“Nothing in biology makes sense except in the light of evolution”
(Th. Dobzhansky)

Alzheimer´s disease -

an evolutionary perspective

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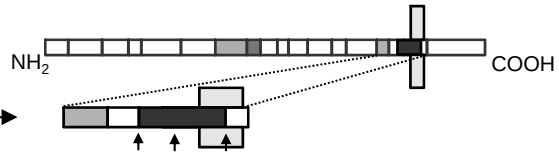
3rd Alzheimer’s Focused #C4CT Concussion
Awareness Summit at United Nations

Prevailing concepts

amyloid cascade hypothesis

PSEN1/2 & APP
FAD mutations



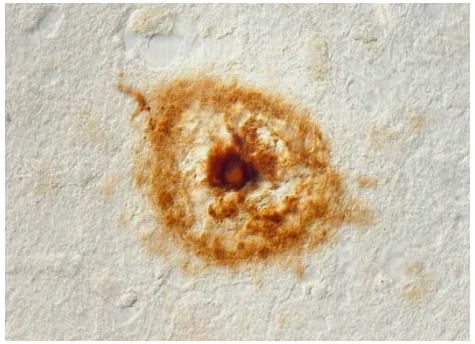
APP

β α γ secretases

Aß-peptide

Aß-aggregates

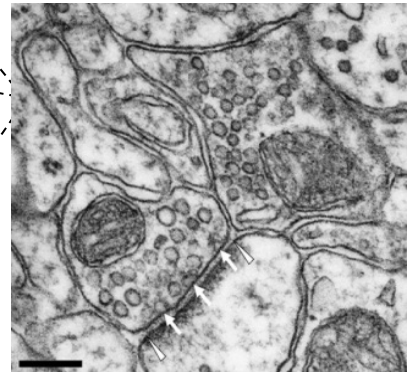
Aß-plaques



hyperphosphorylation and
aggregation of tau-protein

neurofibrillary tangles

loss of synapses



Neuronal dysfunction and death

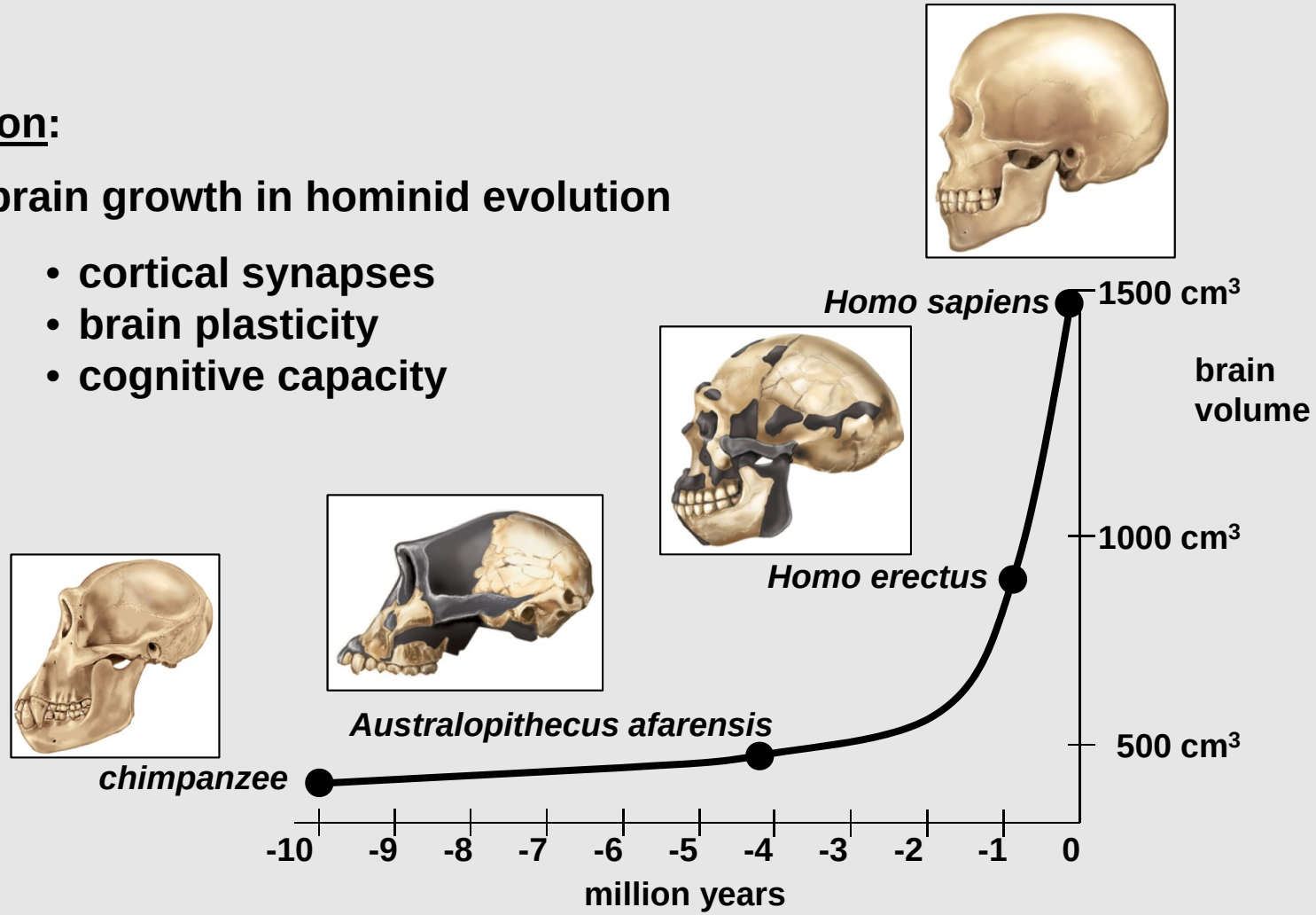
Why do we get Alzheimer´s disease ?

- AD is unique to human
- major genetic risk factor: ApoE polymorphism is unique to human

<u>Cerebralization</u>:

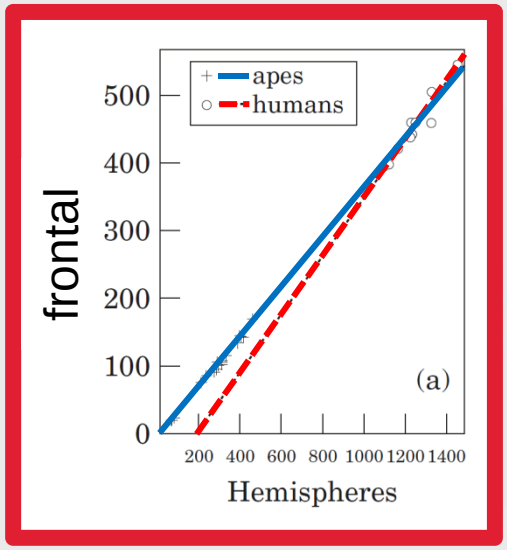
accelerated brain growth in hominid evolution
increase in:

- **cortical synapses**
- **brain plasticity**
- **cognitive capacity**

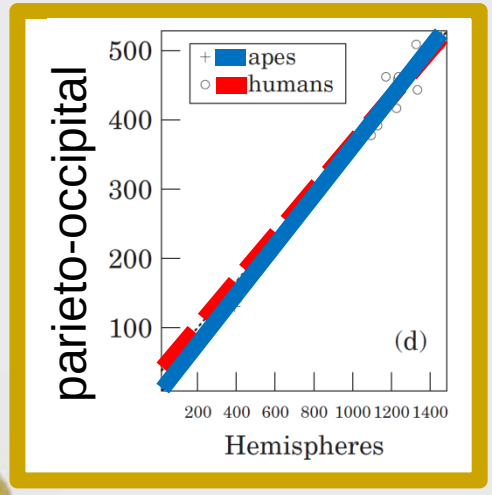


Why do we get Alzheimer´s disease ?

brain regions, highly vulnerable to AD-pathology have been elaborated in most recent hominid evolution

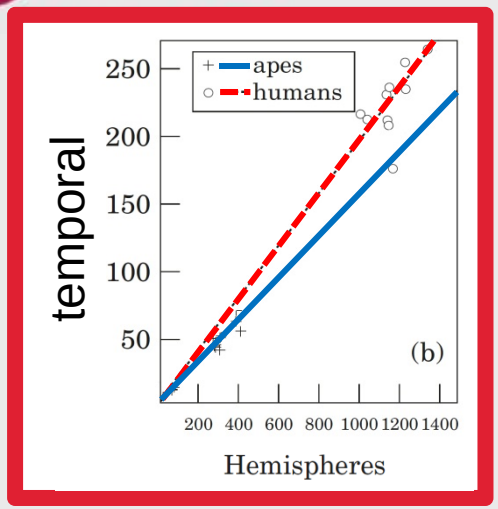


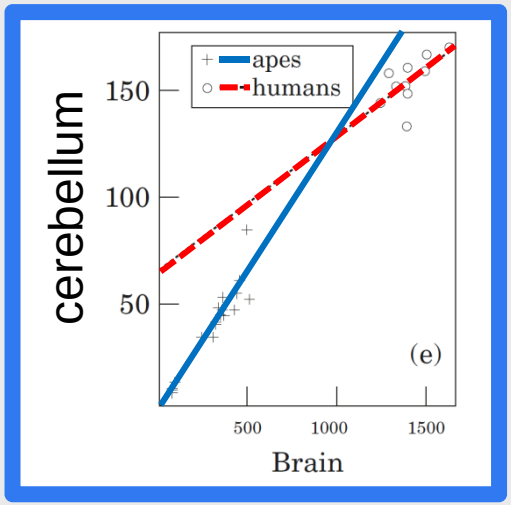
AD vulnerability



deceleration

acceleration



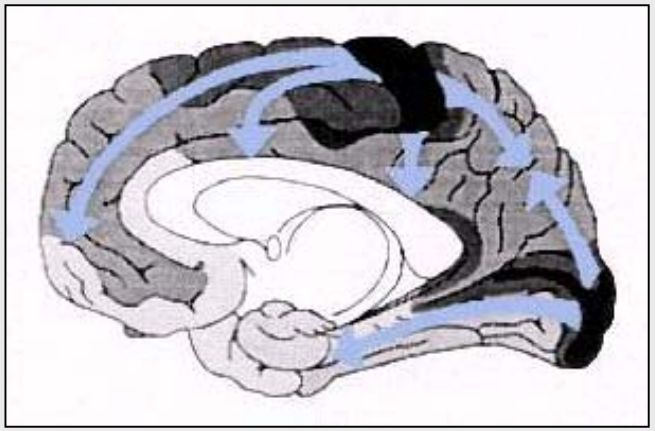


Allometric volume plots

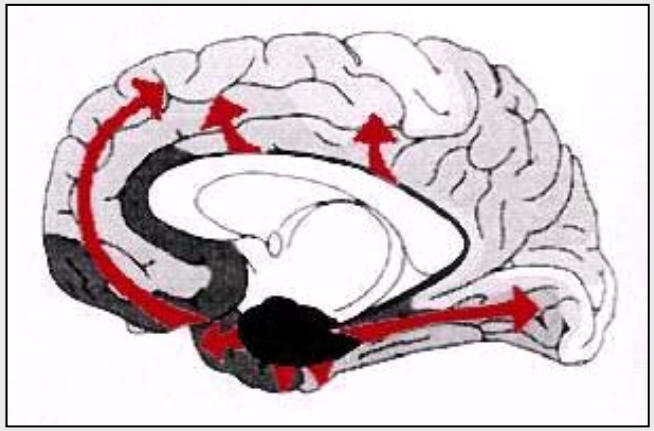
Katerina Semendeferi & Hanna Damasio,
J. Human Evolution (2000) 38:317-332.

Development of neurofibrillary degeneration inversely recapitulates brain development

progression of myelination
[acc. to Flechsig]



progression of neurofibrillary degeneration [acc. to Braak]



brain structure: last in – first out

development

primary sensory & motor cortex	primary sensory association cortex	non-primary association cortex	limbic cortex

degeneration / regression?

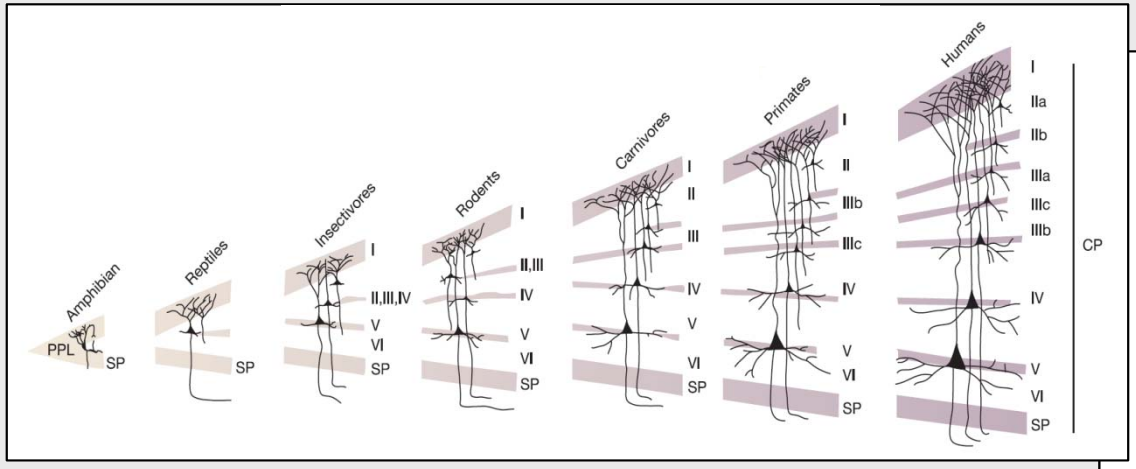
Reversal of developmental behavioural hierarchy in AD
„ last in - first out “

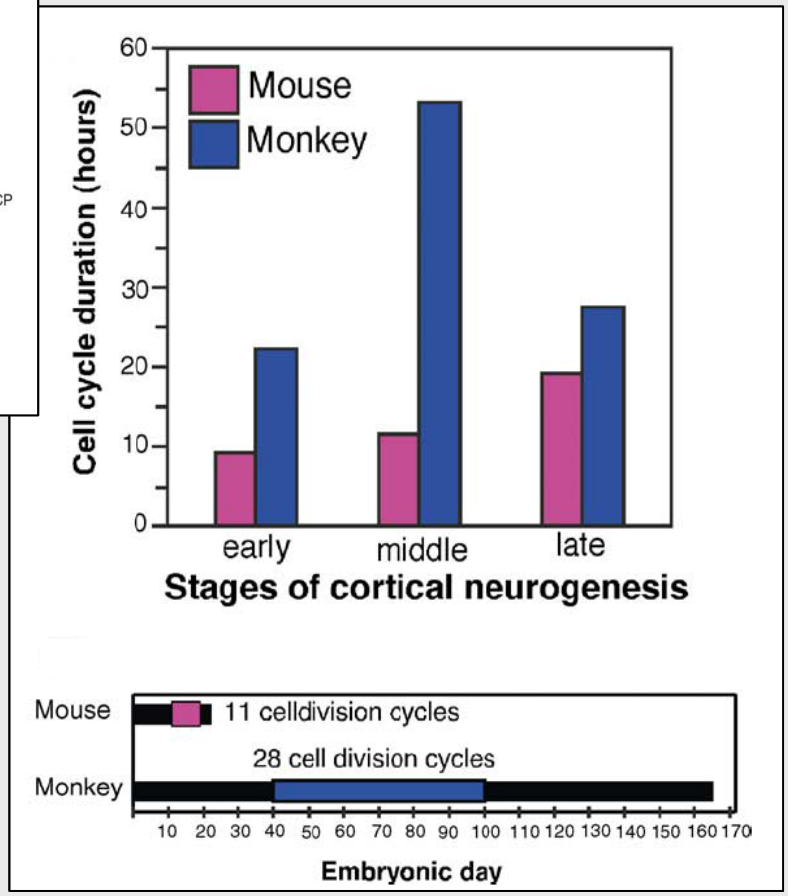
Sequence at which function is acquired during development (J. Piaget)

- Perform complex activities of daily life
- Put on clothing properly
- Perform mechanics of toileting correctly
- Maintain urinary continence
- Maintain fecal continence
- Say a few intelligible words
- Walk independently
- Sit up independently
- Smile
- Hold up head independently

Sequence at which function is lost in AD

How to make a bigger brain ?





expansion and laminar elaboration of primate neocortex:

accelerated cell-cycle kinetics with delayed maturation

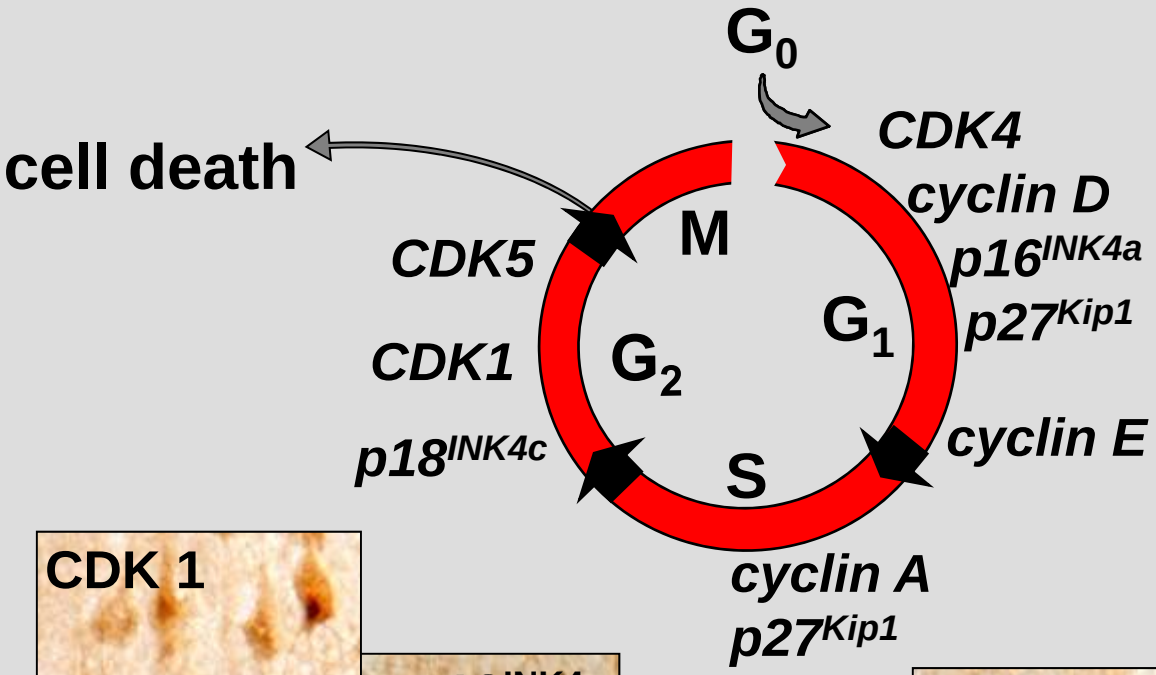
- **extended duration of cell cycle**
- **more total rounds of cell division**

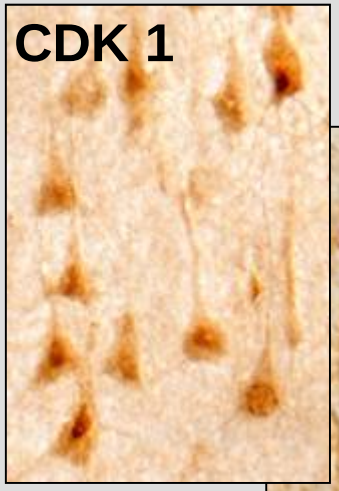
Kornack & Pasko Rakic PNAS (1998) 95: 1242-1246.
Krubitzer & Kahn Prog. Neurobiol. (2003) 70: 33-52.
Hill & Walsh; Nature (2005) 437: 64-67.

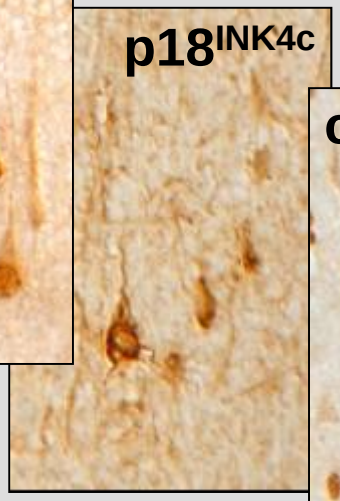
➡ **Achilles heel**

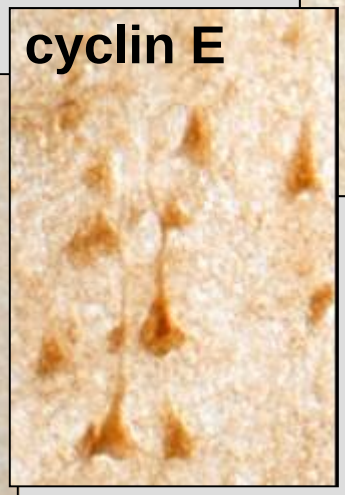
- **increased risk of mitotic errors**
- **special requirements of differentiation control**

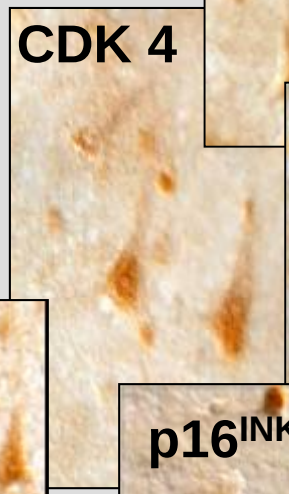
Re-expression of cell cycle markers in AD

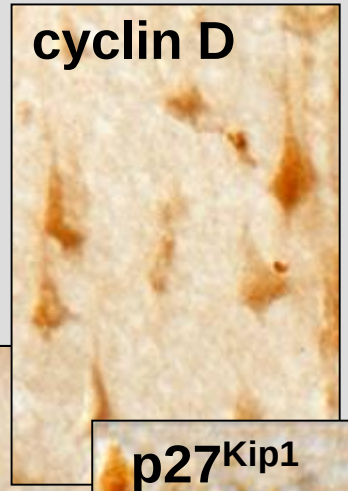


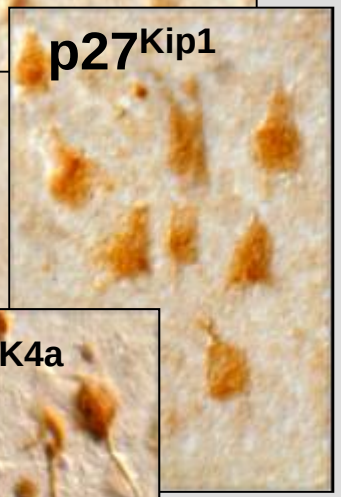






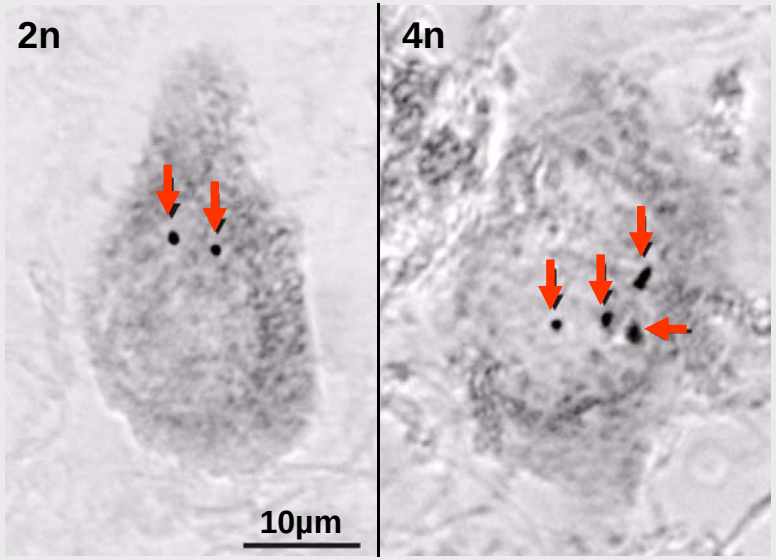


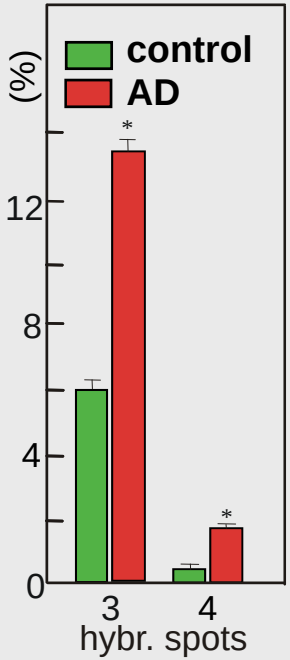


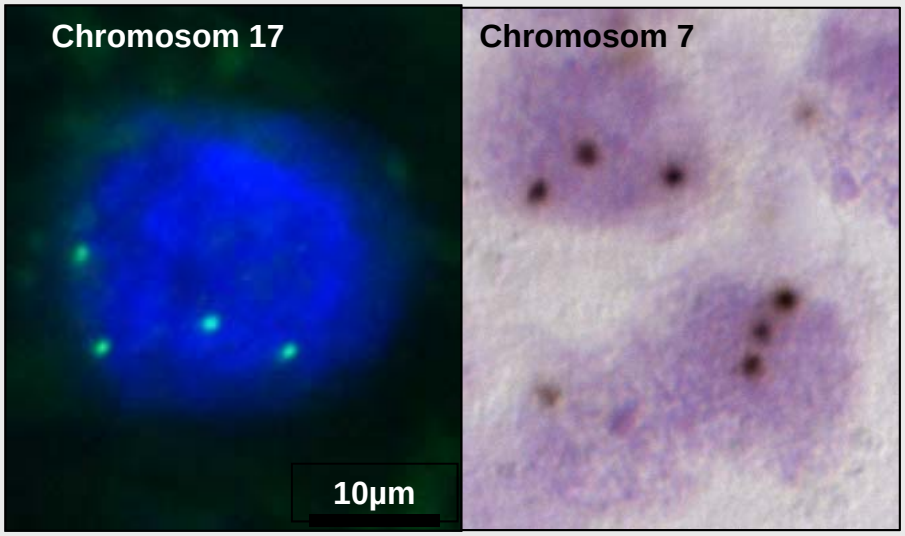


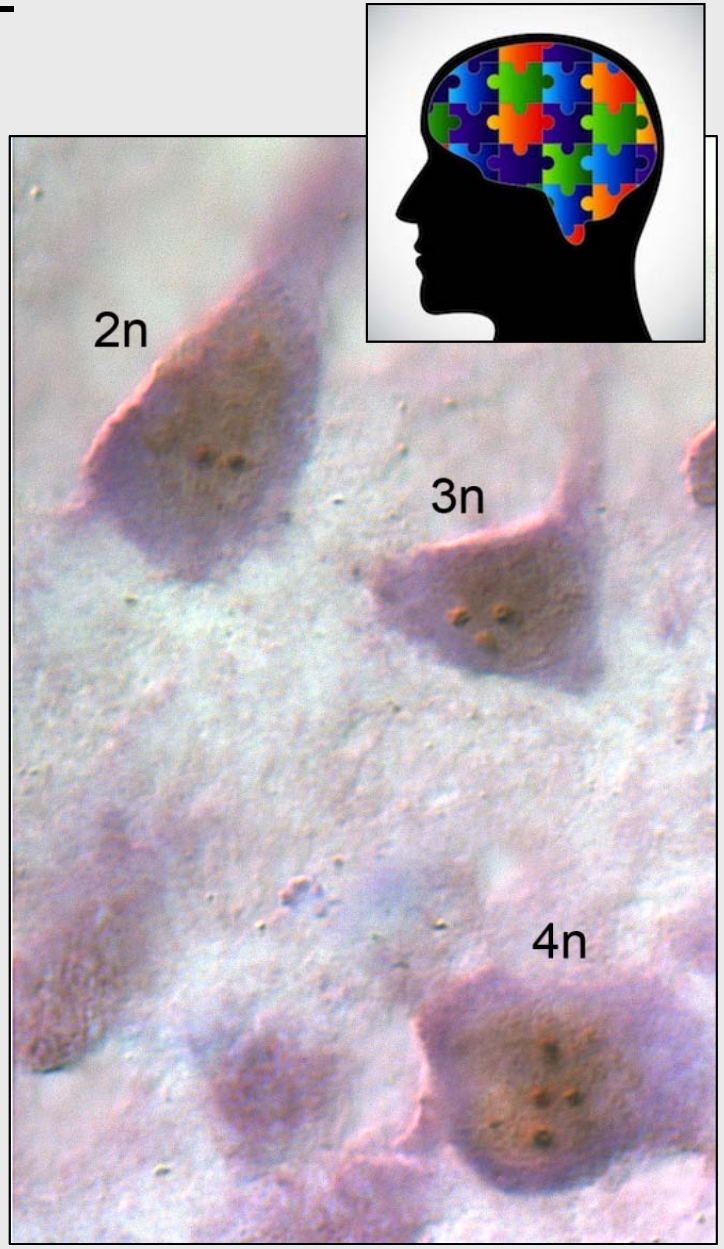
Gärtner et al. Neuroreport (1995)
Arendt et al. Hoppe Seyler (1993), Neurorep. (1995), Neurosci. (1996)

The human brain is a mosaic with hyperploid neurons





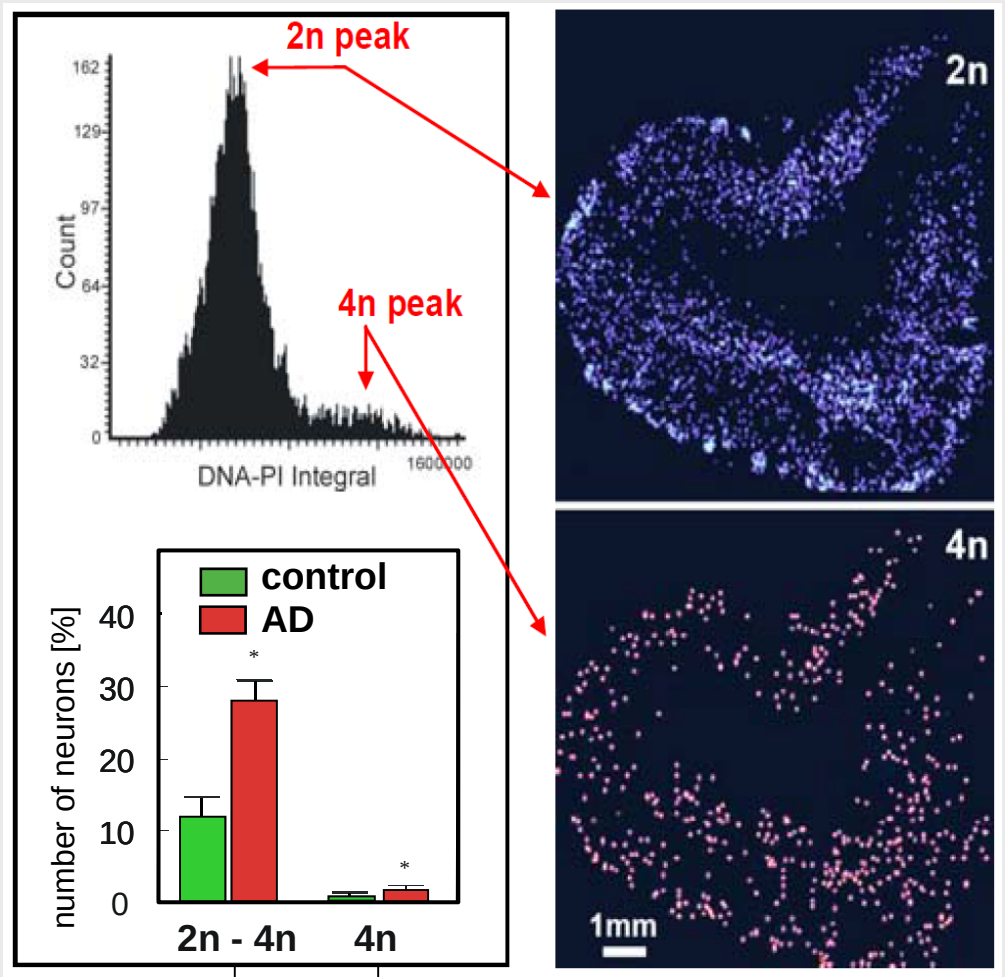




Mosch et al. J.Neurosci. 2007; Arendt et al. Am.J.Pathol. 2010

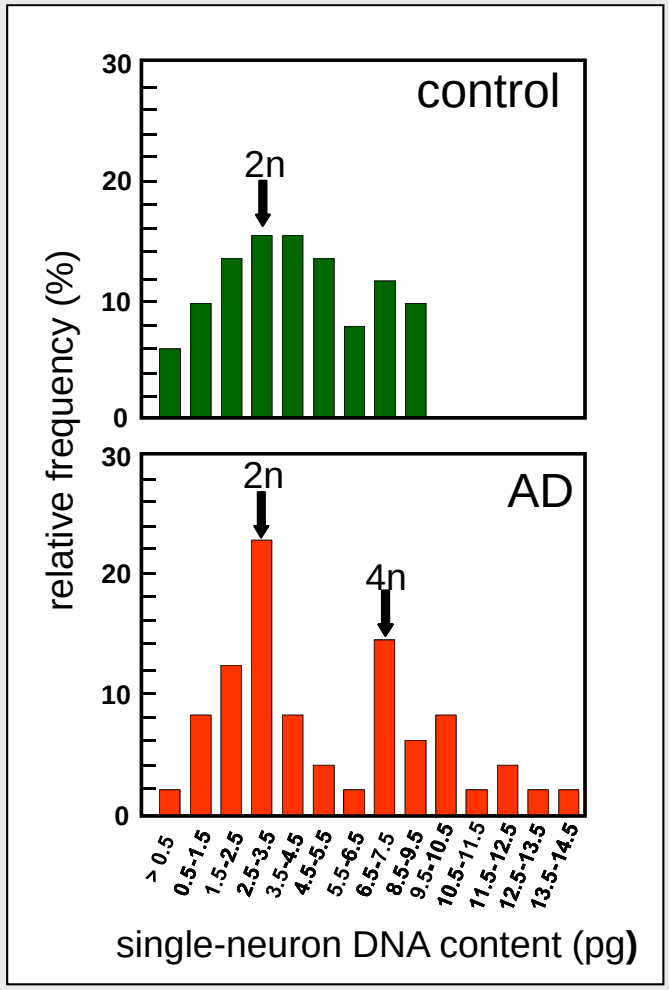
AD: 50% increase in single cell DNA content

Slide based cytometry



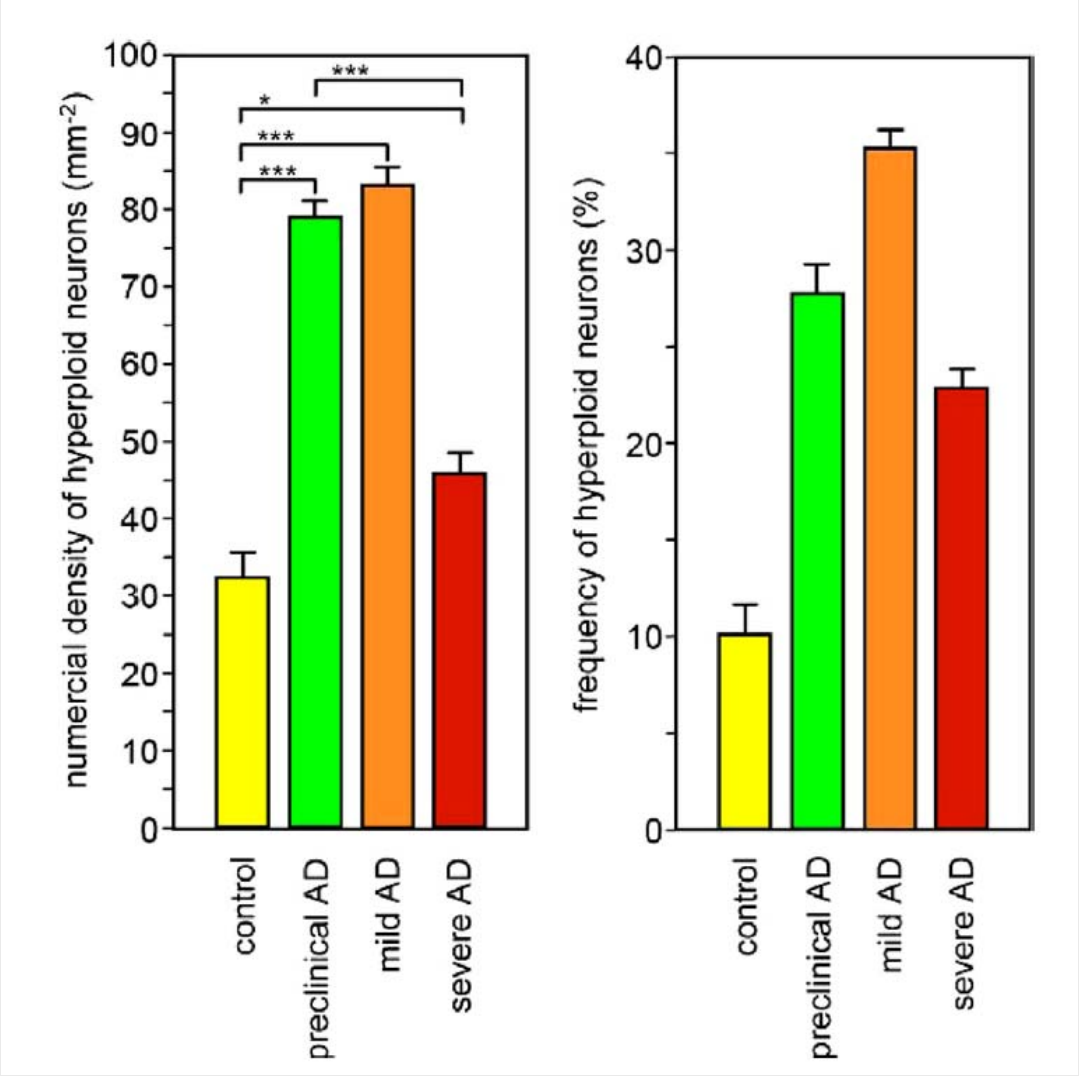
Control	12%	0.4%
AD	29%	1.1%

PCR amplification of alu repeats



Lenz et al. Progr.Biomed.Opt.Imaging 2004, 5322:146-56.
Mosch et al. Cytometry A. 2006, 69:135-8
Mosch et al. J. Neurosci. 2007, 27:6859-67
Arendt et al. Int. J.Mol.Sci. 2009, 10:1609-27

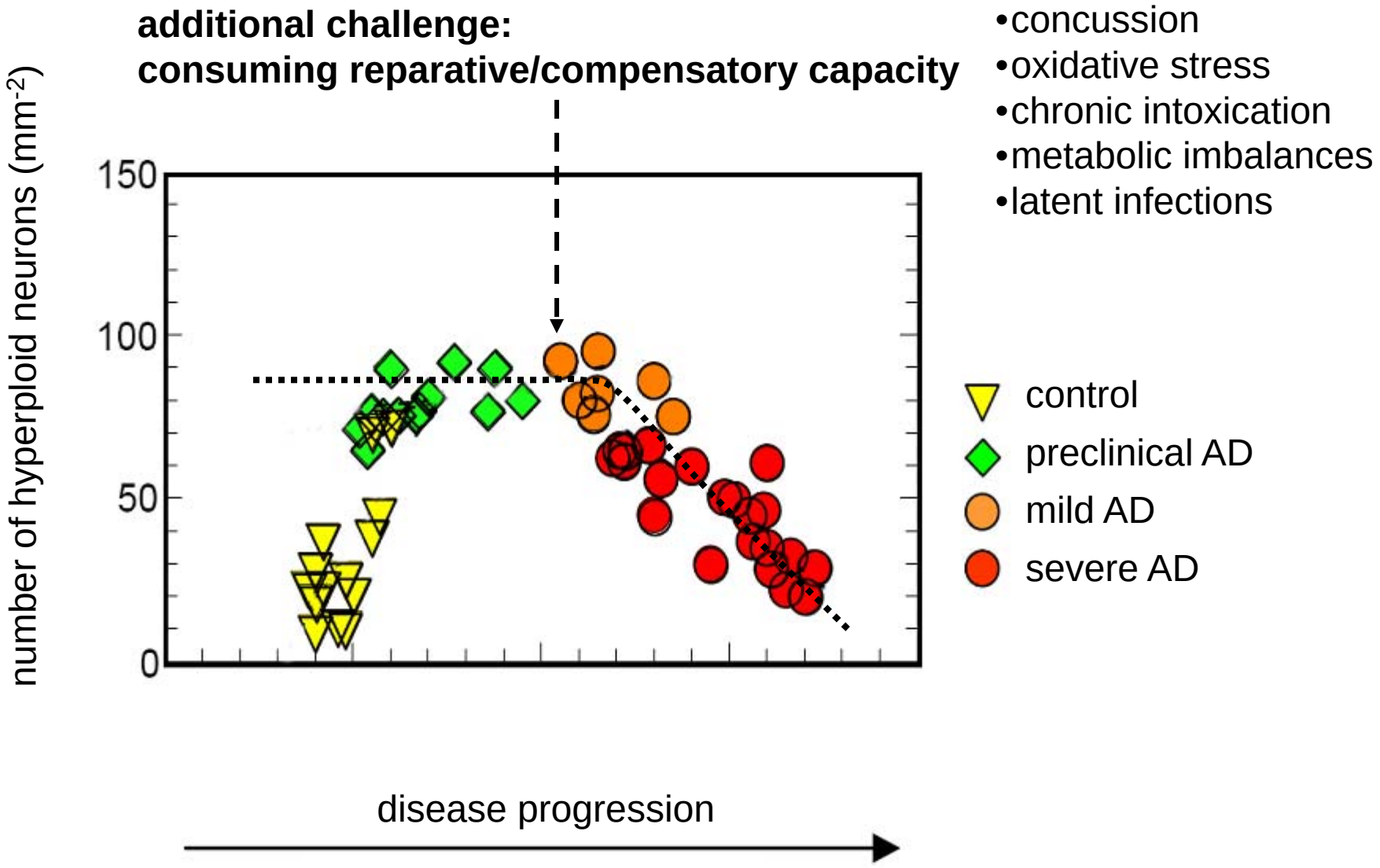
Hyperploidy is an early (preclinical) event



	control	preclinical AD	mild AD	severe AD
CDR	0	0	0.5	3
Braak	0	I-II B	III-IV B-C	V-VI C
CERAD	normal	possible	probable	definite
NIA	negative	low-intermediate	Intermed.	high

Arendt et al. Am.J.Pathol. 2010, 177: 15-20

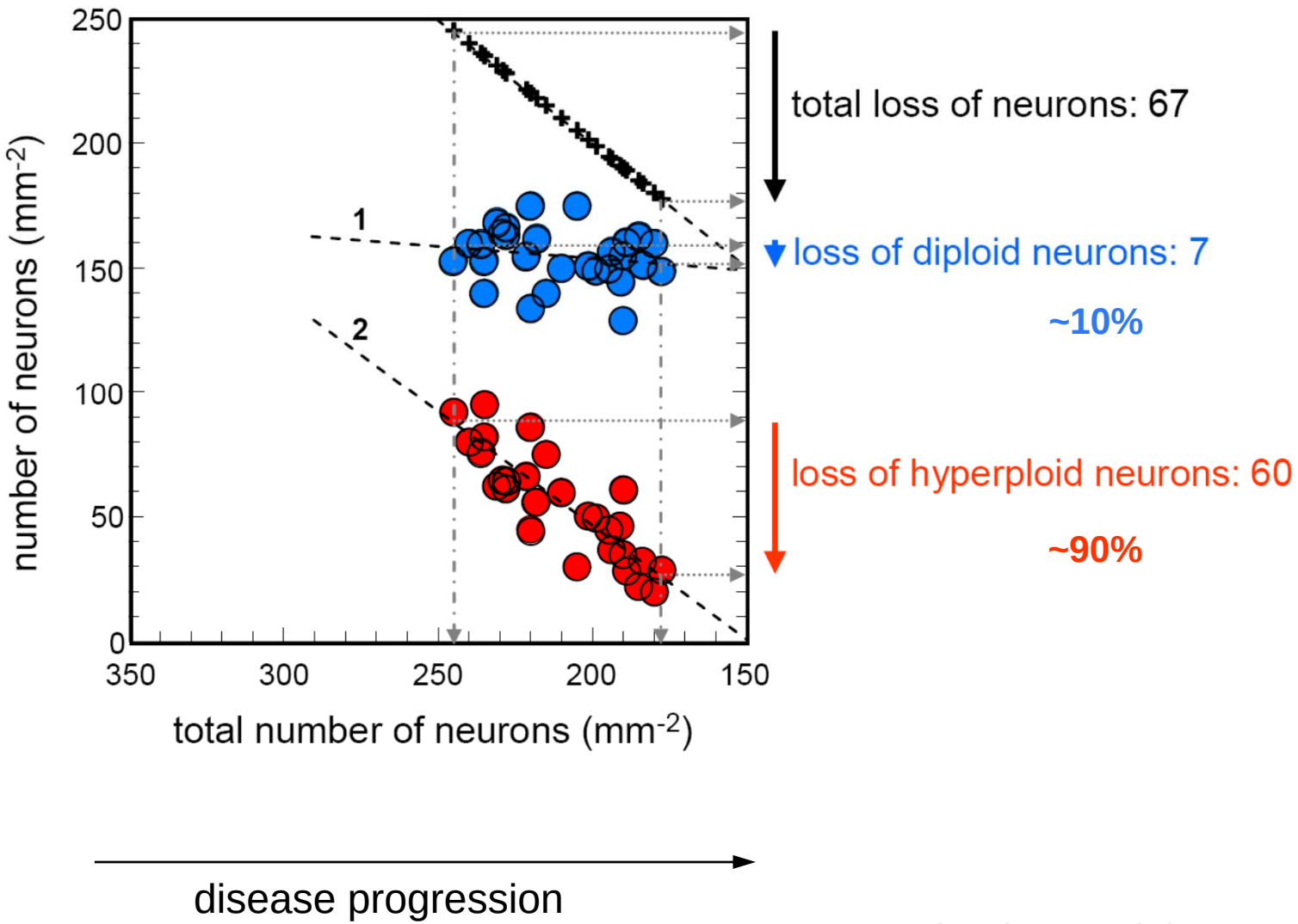
Hyperploidy occurs prior to cell death



Arendt et al. Am.J.Pathol. 2010, 177: 15-20

Selective cell death of hyperploid neurons

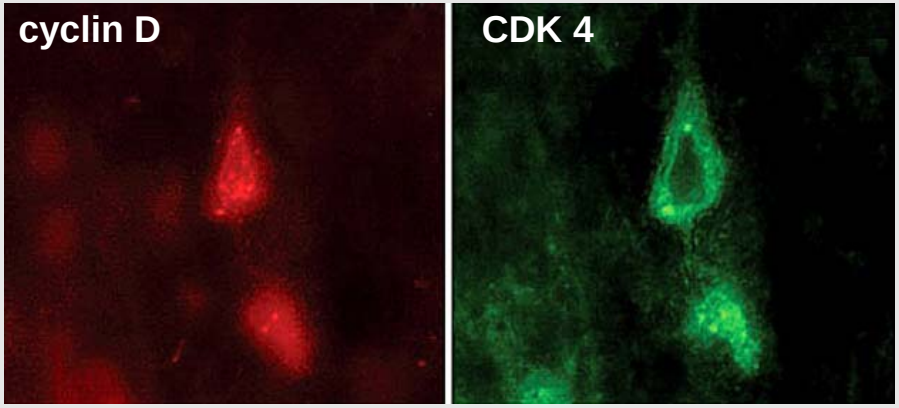
entorhinal cortex (n=28)



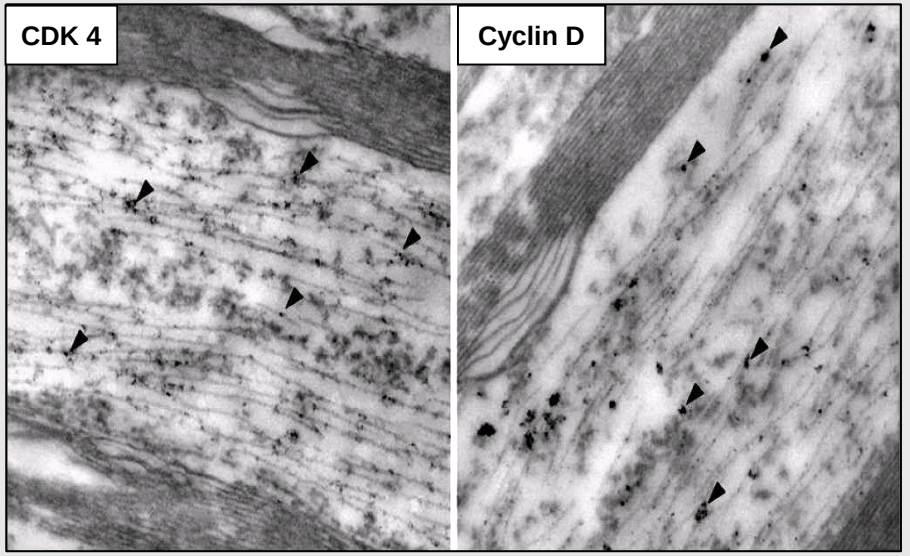
Arendt et al. Am.J.Pathol. 2010, 177: 15-20

Cell cycle proteins subserve alternative functions in differentiated neurons: regulation of synaptic plasticity

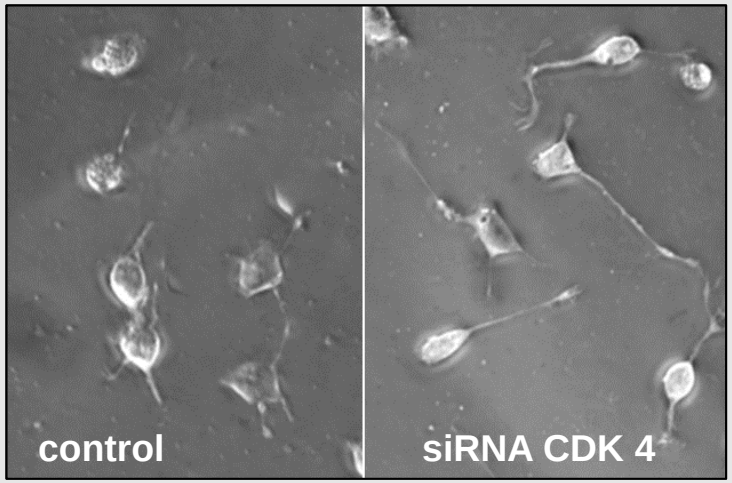
constitutive expression

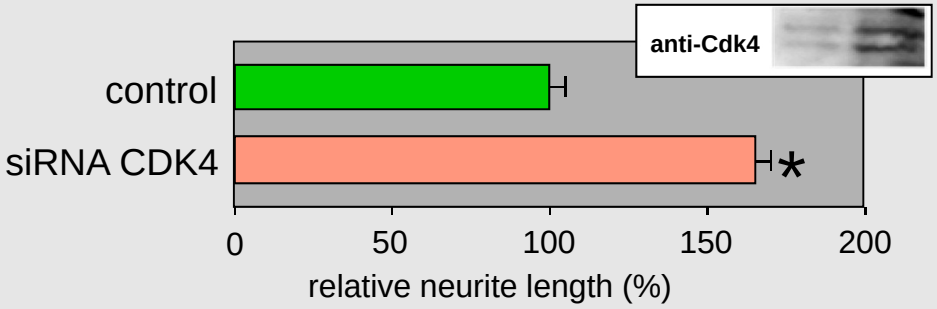


axonal localisation



CDK 4 regulates structural plasticity





Schmetsdorf et al. Cerebral Cortex (2007)
Schmetsdorf et al. Eur.J.Neurosci. (2009)

The dual functions of cell cycle regulators in neurons

“canonical cell cycle regulators”
(e.g. CDKs, cyclins, CDK-inhibitors …)

development

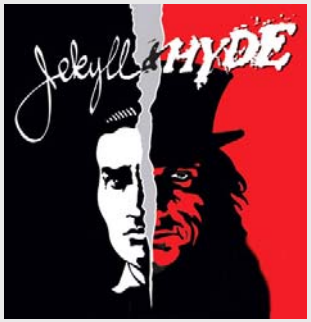
alternative effector pathways

adult

maturation (differentiation)

developmental switch

control of the cell cycle



control of synaptic plasticity

neurodegeneration (de-differentiation)

degenerative switch

'Dr. Jekyll & Mr. Hyde concept'

Is the **risk of a phylogenetic regression** based on the persistence of developmentally primitive aspects in a highly developed biological system.

non-neuronal dividing cells (e.g. fibroblasts)

loss of neighbouring cells

↓

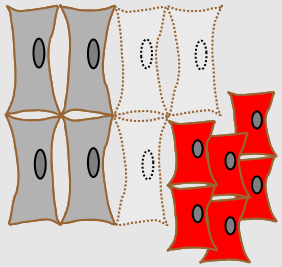
loss of contaction inhibition

↓

proliferation

↓

tissue repair



Cellular evolution:

synapse formation

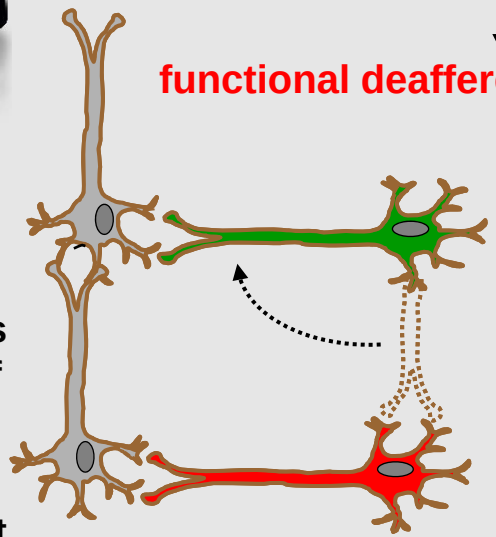
on the expense of the ability to proliferate

postmitotic neurons (non-dividing)

network re-organisation

↓

functional deafferentation



↓

re-activation of proliferation

↓

neuronal death

Regression:

loss of synaptic input is mis-regarded as loss of contact inhibition

triggers ancient programm of repair that involves cell cycle activation

Hibernation: a model for repeated cycles of synaptic regression

metabolic rate depression

⬇

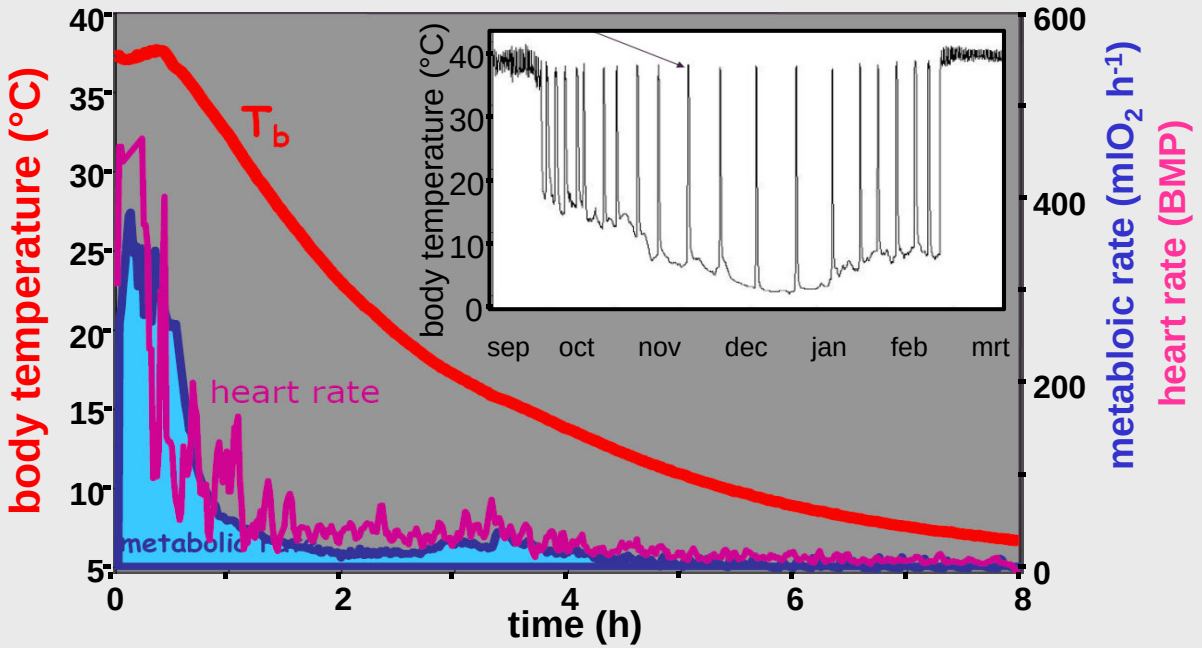
body temperature

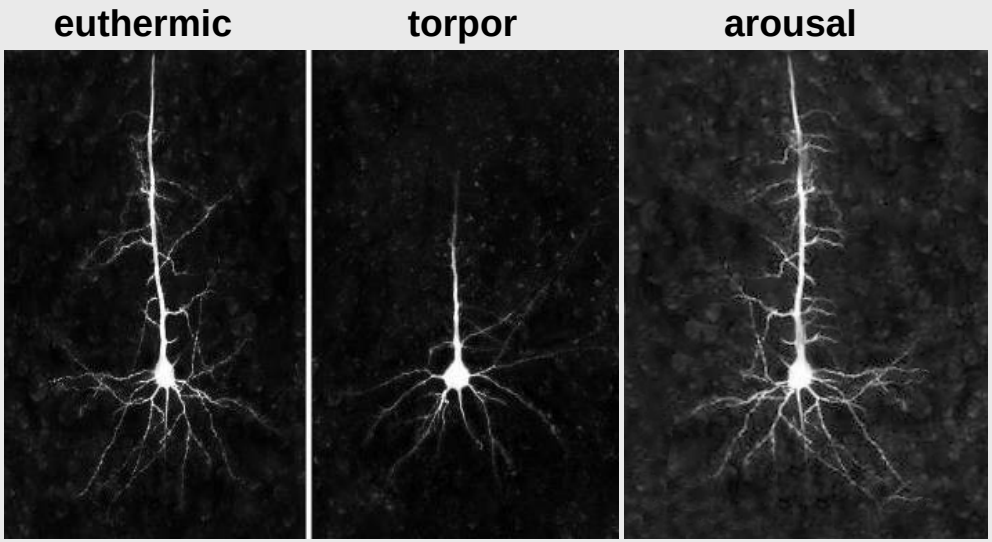
⬇

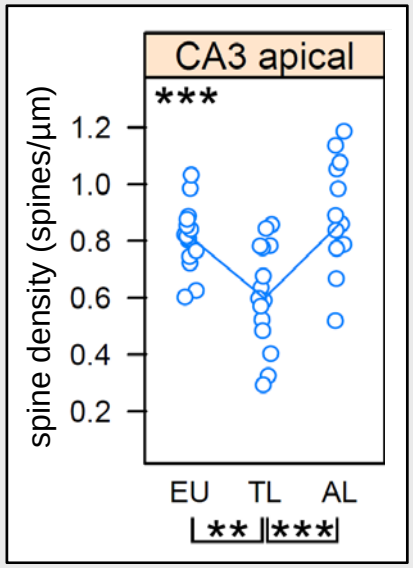
energy expenditure

⬇

reversible „brain shrinkage“

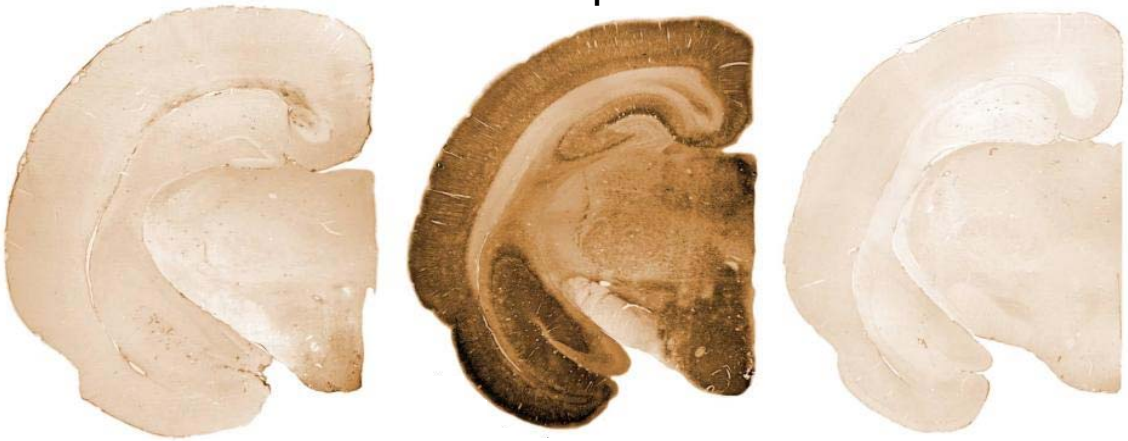






AD (PHF)-like phosphorylation of tau in hibernation

euthermic torpor arousal



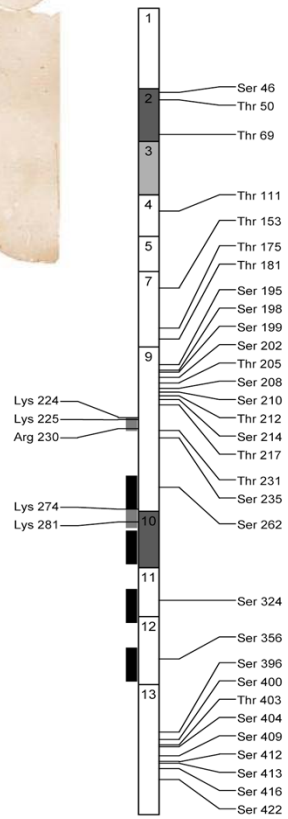
pS202+pT205 (AT8)

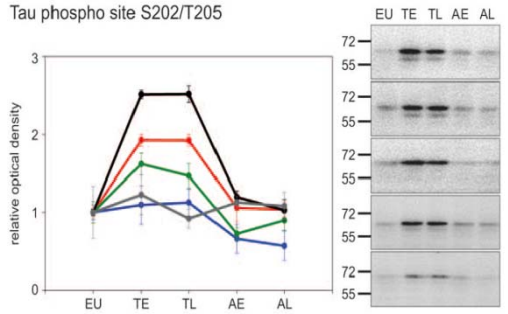
Brown bear *(Ursus arctos)*

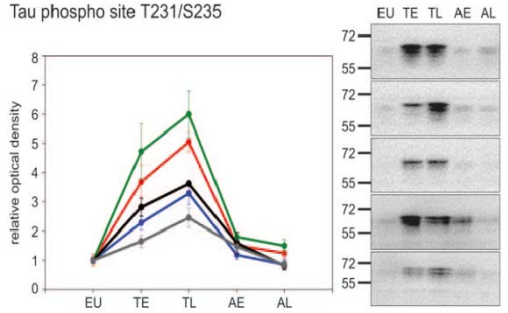
Hamster *(Cricetinae)*

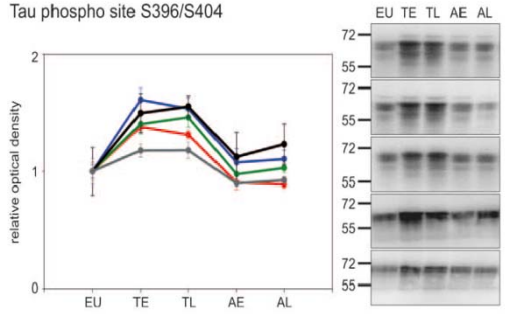
European ground squirrel

Arctic ground squirrel
(Spermophilus parryii)









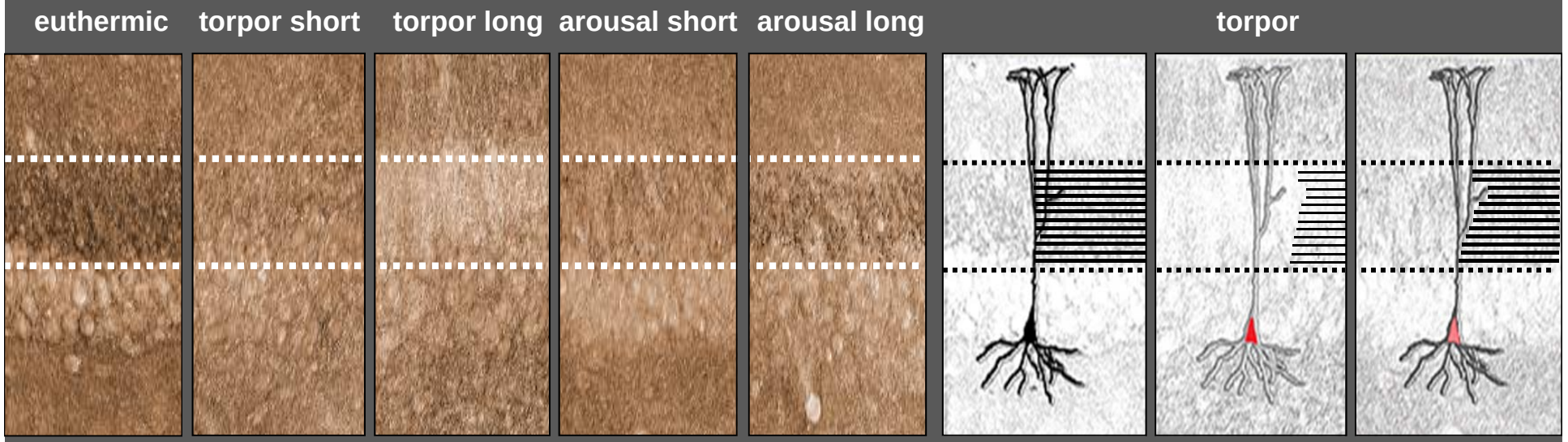
Neocortex
Hippocampus
Cerebellum
Midbrain
Brainstem

Linking metabolic depression (diabetes ?) to AD-type pathology

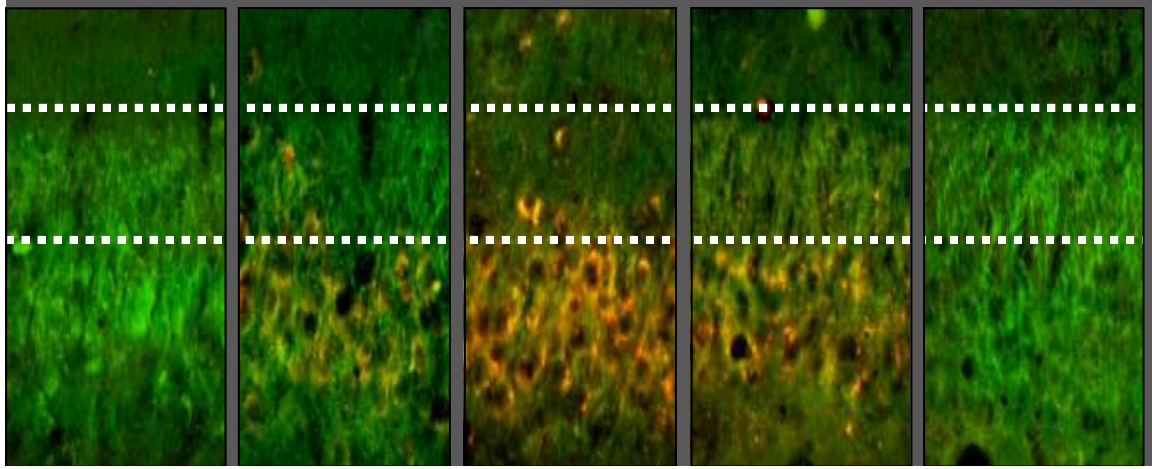
Arendt et al. J.Neurosci. (2003)
Härtig et al. Eur.J.Neurosci. (2007)
Stieler et al. (2008), Stieler et al. PlosOne (2011)

Accumulation of PHF-tau at postsynaptic sites coincides with synaptic detachement of excitatory afferentation

synaptophysin (stratum lucidum): mossy fibre input



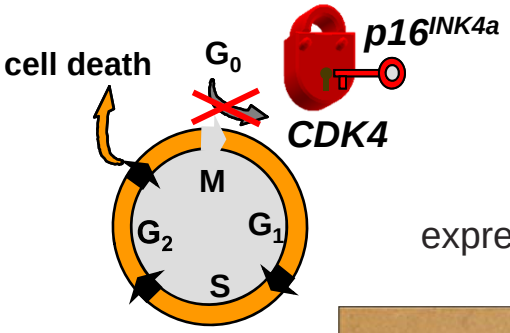
MAP 2 (green) / **PHF-tau**: AT8 (red)



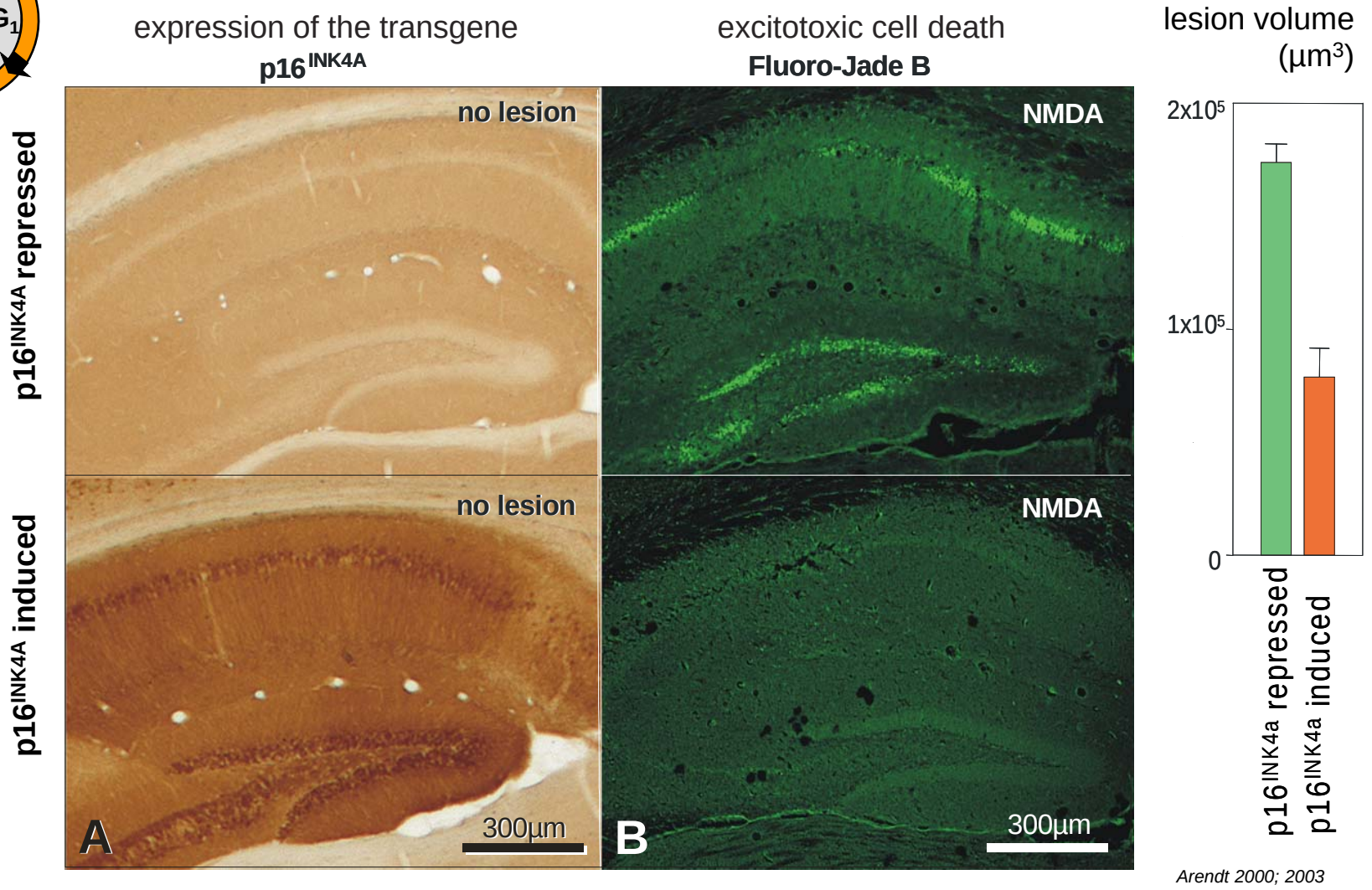
synaptic detachement

gradual re-appearance of synaptic afferentation

Blocking cell cycle activation by p16^{INK4A} is neuroprotective



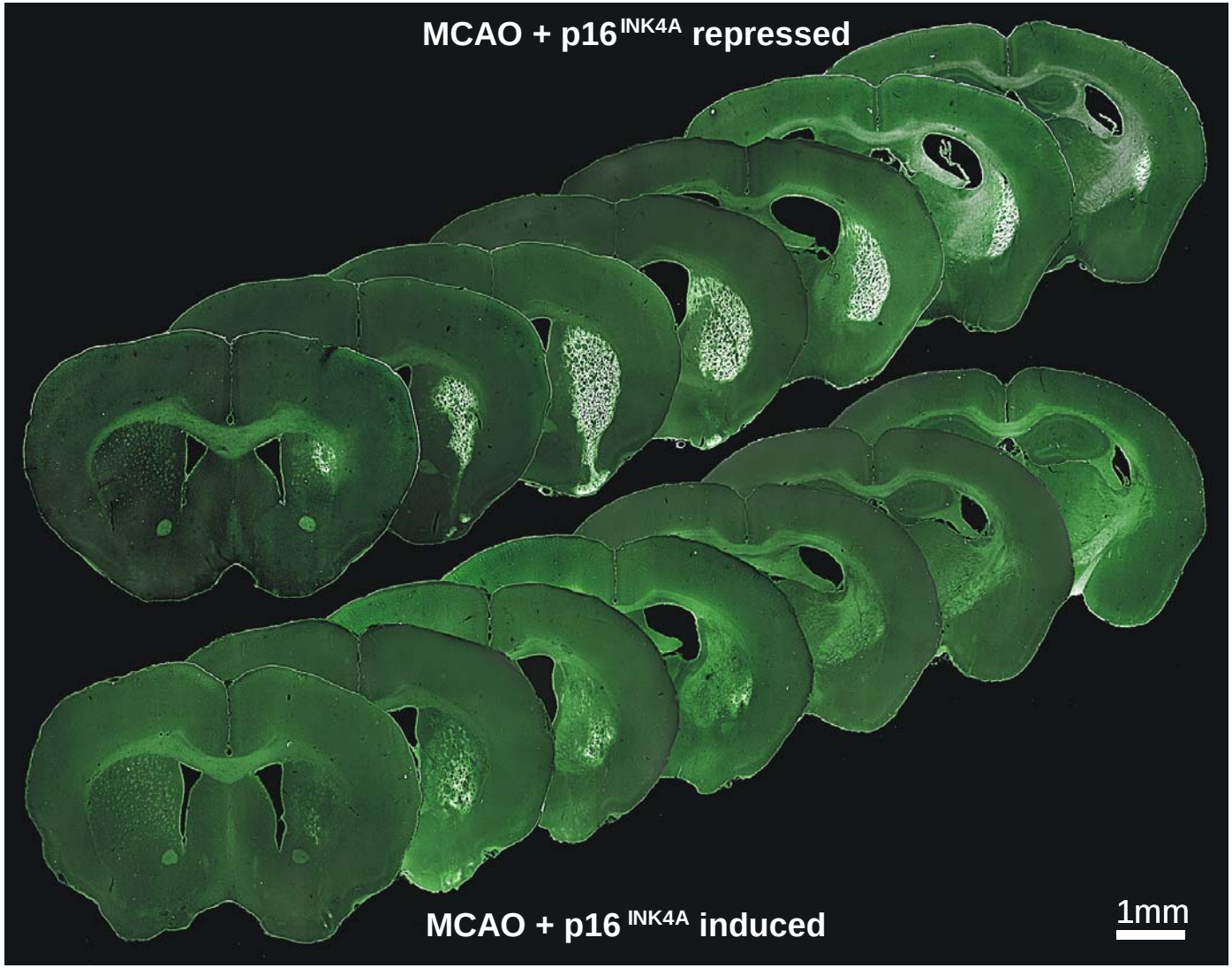
conditional (tet), neuron-specific (CamKII) expression of p16^{INK4A} protects against NMDA- induced cell death

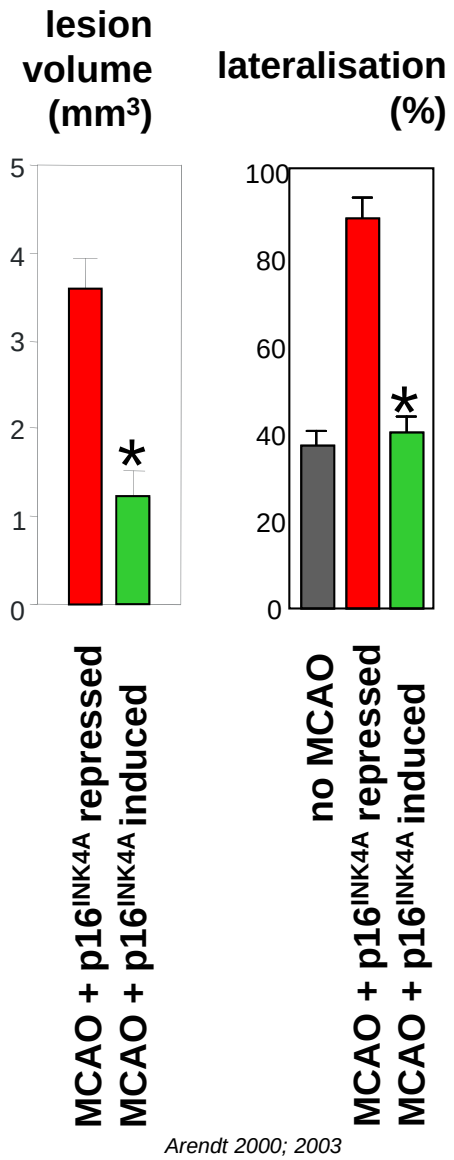


Arendt 2000; 2003

Expression of p16^{INK4a} as universal mechanism of neuroprotection

ischemic cell death (middle cerebral artery occlusion; MCAO)

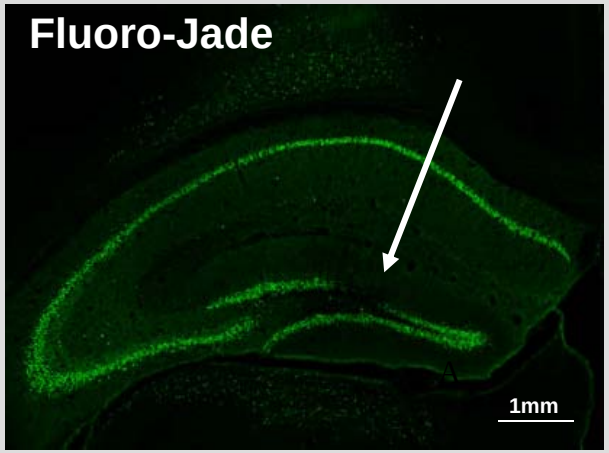


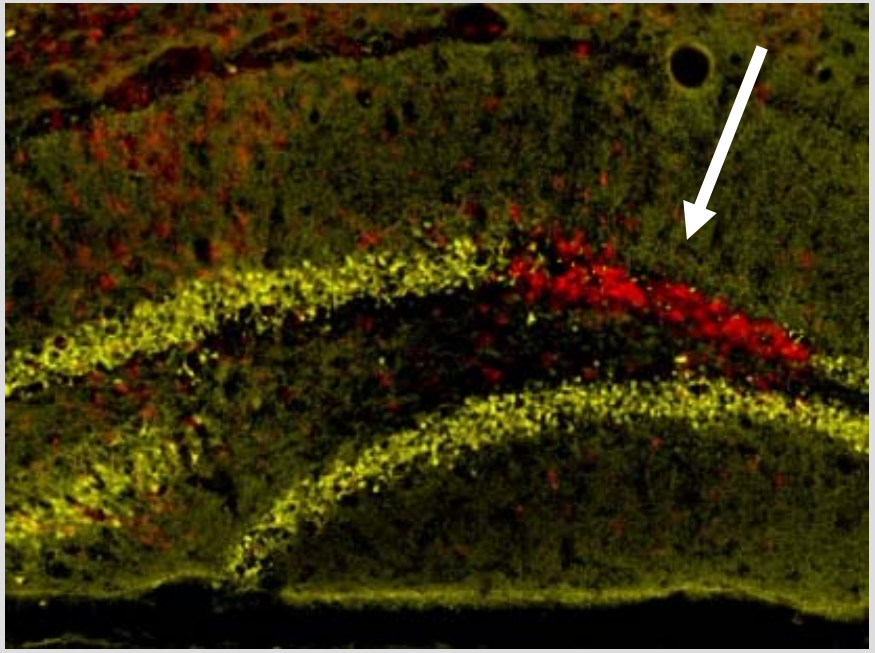


Arendt 2000; 2003

Our vision: neuroprotection by gen-transfer of $p16^{INK4A}$

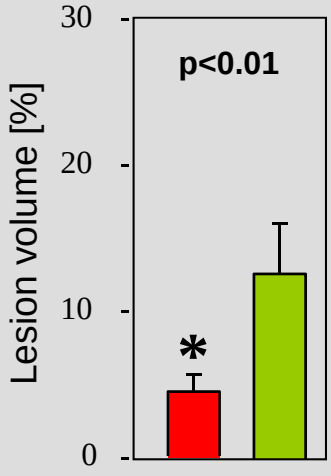
$p16^{INK4A}$ injection side

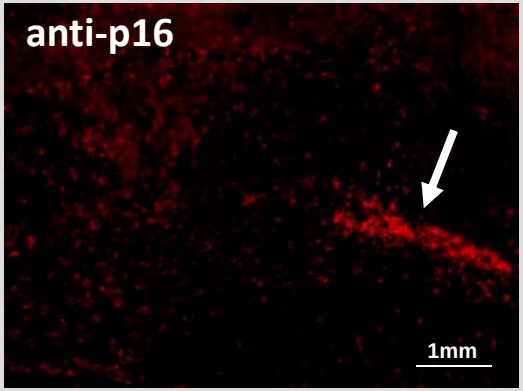


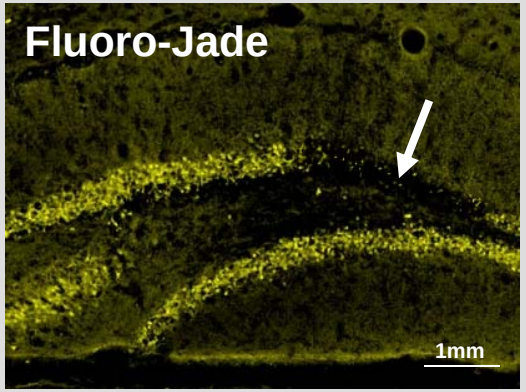


anti-p16

NMDA-induced neurone death (Fluoro-Jade)



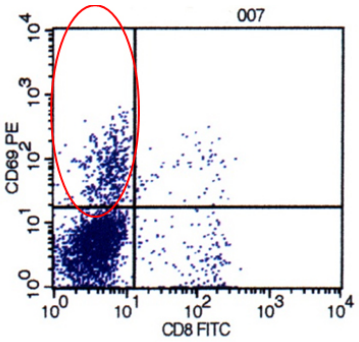




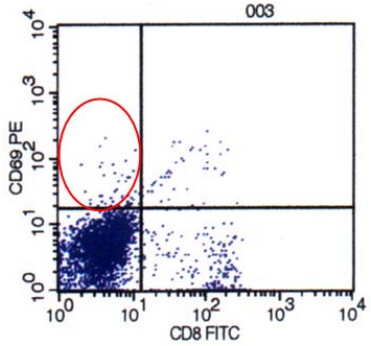
Cell cycle dysregulation on peripheral lymphocytes as diagnostic blood biomarker of AD

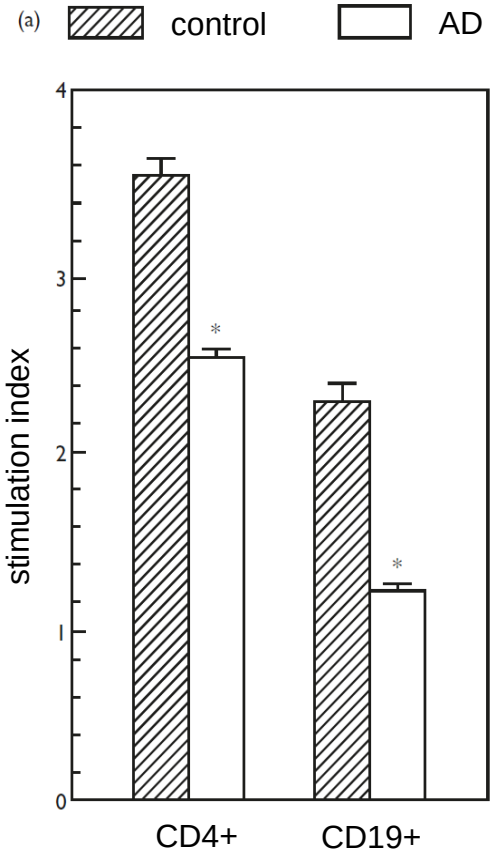
Stieler et al. Neuroreport (2001) 12:3969-3972

Normal subject

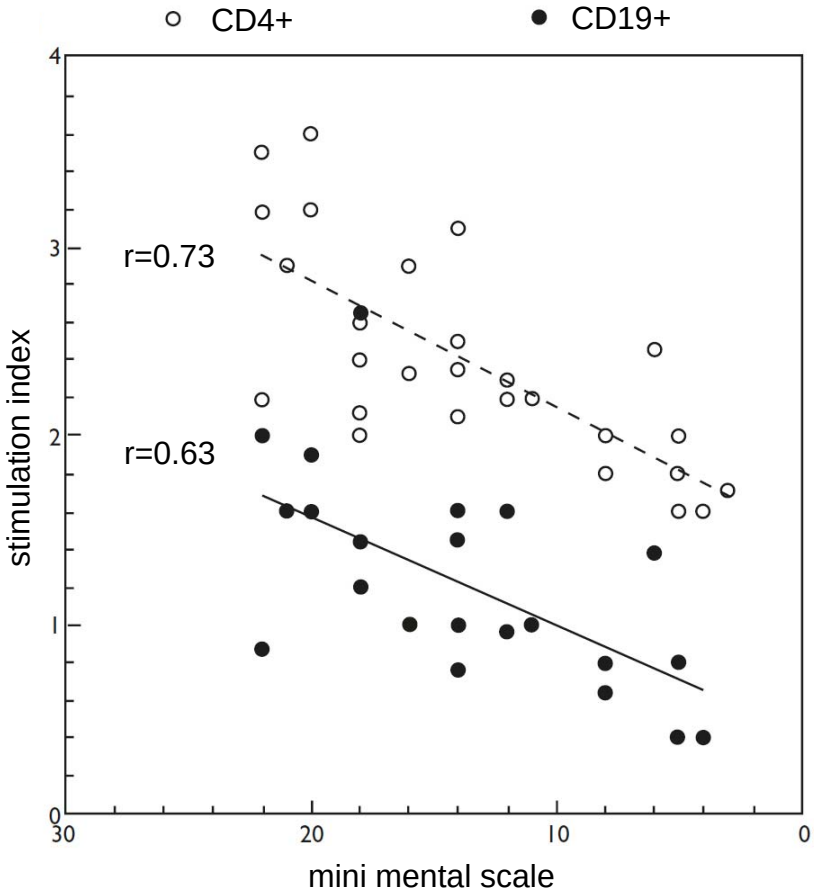


AD - patient





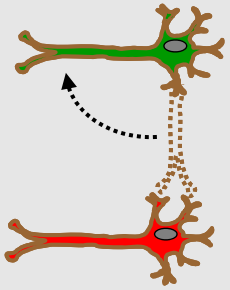
LymPro Test®



AD: n=43; n=27;
MCI: n=14;
control: n=18 n=45

CD69 expression after mitogenic stimulation (PHA, 12µg/ml)
FACscan flow cytometry

The evolutionary '**Dr. Jekyll & Mr. Hyde concept**' of AD and emerging diagnostic & therapeutic targets

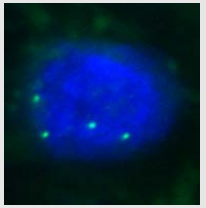


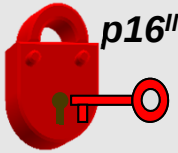
synaptic detachement &
abnormal synaptic turnover

amyloid cascade

phylogenetic
regression

LymPro Test® → cell cycle activation & partial DNA replication





gentherapy

second challenge –
consuming reparative capacity

neuronal death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