Neurodevelopment of ADHD: 
Significance for Assessment and Therapy

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How far are we?

Neurobiology of ADHD and Its Development

Preschool, School ADHD and Adult ADHD
MZ correlation = 0.78 (0.76 – 0.81), DZ correlation = 0.30 (0.26 – 0.35)

Heritability = 0.84 (0.82 – 0.86)

Rijsdijk, Curran, Asherson, unpublished data
Neuropsychological deficits can be observed among preschool children with hyperactivity, particularly when comorbid oppositional-defiance is present.
Aggressive pre-school children showed poorer inhibition than normal children.

Boys performed worse on inhibition than girls.

This association between aggressive behavior and inhibition deficits was maintained after controlling for attention problems.

Boys more impairment in Executive Functioning than girls.
And hyperactive impulsive symptoms predict in Pre-school Children brain structure
Why do the symptom dimensions predict brain functioning?

Parent Conners Scores

Inattention

Hyperactivity
Neuropsychological Tasks Separate ADHD From Controls: Meta-analytic Findings

- Visual WM (meta)
- CPT Hits
- CPT Omis
- Digit Span
- Trails B
- SSRT (meta Lijffijt)
- CPT Comm
- Letter Fluency
- Verbal WM (meta)
- Category Fluency
- CPT MRT
- WCST-Perseveration
- Stroop Interference
- WCST-Categories
- WCST-Set Failure
- Full Scale IQ
- Verbal IQ
- Performance IQ
- Non-EF Measures
- Stroop Colour
- Stroop Word

Structural MRI Effect size
Fig. 2. Regions where the ADHD group had delayed cortical maturation, as indicated by an older age of attaining peak cortical thickness.
**Brain development and genetics related to ADHD symptom remission**

*DRD4* 7-repeat allele associated with a thinner right orbitofrontal/inferior prefrontal and posterior parietal cortex.

ADHD participants with *DRD4* 7-repeat allele had a better clinical outcome. A distinct trajectory of cerebellar development and normalization of right parietal cortical region (orienting attention system).
Decreased Frontostriatal Microstructural Organization in Attention Deficit/Hyperactivity Disorder

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![Image of brain scan and graph showing fractional anisotropy]
ADHD more than a “cognitive” disorder, what is the role of emotion in the disorder?
The ADHD SPECTRUM: A disorder of Self-regulation with emotional dysregulation

- Family disruption
- Disruptive behaviour
- Complex learning difficulties
- Lack of motivation
- Conduct disorder
- Substance abuse
- Poor social skills
- Learning problems
- Oppositional defiant disorder
- Mood disorder
- Provocative behaviour
- Antisocial behaviour

ADHD only
What is the evidence of an Association between ADHD and Emotionality

Strine et al (2006) using SDQ in N = 8681 children 4 – 17 yrs showed that there was indeed considerable association between ADHD and emotionality versus children without ADHD rating.

**Figure 1.** Results of Strengths and Difficulties Questionnaire, based on parent-report, 2003 National Health Information Survey: percentage of children with different problem types.
ADHD & Emotional Lability

- ADHD & Emotional Lability often associated with:
  - irritability, hot temper, low frustration tolerance, unpredictable mood shifts & reduced emotional regulation:
    - **Child ADHD**
      (Melnick & Hinshaw, 2000; Walcott and Landau, 2004; Maedgen & Carlson, 2000)
    - **Adult ADHD**
      (Reimherr et al., 2005; Kooij et al., 2001; Asherson et al., 2007; Wender et al., 2001)
    - **More strongly in ADHD-CT than in ADHD-I**
      (Braaten, 2000; Landau & Milich, 1988; Sanson et al., 1993; Barkley et al., 1990)

- Regulation problem or increased emotional reactivity?
  (Carroll et al. 2006; Braaten & Rosen 2000; Rapport et al. 2002; Melnick & Hinshaw, 2000; Hinshaw 2003)

- Early EL predicts poor social functioning / competence & peer rejection. Even after controlling for ADHD severity.
  (Eisenberg et al., 1997; Hinshaw et al, 1999, Caspi et al, 1994; Melnick et al, 2000; Maedgen et al, 2000)
Emotional Lability: ADHD and Comorbid psychiatric disorders: Severe EL associated with ODD, CD, Anx & Dep

Primary Authors Esther Sobanski & Tobias Banaschewski
EI: impatience, low frustration tolerance, hot-temperedness, quickness to anger, irritability, and easily emotionally excitable
Emotional processing of “delay”? Delay is not simply “cognitive” but effects the amygdala.

Nucleus Accumbens: Selective increased activation when *anticipating* reward and passed on to the ventral frontal cortex. May have a key role in frustration.  *Knutson et al.*

Structural MRI no difference in size between ADHD controls
Affective mechanism: amygdala regulation

aMCC inhibitory

SgACC excitatory effect

With amygdala

Pezawas, Meyer-Lindenberg et al. Nat Neurosci 2005
Overlap Emotion and Cognition

ALE = activation likelihood estimate

The integration of negative affect, pain and cognitive control in the cingulate cortex

Alexander J. Shackman, Tim V. Salamone, Helen A. Siegle, Andrew S. Fox, Jameel J. Winter and Richard J. Davidson
Ventral striatum (nucleus accumbens) underactivated in ADHD
ERPs associated with monitoring and evaluation of monetary reward and punishment in children with ADHD

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ADHD-treatment: targeting the iceberg

Core symptoms
Sleep problems
Emotional lability
Reward dysfunction
Executive dysfunction
.....

What does Neurobiology have to teach us?
Improvement on trained tasks

Training curve

$N = 430$

Day of training

WM capacity index

0 5 10 15 20 25 30

60 65 70 75 80 85 90 95 100 105
102 children ADHD performed either 36 sessions of NF training or a computerised attention skills training within two blocks of about four weeks each (randomised group assignment). The combined NF treatment consisted of one block of theta/beta training and one block of slow cortical potential (SCP) training.

For parent and teacher ratings, improvements in the NF group were superior to those of the control group the effect size was .60.

Comparable effects were obtained for the two NF protocols (theta/beta training, SCP training).
Conventional vs tomographic Neurofeedback

- **Conventional** Neurofeedback
  - few electrodes
  - e.g. Cz: activities mixing at vertex

**Tomographic** Neurofeedback

- Many electrodes, source estimation
- Feedback of regional brain activity,
  e.g. from Anterior Cingulate (ACC), targeting affected regions

➢ ADHD: ACC hypoactivation
Effect-sizes of controlled studies (Arns et al, 2009)

Inattention: 0.81

Hyperactivity: 0.39

Impulsivity: 0.68
Pharmacology: Cognitive & Emotional Regulation
Long-term follow up of unmedicated ADHD patients shows that the typical frontostriatal dysfunction observed in ADHD children in both (a) interference inhibition and (b) attention allocation, is observed in Adult ADHD patients with persistent symptoms. **Hence, this difference is not due to medication** (Cubillo, Halari, Giampietro, Taylor & Rubia, 2011).
Effect of a single dose of MPH is to *normalize* brain function in medication naïve ADHD youth:

a) Placebo significantly reduced activation in ADHD group

b) Single dose: brain activation differences between groups no longer observed in the right inferior/dorsolateral prefrontal cortex and the left caudate/thalamus/ventromedial frontal lobe.
Medication Normalizes ADHD Amygdala Processing of Emotional Stimuli

Abnormal Amygdalar Activation and Connectivity in Adolescents With Attention-Deficit/Hyperactivity Disorder

Both cognitive and emotional conflict monitored in the Dorsal Anterior Cingulate Cortex (daMCC) and at the insula.

Cognitive conflict monitoring improved with medication in ADHD adults. (Bush et al, 2008)
Transcranial magnetic stimulation (TMS)

**TMS:** Weak electromagnetic currents -> rapidly changing magnetic fields 2-3cm into brain 20-80ms duration

In ADHD to test intracortical inhibition (Moll, Richter, Buchmann)

**Therapeutic rTMS:** Depression, OCD, PD, migraine, ED

⇒ Therapeutic use in ADHD?
   ⇒ upregulate dysfunction
   ⇒ downregulate DMN
Repetitive transcranial magnetic stimulation in ADHD
Effect of Cognitive-Behavioural Training: Network Effects

Figure 1.
Statistical parametric maps depicting increases in BOLD response after cognitive training. Whole-brain random effects analyses. (A) Regions of increased activation on the task of response inhibition after cognitive training; (B) regions of increased activation on the task of selective attention after cognitive training; (C) regions of increased activation on the task of response inhibition displayed on surface maps.
Differences in Connectivity between ADHD and Typically Developing Children

Fair et al, (under review)
Summary

- Clear evidence that:
  1) Anxiety and Depression associated with ADHD
  2) Emotional lability particularly in ADHD-CT often present.

- The neurobiological studies suggest wide regions of the brain involved in emotional experience, emotional control.
  - The Cold – Hot distinction a false dichotomy
  - Adaptive control involves both cognitive and affective processes.

- Assessment of ADHD patients requires extensive emotional evaluation.
- Medication important in ADHD emotional management.