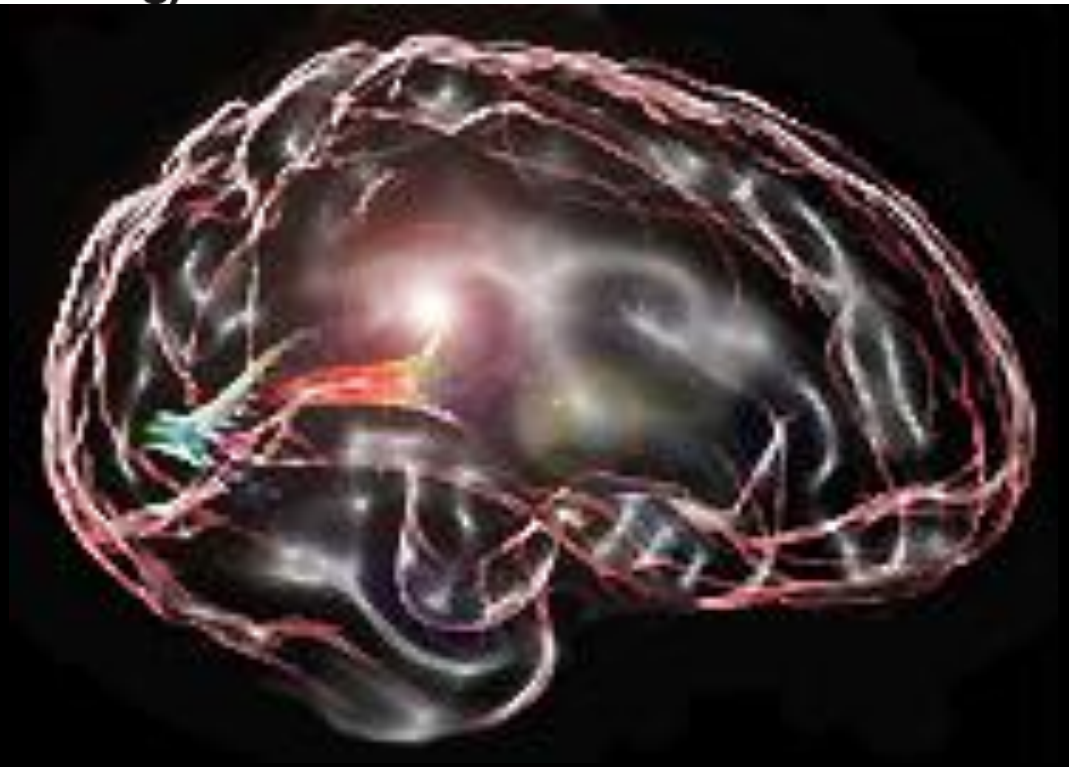
THE UNIVERSITY OF AUCKLAND
FACULTY OF SCIENCE
School of Psychology

CENTRE FOR BRAIN RESEARCH
THE UNIVERSITY OF AUCKLAND
Te Whare Wānanga o Tāmaki Makaurau



Genes, environment and cognitive training in ADHD

A/Prof Karen E Waldie, PhD

ADHD Awareness Day, Sunday 30 Oct, Ellerslie Events Centre

Developmental disorders: A group of conditions identified in childhood that involve serious impairment in different areas

Dyslexia: phonological awareness

Dyscalculia: number sense

ADHD: executive functioning

ASD: social awareness

My research: Cognitive and biological markers; comorbidity

- Outline:
  1. Genes, environment (neuroplasticity) and early brain development
  2. Genes, environment and ADHD
  3. New remediation programme

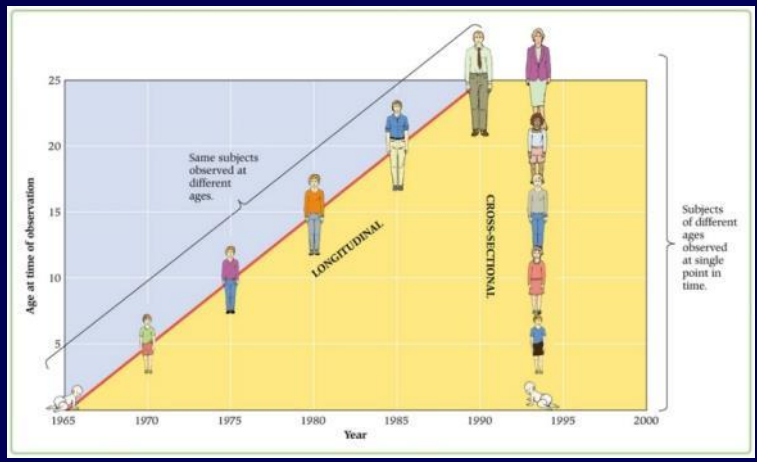
My background: longitudinal research

The Relationship Between Learning Disabilities and Persisting Delinquency

Karen Waldie and Otfried Spreen

Recidivism of delinquency in juveniles with learning disabilities (LD), the focus of the present study, has been virtually unexplored in previous research. Data from a longitudinal study initiated in 1978 are examined. Sixty-five subjects with LD (47 males and 18 females) who had been diagnosed and assessed between the ages of 8 and 12 years were located and, during a personal structured interview at the median age of 18 years, reported police contact. This population was subdivided into two groups on the basis of whether police contact had continued or discontinued, as reported in a second personal interview at the age of 25 years. Discriminant analysis on parent and subject variables correctly classified 75% of the subjects and revealed that certain personality characteristics, such as impulsivity and poor judgment, discriminate between persisting and nonpersisting delinquency in youth with learning disabilities.

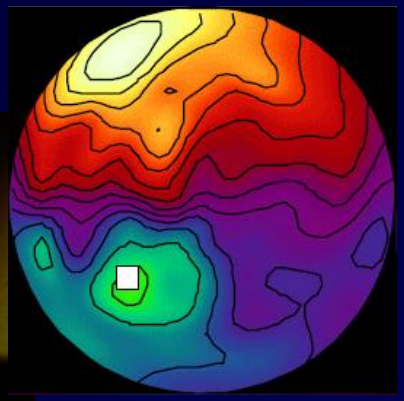
Journal of Learning Disabilities, 26(6), 1993, 417-23.



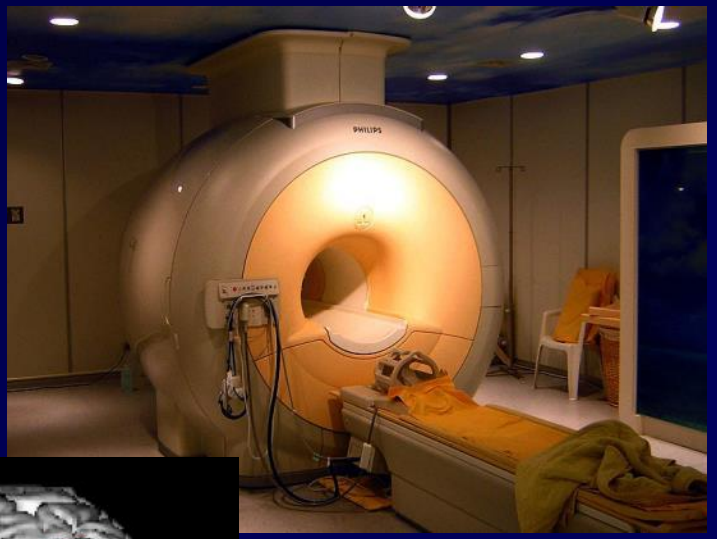
1. DMHDS
2. ABC Study
3. Growing Up in NZ (www.growingup.co.nz)

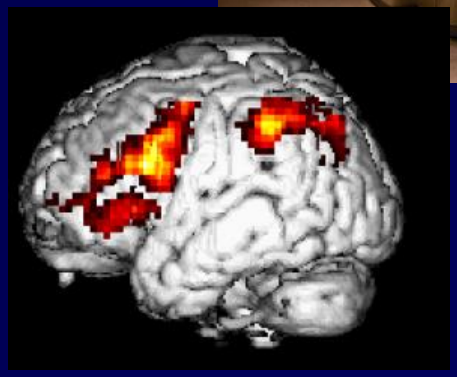
Modern brain imaging methods

In the last 20 years, the field of cognitive neuroscience has developed non-invasive methods for studying healthy human brains in action, in adults and now children.



Electro-encephalography (EEG)





Functional magnetic resonance imaging (fMRI)

My background: brain scanning

CENTRE FOR Advanced MRI

fMRI allows us to map increases in oxygenated blood flow that accompany local brain activity during mental tasks

1. Neuroplasticity (gene-environment)

General introduction

My 1st developmental psychology lectures:

1. Born with 100 billion brain cells
2. Following ~ the first 3 years of life the brain was relatively static

- neurogenesis occurs in humans up to 72 years of age
- stress inhibits neurogenesis
- environmental enrichment enhances neurogenesis

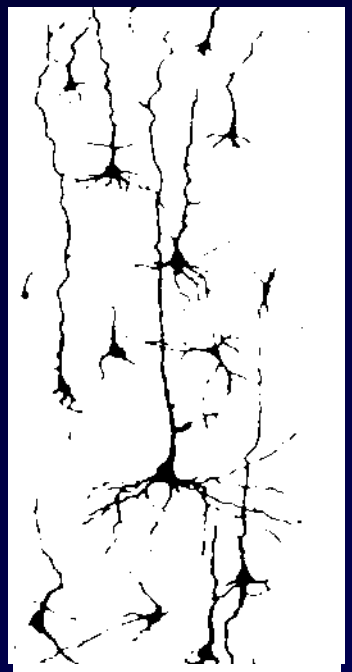
– The capacity of the brain to rewire through experience

1. Neuroplasticity

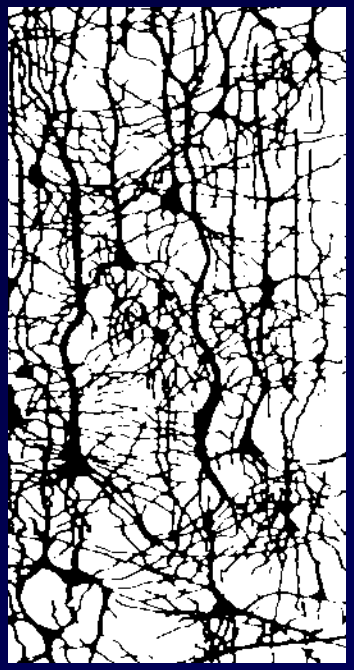
Progressive synapse elimination:

- Brain cells make connections (dendrites, synapses), then prune those which are not used. This process continues into adulthood

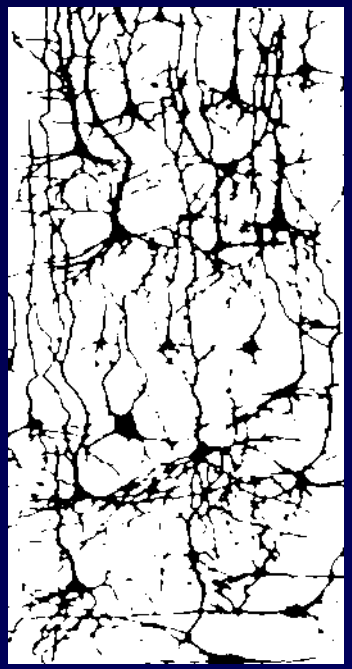
Gabel et al. (2010), Neurobiology of disease



Birth



6 yrs



14 yrs

1. Neuroplasticity

Responsiveness to experiences:

- <u>Can be negative</u>
  - Vulnerable to damage
  - Antenatal maternal perceived stress, smoking
  - Gene x environment

ACTA PÆDIATRICA
NURTURING THE CHILD

Acta Paediatrica ISSN 0803-5253

REGULAR ARTICLE

Maternal stress during pregnancy is associated with moderate to severe depression in 11-year-old children

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Keywords
Child depression, Maternal stress during pregnancy, Risk factors

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DOI:10.1111/apa.12787

ABSTRACT

Aim: Maternal stress during pregnancy has been associated with negative outcomes in children. We examined the risk factors for symptoms of depression in 11-year-old children, including the interaction between birthweight and other variables.

Methods: We collected maternal, obstetric and demographic information from birth through to the age of 11. Approximately, half of the 609 children were born small-for-gestational-age (SGA). Information collected at 3.5 and 7 years of age included intelligence testing and parent-reported behavioural and emotional development. At 11 years of age, the children completed the Center for Epidemiological Studies Depression Scale for Children. Multivariable logistic regression analysis examined the relationship between self-reported symptoms of moderate to severe depression at the age of 11 and explanatory variables.

Results: Symptoms of moderate to severe depression were related to increasing maternal stress during pregnancy, young maternal age, lower intelligence test scores at 7-years-old and being bullied at school in the previous 6 months. There was also a significant interaction between maternal stress in pregnancy and symptoms of depression in 11-year-old children born SGA.

Conclusion: Increasing maternal stress during pregnancy was associated with increased risk of symptoms of moderate to severe depression in 11-year-old children, especially those who were born SGA.

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journal homepage: www.elsevier.com/locate/jad

Research paper

Environmental and genetic determinants of childhood depression: Th roles of *DAT1* and the antenatal environment

Stephanie D'Souza[a], John M.D. Thompson[b], Rebecca Slykerman[b], Gareth Marlow[c], Clare Wall[c], Rinki Murphy[d], Lynnette R. Ferguson[c], Edwin A. Mitchell[b], Karen E. Waldie[a]

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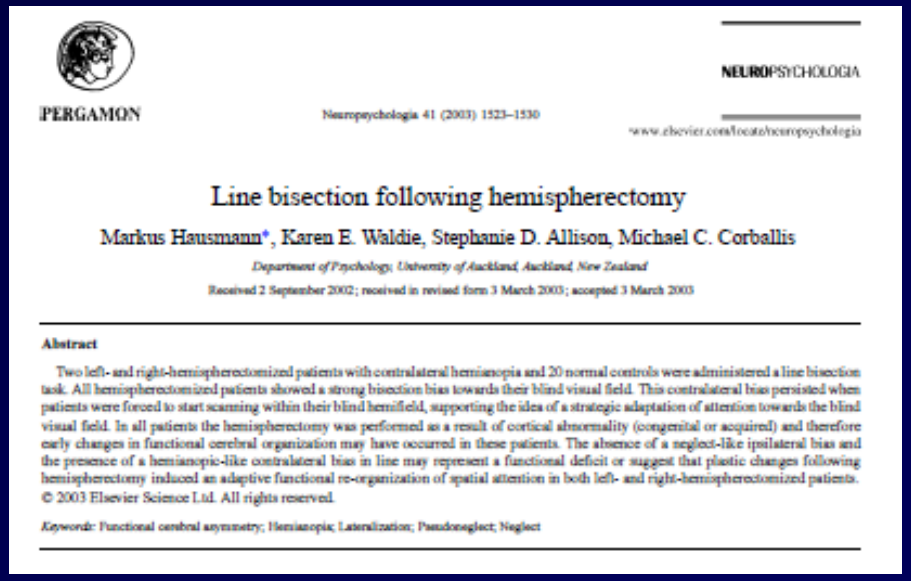
Keywords:
BDNF
IQ
Genotype
Gene–environment
Maternal smoking

Maternal smoking in pregnancy has been separately linked with both lower IQ scores and epigenetic modifications of the brain-derived neurotrophic factor (BDNF) gene in offspring. The purpose of this study was to investigate whether maternal smoking exposure interacts with the BDNF single nucleotide polymorphism (SNP) rs6265 to affect offspring IQ across multiple ages during childhood. Participants are 546 members of a longitudinal study of 871 Caucasian infants sampled disproportionately for small for gestational age: approximately half had birthweight <10th percentile when delivered at term. Perinatal events assessed here were birthweight, maternal school leaving age, and exposure to maternal smoking in-utero. Childhood factors assessed were gender, BDNF, and IQ measured at ages 3.5, 7 and 11 years (repeated measures outcome). We found a significant interaction between rs6265 genotype and maternal smoking in pregnancy on IQ scores, controlling for birthweight. IQ scores of Met-BDNF carriers were significantly lower when mothers smoked during pregnancy (over 8 IQ points) compared to when they did not. This was of borderline statistical significance when maternal school leaving age was controlled ($p = 0.052$).

1. Neuroplasticity

Responsiveness to experiences:

- Can be negative:
  - Vulnerable to damage
  - Antenatal maternal perceived stress, smoking
  - Gene x environment
- Can be positive:
  - Aids in recovery from brain damage/injury (e.g., hemispherectomy)



PERGAMON

Neuropsychologia 41 (2003) 1523–1530

NEUROPSYCHOLOGIA

www.elsevier.com/locate/neuropsychologia

Line bisection following hemispherectomy

Markus Hausmann*, Karen E. Waldie, Stephanie D. Allison, Michael C. Corballis

Department of Psychology, University of Auckland, Auckland, New Zealand

Received 2 September 2002; received in revised form 3 March 2003; accepted 3 March 2003

Abstract

Two left- and right-hemispherectomized patients with contralateral hemianopia and 20 normal controls were administered a line bisection task. All hemispherectomized patients showed a strong bisection bias towards their blind visual field. This contralateral bias persisted when patients were forced to start scanning within their blind hemifield, supporting the idea of a strategic adaptation of attention towards the blind visual field. In all patients the hemispherectomy was performed as a result of cortical abnormality (congenital or acquired) and therefore early changes in functional cerebral organization may have occurred in these patients. The absence of a neglect-like ipsilateral bias and the presence of a hemianopic-like contralateral bias in line may represent a functional deficit or suggest that plastic changes following hemispherectomy induced an adaptive functional re-organization of spatial attention in both left- and right-hemispherectomized patients.

Keywords: Functional cerebral asymmetry; Hemianopia; Lateralization; Pseudoneglect; Neglect

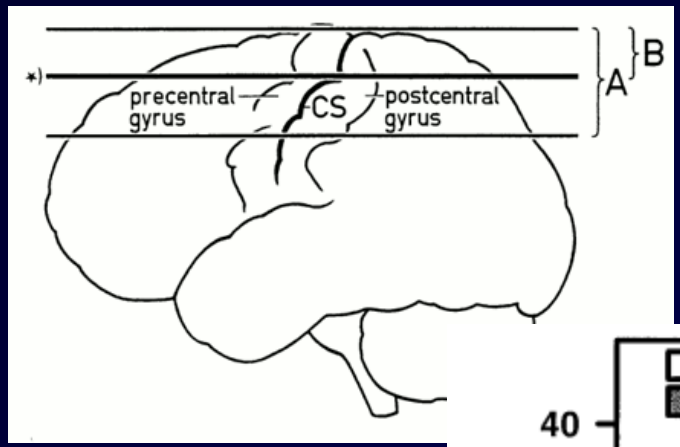
1. Neuroplasticity

Responsiveness to experiences:

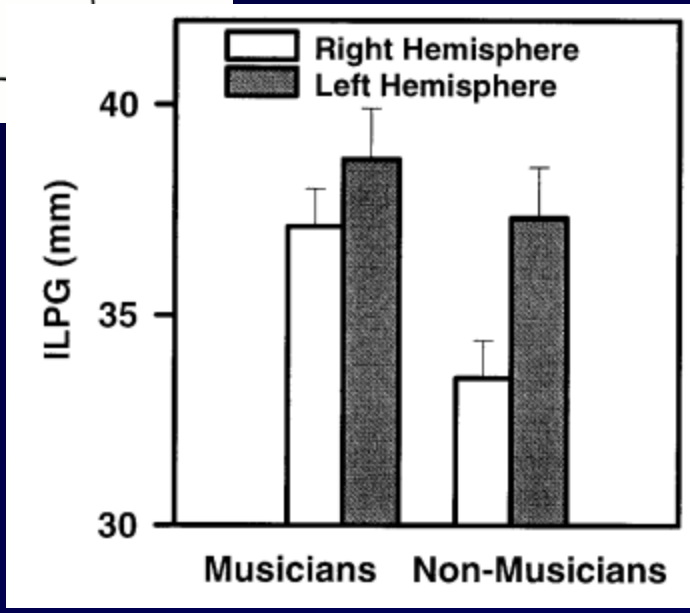
- Can be negative:
  - Vulnerable to damage
  - Antenatal maternal perceived stress, smoking
  - Gene x environment
- Can be positive:
  - Aids in recovery from brain damage/injury (e.g., hemispherectomy)
  - Can benefit from stimulation (e.g., playing a musical instrument; learning a new language; cognitive intervention)

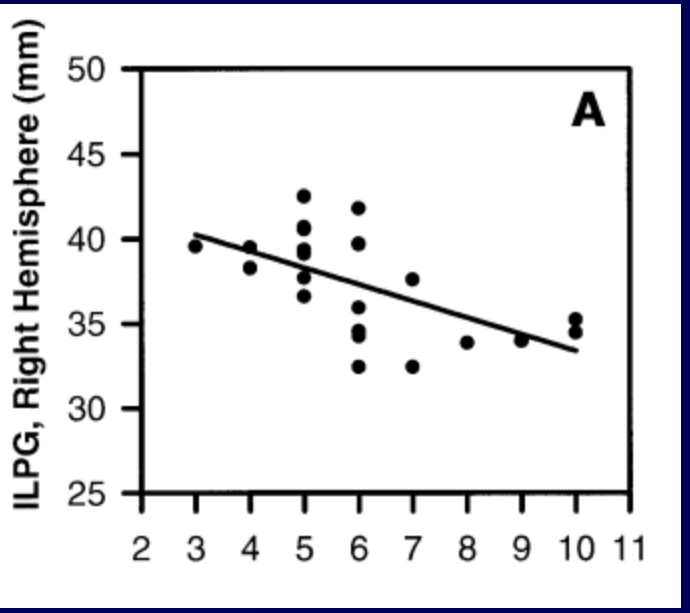
1. Neuroplasticity

Playing a musical instrument:



- Right motor cortex in musicians is expanded in size
- The earlier they started learning – the bigger!





Amunts et al. (1997), *Human Brain Mapping*

1. Neuroplasticity

Learning a new language:

Neuropsychologia 50 (2012) 688–695

Contents lists available at SciVerse ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Language lateralisation in late proficient bilinguals: A lexical decision fMRI study

Haeme R.P. Park, Gjurgjica Badzakova-Trajkov, Karen E. Waldie*

Research Centre for Cognitive Neuroscience, Department of Psychology, The University of Auckland, Auckland, New Zealand

ARTICLE INFO

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Neuroimaging
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L2
Monolingual

ABSTRACT

Approximately half the world's population can now speak more than one language. Understanding the neural basis of language organisation in bilinguals, and whether the cortical networks involved during language processing differ from that of monolinguals, is therefore an important area of research. A main issue concerns whether L2 (second language) is processed using the same neural mechanisms that mediate L1 (first language) processing. Moderating factors include the age of L2 acquisition and the level of proficiency. Here we used a lexical decision task with five conditions during functional magnetic resonance imaging (fMRI) to investigate language processing in eight late proficient bilinguals when using Macedonian (L1) and English (L2). Bilinguals had greater bilateral activation during both L1 and L2 processing, and therefore weaker language lateralisation, compared to matched control English monolinguals. A greater amount of overall activation was also seen in bilinguals, especially during L2 conditions. Late proficient bilinguals living in their L2 environment employ a more extensive neural network than monolinguals when processing their second language.

1. Neuroplasticity

Responsiveness to experiences:

- Can be negative:
  - Vulnerable to damage
  - Antenatal maternal perceived stress, smoking
  - Gene x environment
- Can be positive
  - Aids in recovery from brain damage/injury (e.g., hemispherectomy)
  - Can benefit from stimulation (e.g., playing a musical instrument; learning a new language; cognitive intervention)
  - Can compensate when areas are not functioning optimally

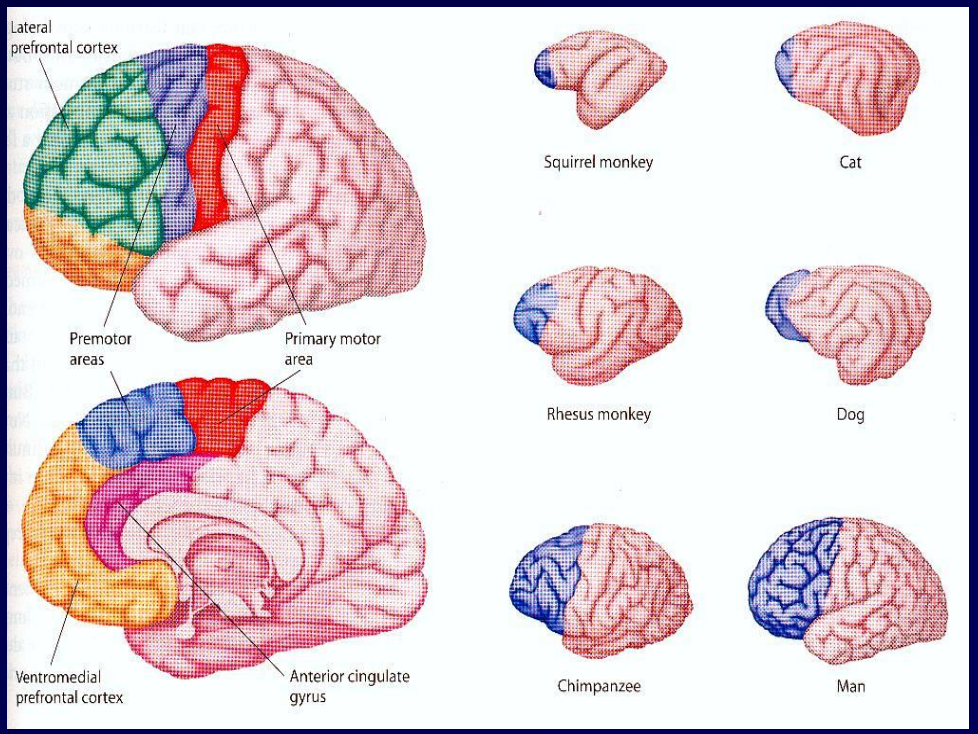
Bottom line: Allows for *adaptability*

2. Neuroplasticity and ADHD

ADHD and the frontal lobe:

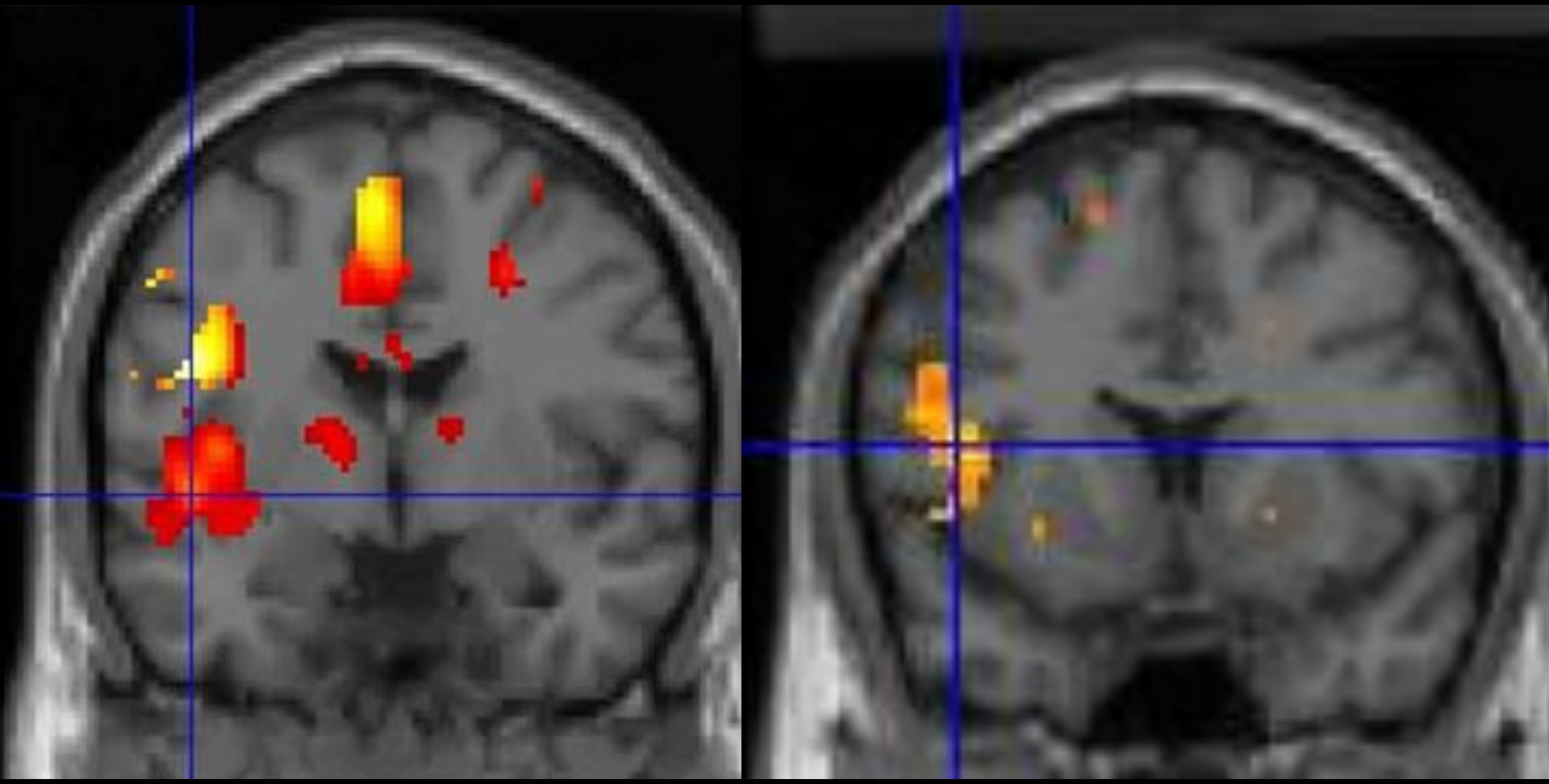
Frontal lobe under-activity

- Reduced size / density (MRI)
- Decreased blood flow (activation) during executive tasks (PET, fMRI)



2. Neuroplasticity

ADHD and the frontal lobe:



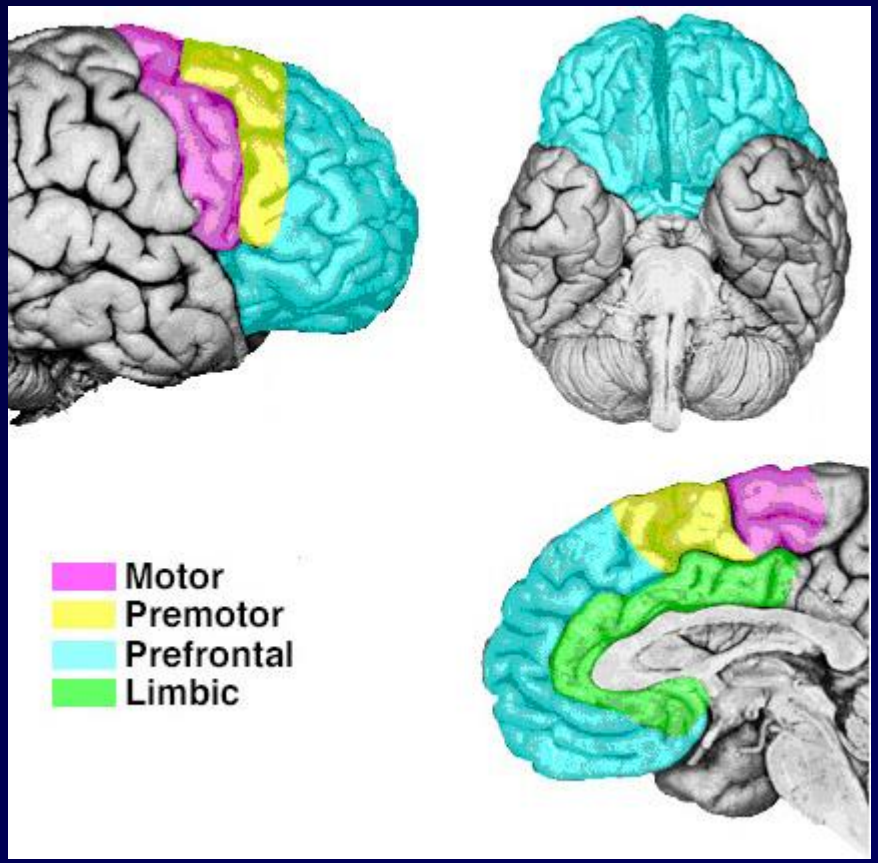
Due to a genetic impairment in neurotransmitter metabolism

2. Neuroplasticity

ADHD and the frontal lobe:

Executive functions:

- Planning
- Inhibition
- Response selection
- Top-down allocation of attention
- Regulation of emotion
- Working memory

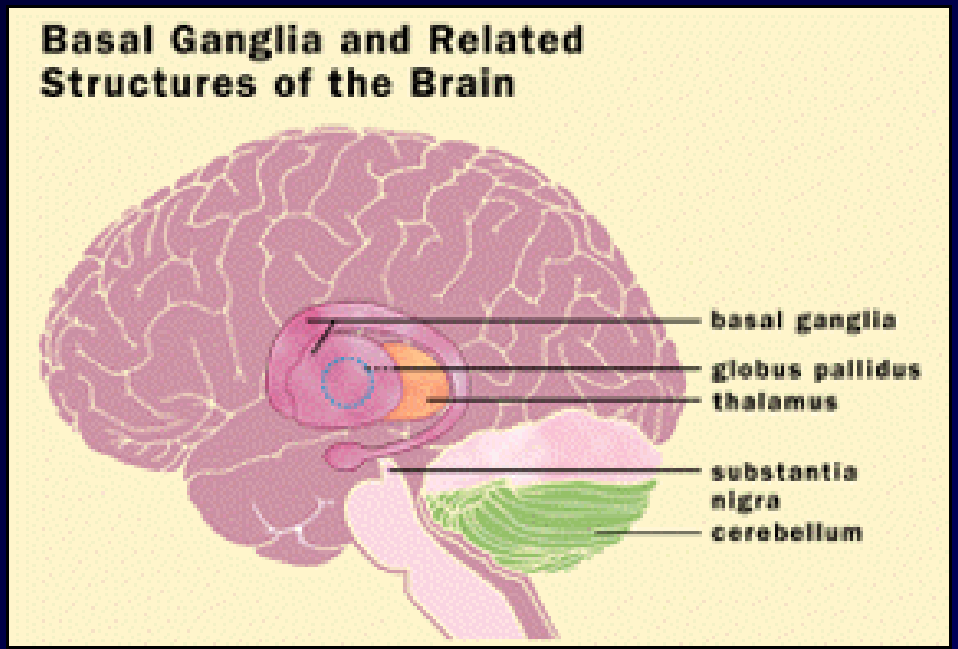


2. Neuroplasticity

ADHD and the frontal lobe:

Frontal lobe under-activity

- Frontal cortex has the most connections
- Fronto-striatal pathway inadequate in ADHD



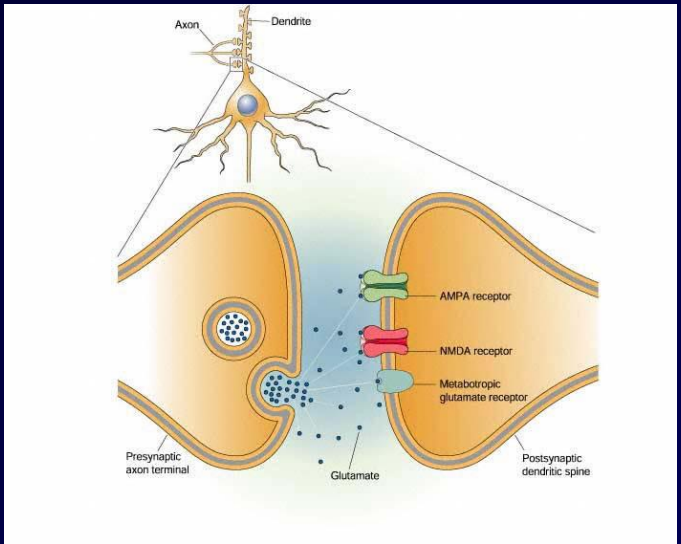
= Inattention and failure to inhibit motor responses

2. Neuroplasticity

ADHD and the frontal lobe:

- These areas under-active because of neurotransmitter depletion (faulty metabolism of dopamine and/or norephinephrine at the synapse)

  = poor transmission of neural impulses in fronto-striatal pathway



Neurocase (2007) **13**, 301–310
http://www.psypress.com/neurocase
ISSN: 1355-4794 print / 1465-3656 online
DOI: 10.1080/13554790701770850

Psychology Press

Dexamphetamine Normalises Electrophysiological Activity in Attention Deficit-Hyperactivity Disorder during the Stroop Task

S. L. HORROBIN, N. A. McNAIR, I. J. KIRK and K. E. WALDIE

Department of Psychology, Research Centre for Cognitive Neuroscience, University of Auckland, Auckland, New Zealand

A case study was conducted to investigate whether dexamphetamine enhances interference control in an adult with attention deficit/hyperactivity disorder. Continuous electroencephalography was recorded both on and off dexamphetamine during performance on a Stroop task. An age-, gender- and IQ-matched control also completed the same task. Event related potentials for the control participant revealed a positive potential to incongruent stimuli between 270 and 440 ms, whereas for the participant with attention deficit/hyperactivity disorder off medication, the reverse polarity was observed in a later time window. Following administration of dexamphetamine, however, the event-related potentials for the incongruent condition closely resembled those in the control, suggesting that dexamphetamine successfully normalises electroencephalographic activity.

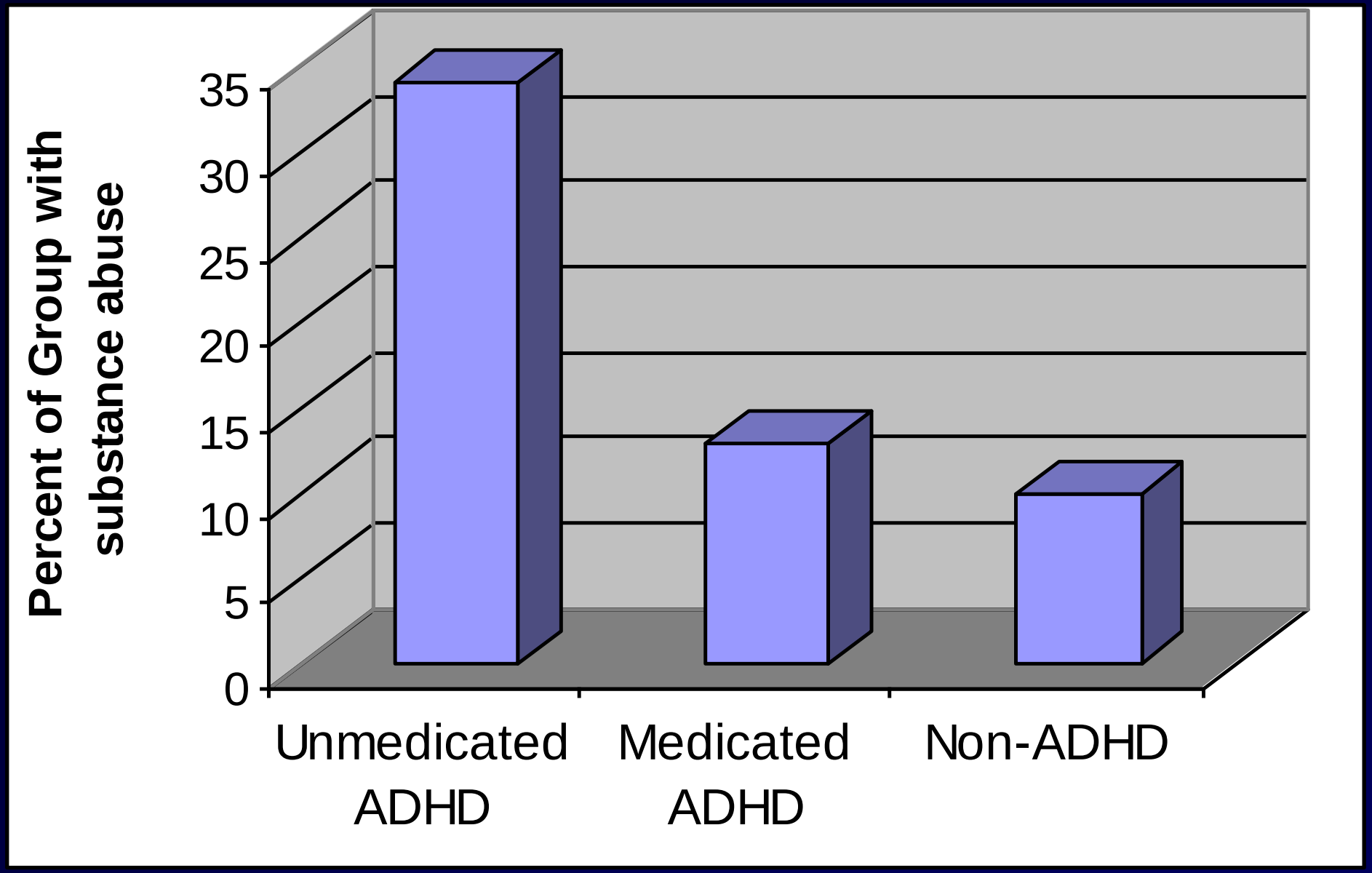
Challenge: non-pharmaceutical intervention to normalize the frontal lobe (see: http://movincog.org/)

Long-term safety?

Medicine must have the following characteristics:

1. Has been used for a long time
2. Many individuals have taken it for extended periods of time
3. Has a high public profile
4. Individuals who take it are regularly examined

See: Long-term stimulant treatment of ADHD: results from a population-based study. *Journal of Developmental & Behavioral Pediatrics*, 2006, 27, 1-17.



Treatment with Ritalin reduces substance abuse in ADHD (from Biederman, et al., *Pediatrics*, 1999)

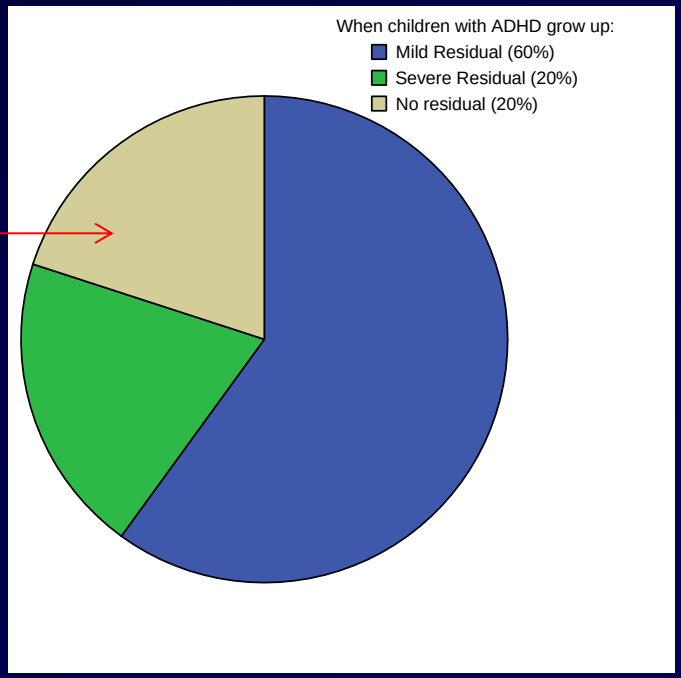
2. Neuroplasticity

ADHD and developmental course:

20% completely outgrow ADHD after ~ 18 years of age

- 80% will not: 60% mild residual, 20% severe residual

Why?



Impossible to complete projects, procrastination, ‘tune out’, difficult to relax, frustration, organization, addiction, verbal impulsivity, spend $, poor memory, risks…

Risk Factors

Genetic Defects

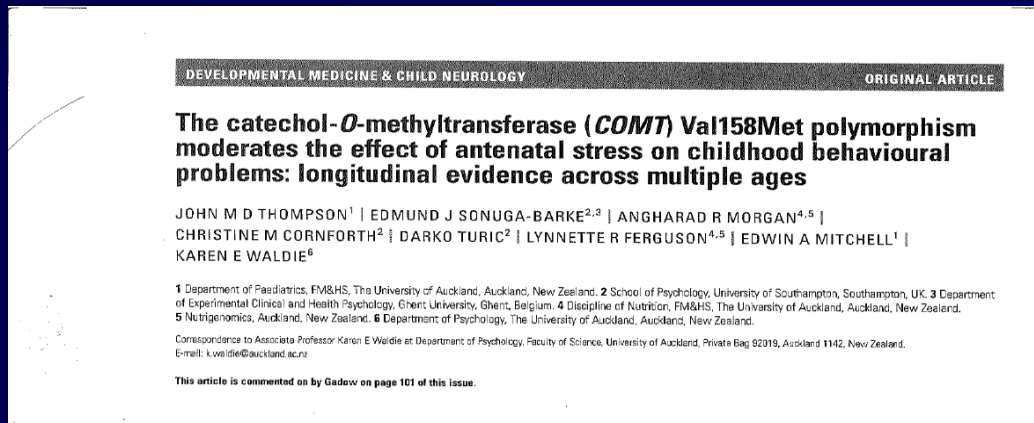
Concordance rates: if one identical twin has it, the other will too:

Ranges from 70-90%

- ADHD genes are common in the general population. When genes from both parents combine – additive effect to cause condition

If genetic susceptibility:

- Low birth weight, Adverse environment,
- Smoking/alcohol during pregnancy
- Stress during pregnancy



DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY ORIGINAL ARTICLE

The catechol-*O*-methyltransferase (*COMT*) Val158Met polymorphism moderates the effect of antenatal stress on childhood behavioural problems: longitudinal evidence across multiple ages

JOHN M D THOMPSON[1] | EDMUND J SONUGA-BARKE[2,3] | ANGHARAD R MORGAN[4,5] | CHRISTINE M CORNFORTH[2] | DARKO TURIC[2] | LYNNETTE R FERGUSON[4,5] | EDWIN A MITCHELL[1] | KAREN E WALDIE[6]

1 Department of Paediatrics, FM&HS, The University of Auckland, Auckland, New Zealand. **2** School of Psychology, University of Southampton, Southampton, UK. **3** Department of Experimental Clinical and Health Psychology, Ghent University, Ghent, Belgium. **4** Discipline of Nutrition, FM&HS, The University of Auckland, Auckland, New Zealand. **5** Nutrigenomics, Auckland, New Zealand. **6** Department of Psychology, The University of Auckland, Auckland, New Zealand.

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This article is commented on by Gadow on page 101 of this issue.

Some examples of other “ADHD genes”

Gene	Effect of the gene
• Dopamine transporter gene (DAT1 gene*)	• Excessive re-absorption of dopamine by nerve
• Dopamine receptor D4 gene (DRD4 gene*)	• Blunted response to dopamine by receptor (“novelty-seeking gene”)
• Dopamine beta-hydroxylase	• Decreased dopamine synthesis
• DOPA decardoxylase gene	• Reduced amount of dopamine stored in vesicles
• Adrenergic $_{2A}$ receptor gene	• Blunted response to norepinephrine by receptor

*most studied; DRD4 is longer than normal

Comorbidity

- The tendency of a condition to co-exist with another
- From med term “morbidity”: the proportion of people having a particularly disorder (vs. mortality)

Conditions that are more common in ADHD

- Tic disorder
- Dyslexia
- Asperger syndrome
- Depression
- Anxiety disorder
- Obsessive compulsive disorder
- Bipolar disorder
- Oppositional disorder
- Conduct disorder

Severity of defiant behaviour

Oppositional disorder (20-25%)

- Milder form of conduct disorder
- 25% w ADHD “Jekyll and Hyde” – every discussion is an argument. Time out? Destroy possessions

Conduct Disorder (7%)

- problems attract a greater degree of social disapproval – often results in law-breaking

"passionate, deviant, spiteful, and lacking inhibitory volition"

Country	Prevalence	Age
NZ	7%	11
USA	8%	6-9
Canada	6%	4-16
Puerto Rico	9%	4-16
UK	5%	6-8
Hong Kong	9%	7

Has become the *most* studied developmental disorder in childhood

Research Article

Hemispheric Coherence in ASD with and without Comorbid ADHD and Anxiety

A. Saunders, I. J. Kirk, and K. E. Waldie

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Correspondence should be addressed to K. E. Waldie; k.waldie@auckland.ac.nz

Received 14 December 2015; Accepted 6 March 2016

Academic Editor: Eiji Kirino

There is a growing body of evidence suggesting that altered brain connectivity may be a defining feature of disorders such as autism spectrum disorder (ASD), anxiety, and ADHD. This study investigated whether resting state functional connectivity, measured by 128-channel EEG oscillation coherence, differs between developmental disorders. Analyses were conducted separately on groups with and without comorbid conditions. Analyses revealed increased coherence across central electrodes over the primary motor cortex and decreased coherence in the frontal lobe networks in those with ASD compared to neurotypical controls. There was increased coherence in occipital lobe networks in the ADHD group compared to other groups. Symptoms of generalised anxiety were positively correlated with both frontal-occipital intrahemispheric (alpha only) coherence and occipital interhemispheric coherence (alpha, approaching theta band). The patterns of coherence in the ASD pure group were different when comorbid conditions were included in the analyses, suggesting that aberrant coherence in the frontal and central areas of the brain is specifically associated with ASD. Our findings support the idea that comorbid conditions are additive, rather than being symptoms of the same disorder.

Summary

Developing critical consumers

- Community outreach from Centre for Brain Research
- More neuroscience / psychology in teacher training
- Debunking neuromyths

Next steps:

- Understanding the limits of plasticity
  - Earlier instruction/intervention more effective?
  - Our new remediation programme

movincog.org

- 4-year goal: Designing, testing and implementing a program that is: Evidence-based, free of charge, offered to anyone who needs it

Behavioural Interventions to Remediate Learning Disorders: A Technical Report

23 March 2015

George Dawson & Stephanie D'Souza

Supervised by:

Dr. David Moreau PhD & A/Prof. Karen Waldie PhD

Centre for Brain Research and School of Psychology

The University of Auckland

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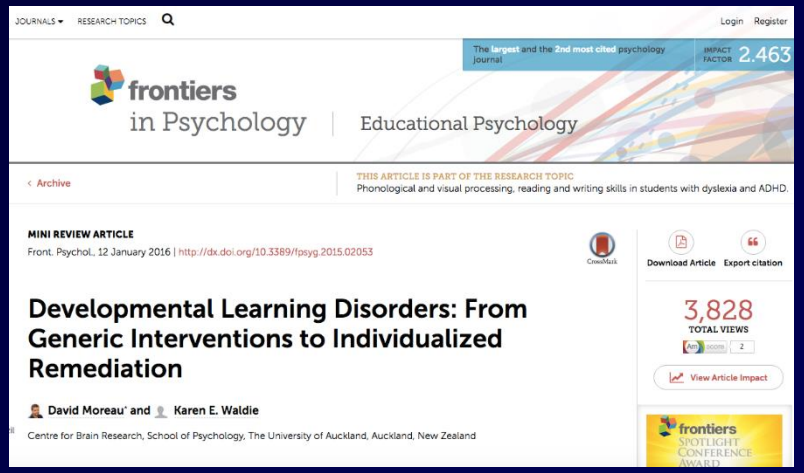
Programme	Overview & Implementation	Cost/Fees *NZD est. based on exchange rate 9/15	Research-Based Evidence
Arrowsmith Program	Aims to **strengthen weak cognitive capacities** underlying learning disabilities through specific cognitive exercises. **Replaces regular school for 3 to 4 years.** Students spend 4 periods per day, 5 days per week with specially-trained teachers in a 1:10 classroom performing computer, auditory, and pen and paper exercises. Claims a **wide range of learning-disabled** students will be able to participate in age-appropriate academic curriculum upon completion.	**Annual Tuition:** NZ$15,000 per student **Training workshop:** NZ$5,600 + travel to Toronto	**No published, peer-reviewed evidence** available evaluating the efficacy of the programme. Anecdotal evidence and unpublished research conducted by Arrowsmith company claims large academic gains, however, the present scientific literature does not provide support for the use of the Arrowsmith programme in the remediation of learning disabilities.
Brain Gym	System of **"educational kinesiology"** (learning through movement); based on the notion that learning difficulties arise from poor coordination between the brain and body. Uses 26 distinct exercises to **improve integration of specific brain functions with body movements.** Offered as intensive 2-3 day training courses, typically 8 hours per day. Targeted at **all ages and abilities.**	**Introduction to Brain Gym course:** NZ$150 **One-on-one training:** 8 sessions: NZ$800 10 sessions: NZ$1,000	Limited peer-reviewed research support; publications in self-funded "Brain Gym Journal" claim gains in cognition. Other peer-reviewed work has labeled Brain Gym as **"pseudoscience,"** due to **invalid theoretical assumptions** (neurological repatterning procedures invalidated, idea that cerebral dominance affects learning repeatedly refuted, and no demonstrated support for impacts of perceptual-motor training on learning).
Brain Time Interactive Metronome	Biometric technology that **measures and improves timing** with specialised computer equipment, targeting the ability to focus, accuracy and efficiency of information processing, executive functions, and motor coordination. Used with a **wide range of neurological conditions** in adults and children, as well as athletes enhancing **sports performance.** Private home training occurs 3-5 days per week for 5, 8, or 12 weeks (15-40 hours) with ongoing professional consultation. Also available for school-based implementation.	**School package** (training, support, and equipment): NZ$12,000 **Home training:** equipment: NZ$625 5 week tuition: NZ$325 8 week tuition: NZ$800 12 week tuition: NZ$1,200	Several published, peer-reviewed studies (about half of which are case studies) have reported **varied significant positive effects of treatment** with isolated clinical and nonclinical populations, including boys with ADHD, elementary math students, soldiers with blast-related traumatic brain injury, and golfers. However, each of these studies evaluated and reported on different cognitive and motor functions, **with conflicting evidence regarding the overall efficacy** of Interactive Metronome training as a general therapeutic treatment tool.

Too few individuals have access to the cognitive remediation programs they need (financial costs, limited evidence)



Physical Space

High Intensity (HIT), video-based exercise. **Classroom-friendly, Standardized**

Short-term: Priming children for learning; **Long-term**: Increase neurogenesis

Cerebral Space

- Key idea: **adaptive training.** Software adapts to core deficits by allocating more time to tasks where performance is lower. Allows combining **domain-general training** (needed for everyone) and **domain-specific** (impaired in a particular learning disorder)

MovinCog

Conclusions

Three key points

1. The brain is “plastic” – it can change in response to experience, stimulation and training.
2. Science has shown that the ADHD brain is often lacking typical chemical and neurological functioning in the frontal cortex (and projections to the motor and mood areas of the brain). Genes and environment both contribute to the likelihood of ADHD.
3. The next step is to provide kids with a new cognitive training programme that will be used in schools and will be freely available.

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