Update on the neurobiology of Attention-deficit/hyperactivity disorder

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Disclosure

I have no financial relationships to disclose.

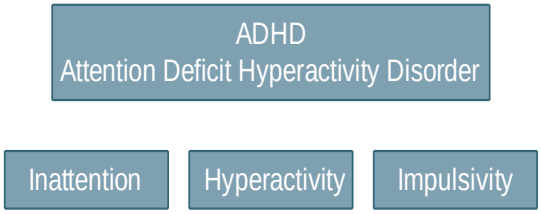
I will discuss off label use of clonidine, guanfacine, psychostimulants in children under 6 years of age, modafinil.

Objectives

- Understand the process of diagnosing ADHD
- Review the primary pharmacological treatments for ADHD
- Review the evidence on the effects of psychostimulants on the human brain.

What is ADHD?

- IMPAIRMENT
  - At school
  - At home
  - With peers
- If a child is not impaired, s/he does not have ADHD



Inattention

- Careless mistakes
- Can't sustaining attention
- Doesn't seem to listen
- Doesn't follow instructions and fails to carry out duties
- Difficulty organizing tasks and activities
- Reluctant to complete tasks that require sustained mental effort
- Often loses things
- Easily distracted by extraneous stimuli
- Is often forgetful

Hyperactivity

- Fidgets or squirms
- Can't stay in his/her seat when expected to do so
- Children may run or climb at inappropriate times, and adults may seem restless
- Difficulty playing quietly
- Always "on the go"
- Talks excessively

Impulsivity

- Blurts out answers to questions before question is completed
- Can't wait for his or her turn
- Interrupts

Diagnosing ADHD

- Need more than one informant
  - Parent
  - Teacher
  - Child
- Use structures scales (e.g.Conner's Scales, Child Behavior Checklist)

The differential

- Make sure it's not something else entirely
  - Anxiety disorder
  - Depression
  - Epilepsy (petit mal)
- Make sure you don't miss comorbid problems
  - Learning disability (50%)
  - Oppositional defiant disorder/conduct disorder (50%)
  - Anxiety/depression (33%)

Peter 6yo

- Main problem is 'he can't sit still'.
  - Since birth mother says he's been 'hyper hyper'. Mum is exhausted and worries she is thinking 'I love my child, but I really don't like him".
  - At pre-K completely unable to sit still .complete any tasks, look disengaged- struggling to keep up.
  - With peers he is very dominant, constantly interrupts, unable to take turns in games.
  - Otherwise a happy, sweet kid. Very interested in others. Aware he is doing poorly and describes himself as 'really stupid'.

Susan- 6yo

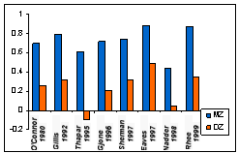
- Main problem is her 'bad behavior'
  - She answers every request with an autmoatic 'no'. Refuses to follow any instructions.
  - Has been in constant fights and described by a teahcer as the 'class bully'. Steals from her mother and shops. Has set one fire when her mother wouldn't buy her a toy. Cruel to animals.
  - A little fidgety but not more so than anyone else in her classroom
  - Never finishes tasks but because 'I don't want to'
  - No friends and she is unconcerned about this.
  - Also can be charming and fun; great energy; close to her grandmother and a very bright child.

Is ADHD a real disorder?

- YES
  - Reliably diagnosed
  - Valid in sense it predicts current and future impairment, socially, academically and occupationally.
  - Rates similar across many cultures and nations
- NO
  - *'No biological marker'* **BUT all mental disorders lack this**
  - *Just a variant of 'normal childhood'*- **BUT the core of the diagnosis if impairment in multiple settings and this is never 'normal'**
  - *'Created by drug companies'* **BUT rates of diagnosis are similar in countries where generic drugs are used (and much less profit for drug companies).**

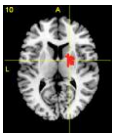
What causes ADHD: Genes

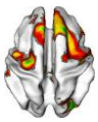
- Heritability estimates (derived from comparing MZ and DZ twins) >0.80
- High sibling risk ratios (4-8)
- Adoption studies demonstrate increased frequency in biological relatives of probands

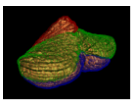


What's happening the brain?

- ADHD is characterized by:-
  - Overall reduction in brain volume- 3-4%
  - Most affected are the
    - Prefrontal cortex
    - Basal ganglia
    - Cerebellum



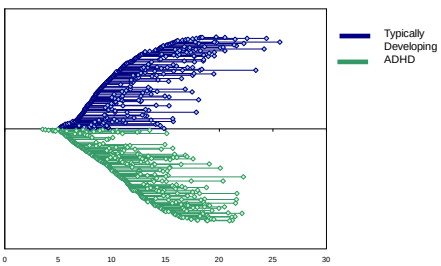




ADHD: delay or deviance?

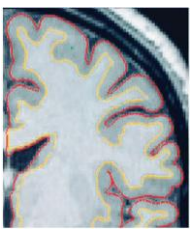
- Delay
  - "The diagnosis of minimal brain dysfunction (ADHD) is based on findings that are abnormal only with reference to the child's age: if the child were younger the findings would be regarded as normal" (Kinsbourne 1970)
  - EEG and fMRI: similar response to slightly younger healthy peers at rest and in response to cognitive probes (El-Sayed et al 2003, Rubia et al 2001).
- Deviance
  - Behavioral excesses never appropriate
  - Unique architecture in EEG (Chabot et al 1996; Clarke et al 2001).

The participants



Comorbidity: ODD 37%; CD 6%; Mood 4%; Anxiety 8%; Tics 3%; high IQ

Cortical thickness

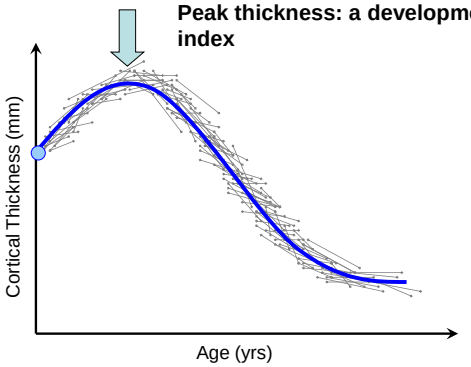


Reflects columnar organization of the cortex

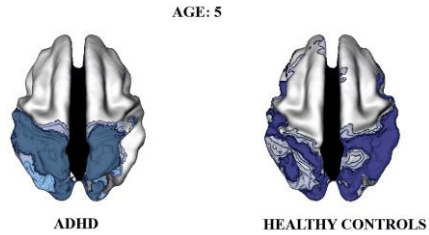
Method validated against manual estimates (Kabani et al 2003, 2008)

Captures pathological confirmed progression of disorders (eg Alzheimer's- Lerch et al 2005)

Peak thickness: a developmental index



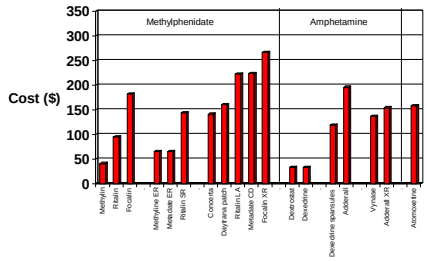
Comparison of cortical maturation
Index: peak in cortical thickness



TREATMENT
Psychostimulants: still first-line treatment

- Psychostimulants are extremely effective
  - Little to choose between amphetamine and the methylphenidate
  - One agent only ----65-75%
  - Switching agents---85%
- Short and long acting equally efficacious (Steele et al 2006) but greater compliance with longer acting (Marcus et al 2005)
- Prodrug- lisdexamfetamine (Vynase)- effective, possibly less misuse potential (activated by contact with GI); smoother release (biederamn et al 2007)?

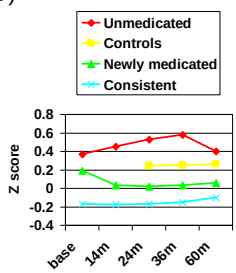
Average wholesale price for 30 days treatment
(1mg/kg MPH equivalent for 40 kg child)



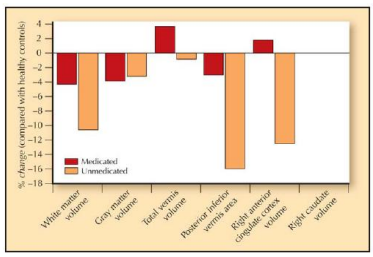
Data from NIH Clinical Center, Pharmacy Department Procurement Section (Average Wholesale Price used) and Ms Geraldine

Side effects of psychostimulants:
What's new- growth retardation (Swanson et al 2007)

- Height and weight retardation
  - 1.3cm/year (PATS)
  - 1.3kg/year to 2.5kg/year (PATS/MTA)
  - Is this effect constant over treatment duration
  - No: effect more marked in early stages

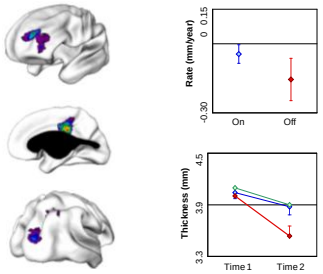


Summary of structural slides



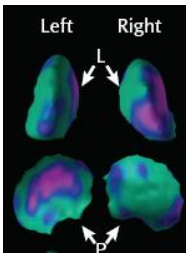
Does this extend to the brain?

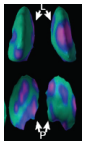
Psychostimulants and the cortex:
Regions where growth differs by treatment



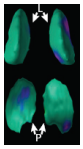
Effects of stimulants on basal ganglia shape (Sobel et al 2010)

ADHD vs NV- PUTAMEN
Inward deformations in purple





Unmedicated ADHD drives the finding



Medicated ADHD
No sig difference from healthy controls

Side effects of psychostimulants

What's new- cardiac concerns

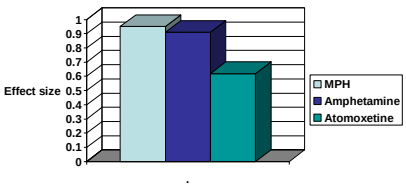
- Cardiovascular
  - FDA Pediatric Advisory: sudden deaths in children on psychostimulants 1992-2005 (during trials and surveillance reports)
    - 11 MPH----------2 per million treated
    - 13 amphetamines----------3 per million
    - 3 atomoxetine (2003-5)---------- 5 per million
    - Recent case control comparing sudden death and RTAs- found higher rates of psychostimulant use in the sudden cardiac deaths.
  - BUT
    - Mechanism is unknown
    - Baseline 8 -62 per million
    - : Retrospective cohort – 10yrs of Medicaid claims 55,000 3-25yr with ADHD – 32,000 taking stimulants and 22,000 not (Winderstein et al 2008 Pediatrics)
      - 5 died due to cardiac cause- none were on psychostimulants
      - 21% increase (CI 6-38%) in hazard for ER visit due to cardiac cause in current (not past) psychostimulant users—but not necessarily severe heart disease
  - History and examination is enough for most children.
    - Familylpersonal history of cardiac disease/ sudden death
    - Unclear is ECG would detect most troublesome causes
      - Will detect WPW, long QT syndrome, and some arrhythmias
      - Unlikely to detect most HOCM

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 vyvanse is an option).

Second line agent: atomoxetine

(Met-analysis of studies)

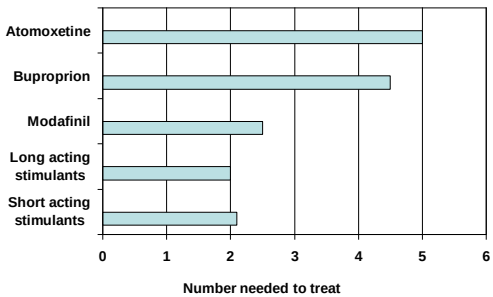


Newcorn et al 2008: N=516; 6 weeks; Atomoxetine 45% response vs. MPH 56% vs. placebo 24%

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

Adults with ADHD (Faraone et al 2010)



Conclusions

- ADHD is a common disorder
- Some insights into its neurobiology are emerging
- Treatment remains psychostimulants