CP-konferansen
Oslo 18. Mars 2019

Karolinska Institutet

Evidensbaserad behandling för barn med cerebral pares- betydelse av motorisk inlärning och träning

Hans Forssberg, MD, PhD
Neuropaediatrics
Karolinska Institutet

CP definition
(SCPE DMCN 2000, Rosenbaum DMCN 2007)

Five key elements

- a **group** (several different disorders)
- of **permanent** but not unchanging
- disorders of **movement, posture** and **motor function**,
- due to a **non progressive**
- interference/**lesion**/abnormality of the **immature brain**

Clinical characterisation of CP

- **Type:** spastic, ataxic, dyskinetic
- **Distribution:** uni- or bilateral
- **Functional level of motor abilities**
  → GMFCS, MACS, CFCS, EDACS
- **Accompanying impairments**
  → Sensation, perception, cognition
  → Communication and behaviour
  → Epilepsy
  → Secondary musculoskeletal problems
- **Brain pathology** (MRI, CT)
  → Identify cause and timing

cerebral palsy treatment

Discover Dr. Nuzzo's method | for children with cer. palsy

Annons www.kids2walk.com/

Kids2Walk help children with **cerebral palsy** to restore mobility with the SPML method. Find out the prerequisites for undergoing the SPML method and the evaluation process.

Get to know kids2walk · Which kids can benefit · Check the SPML Videos

Stem Cell Institute for CP | Cerebral Palsy Therapy

Annons www.stemcell-host.com/

Visible improvements, packages from $8K usd with **therapy**, lodging and transport. More than 500 patients. Latam`s FACT approved lab. 24/7 Follow up. 80% Success rate. English speaking driver. Point of interest visits. Inprove quality life. Lodging included. Amenities: Lodging, Pool access, Wifi.

Stem Cell for Autism · Stem Cell Blog · Stem Cell for CP · HOST Medical Tourism

Treatment For Cerebral Palsy | Treatment For Cerebral Palsy.

Annons no.informationvine.com/Svar

Finn relevante resultater med informationvine.com på nett. Lær mer. Søk og finn nå. Finn relevant informasjon. Raske og enkle svar. Typer: Finans, Business, Teknologi, Helse, Reise.

Therapeutic approaches to improve motor activity in CP

Bobath/NDT
Conductive education
Sensory integration
Vojta
Adeli suit
Aim-oriented management
Advance neuromotor rehabilitation
Biofeedback
Dohsa-Hou
Electrical stimulation
Massage
Heat Therapy
Locomat
CIMT

Early intervention (Portage)
Functional PT
MOVE
Patterning (Doman-Delacato)
Pelvic positioning
Physical activity training
Strength training
Targeted training
Training by Phelps (15 modal)
Recreational (hippo-, hydro-)
Hyperbar oxygen
Acupuncture
Shock therapy
Manipulation of spine (Kozyavkin)

Dolphin Assisted Therapy

Significant improvements of your health by getting closer to nature!

Dr. Lukina was the first in the world scientist to receive Doctoral Degree based on findings in the field of Dolphin Assisted Therapy..

THE DOLPHIN THERAPY PROGRAM.

The Dolphin Assisted Therapy program is a result of 35 years of continuous scientific work with dolphins.

Over the years family doctors advised alternative treatments (Dolphin Assisted Therapy) to more than 2,000 patients because traditional therapy did not work for them. Those who participated in Dr. Lukina's therapy showed significant improvements in their health conditions over the years.

In particular, interactions with dolphins showed dramatic effects in the treatment of patients with Cerebral Paralysis, Stammering, and Specialized Phobias.

Dolphin Assisted Therapy is not a miracle. **A filing of a joy and harmony during the treatment sessions in the hearts of children, their parents and support team is a guaranteed outcome. Contacts with the friendliest creatures of the sea and therapy sessions are like a game for patients and others. It is, nevertheless, a very important part of a therapy sessions.**

The unification of psychological treatments and physical interactions during the treatment sessions provide stable positive results for the patients.

read more about D.A.T. program history...

PRACTICAL RECOMMENDA

1. Dolphin therapy is recommended in the following cases:

- Dolphin therapy is recommended in the following cases. Patients (adults a

· Chronic fatigue syndrome;
· Emotional stress;
· Phobias;
· Depression syndrome;
· Neurasthenia.

The main expected ef s significant improvement of health conditions.

Children suffering from:

· Cerebral palsy.

The main expected effe increase in activity and ability to adapt socially.

2. In selecting patients for dolphin therapy one sho as vulnerability to epileptic seizure.

3. During the formation of the dolphin therapy prog

- the healing effect of the dolphin is most complete dolphin-patient;

- the process of dolphin therapy should include stages of psychological prep and in the water, relaxation procedures after the contact of the patient with conclusion of sessions involving direct contact with the dolphin;

- the optimal duration of dolphin-patient direct contact is 15-20 minutes onc

HELP THE UNFORTUNATE CHILDREN

Therapy Hot News

When you are present at the Dr. Lukina's team treatment therapy sessions you are changing physically and mentally. The Dolphin Assisted Therapy opens the internal power of patient's personality. Of course, it's not the game. It's a process thought out to a

by nature. She spends a lot of time with Barbie.

HBOToday.com

Chico Hyperbaric Center

hyperbaric oxygen treatment facility

Welcome...

The Chico Hyperbaric Center is quickly becoming the hyperbaric oxygen (HBO) treatment facility of choice for people living throughout the United States and Canada.

Why are so many people committed to the Chico Hyperbaric Center for their HBO therapy? Part of the reason has to do with the truly unique and compassion-driven way in which Chico Hyperbaric Center (CHC) was founded. See Why We Are Here to understand how a dedicated group of Chico residents banded together to bring a "state of the art" hyperbaric facility to northern California. Discover how these people made a difference in the lives of local residents—including many children—and in the lives of people across North America.

- Home
- What's New!
- About CHC
- Treatment
- Travel & Accommodations
- Contact Us
- Links
- Site Map

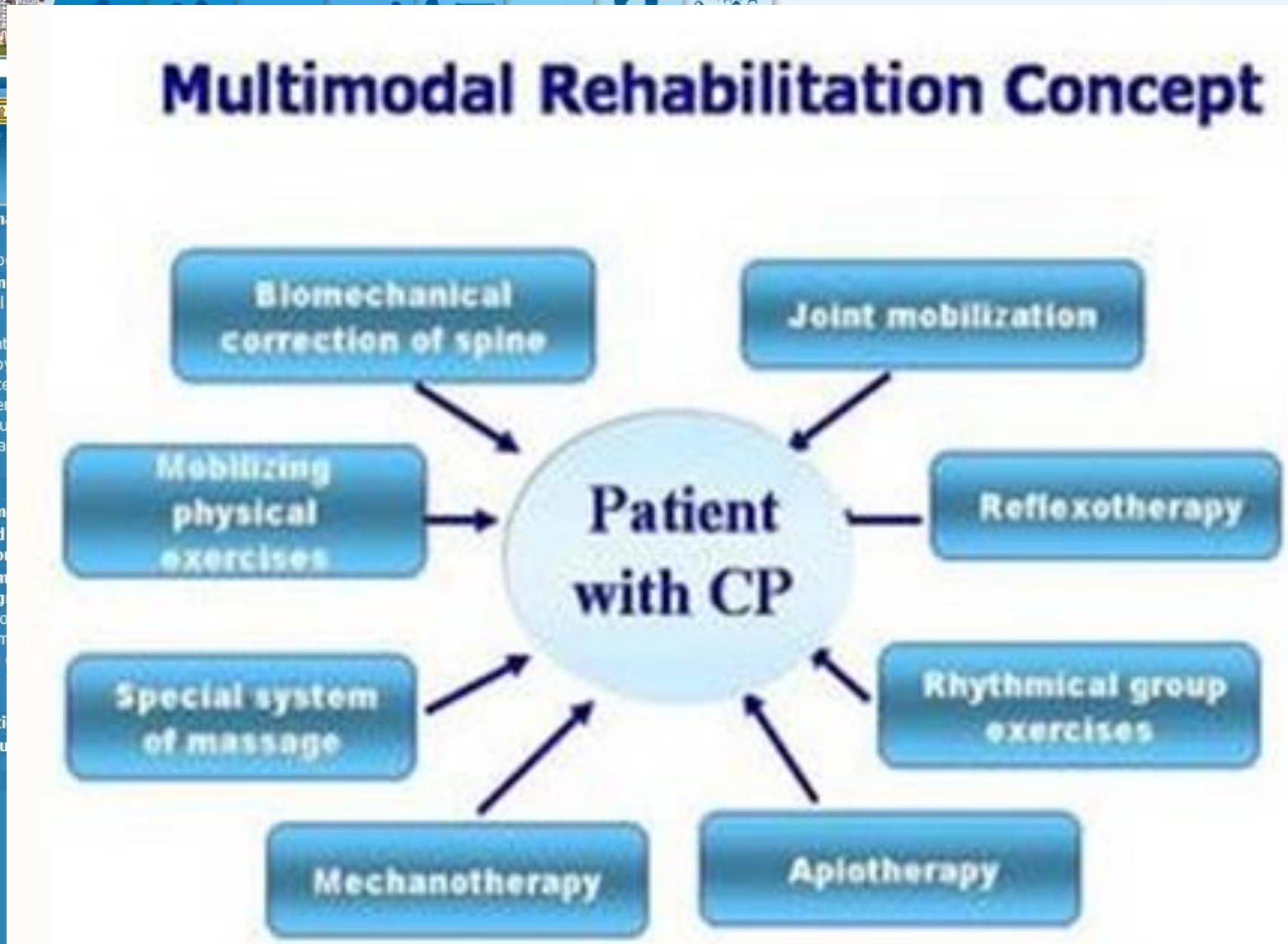
Click on photo to zoom in.

You can also discover how we have taken the hassle out of arranging accommodations during treatment in Chico. We hope our Travel & Accommodations section will answer most of your questions. You can also see Our Facilities to learn about one patient's experience of traveling to Chico and the support he received while living here and taking treatment at the Chico Hyperbaric Center.

If you are new to HBO therapy we recommend our Treatment section. Specifically, What Is HBO Therapy and How Is HBO Therapy Administered are designed to answer most of your questions about HBO therapy itself. Note our special descriptions of:

- Lyme Disease and HBO Therapy
- Cerebral Palsy and HBO Therapy
- Stroke and Traumatic Brain Injury and HBO Therapy

Chico Hyperbarics is committed to advancing the scientific body of evidence that supports the use of HBO therapy for conditions currently considered "investigational" in nature. Please view Our Published Research to read our latest



SEARCH
ENTER THE
General Inform
History
Pathophysiolo
Main componen
Biomechanical the spine
Extremity Joint
Reflexotherapy
Massage syste
Mobilizing exer
Rhytmical grou
Mechanothera
Apitherapy
Video
A day of treatm
Indications and
Contraindicatio
Biodynamical m
correction prog
Program of bio correction of m
Hand training
Training chair
Spider
Early interventi
Treatment Resu
Forum

formation
S IN SHORT
08.04.2010 nternational erebral Palsy ymposium in ruskavets
05.01.2010 rof Hubertus on Voss warded with krainian rder of Merit
01.12.2009 isit of Prime inister
28.09.2009 cheduled reatment ourses for ear 2010
05.09.2009 re congress ymposium in ruskavets

19% began to walk

87% opened the fist

and Truskavets (Ukraine). In July, 2003, the International Clinic of Rehabilitation was opened in Truskavets. It offers the latest technology in Medical Rehabilitation.

Home

The XCell-Center is a private clinic group and institute for regenerative medicine located in Düsseldorf and Cologne, Germany. Bringing together therapeutical use of autologous adult stem cells and medical research, it is our mission to:

- Provide therapeutic application of autologous adult stem cells to patients at the highest medical standard;
- Extend existing knowledge on the effects of autologous adult stem cells by supporting pre-clinical and clinical research.

We offer patients with degenerative diseases the opportunity to undergo an innovative and promising stem cell treatment.

Since the start in January 2007, **more than 2400 patients** have safely undergone our various stem cell treatments.

Therapeutic use

The XCell-Center treats patients with their own autologous adult stem cells. It is the first private clinic worldwide to [illegible] official license for the extraction and approval of stem cell material for autologous treatment.

Therapy focuses on the treatment of cerebral palsy, spinal cord injuries, diabetes mellitus (types 1 and 2 as well as sequelae) and neurological diseases/disorders such as Parkinson's and stroke. Further indications include multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), and Alzheimer's as well as arthritis, heart disease, and eye diseases such as macular degeneration.

Advisory board

News

FOLLOW US ON twitter

Stem cells and tumor risk more...

March 25, 2010
Video Documentary of Dementia Patient, Giulia Serafini's Remarkable Recovery Following Stem Cell Therapy more...

March 10, 2010
Encouraging Stroke Treatment Results Now Available more...

March 10, 2010
NBC News Video Feature "Small Miracles: How life has changed for Dom and H" (cerebral palsy) more...

March 9, 2010
60% of Spinal Cord Injury Patients Improved - The Latest Statistics for 140 Spinal Cord Injury Patients more...

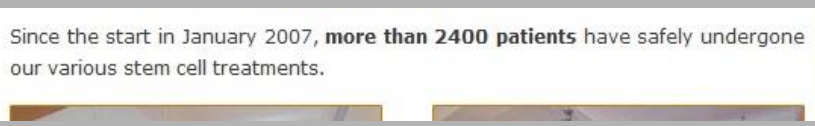
March 8, 2010
XCell-Center Presents Impressive Results from Cerebral Palsy Stem Cell Treatment more...

February 16, 2010
The Lewiston Morning Tribune: Stem Cell Therapy Works for Cousins more...

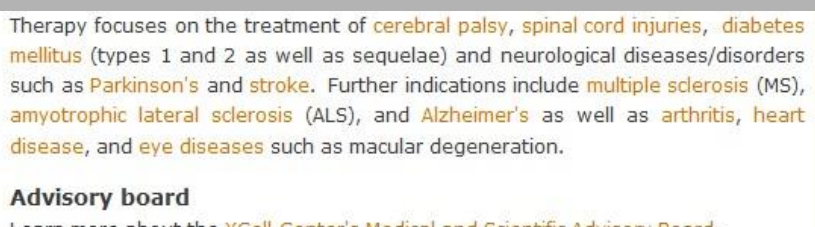
February 9, 2010
Saving Limbs: Autologous Mesenchymal cells for the treatment of patients with critical

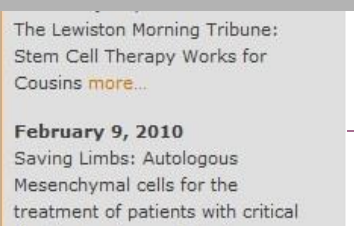
XCell-Center Presents Impressive Results from Cerebral Palsy Stem Cell Treatment

The XCell-Center, Europe's leading stem cell therapy provider has released impressive results from a follow-up study of 100 cerebral palsy patients treated with autologous bone marrow stem cells.



"*Griffin underwent his first stem cell treatment at the XCell-Center in April 2009. Cognitive improvements materialized after about 3 weeks and physical improvements started at 3 - 6 months. Griffin's muscle tone improved along with his attention span and ability to engage others. He no longer required Botox which he needed twice before stem cell therapy,"*





Saturday 29 October 2011

The Telegraph

Karolinska Institutet

Experts in stem cell research had accused the clinic of preying on vulnerable patients, desperately seeking a cure for such illnesses and diseases as cerebral palsy, multiple sclerosis, autism, Parkinson's, Alzheimer's, heart disease, diabetes and spinal cord injuries.

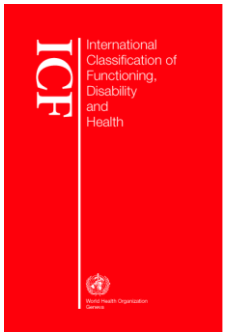
Europe's largest stem cell clinic shut down after death of baby

Ira Hermann, who runs the German stem cell network which funds scientific research projects, said: "XCell was offering unproven treatments and taking a lot of money from very vulnerable people.“

Professor Chris Mason, chair of regenerative medicine at University College London, said: "This is excellent news for the European cell therapy industry. XCell had failed to demonstrate its treatments were either safe and effective or had scientific rationale.“

Principles for evidence based interventions in childhood disability

1. **Reliable and valid methods to measure treatment results**
2. **Clinical trials**
3. **Science based framework predicting/explaining treatment results**

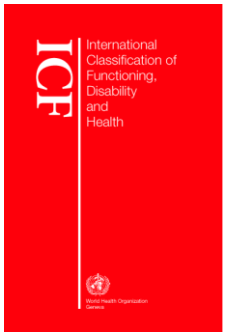


Measurements in motor domain

Health

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

Environment **Personal factors**



Measurements in motor domain

Health

Ashworth scale
Tardieu
HAT

GMFM-66

Body function
&
Body structure

ROM
SMC
Strength
Muscle fatigue
Sensibility
SAROMM
Gait analysis

Activity

PEDI FSS
AHA

Participation

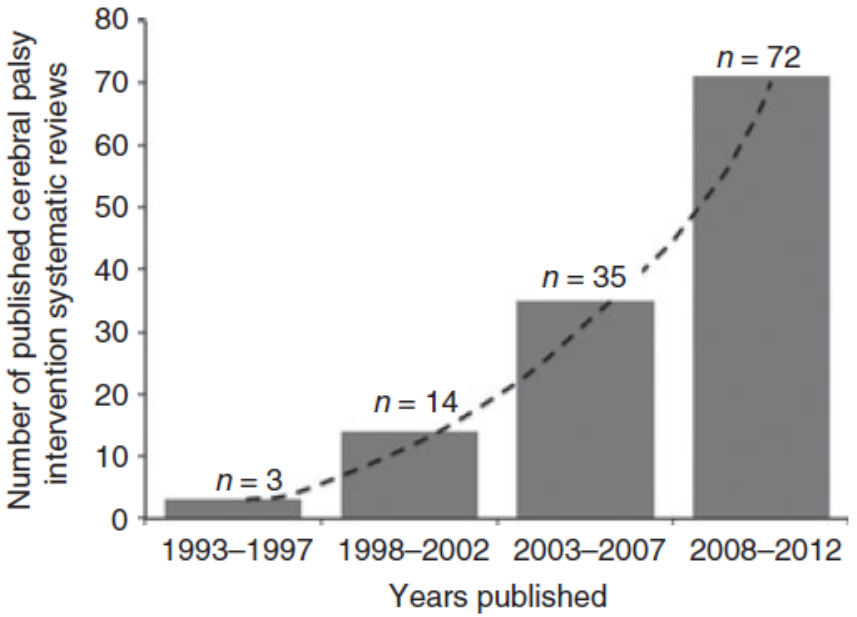
CAPE & PAC
PEDI CAS
PMP

Environment

Personal factors

Principles for evidence based intervention in childhood disability

1. Reliable and valid methods to measure treatment results
2. **Clinical trials**



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

RCT
Randomized Controlled Trial

- Two arms
  - →Treatment group
  - →Control group
- Randomization
- Placebo (control group)
- Blind; both patient and treatment provider
- Stratification; similar characteristics (sex, age, level)
- Statistical power

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

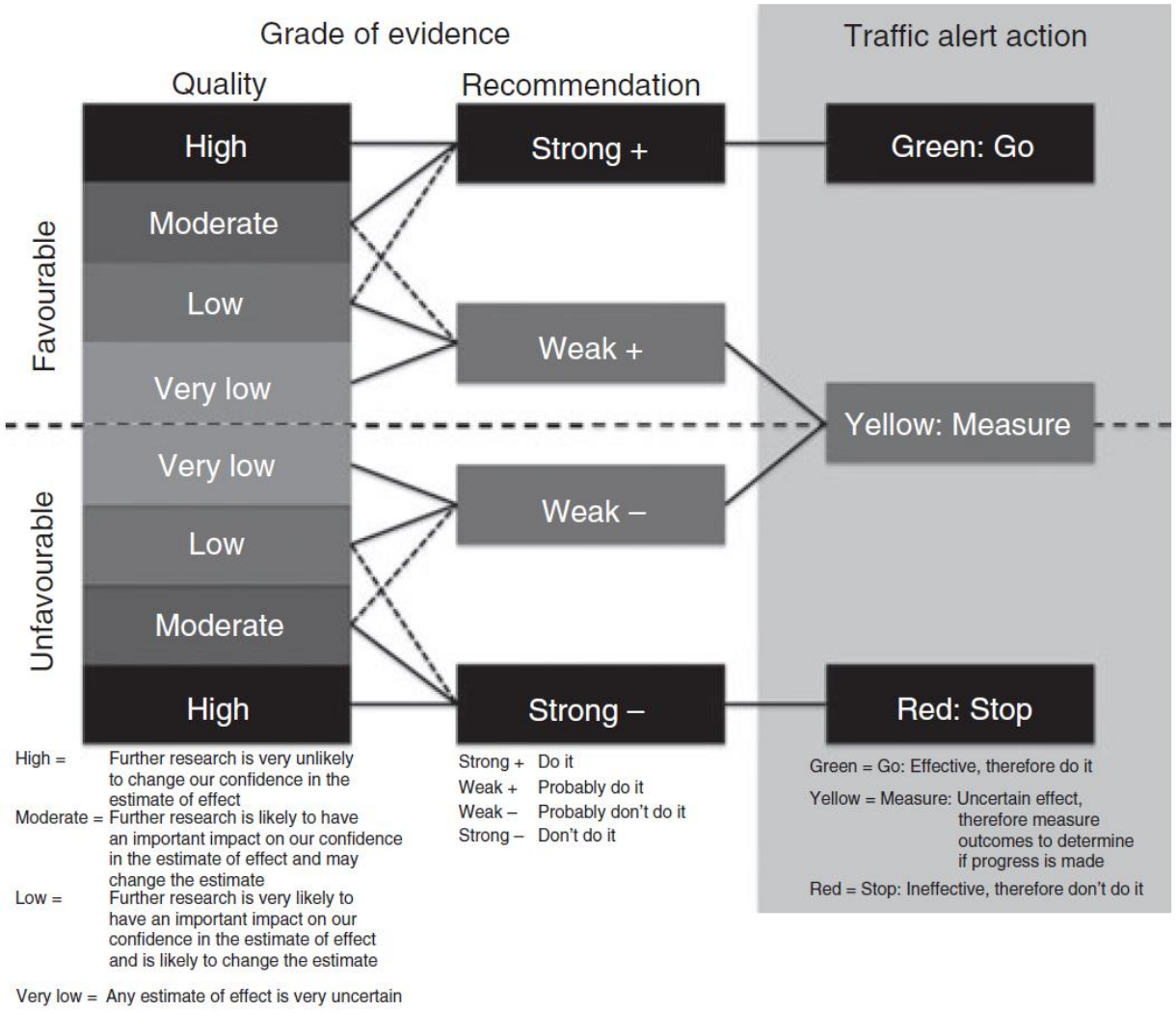
IONA NOVAK[1,2] | SARAH MCINTYRE[1,2] | CATHERINE MORGAN[1,2] | LANIE CAMPBELL[2] | LEIGHA DARK[1] | NATALIE MORTON[1] | ELISE STUMBLES[1] | SALLI-ANN WILSON[1] | SHONA GOLDSMITH[1,2]

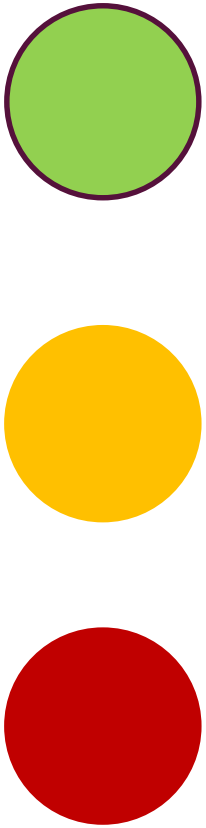
Developmental Medicine & Child Neurology 2013, 55: 885–910

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.

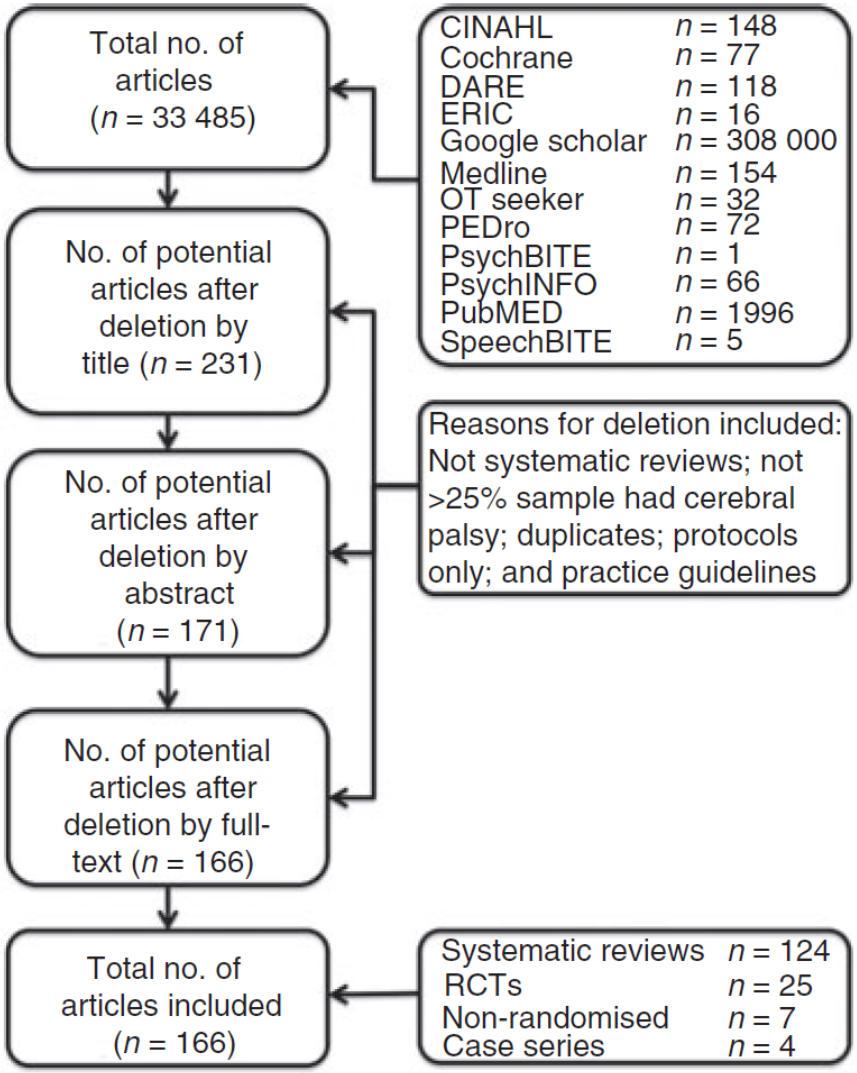
A systematic review of interventions for children with cerebral palsy: state of the evidence





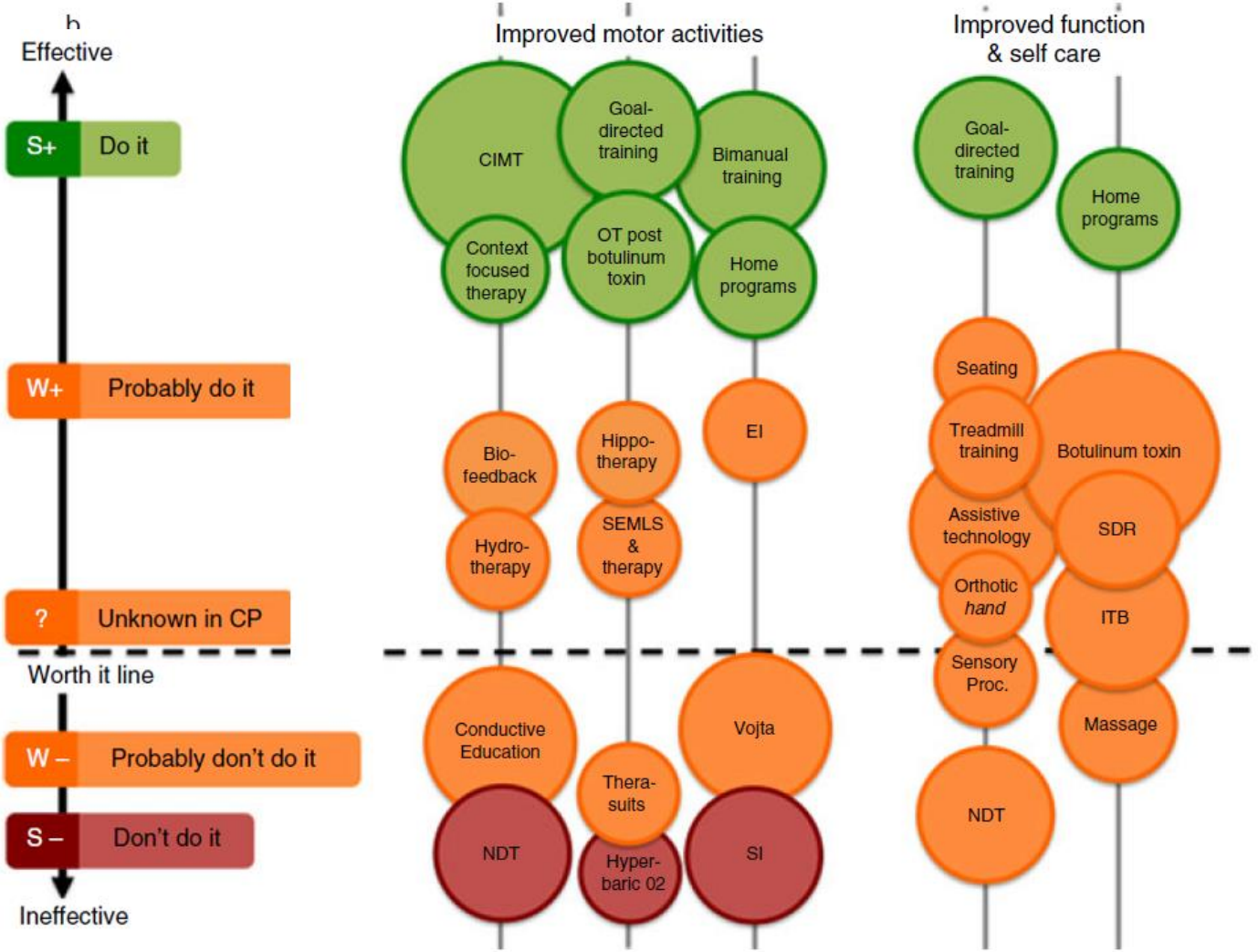
Developmental Medicine & Child Neurology
Volume 55, Issue 10, pages 885-910, 21 AUG 2013 DOI: 10.1111/dmcn.12246
http://onlinelibrary.wiley.com/doi/10.1111/dmcn.12246/full#dmcn12246-fig-0001

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



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



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

APPRAISAL OF GUIDELINES FOR RESEARCH & EVALUATION II

AGREE II

INSTRUMENT

WHO Universal Coverage – Rehabilitation 2030: a call for action
Package of rehabilitation guidelines
Appraisal of guidelines for research & evaluation (AGREE II)

Principles for evidence based interventions in childhood disability

1. Reliable and valid methods to measure treatment results
2. Clinical trials
3. **Science based framework predicting/explaining treatment results**

Cerebral Palsy
Movement Disorders

+

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

-

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

Intervention Cerebral Palsy (+)

- **Spasticity**
  - → Pharmacology
    - systemic
    - muscle
    - intra-thekal
  - → Surgery
    - orthopedic
    - neurosurgery
  - → Physiotherapy
  - → Casting, splinting

- **Musculoskeletal malformations**
  - → Ibid

- **Dyskinesia/Dystonia**
  - → Pharmacology
  - → Deep Brain Stimulation

- **Developmental reactions**
  - → ?

Intervention
Cerebral Palsy (-)

- **Paresis**
  - → **Training muscle strength**
- **Central Dys-coordination**
  - → **Motor Learning**
  - → **Motor Training**

DEVELOPMENTAL MEDICINE & CHILD

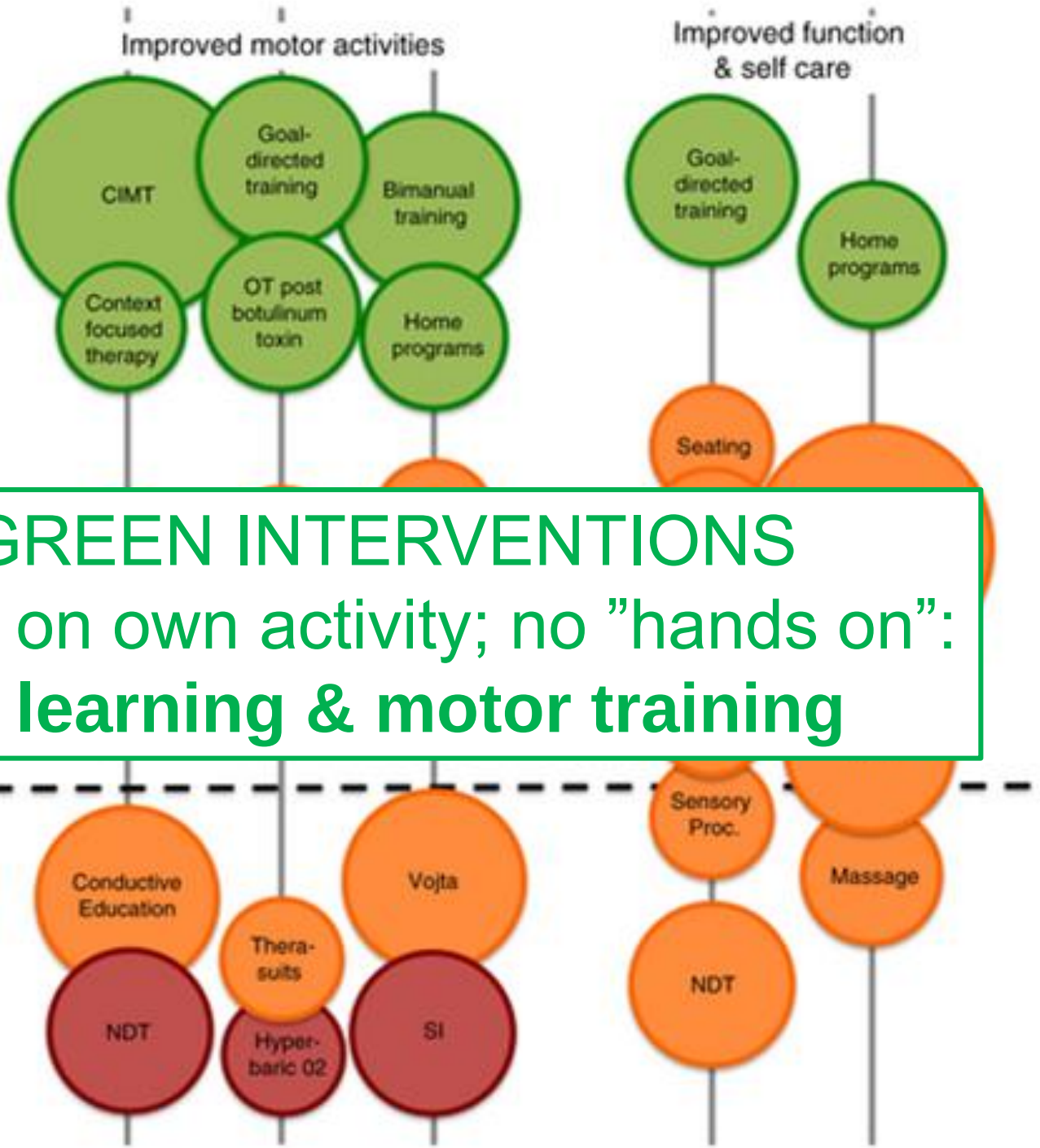
A systematic review
palsy: state of the ev

IONA NOVAK[1,2] | SARAH MCINTYRE
NATALIE MORTON[1] | ELISE STUMBI

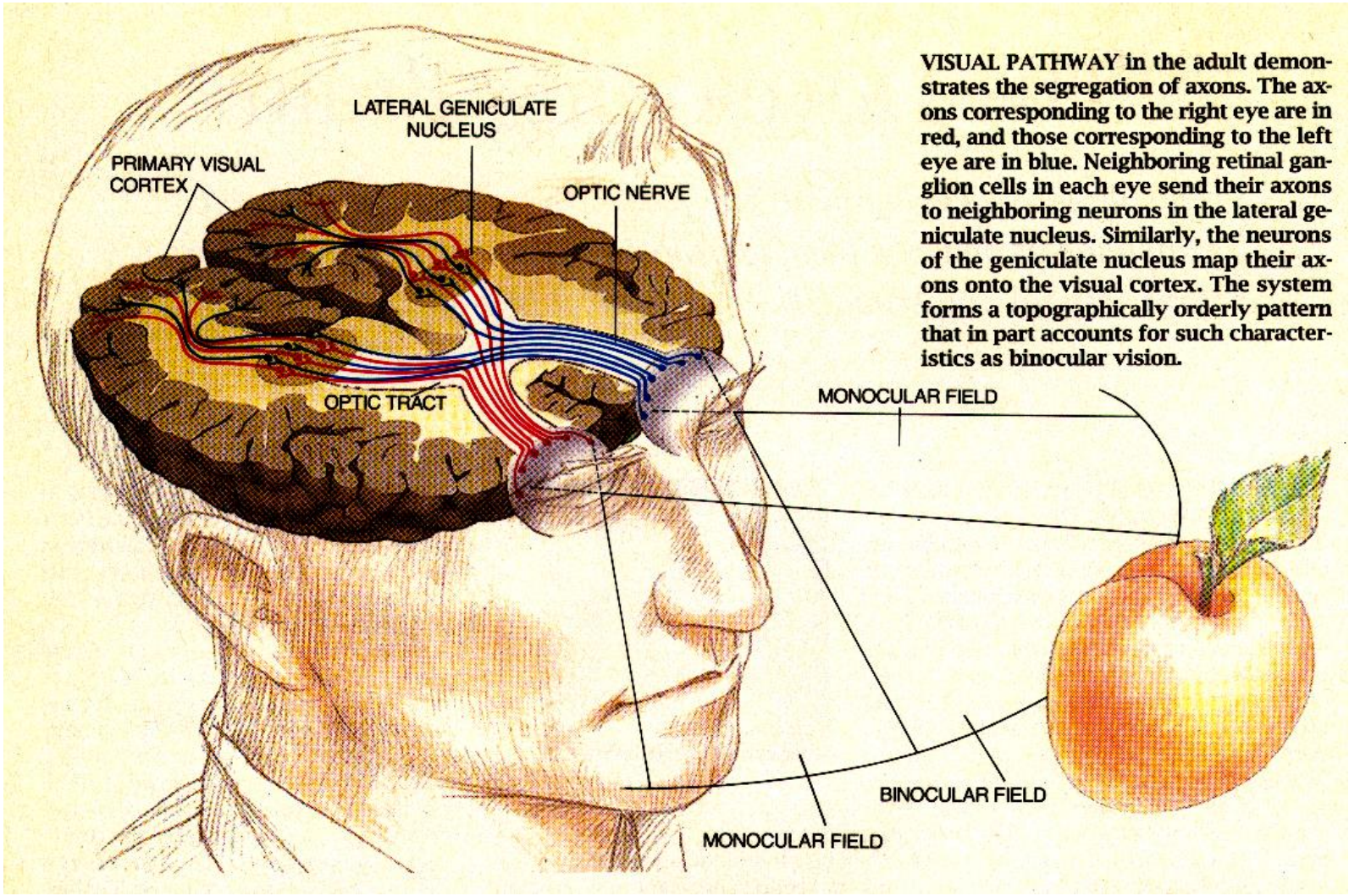
Developmental Medicine

Wh

- Of 6
- 70%
- 6% are proven to be i
- Effective interventions
  knowledge.
- All effective interventi



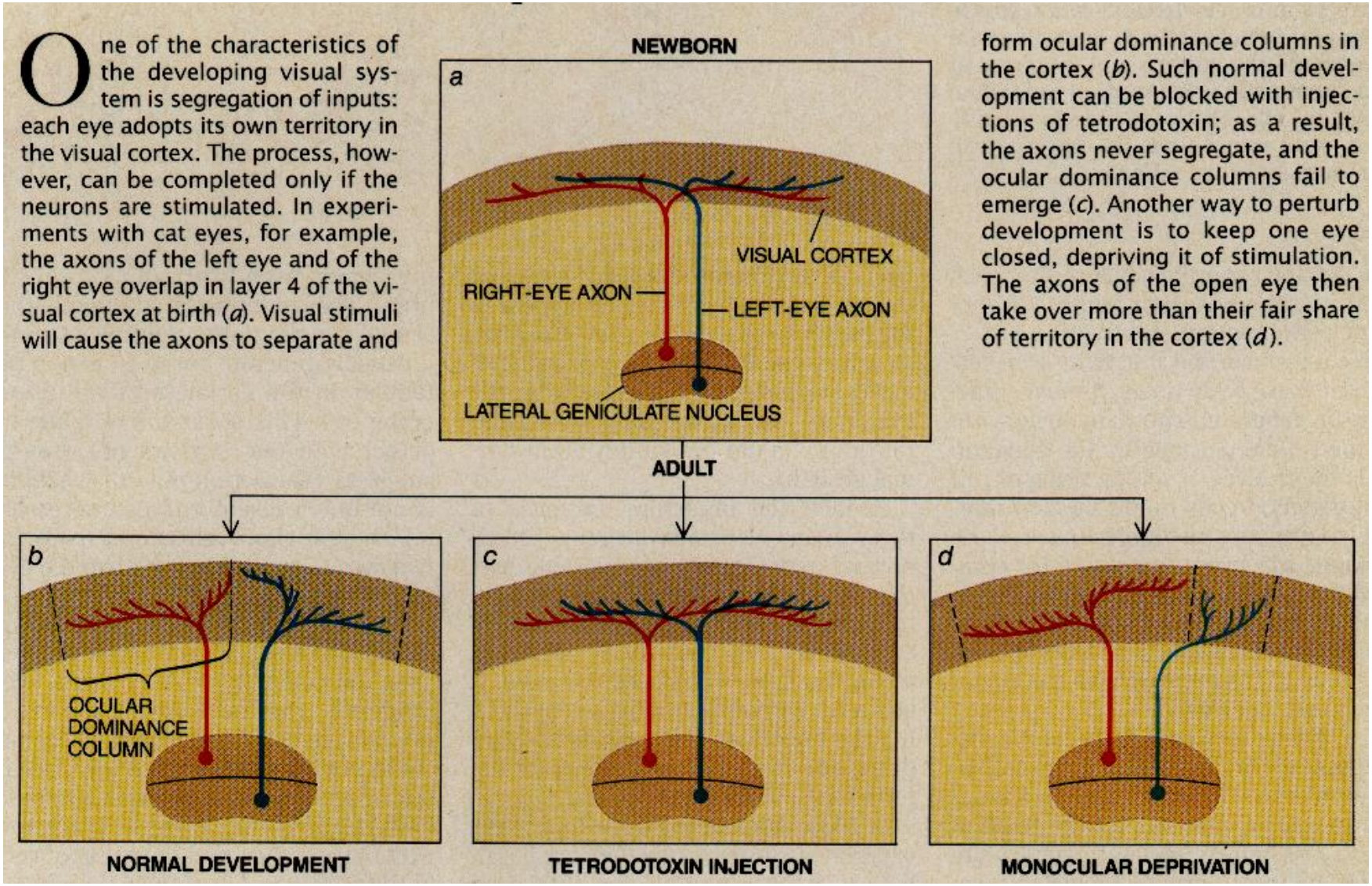
All ”GREEN INTERVENTIONS
are based on own activity; no ”hands on”:
motor learning & motor training



VISUAL PATHWAY in the adult demonstrates the segregation of axons. The axons corresponding to the right eye are in red, and those corresponding to the left eye are in blue. Neighboring retinal ganglion cells in each eye send their axons to neighboring neurons in the lateral geniculate nucleus. Similarly, the neurons of the geniculate nucleus map their axons onto the visual cortex. The system forms a topographically orderly pattern that in part accounts for such characteristics as binocular vision.

Plasticity of the visual system

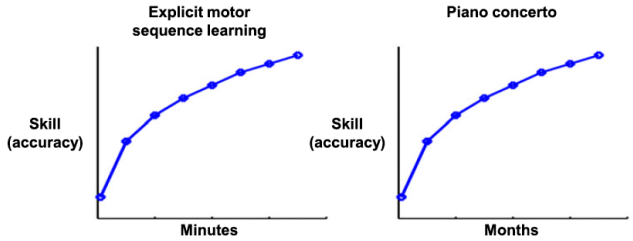
One of the characteristics of the developing visual system is segregation of inputs: each eye adopts its own territory in the visual cortex. The process, however, can be completed only if the neurons are stimulated. In experiments with cat eyes, for example, the axons of the left eye and of the right eye overlap in layer 4 of the visual cortex at birth (*a*). Visual stimuli will cause the axons to separate and form ocular dominance columns in the cortex (*b*). Such normal development can be blocked with injections of tetrodotoxin; as a result, the axons never segregate, and the ocular dominance columns fail to emerge (*c*). Another way to perturb development is to keep one eye closed, depriving it of stimulation. The axons of the open eye then take over more than their fair share of territory in the cortex (*d*).



Hubel & Wiesel

Motor skill learning/motor training

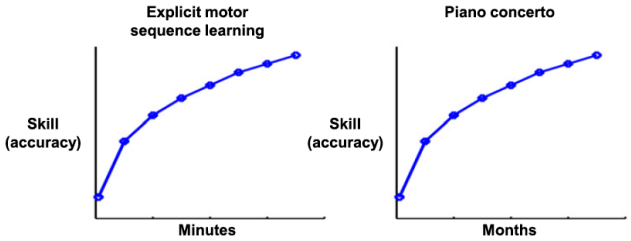
- Learning curve



Dayan & Cohen 2011

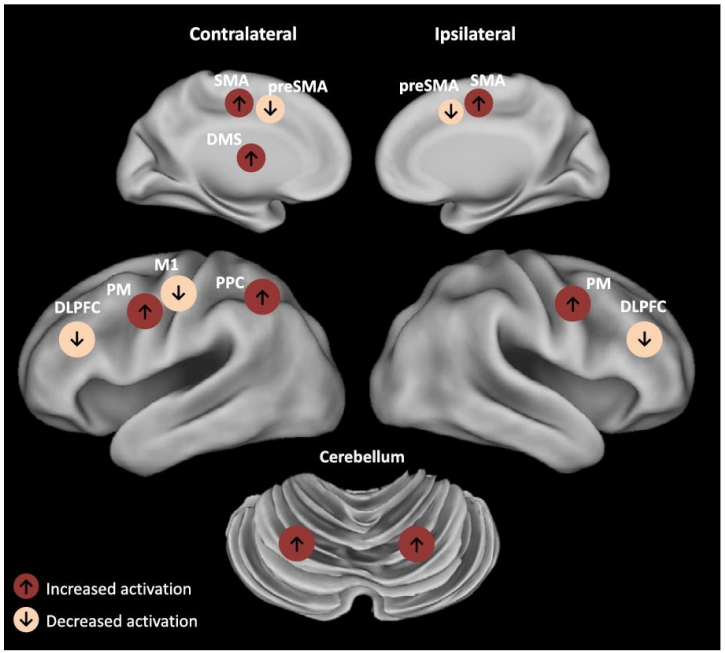
Motor skill learning/motor training

- Learning curve



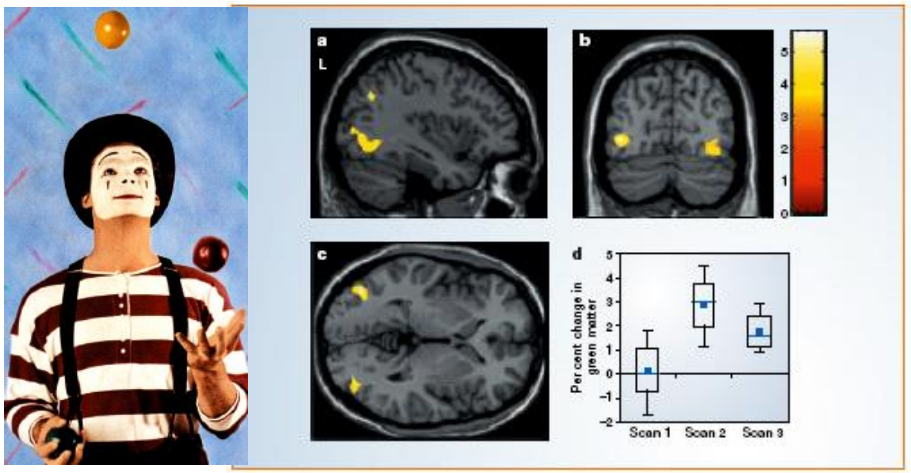
Dayan & Cohen 2011

- fMRI changes



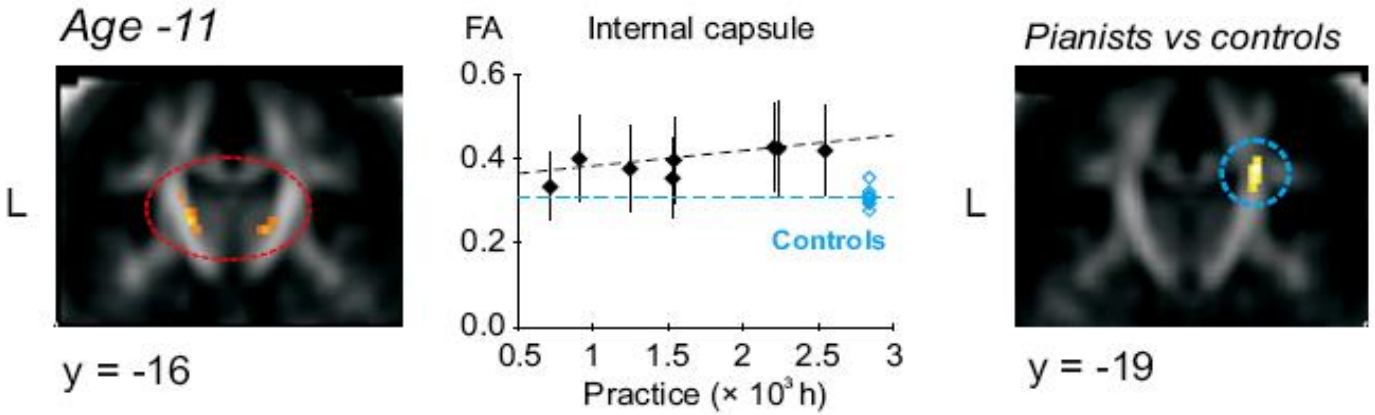
Motor skill learning/motor training

- Learning curve
- fMRI changes



Draganski et al 2004

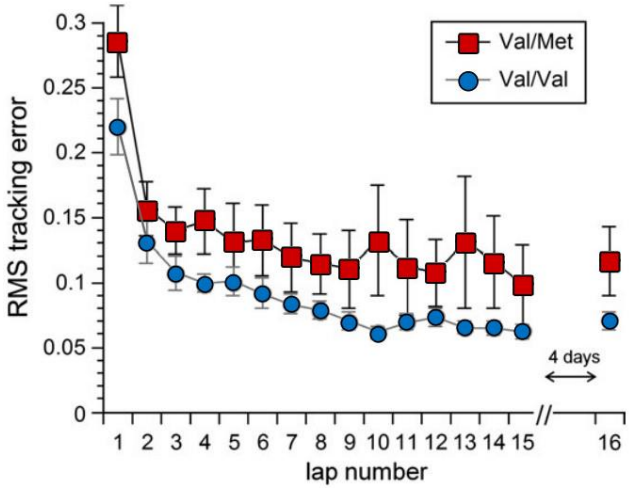
- Grey and white matter changes

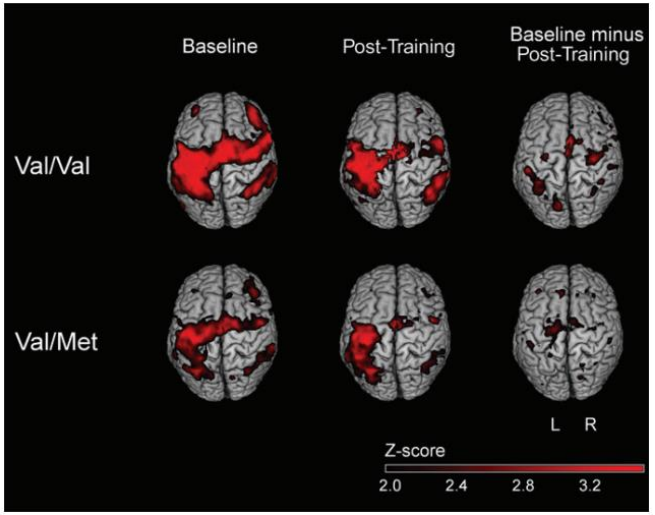


Bengtsson et al, Nature Neurosci 2005

Motor skill learning/motor training

- Learning curve
- fMRI changes
- Grey and white matter changes
- **Genetic variation of BDNF**





McHughen et al. 2010

Motor skill learning/motor training

Gene variants of Dopamine markers

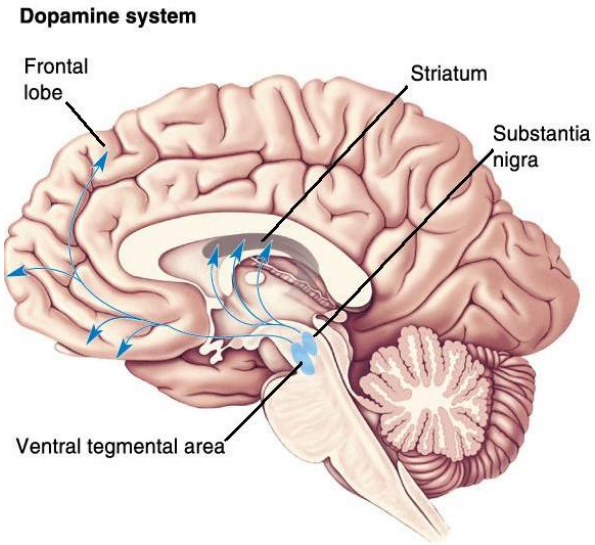
Table 1. Summary of polymorphisms and classification for gene score.

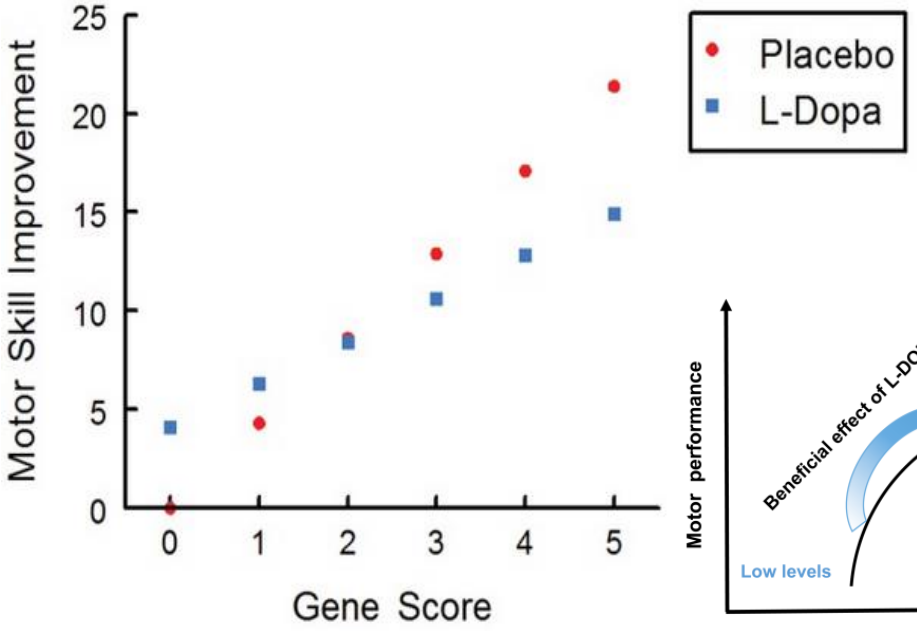
	DRD1 rs4532			DRD2 rs1800497			DRD3 rs6280			COMT rs4680			DAT rs28363170		
	A/A	A/G	G/G	Glu/Glu	Glu/Lys	Lys/Lys	Ser/Ser	Ser/Gly	Gly/Gly	Val/Val	Val/Met	Met/Met	9/9	9/10	10/10
Classification	0	1	1	1	0	0	0	1	1	0	1	1	1	1	0
Predicted Frequency	0.47	0.49	0.04	0.48	0.4	0.14	0.5	0.35	0.15	0.37	0.49	0.15	0.06	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

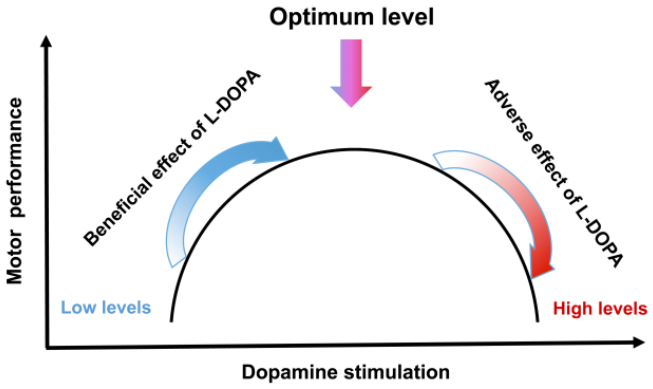
The five polymorphisms related to brain dopamine neurotransmission are listed. Each was in Hardy-Weinberg equilibrium

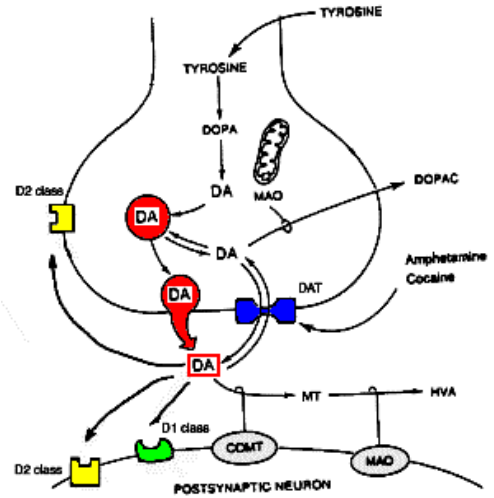
doi:10.1371/journal.pone.0061197.t001

Pearson-Fuhrhop KM et al 2013,

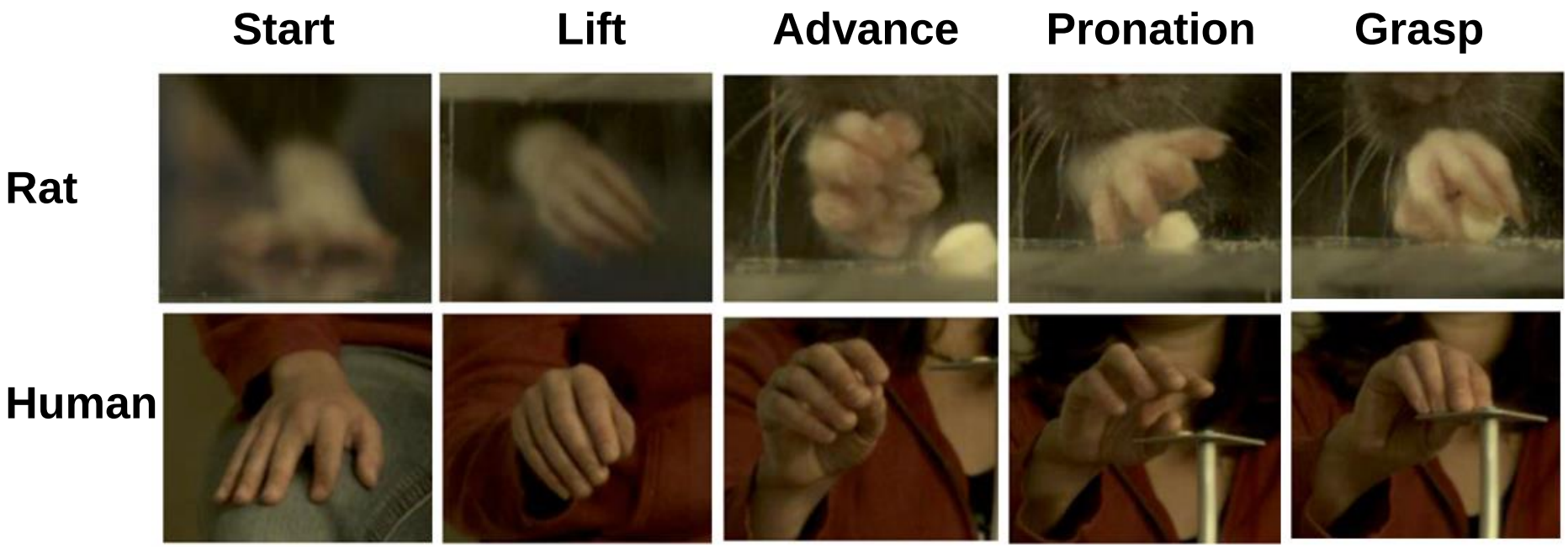






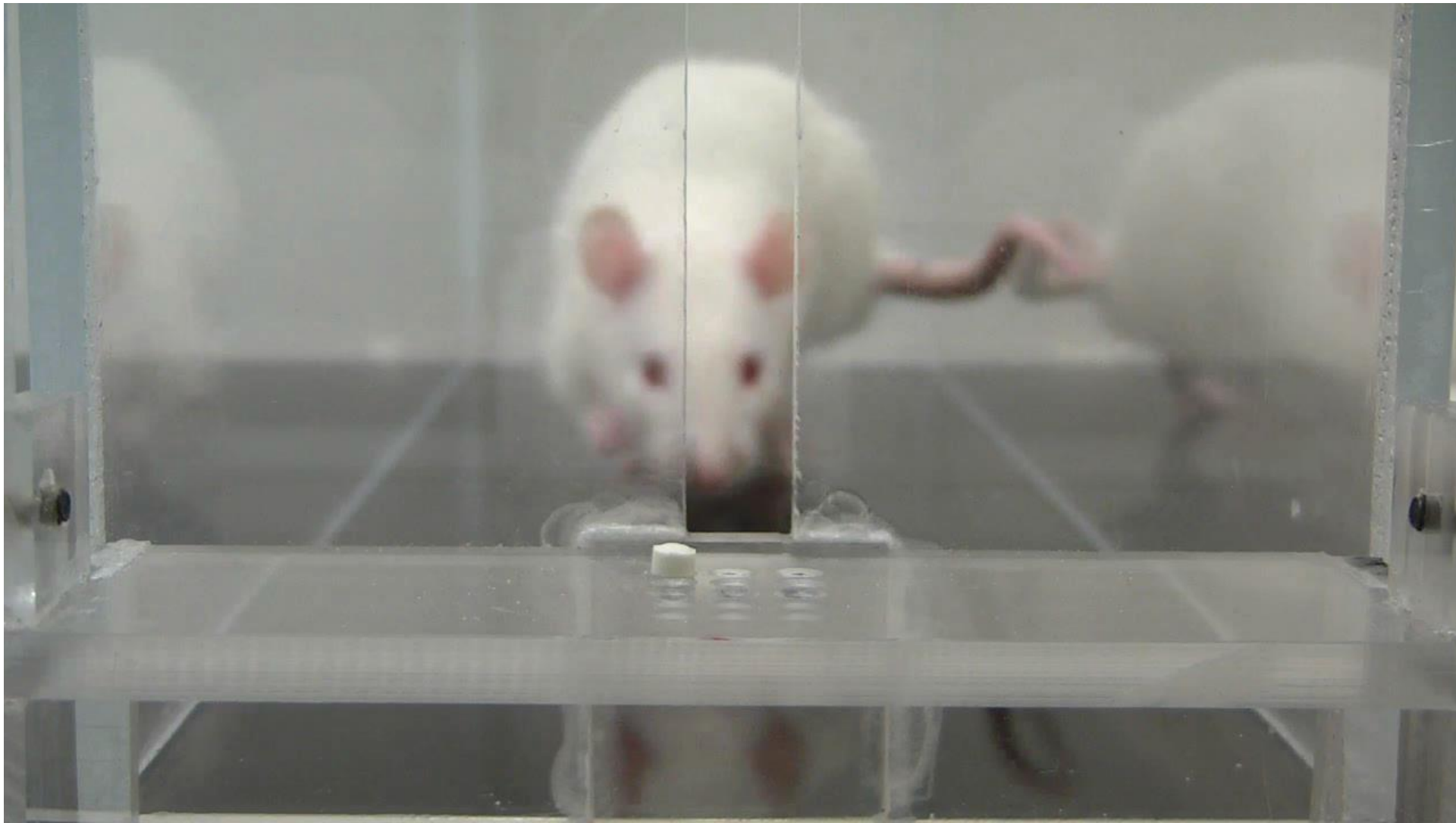


Skilled Reaching in Rats and Humans



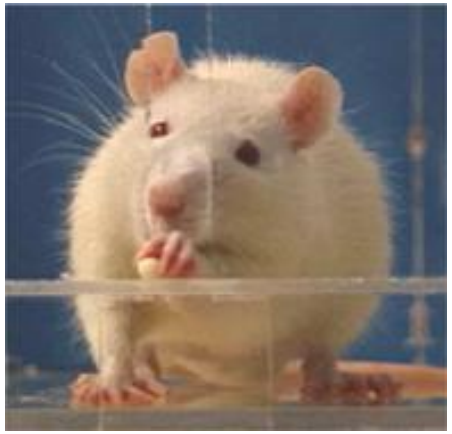
Sacrey et al. *Behavioural Brain Research* 2009

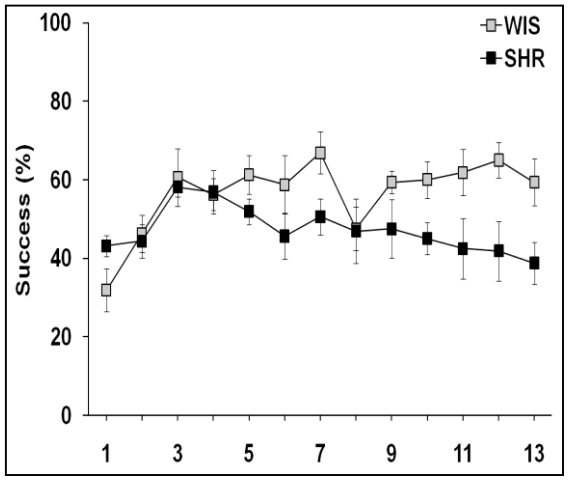
Skilled reaching task paradigm



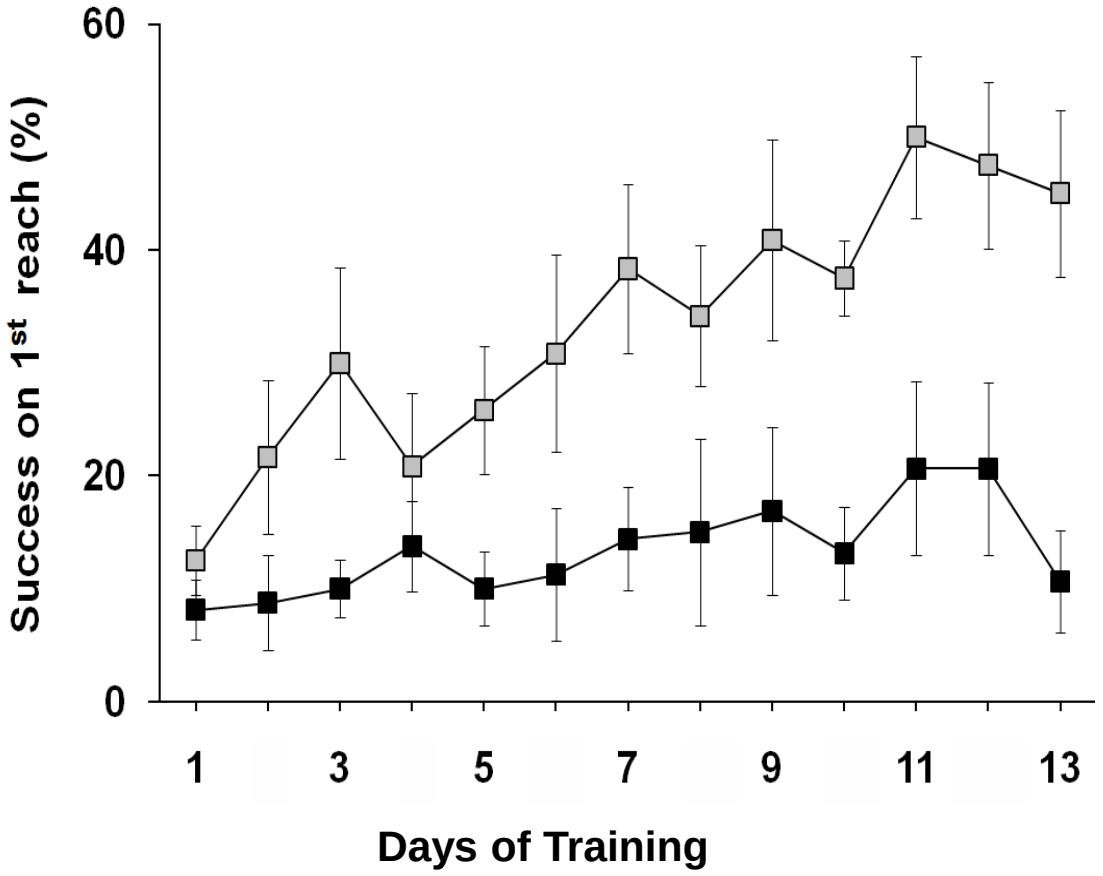
Skilled motor learning in a genetic animal model of ADHD

SHR



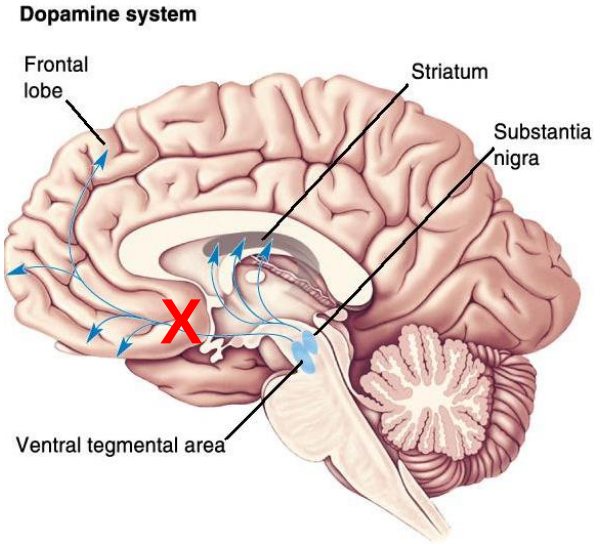


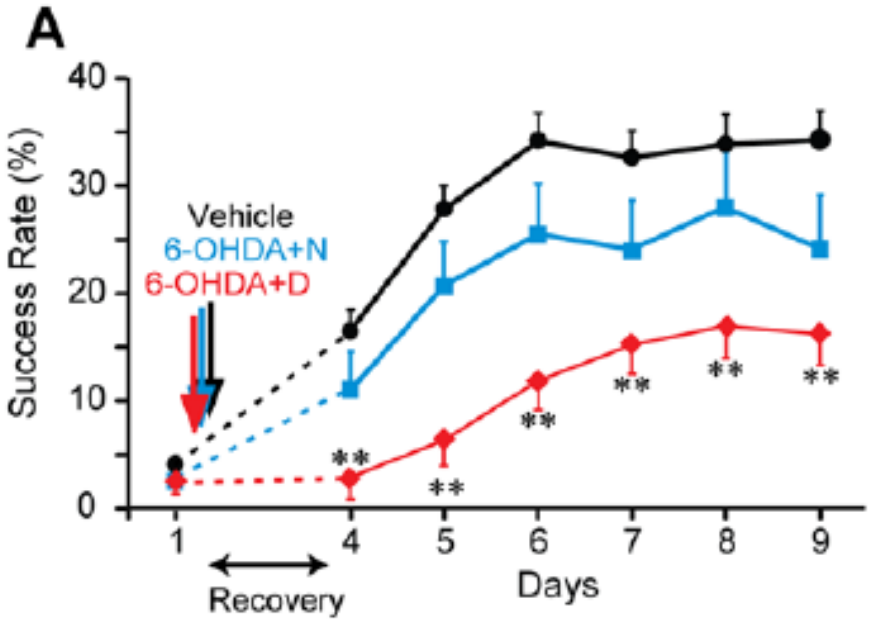
Days of Training

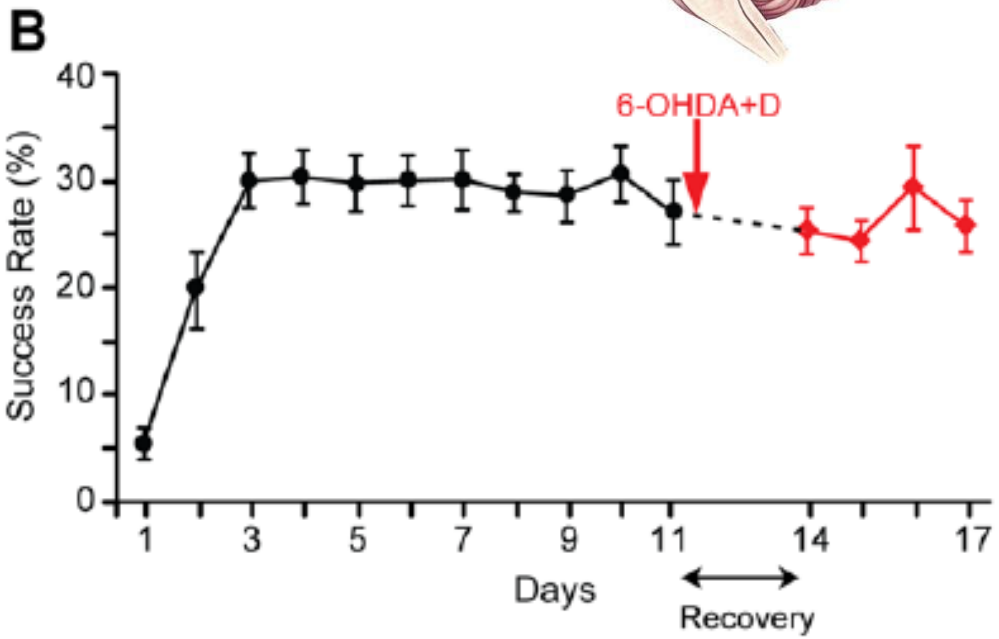


Qian et al 2010

Dopamine in M1 is necessary for optimal motor skill acquisition but not for movement execution







K Molina-Luna 2009, PLOS-One

Dopamine system

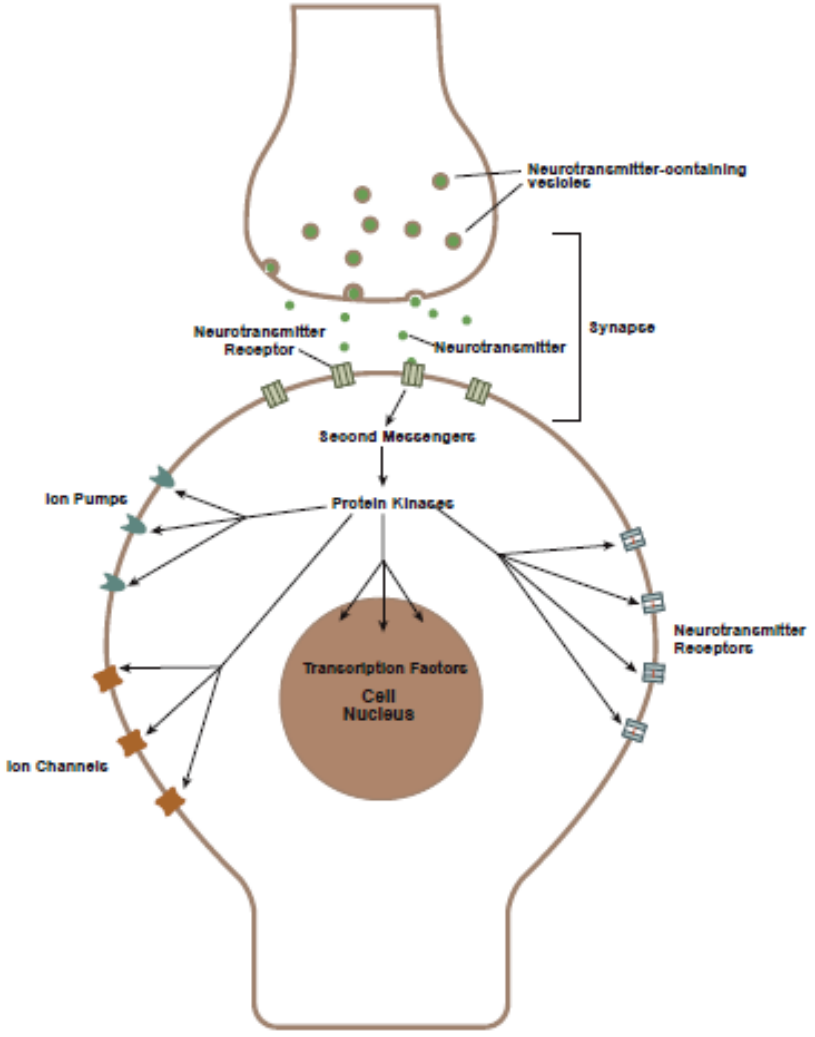
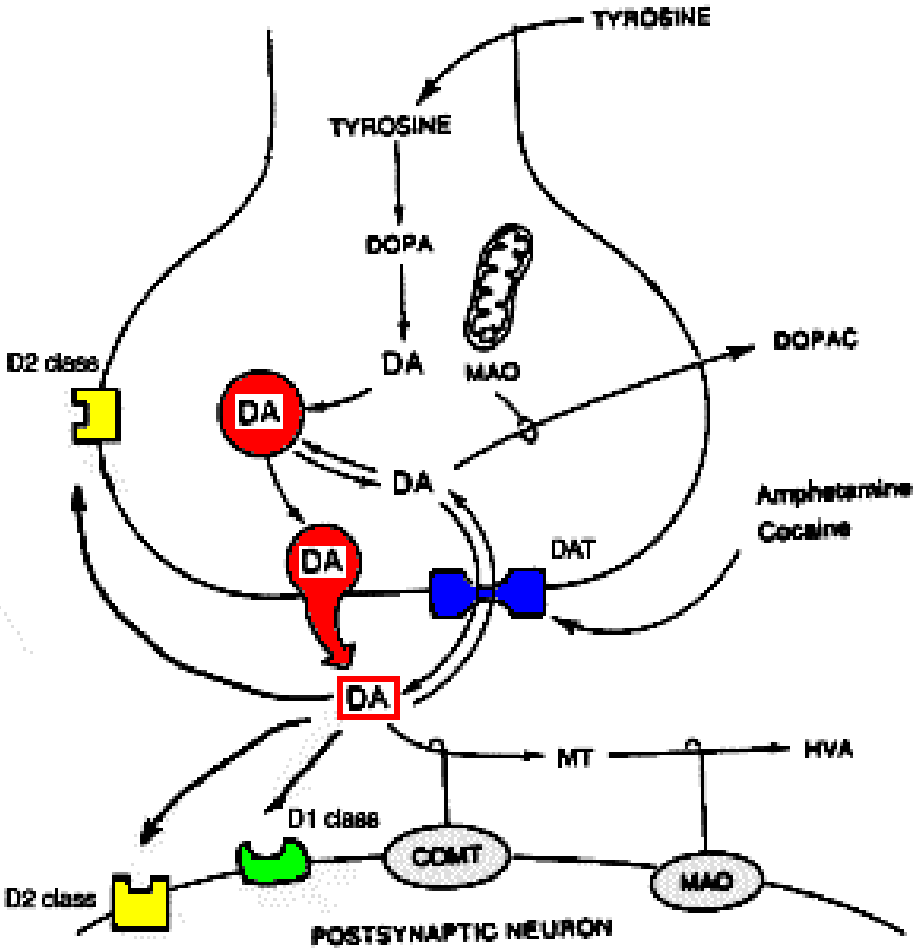
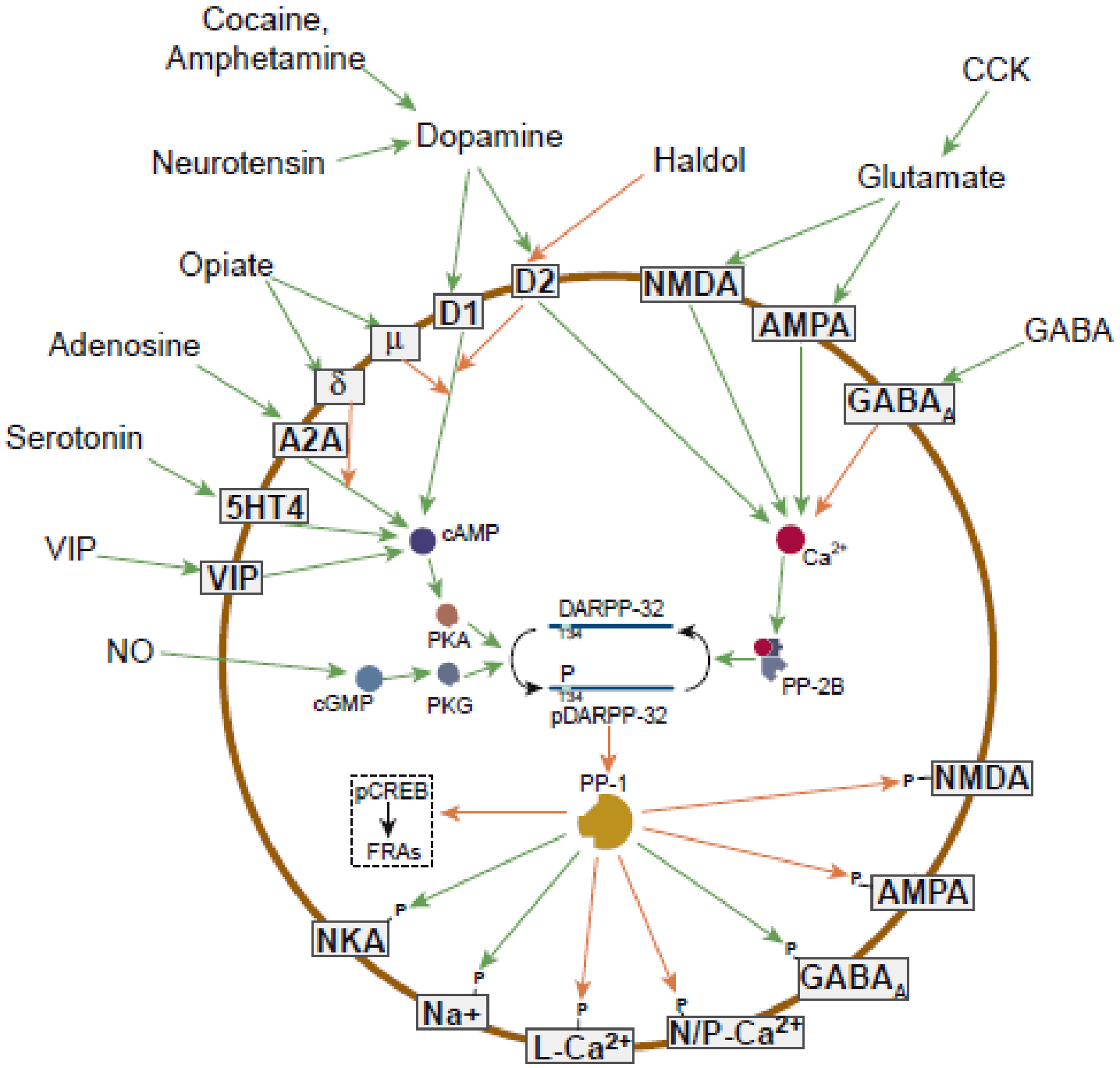
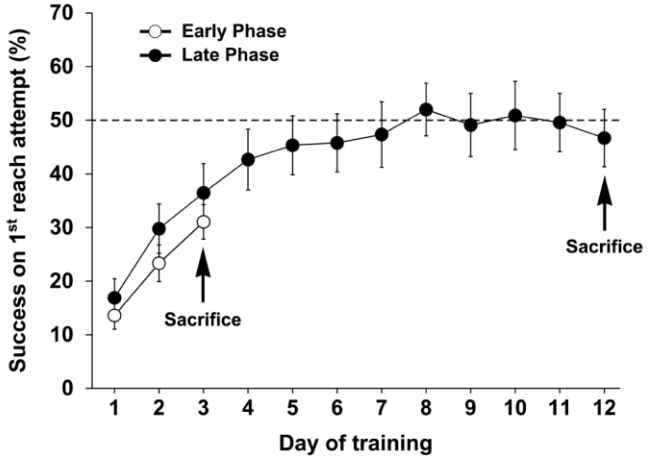


Fig. 1. Some of the signaling pathways of slow synaptic transmission.

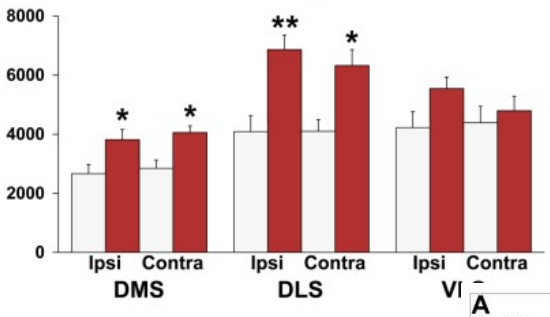


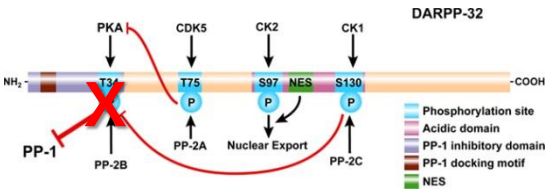

Cocaine,
Amphetamine
Dopamine
Neurotensin
Haldol
CCK
Glutamate
Opiate
D2
NMDA
D1
AMPA
μ
GABA
Adenosine
δ
GABA$_A$
A2A
Serotonin
5HT4
cAMP
Ca^{2+}
VIP
VIP
DARPP-32
Thr34
PKA
NO
P
Thr34
cGMP
PKG
PP-2B
pDARPP-32
PP-1
pCREB
FRAs
P
NMDA
P
AMPA
NKA
P
P
GABA$_A$
Na+
P
L-Ca^{2+}
P
N/P-Ca^{2+}

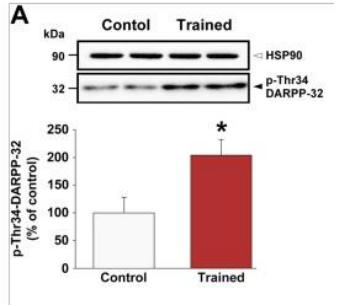
Motor skill learning/motor training
Alteration of dopamine signalling

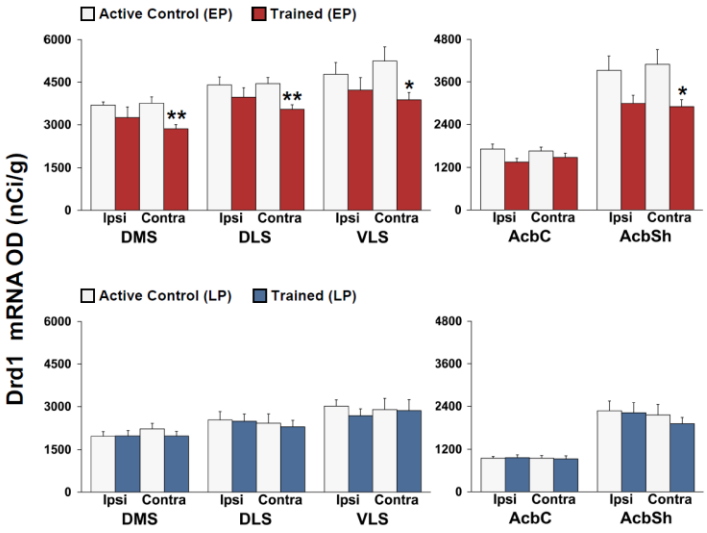


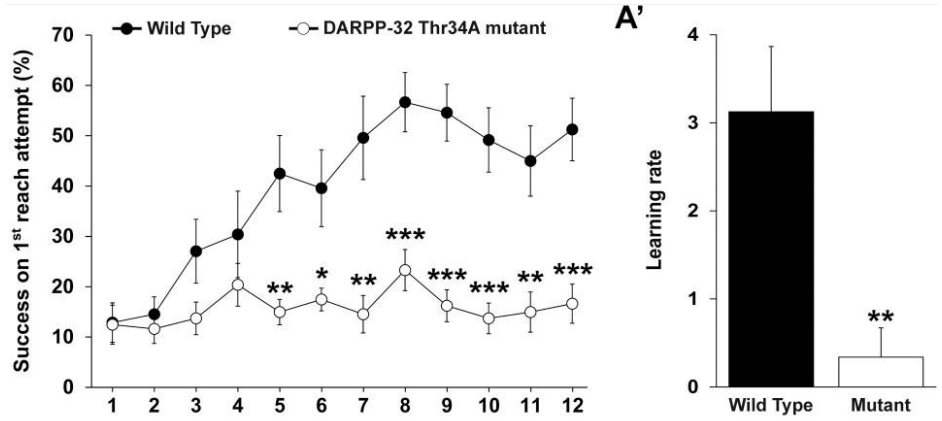
DARPP-32 mRNA expression





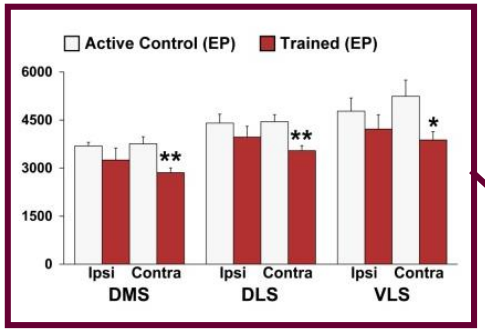


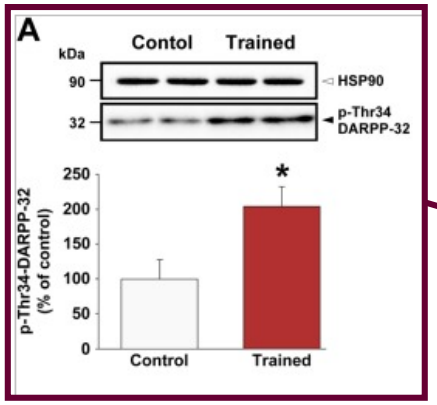


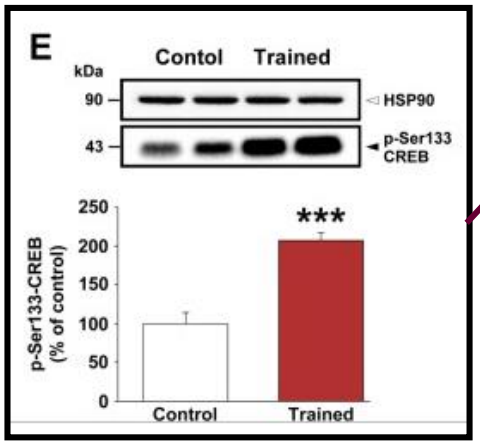


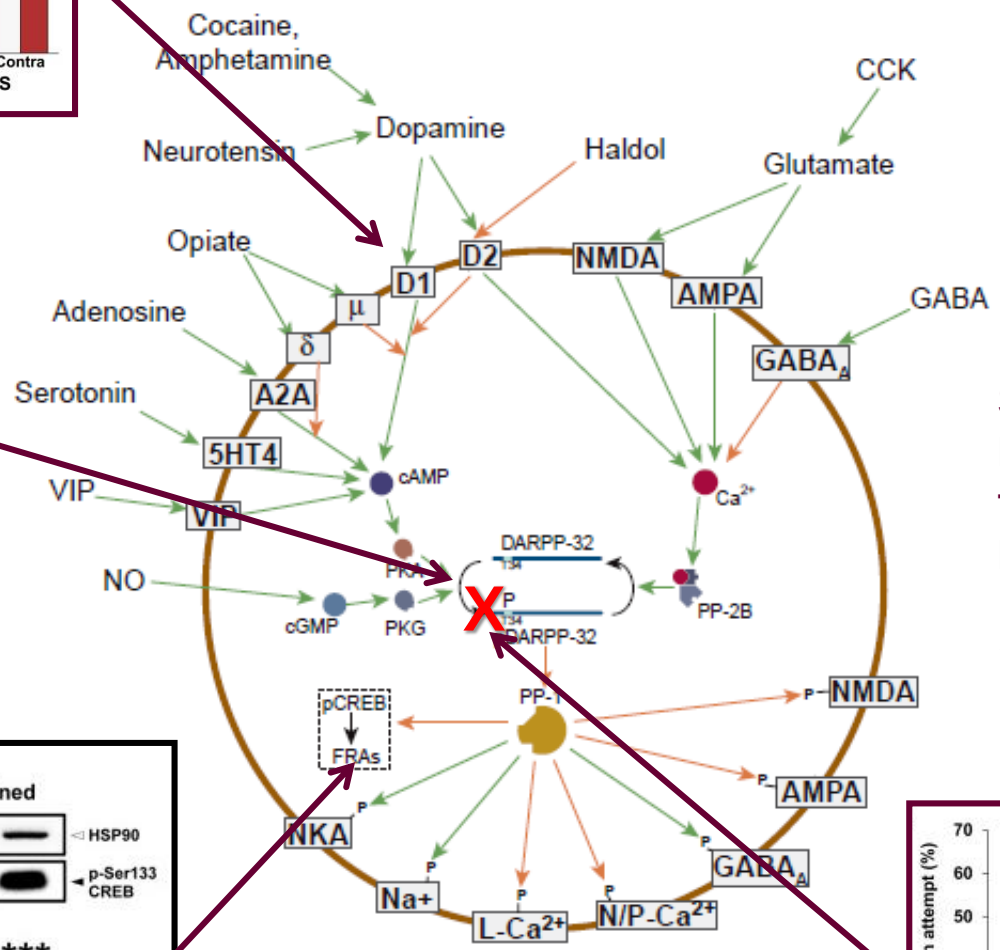
Qian Y et al, PLoS ONE 2015

Summary 1:
Motor learning is associated with modulation of intracellular DA signalling

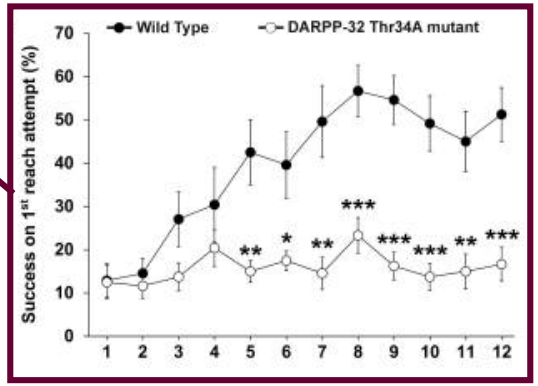








Summary 2:
Interruption of the intracellular DA signalling impairs motor learning



Contents lists available at ScienceDirect
EBioMedicine
journal homepage: www.ebiomedicine.com

Research Paper

Genetic Variation in the Dopamine System Influences Intervention Outcome in Children with Cerebral Palsy

Rochellys Diaz Heijtz [a], Rita Almeida [a], Ann Christin Eliasson [b], Hans Forssberg [b,*]

[a] Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden
[b] Department of Women's and Children's Health, Karolinska Institutet, Astrid Lindgren Children's Hospital, Stockholm, Sweden

Does genetic variation in the dopamine system influence treatment response?

Background:

Evidence based clinical research conclude that activity based interventions (motor learning & training) are most effective

Experimental research suggests that dopamine neurotransmission (and brain-derived neurotrophic factor (BDNF)) are involved in motor learning and plasticity

Clinical trials:

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY INVITED REVIEW

Meaningfulness of mean group results for determining the optimal motor rehabilitation program for an individual child with cerebral palsy

DIANE L DAMIANO

Volume 56, Issue 12
December 2014
Pages 1141-1146


junior

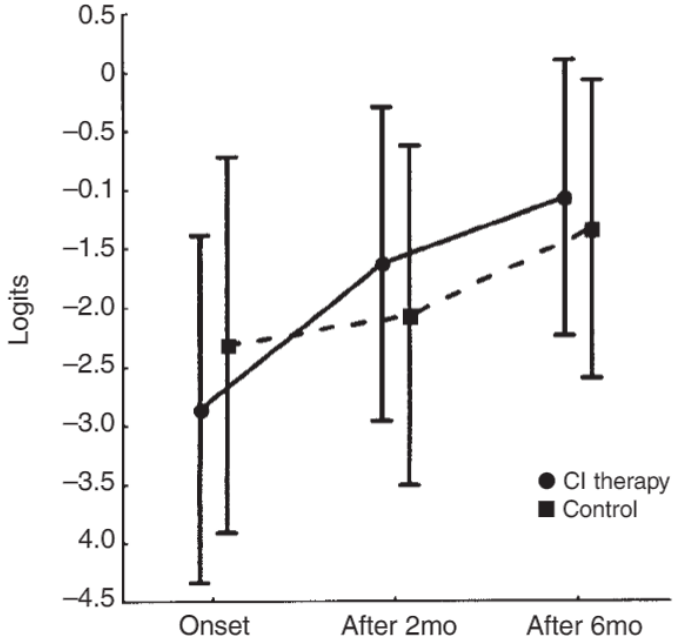
DMCN Developmental Medicine & Child Neurology

Volume 47, Issue 4
April 2005
Pages 266-275

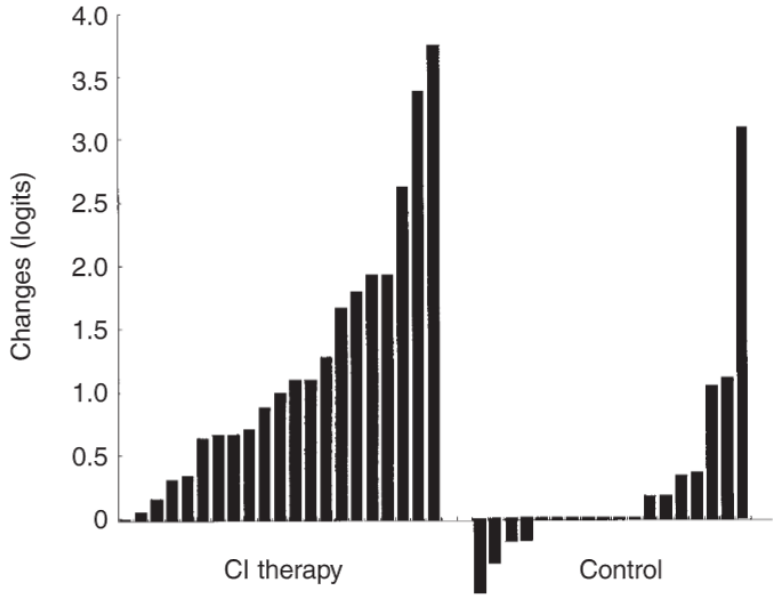
Free Access

Effects of constraint-induced movement therapy in young children with hemiplegic cerebral palsy: an adapted model

Ann-Christin Eliasson PhD OT, Lena Krumlinde Sundholm PhD OT, Karin Shaw MSc PT, Chen Wang MD PhD



Interaction between group and treatment, demonstrated by mean and 95% confidence interval



Individual changes after 2 months Intervention (CIMT)

Contents lists available at ScienceDirect
EBioMedicine
journal homepage: www.ebiomedicine.com

Research Paper

Genetic Variation in the Dopamine System Influences Intervention Outcome in Children with Cerebral Palsy

Rochellys Diaz Heijtz [a], Rita Almeida [a], Ann Christin Eliasson [b], Hans Forssberg [b,*]

[a] Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden
[b] Department of Women's and Children's Health, Karolinska Institutet, Astrid Lindgren Children's Hospital, Stockholm, Sweden

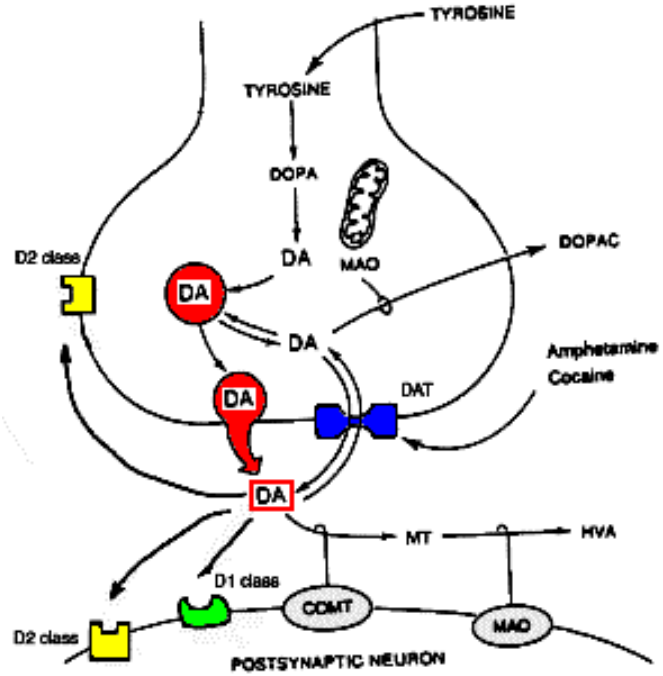
Study design

- Recruited 33 children, 18–60 months with unilateral CP, from previous intervention programmes
- Assessed before and after with AHA
- Saliva was collected for genotyping
- 5 dopamine gene score
  → COMT, DAT, DRD1, DRD2, DRD3

Sex, age, and AHA-unit distribution per polygenic dopamine gene score unit.

	All	DA score 0	DA score 1	DA score 2	DA score 3	DA score 4	DA score 5	p
N	33	0	3	9	4	14	3	
Male	21		3	4	4	9	1	
Female	12		0	5	0	5	2	
Age			24·3 ± 2·9	26·7 ± 5·4	28·5 ± 11·6	33·1 ± 11·6	23·7 ± 7·4	0·262
AHA			38·7 ± 23·1	59·0 ± 10·7	34·5 ± 33·0	43·0 ± 13·9	36·0 ± 21·9	0·184

Mean and SD values are given. p-values are for the correlation between age or baseline AHA unit and dopamine (DA) score.



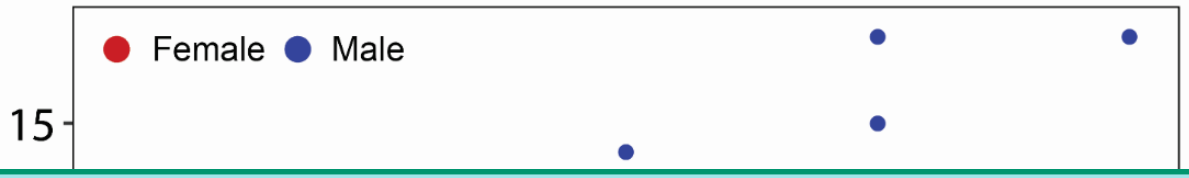
Contents lists available at ScienceDirect
EBioMedicine
journal homepage: www.ebiomedicine.com

Research Paper

Genetic Variation in the Dopamine System Influences Intervention Outcome in Children with Cerebral Palsy

Rochellys Diaz Heijtz [a], Rita Almeida [a], Ann Christin Eliasson [b], Hans Forssberg [b,*]

[a] Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden
[b] Department of Women's and Children's Health, Karolinska Institutet, Astrid Lindgren Children's Hospital, Stockholm, Sweden



Naturally occurring genetic variation in the dopamine system can predict treatment outcome

Children with high dopamine score (endogenous dopamine level) have a greater gain

Can outcome be improved by boosting the dopamine system?

1)

2) Younger children had greater gains than older children
3) When baseline was introduced in the model; lower levels had greater gain

Conclusion

- Evidence based interventions improving motor function in children with CP include active motor learning and training
- Skilled motor learning involves >two molecular pathways
  - → Dopamine system
  - → Microglia – BDNF
- Dopamine system
  - → Interruption of the dopamine pathways impair motor learning
    - Lesions of the striato-frontal pathways
    - KO intracellular pathway (DARPP-32)
  - → Training induced improvement of motor skill is associated with regulation of
    - DRD1; DARPP-32; p-Thr-34-DARPP32; p-Ser-133-CREB
- Dopamine gene score can predict intervention outcome in children with CP
- Early intervention in CP promising; but not yet evident

Acknowledgements

Ann Christin Eliasson

Rochellys Diaz Heijtz

Rita Almeida

Yui Qian