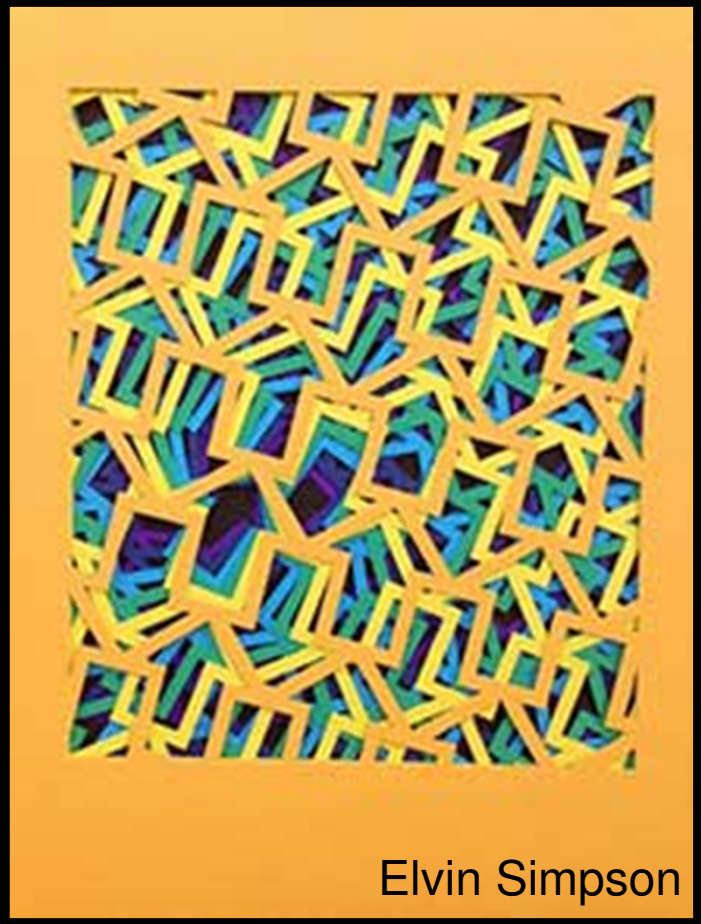
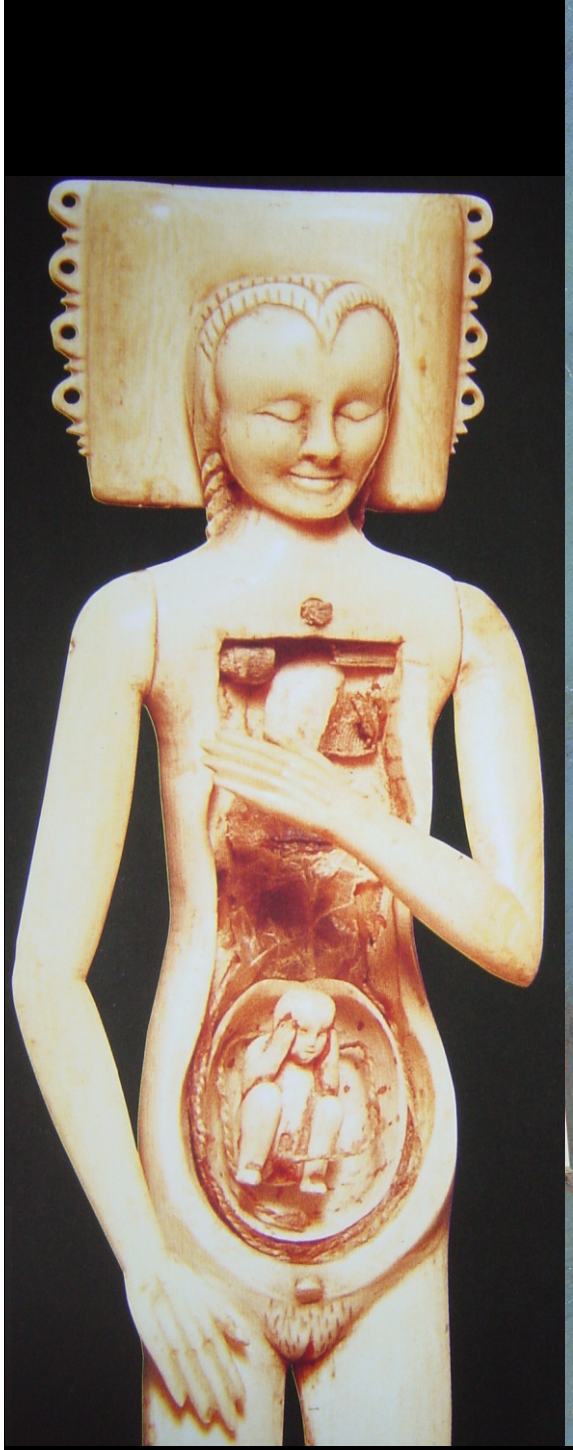
Share experience
Share values
Plan actions

Bernard Dan, Jean Kerver,
Anthony Staines, Nigel Paneth


Elvin Simpson

DOCTRID
DAUGHTERS OF CHARITY
TECHNOLOGY AND RESEARCH INTO DISABILITY



Developmental neurology

Theories of development

maturationism

- Scientific method
- Reflex activities
- Orderly milestones
- Immaturity
- Linear development

=> delay/retardation

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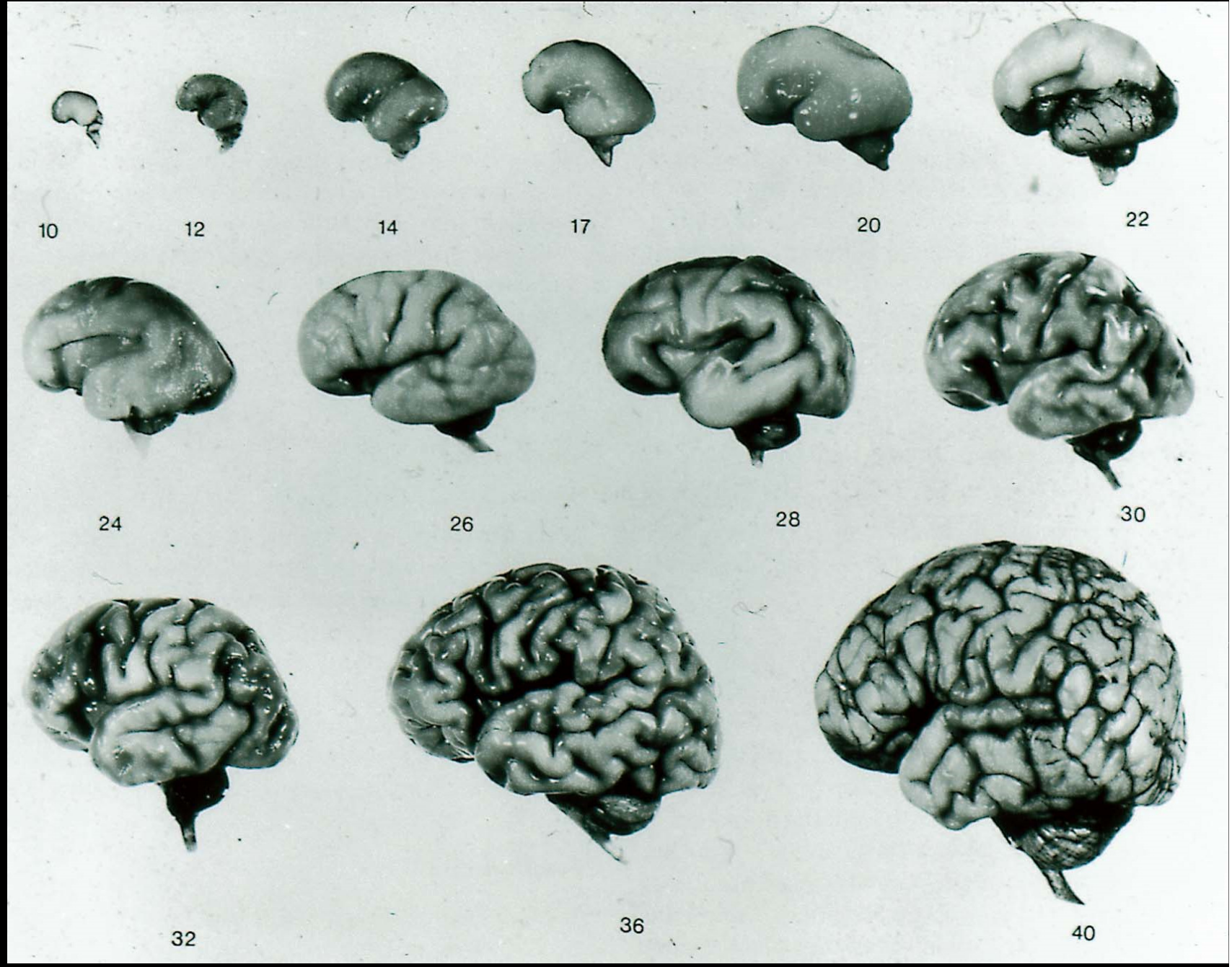
Development

- **Maturation**
- **Experience**
- **Chance**



Brain Development in Early Life Sets Trajectories for Development Throughout Life - Experience-driven processes

Neurodisability describes a group of congenital or acquired long-term conditions that are attributed to impairment of the brain and/or neuromuscular system and create functional limitations. A specific diagnosis may not be identified. Conditions may vary over time, occur alone or in combination, and include a broad range of severity and complexity. The impact may include difficulties with movement, cognition, hearing and vision, communication, emotion, and behaviour.

Morris et al. *Dev Med Child Neurol* 2013

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Health Condition (disorder/disease)

Body function & structure *(Impairment)*

Activities *(Limitation)*

Participation *(Restriction)*

Environmental Factors

Personal Factors

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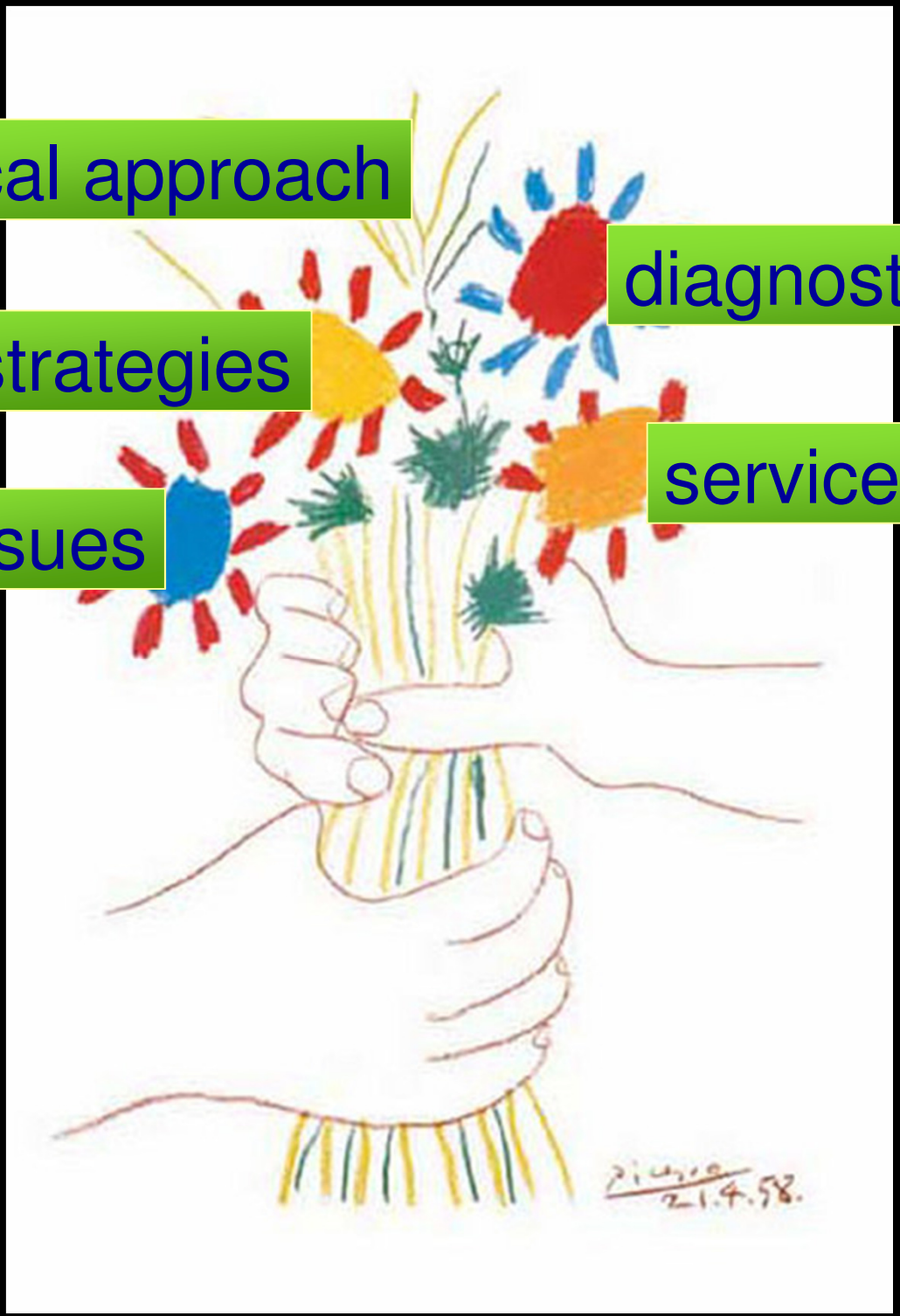
clinical approach

diagnostic work-up

prevention strategies

service organisation

ethical issues



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TECHNOLOGY AND RESEARCH INTO DISABILITY

Generic conditions

e.g. intellectual disability, autism spectrum disorder, ADHD, sensory impairment, cerebral palsy

- clinical approach
- diagnostic work-up
- prevention strategies
- service organisation
- ethical issues

Aetiology-defined conditions

Generic conditions

e.g. intellectual disability, ASD,ADHD, sensory impairment, cerebral palsy

- Advantages
- Limitations

e.g. reflection on changes in the prevalence of ID in general: difficult, maybe rather groups (PKU, kernicterus);
Down syndrome vs intellectual disability;
Rett syndrome vs ASD; ADHD

A DIFFERENT VIEW

Acta Pædiatrica ISSN 0803–5253

The ADHD Tetragrammaton taken in vain in neurogenetic disorders?

Karine Pelc, Bernard Dan (bernard.dan@ulb.ac.be)

Aetiology-defined conditions

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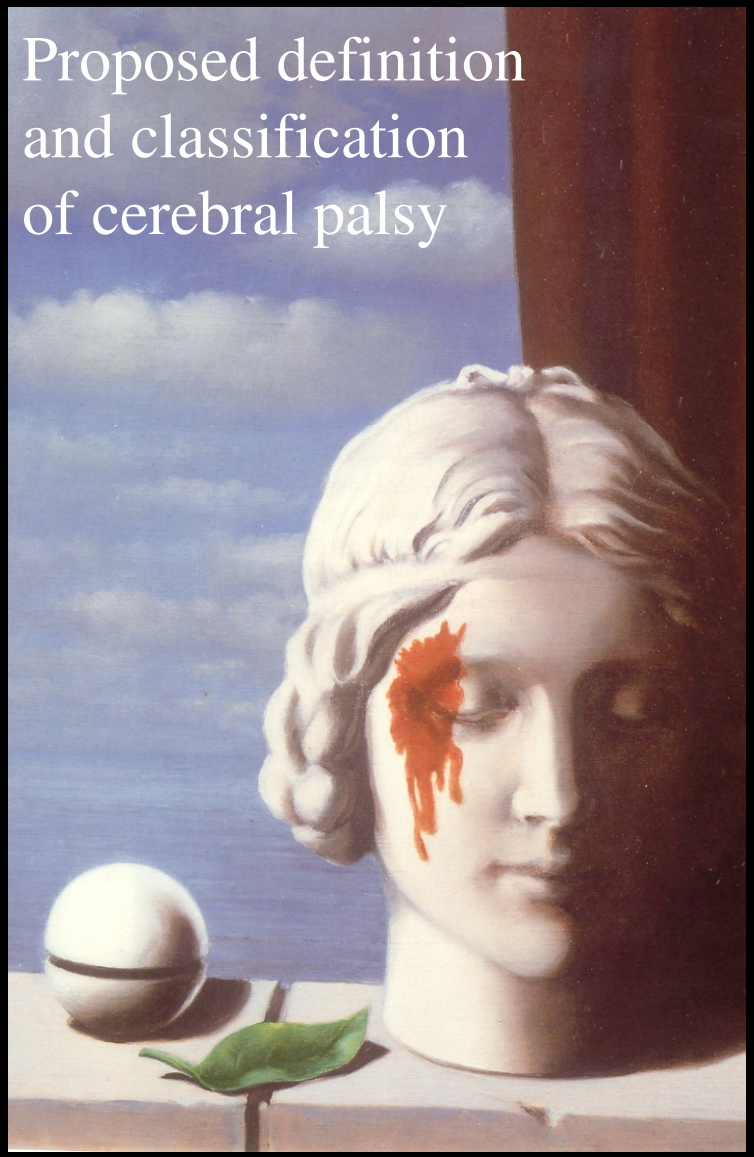
TECHNOLOGY AND RESEARCH INTO DISABILITY

National Institute of Health – National Institute of Neurological Disorders and Stroke

Definition of Cerebral Palsy

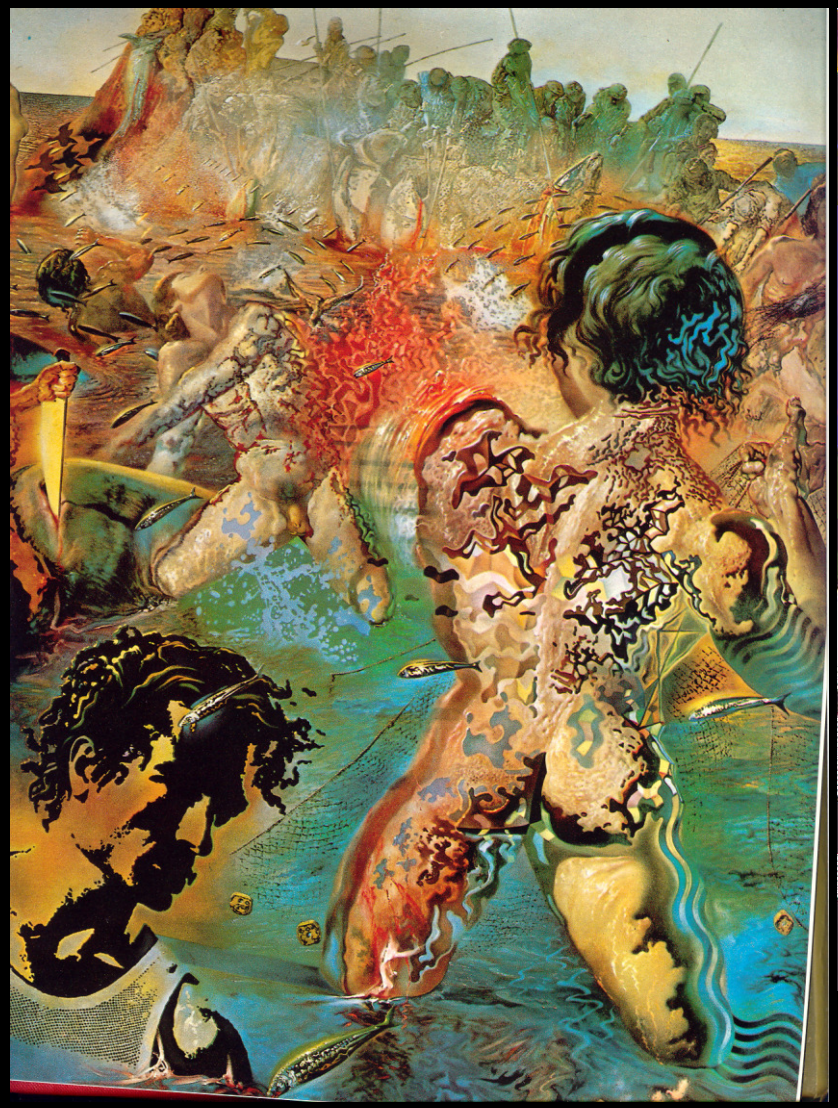
P. Rosenbaum, N. Paneth, A. Leviton, M. Goldstein, M. Bax, D. Damiano, B. Dan, B. Jacobsson.

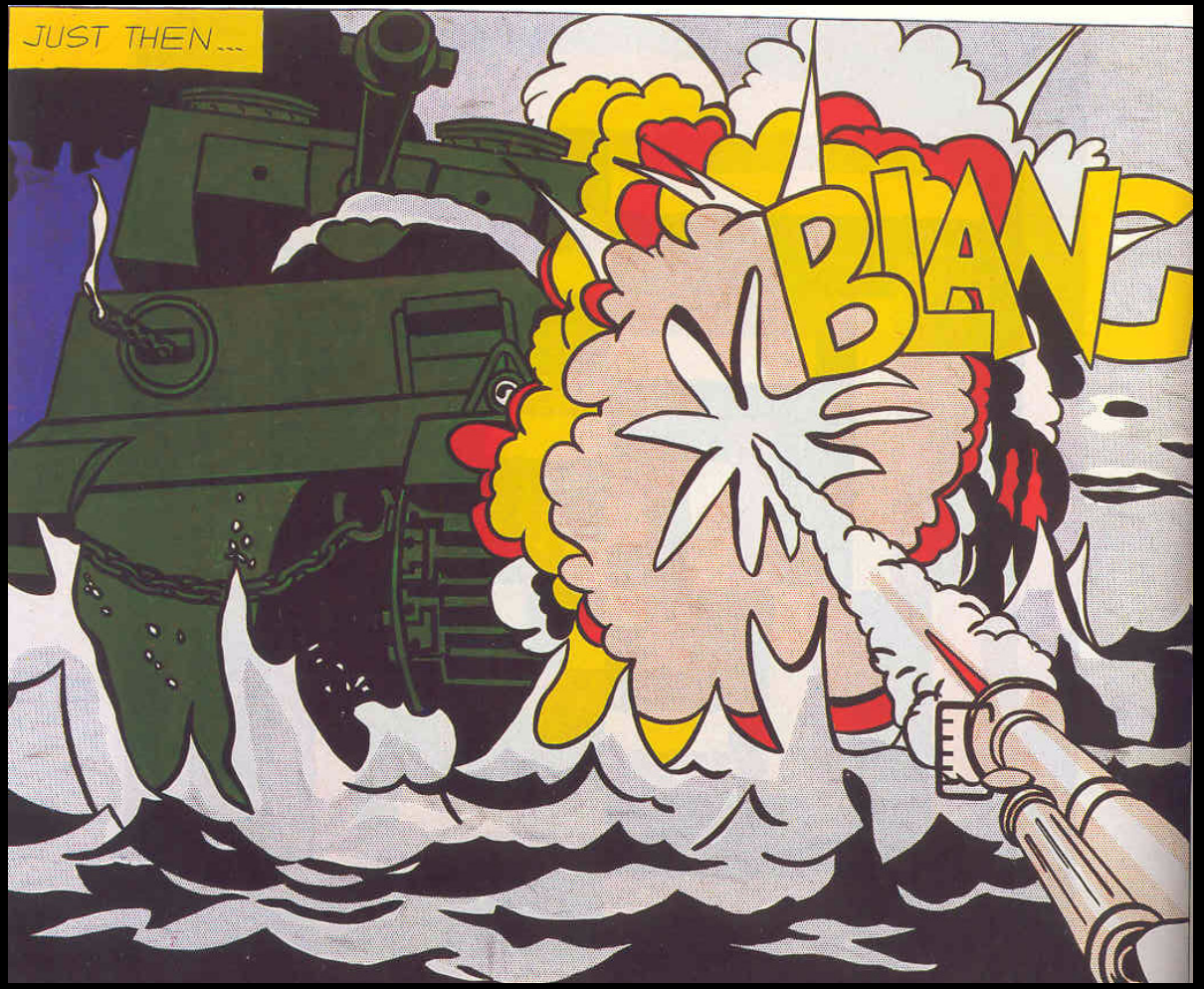


Cerebral palsy (CP) describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behaviour, by epilepsy, and by secondary musculoskeletal problems.

Developmental Medicine and Child Neurology
Feb 2007; 109(Suppl): 8-14

- No aetiological reference
- Much heterogeneity





e.g. vision may be affected, both as a function of the 'primary' disturbance(s) to which CP is attributed, and as a secondary consequence of activity limitation that restricts learning and perceptual development experiences

Phenotype

- **Phenomenology**
- **Pathophysiological** reasoning
- **Management** planning
- **Outcome** measurement

A behavioural phenotype represents a distinctive association of abnormalities in domains such as cognition, language, social skills and motor control, which is consistently accompanied by a biological disorder
(O'Brien and Yule 1995)

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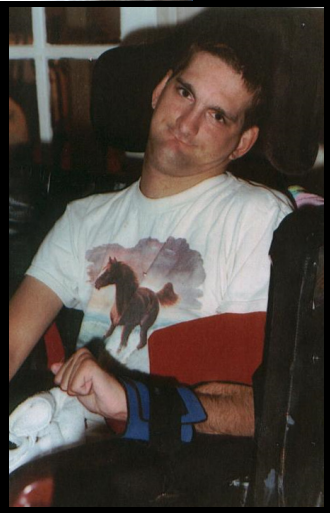
TECHNOLOGY AND RESEARCH INTO DISABILITY

Behavioural phenotype

1961 Williams syndrome
1964 Lesch-Nyhan syndrome
1965 Angelman syndrome
1966 Rett syndrome
…

1971 Nyhan coined the term



DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY ORIGINAL ARTICLE

Phenotypic plasticity and the perception–action–cognition–environment paradigm in neurodevelopmental genetic disorders

BERNARD DAN[1,2] | KARINE PELC[1] | LINDA DE MEIRLEIR[3] | GUY CHERON[2]

DMCN Developmental Medicine & Child Neurology

Special Article

From Eugenic Euthanasia to Habilitation of "Disabled" Children: Andreas Rett's Contribution

Gabriel M. Ronen, MD, MSc, Brandon Meaney, MD, Bernard Dan, MD, PhD, Fritz Zimprich, MD, PhD, Walter Stögmann, MD, and Wolfgang Neugebauer, PhI

Journal of Child Neurol ogy 2009, 24: 115-27

POSTURAL CONTROL IN CHILDREN WITH ANGELMAN SYNDROME AND RETT SYNDROME

Bernard Dan and Guy Cheron

Stereotypic hand movements, breathing disturbances, bruxism, impaired sleep, abnormal muscle tone, inappropriate laughing and screaming, eye-pointing behaviour

Molecular Syndromology

Mol Syndromol 2011;2:113–127
DOI: 10.1159/000337637

Published online: April 16, 2012

Rett Syndrome

E.E.J. Smeets[a] K. Pelc[b] B. Dan[b]

[a]Department of Clinical Genetics, Maastricht University Medical Center, Maastricht, The Netherlands;
[b]Department of Neurology, Hôpital Universitaire des Enfants Reine Fabiola, Université Libre de Bruxelles (ULB), Brussels, Belgium

2013 Round-up

THE LANCET
Neurology

Paediatric neurology: a year of DNA technology

Bernard Dan
Peter Baxter

In 2013, rapid technological improvement in DNA methods has radically changed paediatric neurology. Advances have made exome sequencing more reliable and affordable, revolutionising the diagnostic process in much of paediatric neurology. This change has also enabled the recognition of novel conditions, expansion of the phenotype of previously known ones, and has led to new treatments, belying the old adage that neurology is only concerned with diagnosis; as a corollary, it is also providing fresh clinical challenges.

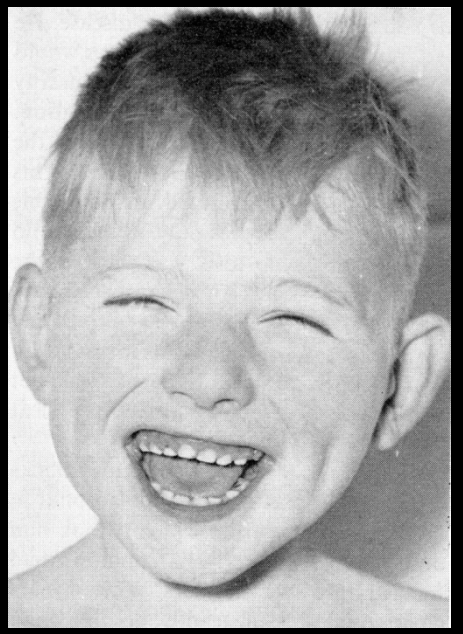
In the past few years comparative genomic hybridisation (CGH)-array studies have replaced karotyping as a routine first-line investigation in children with intellectual disability, yielding up to 20% infantile spasms (West's syndrome) and Lennox-Gastaut syndrome—two devastating developmental epileptic encephalopathies—this approach has been considerably strengthened since the Epi4K exome-sequencing study of 264 patients (actually 264 probant-parents trios) with either condition.[2] The authors recorded 329 de-novo mutations including in known epilepsy-related genes (*SCN1A*, *STXBP1*, *GABRB3*, *CDKL5*, *SCN8A*, *SCN2A*) associated with other presentations, and in other genes (*ALG13*, *DNM1*, *HDAC4*). With continuing advances in this specialty, in the same way as many children are currently referred for a neurology opinion with already-performed MRI, more children are likely to be referred in the future with gene panel results

Develop. Med. Child Neurol. 1965, **7,** 681-688

‘Puppet’ Children

A Report on Three Cases

Harry Angelman



Angelman Syndrome

Clinical diagnostic criteria

A. Consistent features (100%)

Developmental delay, functionally severe

Movement or balance disorder, usually ataxia of gait, and/or tremulous movement of limbs

Behavioural uniqueness: happy demeanour, excitable personality, hypermotoric behaviour

Speech impairment, none or minimal use of words; receptive and non-verbal communication skills higher than verbal ones

B. Frequent features (> 80%)

Delayed head growth

Seizures

Abnormal EEG, with a characteristic pattern (Dan and Boyd 2003)

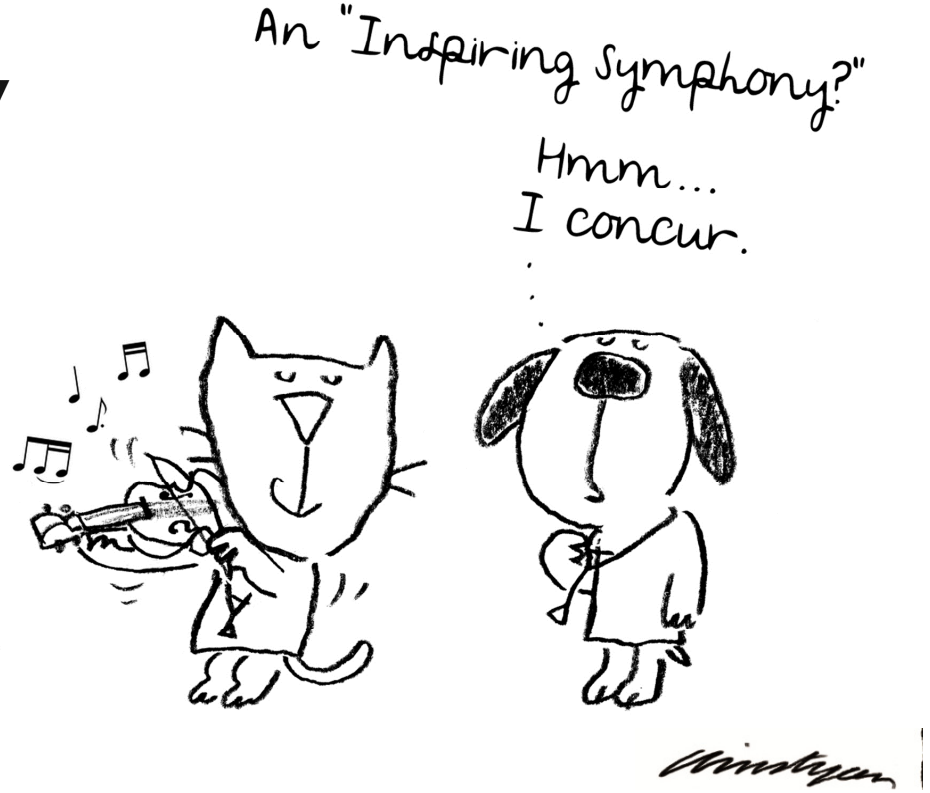
C. Associated features (20%–80%)

Flat occiput, protruding tongue, tongue thrusting; suck/swallowing disorders, feeding problems during infancy, prognathia, wide mouth, wide-spaced teeth, frequent drooling, excessive chewing/mouthing behaviours

Adapted from *Williams et al, Am J Med Genet 2006*

Angelman Syndrome

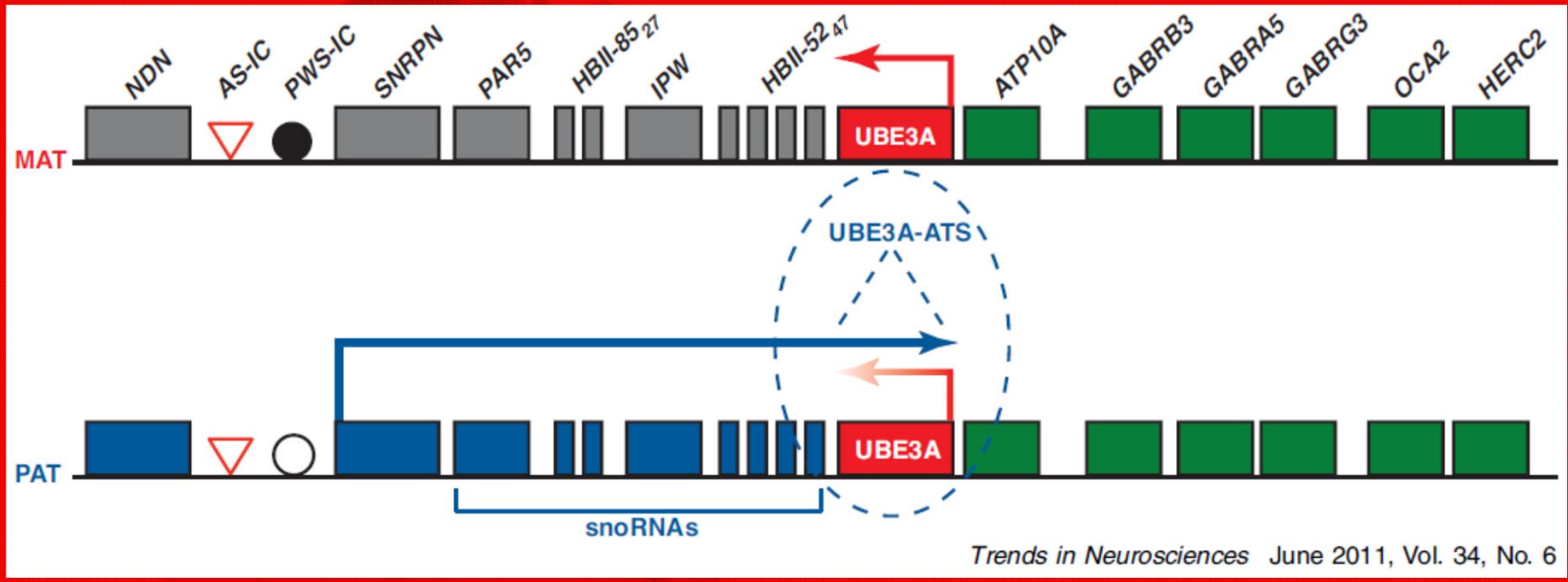
an inspiring molecular, physiological and clinical symphony



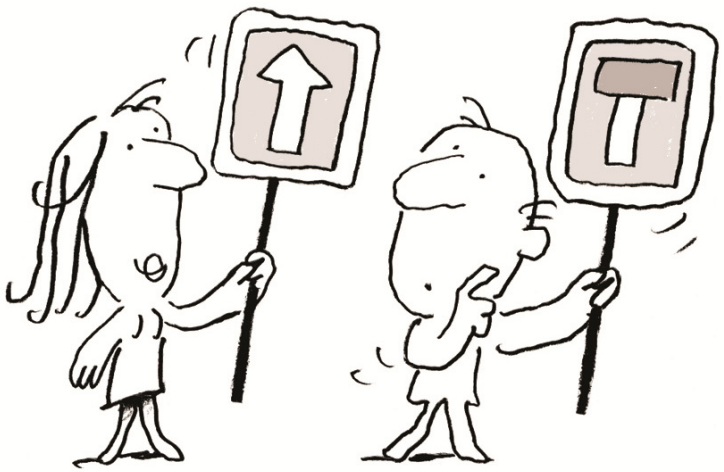
Angelman Syndrome

Bernard Dan

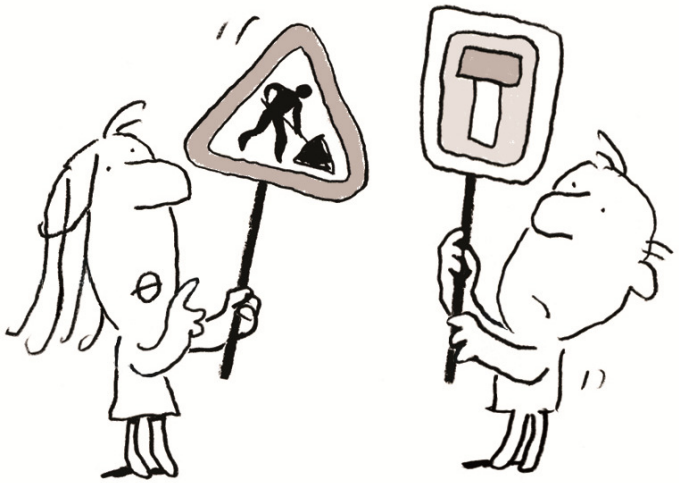
Imprinting



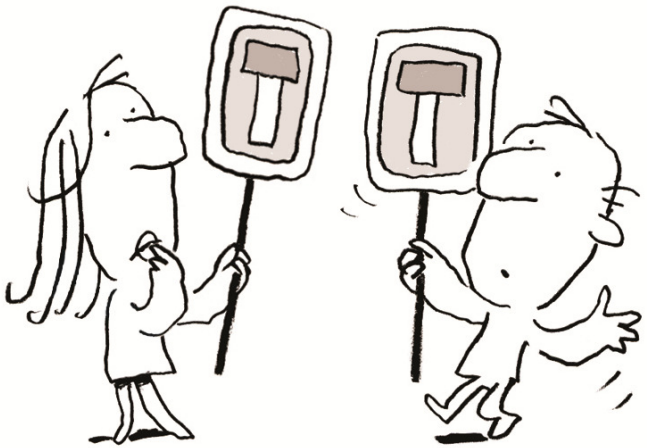
Trends in Neurosciences June 2011, Vol. 34, No. 6



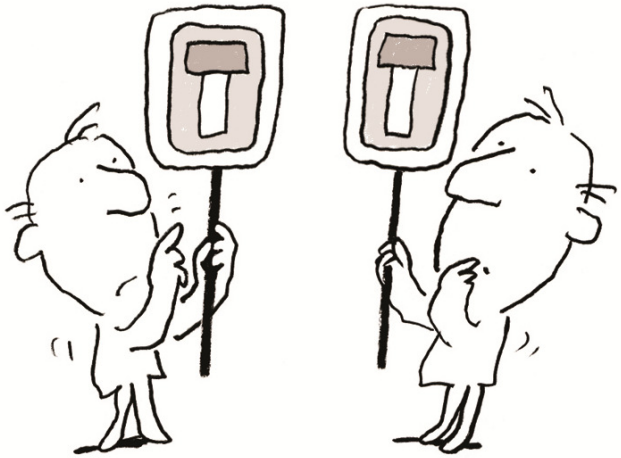
1. Typical



2. Deletion/Mutation
70% 5-10%



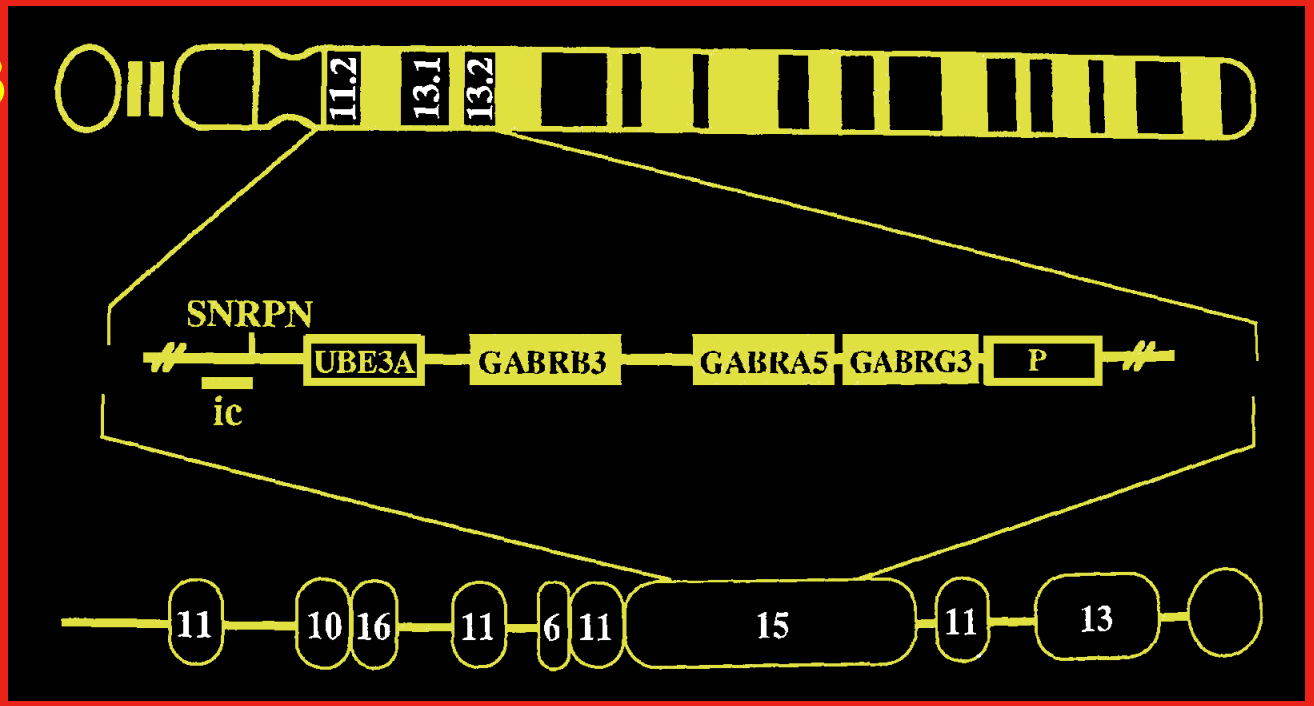
3. Imprinting Defect
3-5%



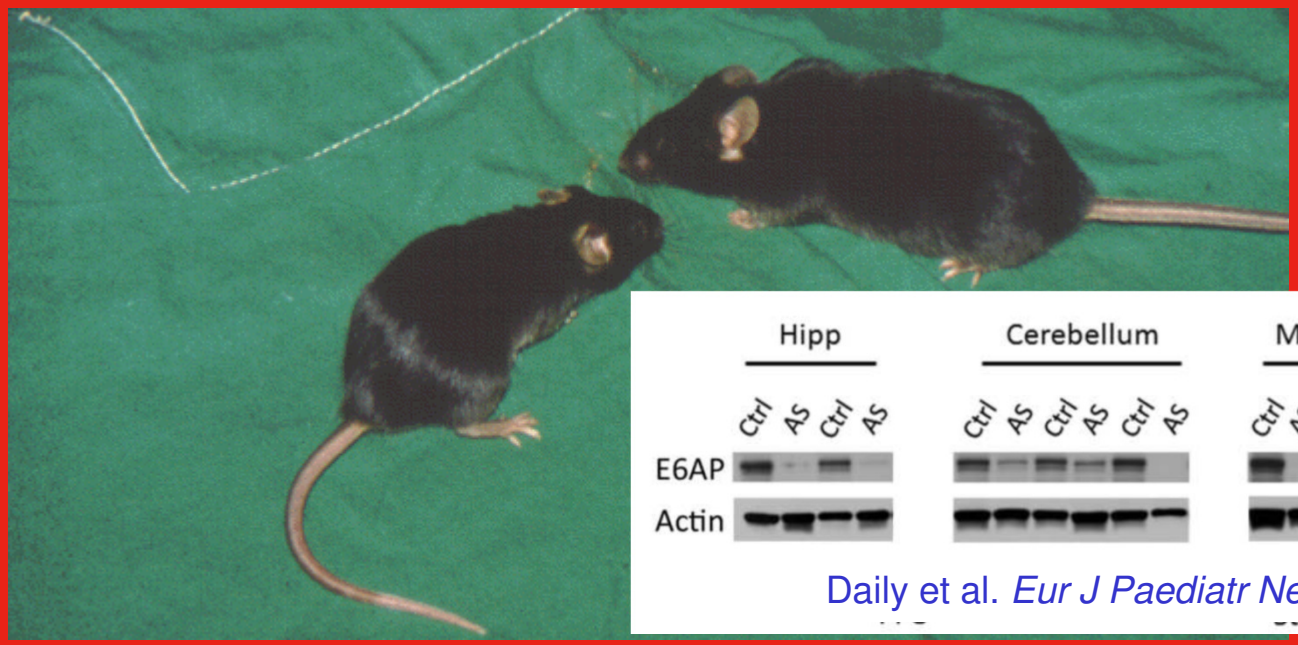
4. Uniparental disomy
2-3%

Dan, Eur J Paediatr Neurol 2012

15q11-q13



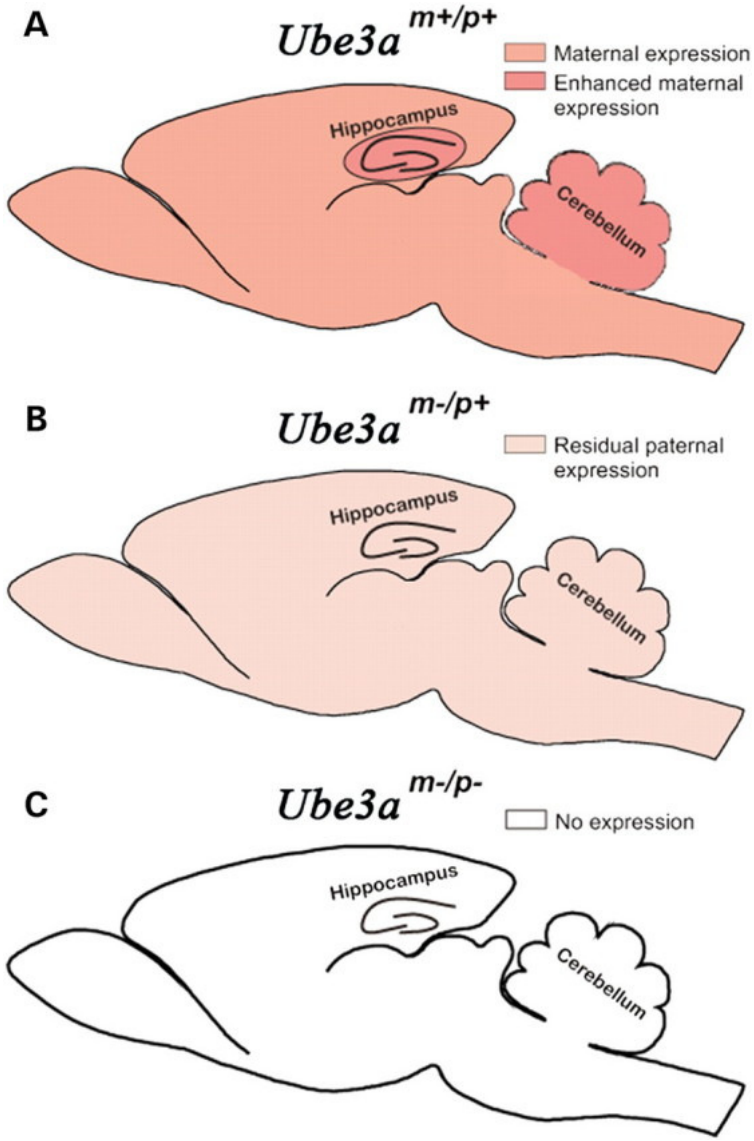
7C



Daily et al. *Eur J Paediatr Neurol,2012*

Analysis of cerebellar function in *Ube3a*-deficient mice reveals novel genotype-specific behaviors

Detlef H. Heck[2], Yu Zhao[1], Snigdha Roy[2], Mark S. LeDoux[1] and Lawrence T. Reiter[1,*]

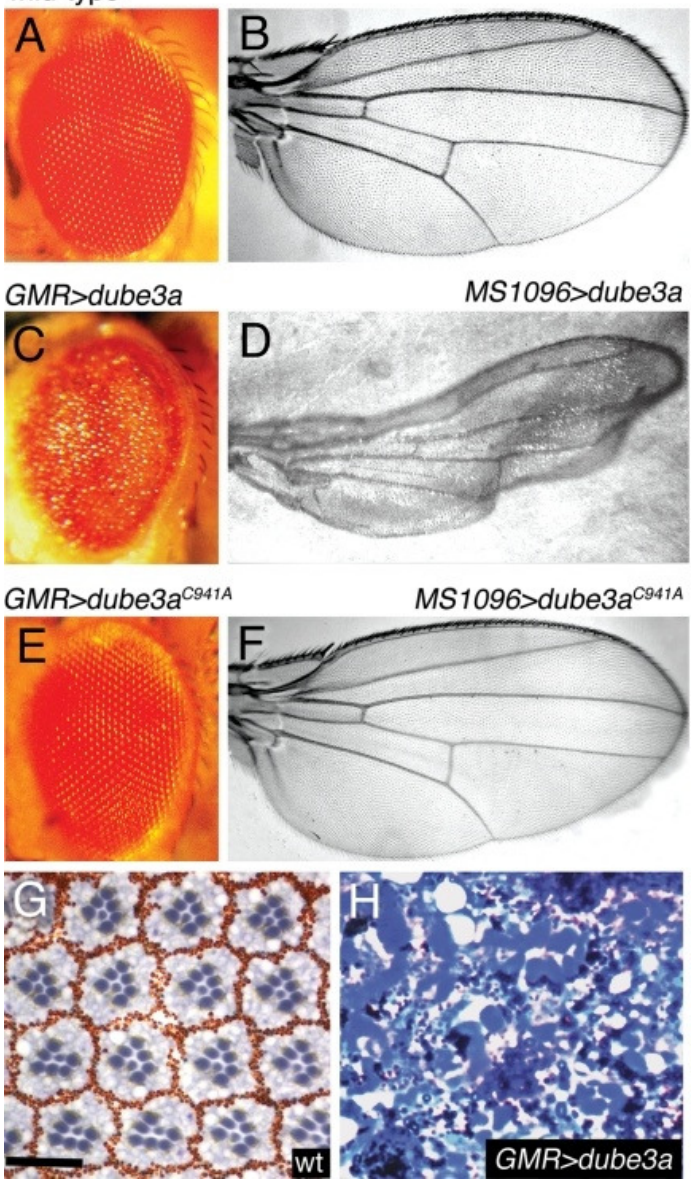


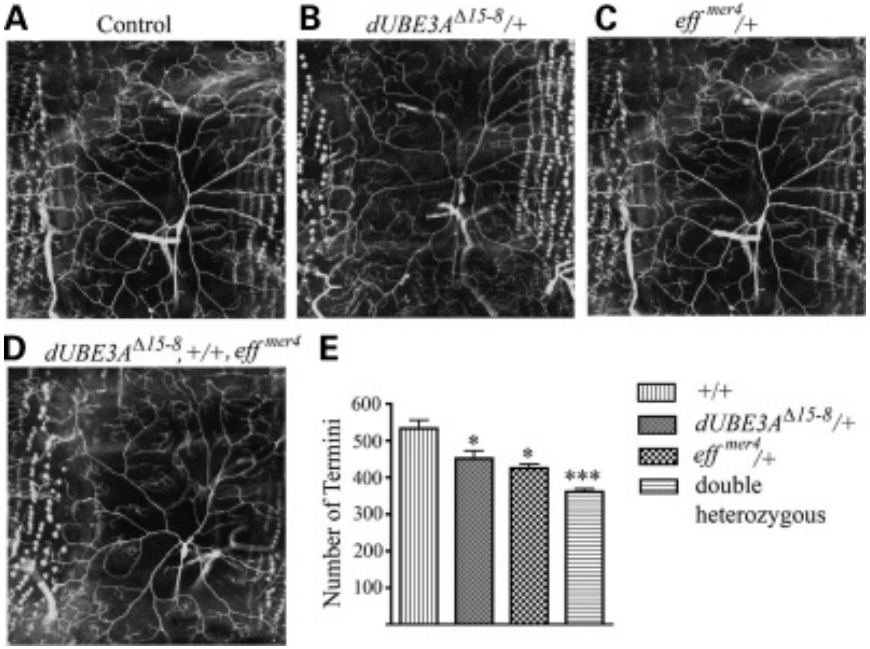
The magnitude of the quantitative differences in licking behaviour correspond to the degree of loss of *Ube3a*.

Human Molecular Genetics, 2008, Vol. 17, No. 14

A *Drosophila* model for Angelman syndrome

Yaning Wu*, Francois V. Bolduc[†‡§], Kimberly Bell[†‡], Tim Tully[†‡], Yanshan Fang[¶], Amita Sehgal[¶], and Janice A. Fischer*





The *Drosophila* homologue of the Angelman syndrome ubiquitin ligase regulates the formation of terminal dendritic branches

Yubing Lu[†], Fay Wang[†,‡], Yan Li[†,¶], Jacob Ferris, Jin-A Lee and Fen-Biao Gao*

Human Molecular Genetics, 2009, Vol. 18, No. 3

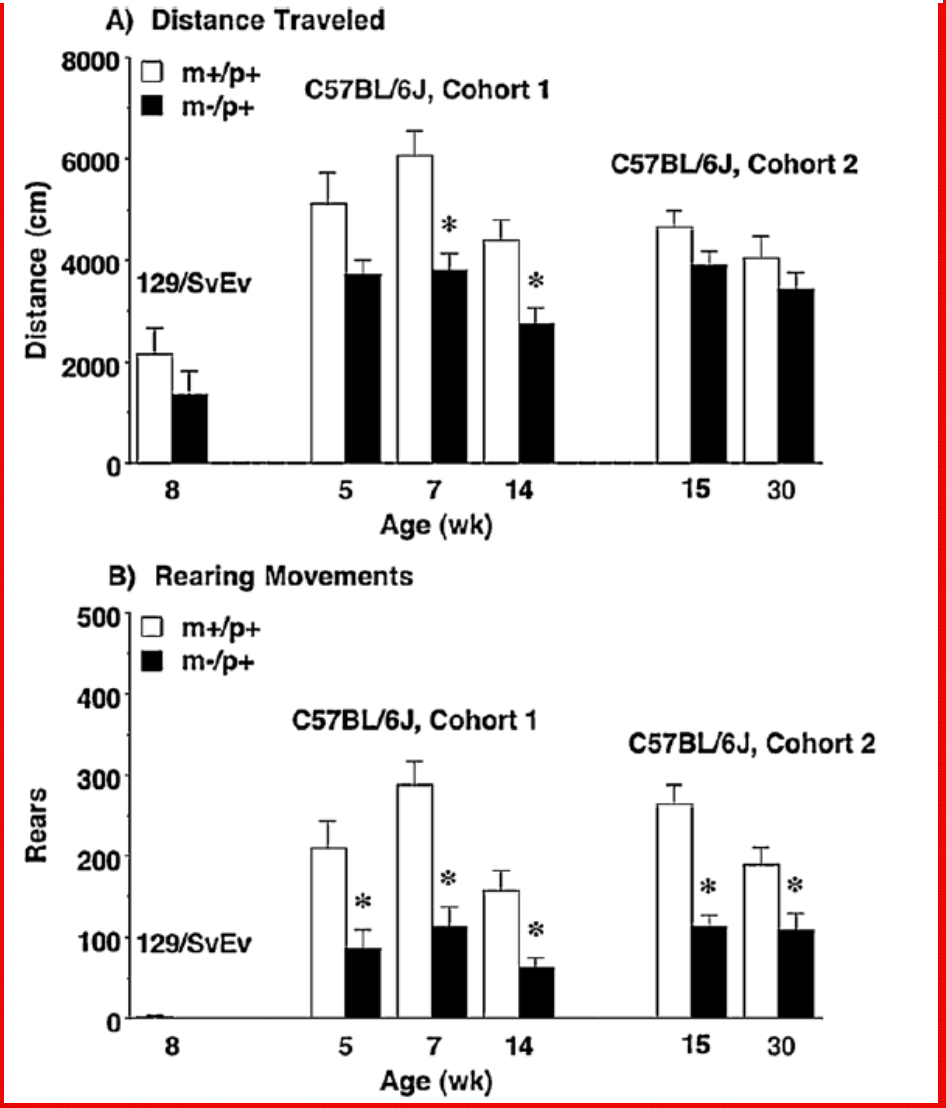
Behavioral deficits in an Angelman syndrome model: Effects of genetic background and age

Behavioural Brain Research 243 (2013) 79–90

Hsien-Sung Huang[a], Andrew J. Burns[a], Randal J. Nonneman[b], Lorinda K. Baker[b,c], Natallia V. Riddick[b,c], Viktoriya D. Nikolova[c], Thorfinn T. Riday[a], Koji Yashiro[a], Benjamin D. Philpot[a,b,d,*], Sheryl S. Moy[b,c,**]

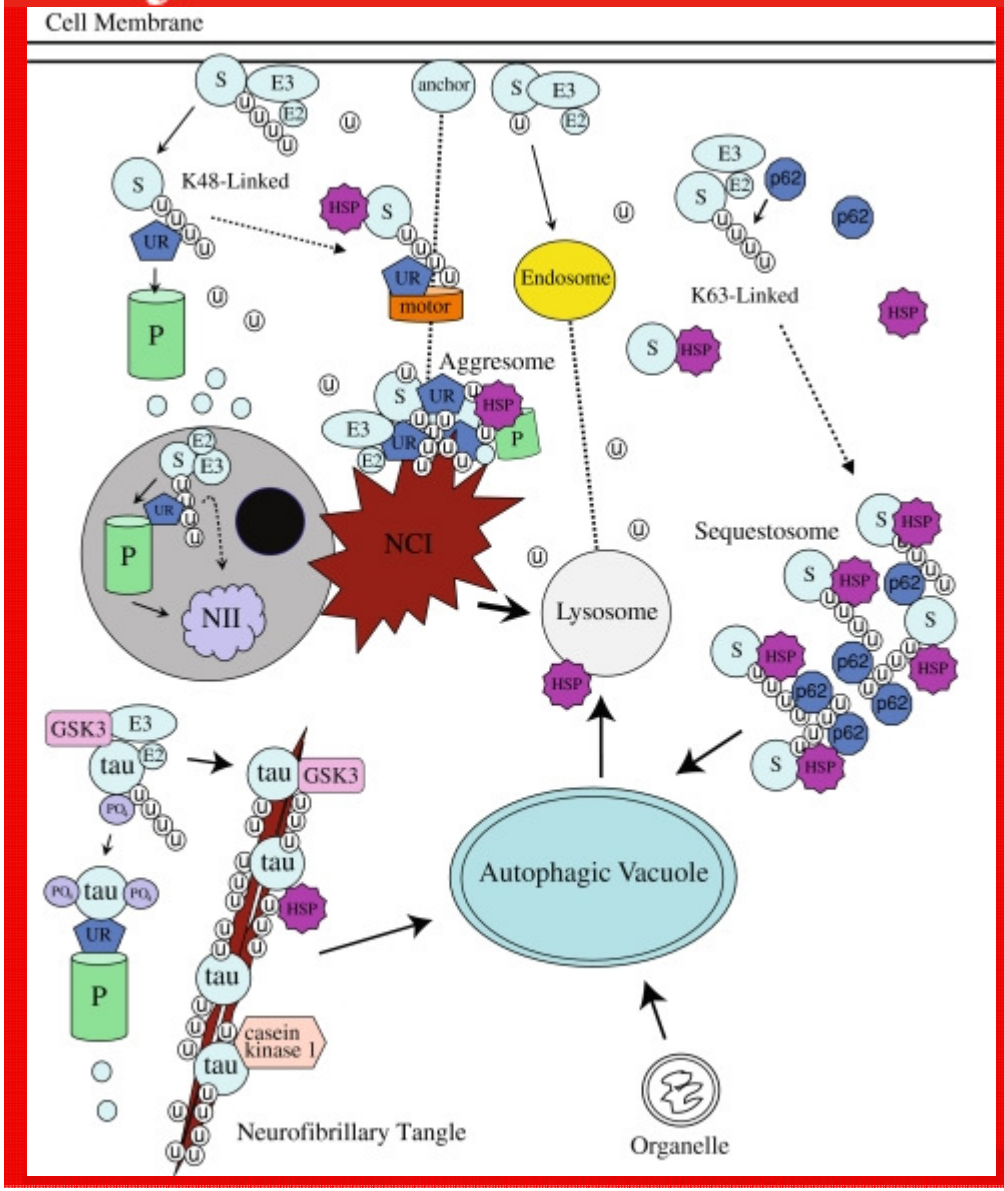
- Behavioural phenotypes vary across ages, cohorts and genetic background of mouse models of AS

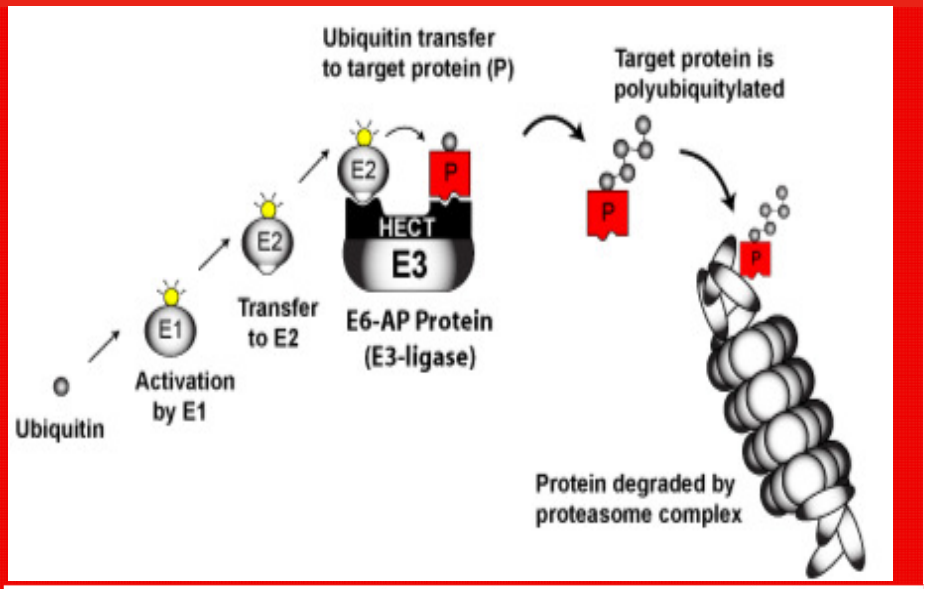
- Motor and spatial deficits seen at 16 w. but not at 8 w.
- Abnormal startle reactivity and sensorimotor gating only in adolescent B6 mice
- Differences between male and female not studied

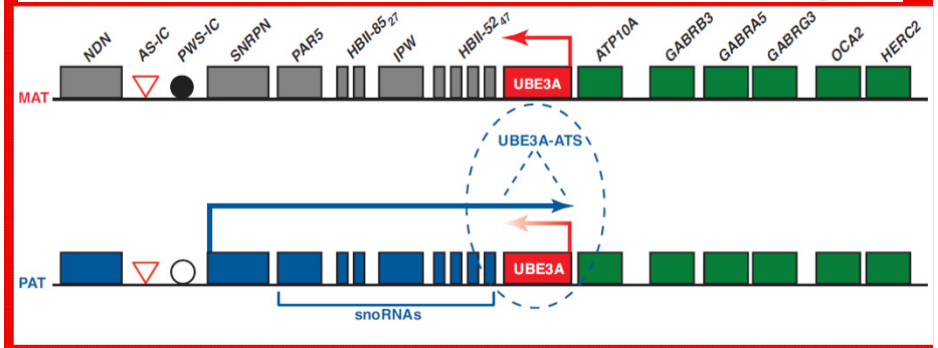


Angelman Syndrome

UBE3A

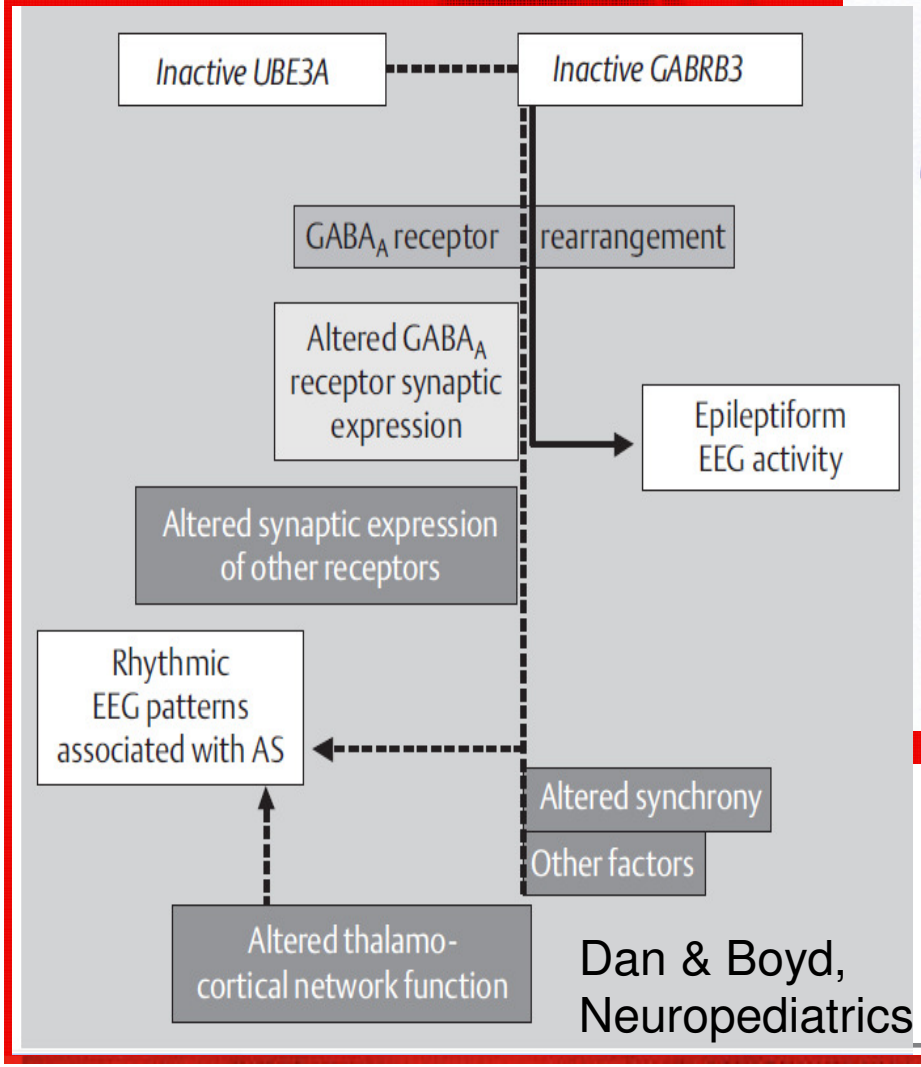






Angelman Syndrome

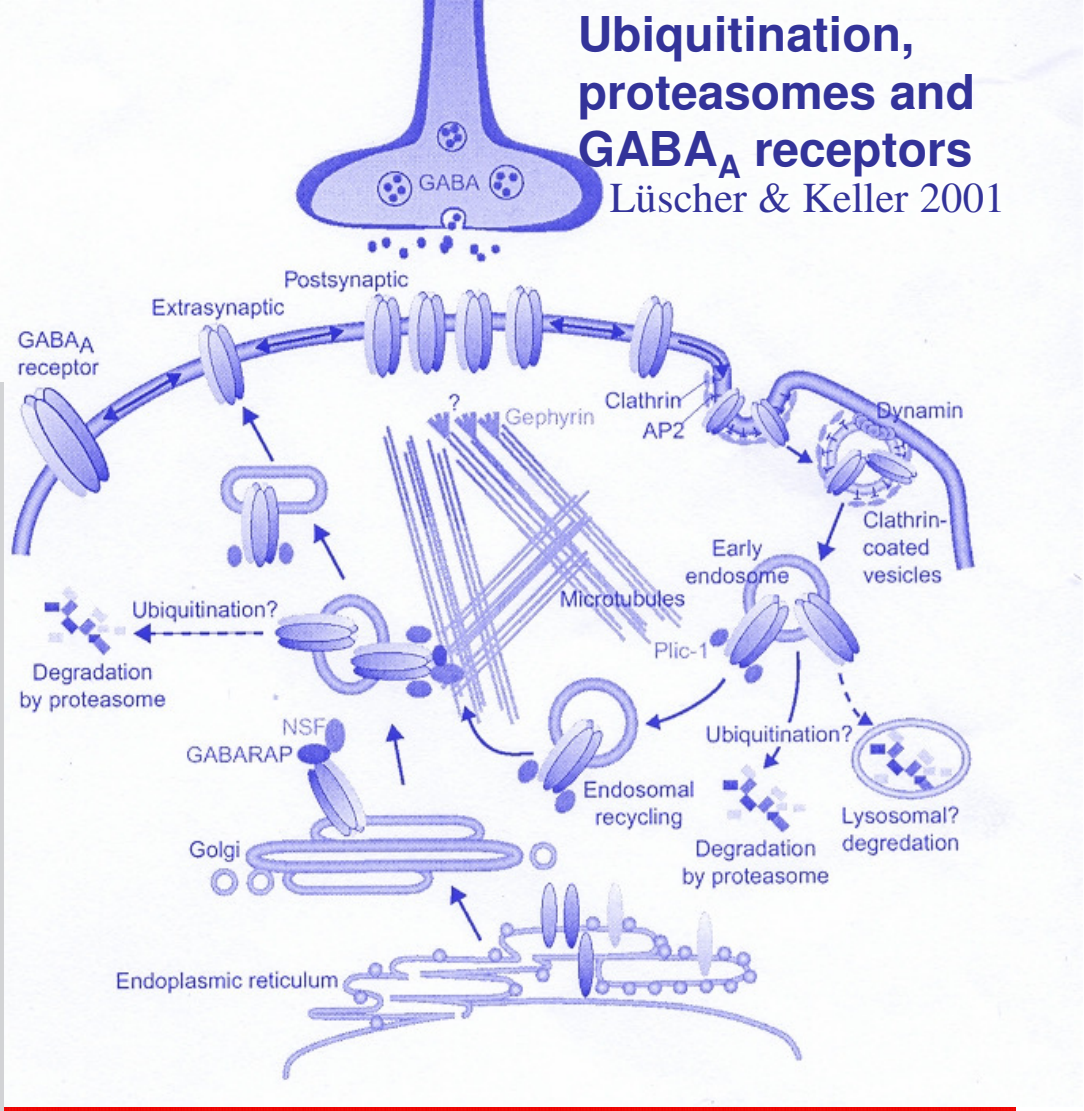
Bernard Dan



Dan & Boyd, Neuropediatrics 2003

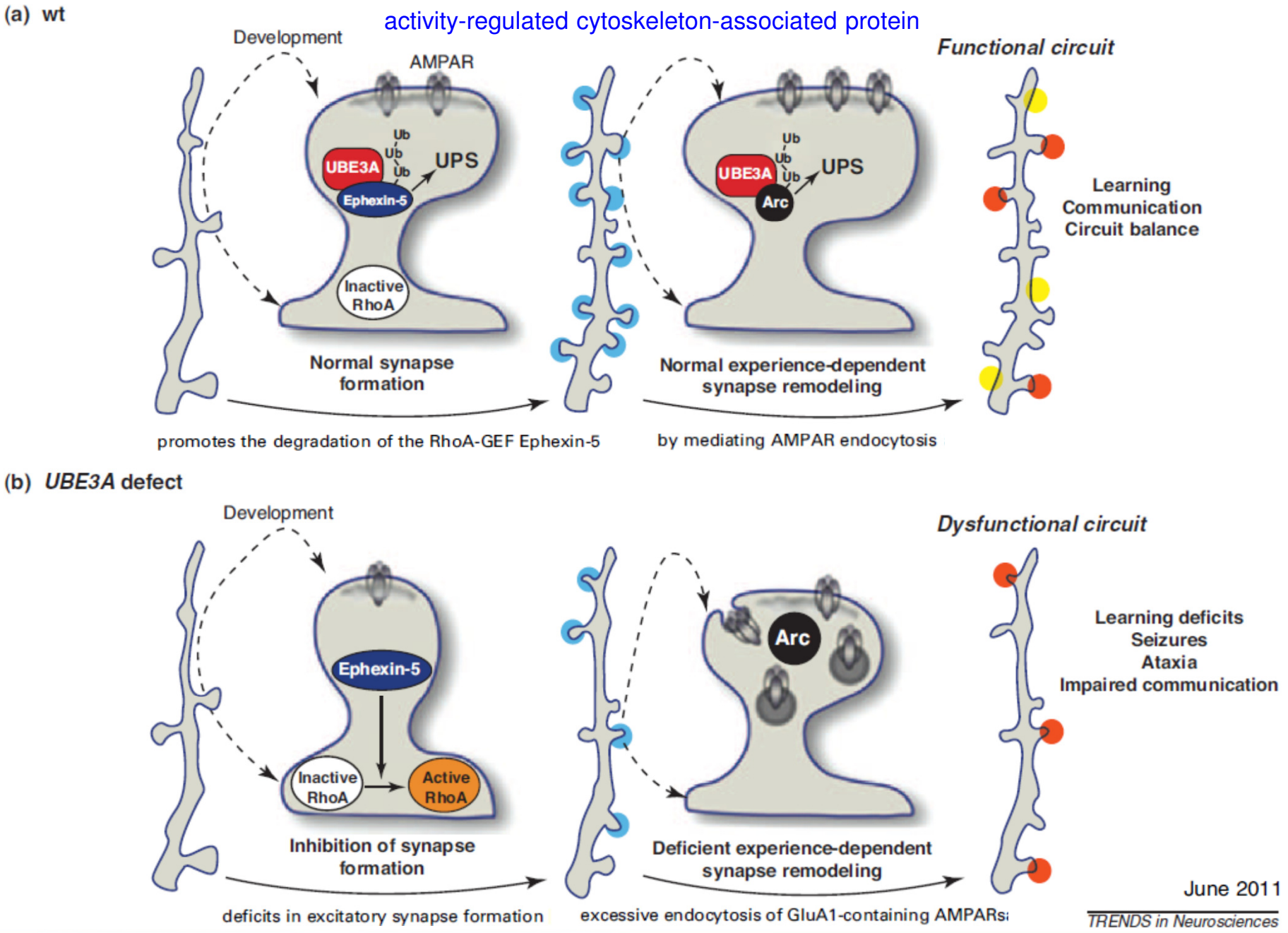
Ubiquitination, proteasomes and GABA$_A$ receptors

Lüscher & Keller 2001



Angelman Syndrome Reviewed from a Neurophysiological Perspective. The *UBE3A-GABRB3* Hypothesis

activity-regulated cytoskeleton-associated protein



June 2011
TRENDS in Neurosciences

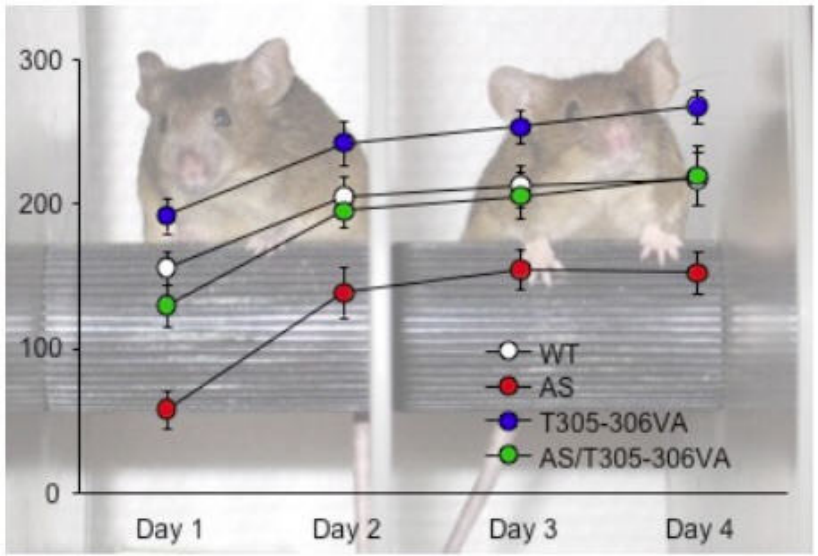


Figure 1. Motor performance. AS mice show impaired motor performance when tested on the rotarod compared to their wild type littermates, which is rescued when the mice are crossed with mice that have a mutation in the CaMKII gene, resulting in less inhibition of CaMKII (AS/CaMKII-305/6$^{+/-}$).

Rescue of neurological deficits in a mouse model for Angelman syndrome by reduction of alphaCaMKII inhibitory phosphorylation

Van Woerden et al.
Nat Neurosci 2007

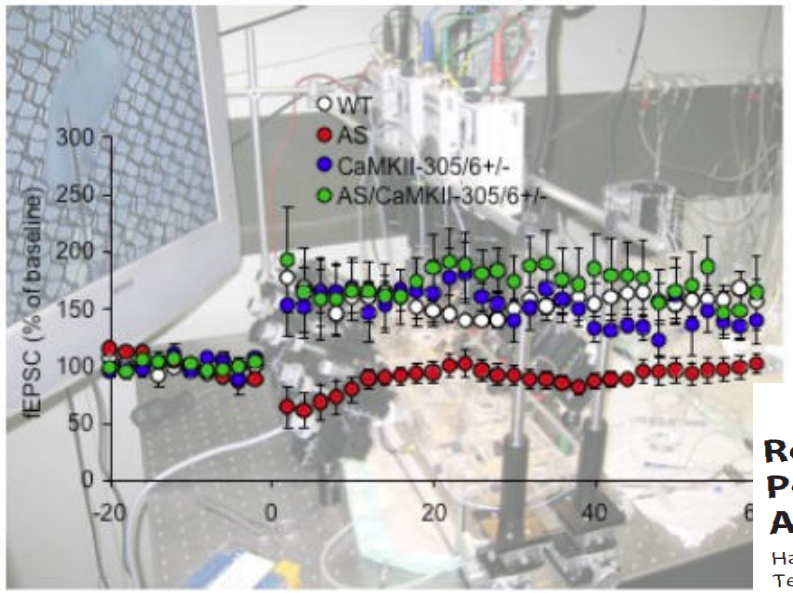
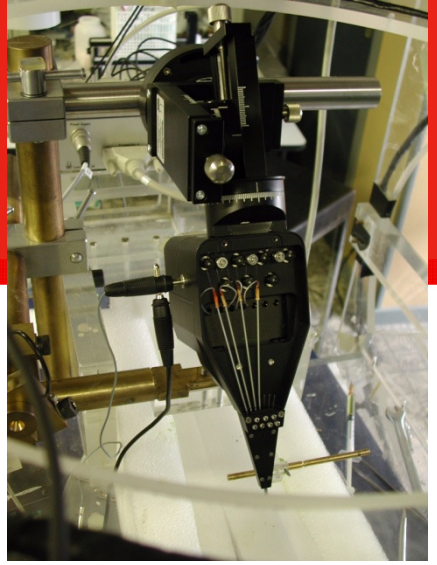


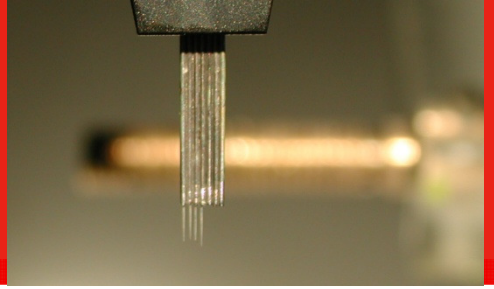
Figure 3. Synaptic plasticity in AS mice. AS mice show impaired Long-Term Potentiation (LTP), which again is restored to Wild-type level when crossed with CaMKII-305/6$^{+/-}$ mice

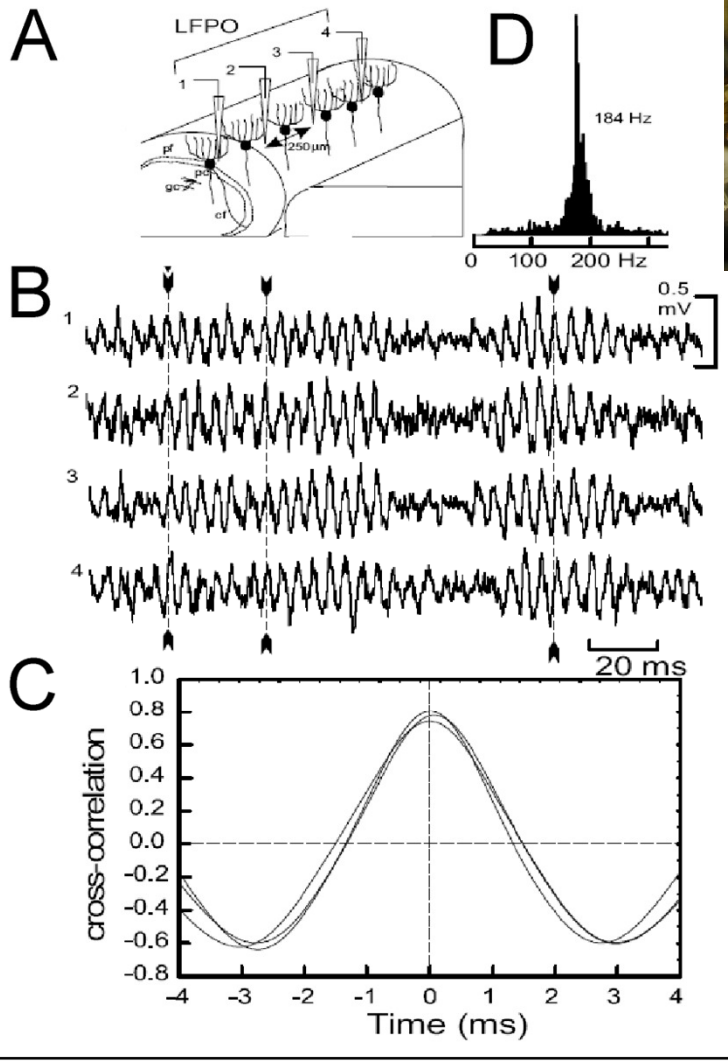
Reversal of Impaired Hippocampal Long-Term Potentiation and Contextual Fear Memory Deficits in Angelman Syndrome Model Mice by ErbB Inhibitors

Hanoch Kaphzan, Pepe Hernandez, Joo In Jung, Kiriana K. Cowansage, Katrin Deinhardt, Moses V. Chao, Ted Abel, and Eric Klann

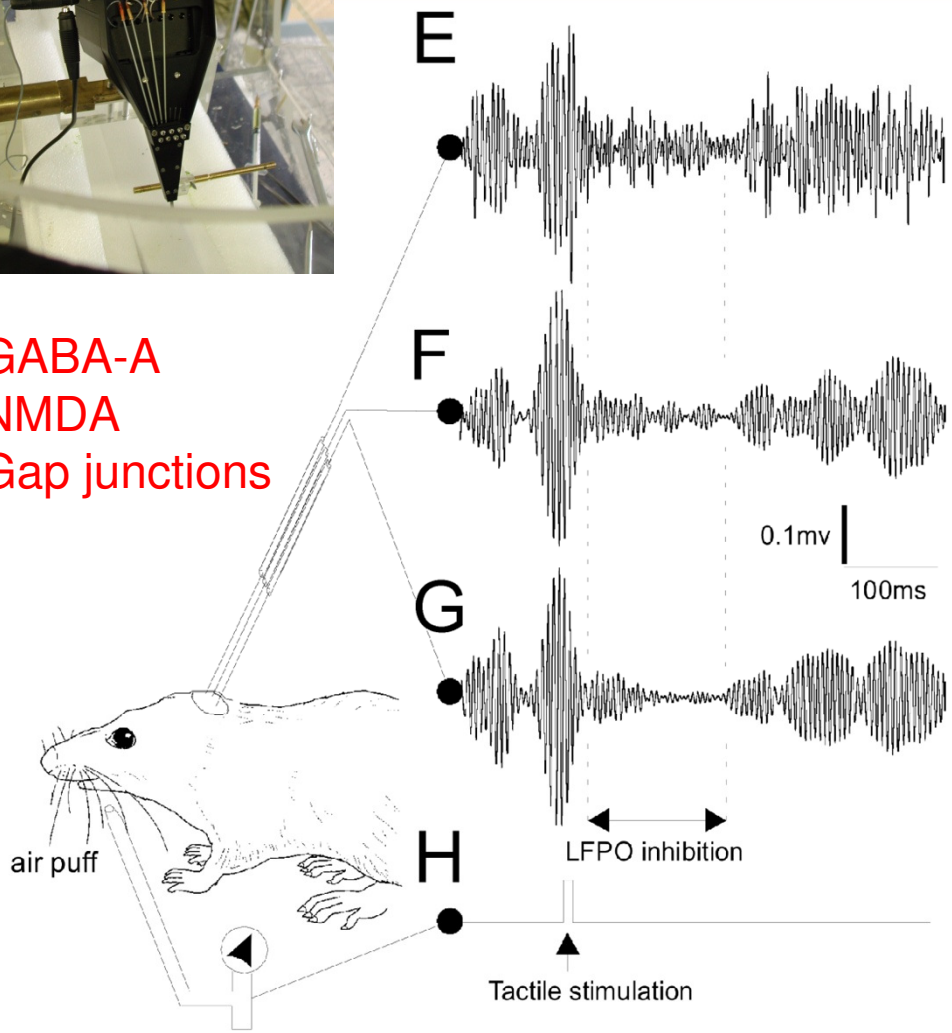
Angelman Syndrome







GABA-A
NMDA
Gap junctions



Cheron et al. *Neuroscience* 2005

Angelman Syndrome

Behaviour and cognition

Bernard Dan

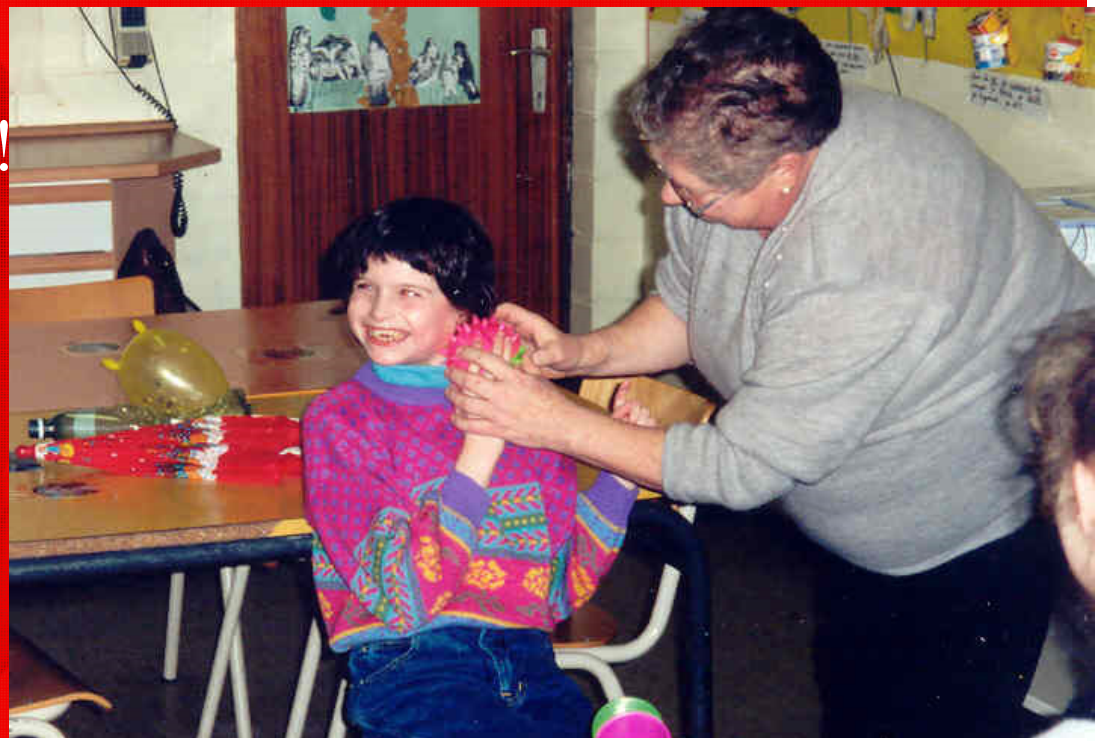
Impaired information processing: intellectual disability

IQ??

Verbal / motor impairment!

Attention! Motivation!

Late learners



J. Summers. Developmental Neurodisability 2012;15(4):239-52.

Neurodevelopmental outcomes in children with Angelman syndrome after 1 year of behavioural intervention.

Angelman Syndrome

Perception

Bernard Dan

Visual perception

Strabismus, low vision, refraction

Hypopigmentation (deletion)
Intellectual disability

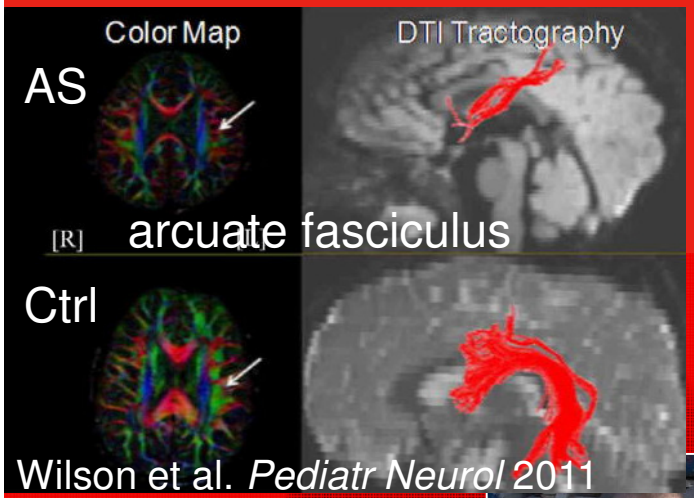
Many patients with treatable eye problems are never seen by an eye doctor

Ophthalmic findings in Angelman syndrome

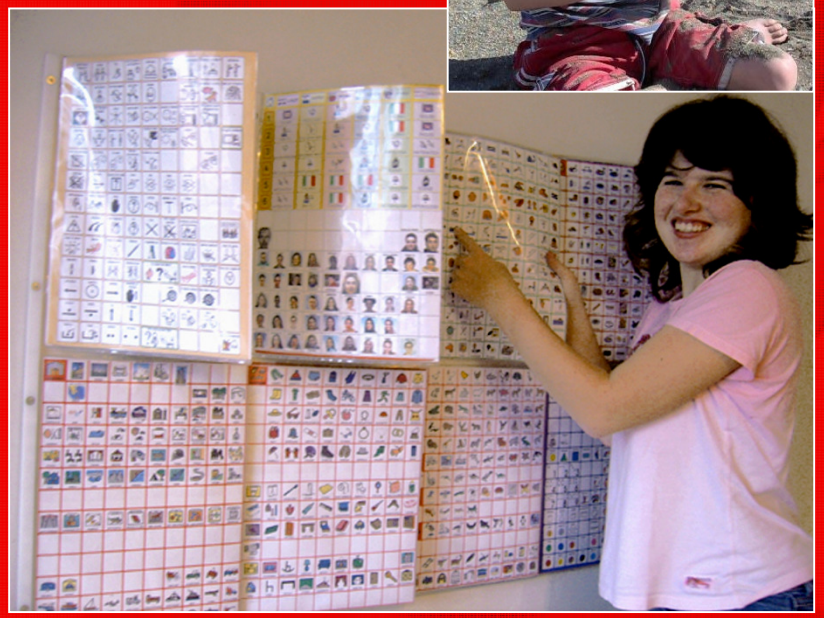
Paola Michieletto, MD,[a] Paolo Bonanni, MD,[a] and Stefano Pensiero, MD[b]

J AAPOS 2011

Communication



Wilson et al. *Pediatr Neurol* 2011



Angelman Syndrome

Bernard Dan

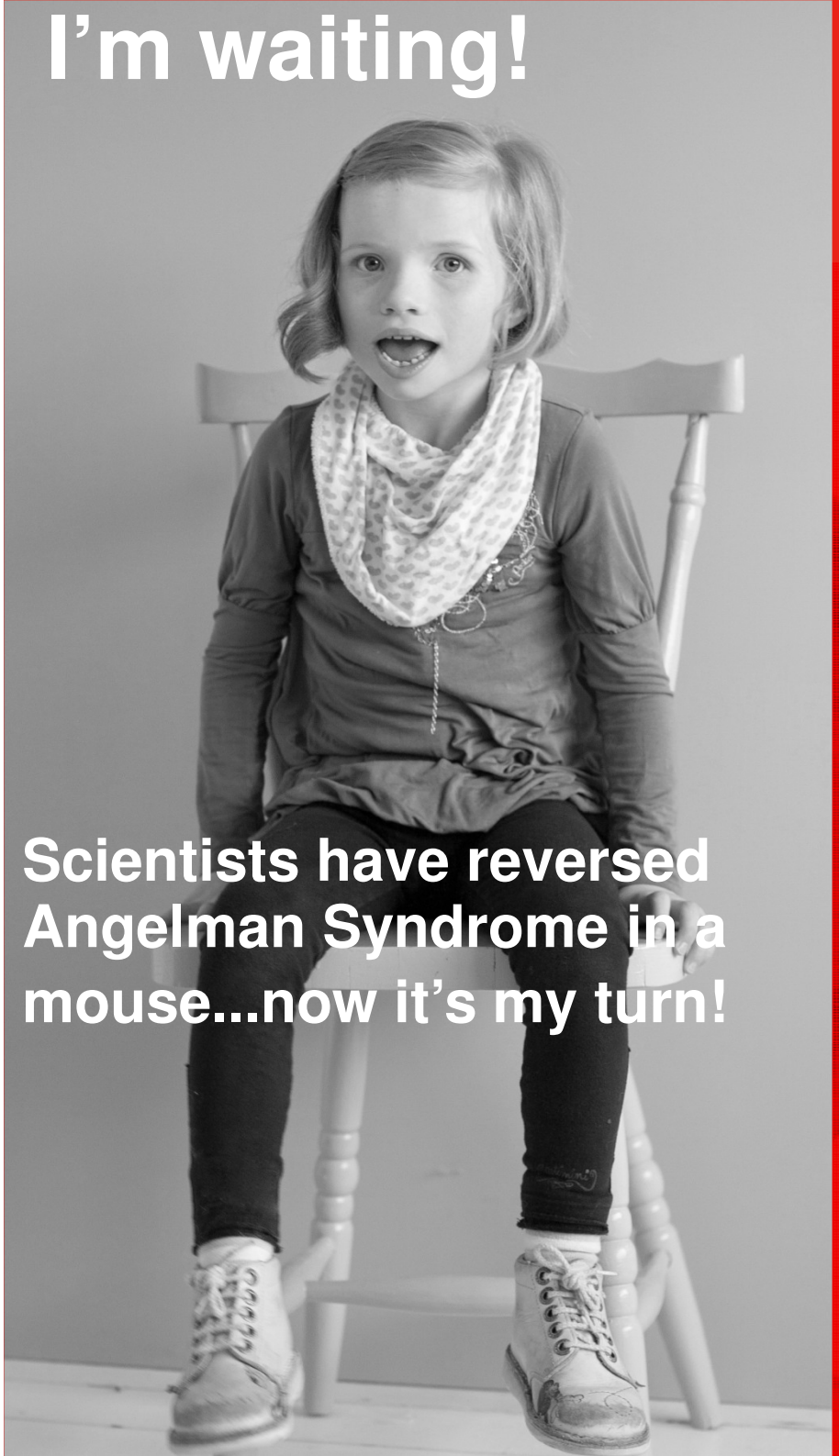
Sleep

reduced total sleep time
increased sleep onset latency
disrupted sleep architecture
frequent awakenings
reduced rapid eye movement sleep
periodic leg movements

no significant interference with daytime alertness

Sleep Medicine 9 (2008) 434–441

I’m waiting!



Scientists have reversed Angelman Syndrome in a mouse...now it’s my turn!

Clinical studies

Epidemiological studies
causation vs risk factors
follow-up (e.g. Apgar)
groupings; cross results

Animal models

document mechanisms, tissue targets, timing of brain injury, functional outcome

test potential therapeutic approaches

not strictly parallel epidemiological findings

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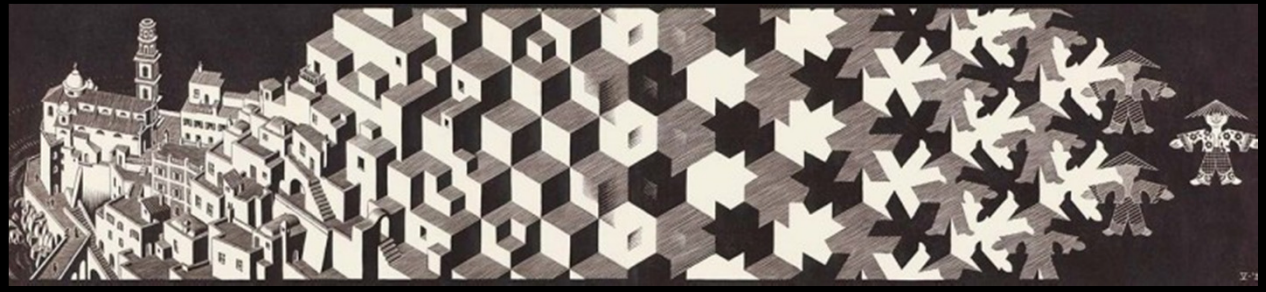
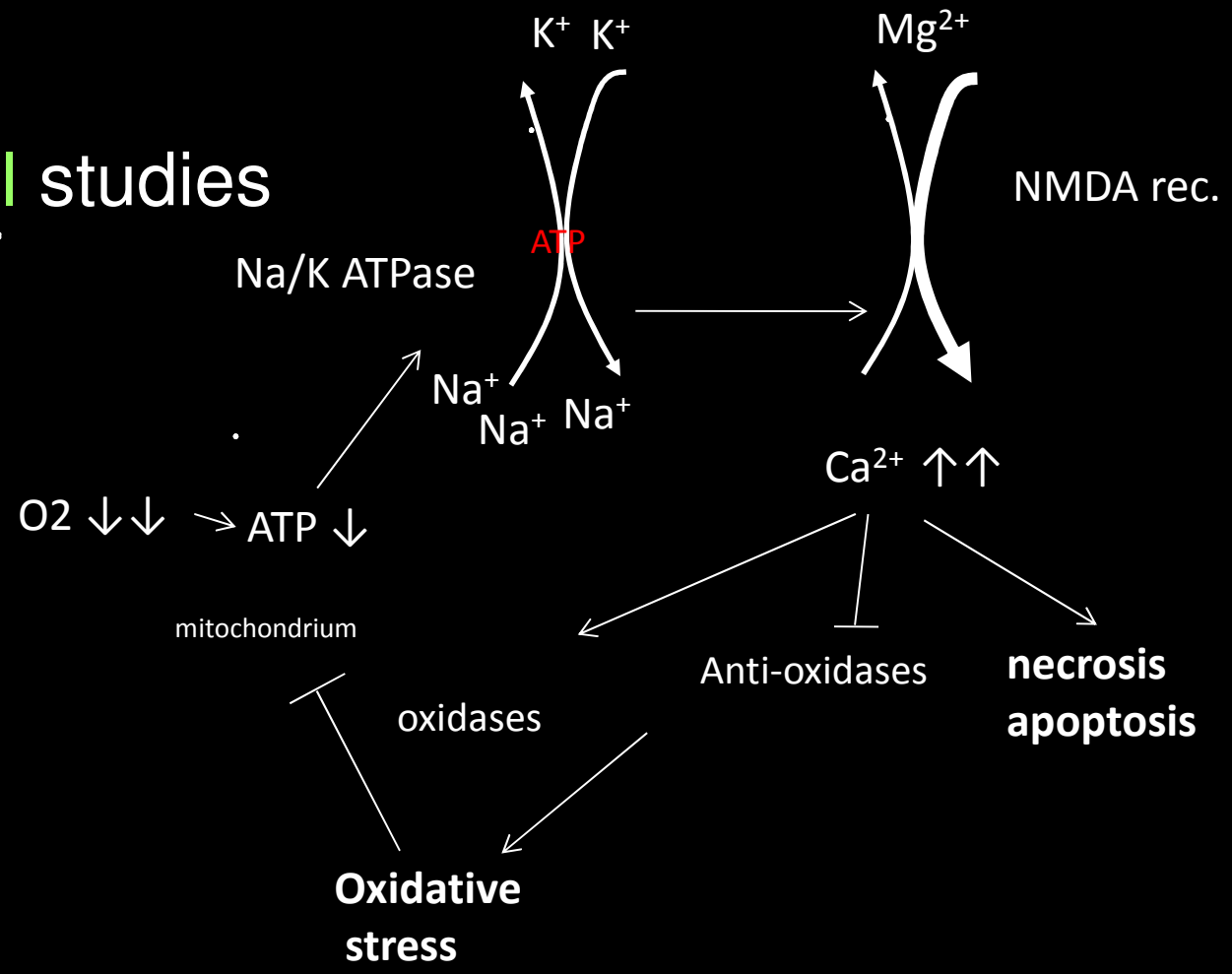
DAUGHTERS OF CHARITY
TECHNOLOGY AND RESEARCH INTO DISABILITY



Clinical studies

Epidemiological studies

Animal models

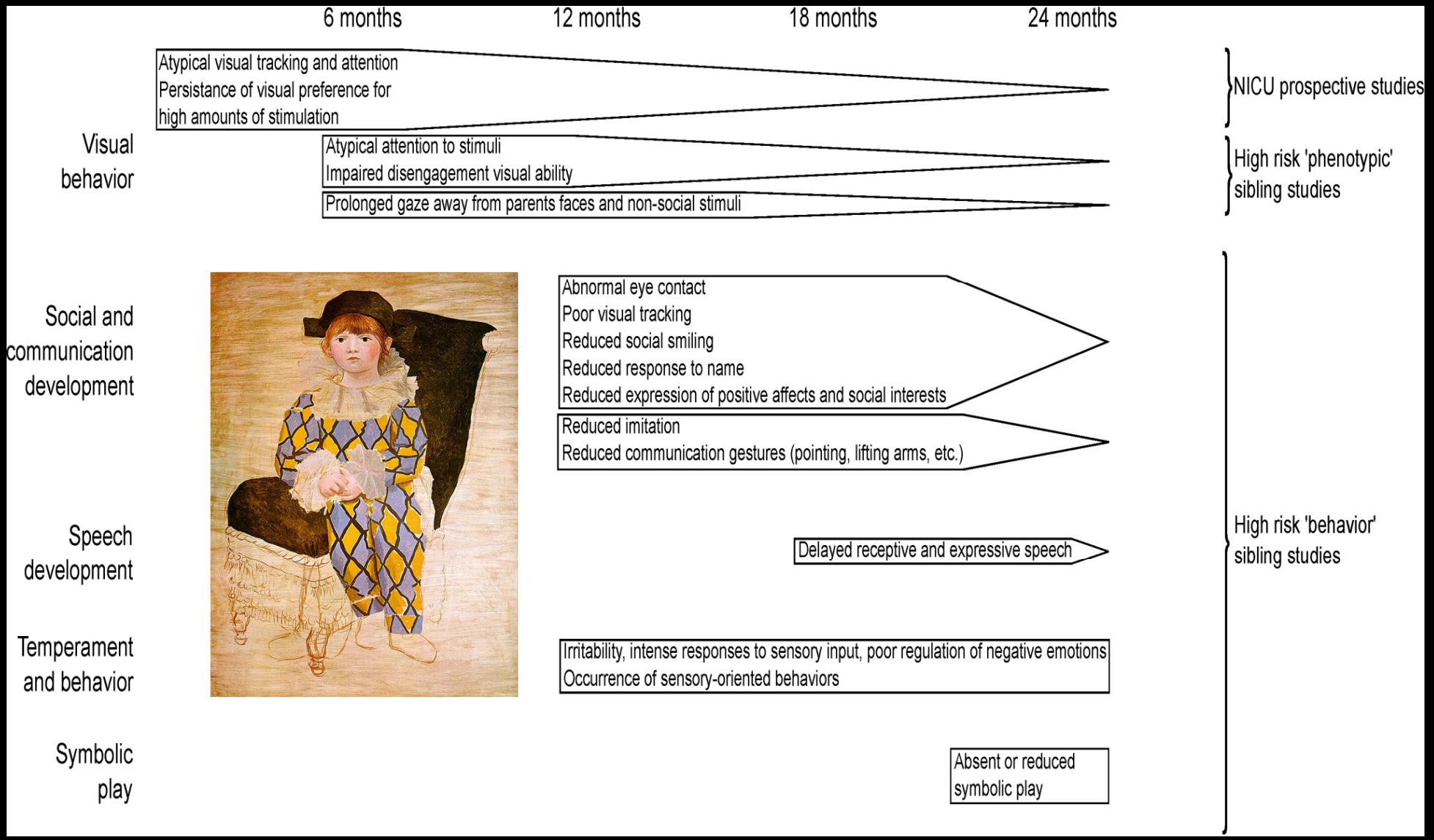


nature REVIEWS DISEASE PRIMERS

Topical Review

Toward Better Recognition of Early Predictors for Autism Spectrum Disorders

Nicolas Deconinck MD, PhD[a,*], Marie Soncarrieu MD[b], Bernard Dan MD, PhD[a]



Developmental exposure

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY INVITED REVIEW

Use of paracetamol during pregnancy and child neurological development

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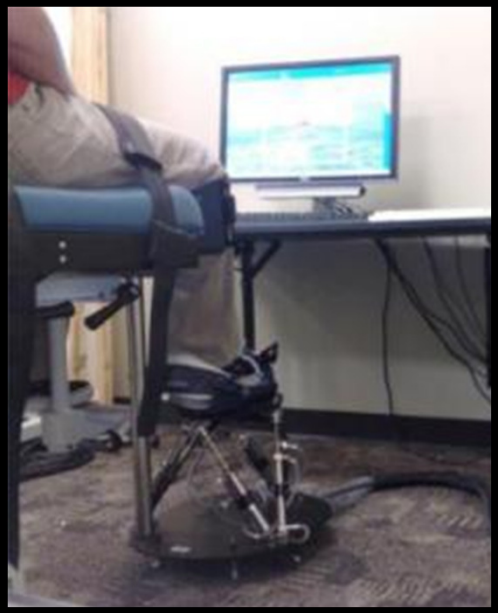
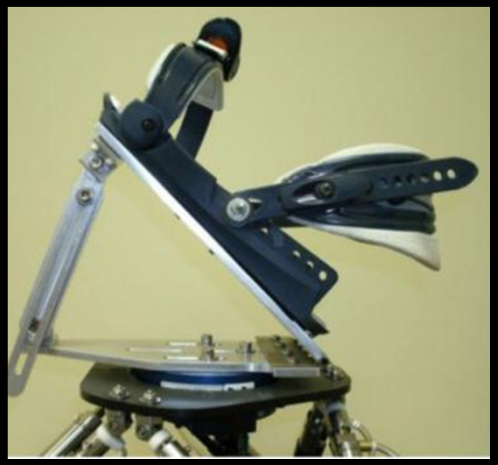
ABBREVIATIONS

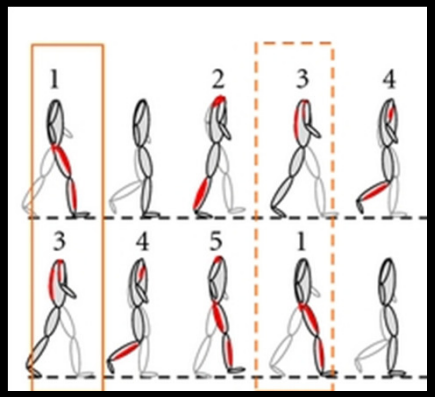
- Animal data suggest that therapeutic doses of paracetamol may alter cognition and behaviour.
- Epidemiological studies suggest a weak to moderate association between antenatal exposure to paracetamol and neurodevelopment or attention-deficit–hyperactivity disorder, but limitations in the studies' design and weakness of the observed associations prevent causal inference.
- Given the current knowledge, paracetamol is still to be considered safe in pregnancy and should remain the first line for the treatment of pain and fever.

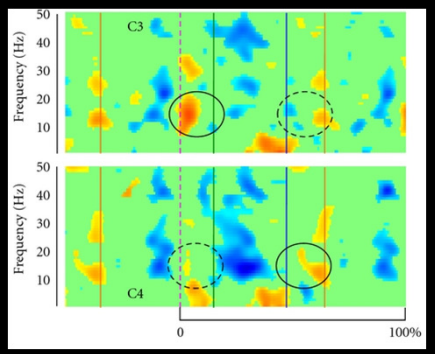
Tertiary prevention

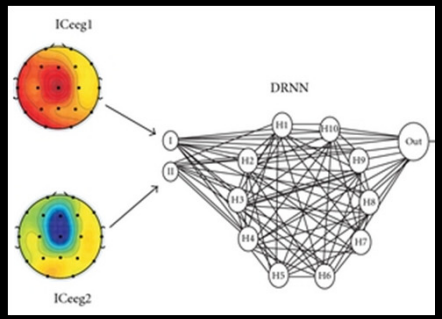




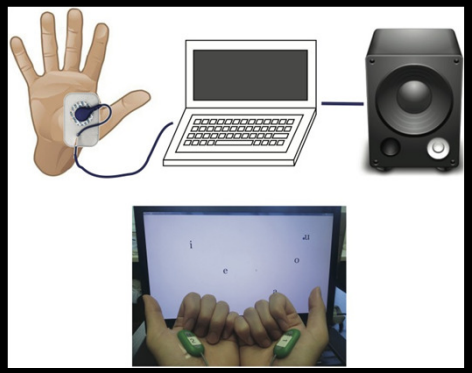
Tele(re)habilitation
Phys Ther 2014

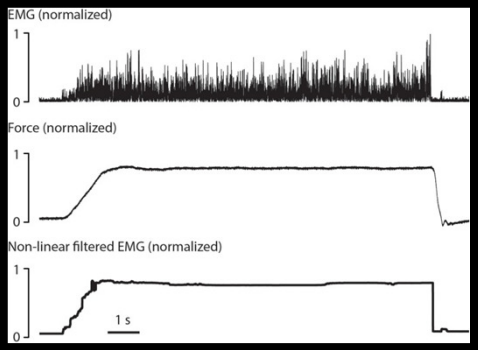


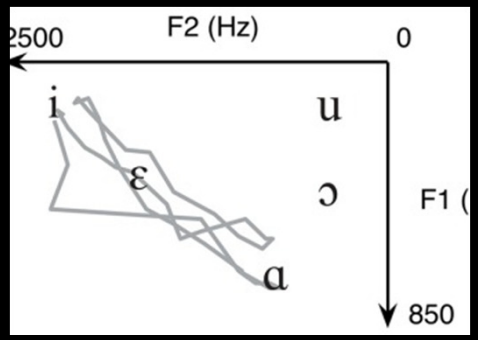




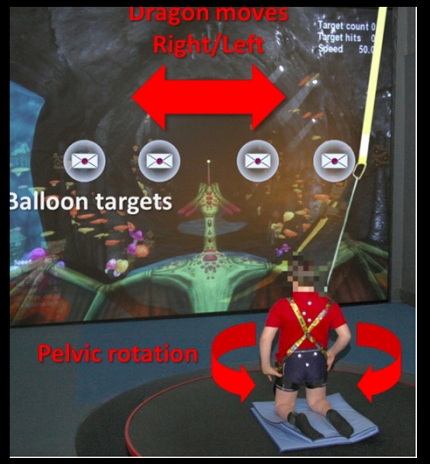
BCI
Neur Plast 2012

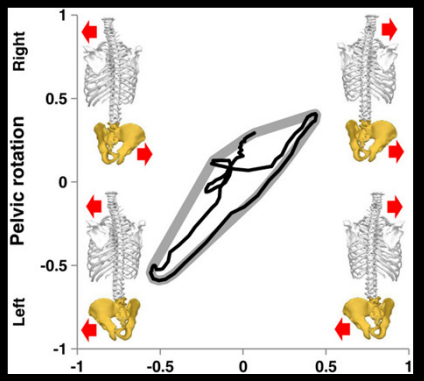


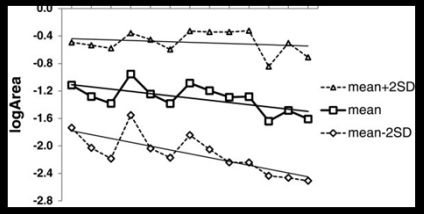




Speech synthesizer
Front Hum Neurosci 2014







Exergame
J Neuroeng Rehab 2013

Primary prevention
stop problem before onset
eliminate agents or increase resistance
prevention of the *existence* of individuals

Secondary prevention
detect and address disease prior to symptoms

Tertiary prevention
reduce negative impact disability or death
rehabilitation and treatment

Primary prevention

folate > spina bifida; HiB vaccination < meningitis;
support > FAS; general welfare programmes
genetic counselling

Secondary prevention

PKU screening; early intervention in high-risk children

Tertiary prevention

optimised care; educational programmes

Aetiology	Examples
1. Preconceptional	
1.1. Chromosomal causes	Prenatal screening (e.g. for Down syndrome)
1.2. Other genetic causes	Newborn screening (e.g. for phenylketonuria)
2. Prenatal	
2.1. Malformations of the central nervous system	Folate therapy during pregnancy, ultrasound screening
2.2. Malformation syndromes	
2.3. Environmental causes	Health education (e.g. about alcohol, drugs and radiation during pregnancy)
3. Perinatal	
3.1. Intrauterine disorders	Optimal prenatal and obstetric care
3.2. Neonatal disorders	Optimal neonatal care
4. Postnatal	
4.1. Head injuries	Health education (e.g. cycling helmets)
4.2. Infections	Vaccinations, health education, optimal care

notion of causation vs factors contributing to pathophysiology

Known or Hypothesised Risk Factors for CP

(not necessarily mutually exclusive)

with Implications for Primary Prevention

- Preterm birth, birth weight, SGA
- Infections
- Genetic factors
- Nutritional factors
- Trauma
- Access to healthcare:

prenatal, perinatal, postnatal and later

- Poverty, socioeconomic factors

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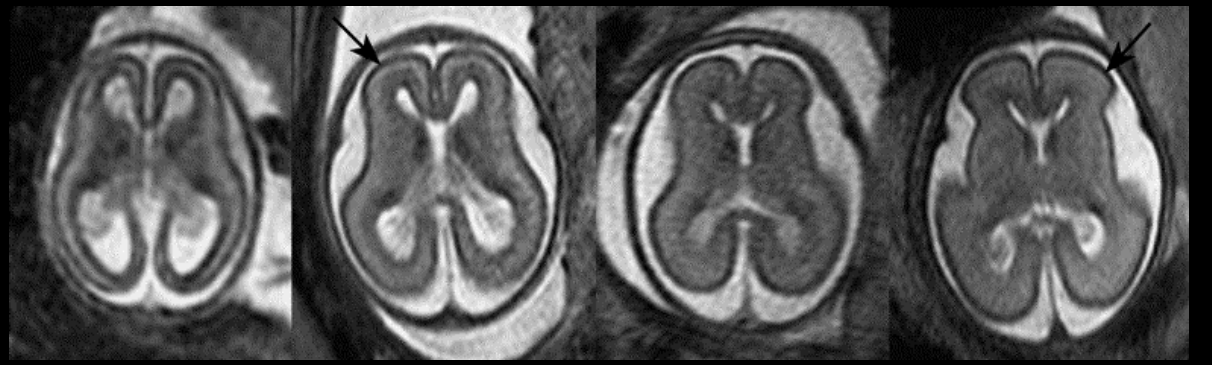
TECHNOLOGY AND RESEARCH INTO DISABILITY

Practical and ethical issues in the prevention of neurodisability in various aetiological categories

1. Preconceptual factors
   - Access to prenatal diagnosis
   - Individual or societal level of prevention
   - Prescriptive or non-prescriptive counselling
2. Prenatal factors
   - Autonomy (e.g. FAS)
   - Ultrasound screening
   - Fetal MRI



3. Perinatal factors
   - Malformation, brain damage, QoL
4. Postnatal factors
   - Large prevention programmes (e.g. vaccination)
   - Parental attitude towards management

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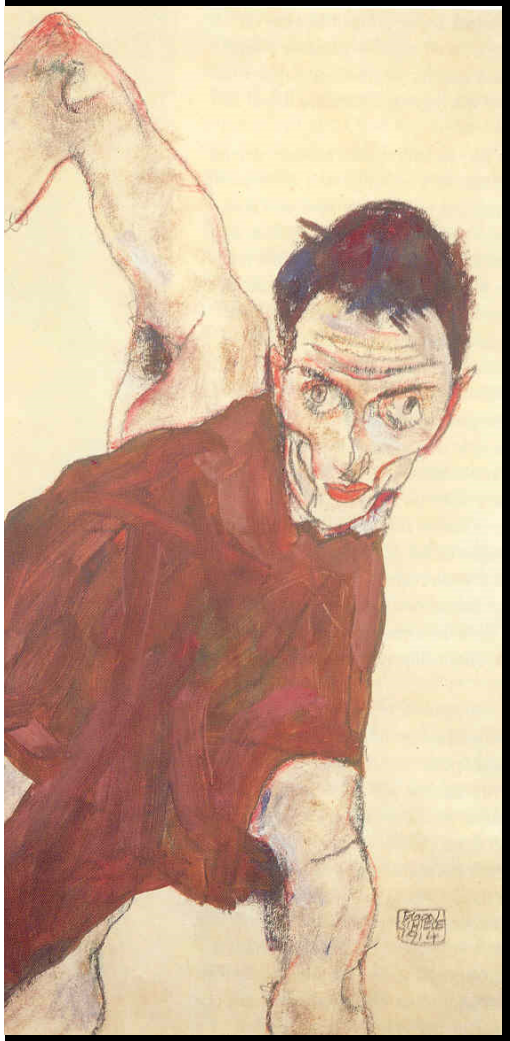
TECHNOLOGY AND RESEARCH INTO DISABILITY



- dynamic and multidimensional concept
- developmental: primary + secondary
- generic vs aetiologically defined conditions
- epidemiology: contributing factors
- animal models (specific limitations)
- strategies for prevention (evaluate!)

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