Neuroscience models of ID, ASD (neuronal circuits)

Nicolas Deconinck

Paediatric neurology

Medical director

Hôpital universitaire des Enfants Reine Fabiola

Intellectual Disabilities

- Most common developmental disorder,
  - ✓ 1/70 individuals,
  - ✓ more than 2 million in Europe
  - ✓ 1.5:1, boys to girls

- Definition

  - ✓ Intelligence quotient (IQ) less than 70 (<2 SD)
  - ✓ 2 or more disorders of adaptive behavior
  - ✓ with onset in childhood

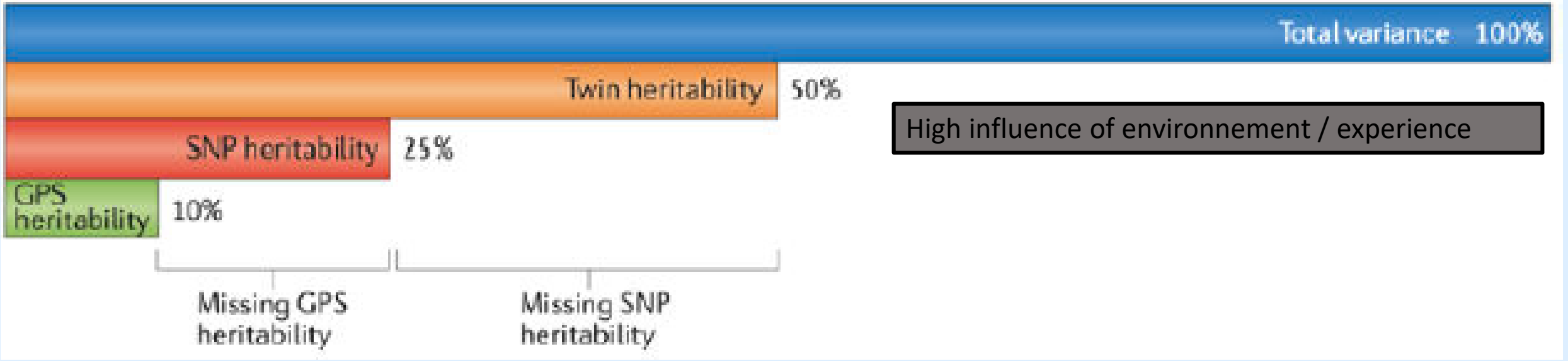
- Adaptive skills: Daily living skills, communication skills or social skills

What is intelligence?

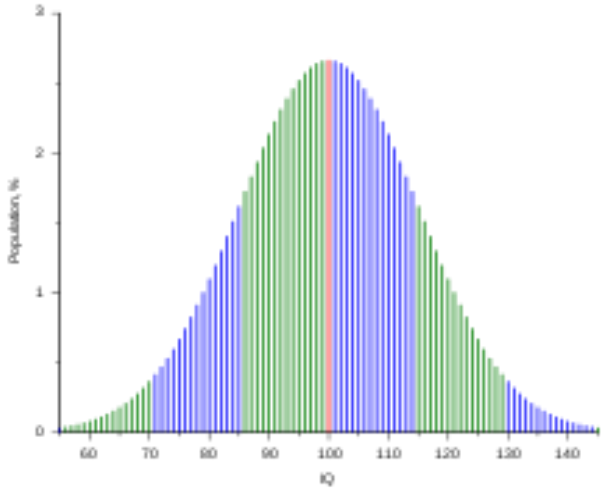
- Defined as the **ability to learn, reason and solve problems**
- Latent trait that cannot be directly observed but is inferred from a battery of diverse cognitive test scores, as in widely used ‘IQ score’
- Variate Psychometric tests (in form and content) :
  - ex: verbal ability and others non-verbal ability,
  - some give strict time limits and some are untimed
- Cognitive test scores, **positively inter-correlated**
  - any differences in test scores that occur within an individual are smaller than test score differences that exist between individuals.
  - “a person who scores high on one type of cognitive test relative to other people will also do comparatively well on other cognitive tests”: positive manifold, **or simply g**, the general factor

What is intelligence?

- Highly heritable



Levels of Intellectual Disability

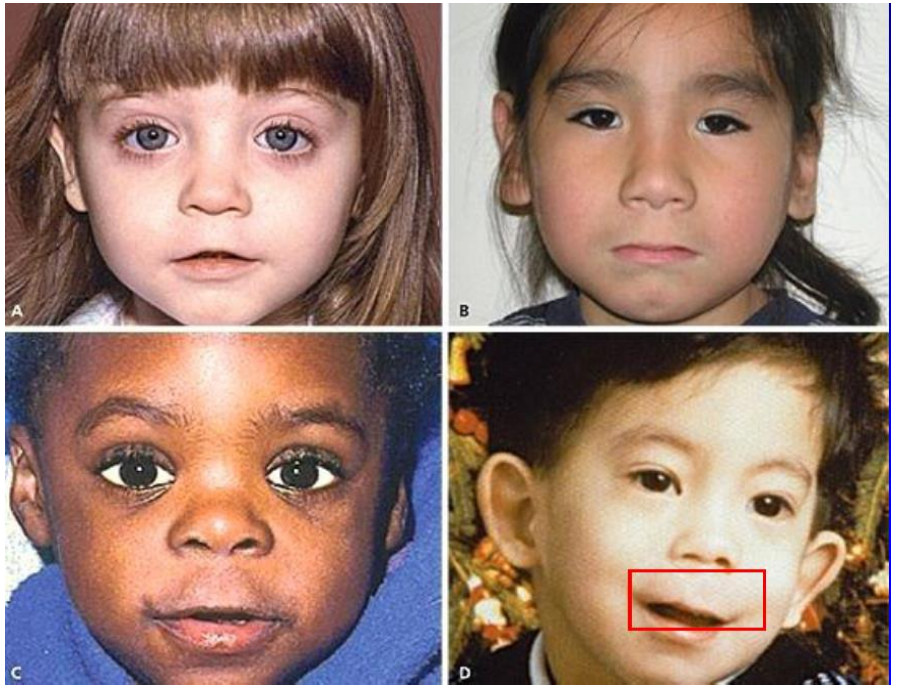


Level	IQ %	Independence
Mild	50-69 (85)	Most work
Moderate	34-49 (10)	With support
Severe	20-34 (3)	None
Profound	<20	None

Most Common Causes of ID

- Most common genetic: Down syndrome (Trisomy 21)
- Most common *inherited*: Fragile X Syndrome
- **Leading global cause**: Iodine deficiency causing thyroid hormone deficiency
- **Leading causes in Europe** : fetal ethanol, psychosocial,

Causes of ID by IQ Level



Mild 80% unidentified,

- psychosocial, toxins, lead,
- fetal alcohol, genetic?

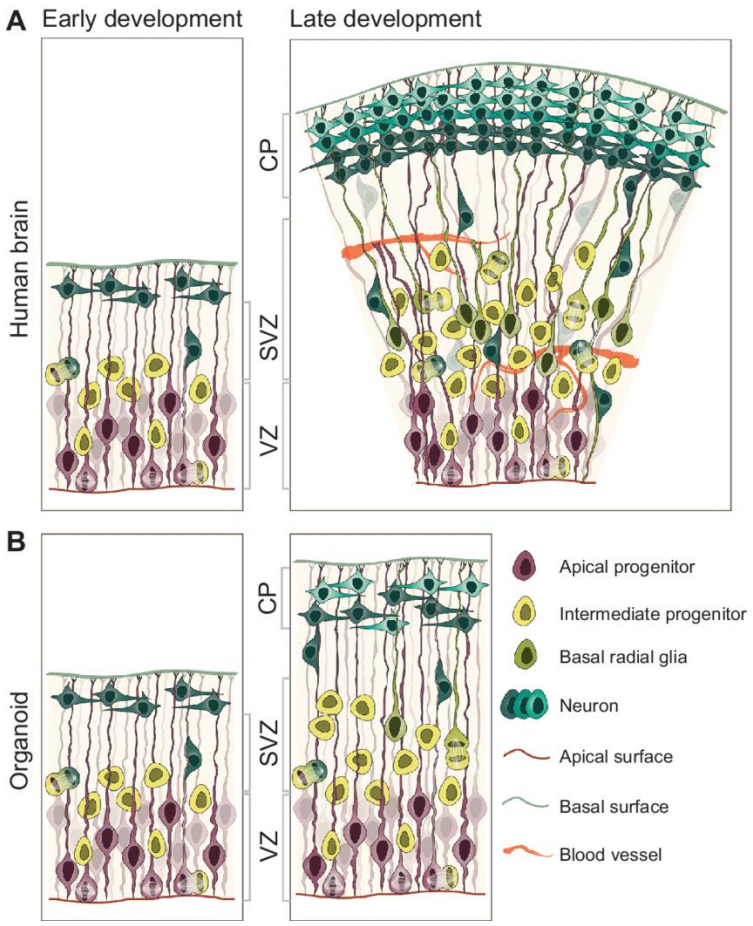
Moderate

- More likely genetic,
  e.g. Down syndrome, Fragile X

Severe

- Genetic more likely especially profound Associated with a syndrome

Early human brain development



5–6 gestational weeks (GW): first neurons progenitors multiplications

Establishment of the ventricular zone VZ.

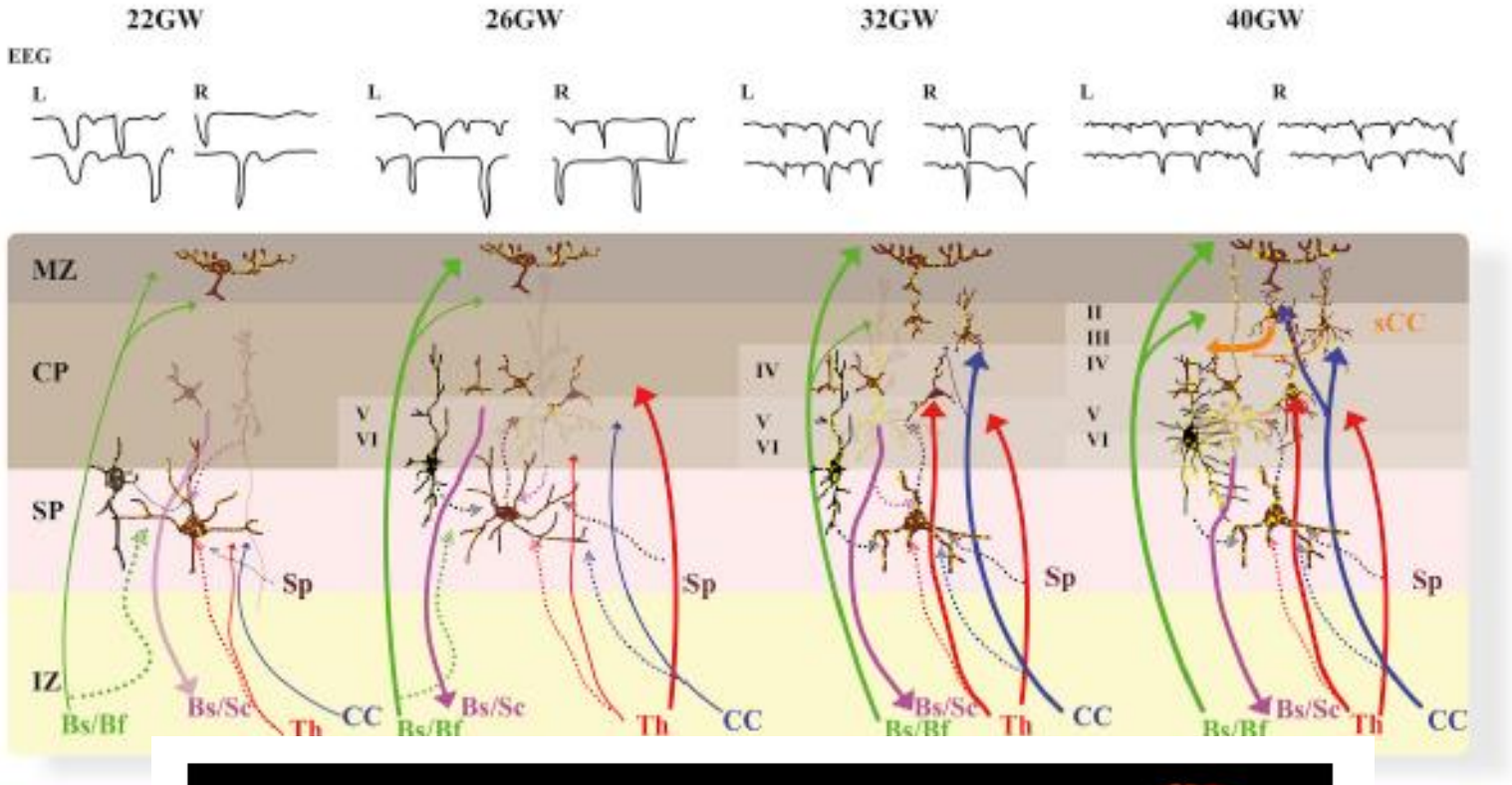
Establishment of an another progenitor layer: the **subventricular zone** (SVZ): intermediate progenitors (IP)

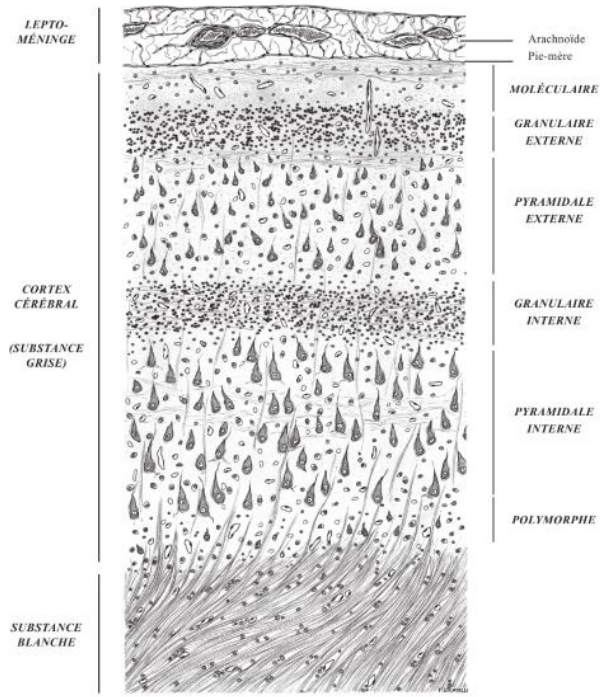
Production of **specific progenitors**: basal radial glia (bRG) or outer radial glia (oRG) in the SVZ

The complexity of the SVZ compartment and the ability of neural progenitors to remain or switch to a “more pro- liferative” state, coupled with the length of neurogenesis, may have contributed to evolutionary expansion of the neocortex (particularly in humans)

All types of **neural progenitors give rise to neurons, which migrate basally**, using the RG processes. Settlement **in well-organized layers, inside out pattern, finally making up the mature, six-layered cortical** plate of an adult neocortex

Next …and in parrallel : Cortical circuiterie development from 22 weeks GA



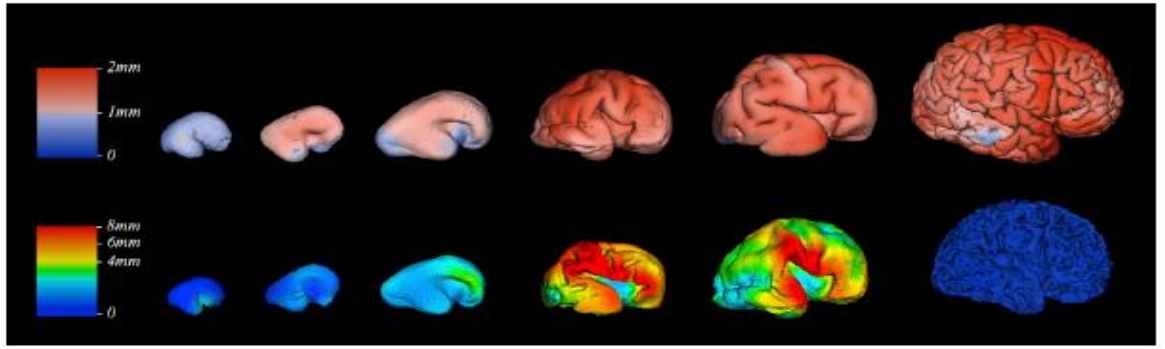


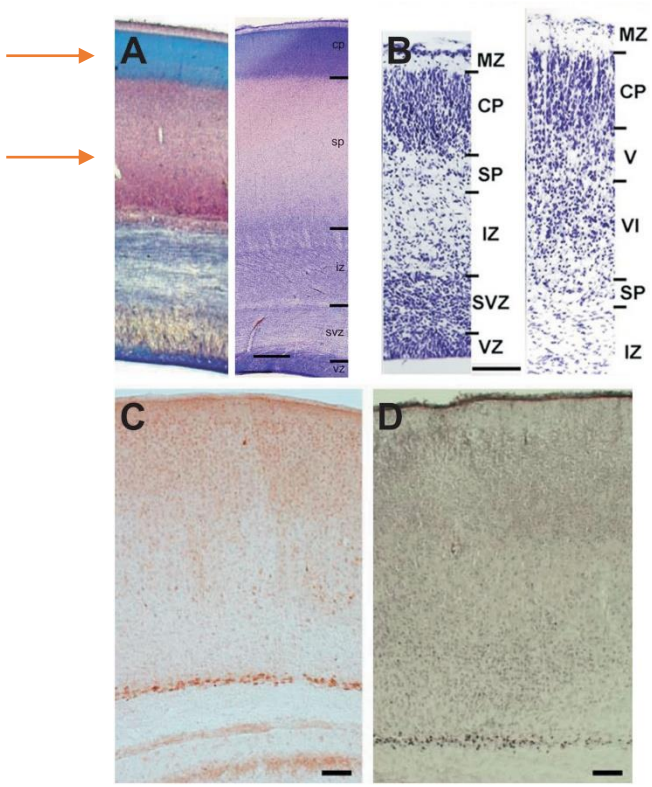
CORTEX CÉRÉBRAL

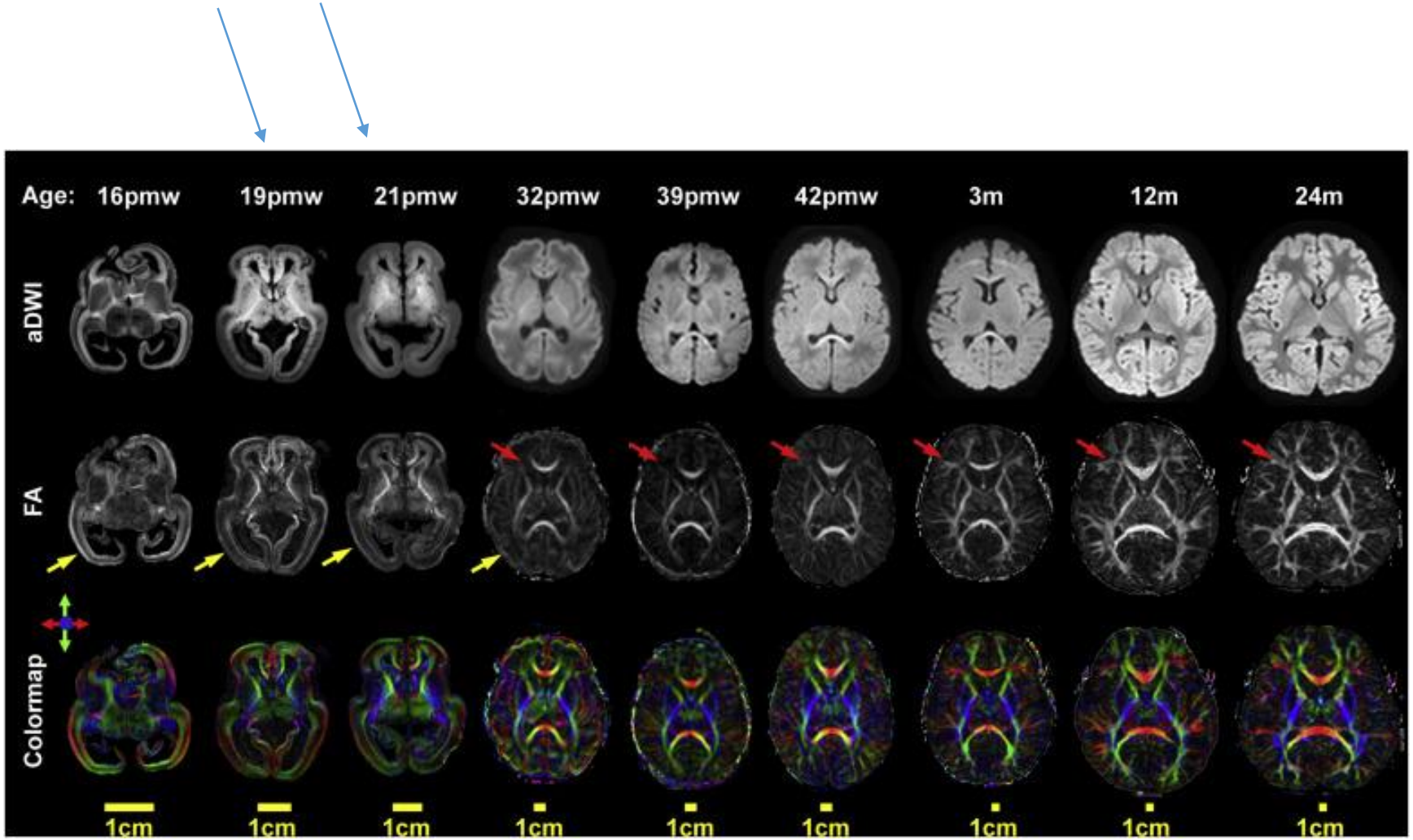
ISOCORTEX HOMOTYPIQUE

Cortex

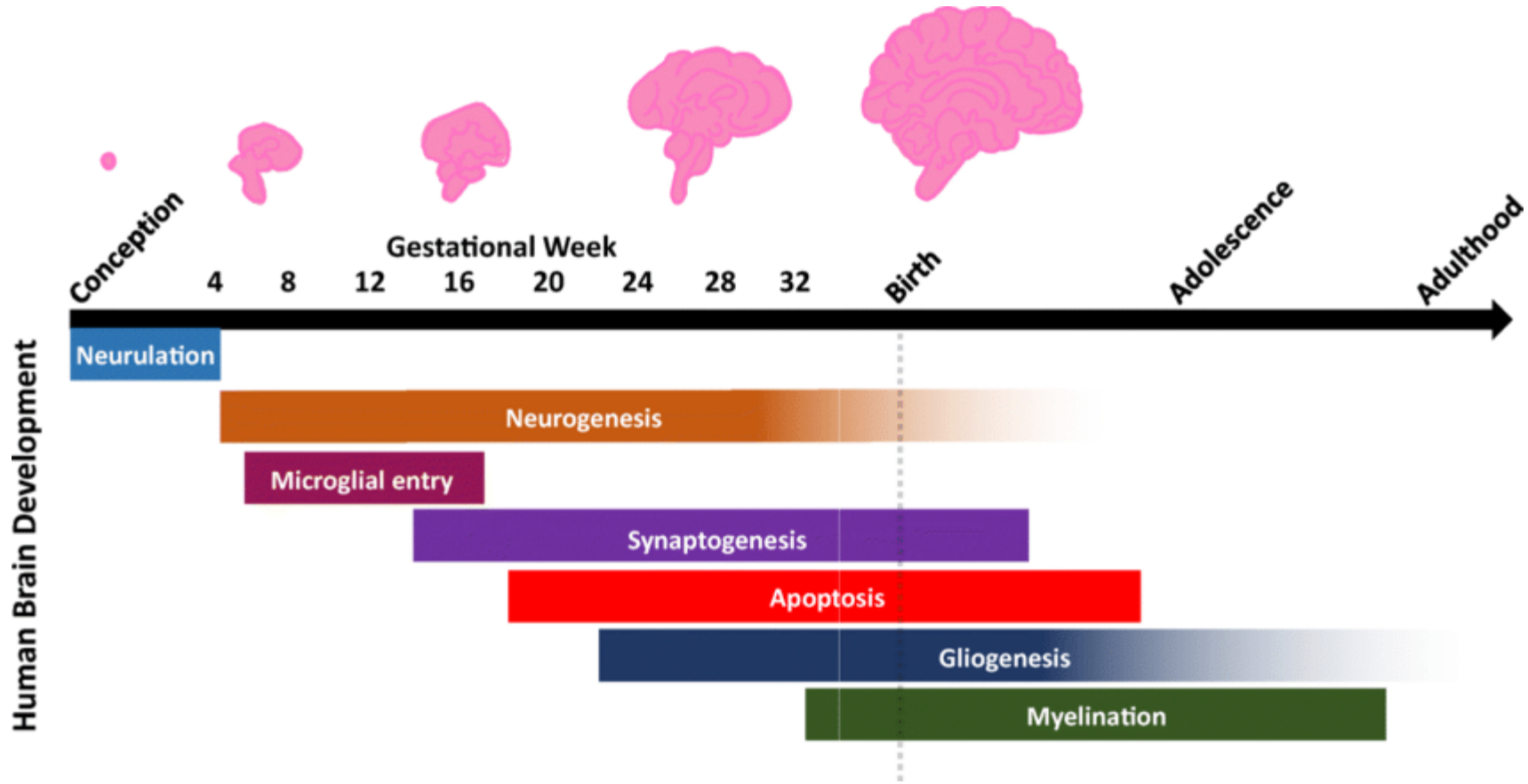
Subplate




A
cp
sp
iz
SVZ
VZ
B
MZ
CP
SP
IZ
SVZ
VZ
MZ
CP
V
VI
SP
IZ
C
D


Age: 16pmw 19pmw 21pmw 32pmw 39pmw 42pmw 3m 12m 24m
aDWI
FA
Colormap
1cm 1cm 1cm 1cm 1cm 1cm 1cm 1cm 1cm

Sequential and parralel development of key elements of the human brain: key for the development of « intelligence »



How is IQ and developing brain interconnected?

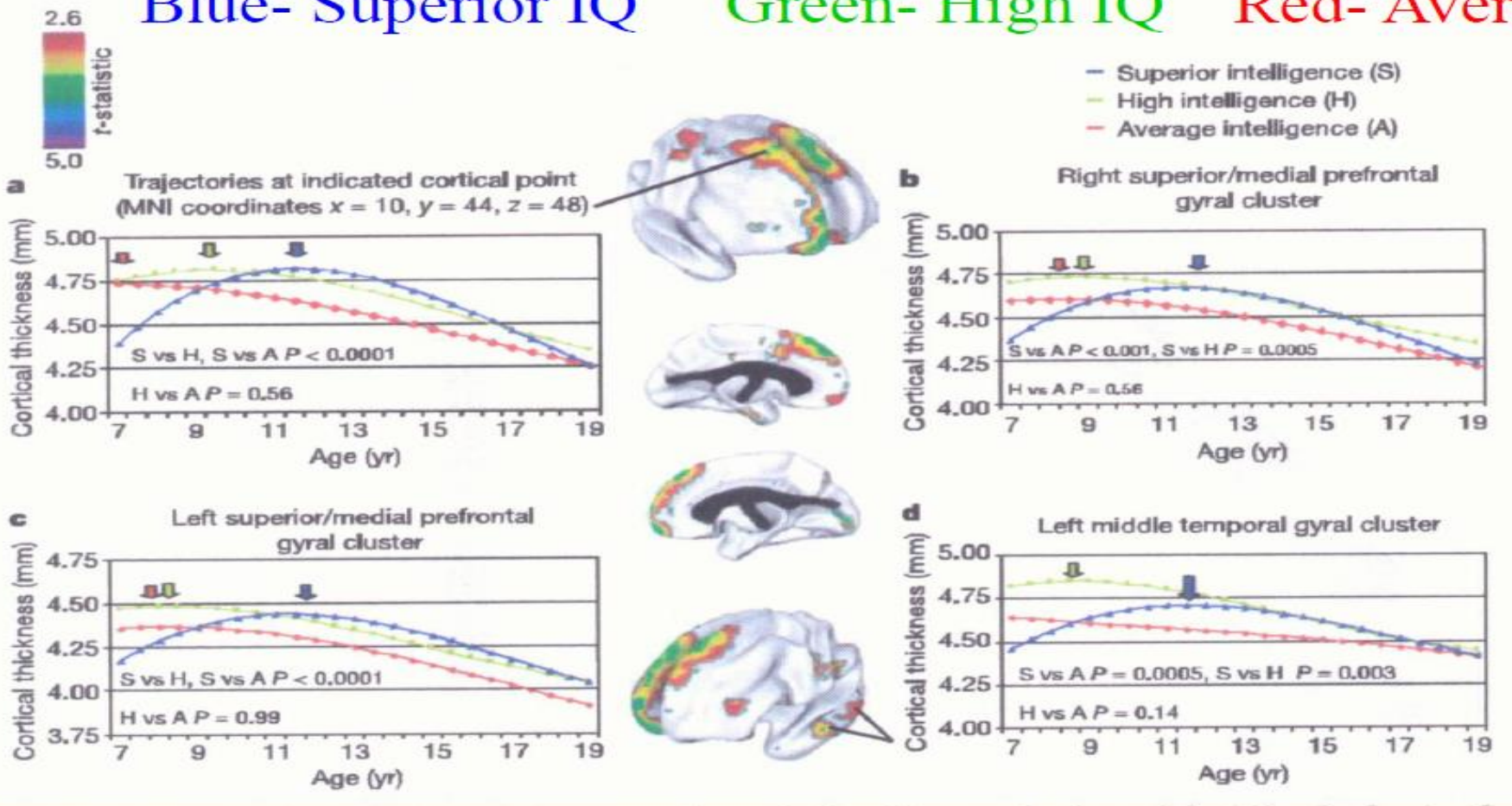
- Repetitive structural magnetic resonance imaging studies in hundreds of healthy subjects revealed that cortical volume and function of specific areas correlate with g (Karama et al., 2009; Choi et al., 2008)

- In particular, areas located in the frontal and temporal cortices with IQ scores: Brodmann areas 21 and 38 (Deary et al., 2010;)

- The key ? Slope and pace of gain of cortical thickness in particular brain areas

Trajectories of Change in Cortical Thickness: Peak Cortical Thickness Delayed in Higher IQ Groups

Blue- Superior IQ Green- High IQ Red- Average IQ

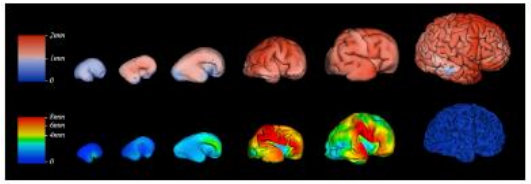


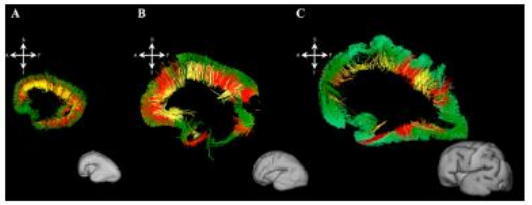
(Superior IQ– 121-149 High IQ – 109-120 Average IQ – 83-108)

Shaw et al, Nature 440:676-679, 2006

What factors might influence this shape of growth ?

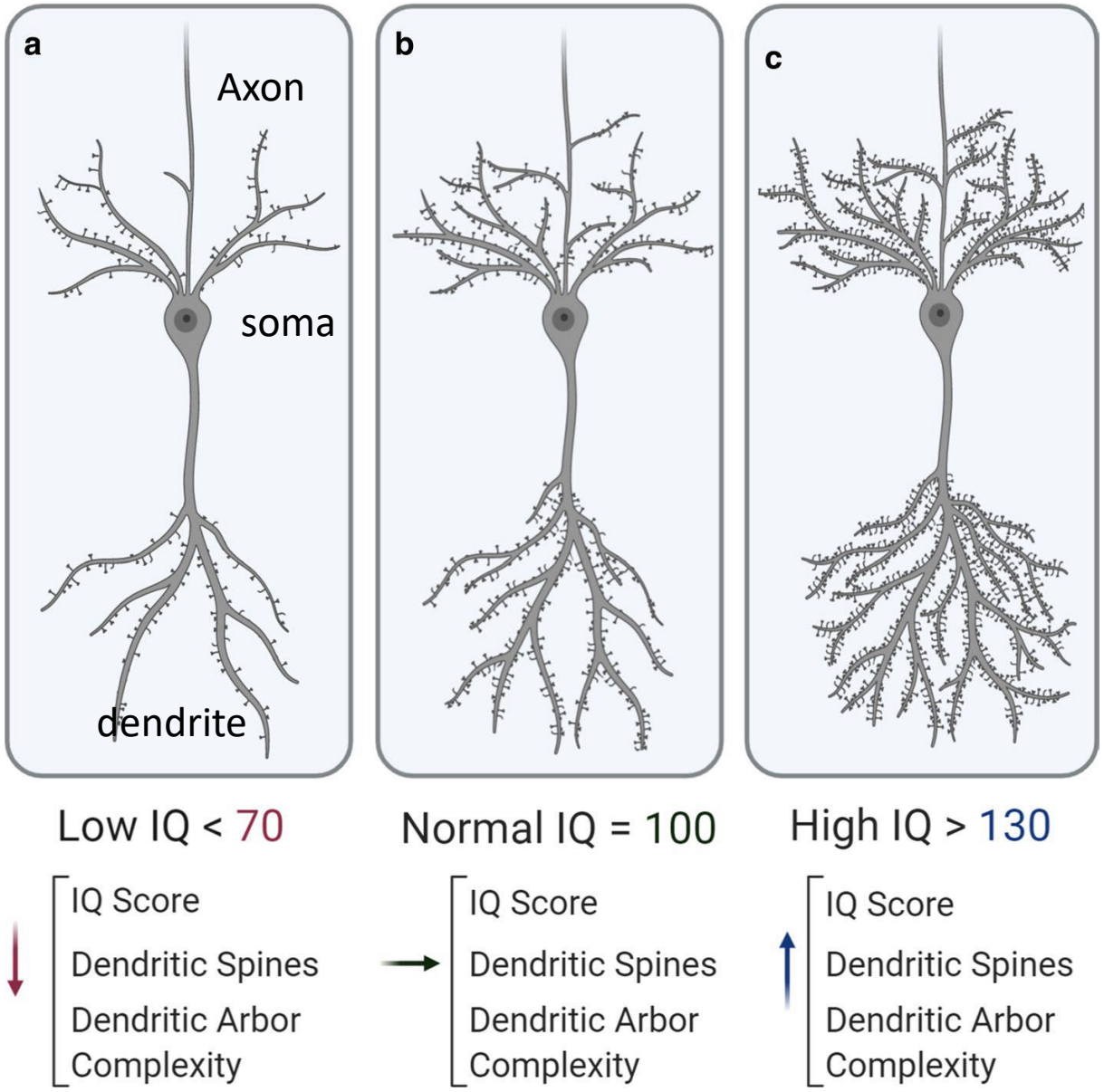
- Number of neurons that collect in the subplate under the cortex during late fetal development ?
- Development of the myelin sheath that insulates the fibres of the neurons?
- Selective elimination at puberty of neuronal connections that are not useful ?
- Length and complexity of dentrites trees?





Cortical thickness associates with larger, more complex dendrites of human pyramidal neurons.

Larger dendritic trees enable pyramidal neurons to track activity of synaptic inputs with higher temporal precision



Goriounova NA, et al (2018) Large and fast human pyramidal neurons associate with intelligence. Elife 7:e41714
Acta Neuropathologica (2021) 141:139–158

What about the relationship between brain neurobiology / development and ID/ MR ?

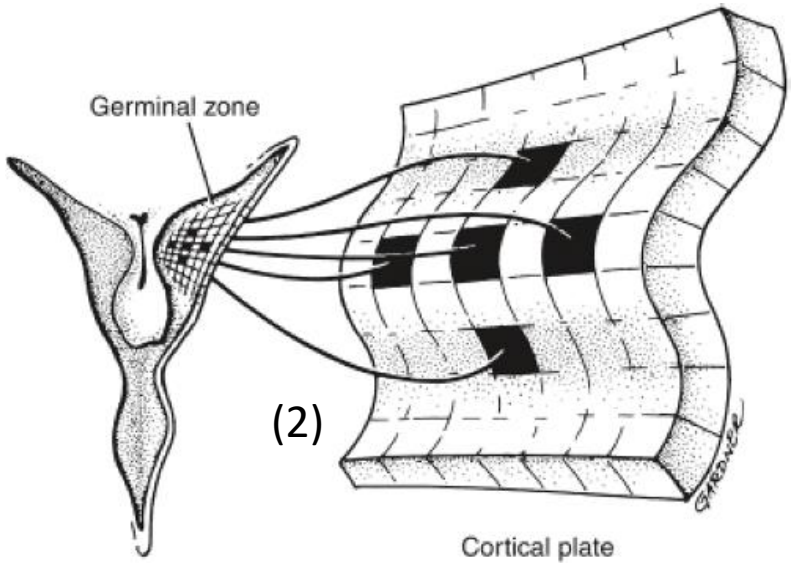
Mary Blue, Ph.D., neurobiologist at the Kennedy Krieger Institute of Johns Hopkins University who studies Rett syndrome, autism, Down syndrome, and other genetic causes of mental retardation.

"The idea that ultimately mental retardation is a problem with synaptic connections in the brain is a fair statement to make—albeit admittedly vague. The synapse is where neurons talk to one another, so whenever that process is disrupted, there are going to be consequences. Ultimately, it is going to be an effect that happens at the synapse"

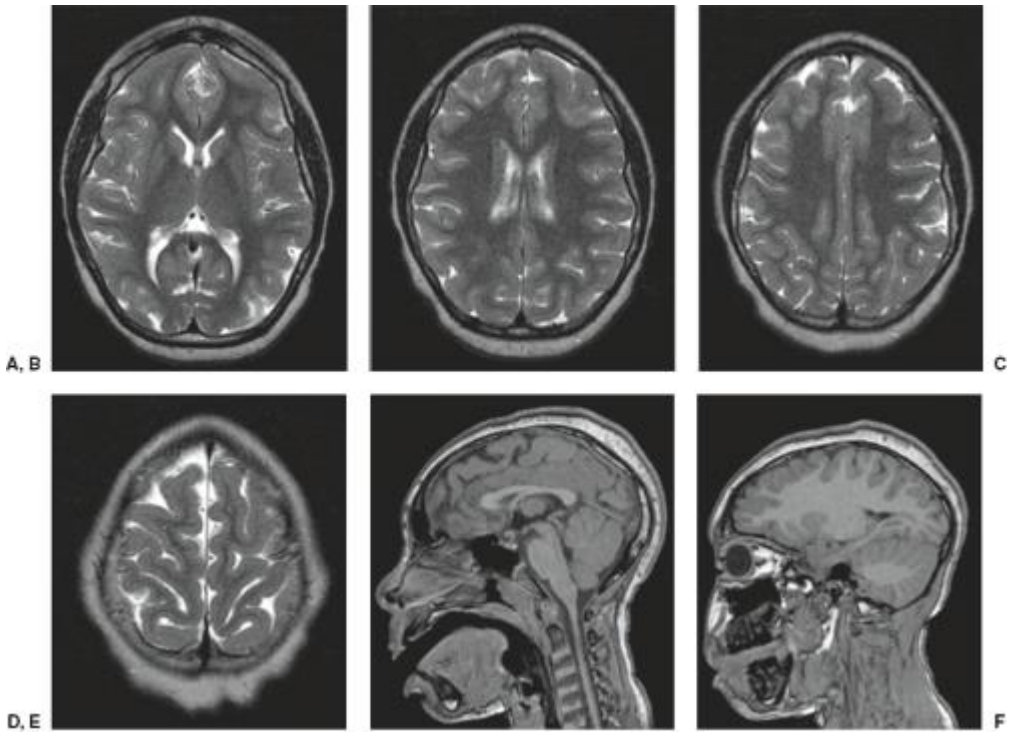
Malformation of Cerebral Cortical Development

3 broad and overlapping steps:

- (1) neural stem cell proliferation and cell-type differentiation,
- (2) neuronal migration,
- (3) **cortical organization and connectivity** (4).
- Any abnormality that interferes with one or more of these processes may result in a malformation of the cortical development:
- (a) gene mutations causing a primary malformation,
- (b) destructive events (e.g., infection or hemorrhage) causing a disruption
- (c) exogenous toxins (e.g., drugs or alcohol from maternal ingestion, or endogenous toxins from metabolic disorders such as Zellweger syndrome).



Neural stem cell proliferation and cell-type differentiation



Microcephaly is defined by a head circumference **< two standard deviations** under the norm for age, gender, and ethnicity (10,11).
May be associated with normal or short stature, normal cortex or malformations of cortical development, and high or severely impaired neurologic and **cognitive function**

Multifactorial but mutated genes cause abnormal:

- mitotic microtubule spindle structure, n
- umerical and structural abnormalities of the centrosome,
- altered cilia function,
- impaired DNA repair,
- DNA damage response signaling and DNA replication,

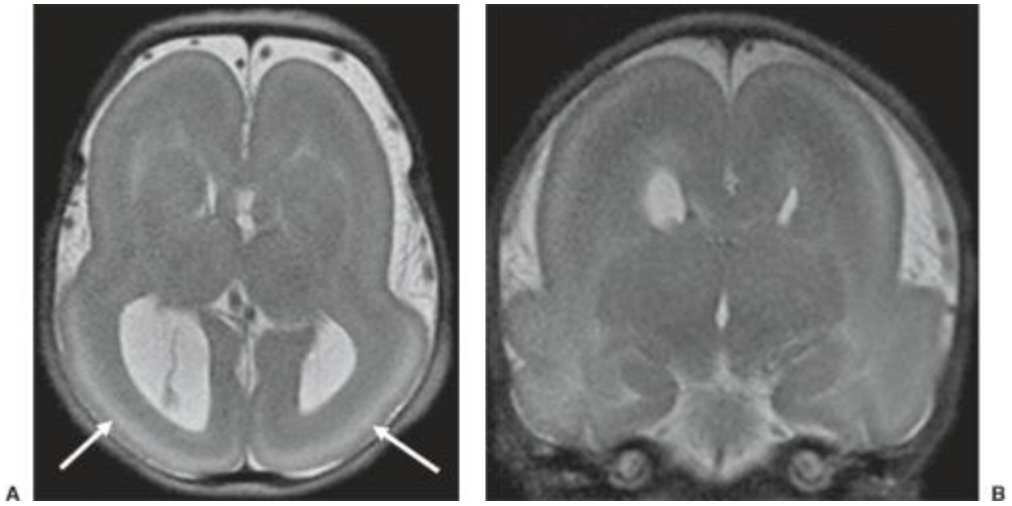
small head and reduced craniofacial ratio
Simplified gyri

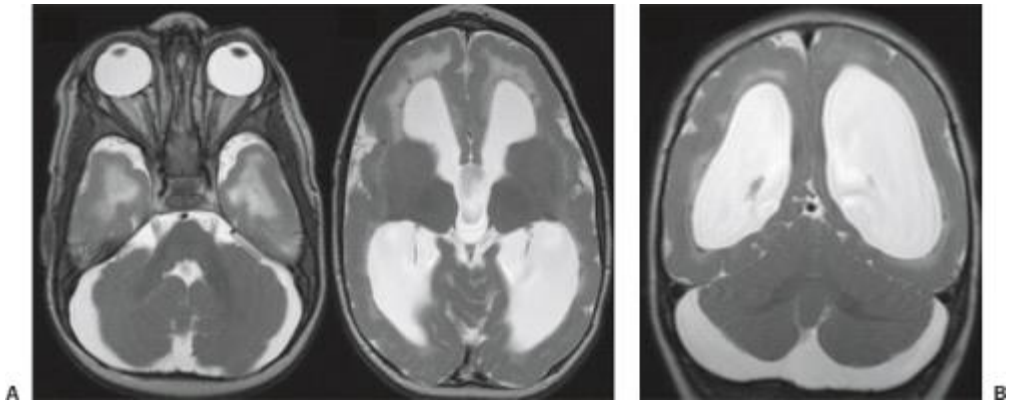
Barkovich et al 2012

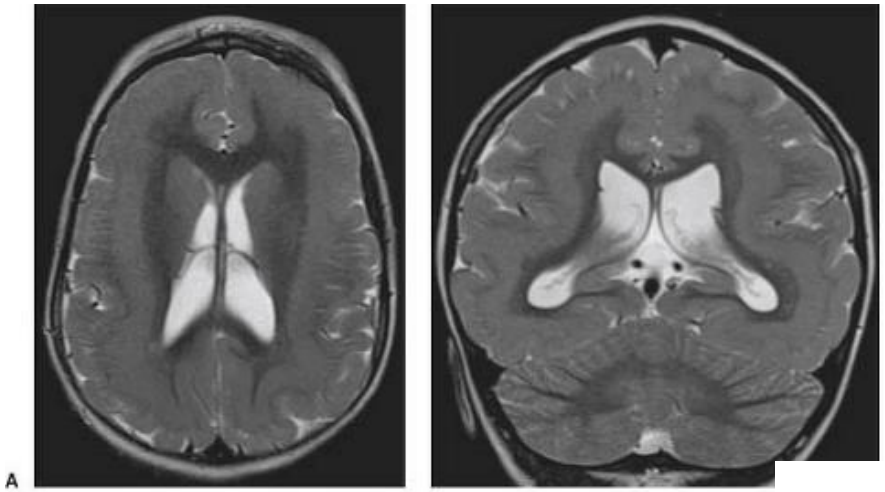
Neuronal migration defect

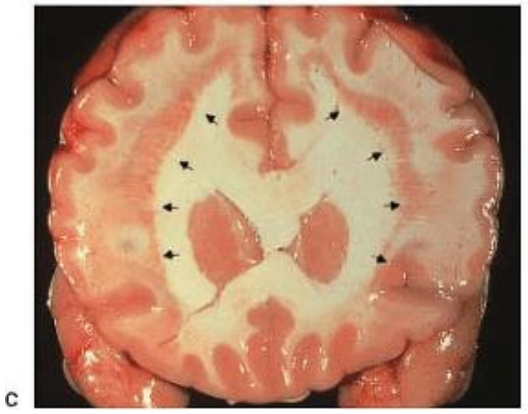
Lissencephaly
Pachygyria
Hemimegalencephaly
Polymicrogyria

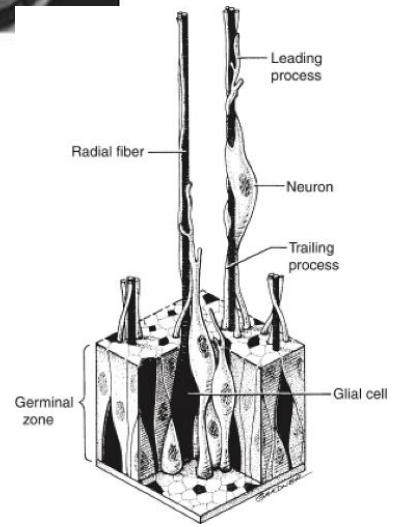
Very low IQ
And often cerebral pasly



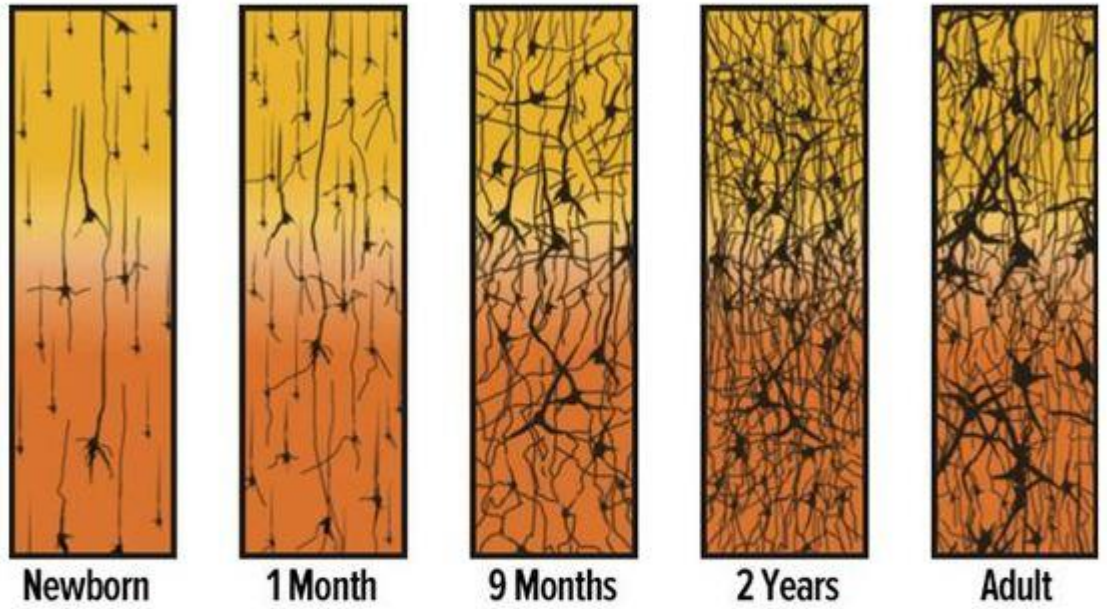








3) Disorders of cortical organization and connectivity

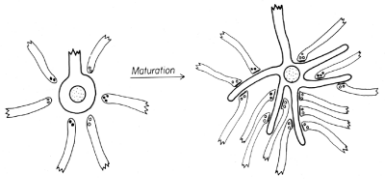


Synapse Density Over Time FIGURE 3

Source: Adapted from Corel, JL. The postnatal development of the human cerebral cortex. Cambridge, MA: Harvard University Press; 1975.

Postnatal synaptic development / maturation in mammalian cerebral cortex

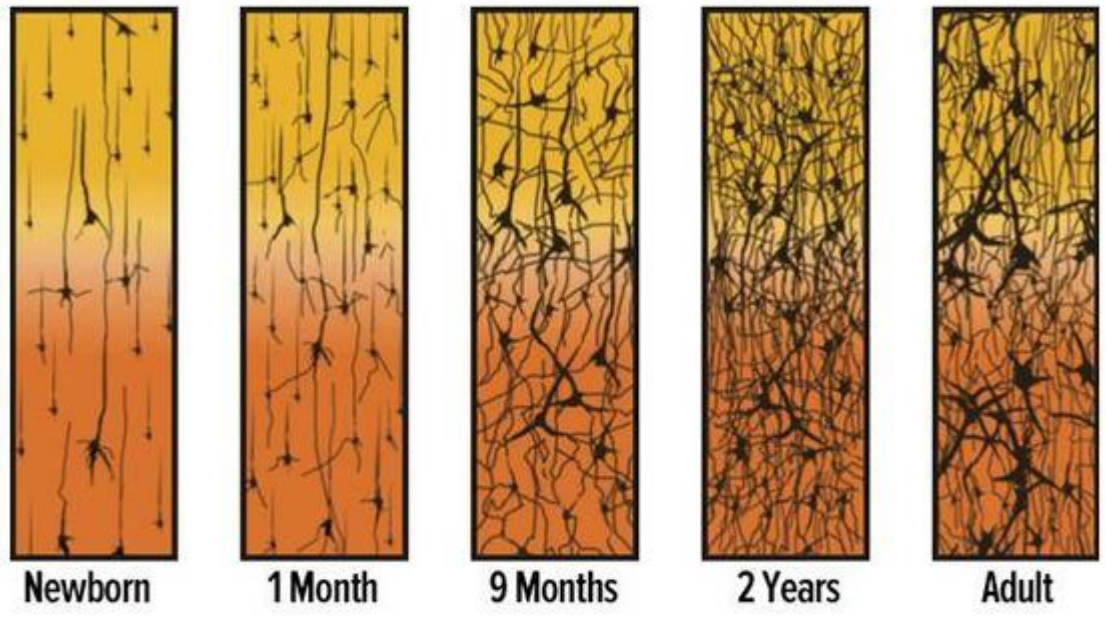
Postnatal synaptic development in mammalian cerebral cortex is a **dynamic process involving concurrent formation and elimination/pruning** (Purves and Lichtman, 1980; Rakic
et al., 1986).



Synapse formation **exceeds pruning at early ages**, yielding excessive excitatory synapses essential for the assembly of neural circuits.
Synaptic elimination subsequently outpaces formation, resulting in net spine pruning from childhood through adolescence.

The density of **dendritic spines peaks in early childhood** and is followed by a steep decline during late childhood and adolescence to adult levels (Penzes et al., 2011)

This process provides **selection and maturation of synapses** and neural circuits.



Synapse Density Over Time FIGURE 3

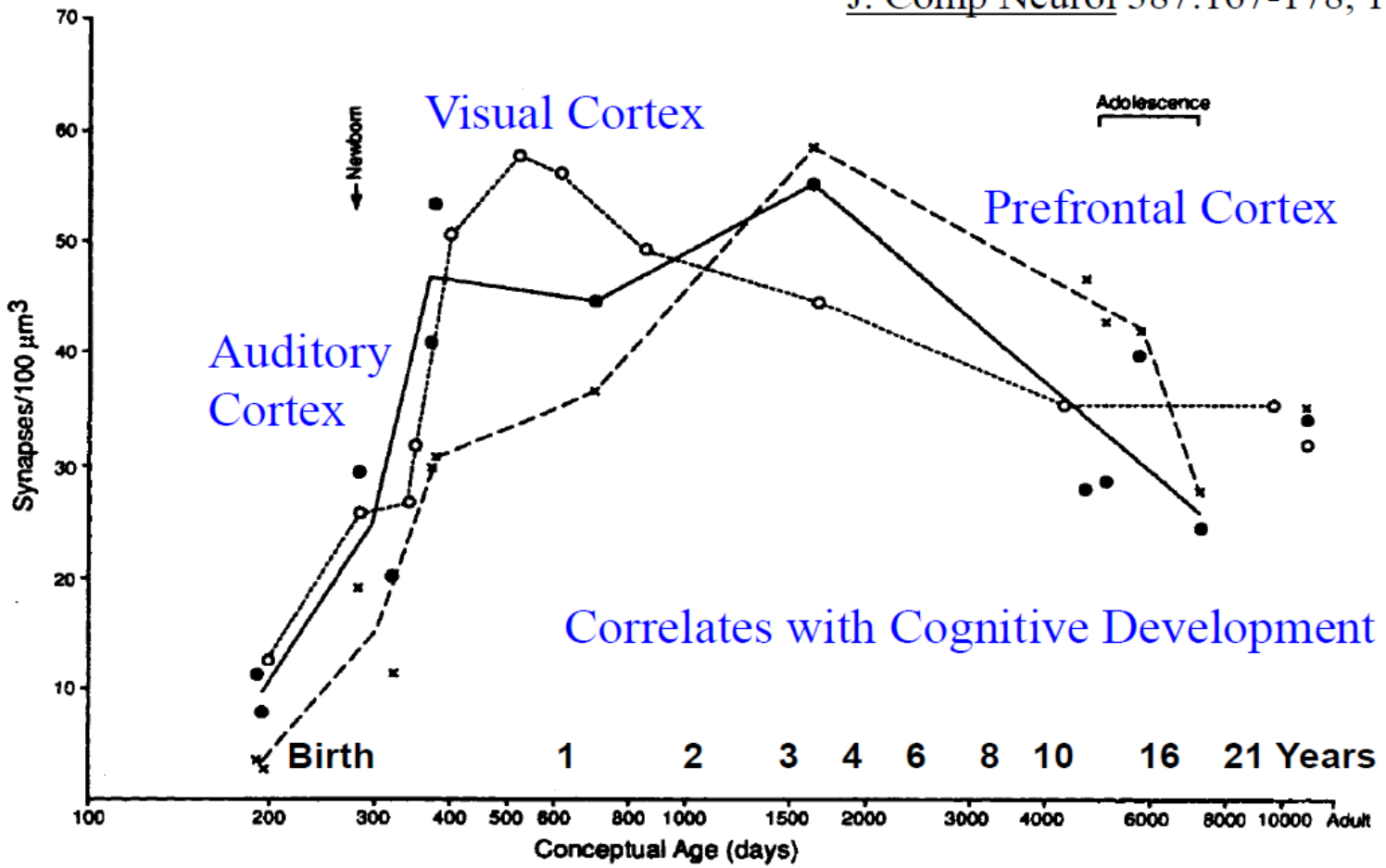
Source: Adapted from Corel, JL. The postnatal development of the human cerebral cortex. Cambridge, MA: Harvard University Press; 1975.

The Developing Brain is Under Construction

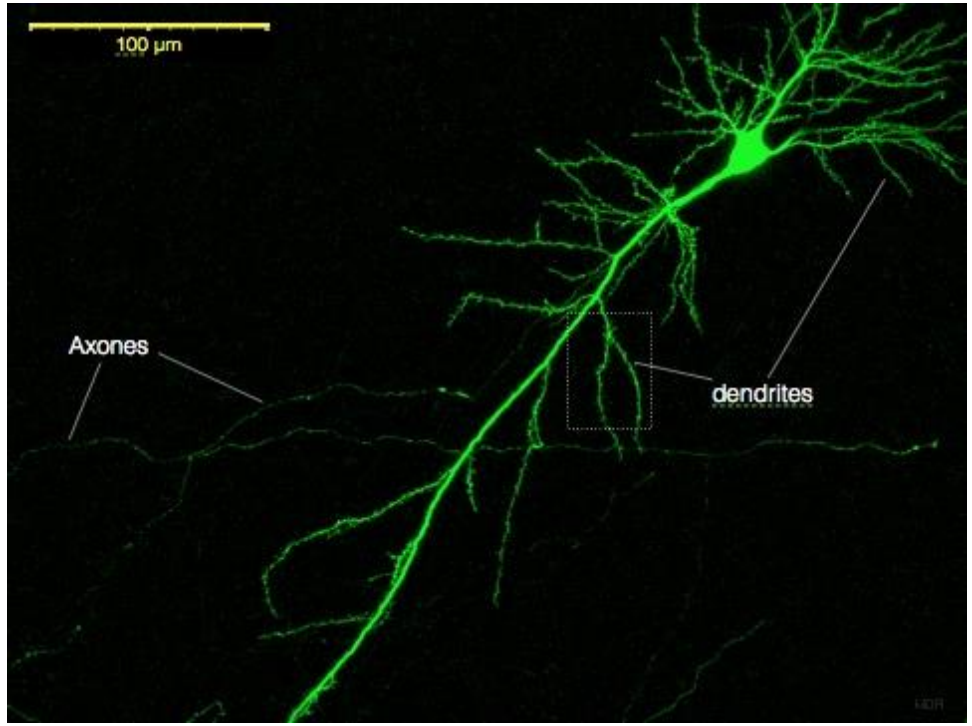
Like this building under construction, the immature brain has connections and structures that will be removed when it is finished.

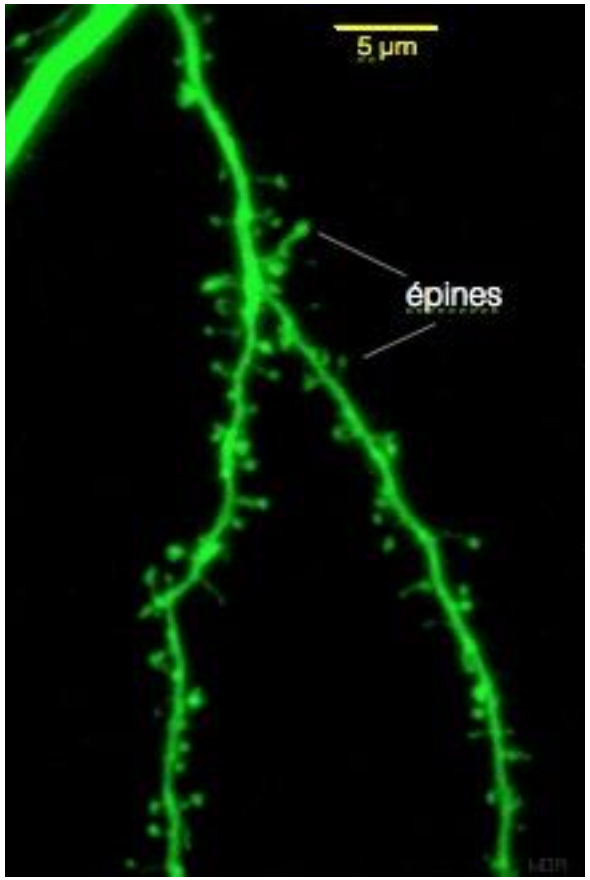
Synaptogenesis in Human Cerebral Cortex

P.R. HUTTENLOCHER AND A.S. DABHOLKAR
J. Comp Neurol 387:167-178, 1997



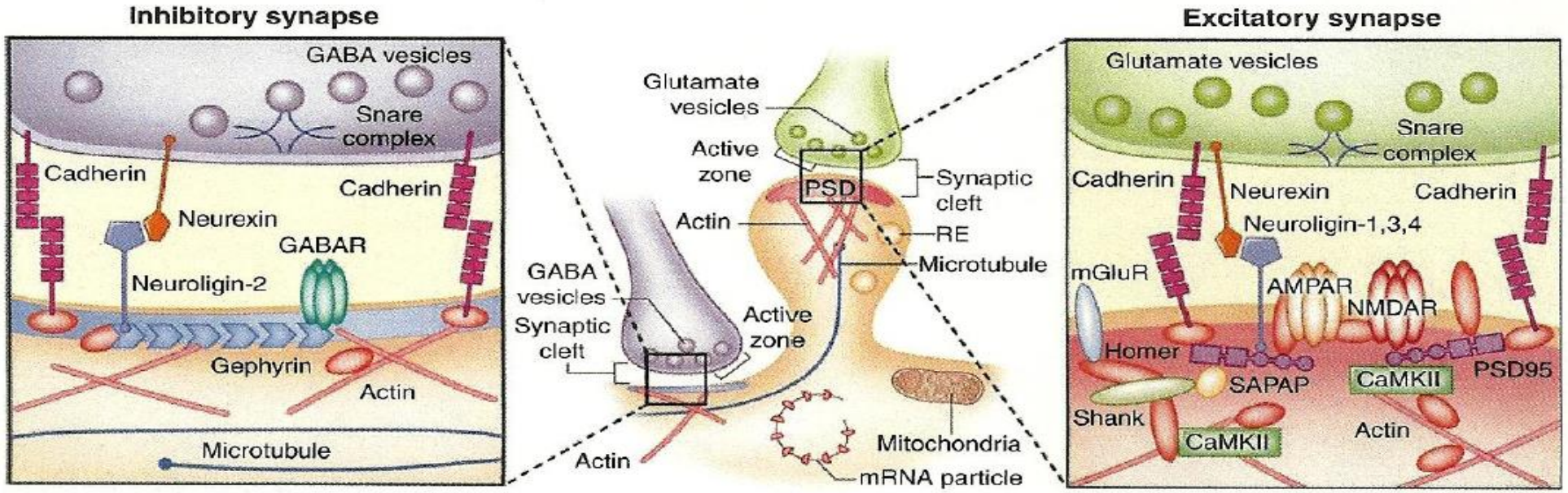
Architecture of neurons connections in development

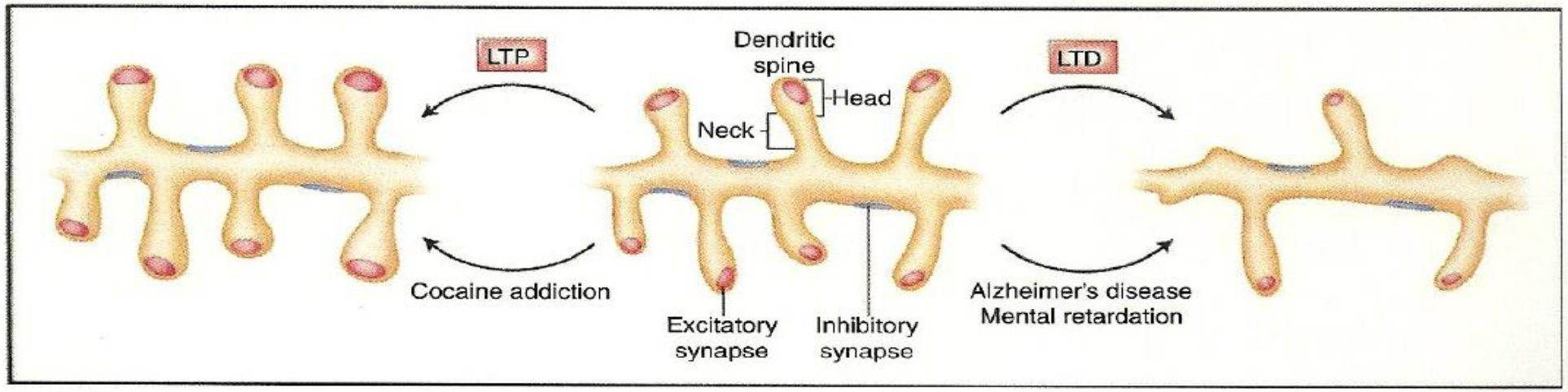




Dentritic spines

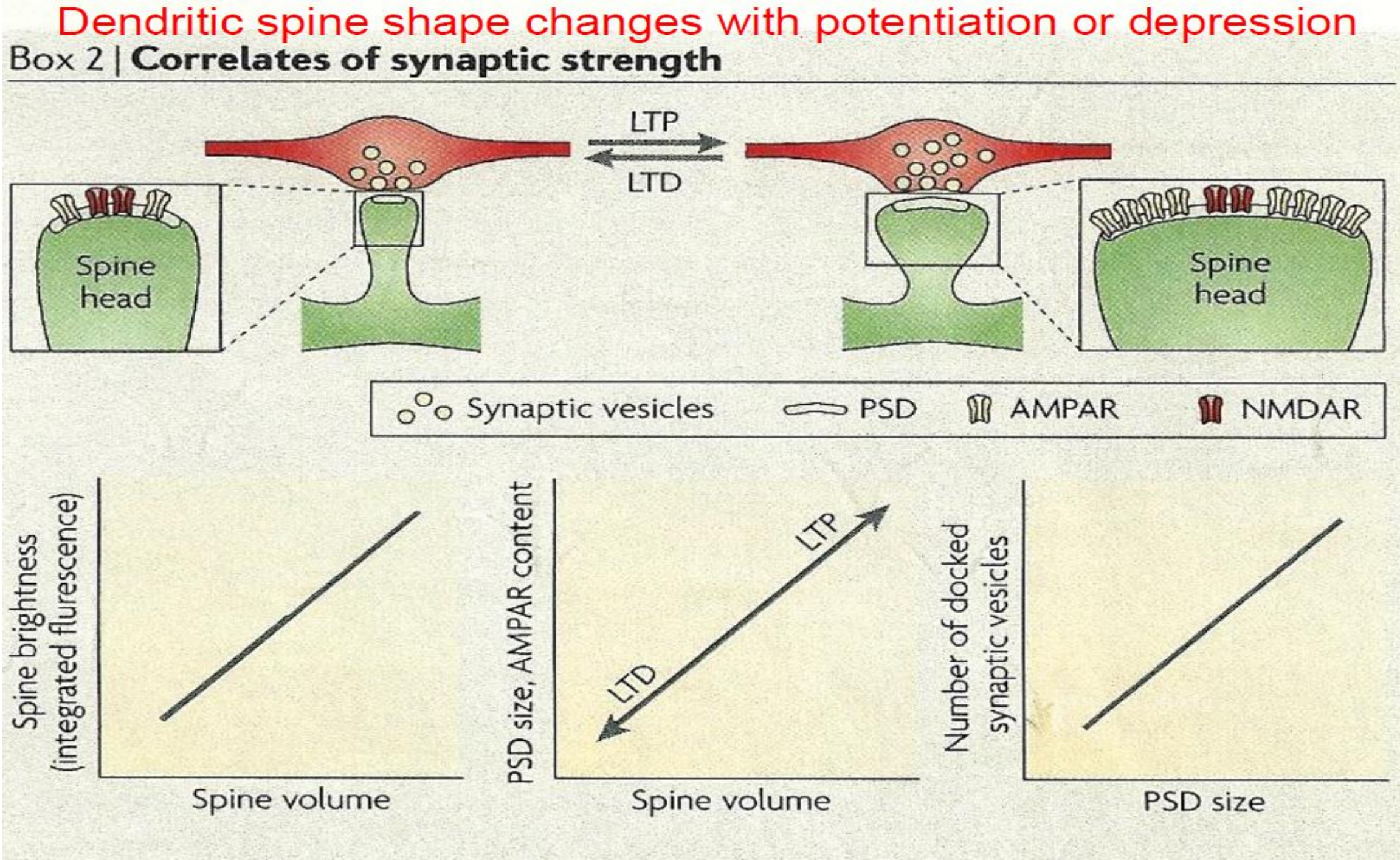
Dendritic spine involved in shaping and refining neuronal connectivity : Long term potentiation and depression





Myrrhe van Spronsen, Hoogenraad, 2010

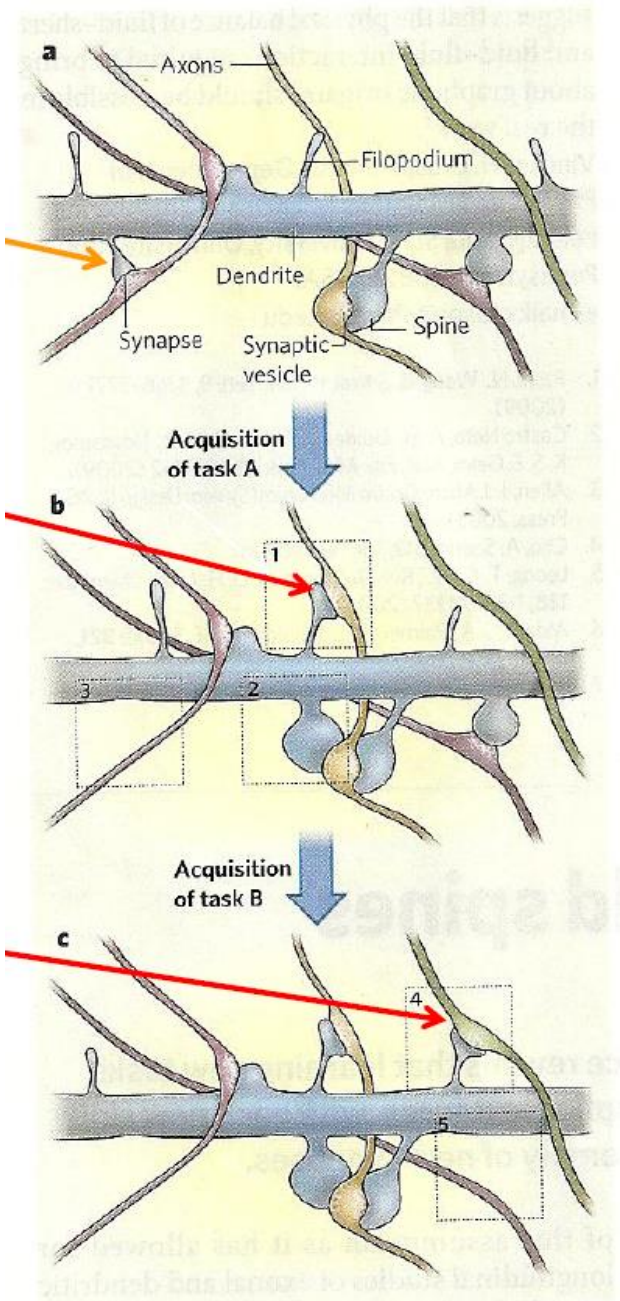
Dendritic spine shape changes with potentiation or depression



Old Synapse

New Synapse

New Synapse



Sequential performance of two new motor learning tasks can lead to formation of new synapses and deletion of others

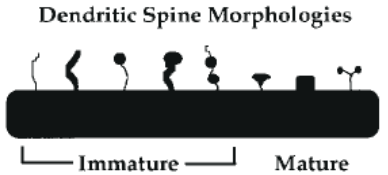
Ziv and Ahissar, Nature 462: 859-862, 2009.

Activity Leads to Plasticity in Dendrites

Learning new motor skills and acquiring new sensory experiences is associated with formation of new synaptic connections in motor and sensory regions of the mouse brain

Abnormal spine densities in ID: first evidence

- **Golgi staining** of post-mortem brain tissue from ID patients:
- Two types of dendritic spine abnormalities in cortical pyramidal neurons of ID patients,
  - dendritic spine loss (paucity of spins)
  - overabundance of long thin ‘immature’ spines.



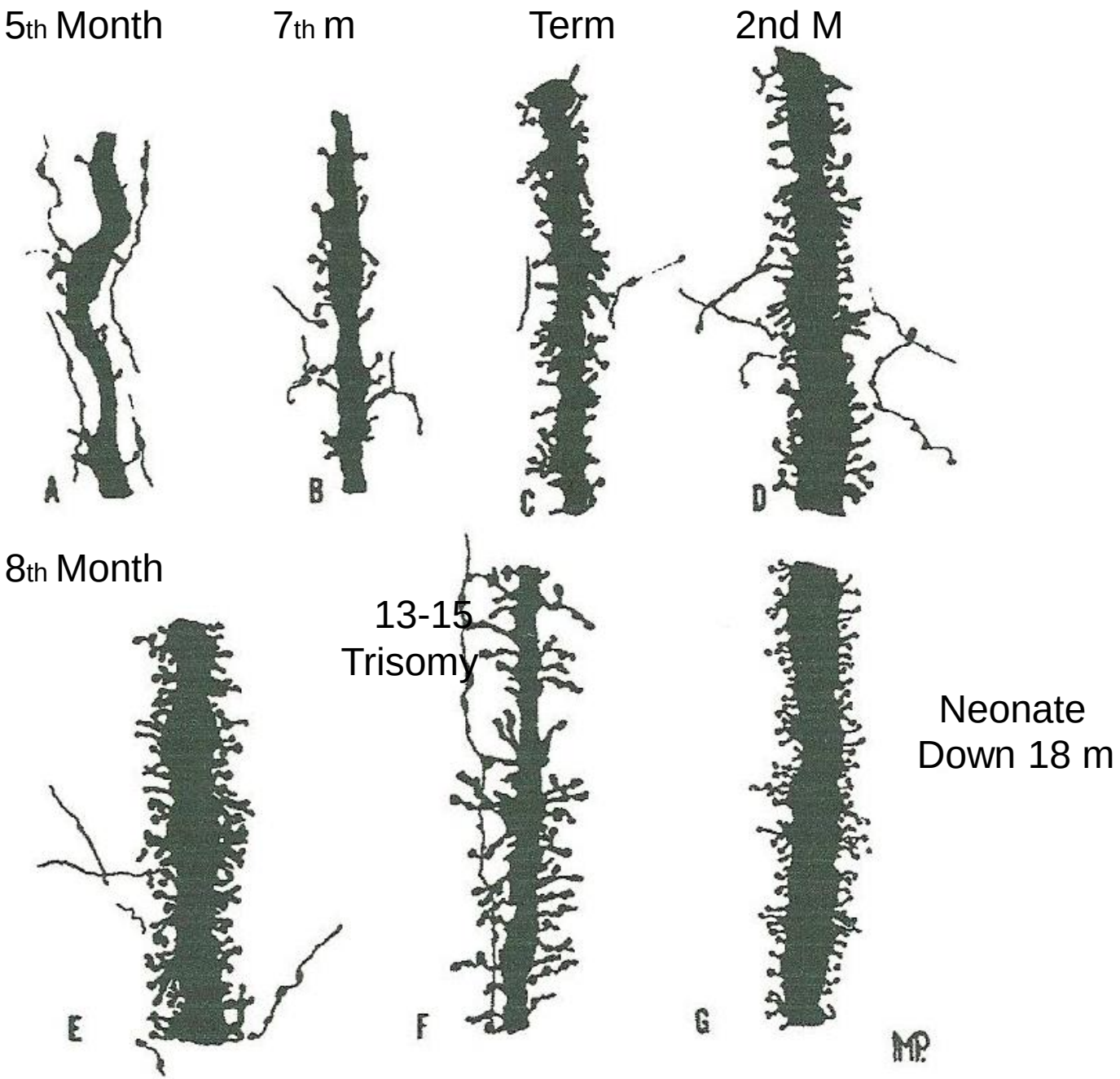
- Golgi staining suffers from limited resolution for imaging dendritic spines, but the first evidence of the association between dendritic spine dysgenesis and ID

Dentritic spines in several known conditions with ID

- Alteration of the dendritic arbor is a consistent feature exhibited by patients with ID across multiple clinical presentations

- Assessed initially on post-mortem neural tissues, with significant alterations of several important CNS areas, …the hippocampus, dentate gyrus, and cerebral cortex
- Reduction in dendritic branching, arborization, and abnormalities in the morphology and density of dendritic spines compared to normal controls
- Highly suggestive of altered neuronal connectivity in ID syndromes

Down syndrome



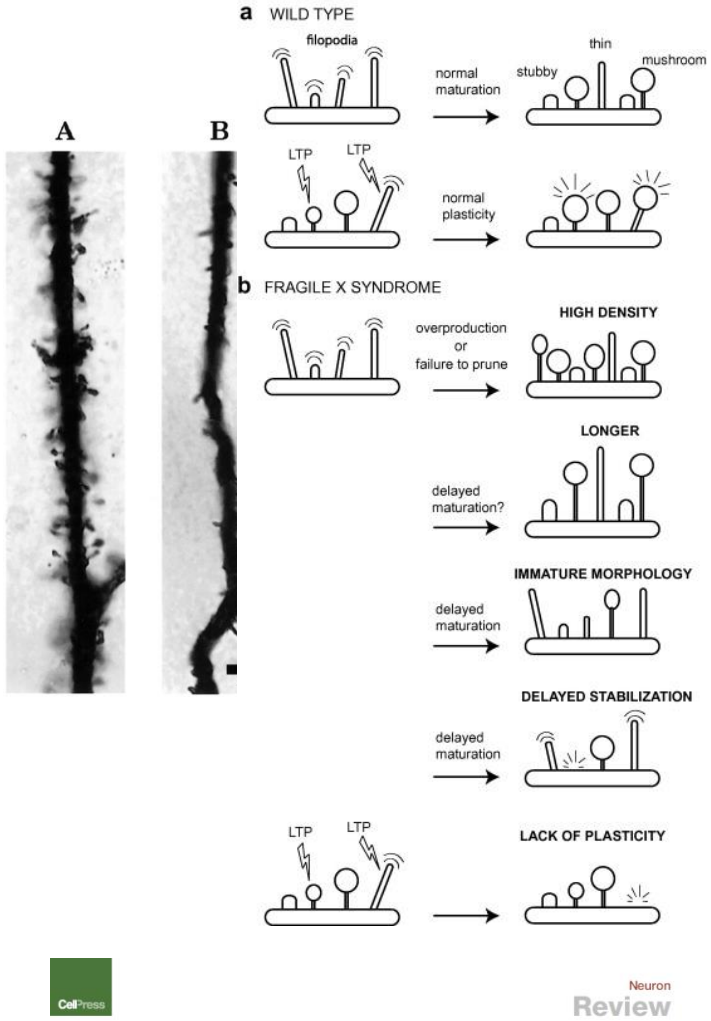
Increased number of shorter spines during normal development Shorter, thinner spines in Down Syndrome

Roberto Keller, J Neurosci 2017

Fragile X syndrome and Fmr1 knock out mice

- No migration defect, number of neurons grossly unaffected
- Increased spine density and increased numbers of long and immature spines:
  - most salient in association with fragile-X syndrome thus far likely to play a role in the cognitive deficits.

- Suggests
  - pruning and maturation may be grossly impaired in fragile-X
  - a role in these processes for FMRP (RNA binding protein)
  - *Fmr1* regulates spine dynamics and experience-dependent plasticity during development



CellPress
Neuron
Review

A Synaptic Perspective of Fragile X Syndrome and Autism Spectrum Disorders

Claudia Bagni[1,2,*] and R. Suzanne Zukin[3,*]
[1]Department of Fundamental Neurosciences, University of Lausanne, Lausanne, Switzerland
[2]Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy
[3]Dominick P. Purpura Department of Neuroscience, Albert Einstein College of Medicine, New York City, NY, USA
*Correspondence: claudia.bagni@unil.ch (C.B.), suzanne.zukin@einstein.yu.edu (R.S.Z.)
https://doi.org/10.1016/j.neuron.2019.02.041

Cerebral Cortex Oct 2000;10:1038–1044; 1047

Rett Syndrome

- Females, signs of neuronal dysfunction: acquired microcephaly, stereotypic movements, seizures, intellectual disability, abnormal breathing, autonomic dysfunction, dystonia, and ataxia
- Loss of function of MECP2
- Neuropathology: Reduced gray matter, neurons packed too close together (Armstrong et al 1992)

Brain Growth Decelerates In Rett Syndrome During The Period of Maximal Synapse Proliferation

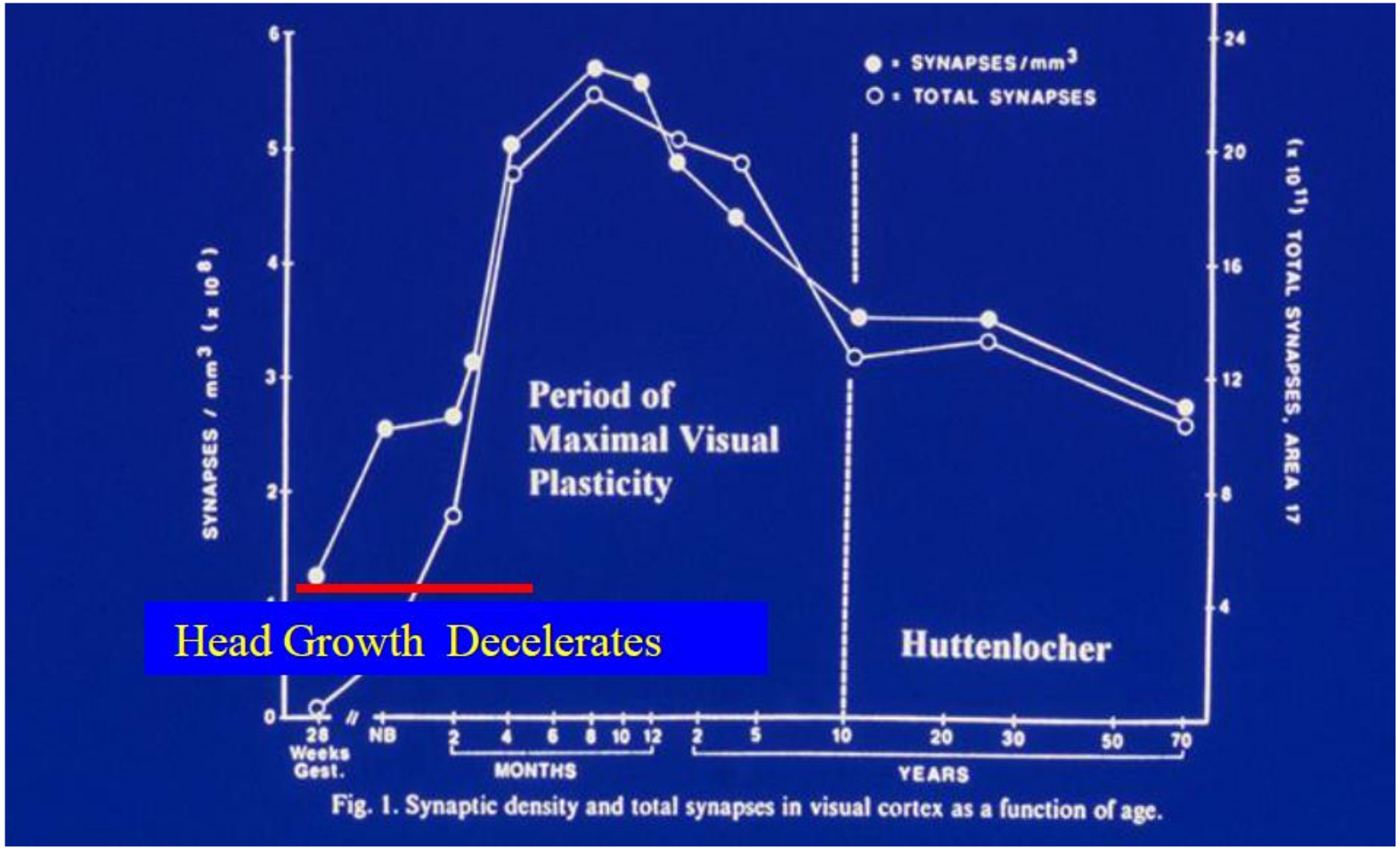
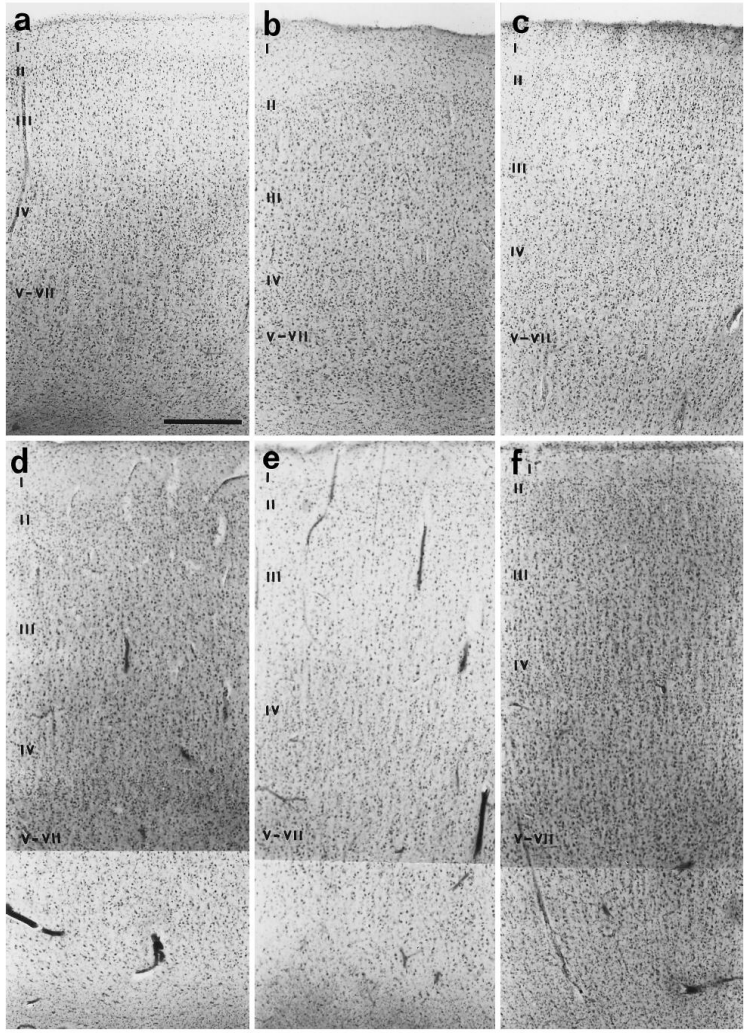
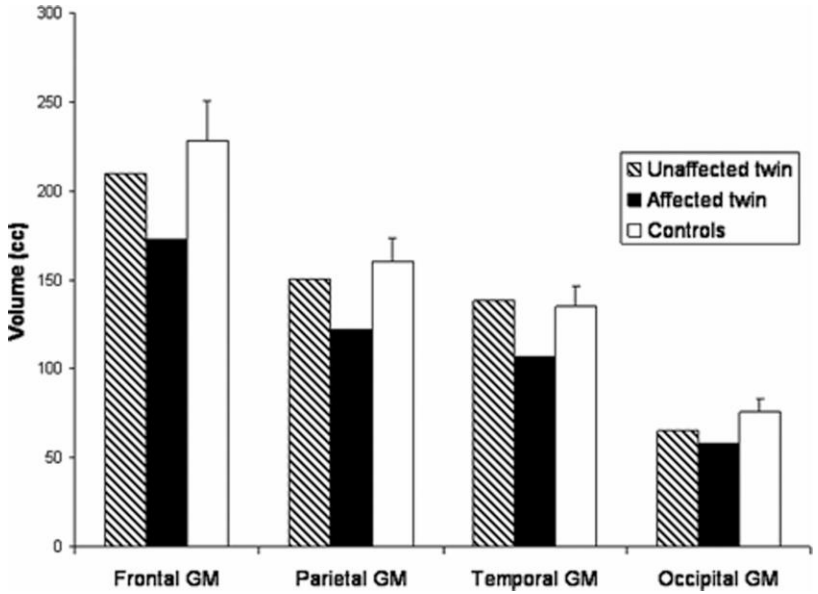


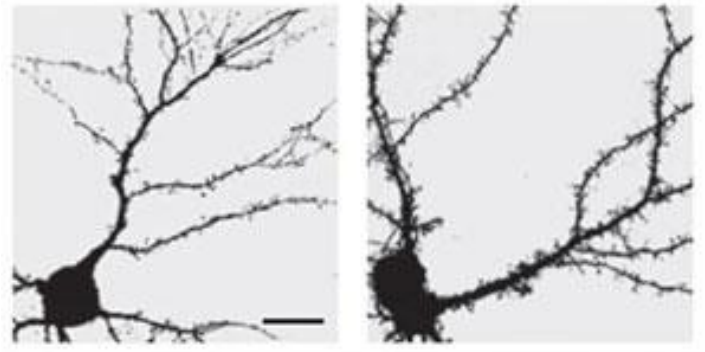
Fig. 1. Synaptic density and total synapses in visual cortex as a function of age.

First brain anatomic studies in Rett syndrome



- Not a migration defect !
- Reduced number of pyramidals cells layer 3 and 5
- Reduced brain volume

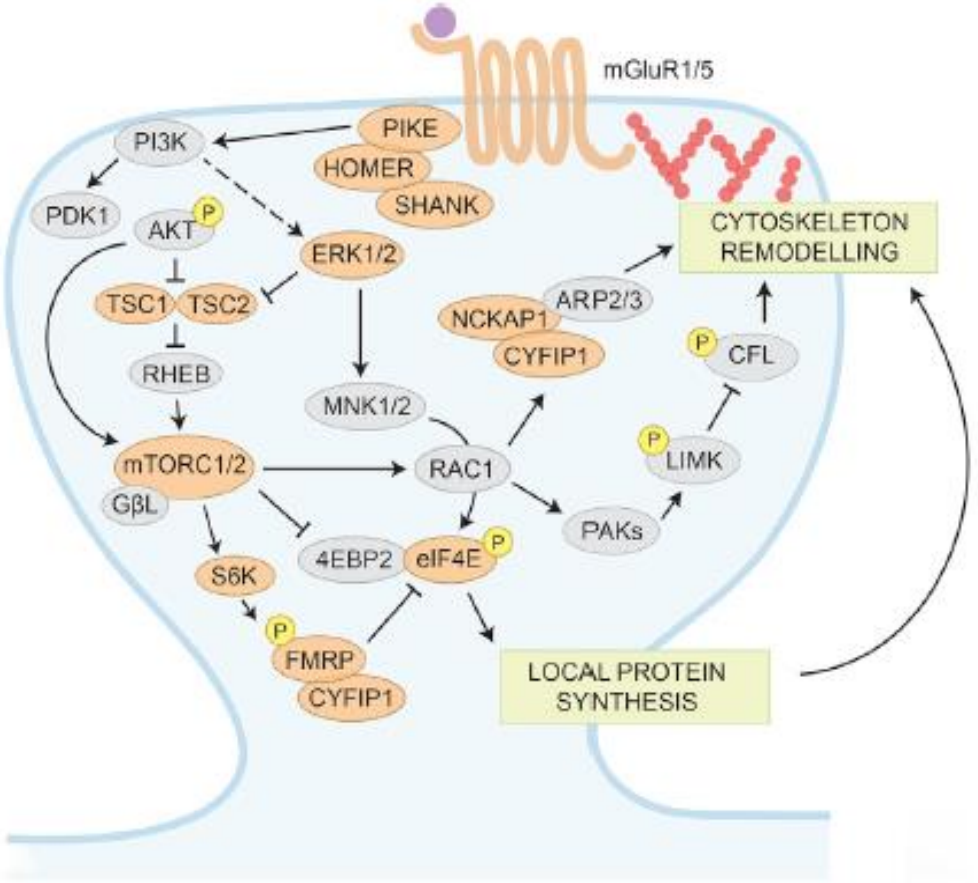




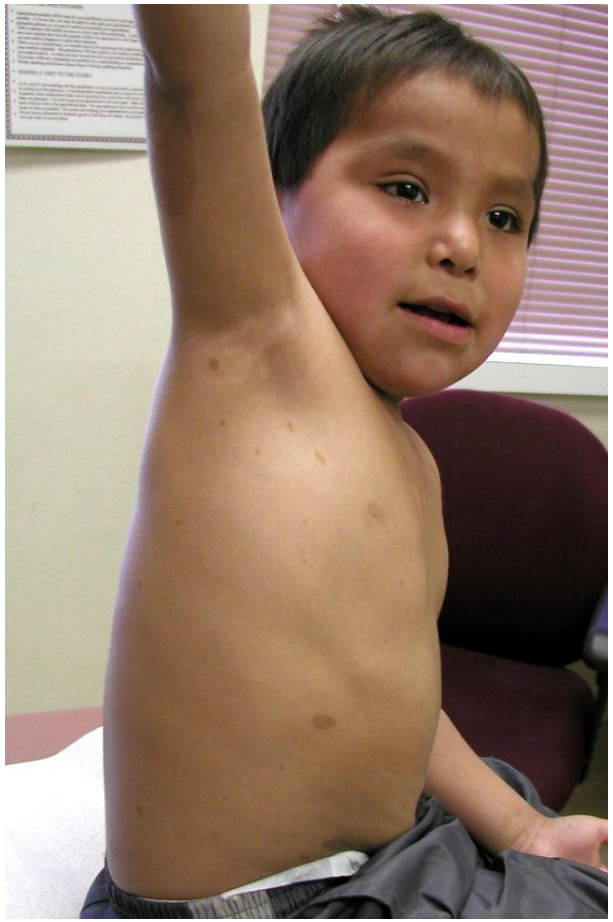
Paucity of spines and the presence of dendrite lengths without spines ("naked dendrites") observed in pyramidal neurons. That may indicate a reduction in synaptic contacts from afferent axons to the pyramidal cells

Carter et al. 2008

Molecular signalling pathways at play in spines involve proteins of which mutations were involved in several genetic forms of ID and or ASD

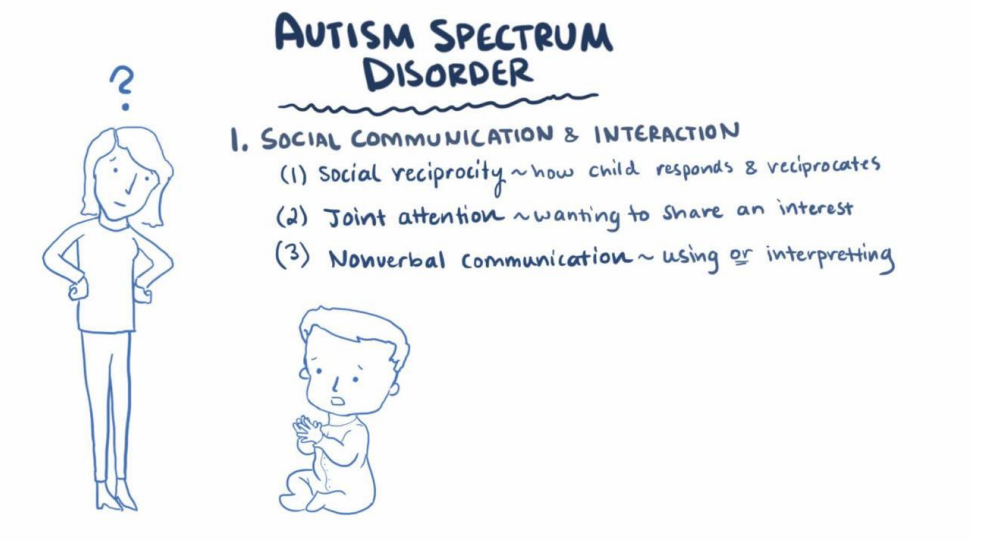


NF1
TSC1-2
PTEN



Claudia Bagni[1,2,*] and R. Suzanne Zukin[3,*]
[1]Department of Fundamental Neurosciences, University of Lausanne, Lausanne, Switzerland
[2]Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy
[3]Dominick P. Purpura Department of Neuroscience, Albert Einstein College of Medicine, New York City, NY, USA
*Correspondence: claudia.bagni@unil.ch (C.B.), suzanne.zukin@einstein.yu.edu (R.S.Z.)
https://doi.org/10.1016/j.neuron.2019.02.041

What about ASD?



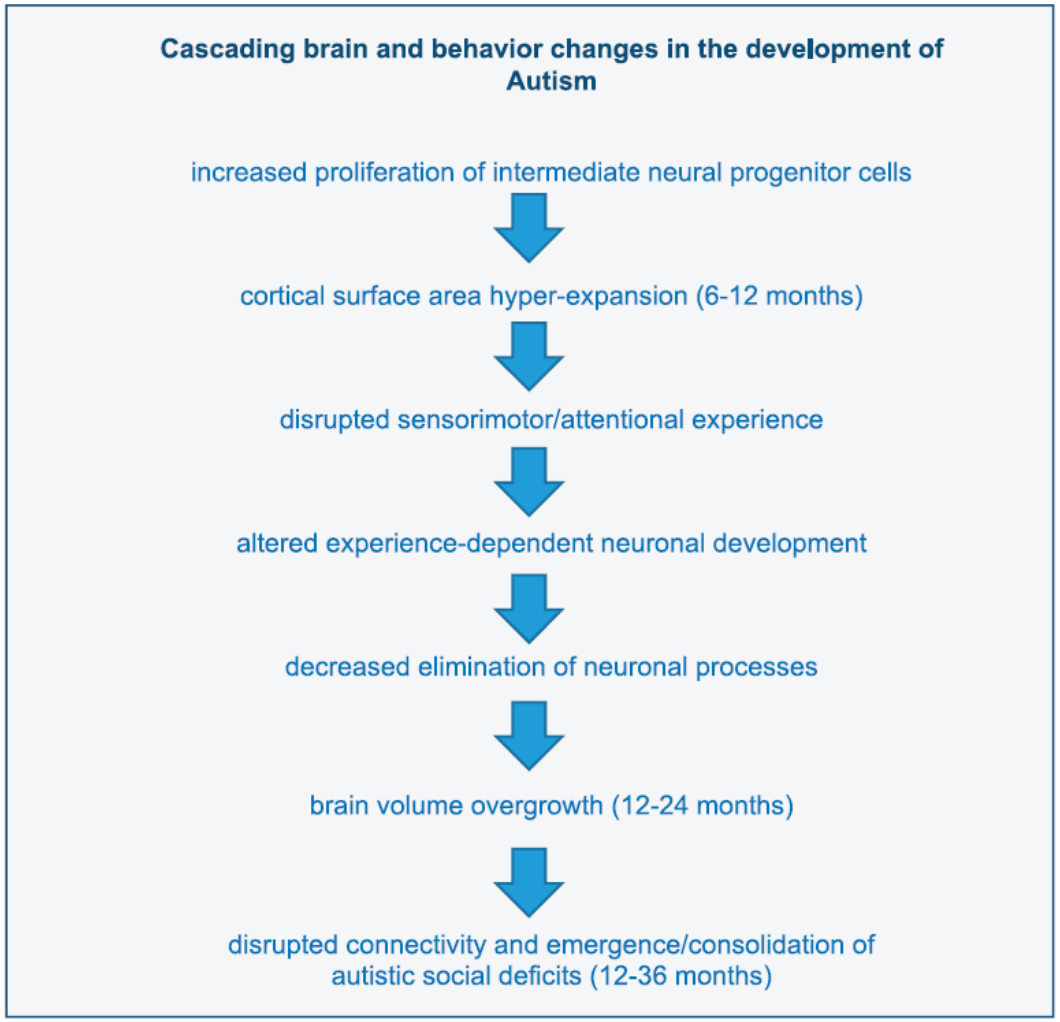
Autism spectrum disorder (**ASD**) is a complex developmental condition that involves

- persistent challenges in social interaction,
- speech and nonverbal communication,
- and restricted/repetitive behaviors.

The effects of **ASD** and the severity of **symptoms** are different in each person

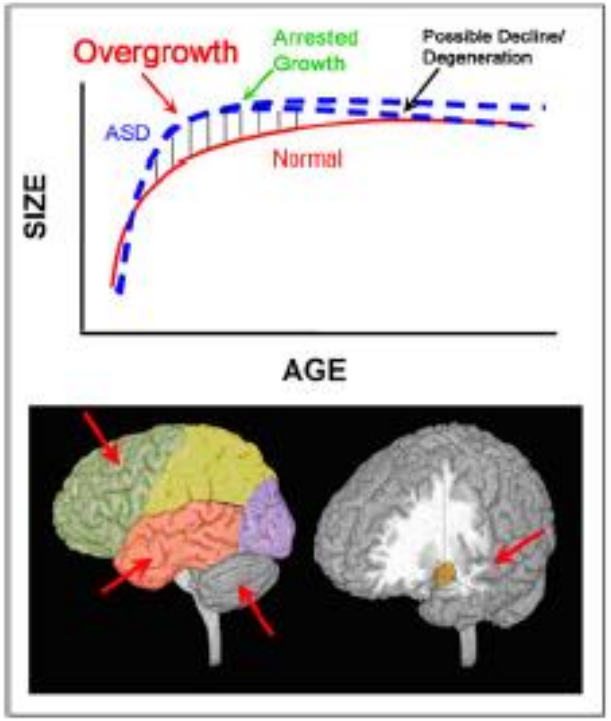
75 % patients with ASD have combined ID

The interaction of early brain development and behavior in ASD: a framework that best integrates our current evidence.

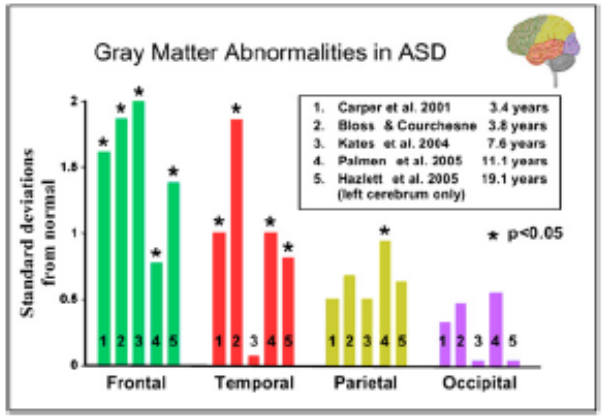


Molecular Psychiatry (2017), 1 – 10

One of the most consistent findings in toddlers with autism is a modest but significant increase in overall brain volume



Toddlers: increase in head circumference



Was not present at birth !

But emerged at the end of first and 2nd year

However, in absolute values present in a small group (15 %) of TSA (> 1.5 SD mean non autististic)

But what about growth rate ?

Hazlett el al. 2005; Courchesnes 2011

Very early, post-natal hyper-expansion of cortical surface areas may play an important role in the development of autism

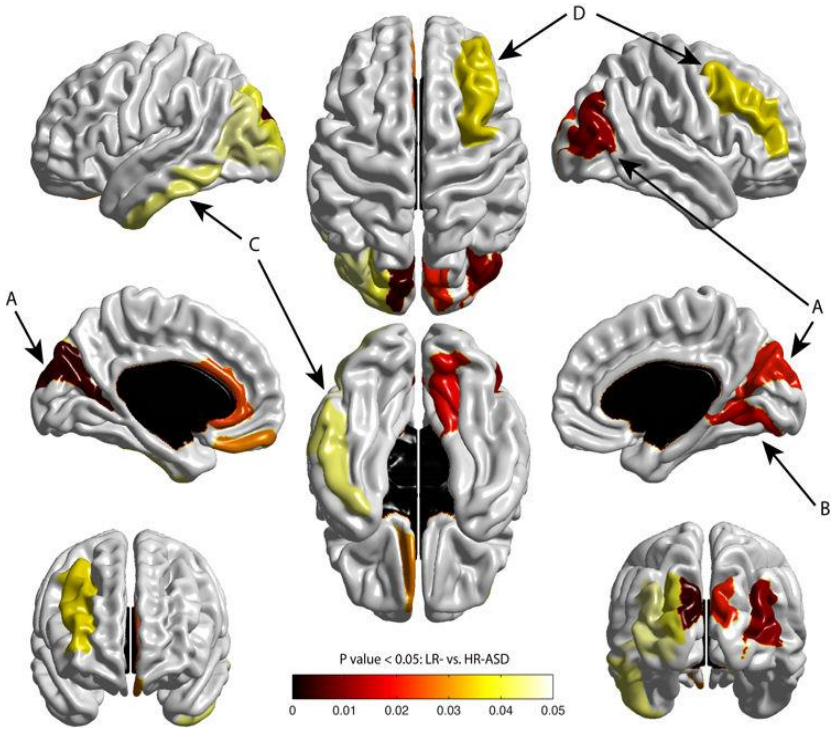
1) **Rate of cortical surface area (SA) expansion** from 6 to 12 months significantly **increased** in individuals diagnosed with **autism** at 24 months,

2) Linked to subsequent **brain overgrowth** which, in turn, linked to the emergence of social deficits.

Suggests a sequence whereby hyper-expansion of cortical surface area is an early event in a cascade leading to brain overgrowth and emerging autistic deficits.

Surface **area hyper-expansion in Y 1 observed in cortical areas linked to processing sensory information (e.g., left middle occipital cortex),** consistent

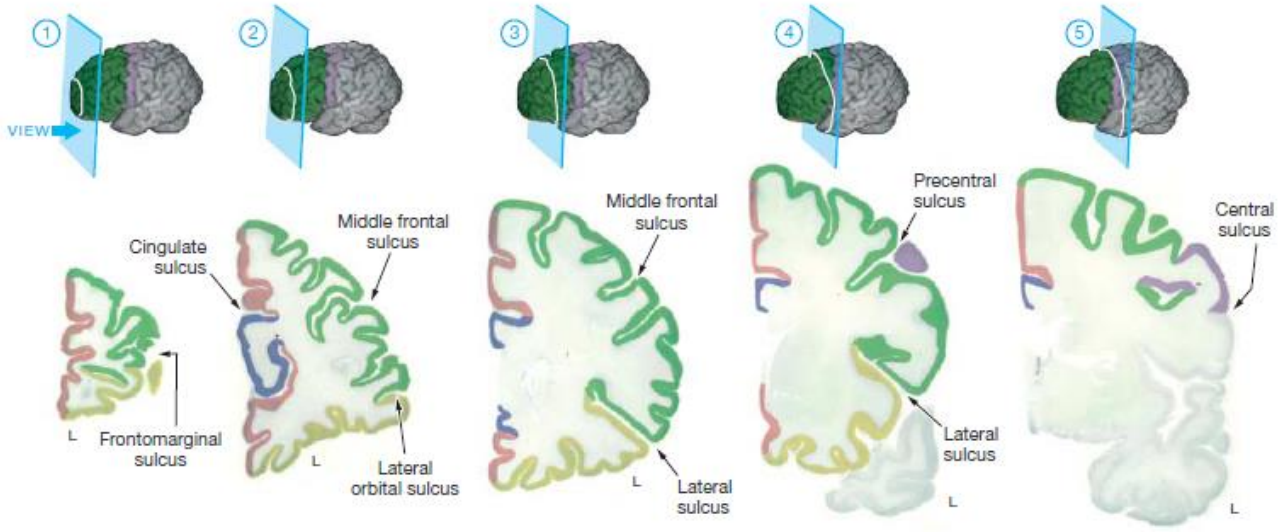
(Hazlett, Nature 2017)



Significant expansion in cortical SA in the left/right middle occipital gyrus and right cuneus (A), right lingual gyrus (B), and to a lesser extent the left inferior temporal gyrus (C), and middle frontal gyrus

Neuron Number and Size in Prefrontal Cortex of Children With Autism

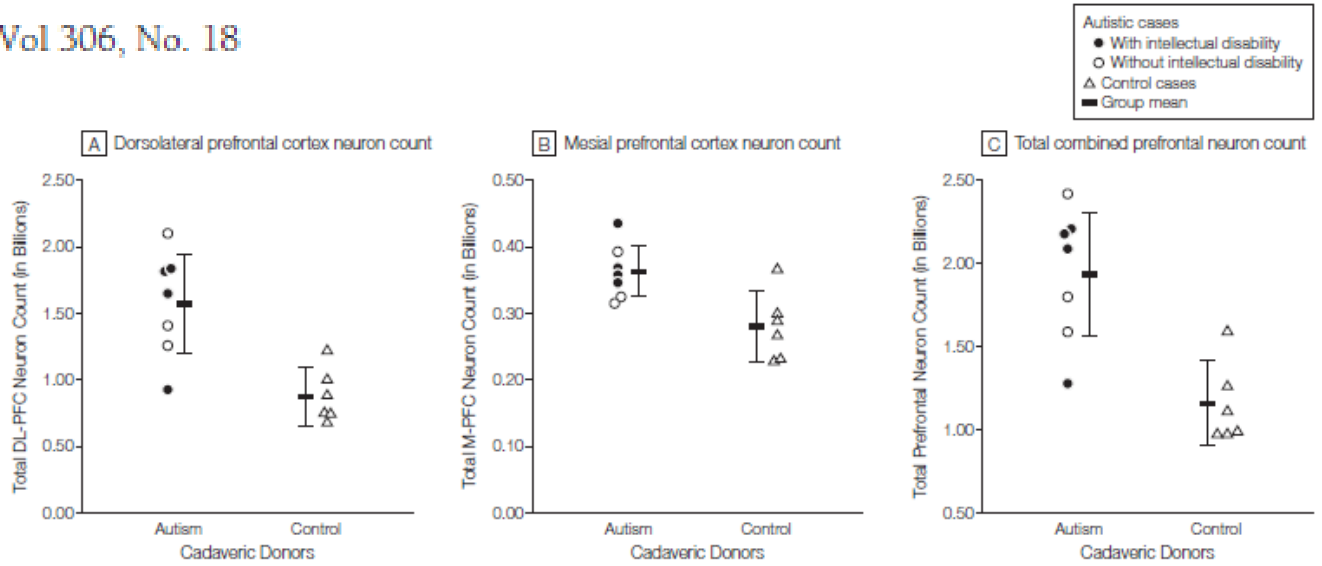
A prunning disorder ?



Eric Courchesne, PhD
Peter R. Mouton, PhD
Michael E. Calhoun, PhD
Katerina Semendeferi, PhD
Clelia Ahrens-Barbeau, BS
Melodie J. Hallet, MS
Cynthia Carter Barnes, PhD
Karen Pierce, PhD

JAMA, November 9, 2011—Vol 306, No. 18

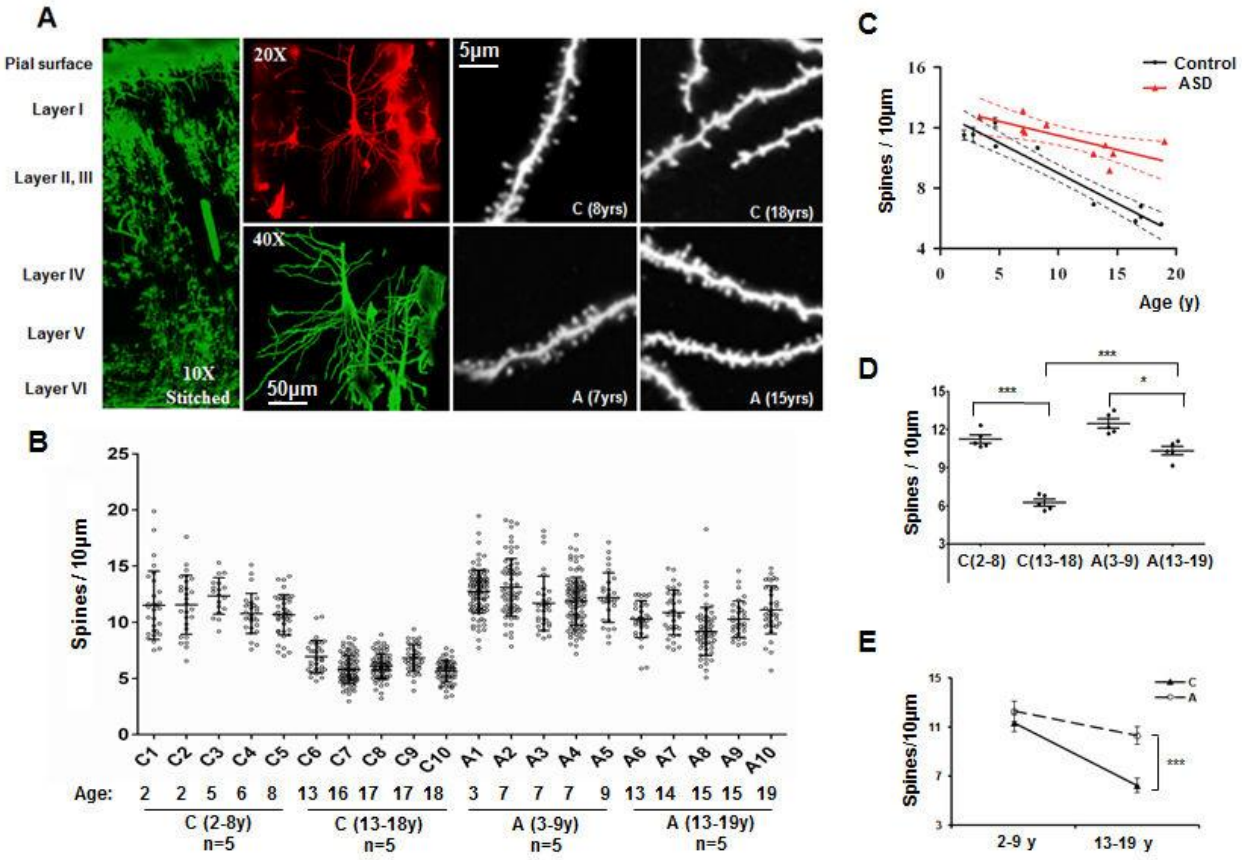
2 to 16
Year old



Spine densities in ASD

- ASD, in contrast to ID, associated *with significantly increased spine density on various neuronal types*, such as layer (L) 2/3 cortical pyramidal neurons in the frontal, temporal, and parietal lobes and neurons in the lateral nucleus of the amygdala.69, 70

Developmental alterations of excitatory synapses are implicated in ASDs



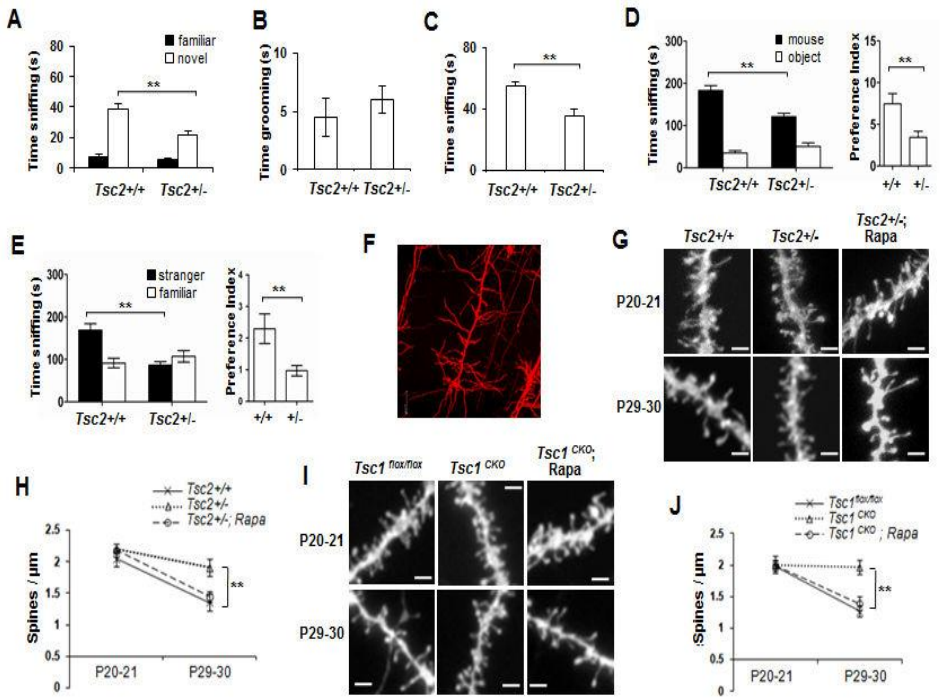
- Increased spine density is observed in frontal, temporal,and parietal lobes in ASD brains (Hutsler and Zhang, 2010).
- Increased dendritic spine density with reduced developmental spine pruning in layer V pyramidal neurons in postmortem ASD temporal lobe
- Correlation with hyperactivated mTOR and impaired autophagy

G. Tang et al. *Neuron*. 2014

Changes in synaptic structure are detected in multiple ASD model mice (Tsc2+:- Example) (Zoghbi and Bear, 2012; G. Tang *Neuron*. 2014)

ASD-like social behaviors

Postnatal spine pruning defects



Correction with mTOR inhibitor rapamycin

TSC inhibition of mTOR is required for postnatal spine pruning
Basal neuronal autophagy is depressed due to mTOR hyperactivation in Tsc mutant ASD
mouse models

PCDH10 and MEF2 recently found at the center of synapse elimination and associted with ASD

Conclusions

- Genes have been discovered for numerous syndromic disorders that prominently feature ASD and ID.
- Gene mutations have been reproduced in animal models that allow more and more a detailed examination of the underlying brain pathophysiology.
- Early neurogenseis and neuro circuitry development is most probably implicated in ASD and ID genesis (neuronal migration, synapse maturation,…)
- Insights gained on how synapses function differently in the face of these mutations may pave the way for novel therapeutic interventions validated in preclinical models

Pregnenolone-methyl-ether enhances CLIP170 and microtubule functions improving spine maturation and hippocampal deficits related to CDKL5 deficiency

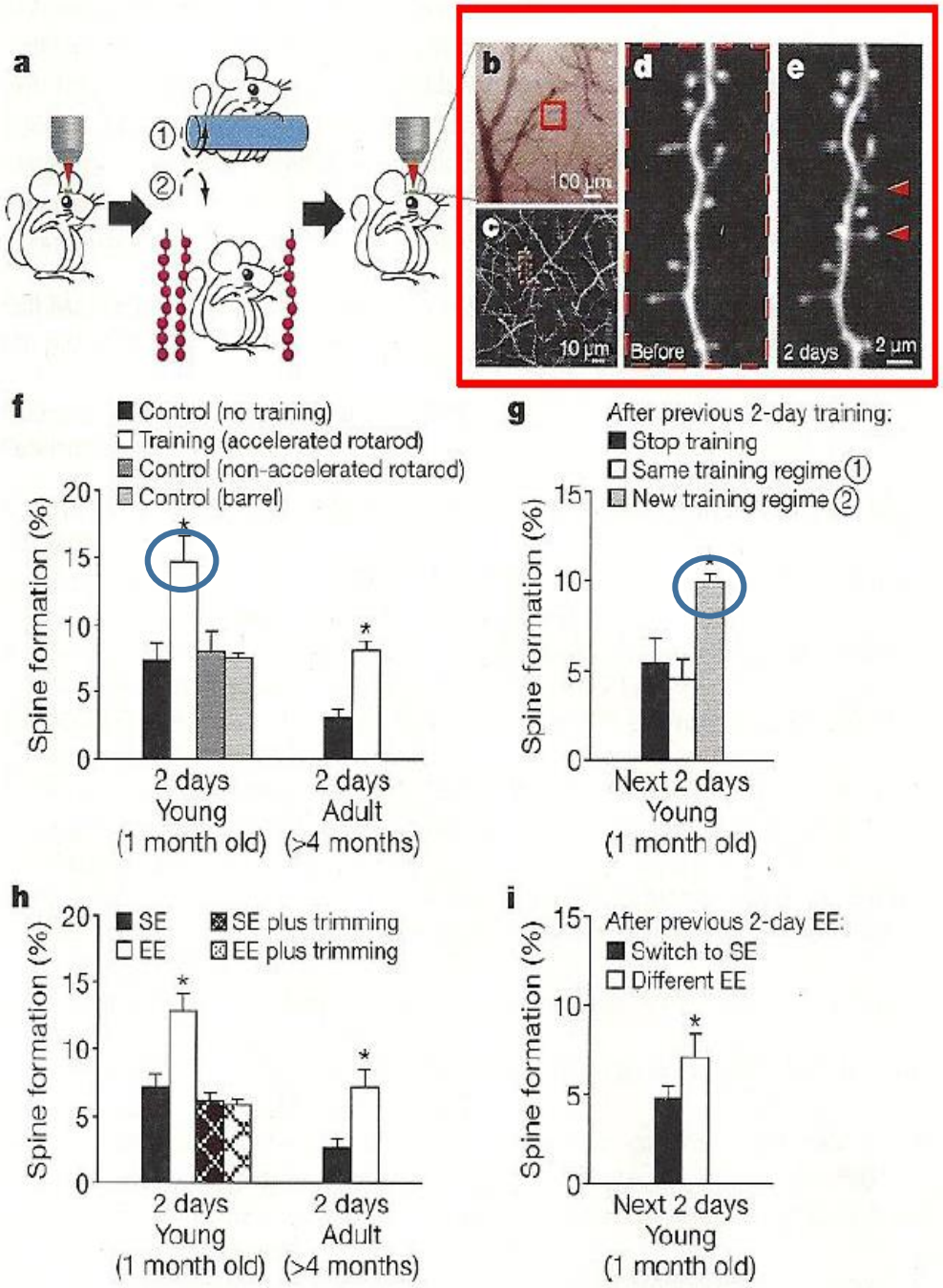
Isabella Barbiero[1,†], Erica Zamberletti[1], Marco Tramarin[1], Marina Gabaglio[1], Diana Peroni[1], Roberta De Rosa[1], Serena Baldin[1], Massimiliano Bianchi[2,3], Tiziana Rubino[1] and Charlotte Kilstrup-Nielsen[1,†,*]

[1]Department of Biotechnology and Life Sciences (DBSV), Centre of NeuroScience, University of Insubria, Busto Arsizio, Italy
[2]Ulysses Neuroscience Ltd., Trinity College Dublin, Dublin, Ireland
[3]Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland
*To whom correspondence should be addressed at: Department of Biotechnology and Life Sciences (DBSV), University of Insubria, Via Manara 7, 21052 Busto Arsizio, Italy. Tel: +39 0331339430; Fax: +39 0331339459; Email: c.kilstrup-nielsen@uninsubria.it

†Co-corresponding authors

Human Molecular Genetics, 2022, Vol. 31, 16, 2738–2750
https://doi.org/10.1093/hmg/ddac067
Advance access publication date: 25 March 2022
Original Article

Back –up slides



Activity Leads to Plasticity in Dendrites

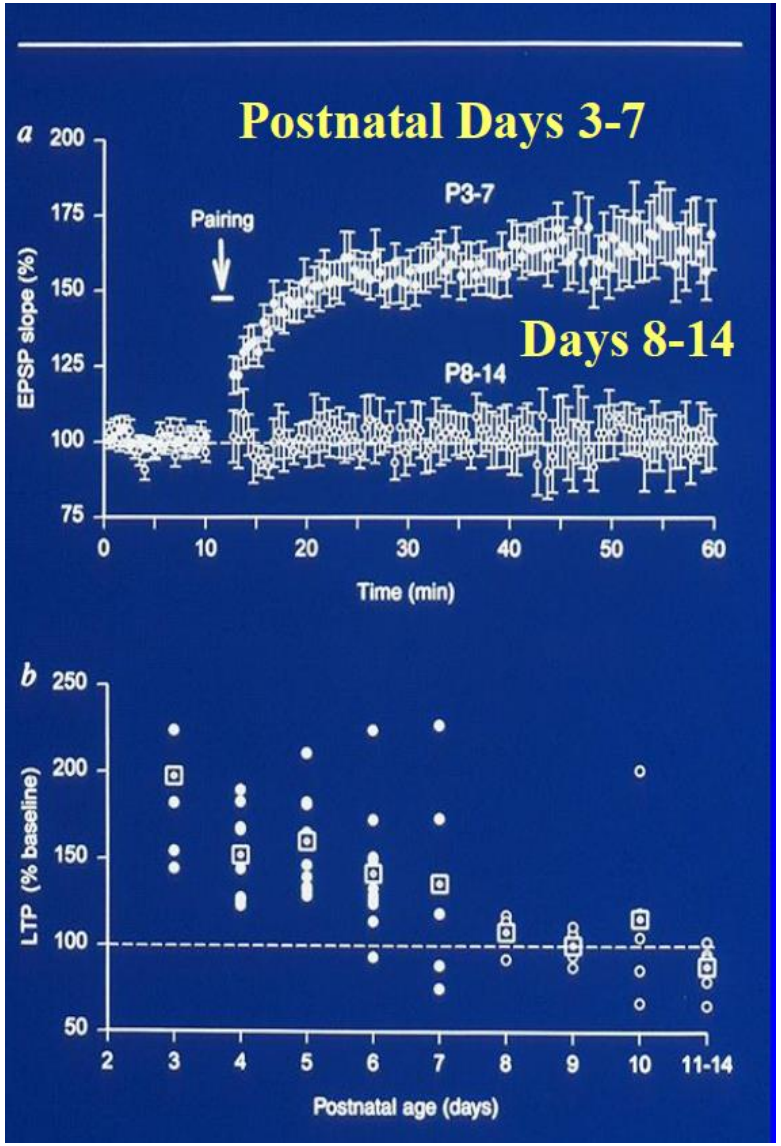
Learning new motor skills and acquiring new sensory experiences is associated with formation of new synaptic connections in motor and sensory regions of the mouse brain

LTP is Enhanced in the Immature Brain

A critical period for long-term potentiation at thalamocortical synapses

Michael C. Crair & Robert C. Malenka

Departments of Psychiatry and Physiology, Center for Neurobiology and Psychiatry, University of California, San Francisco, California 94143, USA

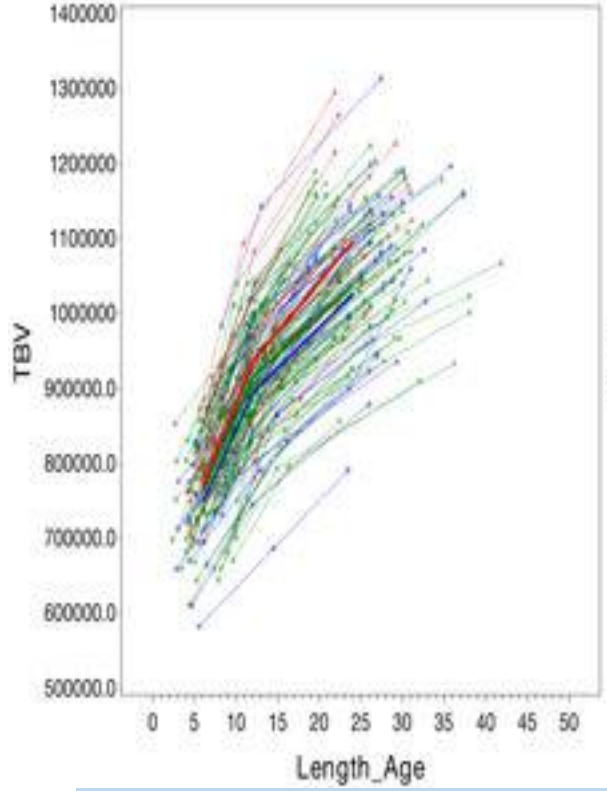


Results from a prospective brain imaging studies of infants at high familial risk for ASD (Hazlett, Nature 2017)

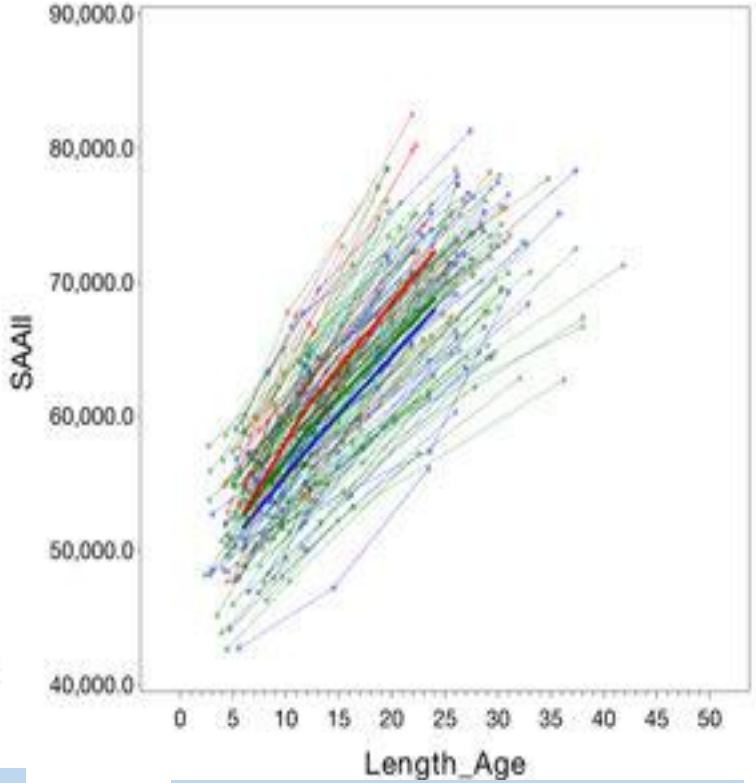
- 106 infants at *high familial risk* of ASD (**15 HR-ASD**; **91 HR- neg**) and 42 ***low-risk*** infants

6, 12 and 24 months

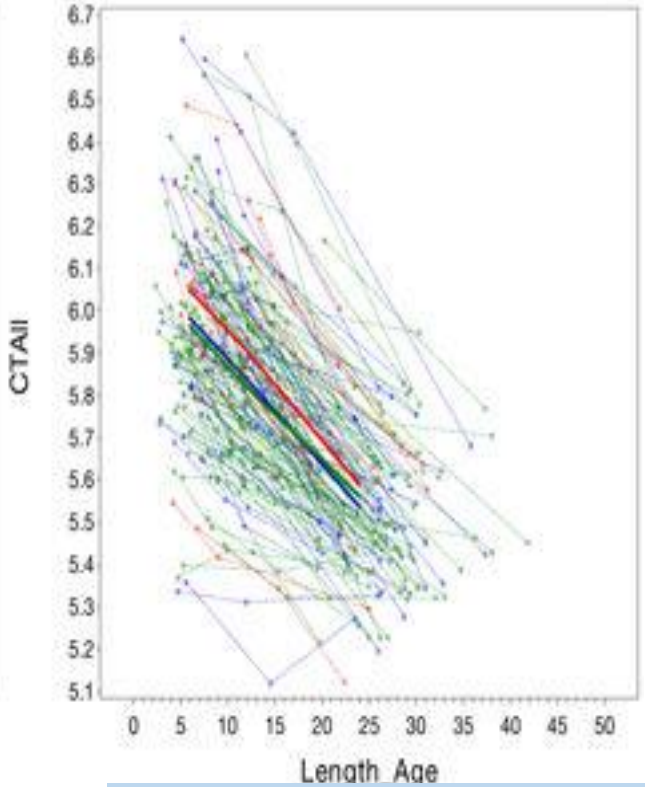
- *behavioral assessments,*
- *high-resolution brain MRI*



Growth slope diff 12-24 M



Growth slope diff 6-12 M



Slope not diff

1) Cortical surface area hyper-expansion between 6-12 months of age precedes brain volume overgrowth between 12-24 months in HR ASD

2) Brain volume overgrowth linked to the emergence and severity of autistic social deficits.

Spine head size correlates with stability:

Enlargement correlates with:

- a remodeling of the postsynaptic density (PSD),
- an increased expression of AMPA receptors (Matsuzaki et al., 2004; Zito et al., 2009),
- a reorganization of the actin cytoskeleton (Honkura et al., 2008).
- depends on protein synthesis and neurotrophin signaling (Tanaka et al., 2008)
- involves increased dynamics of PSD proteins such as PSD-95 and Shank-1 (Steiner et al., 2008).

Changes are directly:

- related to the increase in synaptic strength
- but could also be part of process that provides a better stability to the spine.
- LTP induction is indeed able to switch potentiated spines to a highly stable state, making these spines persistent for several days (De Roo et al., 2008b)

Dendritic spines serve to shape and refine neuronal connectivity

Architecture of developing Synapses

Dendritic spines

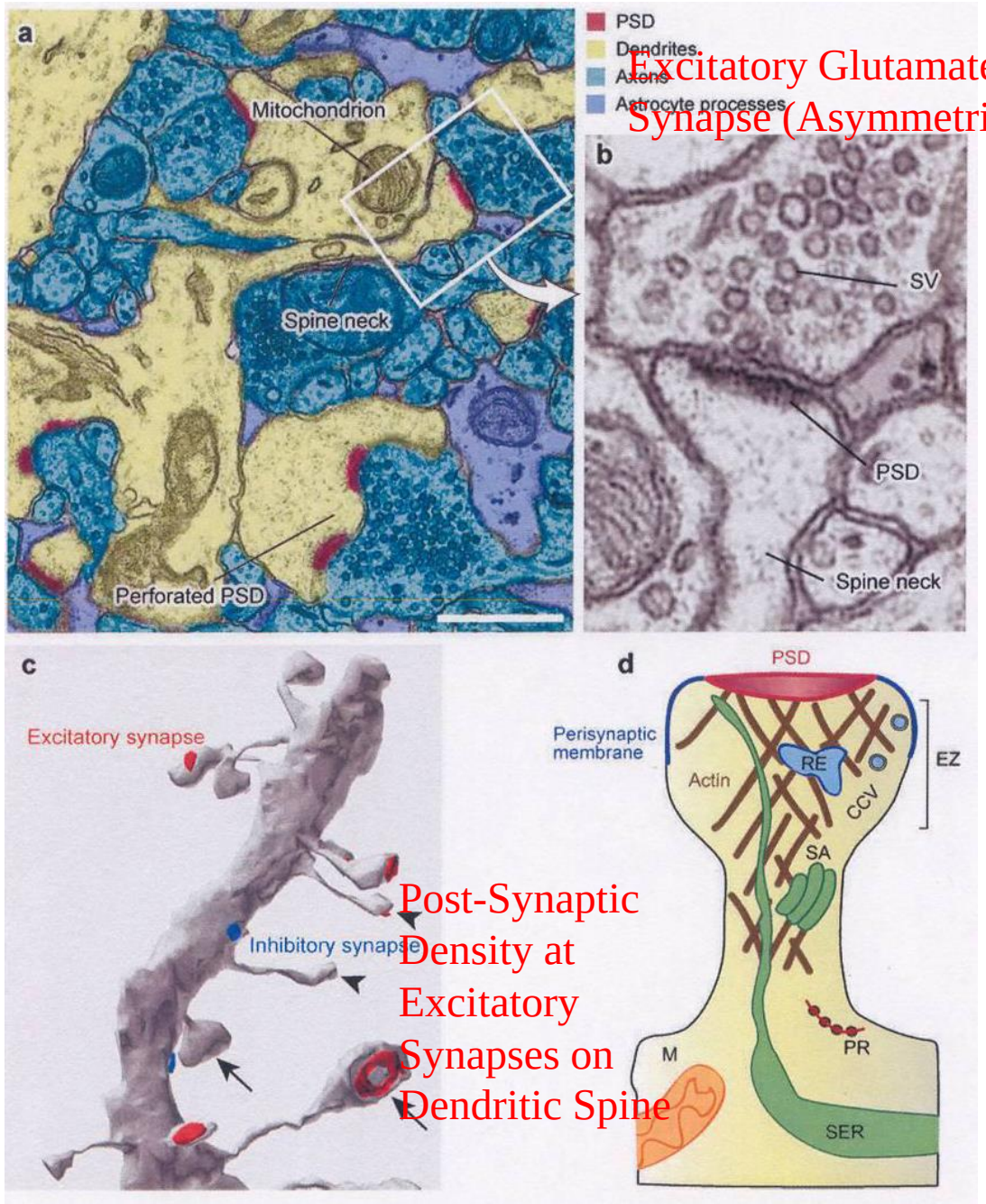
- small membranous protrusion from the dentrite;
- postsynaptic compartments that receive the majority of excitatory input in the brain
- Post synaptic density (PSD)
- Micro domain; Compartimentlizes Ca++
- High Remodelling capacity –high turn over, even after birth

Dendritic shafts have multiple inhibitory synapses.

Shaped by Activity

Excitatory synapses are more likely to be eliminated after birth than inhibitory synapses.

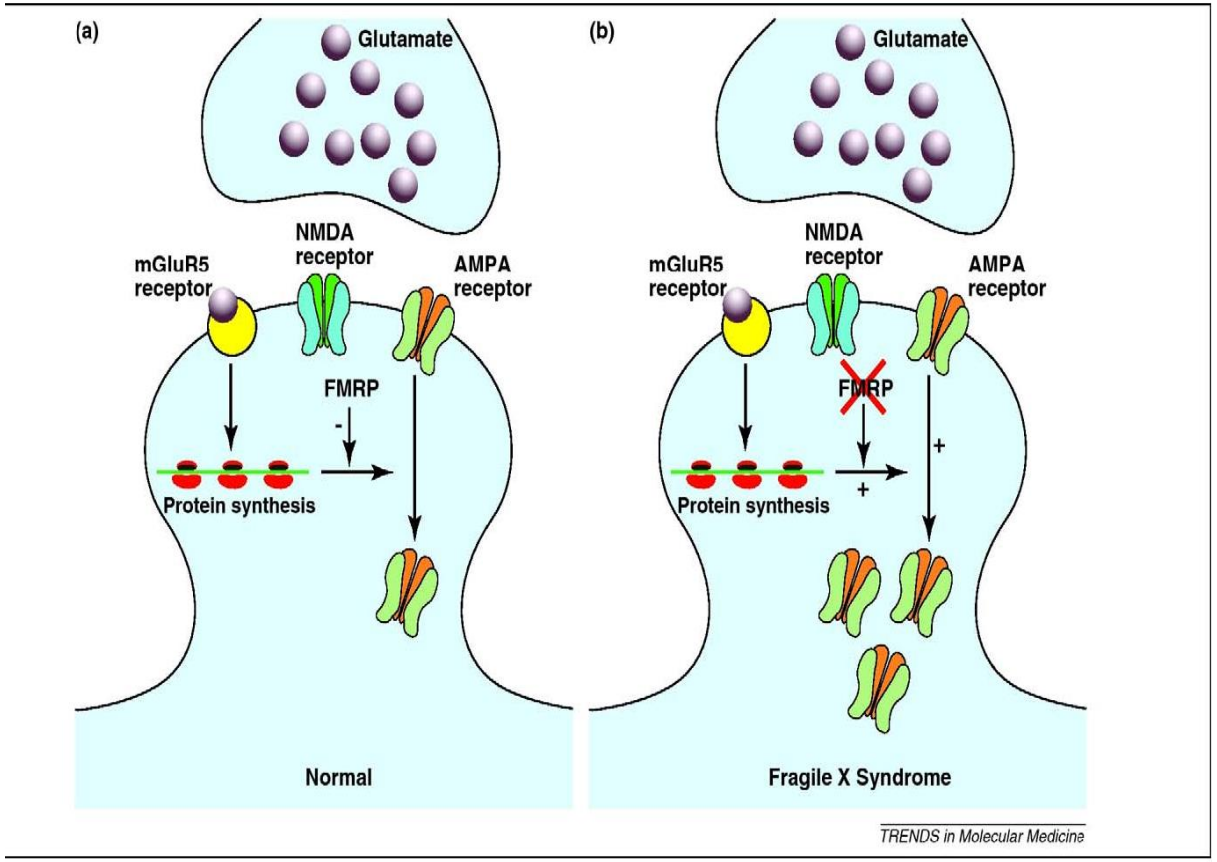
Sheng and Hoogenraad, Ann Rev Biochem 2007, 76:823-47; Glantz et al, Neuroscience, 2007



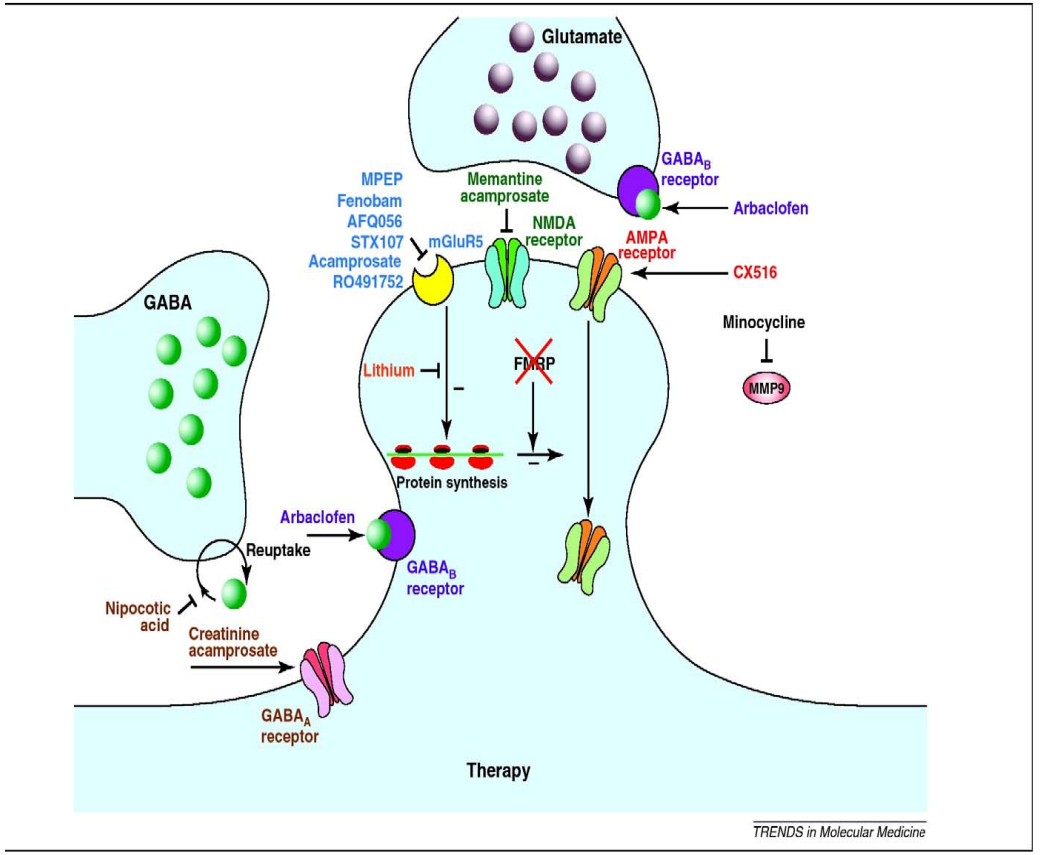
Excitatory Glutamate Synapse (Asymmetric)

Post-Synaptic Density at Excitatory Synapses on Dendritic Spine

FMRP and AMPA receptor internalisation



. The mGluR theory. **(a)** Stimulation of mGluR5 by glutamate induces local mRNA translation at the synapse. Local protein synthesis stimulates the internalisation A receptors, which is essential for long-term synaptic plasticity. FMRP negatively regulates transcription and reduces the internalisation of AMPA receptors. **(b)** By



3. Therapeutic strategies for FXS. Schematic representation of a glutamate receptor excitatory and GABA receptor inhibitory synapse lacking FMRP. Drugs can t with different types of neuronal receptors, which might rescue the disturbed synaptic transmissions in FXS. Negative mGluR5 modulators, GABA$_A$ agonists, R agonists, NMDA receptor antagonists, positive AMPA receptor modulators are potential candidates to rescue the FXS phenotype by correcting altered synaptic

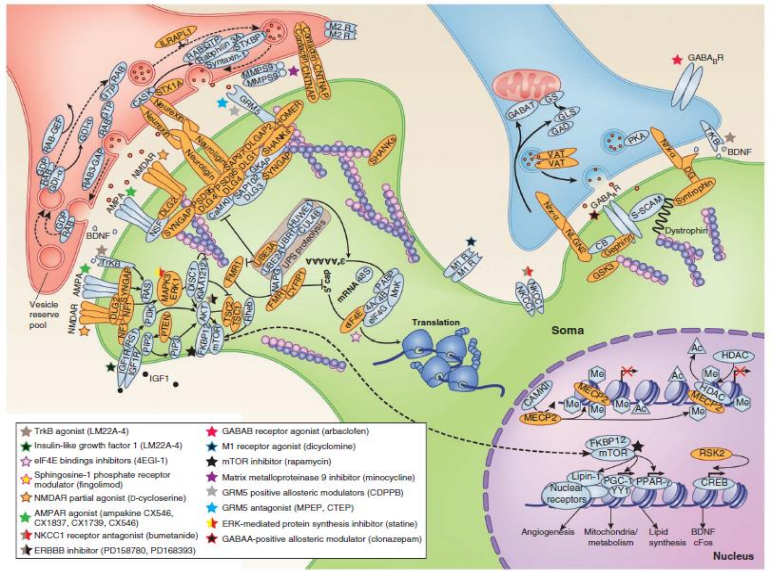
Increased AMPA receptor internalisation
associated with increased LTD !

Pathogenic *SYNGAP1* Mutations Impair Cognitive Development by Disrupting Maturation of Dendritic Spine Synapses

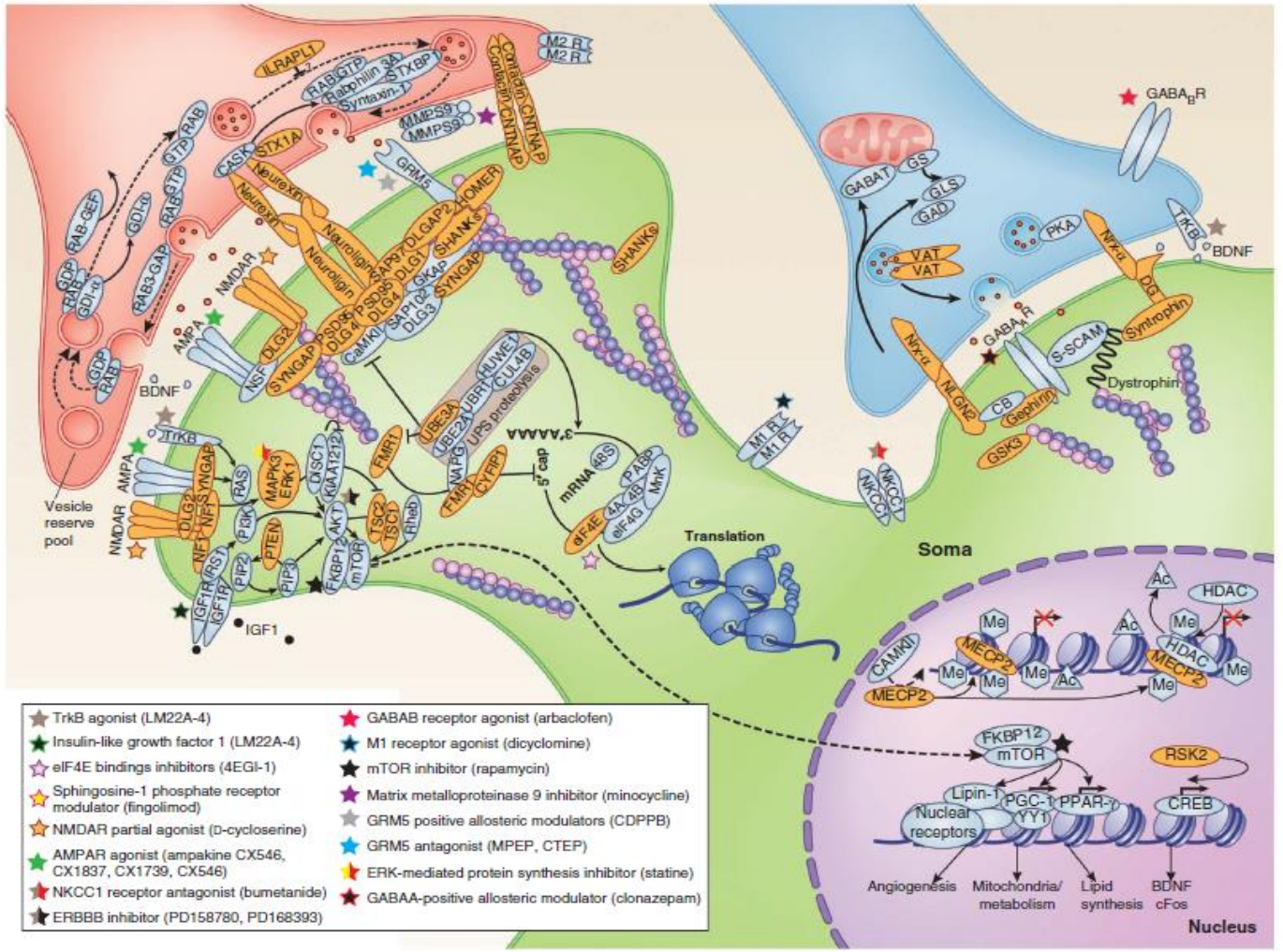
James P. Clement,[1,6] Massimiliano Aceti,[1,6] Thomas K. Creson,[1,6] Emin D. Ozkan,[1] Yulin Shi,[3] Nicholas J. Reish,[4] Antoine G. Almonte,[4] Brooke H. Miller,[1] Brian J. Wiltgen,[5] Courtney A. Miller,[1,2] Xiangmin Xu,[3] and Gavin Rumbaugh[1,*]
[1]Department of Neuroscience
[2]Department of Metabolism and Aging
The Scripps Research Institute, Jupiter, FL 33458, USA
[3]Department of Anatomy and Neurobiology, University of California, Irvine, CA 92697, USA
[4]Department of Neurobiology, University of Alabama at Birmingham, Birmingham, AL 35294, USA
[5]Department of Psychology, University of Virginia, Charlottesville, VA 22904, USA
[6]These authors contributed equally to this work.
*Correspondence: grumbaug@scripps.edu
http://dx.doi.org/10.1016/j.cell.2012.08.045

Cell 151:709-723, 2012

SYNGAP1 mutations cause **intellectual disability and autism**. This protein normally **represses synaptic excitability during development**. Enhanced excitability during development is associated **with premature development of dendritic spines**, which may stunt their growth, thereby impairing intellectual potential.



Mutations found in genes involved in neuronal synaptic formation, maturation and transmission



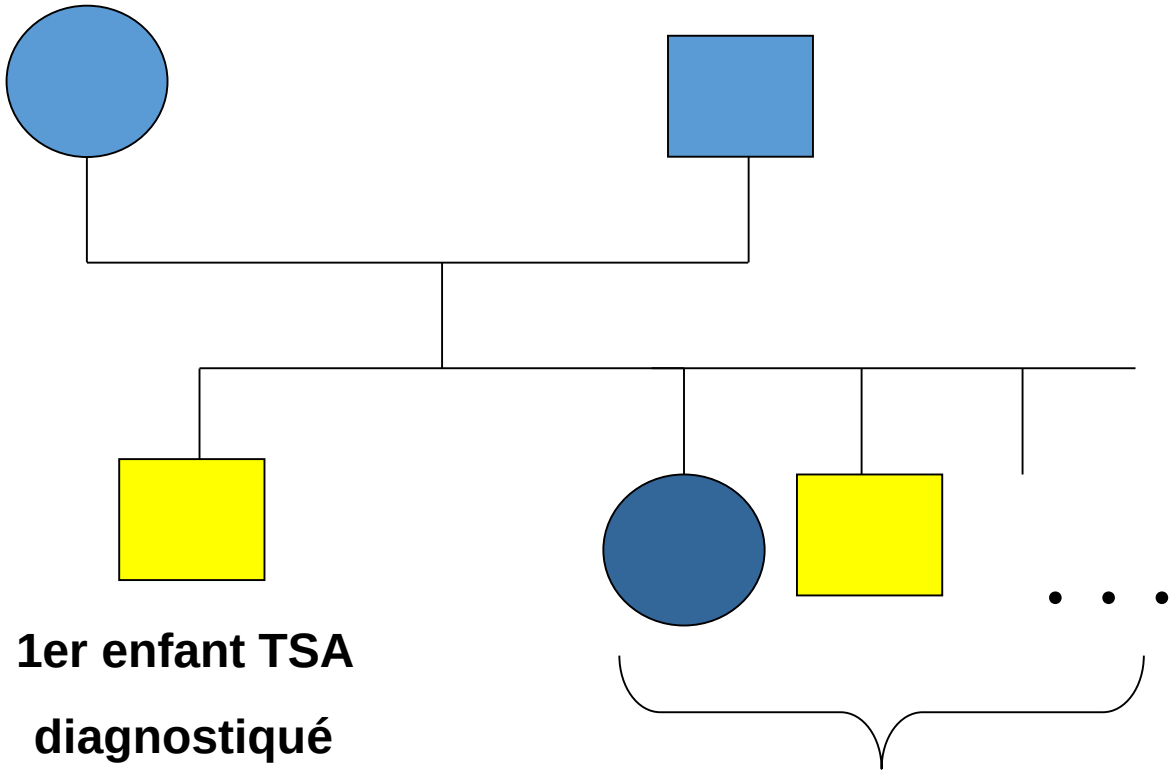
Progress toward treatments for synaptic defects in autism

Richard Delorme[1-4], Elodie Ey[1-3], Roberto Toro[1-3], Marion Leboyer[5,6], Christopher Gillberg[7-9] & Thomas Bourgeron[1-3,6]

nature medicine

Infant siblings studies : Quid?

Fombonne et al, 2011
Prevalence 80/10.000, 0.8 %
(close 1 %)



1er enfant TSA diagnostiqué

. Increased risk

.recurrence (10 à 15 %)

. Early follow up of siblings

Low Risk

High Risk
- negative
- ASD

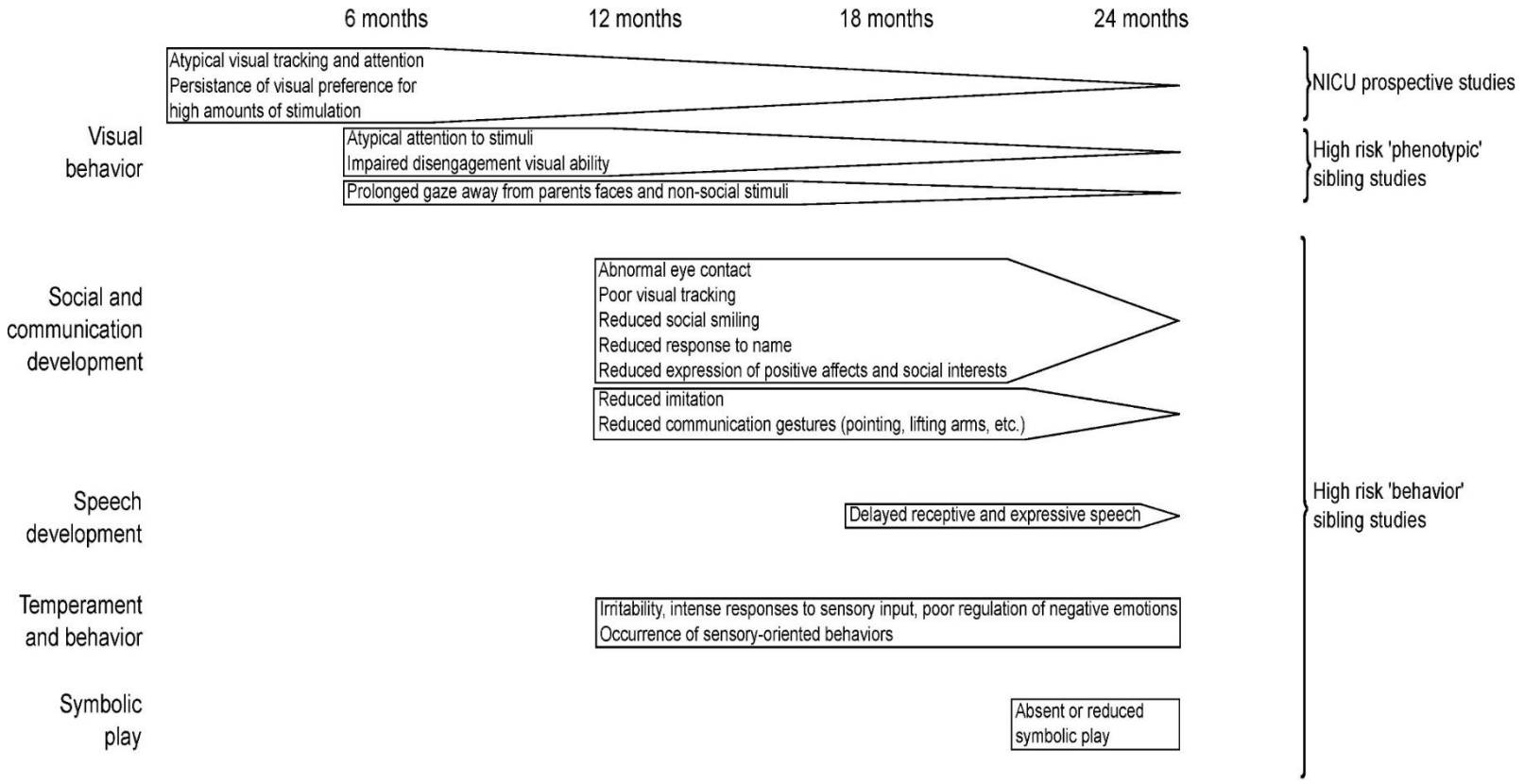
Disorder effect
- LR=HR neg ≠HR ASD

Familial effect
- LR≠ HR neg= HR ASD

Endophenotype effect
- LR≠HR neg≠HR ASD

Ozonoff et al, 2011

Studies of infants at high familial risk for autism have found that characteristic social deficits in ASD emerge during the latter part of the first and in the second year of life



Deconinck, Soncarrieu et al., Pediatric Neurology Septembre 2013

Fragile X

- FXS patients: full length mutation, >200 CGG repeats
- Alters the translation of the **FMR protein (FMRP),** with deficiency observed in FXS
- FMRP :
  - RNA-binding protein;
  - controls the translation of a large array of mRNAs:
  - critical for dendritic arborization and spine structure
  - modulates local protein synthesis in dendrites and optimizes the activity of several signaling cascades through interactions with Rac1, Arc, PSD95, MAP1B, CaMKII, calbindin, and cadherins, which are essential for spine morphogenesis