

School Research Seminar Series

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**ADHD:
History, Development and Current Trends**

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Part 1

History

Sir Alexander Crichton

- Scottish Physician
- 1798 Book: *“An inquiry into the nature and origin of mental derangement: comprehending a concise system of the physiology and pathology of the human mind and a history of the passions and their effects” (1)*
- Chapter on Attention and described “mental restlessness” in a similar way to current descriptions of Inattentive subtypes
- Described certain children with fidgety behaviour, excessive distractibility, etc., .

(1) Crichton A. An inquiry into the nature and origin of mental derangement: on attention and its diseases. *J Atten Disord* 2008 Nov;12(3):200-4.

Dr. Heinrich Hoffman

- German Psychiatrist
- *Der Struwwelpeter* (1845)
- Translated to English in 1878 by Mark Twain while he was trying to make money in Berlin (2)
- 10 stories/pictures.
- Original title: *Lustige Geschichten und drollige Bilder mit 15 schön kolorierten Tafeln für Kinder von 3-6 Jahren*
- Notable :
 - Die Geschichte vom bösen Friederich
 - Die Geschichte vom Zappel-Philipp
 - Die Geschichte von Hans Guck-in-die-Luft

(2) Wortis J. Struwwelpeter Heinrich Hoffmann (1809-1894). *Biol Psychiatry* 1988 Oct;24(6):615-8.





Sir George Frederick Still

- English Paediatrician
- 3 Goulstonian Lectures to the Royal College of Physicians (3;4)
- 43 children with a pattern of excessive defiance, impulsivity, poor emotional control and aggression

(3) Still GF. The Goulstonian Lectures on some abnormal psychical conditions in children. Lancet 1902;1:1163-8.

(4) Still GF. The Goulstonian lectures on some abnormal psychical conditions in children. Lancet 1902;1:1008-12.

Part 2

Clinical Presentation

Background

- Attention-Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental condition affecting children and adults.
- The prevalence of the condition in children has been reported as low as 3% and as high as 12% (5)
- Around half of those children with ADHD will continue to have ADHD-related difficulties in adulthood (6)

(5) Brown RT, Freeman WS, Perrin JM, Stein MT, Amler RW, Feldman HM, et al. Prevalence and assessment of attention-deficit/hyperactivity disorder in primary care settings. *Pediatrics* 2001 Mar;107(3):E43.

(6) Faraone SV, Biederman J, Spencer T, Wilens T, Seidman LJ, Mick E, et al. Attention-deficit/hyperactivity disorder in adults: an overview. *Biol Psychiatry* 2000 Jul 1;48(1):9-20.

Comorbidity

- Around 60-65% of those children with ADHD will suffer some comorbid condition (7)
- In fact, most cases of ADHD have present with some comorbid condition (8)
- The most common conditions are ODD, Anxiety, Depression
- The reported incidence of comorbid anxiety disorders has also varied, from as low as 12% to 22% to as high as 33.5% (7;9)
- Much higher risk compared to non-ADHD children

(7) Elia J, Ambrosini P, Berrettini W. ADHD characteristics: I. Concurrent co-morbidity patterns in children & adolescents. *Child Adolesc Psychiatry Ment Health* 2008;2(1):15.

(8) Ollendick TH, Jarrett MA, Grills-Taquechel AE, Hovey LD, Wolff JC. Comorbidity as a predictor and moderator of treatment outcome in youth with anxiety, affective, attention deficit/hyperactivity disorder, and oppositional/conduct disorders. *Clin Psychol Rev* 2008 Dec;28(8):1447-71.

(9) A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. The MTA Cooperative Group. Multimodal Treatment Study of Children with ADHD. *Arch Gen Psychiatry* 1999 Dec;56(12):1073-86.

Classical Diagnosis (DSM IV)

- Symptoms:
 - 9 Inattentive
 - 9 Hyperactive/Impulsive
- Diagnosis:
 - > 6 of either: that subtype
 - > 6 of both: combined type
 - Onset before age of 7
 - At least 6 months duration
 - Maladaptive and significant impairment in social, academic or occupational functioning
 - Inappropriate to developmental level
 - Impairments should be pervasive (> 2 settings)
- What about DSM V?

Multifaceted Presentation

- Multifaceted presentation: (10)
 - ADHD + Anxiety ("Internalising")
 - ADHD + Mood ("Internalising")
 - ADHD + Conduct ("Externalising")
 - ADHD + Substance Misuse ("Externalising")
 - ADHD + Borderline

(ADHD + PDD/Asperger/Autism)

(10) Schmidt S, Petermann F. Developmental psychopathology: Attention Deficit Hyperactivity Disorder (ADHD). BMC Psychiatry 2009;9:58.

Detailed symptom assessment

- Multiple measurements:
 - Core Symptoms
 - Executive Function
 - Sensation Seeking
 - Maturation Tasks Outcome
 - Quality of Life Outcome

Part 3

Brain

Dopamine

- Prefrontal cortex regulates emotion, attention integration
- PFC is largely dependent on DA and NA
- Too little, too much vs. just right
 - Too little: heightens working memory (12)
 - Too much: weakens working memory (13)
- Dopaminergic dysregulation in the fronto-striatal system (incl. basal ganglia) (14;15) is closely linked to ADHD symptoms

- (11) Castellanos FX, Giedd JN, Marsh WL, Hamburger SD, Vaituzis AC, Dickstein DP, et al. Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. *Arch Gen Psychiatry* 1996 Jul;53(7):607-16.
- (12) Castellanos FX, Lee PP, Sharp W, Jeffries NO, Greenstein DK, Clasen LS, et al. Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *JAMA* 2002 Oct 9;288(14):1740-8.
- (13) Vijayraghavan S, Wang M, Birnbaum SG, Williams GV, Arnsten AF. Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. *Nat Neurosci* 2007 Mar;10(3):376-84.
- (14) Castellanos FX, Giedd JN, Marsh WL, Hamburger SD, Vaituzis AC, Dickstein DP, et al. Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. *Arch Gen Psychiatry* 1996 Jul;53(7):607-16.
- (15) Castellanos FX, Lee PP, Sharp W, Jeffries NO, Greenstein DK, Clasen LS, et al. Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *JAMA* 2002 Oct 9;288(14):1740-8.

Noradrenaline

- NA is also involved in PFC function
- $\alpha 2A$ is highly concentrated in PFC
- Stimulation of $\alpha 2A$ induces improved integration of emotion and behaviour (16)
- Blockade induces ADHD type symptoms (17-19)

(16) Wang M, Ramos BP, Paspalas CD, Shu Y, Simen A, Duque A, et al. Alpha2A-adrenoceptors strengthen working memory networks by inhibiting cAMP-HCN channel signaling in prefrontal cortex. *Cell* 2007 Apr 20;129(2):397-410.

(17) Li BM, Mei ZT. Delayed-response deficit induced by local injection of the alpha 2-adrenergic antagonist yohimbine into the dorsolateral prefrontal cortex in young adult monkeys. *Behav Neural Biol* 1994 Sep;62(2):134-9.

(18) Mo CL, Qi XL, Peng JY, Li BM. Selective deficit in no-go performance induced by blockade of prefrontal cortical alpha 2-adrenoceptors in monkeys. *Neuroreport* 2003 May 23;14(7):1013-6.

(19) Ma CL, Arnsten AF, Li BM. Locomotor hyperactivity induced by blockade of prefrontal cortical alpha 2-adrenoceptors in monkeys. *Biol Psychiatry* 2005 Jan 15;57(2):192-5.

Structural Changes

- Gross changes:
 - Cerebellar
 - Cortical
 - Subcortical
- Overall reduction in brain volume (15)
 - Typical cerebral volume reduction is ~ 3%
 - Frontal lobes account ~ half of the overall reduction (20)
- Basal Ganglia:
 - Abnormalities up until around age 16, then less so (15)
 - There is more debate as abnormalities are less consistent (21)
 - Left vs right
 - Increased vs. Decreased

(15) Castellanos FX, Lee PP, Sharp W, Jeffries NO, Greenstein DK, Clasen LS, et al. Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *JAMA* 2002 Oct 9;288(14):1740-8.

(20) Mostofsky SH, Cooper KL, Kates WR, Denckla MB, Kaufmann WE. Smaller prefrontal and premotor volumes in boys with attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2002 Oct 15;52(8):785-94.

(21) Krain AL, Castellanos FX. Brain development and ADHD. *Clin Psychol Rev* 2006 Aug;26(4):433-44.

Structural Changes

- Cerebellum:
 - A consistent finding is posterior-inferior lobe reduction (21)
- Grey vs White Matter:
 - More likely grey matter reduction on the right (21)
 - More likely white matter reduction on the left (21)

(21) Krain AL, Castellanos FX. Brain development and ADHD. Clin Psychol Rev 2006 Aug;26(4):433-44.

Part 4

Executive Function

Executive Function

- Summary:

- Goal directed
- Forward planning
- Abstract thinking
- Emotional self-regulation

- Why is it important?

- Functional outcome measure
- Treatment target (e.g., Pay Attention program) (22)
- Academic performance measure

(22) Tamm L, Hughes C, Ames L, Pickering J, Silver CH, Stavinoha P, et al. Attention Training for School-Aged Children With ADHD: Results of an Open Trial. *J Atten Disord* 2009 Oct 5.

Executive Function

- Persistent ADHD and Remitted ADHD demonstrate ongoing cognitive executive function deficits vs. controls at 10 year follow-up (ages 15 +) (23).
- Child ratings predict academic performance outcome in adolescence and social functioning (5 year study, females) (24).
- Development of Simple EF → Complex EF supported longitudinally in children aged 5-7: (25)
 - More predictive of inattention than hyperactivity
 - Simple inhibition → Complex inhibition
 - Selective inattention → Working memory problems
- Impact of EF dysfunction may vary depending on ODD/CD comorbidity (26)

(23) Biederman J, Petty CR, Ball SW, Fried R, Doyle AE, Cohen D, et al. Are cognitive deficits in attention deficit/hyperactivity disorder related to the course of the disorder? A prospective controlled follow-up study of grown up boys with persistent and remitting course. *Psychiatry Res* 2009 Dec 30;170(2-3):177-82.

(24) Miller M, Hinshaw SP. Does Childhood Executive Function Predict Adolescent Functional Outcomes in Girls with ADHD? *J Abnorm Child Psychol* 2009 Dec 4.

(25) Brocki KC, Engler L, Thorell LB, Bohlin G. Interrelations Between Executive Function and Symptoms of Hyperactivity/Impulsivity and Inattention in Preschoolers: A Two Year Longitudinal Study. *J Abnorm Child Psychol* 2009 Sep 10.

(26) Barnett R, Maruff P, Vance A. Neurocognitive function in attention-deficit-hyperactivity disorder with and without comorbid disruptive behaviour disorders. *Aust N Z J Psychiatry* 2009 Aug;43(8):722-30

Executive Function

- Treatment:

- Atomoxetine treatment demonstrates improvement across executive function in children over 6 months (27).
- Atomoxetine treatment also shown to improve executive function in adults (28)

- Genetics:

- On fMRI, DAT1 10-repeat (10/10) VNTR shown to be more closely associated with working memory dysfunction than 9/10 variation, but more particularly, at higher loads of working memory than lower, and also DAT1 may have a greater impact on working memory depending on developmental stage (i.e., younger). (29).
- Younger children demonstrate the 9/10 greater activation than 10/10, generally speaking, younger children will involve a wider network of areas for working memory tasks than adults, again suggesting immature processing in younger ages (29).

(27) Maziade M, Rouleau N, Lee B, Rogers A, Davis L, Dickson R. Atomoxetine and neuropsychological function in children with attention-deficit/hyperactivity disorder: results of a pilot study. *J Child Adolesc Psychopharmacol* 2009 Dec;19(6):709-18.

(28) Brown TE, Holdnack J, Saylor K, Adler L, Spencer T, Williams DW, et al. Effect of Atomoxetine on Executive Function Impairments in Adults With ADHD. *J Atten Disord* 2009 Dec 21.

(29) Stollstorff M, Foss-Feig J, Cook EH, Jr., Stein MA, Gaillard WD, Vaidya CJ. Neural response to working memory load varies by dopamine transporter genotype in children. *Neuroimage* 2010 Jan 4.

Part 5

Genetics

Genetics

- Huge amount of genes have been studied
- No single gene mutation which makes sense due to multifaceted presentation
- Likely combination of several gene mutations and environmental exposure lead to someone's particular pattern of ADHD presentation
- Dopamine has been recurrently implicated
- Genetic links e.g., DRD4, DAT1 identified and replicated but actually quite weak individually as contributing to overall ADHD picture.
- Heritability estimated at ~ 0.8 (i.e., very high compared to other major psychiatric disorders) (30).

(30) Kiehl C, Goncalves RR, Tannock R, Castellanos FX. Neurobiology of attention deficit hyperactivity disorder. *Child Adolesc Psychiatr Clin N Am* 2008 Apr;17(2):285-307, viii.

Genetics

- Genes may moderate ADHD-symptom treatment response (31).
- Genotyping success may depend on source of DNA (e.g., buccal vs. Blood) (32)
- Negative study on parent of origin effect on major genes (33).
- Different combinations of gene polymorphisms likely to lead to different clinical picture: Combined vs. Inattentive (34).
- Dopamine genotypes more likely to influence degree of appetite suppression with methylphenidate (35).
- Paternal smoking more than maternal smoking may be an indicator of risk phenotypes of ADHD+/- smoking (36)

(31) McGough JJ, McCracken JT, Loo SK, Manganiello M, Leung MC, Tietjens JR, et al. A Candidate Gene Analysis of Methylphenidate Response in Attention-Deficit/Hyperactivity Disorder. *J Am Acad Child Adolesc Psychiatry* 2009 Oct 23.

(32) Swanson JM, Moysis RK, McGough JJ, McCracken JT, Riddle MA, Kolins SH, et al. Effects of source of DNA on genotyping success rates and allele percentages in the Preschoolers with Attention-Deficit/Hyperactivity Disorder Treatment Study (PATS). *J Child Adolesc Psychopharmacol* 2007 Oct;17(5):635-46.

(33) Kim JW, Waldman ID, Faraone SV, Biederman J, Doyle AE, Purcell S, et al. Investigation of parent-of-origin effects in ADHD candidate genes. *Am J Med Genet B Neuropsychiatr Genet* 2007 Sep 5;144B(6):776-80.

(34) Grizenko N, Paci M, Joobar R. Is the Inattentive Subtype of ADHD Different From the Combined/Hyperactive Subtype? *J Atten Disord* 2009 Sep 18.

(35) Leddy JJ, Waxmonsky JG, Salis RJ, Paluch RA, Gnagy EM, Mahaney P, et al. Dopamine-related genotypes and the dose-response effect of methylphenidate on eating in attention-deficit/hyperactivity disorder youths. *J Child Adolesc Psychopharmacol* 2009 Apr;19(2):127-36.

(36) Altink ME, Slaats-Willemse DJ, Rommelse NN, Buschgens CJ, Filiers EA, rias-Vasquez A, et al. Effects of maternal and paternal smoking on attentional control in children with and without ADHD. *Eur Child Adolesc Psychiatry* 2009 Aug;18(8):465-75.

Genetics

- DRD4: (gene for D4 receptor, located at 11p15.5)
- Particularly implicated in neonatal motor development (37) and < 12 months Activity Level (38).
- Possible association between heritable activity level and novelty-seeking behaviour in children and adults (39) – this was a twin-study of 312 same-sex twins based Boston University Twin Project. However, a limit of this study was power.
- Is generally the most studied of all genes (40;41)
- Possible association with increased irritability and social withdrawal at higher doses of MPH (42)

- (37) Ebstein RP, Levine J, Geller V, Auerbach J, Gritsenko J, Belmaker RH. Dopamine D4 receptor and serotonin transporter promoter in the determination of neonatal temperament. *Mol Psychiatry* 1998 May;3(3):238-46.
- (38) Auerbach JG, Faroy M, Ebstein R, Kahana M, Levine J. The association of the dopamine D4 receptor gene (DRD4) and the serotonin transporter promoter gene (5-HTTLPR) with temperament in 12-month-old infants. *J Child Psychol Psychiatry* 2001 Sep;42(6):777-83.
- (39) Ilott N, Saudino KJ, Wood A, Asherson P. A Genetic Study of ADHD and Activity Level in Infancy. *Genes Brain Behav* 2009 Dec 17.
- (40) Swanson JM, Sunohara GA, Kennedy JL, Regino R, Fineberg E, Wigal T, et al. Association of the dopamine receptor D4 (DRD4) gene with a refined phenotype of attention deficit hyperactivity disorder (ADHD): a family-based approach. *Mol Psychiatry* 1998 Jan;3(1):38-41.
- (41) Swanson JM, Flodman P, Kennedy J, Spence MA, Moyzis R, Schuck S, et al. Dopamine genes and ADHD. *Neurosci Biobehav Rev* 2000 Jan;24(1):21-5.
- (42) McGough J, McCracken J, Swanson J, Riddle M, Kollins S, Greenhill L, et al. Pharmacogenetics of methylphenidate response in preschoolers with ADHD. *J Am Acad Child Adolesc Psychiatry* 2006 Nov;45(11):1314-22.

Genetics

- Possible association with response inhibition (7 repeats better than 4 repeats) likely due to D4 regulatory function in prefrontal cortex (43)
- More likely association with ADHD that persists into adulthood (n=563 study) (44)
- Known association with risk-taking and ADHD, but the same 7R allele is also higher in populations with a history of migration (45).
- Verbal IQ (and not performance IQ) is related to externalising behaviour in ADHD if both DRD4 and DAT1 are present (46)
- DRD4 may also moderate intervention effects on toddlers externalising behaviour (47).

- (43) Kramer UM, Rojo N, Schule R, Cunillera T, Schols L, Marco-Pallares J, et al. ADHD candidate gene (DRD4 exon III) affects inhibitory control in a healthy sample. *BMC Neurosci* 2009;10:150.
- (44) Biederman J, Petty CR, Ten Haagen KS, Small J, Doyle AE, Spencer T, et al. Effect of candidate gene polymorphisms on the course of attention deficit hyperactivity disorder. *Psychiatry Res* 2009 Dec 30;170(2-3):199-203.
- (45) Eisenberg DT, Apicella CL, Campbell BC, Dreber A, Garcia JR, Lum JK. Assortative human pair-bonding for partner ancestry and allelic variation of the dopamine receptor D4 (DRD4) gene. *Soc Cogn Affect Neurosci* 2009 Aug 27.
- (46) Kebir O, Grizenko N, Sengupta S, Joobler R. Verbal but not performance IQ is highly correlated to externalizing behavior in boys with ADHD carrying both DRD4 and DAT1 risk genotypes. *Prog Neuropsychopharmacol Biol Psychiatry* 2009 Aug 31;33(6):939-44.
- (47) Bakermans-Kranenburg MJ, Van IJzendoorn MH, Pijlman FT, Mesman J, Juffer F. Experimental evidence for differential susceptibility: dopamine D4 receptor polymorphism (DRD4 VNTR) moderates intervention effects on toddlers' externalizing behavior in a randomized controlled trial. *Dev Psychol* 2008 Jan;44(1):293-300.

Genetics

- In adults, the DRD4 is associated with volumetric changes (reduced volume in dorsolateral prefrontal cortex and cerebellum) in those with just ADHD, but not in ADHD+BD (48)
- DRD4 associated with poor performance on intelligence, working memory, colour-naming, interference control and verbal working memory (possible endophenotype identification) (49)

(48) Monuteaux MC, Seidman LJ, Faraone SV, Makris N, Spencer T, Valera E, et al. A preliminary study of dopamine D4 receptor genotype and structural brain alterations in adults with ADHD. *Am J Med Genet B Neuropsychiatr Genet* 2008 Dec 5;147B(8):1436-41.

(49) Loo SK, Rich EC, Ishii J, McGough J, McCracken J, Nelson S, et al. Cognitive functioning in affected sibling pairs with ADHD: familial clustering and dopamine genes. *J Child Psychol Psychiatry* 2008 Sep;49(9):950-7.

Genetics

- SLC6A3/DAT1: (gene for dopamine transporter)
- Predicts clinical heterogeneity: the DAT1 is associated with non-Conduct Disorder subtypes of ADHD, and other types are not. This is quite significant. (52).
- Presence reflects maternal positive emotion expression likelihood in relation to conduct problems (53)
- Risk of symptoms of ADHD due to early institutional deprivation moderated by DAT1 (not DRD4 in this study) (54)

(52) Sharp SJ, McQuillin A, Gurling HM. Genetics of attention-deficit hyperactivity disorder (ADHD). *Neuropharmacology* 2009 Dec;57(7-8):590-600.

(53) Sonuga-Barke EJ, Oades RD, Psychogiou L, Chen W, Franke B, Buitelaar J, et al. Dopamine and serotonin transporter genotypes moderate sensitivity to maternal expressed emotion: the case of conduct and emotional problems in attention deficit/hyperactivity disorder. *J Child Psychol Psychiatry* 2009 Sep;50(9):1052-63.

(54) Stevens SE, Kumsta R, Kreppner JM, Brookes KJ, Rutter M, Sonuga-Barke EJ. Dopamine transporter gene polymorphism moderates the effects of severe deprivation on ADHD symptoms: developmental continuities in gene-environment interplay. *Am J Med Genet B Neuropsychiatr Genet* 2009 Sep 5;150B(6):753-61.

Genetics

- Other genes:
 - SLC6A4/5HTT
 - NET1
 - ADRA1A, ADRA2C
 - SNAP25 (opposite alleles associated with schizophrenia vs ADHD - different genes with multiple illness components), ADHD+MDD, tics
 - BDNF (brain maturation)
 - COMT (irritability)
 - DRD5 (age of onset)
 - DBH: converts DA to NA. Patients with ADHD have low levels of DBH, correlating with hyperactivity. Released in response to stimulation.

Part 6

Bipolar Disorder

Bipolar Disorder

- Inflated self-esteem or grandiosity
- **decreased need for sleep** (e.g., feels rested after only 3 hours of sleep)
- **more talkative** than usual or pressure to keep talking
- flight of ideas or subjective experience that **thoughts are racing**
- **distractibility** (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
- **increase in goal-directed activity** (either socially, at work or school, or sexually) or **psychomotor agitation**
- **excessive involvement in pleasurable activities that have a high potential for painful consequences** (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

Bipolar Disorder

- Common & Difficult to Discern Symptoms to both BD and ADHD: (55)
 - Talking excessively
 - Hyperactivity
 - Distractability
 - Flight of ideas vs Difficulty sustaining attention
 - Excessive involvement in pleasurable activities vs Impulsively changing tasks
- Presentation in children of BPAD:
 - A more severe, predominantly manic form of BPAD?
 - A subtype of BPAD (like BPAD I or II)?
 - An affective-dominant ADHD presentation?

(55) Hegerl U, Himmerich H, Engmann B, Hensch T. Mania and attention-deficit/hyperactivity disorder: common symptomatology, common pathophysiology and common treatment? *Curr Opin Psychiatry* 2010 Jan;23(1):1-7.

Bipolar Disorder

- Pre-pubertal vs Post-pubertal: (“Very early onset vs Early onset”)
 - There is less debate in post-pubertal onset due to clinical similarity with adult BPAD (56)
- Presentation in pre-pubertal:
 - Childhood-onset more likely to be with manic symptoms
 - More mixed-episode and rapid-cycling in childhood-onset
 - More males in childhood (adult BPAD is equal)
 - ADHD+CD is present in ~75% of childhood-BPAD cases (10-20% in adult BPAD)
 - Lifetime prevalence of ADHD in Adult BPAD patients is ~ 15% for males and 10% for females (57)
- STEP-BD Study (n=983) of adults with BPAD found 272 (~27%) had onset of symptoms before age 13, 370 (~38%) had onset age 13-18, i.e., ~ 60-65% of adults in this large cohort had onset of BPAD symptoms described < 18 (58).

(56) Kyte ZA, Carlson GA, Goodyer IM. Clinical and neuropsychological characteristics of child and adolescent bipolar disorder. *Psychol Med* 2006 Sep;36(9):1197-211.

(57) Nierenberg AA, Miyahara S, Spencer T, Wisniewski SR, Otto MW, Simon N, et al. Clinical and diagnostic implications of lifetime attention-deficit/hyperactivity disorder comorbidity in adults with bipolar disorder: data from the first 1000 STEP-BD participants. *Biol Psychiatry* 2005 Jun 1;57(11):1467-73.

(58) Perlis RH, Miyahara S, Marangell LB, Wisniewski SR, Ostacher M, Dalbello MP, et al. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). *Biol Psychiatry* 2004 May 1;55(9):875-81.

Bipolar Disorder

- Comorbidity rates:
 - Clinical difficulty lies in symptom overlap between ADHD and PBD
 - Generally, around 60-90% of PBD patients will have comorbid ADHD (59)
 - But, found that it was ~ 90% in children, and ~ 57% in adolescents (59)
 - Furthermore, in adults with BD, there was only a high chance of comorbid ADHD if onset of BD was in adolescence or earlier
 - I.e., age of onset of first manic episode may be the indicator for the form with high comorbidity with ADHD (59).

(59) Biederman J, Mick E, Faraone SV, Spencer T, Wilens TE, Wozniak J. Pediatric mania: a developmental subtype of bipolar disorder? *Biol Psychiatry* 2000 Sep 15;48(6):458-66.

Bipolar Disorder

- Heritability Data for adults is well known:
 - Established familial/heritability for decades now (60).
 - Risk in Siblings of Adults with BPAD: 5-10% (61)
 - Heritability risk: 0.8-0.9 (61)
- Data for child BPAD is sparse:
 - There are studies but methodology is poor – histories based on collaterals rather than clinical diagnostic interviews.
 - Lots of studies looked only at comorbid mood disorders in relatives
 - Comorbidity in a well-designed recent large (n=455, three groups: BPAD, ADHD, Control) familial sample examining risk of psychiatric illness among families of pediatric BPAD patients, showed: (62)
 - Risk of BPAD 4x higher in families of BPAD child compared to controls
 - Risk of BPAD is 3.5x higher in families of BPAD child compared to ADHD group
 - i.e., families of children with BPAD are at significantly higher risk of developing BPAD than the risk of them developing BPAD if they child has ADHD (or not, i.e., the control group).
 - BUT, the BPAD group had high (~85%) ADHD comorbidity.
 - Suggestion: there is a shared affective component in some of those with ADHD which is heritable?

- (60) Faraone SV, Glatt SJ, Tsuang MT. The genetics of pediatric-onset bipolar disorder. *Biol Psychiatry* 2003 Jun 1;53(11):970-7.
- (61) Craddock N, Forty L. Genetics of affective (mood) disorders. *Eur J Hum Genet* 2006 Jun;14(6):660-8.
- (62) Wozniak J, Faraone SV, Mick E, Monuteaux M, Coville A, Biederman J. A controlled family study of children with DSM-IV bipolar-I disorder and psychiatric comorbidity. *Psychol Med* 2009 Nov 6;1-10.

Bipolar Disorder

- Irritability is a common symptom to both: (63-65)
 - BPAD and controls display generally the same behaviour, affect, EEG/ERP responses on standard attention task
 - When a frustration task introduced for negative feedback, became BPAD youth showed altered attention (slower reaction time, negative affect, reduced P300 amplitude which was an index of attention).
 - Same group then studied with MEG, theta band (4-8Hz), anterior cingulate cortex: Theta band power in front-midline areas like AAC thought to be indicative of attention, emotional processing and self-monitoring.
 - Interesting result: *"Our MEG results indicated that, in response to frustration inducing negative feedback, BD youth displayed greater theta power relative to controls in the right ACC and bilateral parietal lobe (i.e. left IPL and right SPL). In contrast, compared to BD youth, controls displayed greater left ACC theta power after positive feedback, with a trend in the same direction in the right ACC."*
 - Also suggested that positive factors to influence affect response may be filtered out
 - There were also problems with the study: high ADHD comorbidity (12 of the total 20 participants) although analysis suggested not a problem), the BPAD without anxiety did not display IPL changes, etc.,

- (63) Rich BA, Schmajuk M, Perez-Edgar KE, Pine DS, Fox NA, Leibenluft E. The impact of reward, punishment, and frustration on attention in pediatric bipolar disorder. *Biol Psychiatry* 2005 Oct 1;58(7):532-9.
- (64) Rich BA, Schmajuk M, Perez-Edgar KE, Fox NA, Pine DS, Leibenluft E. Different psychophysiological and behavioral responses elicited by frustration in pediatric bipolar disorder and severe mood dysregulation. *Am J Psychiatry* 2007 Feb;164(2):309-17.
- (65) Rich BA, Holroyd T, Carver FW, Onelio LM, Mendoza JK, Cornwell BR, et al. A preliminary study of the neural mechanisms of frustration in pediatric bipolar disorder using magnetoencephalography. *Depress Anxiety* 2009 Dec 27.

Bipolar Disorder

• Clinical diagnostic issues:

- American study (n=107) of adults with ADHD: 20 with comorbid BPAD (I and II), almost half (45%) of combined ADHD group (n=66) had ODD (66). But, criteria used for adult diagnosis are based on child “6 of 9” criteria – the study group acknowledged it therefore represents the more severe types of ADHD.
- In Wilens’ 2009 study, you can see the clear dominance of inattentive symptoms. (*Figure 1: Presenting DSM-IV Symptoms....*)

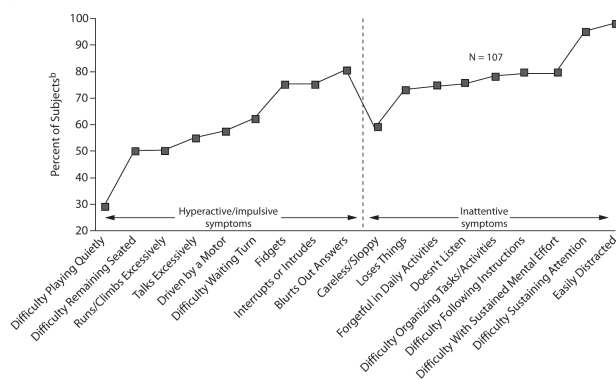
• Motor Function:

- Norwegian study (n=64) of ages 6-18 meeting DSM-IV criteria for BPAD, ADHD or ADHD+BPAD (67)
 - ADHD(C) and ADHD+BPAD group showed significantly more neurological soft signs compared to BPAD group.

(66) Wilens TE, Biederman J, Faraone SV, Martelon M, Westerberg D, Spencer TJ. Presenting ADHD symptoms, subtypes, and comorbid disorders in clinically referred adults with ADHD. *J Clin Psychiatry* 2009 Nov;70(11):1557-62.

(67) Udal AH, Malt UF, Lovdahl H, Gjaerum B, Pripp AH, Groholt B. Motor function may differentiate attention deficit hyperactivity disorder from early onset bipolar disorder. *Behav Brain Funct* 2009;5:47.

Figure 1. Presenting DSM-IV Symptoms in a Clinical Sample of Adults With ADHD^a



^aEndorsed symptoms were reported by adults with ADHD through structured clinical interviews.

^bData are presented as percentage of subjects endorsing each DSM-IV-specific symptom of ADHD.

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition.

Bipolar Disorder

- Neuropsychological Overlap:
 - Generally reported ADHD, PBD have similar deficits
 - Motor function is increased in ADHD and Mania, but may be reduced in Depressive phase of PBD – an indicator?
 - A study (USA) (n=64) on NEAs showed: (69)
 - ADHD: impaired repetitive motor tasks
 - PBD: impaired sequential motor tasks (with or without comorbid ADHD)
 - PBD have deficits in cognitive flexibility, sustained attention and verbal working memory, independent of illness status
 - ADHD patients exhibit deficits in executive functions, attention, vigilance, working memory, planning and response inhibition

(69) Dickstein DP, Garvey M, Pradella AG, Greenstein DK, Sharp WS, Castellanos FX, et al. Neurologic examination abnormalities in children with bipolar disorder or attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2005 Oct 1;58(7):517-24.

Bipolar Disorder

- Brain overlap between ADHD + PBD : (70)
 - fMRI study (USA) with n=41 and three arms (PBD, ADHD, Control, all untreated) on response inhibition
 - Task was inhibition of a motor response when a stop cue presented
 - Both ADHD, PBD had impaired PFC function
 - But only ADHD showed deficit in DLPFC and VLPFC
 - DLPFC is part of a system to select and suppress motor responses
 - VLPFC is involved in interference suppression
 - ADHD group exhibited increased bilateral caudate and left cerebellar activation,
 - PBD group showed decreased activation in a left ventrolateral prefrontal region at the junction of BA 46/47/10, and in right pregenual ACC
 - I.e., similar behavioural problem but different underlying pathophysiology
 - I.e., fronto-striatal region is definitely implicated in the neurobiology of ADHD
 - ADHD: Dorso-frontal-striatal for cognitive (inattention) and motor (hyperactivity); bilateral VLPFC for response inhibition deficit
 - PBD: left VLPFC localised dysfunction (junction of inferior and middle frontal gyri) and ventral right ACC dysfunction for response inhibition deficit

(70) Passarotti AM, Sweeney JA, Pavuluri MN. Neural correlates of response inhibition in pediatric bipolar disorder and attention deficit hyperactivity disorder. *Psychiatry Res* 2010 Jan 30;181(1):36-43.

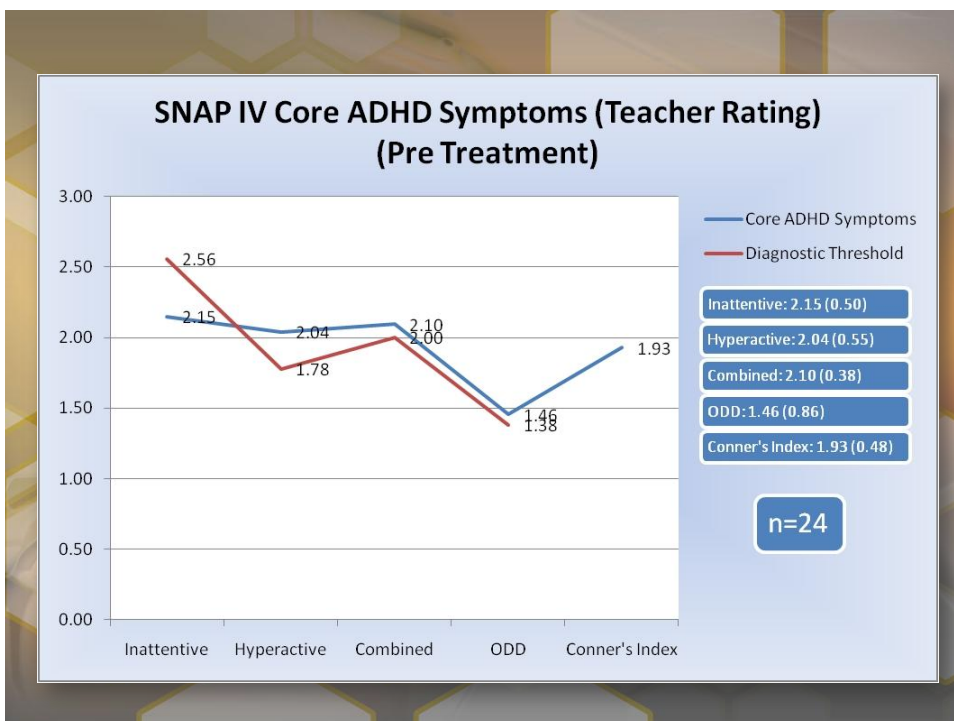
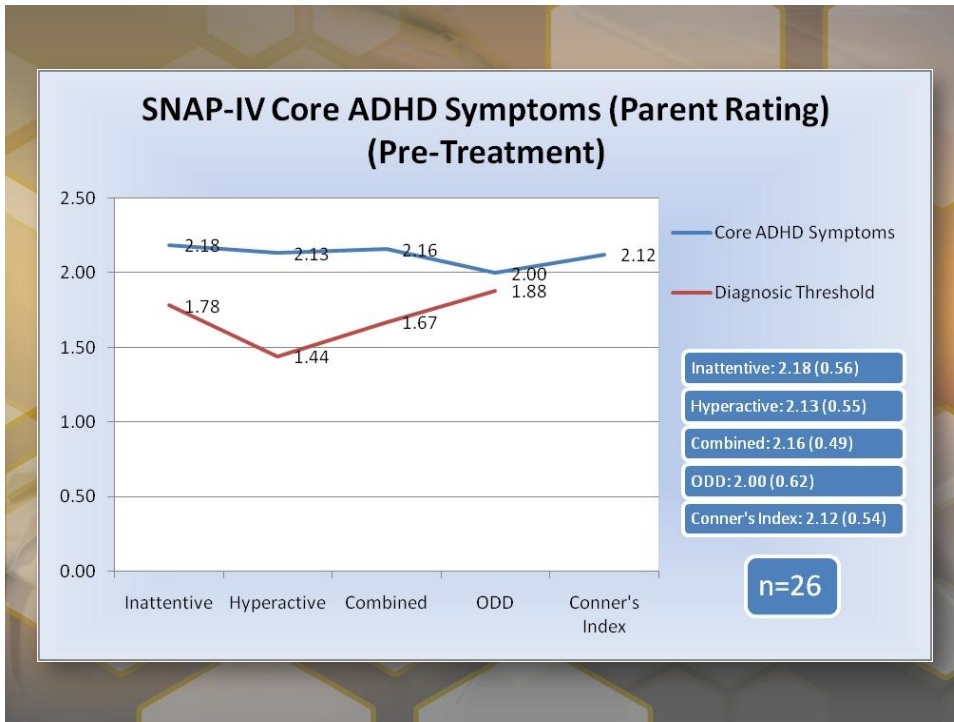
Bipolar Disorder

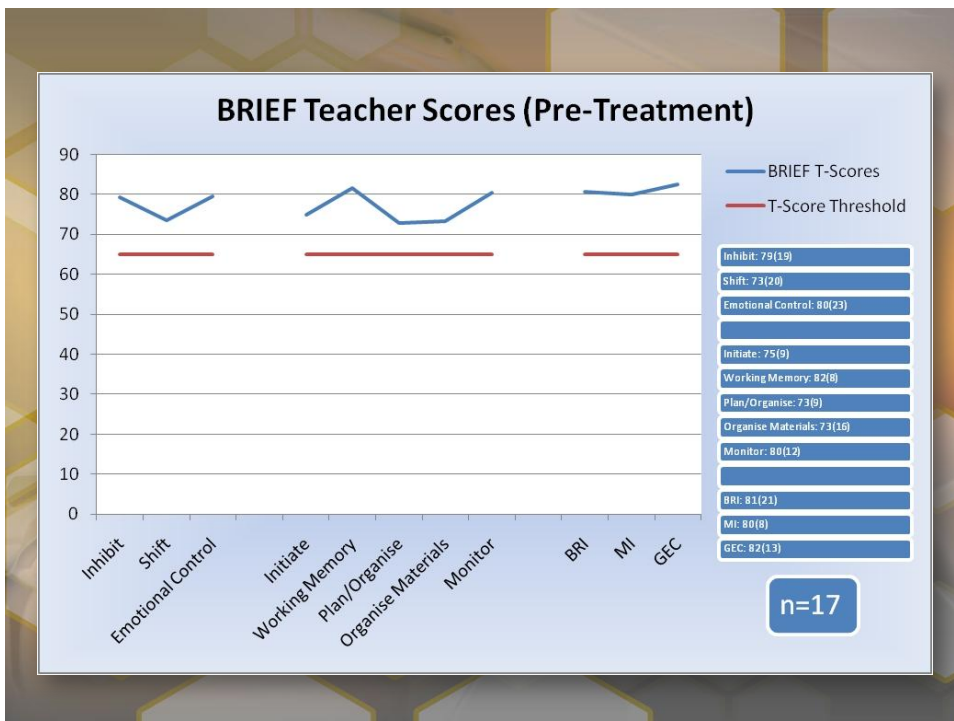
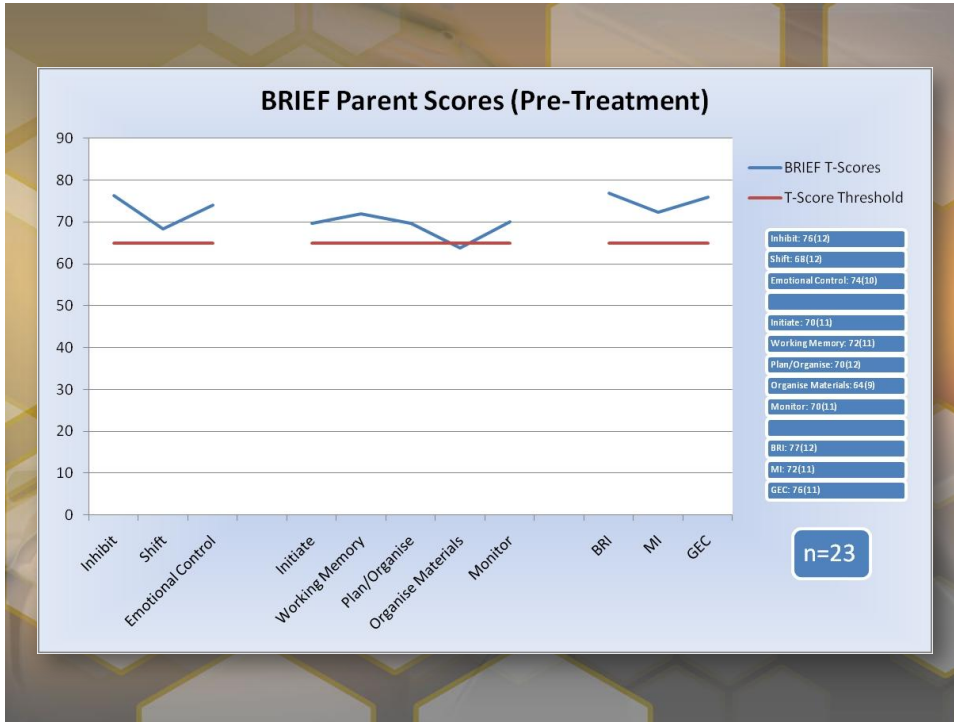
- A study also reported left-amygdala hyperactivity in ADHD when reporting fear of neutral faces vs. Left-amygdala hypoactivation for those with just mood dysregulation (71).

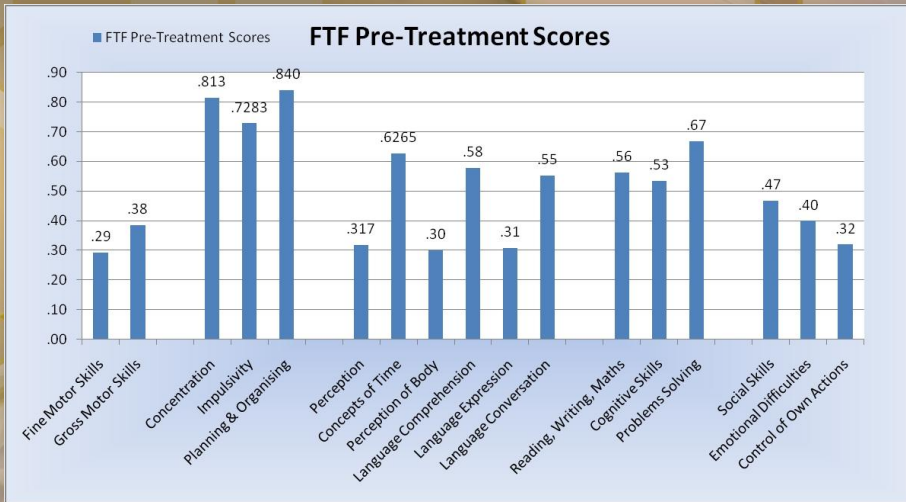
(71) Brotman MA, Rich BA, Guyer AE, Lunsford JR, Horsey SE, Reising MM, et al. Amygdala activation during emotion processing of neutral faces in children with severe mood dysregulation versus ADHD or bipolar disorder. *Am J Psychiatry* 2010 Jan;167(1):61-9.

Part 7

Pre-Treatment Scales







The End!