficit Hyperactivity Disorder throughout the lifespan.

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Objectives

• To show that ADHD can be a challenge not just for children but also for adults

• Examine the subtle changes in brain structure that are associated with ADHD

• Review the genes which confer an increased risk for ADHD

• Stress that while neuroimaging and genetics are exciting research tools, they are not ready for clinical use (yet).
Disclosures

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• I will discuss off label use of:-
  – Psychostimulants in the under 6 year old age group
ADHD

• Recent increase in childhood diagnosis
  – Young children (5-11ys)- estimated 25% (CI 18-32%) increase (Getahun et al 2013)
  – High School – estimated 70% increase over 10 years to 19% diagnosis rates in teenage boys. (CDC survey, 2012)
  – Need for objective markers

• Rapid increase in adult diagnosis
  – From 0.01% to 1.5% in 20 years.
  – Cost per year for each individual $39,500 (range S18-45k).
  – Need for prognostic tools
What do we need to know?

• Are there brain differences associated with ADHD?

• Do these persist into adulthood?

• How can we help?

• What role does the genome play?
How can we find this out?

• The brain: insights from magentic resonance images (MRIs)

• Using longitudinal data to capture development (movies rather than snap shots)
The participants

Comorbidity: ODD 37%; CD 6%; Mood 4%; Anxiety 8%; Tics 3%; high IQ
Looking at the brain in ADHD

- MRI
- Classification
- Extraction of surfaces

Volumetric data (lobes, deep structures)

Cortical thickness, surface area and complexity
Cortico-striatal loops

Motor

Cognitive control

Emotion/attention
Cross-sectional studies of the brain in ADHD.

- ADHD as a brain disorder
  - Overall reduction in brain volume (e.g., Castellanos 2002; many others)
  - Most affected
    - Prefrontal cortex
    - Basal ganglia
    - Cerebellum

Anomalies found in unaffected first degree relatives (Durston et al. 2005)
A longitudinal study of childhood ADHD and the prefrontal cortex
(Shaw et al, 2012 Biol Psychiatry)

![Graphic showing the relationship between age and right prefrontal cortical surface area in typical and ADHD subjects.](image)
A longitudinal study of childhood ADHD and the prefrontal cortex
(Shaw et al, 2012 Biol Psychiatry)
Important limitations

• This alteration of velocity (brain growth) is detected only with large groups: a subtle difference

• No role (yet) for neuroimaging in the diagnosis of ADHD.
Treatment

• Review two pivotal studies
  – Multimodal Treatment of ADHD
  – Preschool ADHD Treatment Study

• Psychostimulants and the developing brain

• Non-pharmacological approaches
Recent important studies: Mulitmodal Treatment of ADHD

- 576 school-age children
- Randomly allocated to
  - Methylphenidate
  - Behavioral management
  - Methyphindate + behavior management
  - Treatment as usual
- At 14 months
  - Med and med+beh highly effective
  - Behavioral treatment alone = treatment as usual
- Hint that some subgroups dervied most benefit from combination treatment (anxious or disruptive comorbid)
Recent important studies: Preschool ADHD Treatment Study (Greenhill et al 2006; Vitiello et al 2007)

- 147 children: 3 and 5.5yrs
- Initial parent training phase (37/279 responded)
- Open label MPH titration; and placebo controlled phases (cross-over and parallel); then open continuation
  
  - Optimal response at lower dose (0.7mg/kg) than older children (1.0mg/kg)- although this increased during open continuation (0.92mg.kg)
  
  - Effect size lower (teacher 0.43 vs 0.75 in MTA; parent 0.35 vs 0.52)
  
  - Higher rate of adverse effects from MPH in younger children
  
  - MPH less effective if more than Oppositional Defiant Disorder as a comorbidity (if three or more comorbidités- ineffective)
Psychostimulants and the brain

- Psychostimulant medication impacts height and weight gain
  - 1.3cm/year less height gain
  - 1.3kg-2.5kg/year less weight gain (Sawnson et al; 2007; MTA)
  - Effect more marked early in treatment
  - Does it extend to the brain?
Neuroanatomic correlates of psychostimulants
(Nakao et al 2011)

Meta-regression of 14 voxel based morphometric studies. Found volume reduction in right putamen and globus pallidus extending to caudate, more prominent in unmedicated
Effects of stimulants on basal ganglia shape
(Sobel et al 2010)

ADHD vs neurotypical- PUTAMEN
Inward deformations in purple

ADHD group not on psychostimulants drives the finding

Medicated ADHD
No sig difference from healthy controls
Second and third line treatments

• Consider when :-
  – Complex cases with multiple comorbidities-adjunctive with psychostimulants
  – Failure to tolerate/ adverse side effects on psychostimulants
  – Possibility of misuse of psychostimulants (although vyvanase is an option).
Second line agent: atomoxetine
(Met-analysis of studies)

Newcorn et al 2008: N=516; 6 weeks; Atomoxetine 45% response vs. MPH 56% vs. placebo 24%

Switch at week 6 for MPD non-responders to atomoxetine under double-blind- 43% responded. Likewise 29 (42%) of the 69 non-responders to initial treatment with atomoxetine responded to MPH). Note- used low dose of Concerta and high dose of atomoxetine.

May be good for comorbid anxiety; tics
Other second and third line medications

• Alpha 2 agonists
  – Clonididine (catapres)- esp if also tics
  – Guanfacine (intuniv)

• Modafinil (provigil)

• Antidepressants (buproprion/ tricyclcsis/ SSRIs?)

• NOT ANTIPSYCHOTICS
Non pharmacological options

• Not all individuals with ADHD are the same…..
• Those with comorbidities need most complex treatment approaches (psychostimulants become less effective the more diagnoses a child)
• **Behavior management**- (MTA and PATS)
  – Efficacious- perhaps most when combined with medication.
• **School accommodation**-
• Other therapies – some initial evidence
  – **Cognitive remediation**- eg working memory training (‘Cogmed’) - recent RCT disappointing (Tannock et al 2012)
  – **Biofeedback** (some mixed evidence).
  – **Early executive function training** (primary prevention).
  – **Social skills training** –meta-analysis found no benefit (ES=0.16, CI=-0.04 to 0.36)- (Storebo et al, 2011)
Social perspective: Why don’t behavioral treatments work better?

• Behavioral treatment: we take child and family out of their usual social context for treatment.

• BUT: children with ADHD may have distinct social problems -inhabit distinct peer network positions

• Position within peer network not only influences the course of the behavioral problems but also may be a phenotype for genomic study.
Significance

• Understanding the social network of a child allows us to intervene more effectively

  – ‘Points of access’
  – Interventions at a classroom level to boost mental health of all children
II. Outcome

What’s happens to children with ADHD as they grow up?
Adult outcome and cerebral trajectories
(Shaw et al, In press, Biol Psychiatry)

Original childhood ADHD cohort (N=202)
Mean age 10 yrs (SD3)

Assessed as adults (N=116)
Mean age 24 (SD 4)

Structural MRI on same scanner, passing quality control (N=92)
The brain and adult outcome

• Do trajectories of cortical growth in adolescence associate with adult ADHD outcome?

• All had repeated scans
  – 40 had 2 scans; 22 had 3 scans; 25 had 4 scans; 8 had 5 or more

• Cortical thickness
  – Cortical morphology is abnormal in adults with ADHD: particularly the cingulate cortex (Proal et al 2011; Makris et al 2007; Bush et al 2009)
Where do rates of cortical change (slopes) predict total symptom count in adulthood?
Inattentive symptoms and cortical slopes

T statistic

-3.2

-6
No significant links with hyperactive-impulsive
Attentional networks

• Trajectories linked with outcome localize to cortical regions which are key hubs in networks supporting attention/executive function.

• Attention network (Posner/Cabeza and Nyberg/Corbetta and Schulman)
  • Cingulate – dorsolateral PFC – inferior parietal cortex

• CAN WE PREDICT OUTCOME USING TRAJECTORIES?
Conclusions

• Childhood ADHD can be partly conceptualized as a disturbance to trajectories of cortical development.

• Adult outcome: different outcomes linked with distinct trajectories of the cortical ‘attention’ system.

• Splitting ADHD into genetic subtypes may accelerate the definition of its brain basis and stimulate new treatments.

• First-line treatment remains psychostimulants.