CPUP, Malmö

20 oktober 2014

Trender inom CP forskning:

Historiska landvinningar och framtida utmaningar

Hans Forssberg, MD, PhD
Neuropediatrics
Karolinska Institutet

Important Steps in Management of Childhood Disability

- **From**
  - Institution to Inclusion
  - Medical Construct to Participation
  - Doctor Centered to Family Based
  - Care Givers to Academic Professionals
  - Empiric Art to Evidence Based Medicine

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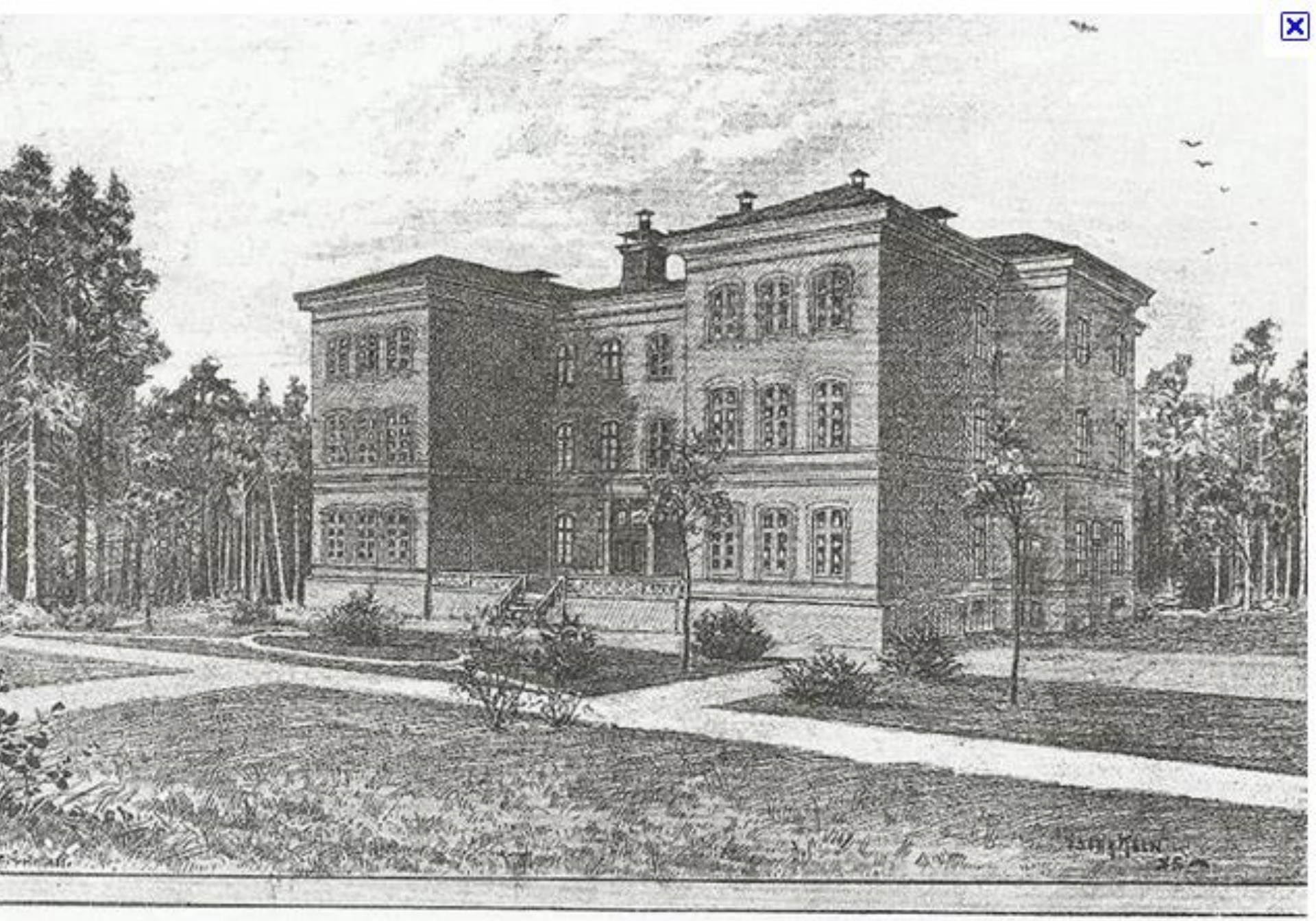
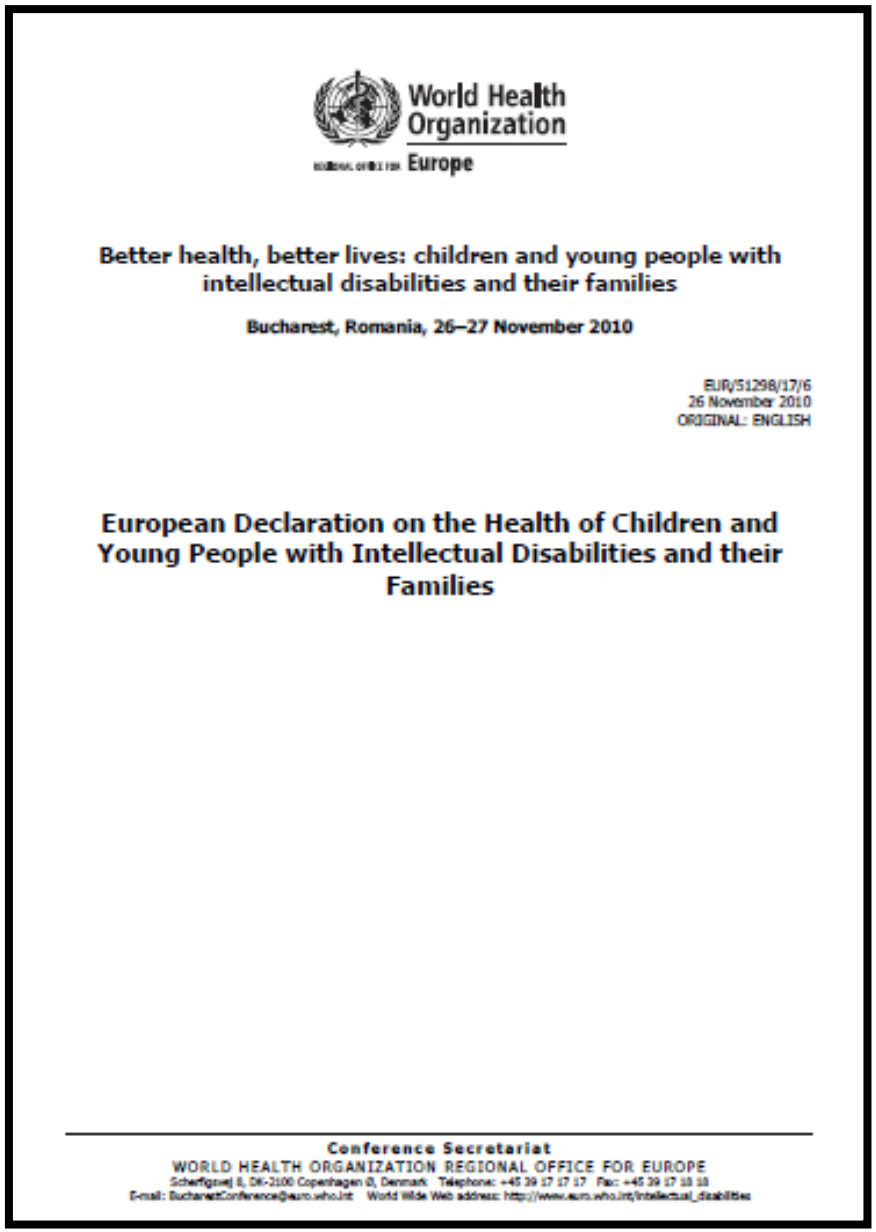


DET NYA EUGENIAHEMMET VID NORRBACKA. Teckning af O. Keen.

1885



World Health Organization
Europe

Better health, better lives: children and young people with intellectual disabilities and their families

Bucharest, Romania, 26–27 November 2010

EUR/51298/17/6
26 November 2010
ORIGINAL: ENGLISH

European Declaration on the Health of Children and Young People with Intellectual Disabilities and their Families

Conference Secretariat
WORLD HEALTH ORGANIZATION REGIONAL OFFICE FOR EUROPE
Scherfigsvej 8, DK-2100 Copenhagen Ø, Denmark Telephone: +45 39 17 17 17 Fax: +45 39 17 18 18
E-mail: BucharestConference@euro.who.int World Wide Web address: http://www.euro.who.int/intellectual_disabilities

Karolinska Institutet

The WHO Europe initiative:

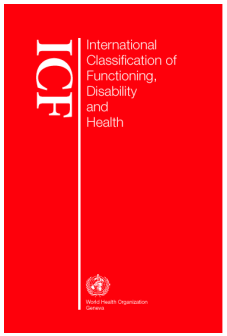
Better health better lives: children and young people with intellectual disabilities and their families

- *aims to ensure that all children and young people with intellectual disabilities are fully participating members of society, living with their families, integrated in the community and receiving health care and support proportional to their needs.*

Important Steps in Management of Childhood Disability

- **From**
  - Institution to Inclusion
  - Medical Construct to Participation

Cerebral Palsy
- Orthopaedic disease - surgery
- Brain Disease – reflexes and posture
- Motor & cognitive dysfunction
- Limitation in activity and participation



Health

Body function & Body structure ⟷ **Activity** ⟷ **Participation**

Environment **Personal factors**

Important Steps in Management of Childhood Disability

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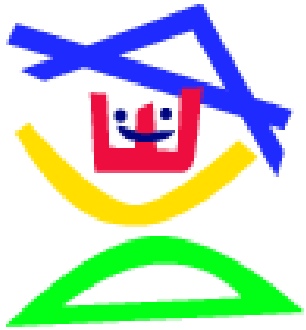
From Doctor Centred to Family Based Services

- Daily life & social interactions
- Autonomy and self determination
  →Informed decisions
- Well informed patients and parents
  →Second opinion
- Integrity of the child

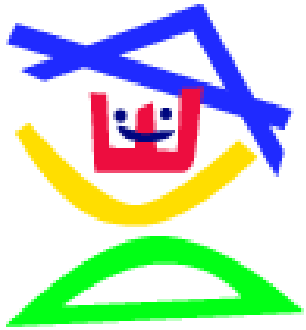
Family Centred Care



- "...a philosophy and method of service delivery for children and parents which emphasizes a **partnership between parents and service providers**, focuses on the family's role in decision-making about their child, and recognizes **parents as the experts** on their child's status and needs."

Rosenbaum et al (1998)
Physical and Occupational Therapy
In Pediatrics 18:1-20.

Historical Perspective on Management of Childhood Disability



- **From**
  - Institution to Inclusion
  - Medical Construct to Participation
  - Doctor Centered to Family Based
  - Care Givers to Academic Professions
    - Multi-professional teams
  - Empiric Art to Evidence Based Medicine

Multi-professional teams

- Multiple skills required around the child
  - Physio-, occupational-, speech and language therapists; psychologists; nurses, teachers; social workers; medical doctors
- University education
  - Research and development

Important Steps in Management of Childhood Disability

- **From**
  - Institution to Inclusion
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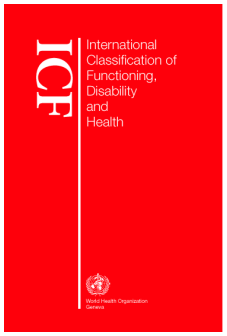
  - Doctor Centered to Family Based
  - Care Givers to Academic Professions
  - Empiric Art to Evidence Based Medicine

Principles for intervention in childhood disability

1. **Reliable and valid methods to measure treatment results**
2. **Evidence based medicine**
3. **A science based theoretical framework predicting the treatment results**



Measurements in motor domain

Health

Ashworth scale
Tardieu
HAT

GMFM-66

Body function
&
Body structure

ROM
SMC

Strength
Muscle fatigue
Sensibility
SAROMM

Activity

PEDI FSS
AHA

Participation

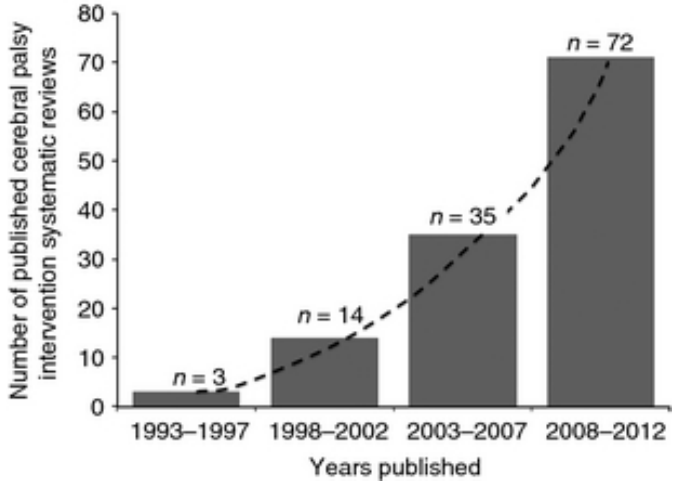
CAPE & PAC
PEDI CAS

Environment

Personal factors

Principles for intervention in childhood disability

1. **Reliable and valid methods to measure treatment results**
2. **Evidence based medicine**
    1. **Clinical trials**
    2. **Systematic reviews**
    3. **Guidelines**



Hierarchy of study designs
(Khan et al 2003)

Description of the design	Levels assigned to evidence based on soundness of design
Experimental study •RCT (with concealed allocation) •Exp. study without randomisation	I
Observational study with control groups •Cohort study •Case-control studies	II
Observational study without control groups •Cross-sectional study •Before-after study •Case-series	III
Case reports Pathophysiologal studies Expert opinion or consensus	IV

A systematic review of interventions for children with cerebral palsy: state of the evidence

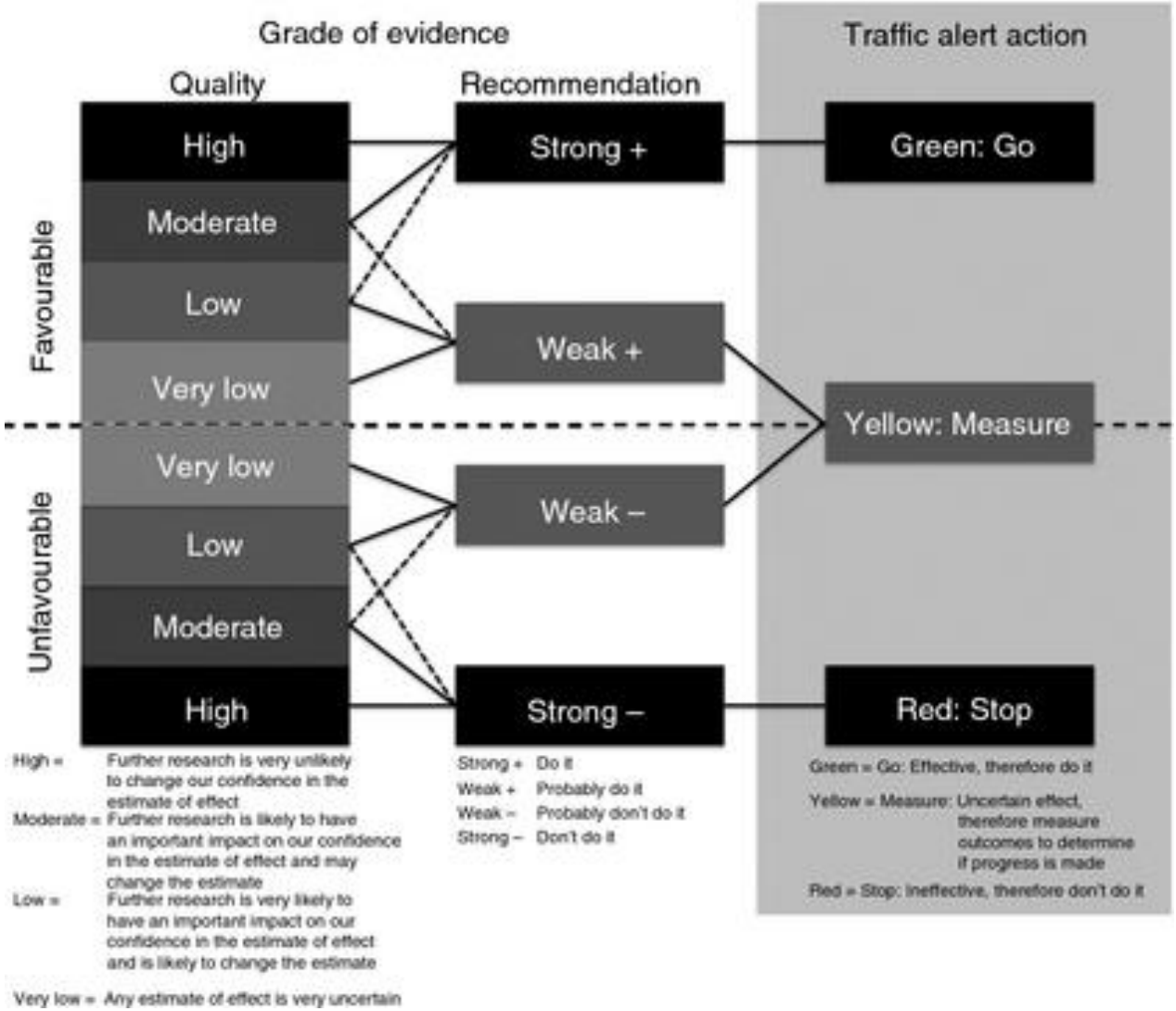
IONA NOVAK[1,2] | SARAH MCINTYRE[1,2] | CATHERINE MORGAN[1,2] | LANIE CAMPBELL[2] | LEIGHA DARK[1] | NATALIE MORTON[1] | ELISE STUMBLES[1] | SALLI-ANN WILSON[1] | SHONA GOLDSMITH[1,2]

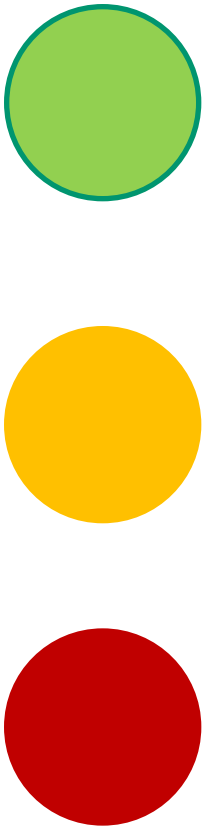
Developmental Medicine & Child Neurology 2013, 55: 885–910

What this paper adds

- Of 64 discrete CP interventions, 24% are proven to be effective.
- 70% have uncertain effects and routine outcome measurement is necessary.
- 6% are proven to be ineffective.
- Effective interventions reflect current neuroscience and pharmacological knowledge.
- All effective interventions worked at only one level of the ICF.

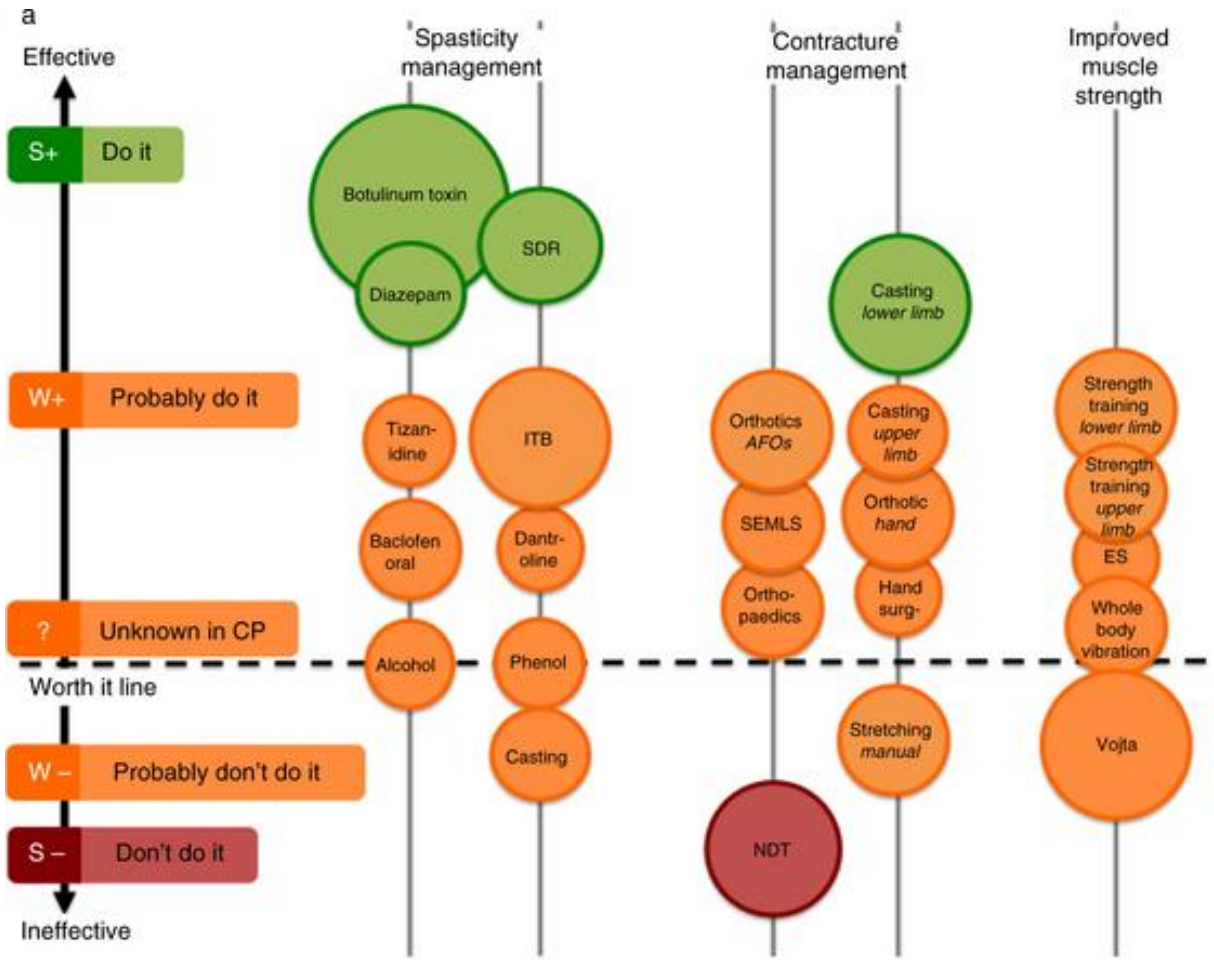
A systematic review of interventions for children with cerebral palsy: state of the evidence





Developmental Medicine & Child Neurology
Volume 55, Issue 10, pages 885-910, 21 AUG 2013 DOI: 10.1111/dmcn.12246
http://onlinelibrary.wiley.com/doi/10.1111/dmcn.12246/full#dmcn12246-fig-0001

A systematic review of interventions for children with cerebral palsy: state of the evidence



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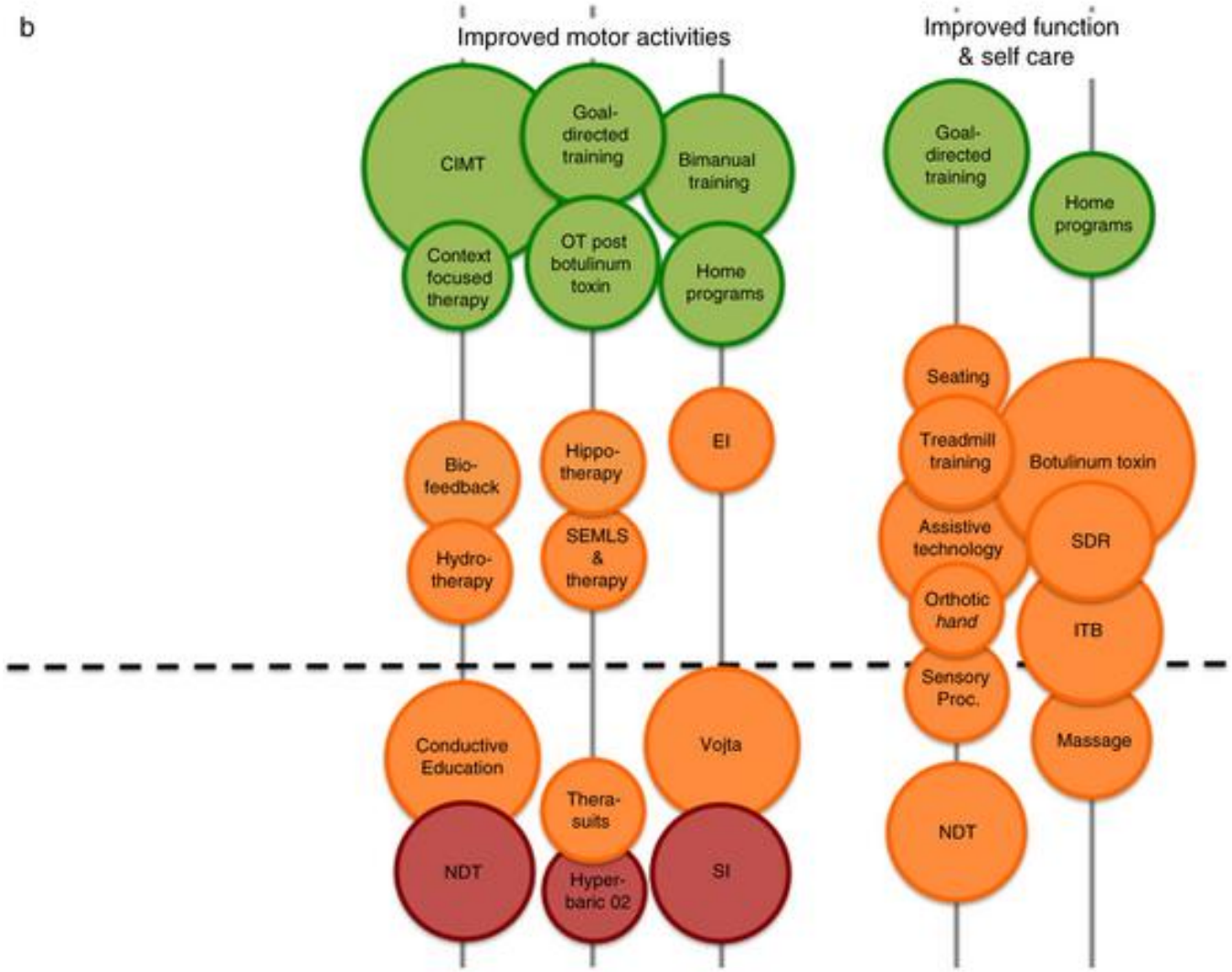

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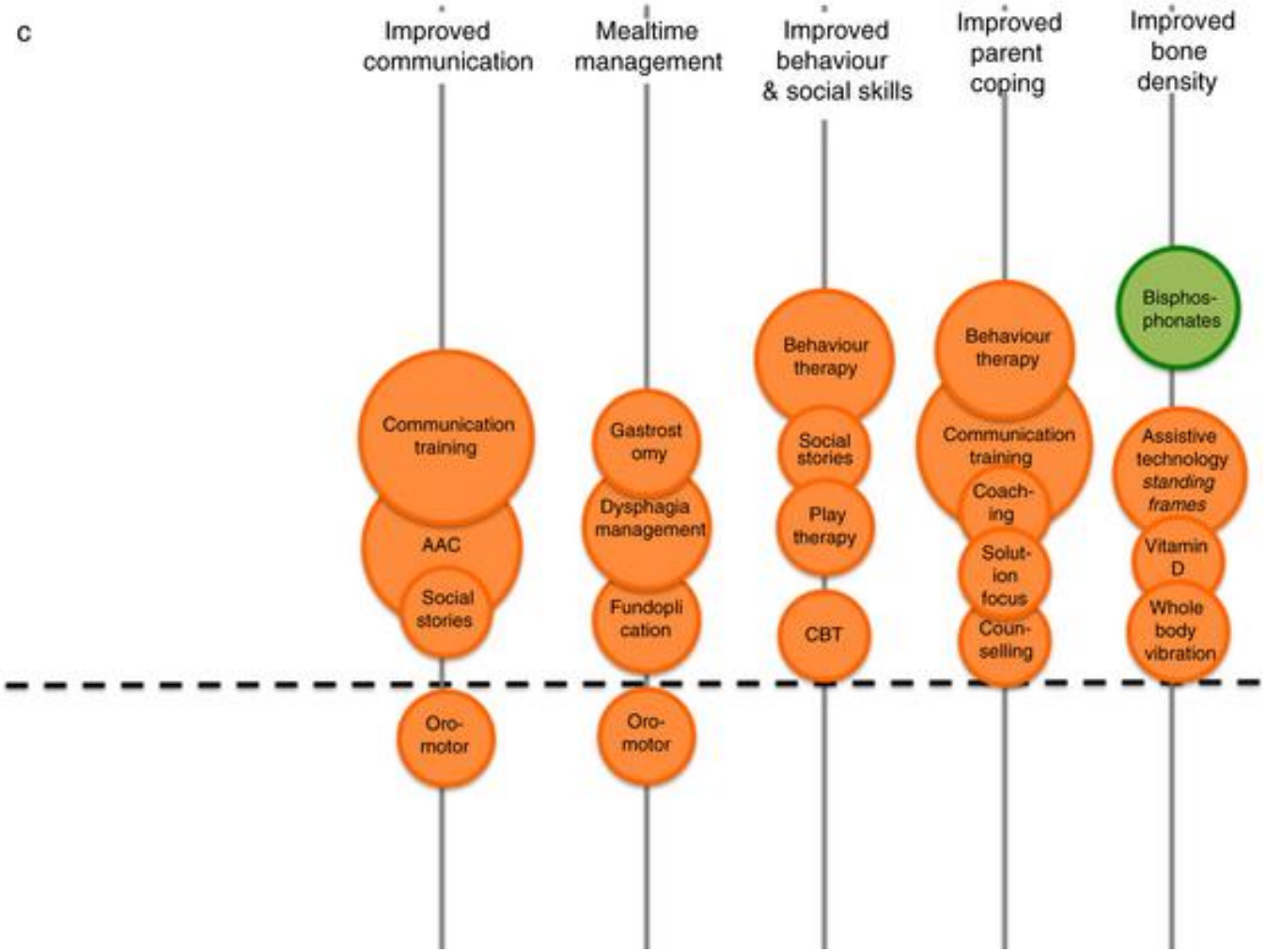

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http://onlinelibrary.wiley.com/doi/10.1111/dmcn.12246/full#dmcn12246-fig-0004

DMCN Developmental Medicine & Child Neurology

Levels of evidence an

I still vividly remember as a medical st
by the way two different experts tre
breast cancer, one by a simple lumpect
by very radical and deforming surgery
both could not always be right and was
tion to the need for evidence-based
responsibility of journals such as *DM*
improve current practice by publishing
statistically validated evidence for, an
interventions in our field.

The recent systematic review by N
example of an attempt to do this for
included an innovative traffic light sys
results of the GRADE scores in an easil
intended to help in knowledge translat
lights have been used in other areas of
the context of management guidelines
National Institute for Clinical Evidence
assessment of a febrile child.[2] This is
create traffic lights for interventions in
ied a group of conditions as the cerebr
more challenging when individual in
either aimed at the primary problems,
sensory neglect, or at secondary effects,
and musculoskeletal problems, or a mix

As pointed out in the ensuing co
lished in this issue, the systematic
several other issues. One is to demons
of the pharmaceutical industry, which i
to fund the vast majority of medical r
Partly this is due to the cost of me
drug licensing requirements, but inevi
heavy emphasis on allopathic medicine
attempted research in other fields is aw
limited funding available, especially as
be even more expensive than a drug tr
tions are so much more complex tha
drug or placebo. Another less expecte
been the interpretation that only green
should be offered. This is clearly incor
must not be used in this way. As poi
paedic and other colleagues, the fact

REFERENCES

1. Novak I, McIntyre S, Morgan C, et al. A systematic review of interventions for children with cerebral palsy: state of the evidence. *Dev Med Child Neurol* 2013; 55: 885–910.
2. National Institute for Health and Clinical Excellence. Feverish illness in children: full guideline. Clinical

A systematic r
palsy: the stat

Pam Thomason[1], H Kerr G
1 Royal Children's Hospital – Hugh
Parkville, Vic.,; 2 Royal Children's
Parkville, Vic., Australia.

Correspondence to: kerr.graham@rc

doi: 10.1111/dmcn.12417

SIR–The systematic revie
concerns. We question t
for the whole field of orth
(CP), including upper lim
surgery, single-event mult
surgery. We will restrict
botulinum toxin A (Bo
because we have experienc

1 Given the breadth of i
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3 There are major differ
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Gregory B Firt
Department of Orth
Johannesburg, Sout

Correspondence to:

doi: 10.1111/dmcn.1

SIR–There are
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2 There is a
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long-term

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1. Novak I, McIntyre
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2. Thomason P, Sell
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2013; 37: 25–8.

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Tim Theologis
Nuffield Orthopaedi

Correspondence to:

doi: 10.1111/dmcn.12401

How to bridge the gap between systematic reviews and clinical guidelines

Ilona Autti-Rämö
Hans Forssberg[2]
1 Research Department
2 Department of Wome
Stockholm; 3 Neuropae
Sweden; 4 Chairman,

Correspondence to: har

doi: 10.1111/dmcn.1241

SIR–There is a
ommendations f

outcomes. Evi
tions are also
what treatmen
implementation
Directive requi
care services p
identified lack
inspired almost
quality interver
in recent years.
step in the pr
guidelines.

Novak et al. reply

Iona Novak[1,2], Sarah McIntyre[1,2], Catherine Morgan[1,2], Lanie Campbell[2], Leigha Dark[1], Natalie Morton[1], Elise Stumbles[1], Salli-Ann Wilson[1], Shona Goldsmith[1,2]
1 Cerebral Palsy Alliance, Sydney; 2 University of Notre Dame Australia, Sydney, Australia.

Correspondence to: inovak@cerebralpalsy.org.au

doi: 10.1111/dmcn.12426

SIR–In responding to the letters that have been sent regarding our paper[1], it is clear we are all passionate about our own specialities; at the same time we believe that the optimal well-being of children with cerebral palsy (CP) must remain at the centre of this debate. We take this opportunity to state that we strongly uphold the principles of evidence-based medicine (EBM), wherein the integration of clinical expertise, client values, and best evidence[2] is considered paramount to quality clinical decision-making. The purpose of a systematic review is to summarize the best available evidence. We provided such a summary, but this should not be misread as a clinical 'cookbook'. We concur with EBM experts that, 'Systematic reviews can define the boundaries of what is known and what is not known… Systematic reviews can aid, but can never replace, sound clinical reasoning.'[3]

Our systematic review used strict, clear inclusion and exclusion criteria, with an emphasis on including systematic review levels of evidence. It is important to note that
GRADE criteria that we employed downgrade the qua
score in response to methodological limitations.[4] In t
field, for reasons the corresponding authors have identifi
this often resulted in a GRADE evidence quality rating
low or very low, which formed a part of the GRADE r
ommendation and the assigned traffic light colour. It
plausible that another systematic review with broader
more specific) inclusion criteria, including other levels
evidence, might produce another result more favoura
for interventions predominated by lower levels of eviden
We believe that this is an area for further discussion
exploration by our whole field, regarding how to reso
these dilemmas commonly faced in research.

We acknowledge that a three-colour code evidence s
tem may risk oversimplifying complex research data
recommendations for some readers. We also acknowle
some may not favour the 'review of reviews' methodolo
however, great variation in care occurs and diverse DM
readership needs exist. In addition to the letters that
are responding to, we have also received positive writ
and verbal feedback from reputable research, clinical,
parent groups about perceived usefulness of the review
sign of positive impact for some readers. None of th
groups (or we) regard this paper as a stand-alone pie
but rather a platform from where to look further for s
cific information.

Principles for intervention in childhood disability

1. **Reliable and valid methods to measure treatment results**
2. **Evidence based medicine**
3. **A science based theoretical framework predicting the treatment results**

Individualized medicine in the heterogeneous CP syndromes

- **Type of CP and severity level**
  - → **GMFCS**
  - → **MACS**
- **Brain pathology**
- **Pathophysiology of Motor Disorder**
- **Registers and patient records**
- **Aetiology**
  - → **Complex disorder?**
- **Intervention based on neuroplasticity**

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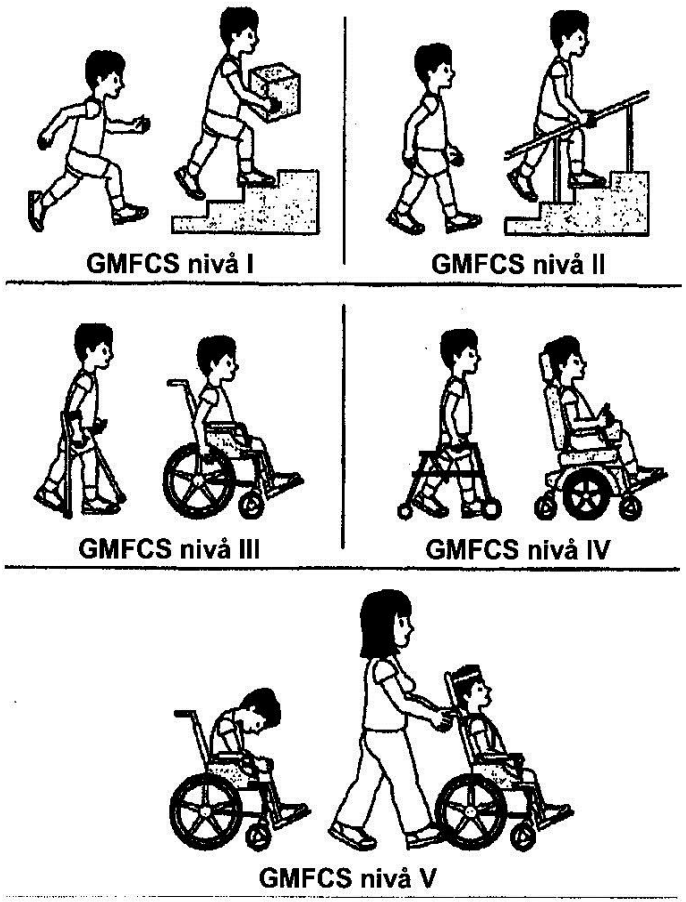
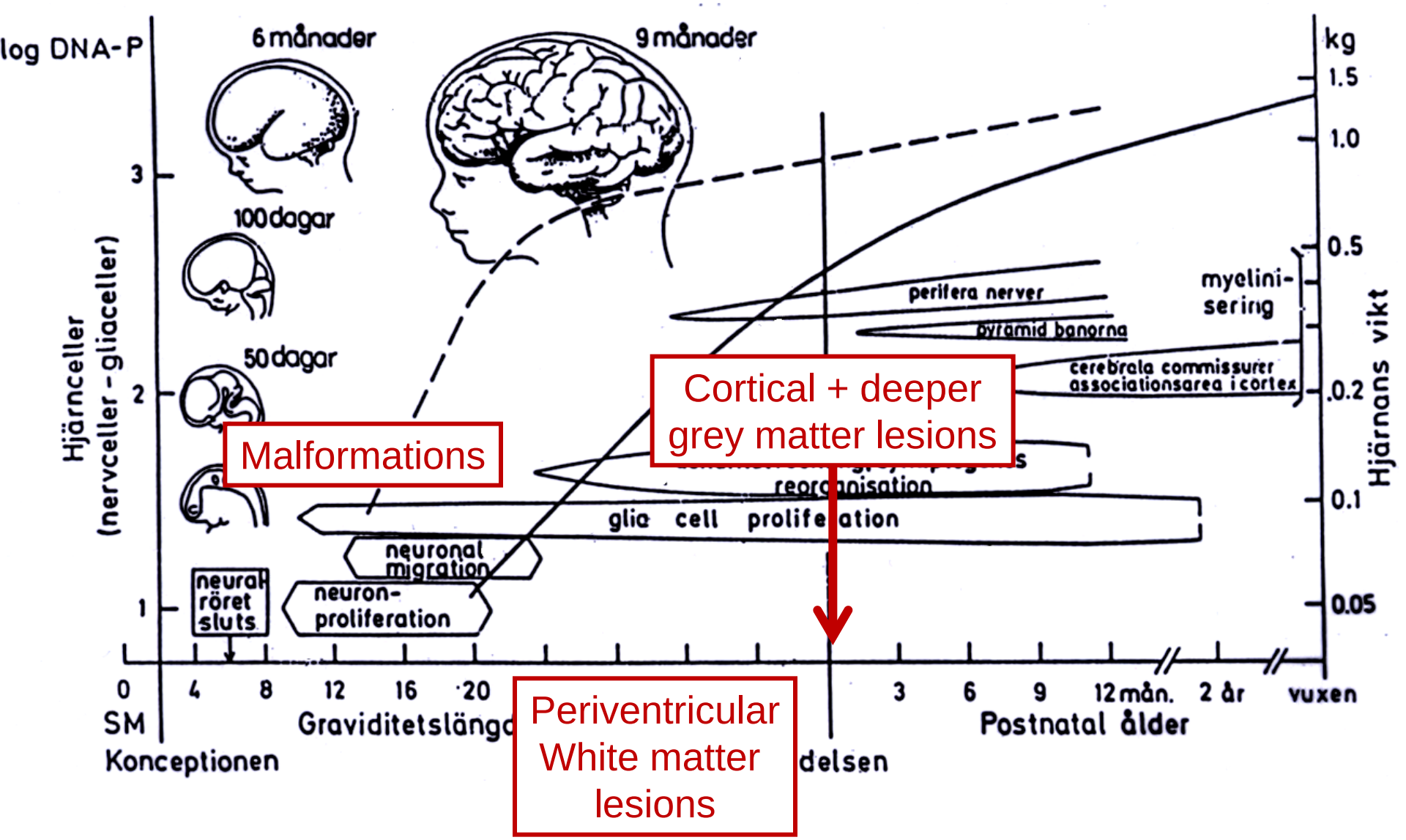
Gross Motor Function Classification System

Level 1-5



Manual Ability Classification System, 2006
www.macs.nu; Free to use on the internet, 21 languages, Instructional video for sale
4 publications; 226 citations


log DNA-P
6 månader
9 månader
100 dagar
50 dagar
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(nervceller - gliaceller)
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1.0
0.5
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0.1
0.05
Hjärnans vikt
perifera nerver
myelini-
sering
pyramid banorna
cerebrala commissurer
associationsarea i cortex
reorganisation
glia cell proliferation
neuronal
migration
neuron-
proliferation
neural
röret
sluts
Malformations
Cortical + deeper
grey matter lesions
Periventricular
White matter
lesions
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4
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12
16
20
3
6
9
12 mån.
2 år
vuxen
SM
Konceptionen
Graviditetslängd
delsen
Postnatal ålder

Clinical and MRI Correlates of Cerebral Palsy

The European Cerebral Palsy Study

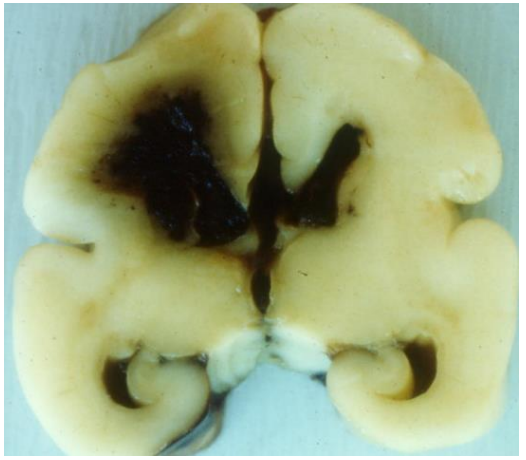
Martin Bax, DM, FRCPCH
Clare Tydeman, BA(Hons)
Olof Flodmark, MD, PhD

Table 3. Magnetic Resonance Imaging (MRI) Pattern Types

MRI Pattern	No. (%)
Malformation	32 (9.1)
White-matter damage of immaturity	149 (42.5)
Focal infarct	26 (7.4)
Cortical subcortical damage	33 (9.4)
Basal ganglia damage	45 (12.8)
Miscellaneous	25 (7.1)
Normal	41 (11.7)
Total	**351 (100)**

JAMA, October 4, 2006

Cerebral Palsy
Movement Disorders



+

- Spasticity
- Musculoskeletal malformations
- Dyskinesis
- Hyperreflexia
- Retained developmental reactions

-

- Paresis
- **Central dys-coordination**
  - → Co-contractions
  - → Mirror movements

Individualized medicine in the heterogeneous CP syndromes

- Type of CP and severity level
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  - → **Complex disorder?**
- Intervention based on neuroplasticity

Surveillance of Cerebral Palsy in Europe

http://www.scpenetwork.eu/

CPUP

UPPFÖLJNINGSPROGRAM FÖR CEREBRAL PARES

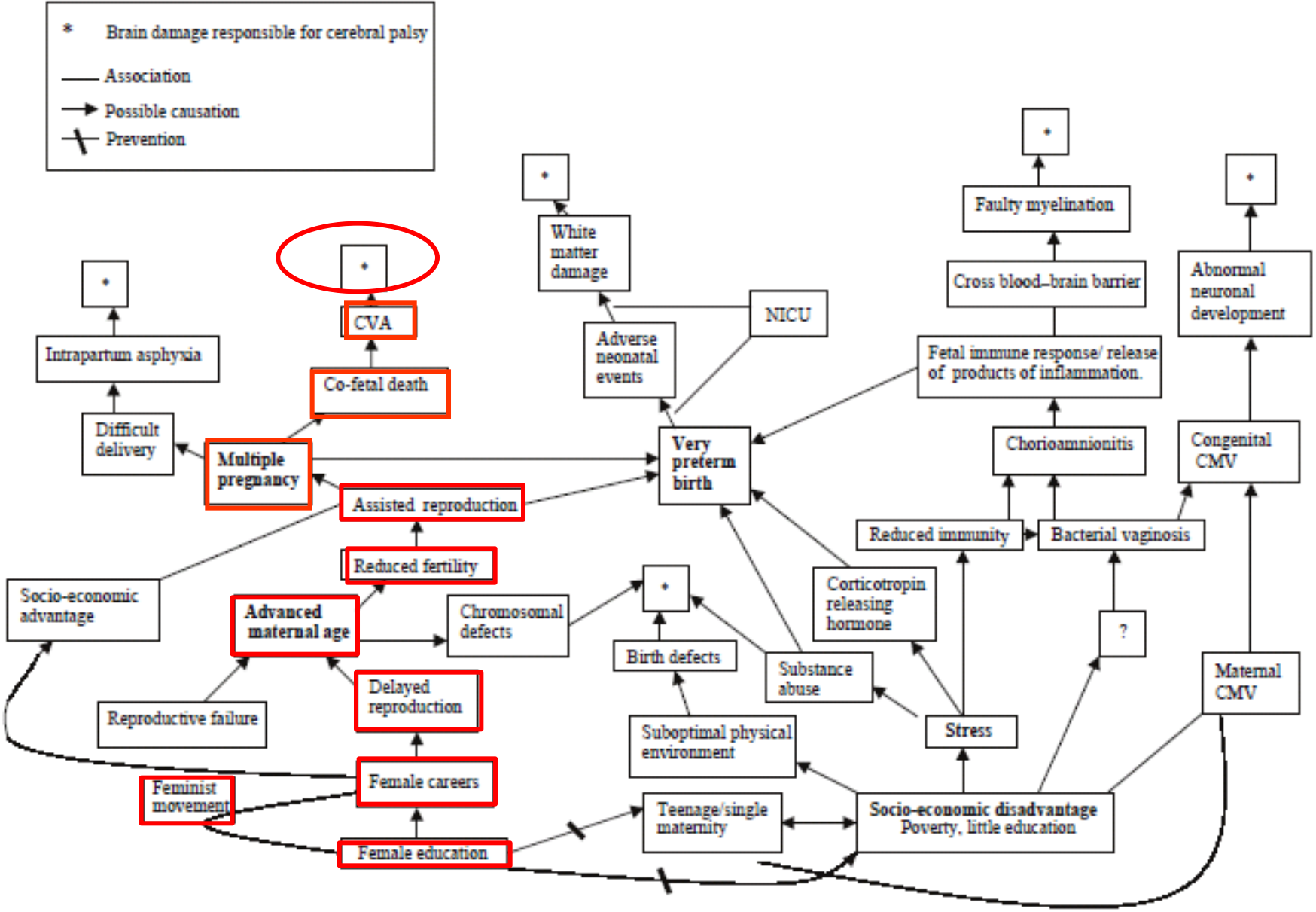
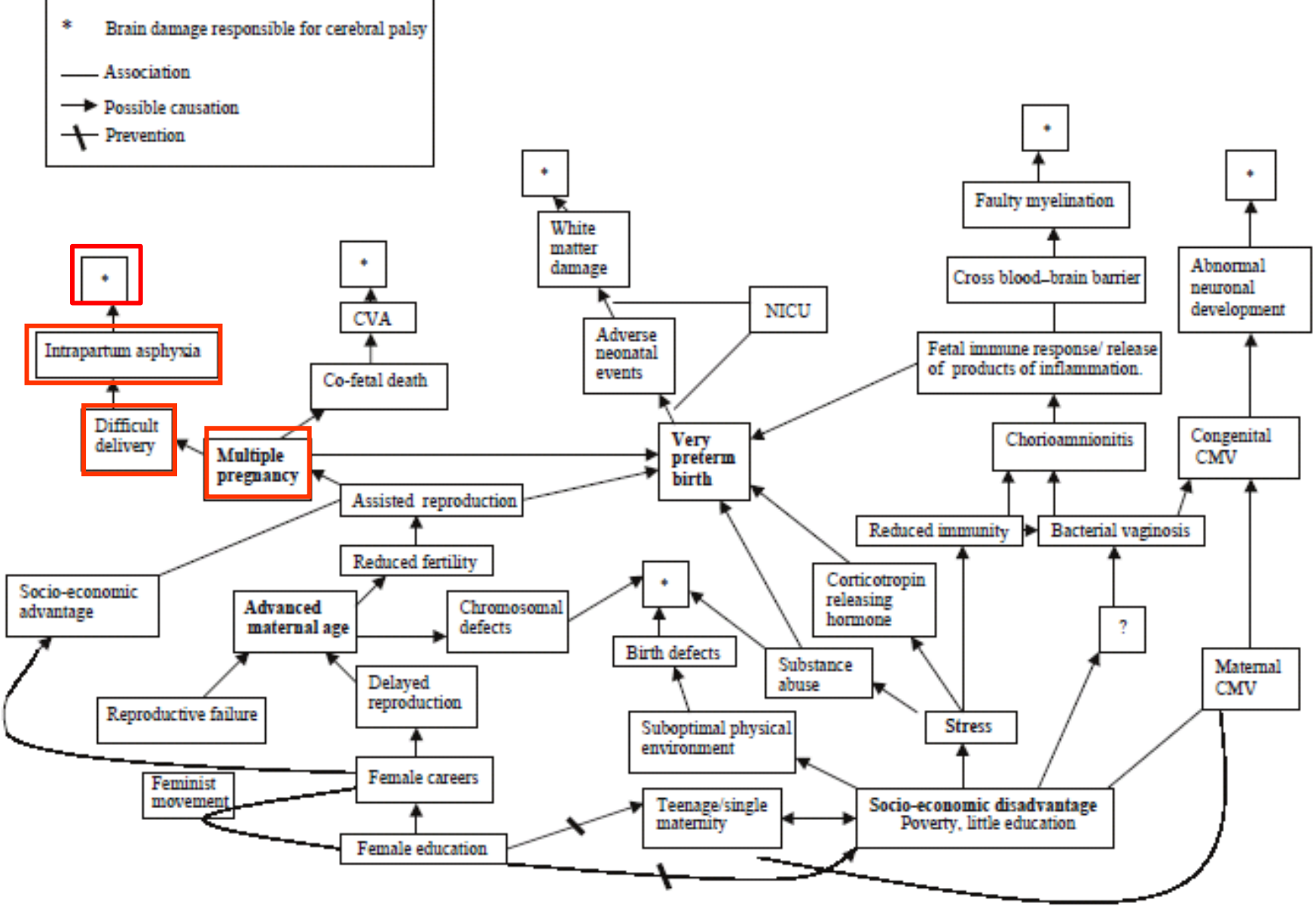


Figure 2 Some causal pathways to CP that interact with very preterm birth.

Blair & Stanley. Current Pediatrics 2002



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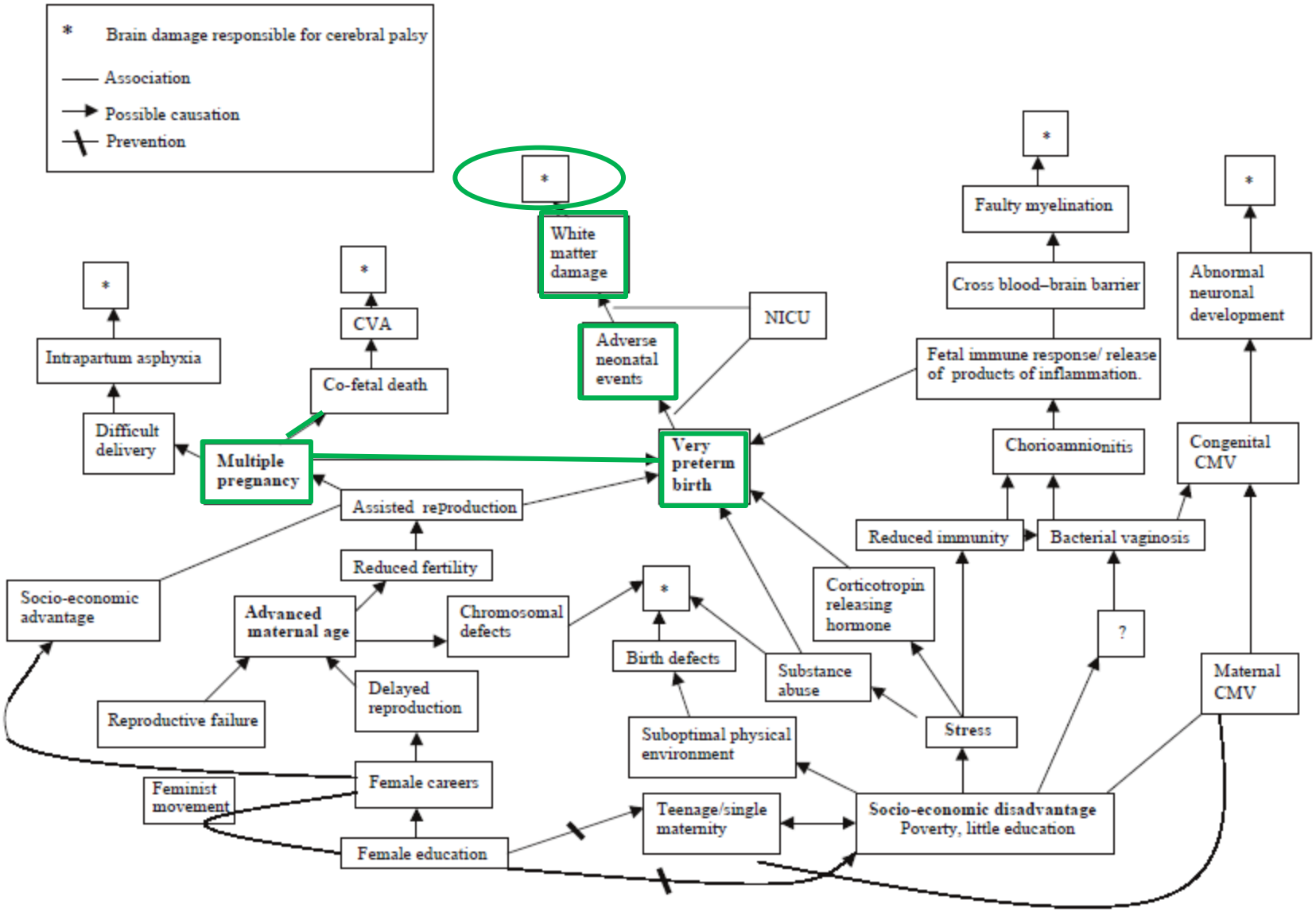

Figure 2 Some causal pathways to CP that interact with very preterm birth.

Blair & Stanley. Current Pediatrics 2002

thebmj

CrossMark

BMJ 2014;349:g4294 doi: 10.1136/bmj.g4294 (Published 15 July 2014)

RESEARCH

Familial risk of cerebral palsy: population based cohort study

Mette C Tollånes *posto*
Dag Moster *associate p*

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Health Sciences, National Institute
Health, Bergen, Norway; [4]Departm

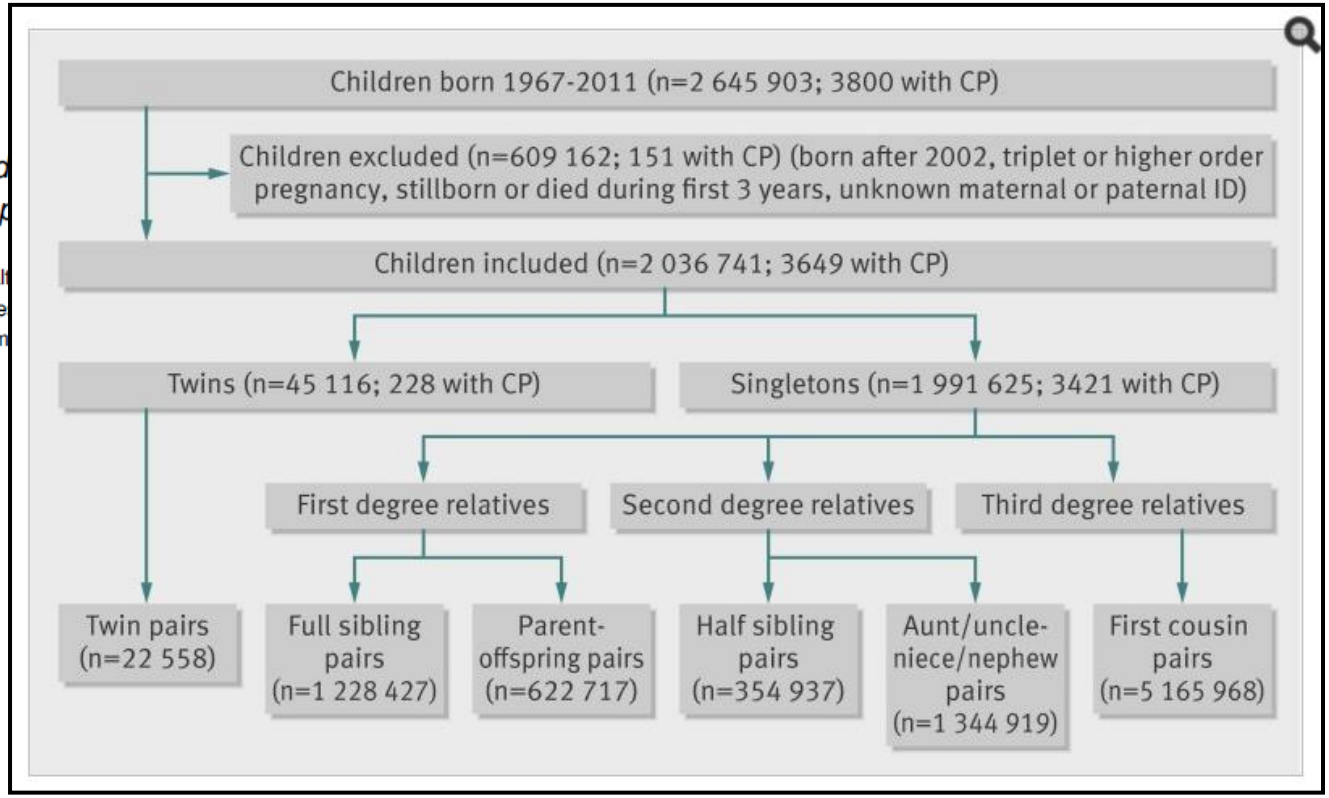


Table 1| **Recurrence of cerebral palsy (CP) among relatives. Singletons and twins born in Norway 1967-2002 surviving first three years of life**

Relatives	Prevalence of CP (per 1000)	Relative risk (95% CI)	
		Crude	Adjusted
Twins			
Prevalence in twin population	228/45 116 (5.1)	1 (reference)	—
Proband-wise concordance rate	18/228 (78.9)	15.6 (9.8 to 24.8)	—
First degree			
Full siblings:			
Sibling without CP	1929/1 226 413 (1.6)	1 (reference)	1 (reference)
Sibling with CP	30/2014 (14.9)	9.5 (6.6 to 13.5)	9.2 (6.4 to 13.1)*
Parent-offspring:			
Parent without CP	813/622 480 (1.3)	1 (reference)	—
Parent with CP	2/237 (8.5)	6.5 (1.6 to 25.6)	—
Second degree			
Half siblings:			
Half sibling without CP	762/354 163 (2.2)	1 (reference)	1 (reference)
Half sibling with CP	5/774 (6.5)	3.0 (1.2 to 7.2)	3.0 (1.1 to 8.6)†
Aunt/uncle-niece/nephew:			
Aunt/uncle without CP	1930/1 342 559 (1.4)	1 (reference)	—
Aunt/uncle with CP	3/2360 (1.3)	0.9 (0.3 to 2.7)	—
Third degree			
First cousin with CP	8472/5 156 811 (1.6)	1 (reference)	—
First cousin without CP	23/9157 (2.5)	1.5 (0.9 to 2.7)	—

Genetic insights into the causes and classification of the cerebral palsies

Andres Moreno-De-Luca, David H Ledbetter, Christa L Martin

	Name	OMIM ID	Inheritance	Reference
GAD1	Glutamate decarboxylase 1	603513	AR	Lynex et al[59]
KANK1	KN motif and ankyrin repeat domains 1	612900	AD	Lerer et al[60]
AP4M1	Adaptor-related protein complex 4, μ1 subunit	612936	AR	Verkerk et al[61]
AP4E1	Adaptor-related protein complex 4, ε1 subunit	613744	AR	Moreno-De-Luca et al[62]
AP4B1	Adaptor-related protein complex 4, β1 subunit	614066	AR	Abou Jamra et al[63]
AP4S1	Adaptor-related protein complex 4, σ1 subunit	614067	AR	Abou Jamra et al[63]

OMIM=Online Mendelian Inheritance in Man. AR=autosomal recessive. AD=autosomal dominant.

Table 1: **Genes associated with cerebral palsy**

Lancet Neurol 2012; 11: 283–92

Individualized medicine in the heterogeneous CP syndromes

- Type of CP and severity level
  - → GMFCS
  - → MACS
- Brain pathology
- Pathophysiology of Motor Disorder
- Registers and patient records
- Aetiology
  - → Complex disorder?
- **Intervention based on neuroplasticity**

Brain Plasticity -
Alteration of the synaptic connectivity

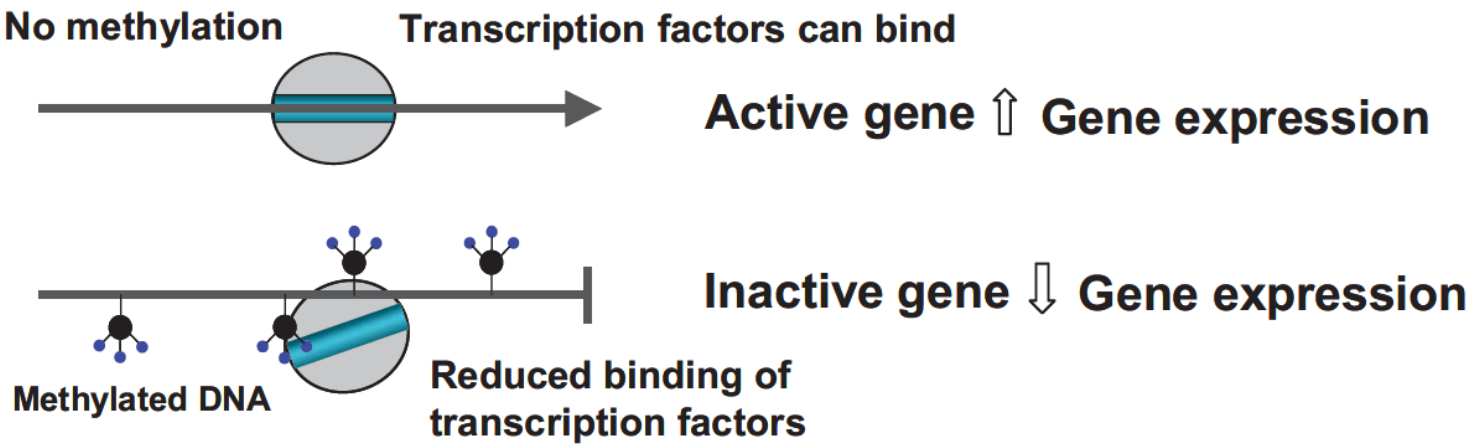
- **Development**
- **Brain lesions**
- **Activation & learning**

- **USE DEPENDENT**

General principles of plasticity

MECHANISMS

- Gene expression (Epigenetics)
  - → Methylation
  - → Histone modifications



General principles of plasticity

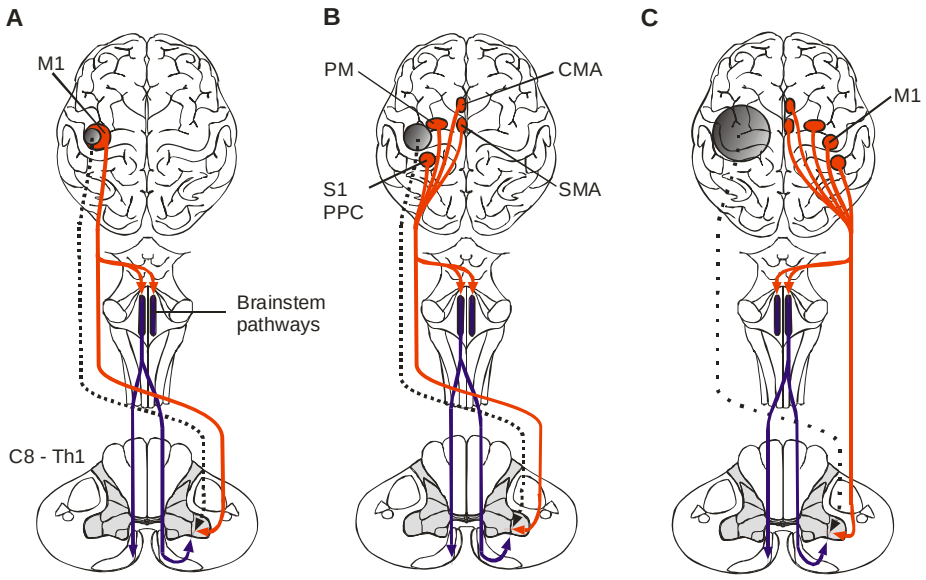
MECHANISMS

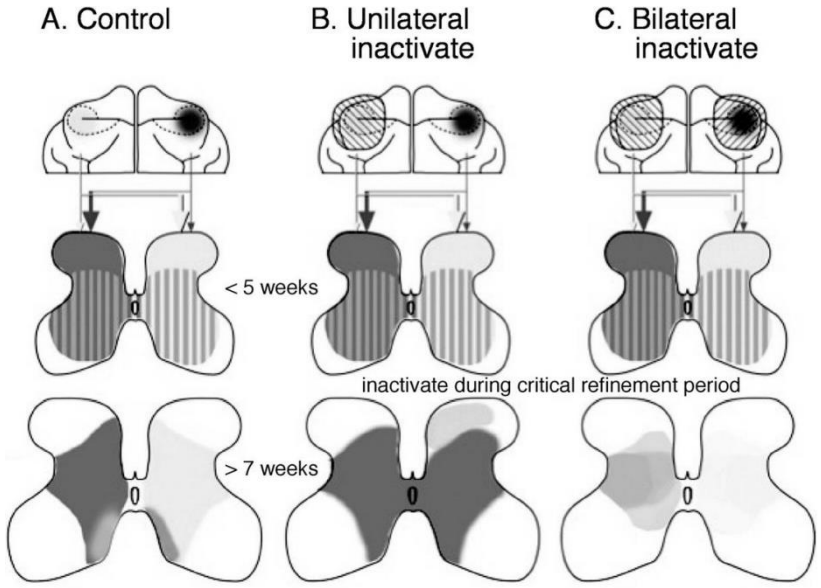
- Gene expression (Epigenetics)
  - → Methylation
  - → Histone modifications
- Molecular/cellular level (proteins)
  - → Trophic factors (BDNF, IGF2)
  - → Neuromodulators (e.g., monoamines)
- Neuronal circuits/network
  - → Synaptic connectivity
    - LTP, LTD
    - Dendritic spine formation
    - Axon retraction/sprouting
- Behavioural/functional

Examples of Motor Plasticity

- Cortical motor maps (network level)
- Axonal growth/Rejection

  → Activity dependent corticospinal projections





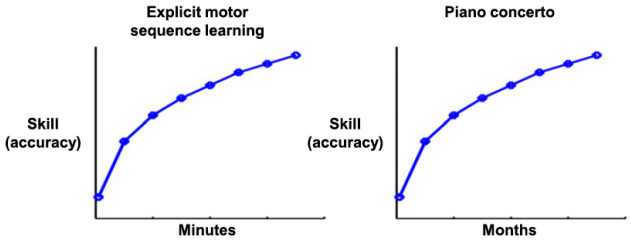
Martin et al, 2011

Examples of Motor Plasticity

- Cortical motor maps (network level)
  - → Activity-dependent driven dynamics
  - → Horizontal intracortical connections
  - → LTP-like mechanisms
  - → Can be modified by neuromodulators, TMS, BDNF
- Axonal growth/Rejection
  - → Activity dependent corticospinal projections
- Motor skill learning/motor training

Motor skill learning/motor training

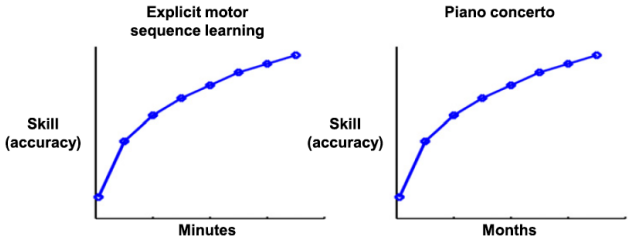
- Learning curve



Dayan & Cohen 2011

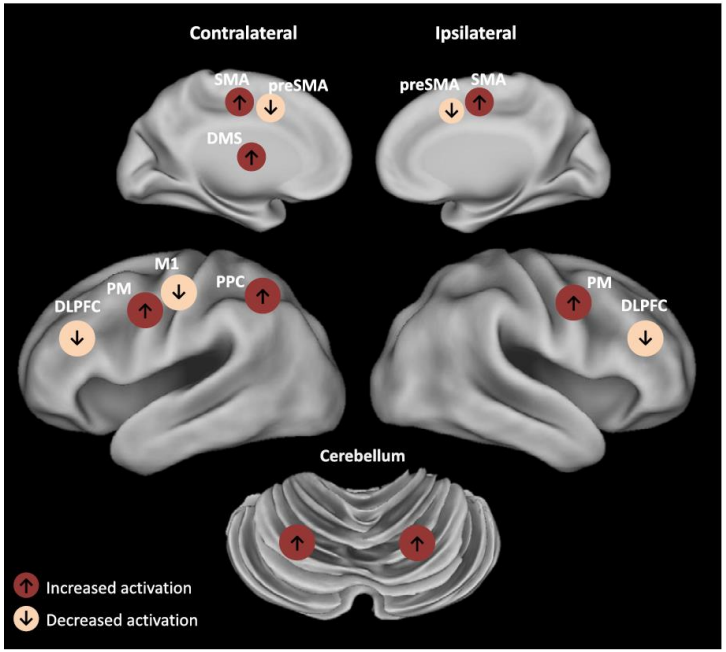
Motor skill learning/motor training

- Learning curve



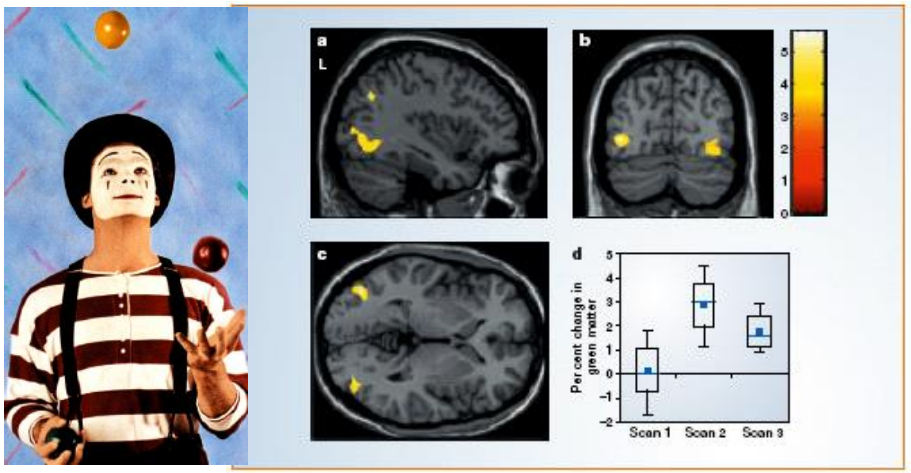
Dayan & Cohen 2011

- fMRI changes



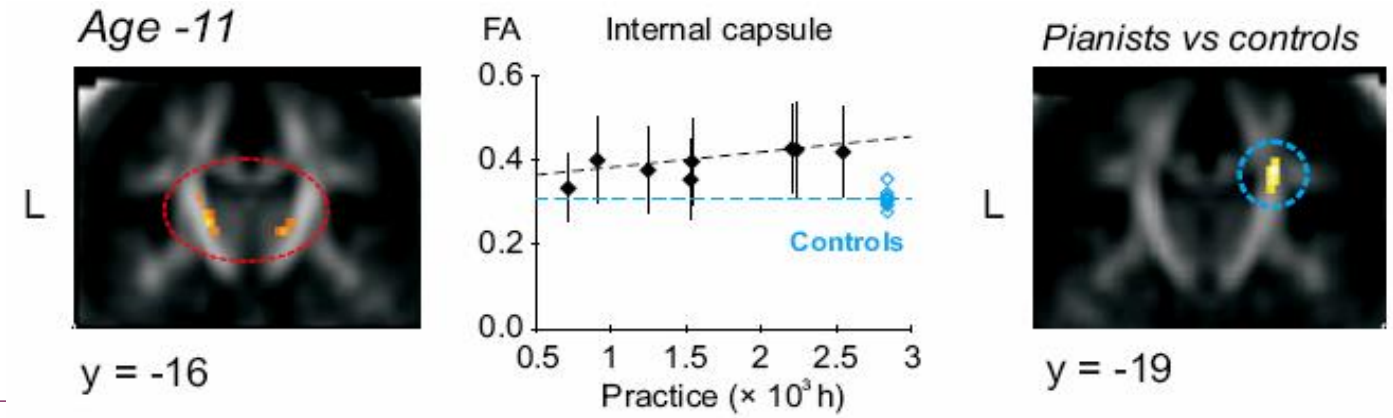
Motor skill learning/motor training

- Learning curve
- fMRI changes



Draganski et al 2004

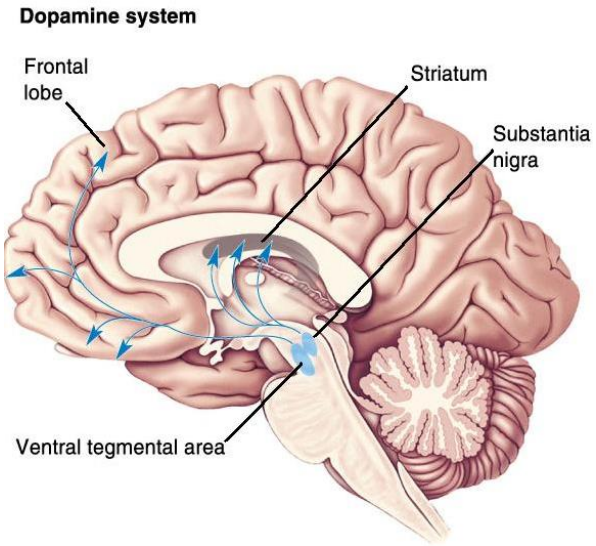
- Grey and white matter changes

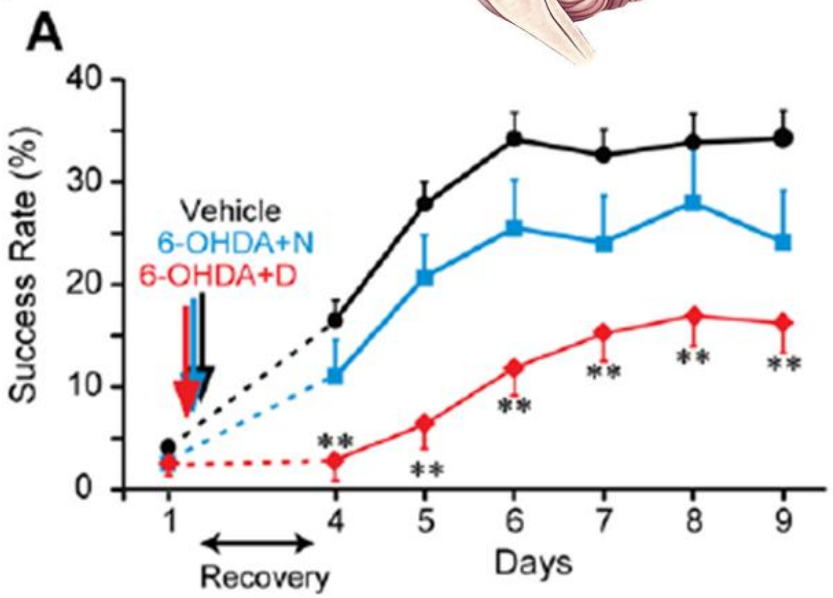


Bengtsson et al, Nature Neurosci 2005

Motor skill learning/motor training

- Learning curve
- fMRI changes
- Grey and white matter changes
- Role of dopamine system

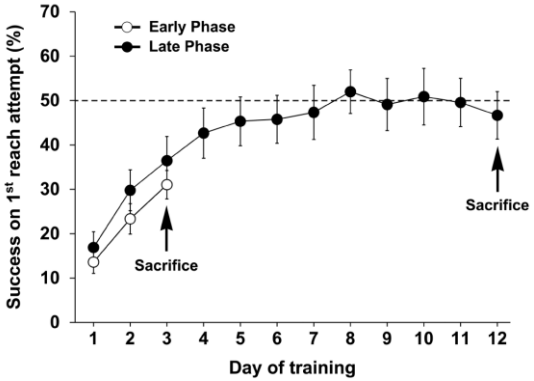


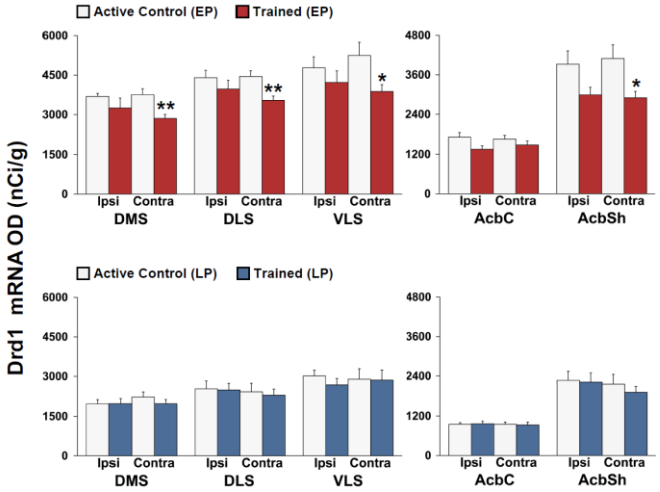


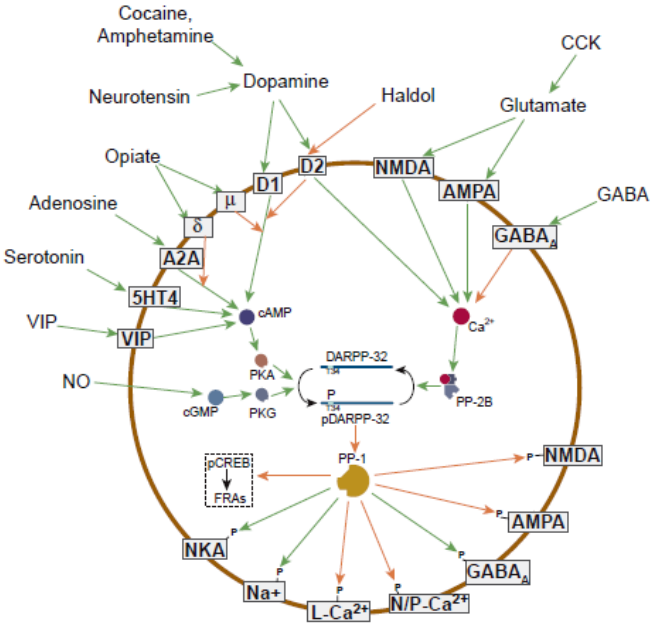
K Molina-Luna 2009, PLOS-One

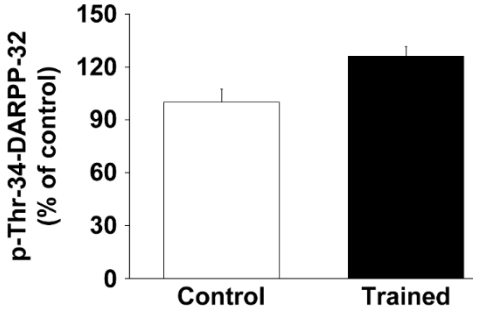
Motor skill learning/motor training

Alteration of dopamine signalling









Qian, Y et al 2013, 2014

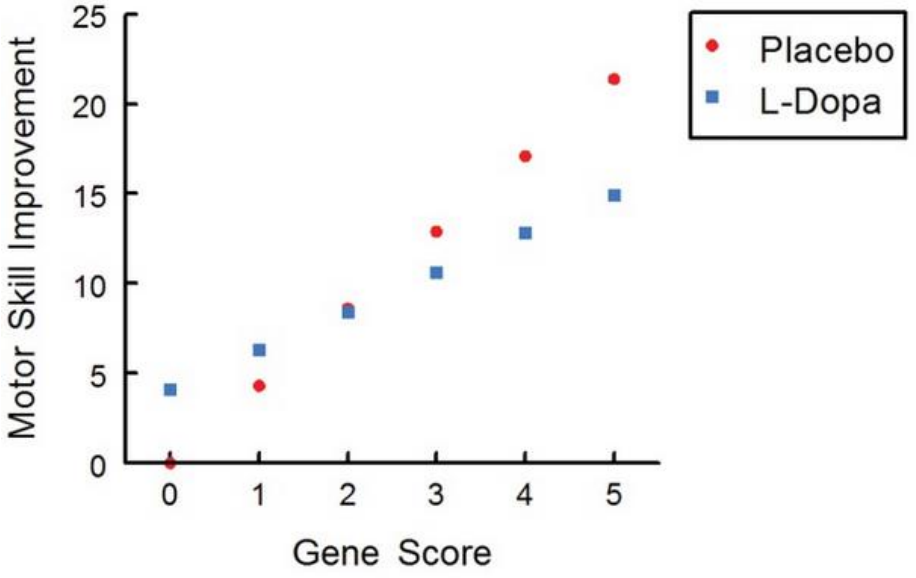
Genetic influence on motor learning and plasticity

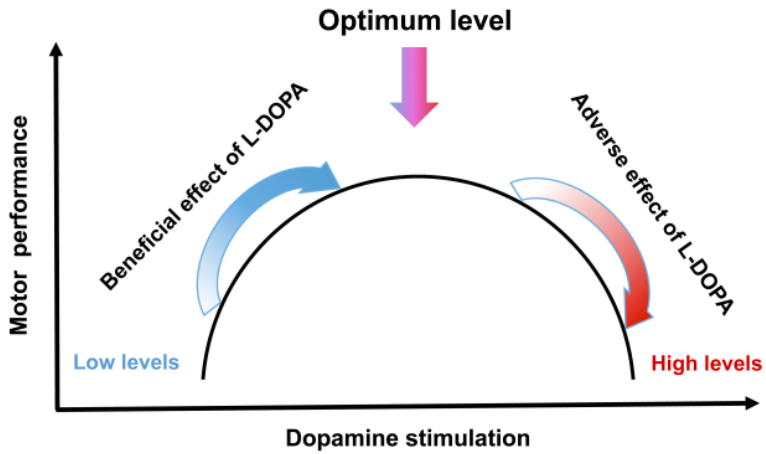
Table 1. Summary of polymorphisms and classification for gene score.

	DRD1 rs4532			DRD2 rs1800497			DRD3 rs6280			COMT rs4680			DAT rs28363170		
	A/A	A/G	G/G	Glu/Glu	Glu/Lys	Lys/Lys	Ser/Ser	Ser/Gly	Gly/Gly	Val/Val	Val/Met	Met/Met	9/9	9/10	10/10
Classification	0	1	1	1	0	0	0	1	1	0	1	1	1	1	0
Predicted Frequency	0.47	0.49	0.04	0.48	0.4	0.14	0.5	0.35	0.15	0.37	0.49	0.15	0.06	0.33	0.56
Number in our sample	27	20	3	19	26	5	22	23	5	19	27	4	1	11	36
Frequency in our sample	0.54	0.40	0.06	0.38	0.52	0.10	0.44	0.460	0.10	0.38	0.54	0.08	0.02	0.22	0.72

The five polymorphisms related to brain dopamine neurotransmission are listed. Each was in Hardy-Weinberg equilibrium.
doi:10.1371/journal.pone.0061197.t001

Pearson-Fuhrhop KM et al 2013,





The 2014 Nobel Prize in Physiology or Medicine

John O’Keefe
Born 1939, USA
University College London

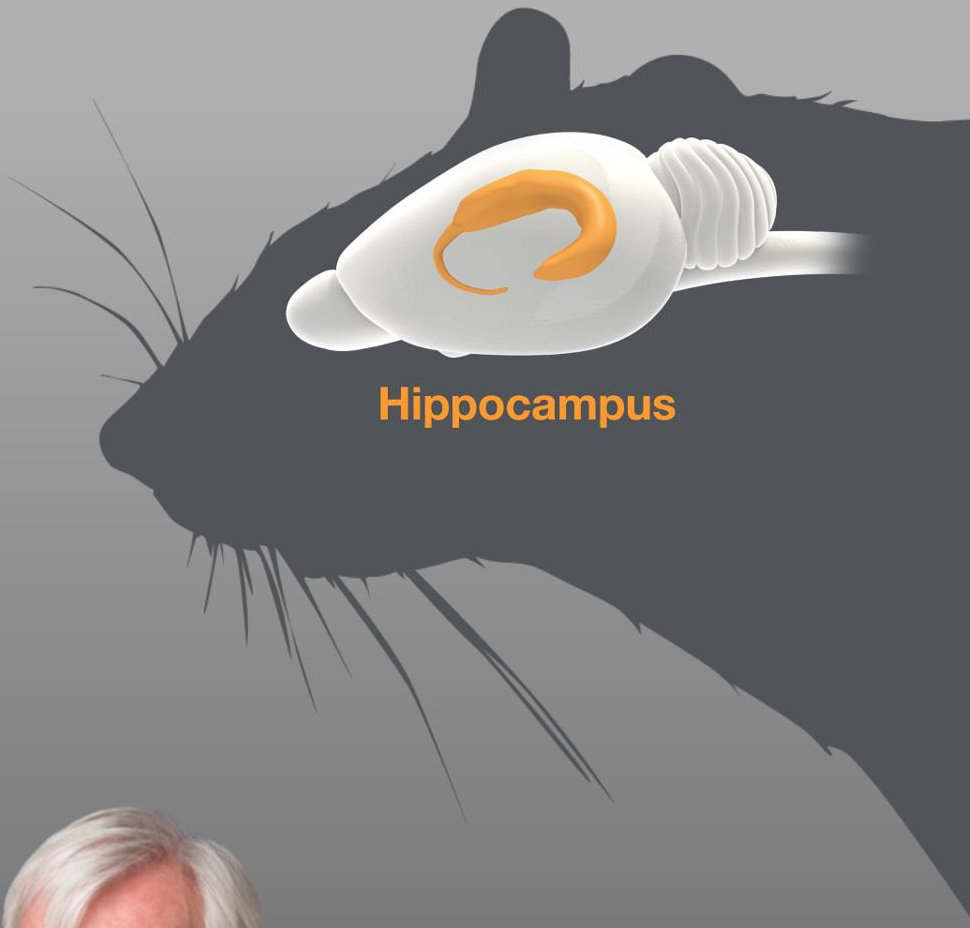
May-Britt Moser
Born 1963, Norway
Norwegian University of Science and Technology, Trondheim

Edvard I. Moser
Born 1962, Norway
Norwegian University of Science and Technology, Trondheim

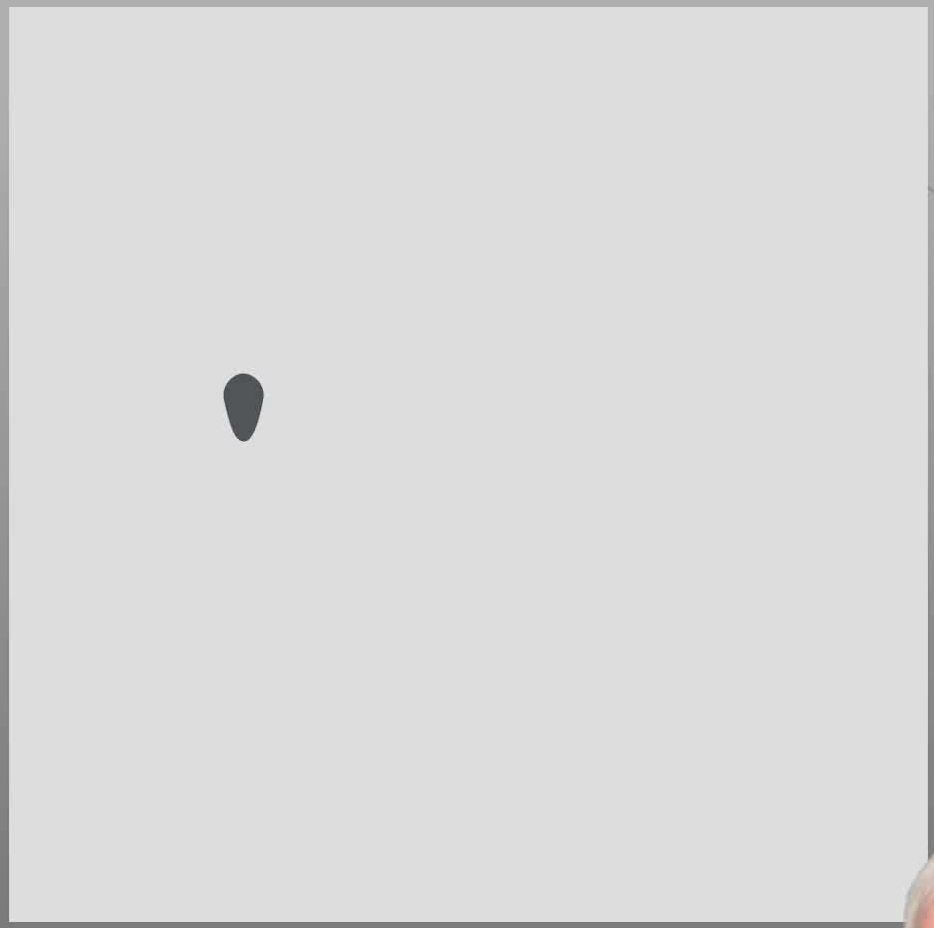

Sveavägen
Vasagatan
Arlanda Express
T-Centralen
Stockholm central
Klarabergsviadukten
Klarabergsgatan
Hötorget
Rådmansgatan
Rådhuset
Tegnérgatan
Torsgatan
Olof Palmes Gata
Bantorget
Norrmalm


Sveavägen
Vasagatan
Arlanda Express
T-Centralen
Stockholm Central
Klarabergsviadukten
Klarabergsgatan
Hötorget
Rådhuset
Radmansgatan
Tegnérgatan
Olof Palmes Gata
Norrmalm

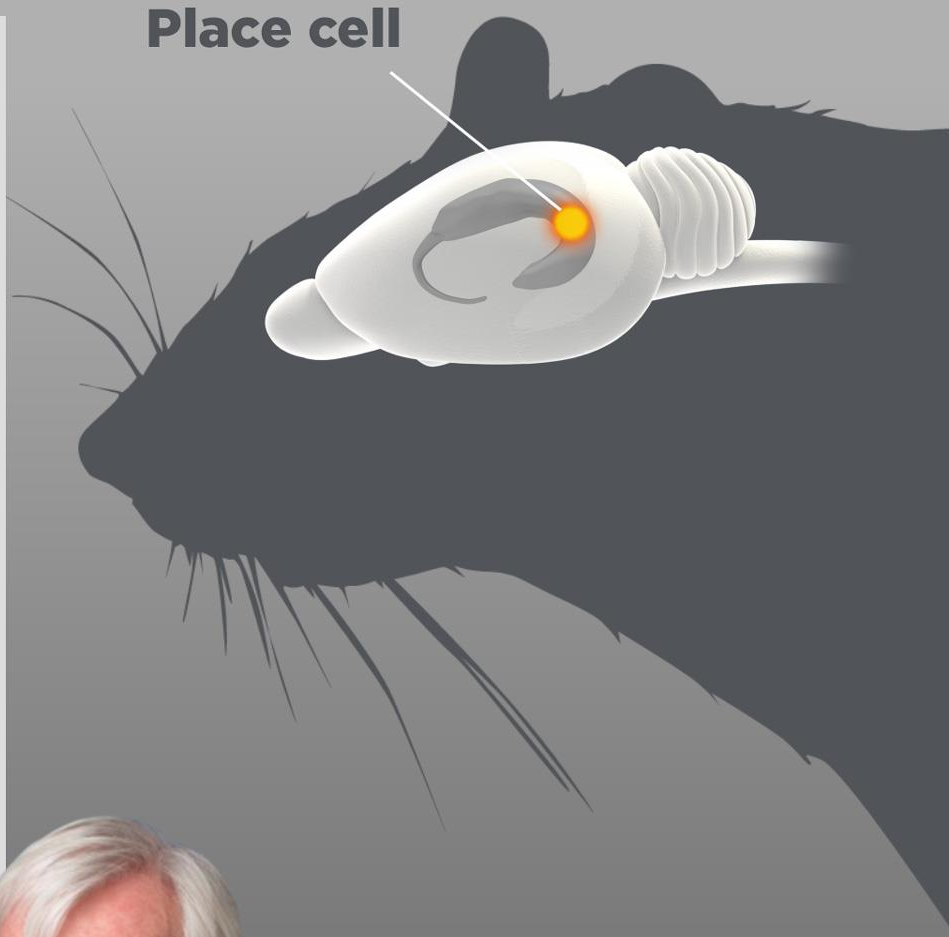
John O’Keefe and the place in space



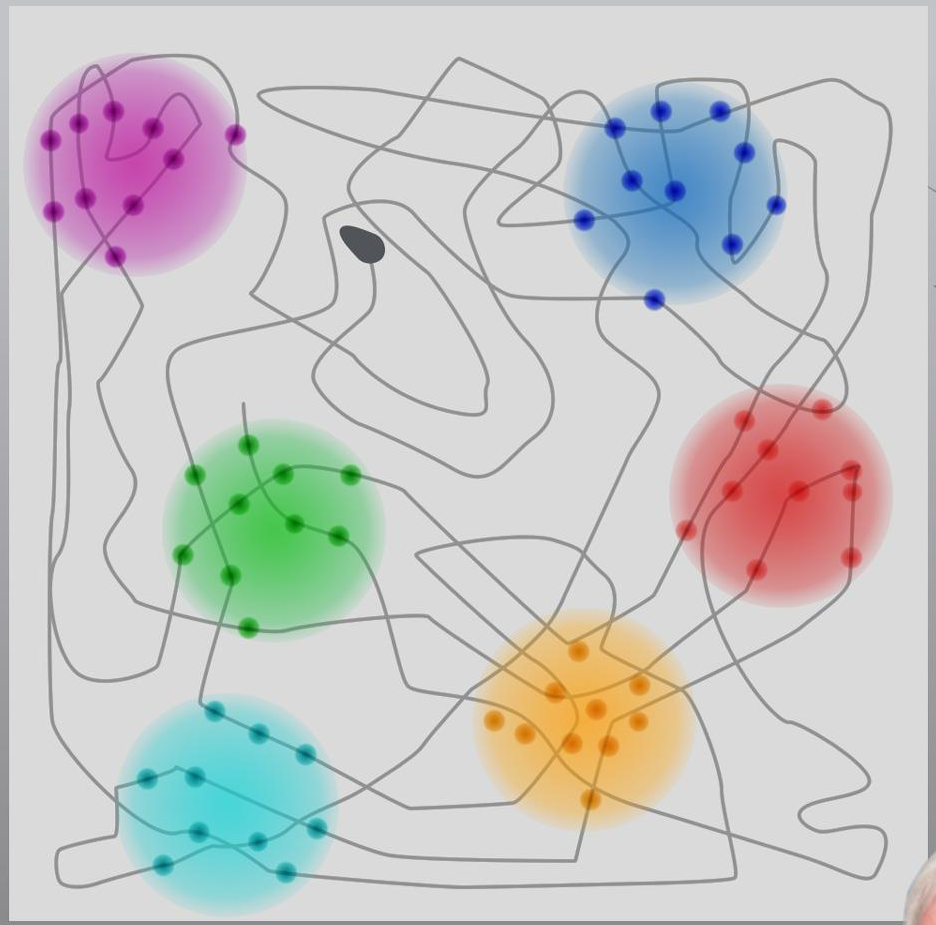
John O’Keefe and the place in space

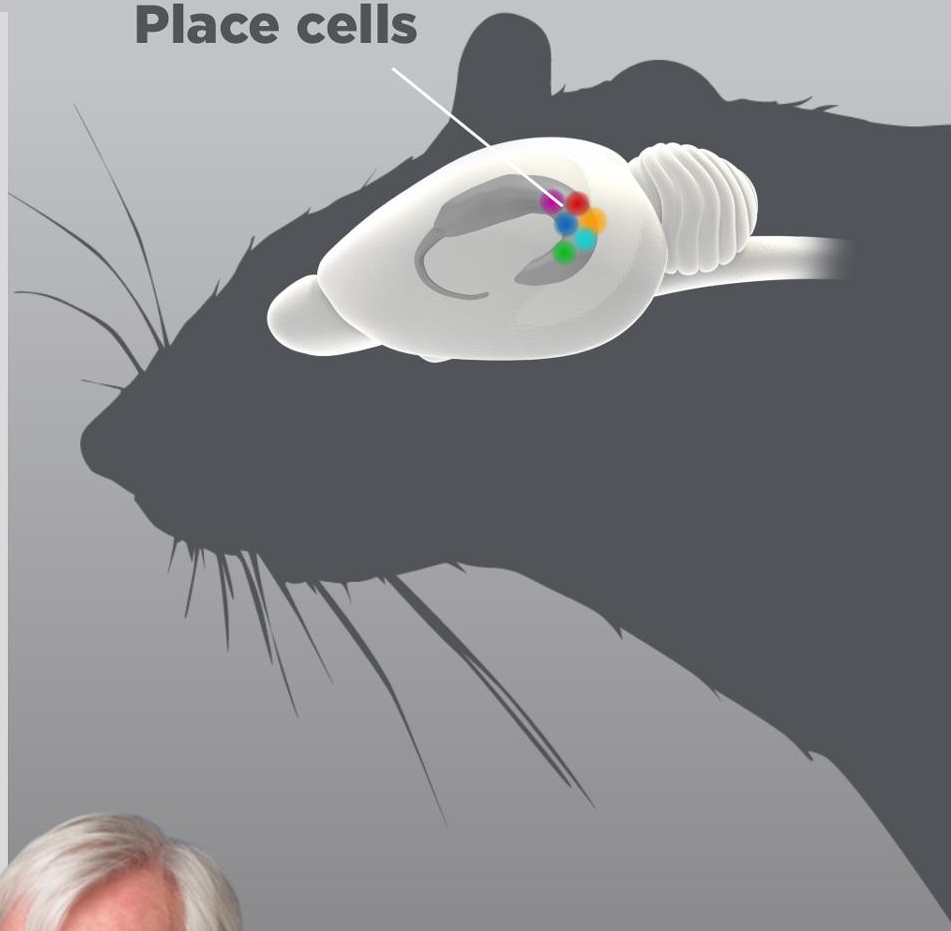


John O’Keefe and the place in space

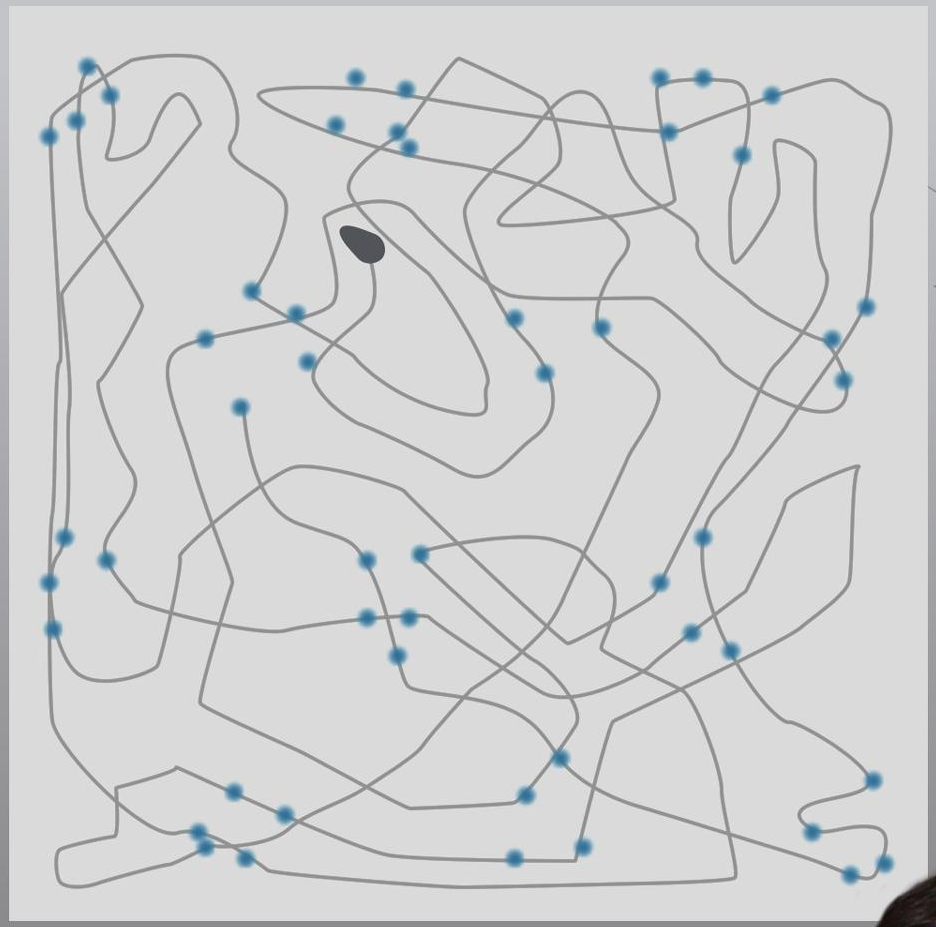


John O'Keefe and the place in space

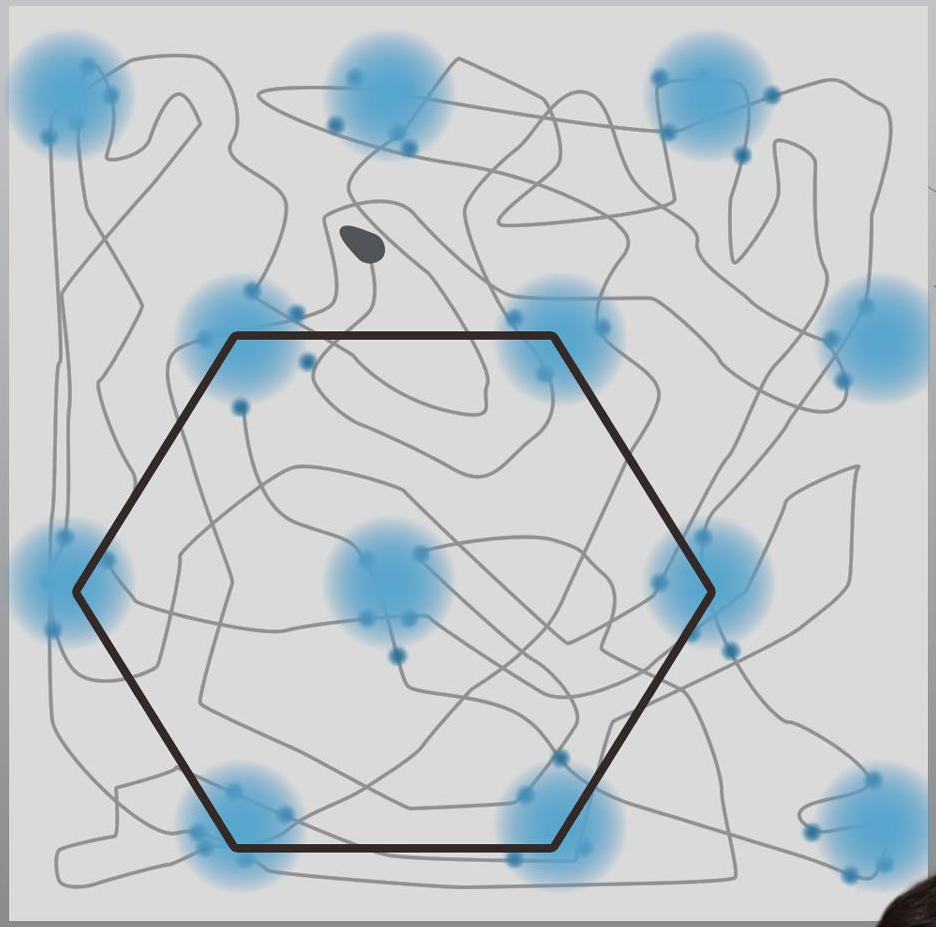




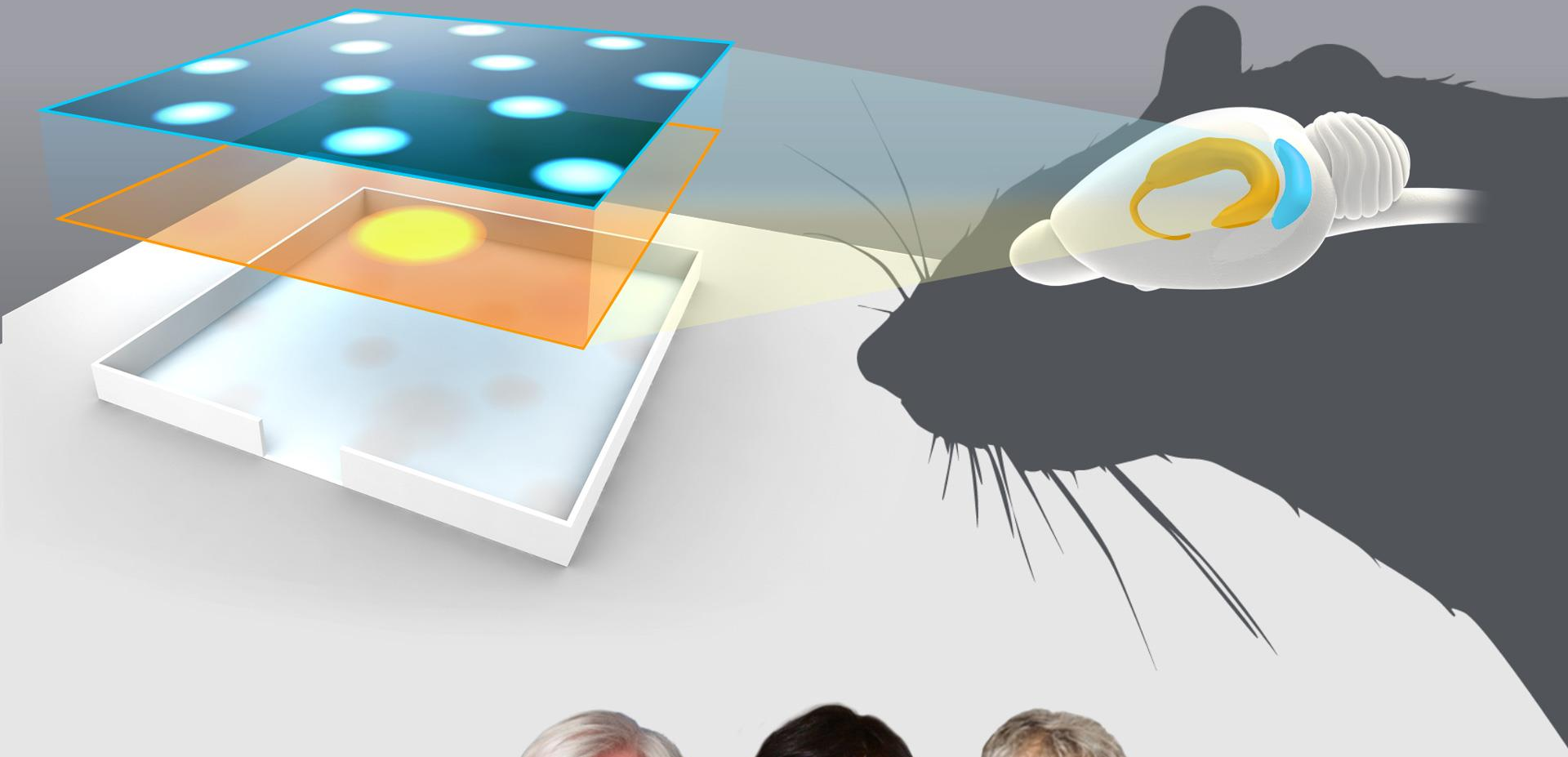
May-Britt Moser & Edvard Moser find the coordinates



May-Britt Moser & Edvard Moser find the coordinates



Place and coordinates are combined in a cognitive map



Personalised Intervention in CP

Brain structure
(MRI, DTI)
Lesion
time, localization, extent

Molecular imaging (PET)
Integrity of signaling systems

Functional plasticity (fMRI, MEG)

Behavioral phenotype

Genotype
e.g., SNPs, CNVs
epigenetics

Pharmacology
Monoamine enhancers
”Opening up plasticity window”

Challenge the Boundaries

Stockholm 1–4 June 2016

5th ICPC | 1st IAACD | 28th EACD

Save the date!

1 - 4 June, 2016

International Conference on Cerebral Palsy and other Childhood-onset Disabilities

5th International Conference of Cerebral Palsy (ICPC)

28th Annual Meeting of the European Academy of Childhood Disability (EACD)

1st Biennial Meeting of the International Alliance of Academies of Childhood Disability (IAACD)