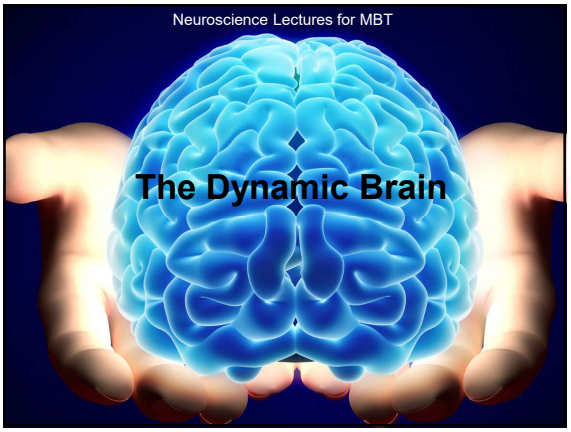
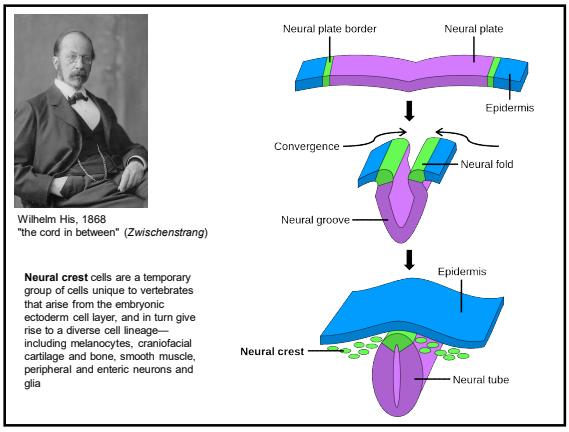
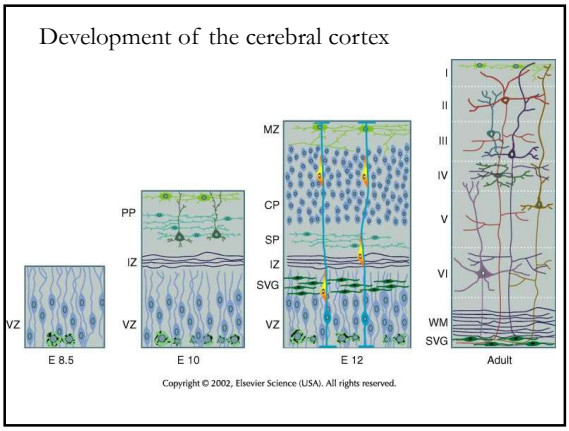
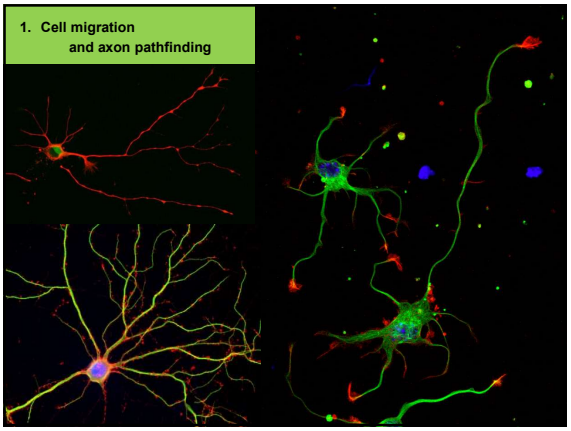


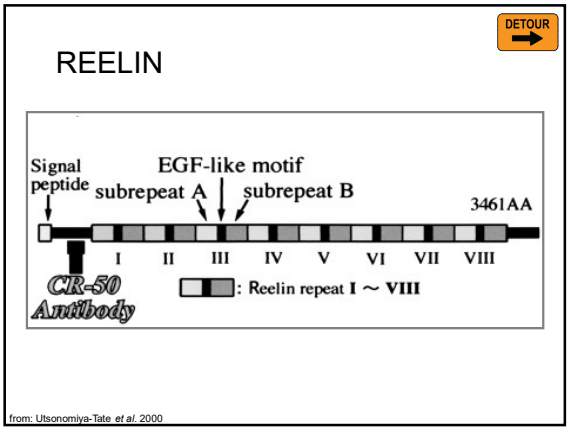


Index

1. Cell migration and axon pathfinding
2. Cell death
3. Synaptic pruning
4. Neuroplasticity
5. Adolescence
6. Stress and the brain
7. The ageing brain



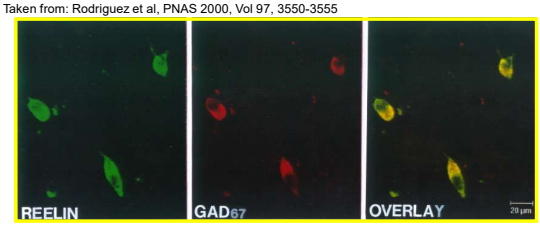




Reelin is Expressed in GABAergic Neurons in Layers I, II and III of the Baboon PFC

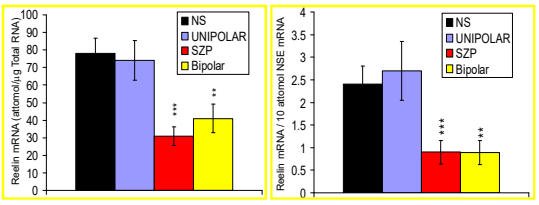
DETOUR

Taken from: Rodriguez et al, PNAS 2000, Vol 97, 3550-3555



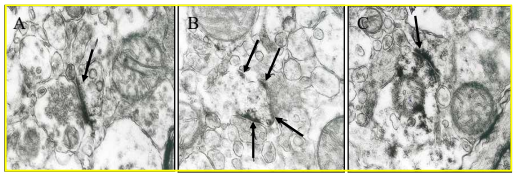
Reelin expression is reduced in prefrontal cortex of schizophrenia patients

DETOUR



**p<0.01; ***p<0.001 - ANOVA followed by Bonferroni post hoc analysis

Electron Micrographs of Reelin-immunostaining in Thin Sections Taken from Layers I-II of Prefrontal Cortex Human Brain with 6 Hours PMI



Mag. = 50,000X

DETOUR

Criteria for assessing the validity of animal models of human behavioral research

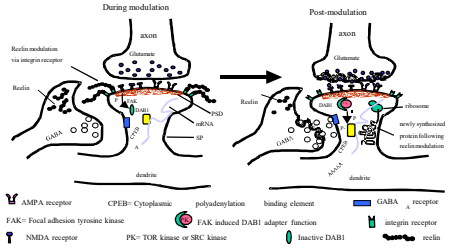
Face validity: perceived resemblance between the animal model and the situation or process in humans (qualitative)

Predictive validity: accuracy with which the animal model predicts the course or outcome of the human phenomenon (empirical)

Construct validity: the extent to which both the animal model and the human phenomenon can be explained (e.g. in terms of origin, underlying mechanisms, and function) by the same theory (theoretical)

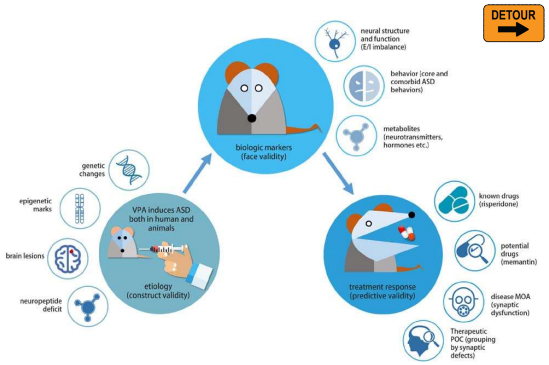
P. Willner (1984). The validity of animal models of depression. Psychopharmacology

Integrin Stimulation by Reelin Constitutive Release: Putative Modulation of Dendritic Resident mRNA Translation



DETOUR

DETOUR



DETOUR

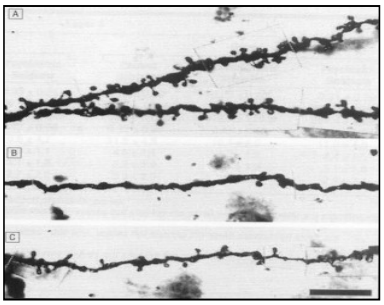
Can we really model in mouse dissociative thinking?

The endophenotype concept in psychiatry: Gottesman and Gould

The concept of endophenotypes, measurable components unseen by the unaided eye along the pathway between disease and distal genotype, has emerged as an important concept in the study of complex neuropsychiatric diseases. Endophenotypes may be neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological (including configured self-report data) in nature. This concept has gained attention especially in the field of complex diseases.

Gottesman, II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry 2003; 160: 636-645.

Reduced spine density in prefrontal cortex pyramidal neurons of schizophrenia patients



DETOUR

A: non psychiatric B and C: schizophrenia

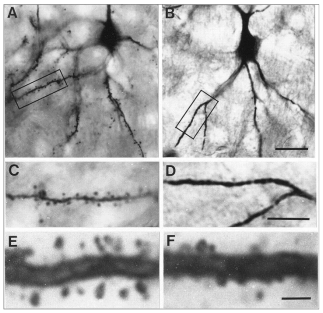
Glantz et al 2000

Photo courtesy of Mouse Mutant Resource at The Jackson Laboratory. http://www.jax.org/mmr/index.html J:110244

DETOUR

Relnrl/Relnrl mice exhibit an ataxic gait, dystonic posture and tremors starting around 2 weeks of age. These mutants are incapable of maintaining their hindquarters upright and often fall over during locomotor activity.

Golgi staining of pyramidal neurons (layer III) of wild type (A, C, E) and heterozygous reeler mice (B, D, F)



DETOUR

DETOUR

Genetic Background

B6C3Fe a/a-Reln^{rl}/J

Photo courtesy of Mouse Mutant Resource at The Jackson Laboratory http://www.jax.org/mmr/index.html J:110244

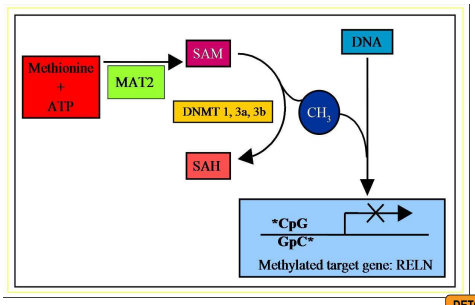
L-Methionine Induced Aggravation of Schizophrenia Symptoms *

No.	Age/ Sex	Diagnosis	Hospital years	Reaction to methionine **
1	60/F	Hebephrenic Schizophrenia	25	Toxic psychosis followed by acute schizophrenic symptoms
2	46/F	Hebephrenic Schizophrenia	10	Acute Schizophrenia symptoms
3	59/F	Schizophrenia	29	Non reactor
4	55/F	Schizophrenia	37	Non reactor
5	57/F	Schizophrenia	25	Become more suspicious, negativistic and withdrawal. Manifest persecutory delusion and auditory hallucination
6	51/M	Hebephrenic Schizophrenia	20	Auditory hallucination, paranoid delusion, withdrawal, thought block, lack of concentration
7	53/M	Catatonic Schizophrenia	16	Marked increase of symptoms
8	55/M	Paranoid Schizophrenia	27	Non reactor
9	58/M	Schizophrenia	36	Non reactor
10	51/M	Paranoid Schizophrenia	14	Aggravated
11	49/M	Catatonic Schizophrenia	12	Exaggerated negativism, withdrawal

DETOUR

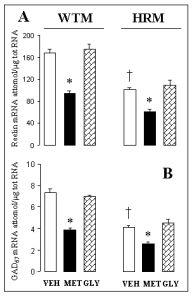
* Summary from Antun et al. (11).
** 20 g of L-amino acid daily during the first week and 10 g daily during the second week.

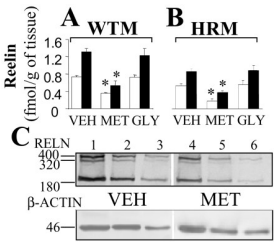
Working hypothesis: Methionine epigenetic effect



DETOUR

Protracted methionine administration* reduced reelin and GAD_{67} expression in mouse frontal cortex



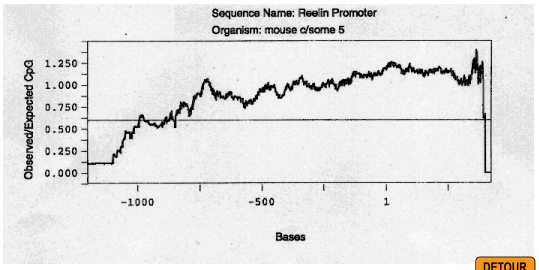


*p<0.05 *vs.* VEH

*MET 6.6 mmol/kg s.c. twice daily 15 days; GLY 13.2 mmol/kg

DETOUR

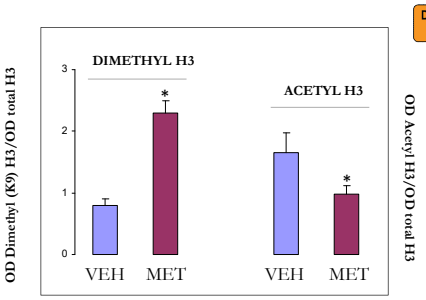
Strctural analysis of reelin promoter in mouse reveals a CpG island



DETOUR

Protracted methionine administration § increased methyl-H3 histone content in mouse frontal cortex

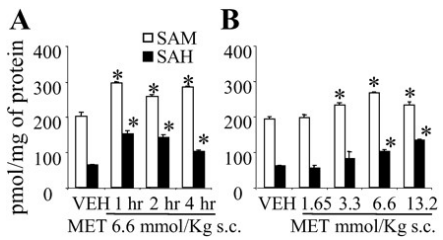
DETOUR



§MET 6.6 mmol/kg s.c. twice daily 15 days

*p<0.05

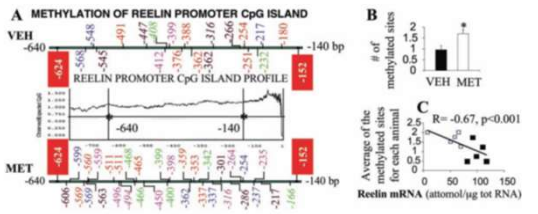
Methionine administration increases SAM and SAH in mouse frontal cortex



*p<0.05 *vs.* VEH

DETOUR

Protracted methionine administration § increased reelin promoter methylation in mouse frontal cortex



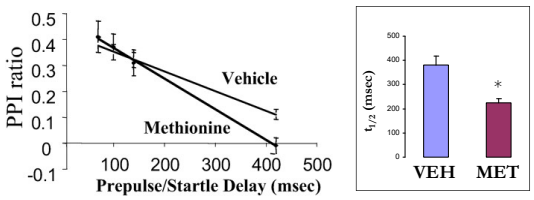
§MET 6.6 mmol/kg s.c. twice daily 15 days

DETOUR

Protracted methionine administration facilitates the extinction of the inhibitory reflex induced by the pre-pulse

(PREPULSE INHIBITION OF STARTLE, PPI)

MET 6.6 mmol/kg s.c. twice daily for 15 days



$n = 7$, mean ± SE. *p<0.001, Student's t-test

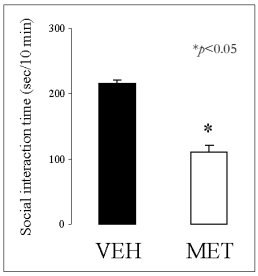
DETOUR

VPA prevents schizophrenia-related endophenotypes elicited by methionine administration

	Reelin promoter methylation	Reelin and GAD67 mRNA	Reelin protein	Alterations of sensory gating and social interaction
MET	↑	↓↓	↓	yes
VPA + MET	↔	⇅	↔	no

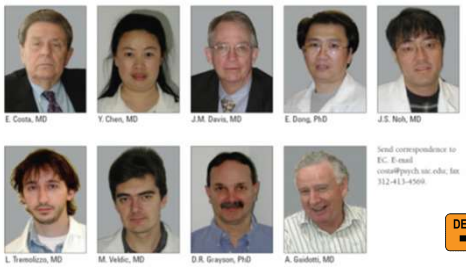
DETOUR

Social interaction decreases in methionine treated mice



MET 6.6 mmol/kg s.c. twice daily for 15 days

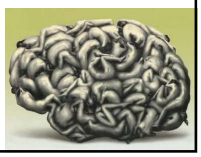
DETOUR



DETOUR

REELIN and schizophrenia: a disease at the interface of the genome and the epigenome. Costa E et al. Mol Interv. 2002 Feb;2(1):47-57.

Thanks for your attention!



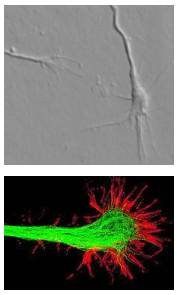
The epigenetic mouse model recapitulates some major endophenotypes associated to schizophrenia

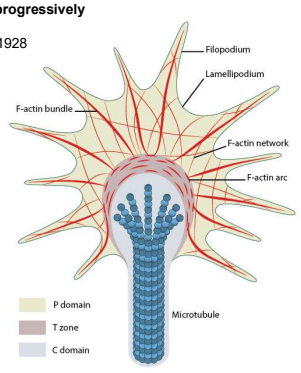
	Reelin promoter methylation	Reelin and GAD67 mRNA	Reelin protein	Alterations of sensory gating and social interaction
Epigenetic mouse model	↑	↓↓	↓	yes
Schizophrenia patients	?↑	↓↓	↓	yes

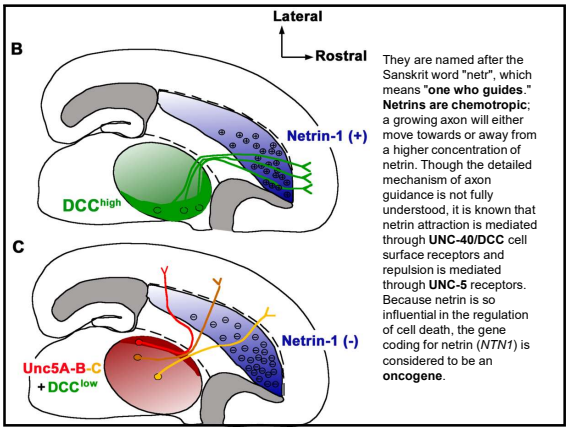
DETOUR

'At first, many imperfect connections are formed, and many errors of distribution occur … But these incongruences are progressively corrected.'

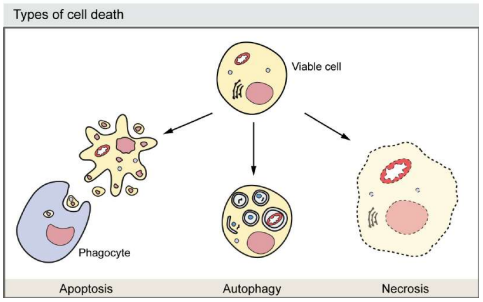
Santiago Ramón y Cajal, 1928







They are named after the Sanskrit word "netr", which means "**one who guides**." **Netrins are chemotropic**; a growing axon will either move towards or away from a higher concentration of netrin. Though the detailed mechanism of axon guidance is not fully understood, it is known that netrin attraction is mediated through **UNC-40/DCC** cell surface receptors and repulsion is mediated through **UNC-5** receptors. Because netrin is so influential in the regulation of cell death, the gene coding for netrin (*NTN1*) is considered to be an **oncogene**.

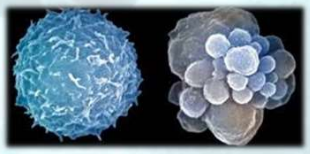


1. Cell migration and axon pathfinding

TAKE HOME MESSAGE:
– CHEMICAL CUES GUIDE MIGRATING NEURONS AND GROWING NERVE FIBRES –

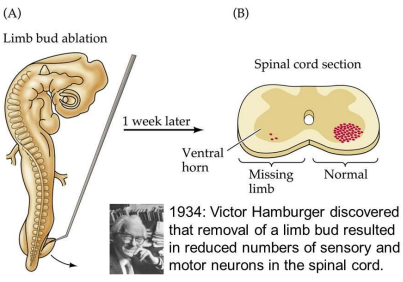
Apoptosis
programmed cell death

- Form of cell death, in which a 'suicide' program is activated within the cell, leading to:
- fragmentation of the DNA.
- shrinkage of the cytoplasm.
- membrane changes and cell death without lysis or damage to neighboring cells.



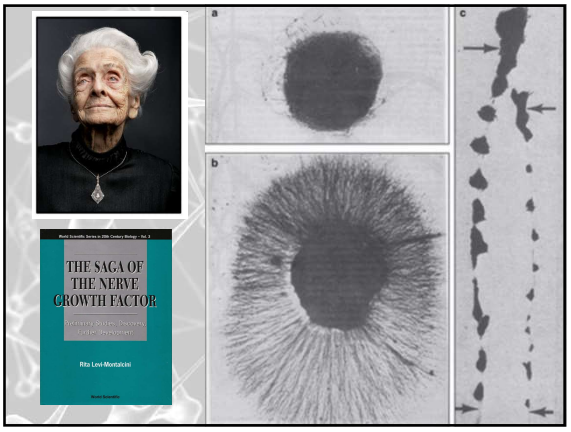
2. Cell death

By the time I was born, more of me had died than survived
Lewis Thomas, 1992



1934: Victor Hamburger discovered that removal of a limb bud resulted in reduced numbers of sensory and motor neurons in the spinal cord.

RLV '40s - repeats experiments: conclude that cell death occurs **not** because of lack of a signal that makes them divide and differentiate, but because of a lack a signal that promotes their growth.

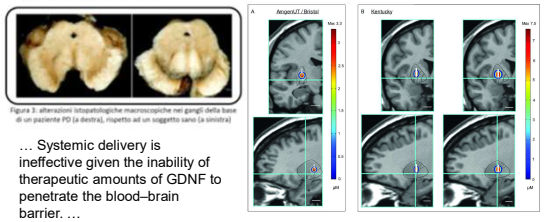


PD & glial derived neurotrophic factor (**GDNF**)

DETOUR

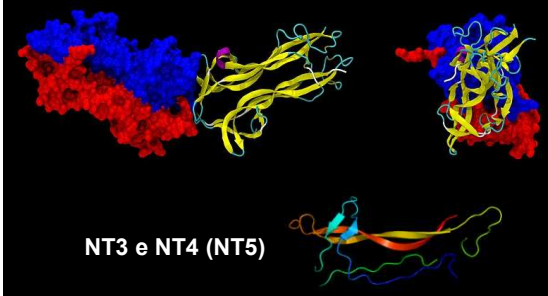
Convective delivery of glial cell line–derived neurotrophic factor in the human putamen

PAUL F. MORRISON, PH.D.,[1] RUSSELL R. LONSER, M.D.,[2] AND EDWARD H. OLDFIELD, M.D.[2]
[1]Division of Bioengineering and Physical Science, Office of Research Services; and [2]Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland



… Systemic delivery is ineffective given the inability of therapeutic amounts of GDNF to penetrate the blood–brain barrier. …

BDNF: brain-derived neurotrophic factor
- Memory and synaptic plasticity



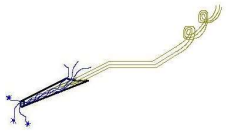
NT3 e NT4 (NT5)

Neurotrophic electrode

DETOUR

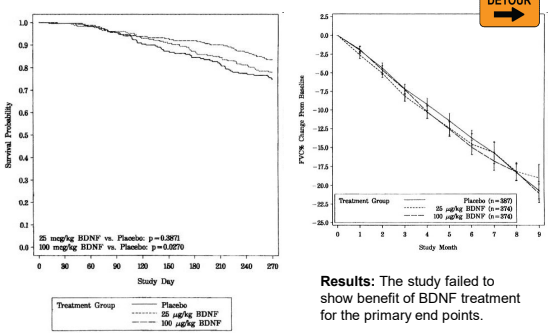
Philip Kennedy → 1996 Roy Bakay

…the device gets its name from the fact that it is coated with Matrigel and nerve growth factor to encourage the expansion of neurites through its tip.



A controlled trial of recombinant methionyl human BDNF in ALS: The BDNF Study Group (Phase III).
Neurology. 1999 Apr 22;52(7):1427-33.

DETOUR



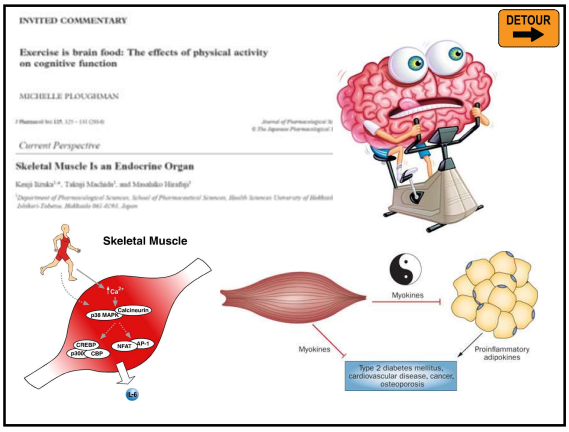
Results: The study failed to show benefit of BDNF treatment for the primary end points.

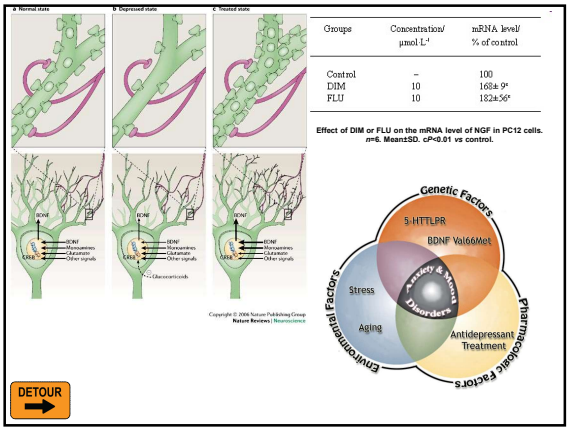
Research Articles

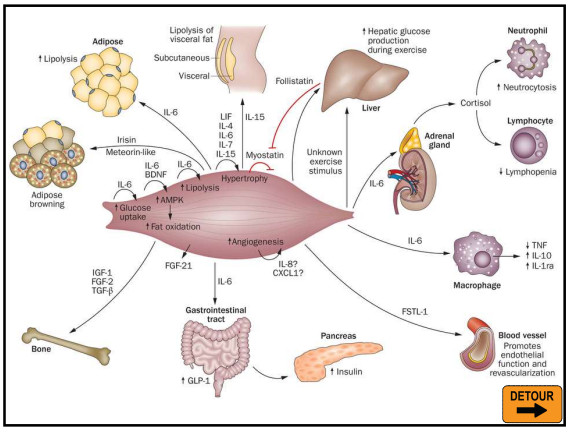
DETOUR

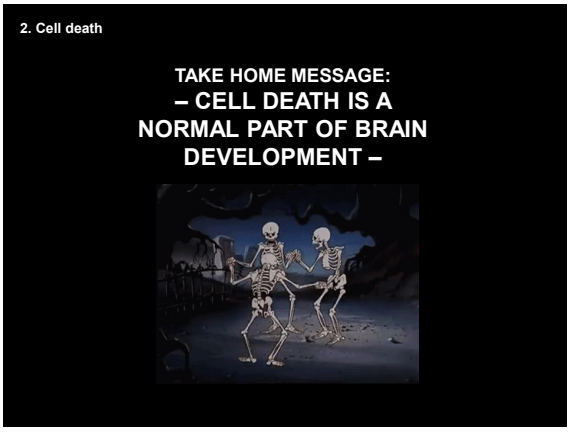
Enriched Environment Improves Motor Function and Increases Neurotrophins in Hemicerebellar Lesioned Rats

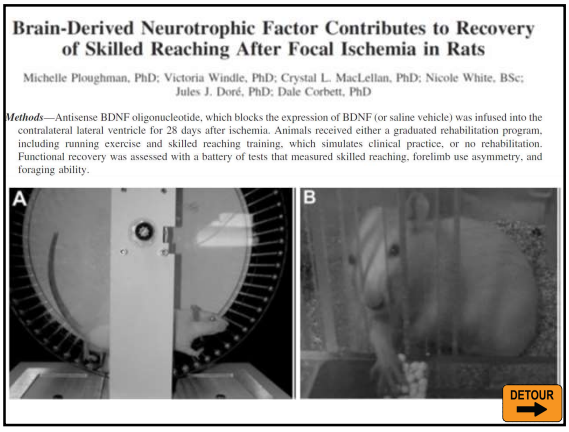
Francesca Gelfo, PhD[1,2], Debora Cutuli, PhD[1,3], Francesca Foti, PhD[1,3], Daniela Laricchiuta[1,3], Paola De Bartolo, PhD[1,3], Carlo Caltagirone, MD[1], Laura Petrosini, PhD[1,3], and Francesco Angelucci, PhD[1]

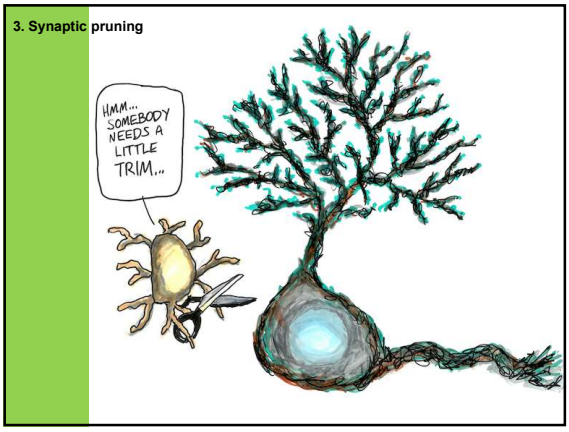

INVITED COMMENTARY
Exercise is brain food: The effects of physical activity on cognitive function
MICHELLE PLOUGHMAN
Current Perspective
Skeletal Muscle Is an Endocrine Organ
Skeletal Muscle
Myokines
Myokines
Proinflammatory adipokines
Type 2 diabetes mellitus, cardiovascular disease, cancer, osteoporosis
DETOUR

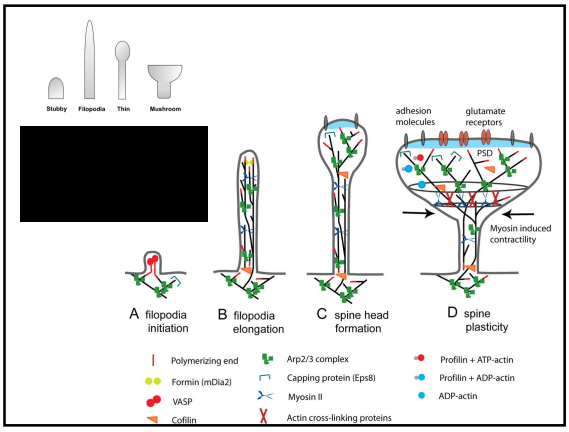

Groups
Concentration/ μmol·L⁻¹
mRNA level/ % of control
Control – 100
DIM 10 168± 9*
FLU 10 182±56*
Effect of DIM or FLU on the mRNA level of NGF in PC12 cells. n=6. Mean±SD. cP<0.01 vs control.
Genetic Factors
5-HTTLPR
BDNF Val66Met
Stress
Aging
Antidepressant Treatment
Environmental Factors
Pharmacologic Factors
DETOUR


Adipose
↑ Lipolysis
Lipolysis of visceral fat
Subcutaneous
Visceral
Follistatin
↑ Hepatic glucose production during exercise
Liver
Neutrophil
↑ Neutrocytosis
Cortisol
Lymphocyte
↓ Lymphopenia
Adrenal gland
Irisin
Meteorin-like
Adipose browning
IL-6
LIF
IL-4
IL-6
IL-7
IL-15
Myostatin
Unknown exercise stimulus
Hypertrophy
↑ Lipolysis
↑ AMPK
↑ Glucose uptake
↑ Fat oxidation
↑ Angiogenesis
FGF-21
IL-8?
CXCL1?
Macrophage
↓ TNF
↑ IL-10
↑ IL-1ra
IGF-1
FGF-2
TGF-β
Bone
Gastrointestinal tract
↑ GLP-1
Pancreas
↑ Insulin
FSTL-1
Blood vessel
Promotes endothelial function and revascularization
DETOUR


2. Cell death
TAKE HOME MESSAGE:
– CELL DEATH IS A NORMAL PART OF BRAIN DEVELOPMENT –


Brain-Derived Neurotrophic Factor Contributes to Recovery of Skilled Reaching After Focal Ischemia in Rats
Michelle Ploughman, PhD; Victoria Windle, PhD; Crystal L. MacLellan, PhD; Nicole White, BSc; Jules J. Doré, PhD; Dale Corbett, PhD
Methods—Antisense BDNF oligonucleotide, which blocks the expression of BDNF (or saline vehicle) was infused into the contralateral lateral ventricle for 28 days after ischemia. Animals received either a graduated rehabilitation program, including running exercise and skilled reaching training, which simulates clinical practice, or no rehabilitation. Functional recovery was assessed with a battery of tests that measured skilled reaching, forelimb use asymmetry, and foraging ability.
A
B
DETOUR


3. Synaptic pruning
HMM... SOMEBODY NEEDS A LITTLE TRIM...



Published in final edited form as:
Neuron. 2012 May 24; 74(4): 691–705. doi:10.1016/j.neuron.2012.03.026.

Microglia Sculpt Postnatal Neural Circuits in an Activity and Complement-Dependent Manner

Dorothy P Schafer[1], Emily K Lehrman[1,*], Amanda G Kautzman[1,*], Ryuta Koyama[1], Alan R Mardinly[2], Ryo Yamasaki[3], Richard M Ransohoff[4], Michael E Greenberg[2], Ben A Barres[2], and Beth Stevens[1]

'Through experience, the brain works to select, out of this mass of possible circuits, a very small subset.'
Jeff Lichtman, 2012

...while past work has focused on the role of these cells during disease, recent imaging studies reveal dynamic interactions between microglia and synaptic elements in the healthy brain.
Despite these intriguing observations, the precise function of microglia at remodeling synapses and the mechanisms that underlie microglia-synapse interactions remain elusive...

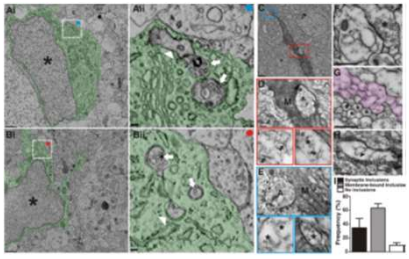
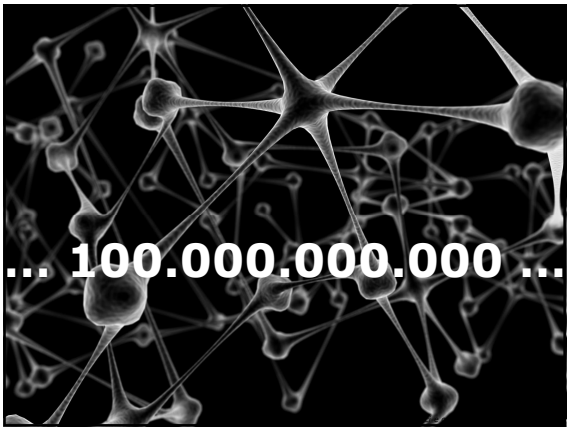
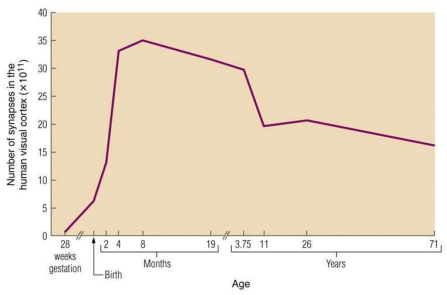
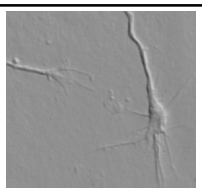


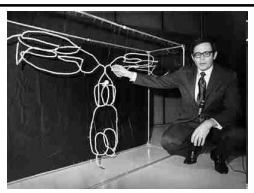
Figure 4. Microglia engulf presynaptic elements undergoing active synaptic pruning



Visual Synapses Peak at 1 Year of Age

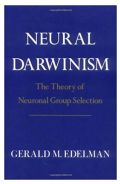




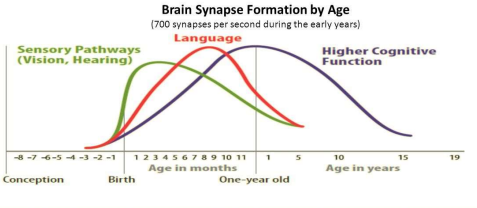


Gerald Edelman (1978)

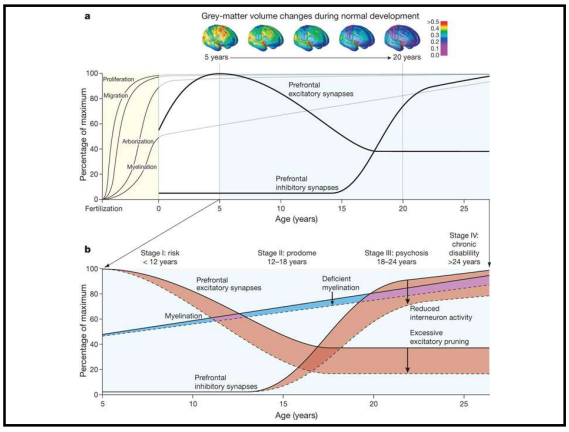
- The human genome alone cannot specify the whole complex structure of the brain
- Individual brains are wildly diverse
- "Neural Darwinism": application of Jerne's "selectional" theory of the immune system to the brain
- The brain develops categories by selectively strengthening or weakening connections between neural groups
- Neural groups "compete" to respond to environmental stimuli
- Each brain is different because its ultimate configuration depends on the stimuli that it encounters during its development

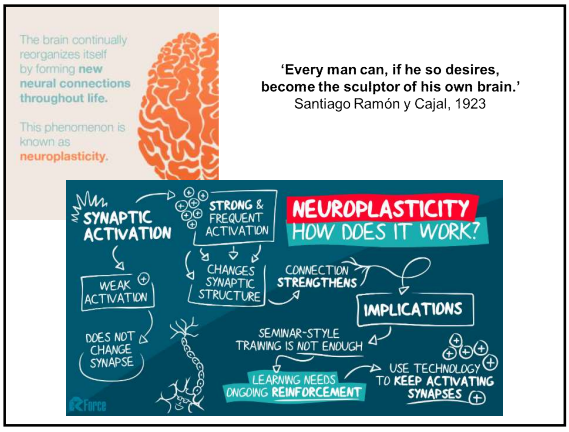


Major Milestones in Brain Development



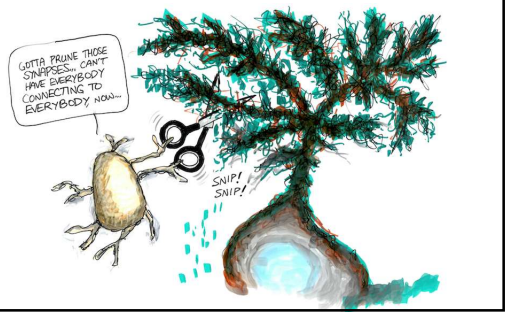
Penn Center on the States Home Visitation Campaign. (2000). [Image adaptation] Nelson, C.A. (2000). In Jack P. Shonkoff and Deborah A. Phillips (Eds.), From Neurons to Neighborhoods: The Science of Early Childhood Development (p. 188). Washington, DC: National Research Council and Institute of Medicine, National Academy Press.

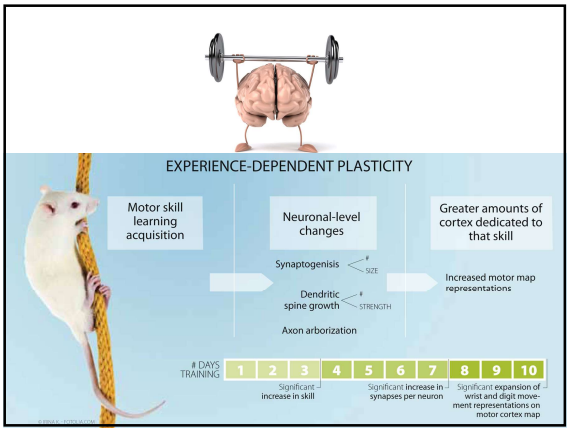




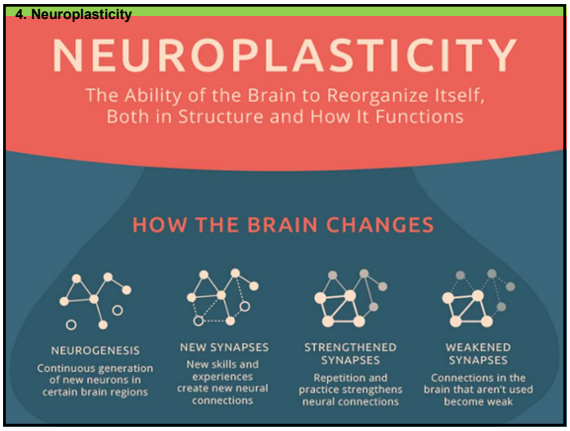
3. Synaptic pruning

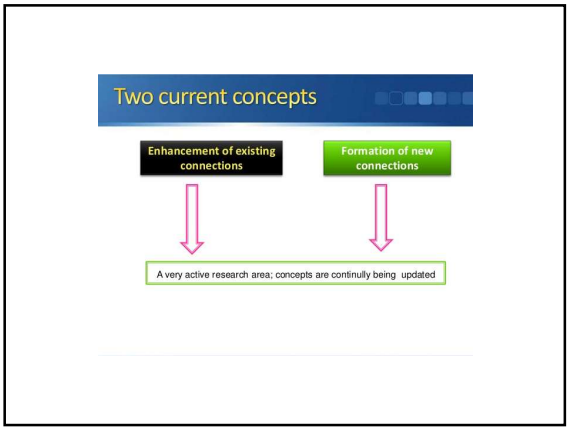
TAKE HOME MESSAGE:
– THE BRAIN ELIMINATES UNWANTED SYNAPSES –





4. Neuroplasticity

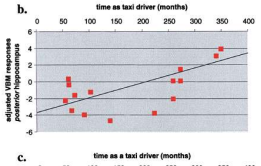


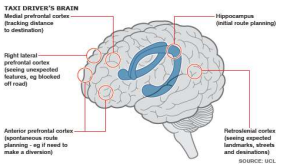


Types of Neuroplasticity

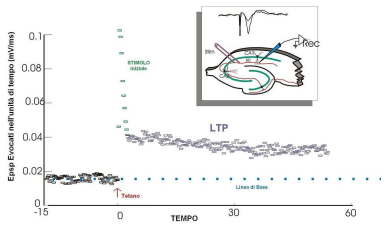
Type	Mechanism	Duration
1. *Enhancement of existing connections*		
A. Synapse development	Physiological	ms^{-1} to hours
B. Synapse strengthening	Biochemical	hours to days
2. *Formation of new connections*		
A. Unmasking	Physiological	minutes to days
B. Sprouting	Structural	days to months

Eleanor Maguire, UCL



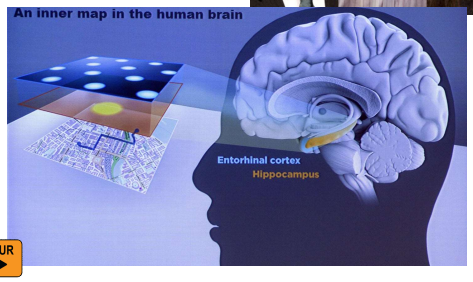


The **Ig Nobel** Prizes honor research that first make people **laugh**, and then make them **think**



long-term potentiation (**LTP**) is a persistent strengthening of synapses based on recent patterns of activity. These are patterns of synaptic activity that produce a long-lasting increase in signal transmission between two neurons. The opposite of LTP is long-term depression, which produces a long-lasting decrease in synaptic strength.

The Nobel Prize for physiology or medicine has been awarded to three scientists who discovered the brain's "GPS system".
UK-based researcher Prof John O'Keefe as well as May-Britt Moser and Edvard Moser share the award.



DETOUR

Historical Background

- Until 1970 : brain structure is relatively immutable in adulthood.

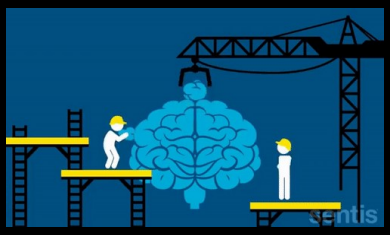
History Contd...

- David Hubel and Torsten Wiesel:
  - Study with kittens
  - The experiment involved sewing one eye shut and recording the cortical brain maps
  - the portion of the kitten's brain associated with the shut eye was not idle, as expected. Instead, it processed visual information from the open eye.
  - "... as though the brain didn't want to waste any 'cortical real estate' and had found a way to rewire itself."

1960s
1981 Nobel Prize

4. Neuroplasticity

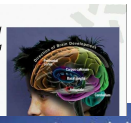
TAKE HOME MESSAGE:
– LIFE EXPERIENCES REORGANIZE THE BRAIN –



5. Adolescence

'The young are heated by nature as drunken men by wine.'
Aristotle, c. 350 BC

A teenager's brain "has a well-developed accelerator but only a partly developed brake."
Laurence Steinberg

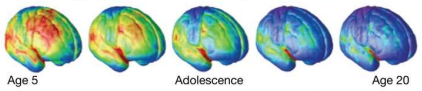


'Accelerating the intensity of emotional and motivational tendencies … is, metaphorically, like revving the engine without a skilled driver.'
American psychiatrist Ronald Dahl, 2003

Normative Adolescent Development
Dr. Laurence Steinberg (2007, 2008, 2009)

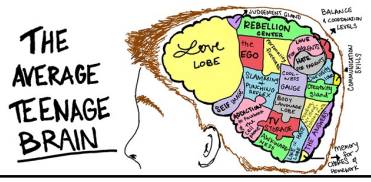
- Impulsivity Declines with Age
- Sensation-Seeking Declines with Age
- Risk-Taking Peaks in Mid-Adolescence
- Risk Perception Decreases Then Increases
- Future Orientation Increases with Age
- Delayed Gratification Increase with Age
- Time Spent Problem-Solving Increases with Age
- Susceptibility to Peer Influence Declines with Age

Dynamic mapping of human cortical development

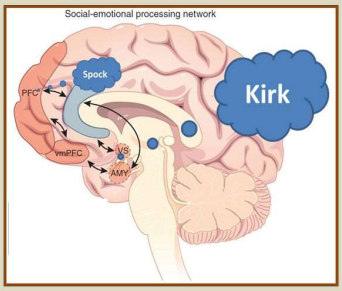


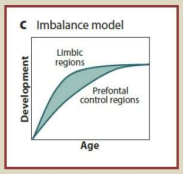
Age 5 Adolescence Age 20

Adolescence is a uniquely human phenomenon, a period of life marked by a peak in risk-taking behaviour.
New research shows that the brain continues to mature throughout adolescence and into early adulthood.
This results in a prolonged period of plasticity that makes teenagers highly vulnerable, but it may also have conferred an important evolutionary advantage.

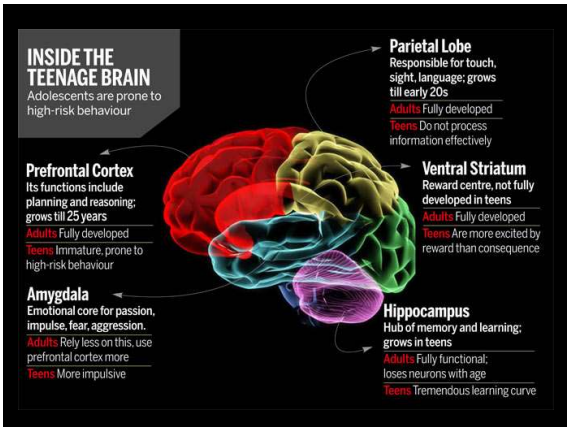


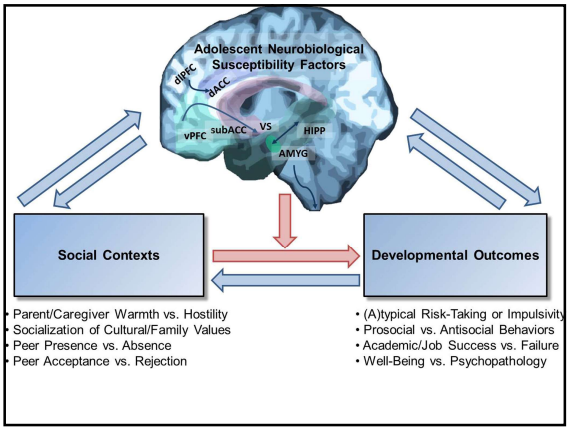
Imbalance Model of the Adolescent Brain





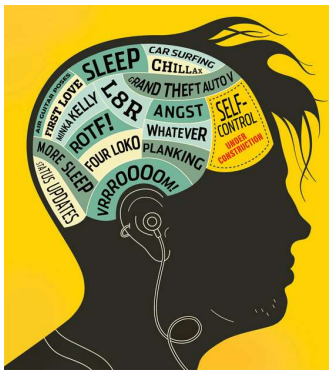
Casey (2015). Beyond simple models of self-control to circuit-based accounts of adolescent behavior. Annual Rev Psychology 66:6.1-6.25



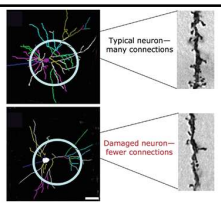


5. Adolescence

TAKE HOME MESSAGE:
– TEENAGE RISK-TAKING BEHAVIOUR MAY BE AN EVOLUTIONARY ADAPTATION –



Normal

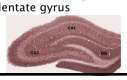


Toxic stress

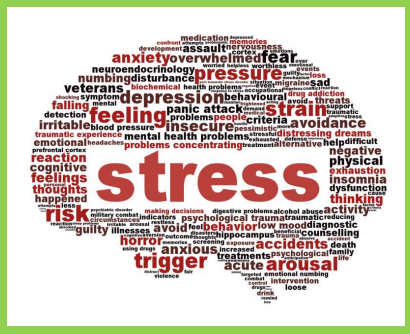
Stress and the Hippocampus

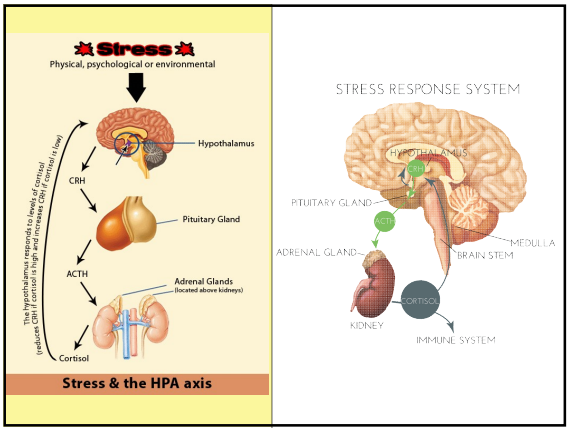
- Within the Hippocampus, is the dentate gyrus, a structure which seems to play a role in the memory of sequences of events
- It has high plasticity and is constantly producing new neurons, even throughout adult life.
- Certain types of stress suppress neurogenesis and cell survival in the dentate gyrus

Prefrontal Cortex and Hippocampus

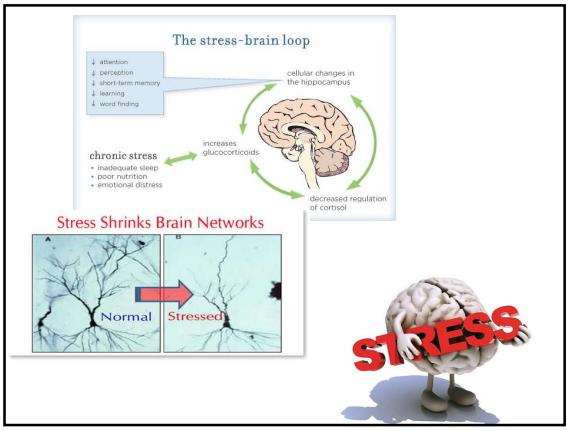


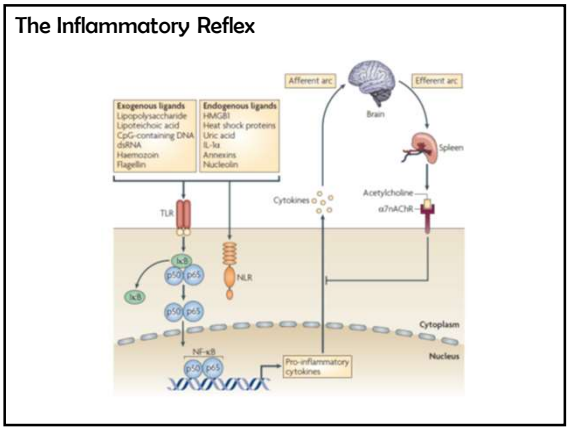
6. Stress and the brain





Stress & the HPA axis





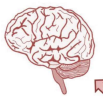
'It is easier to build strong children than to repair broken men.'
American social reformer Frederick Douglass, 1849

Types of stress responses

A normal and essential part of healthy development
EXAMPLES
getting a vaccine, first day of school

Response to a more severe stressor, limited in duration
EXAMPLES
loss of a loved one, a broken bone

Experiencing strong, frequent, and/or prolonged adversity
EXAMPLES
physical or emotional abuse, exposure to violence



Possible Mechanisms By Which Microbiota Affect CNS Function:

Adult Hippocampal Neurogenesis:
- Involved in learning and memory [79]
- Decreased in elderly [80]
- Affected by inflammation [80]

Vagus Nerve:
- Conveys peripheral immune status [61]
- Essential in the microbiota-brain pathway [62]

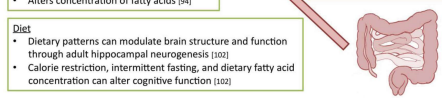
Energy Metabolism:
- SCFAs and other microbiota-derived molecules affect metabolism, inflammation, mitochondrial function, neurotransmitter levels, histone acetylation [8,77]

Immune Activation:
- Decline in function in elderly [57]
- Bidirectional communication between the immune system and CNS [65]
- Blood brain barrier and microglia involvement [67,68]

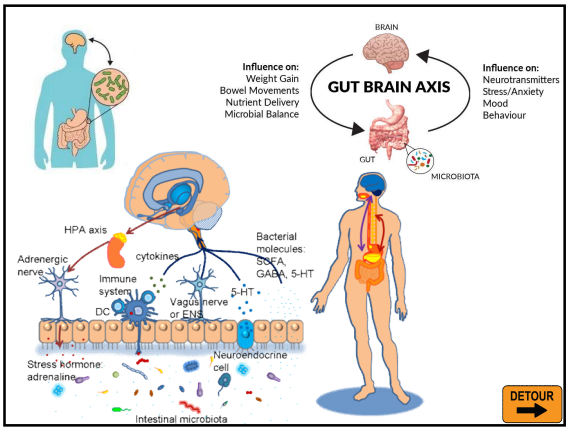
Possible Treatment Strategies:

Probiotics
- Decreases anxiety-like behaviour in rats and humans [91]
- Alters expression of GABA receptors [62]
- Alters concentration of fatty acids [94]

Diet
- Dietary patterns can modulate brain structure and function through adult hippocampal neurogenesis [102]
- Calorie restriction, intermittent fasting, and dietary fatty acid concentration can alter cognitive function [102]



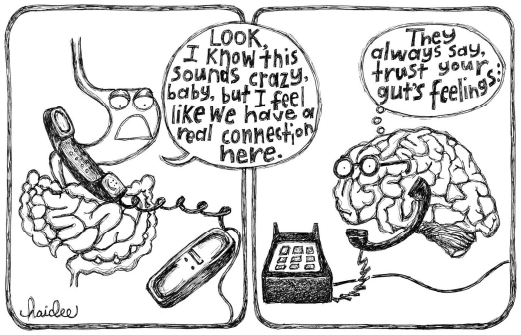
DETOUR



DETOUR

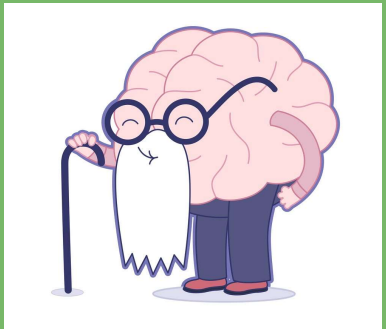
6. Stress and the brain

TAKE HOME MESSAGE:
– PROLONGED STRESS IS TOXIC TO THE BRAIN –



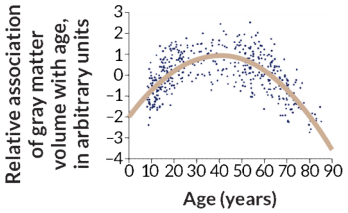
DETOUR

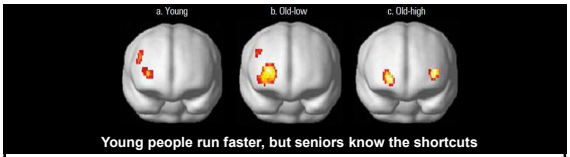
7. The ageing brain



'Man when he grows old … can no more learn much than he can run much; youth is the time for any extraordinary toil.'
Plato, c. 350 BC

Gray matter volume varies with age



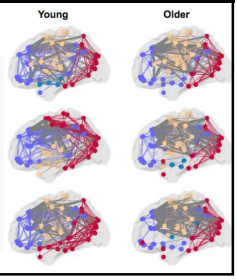


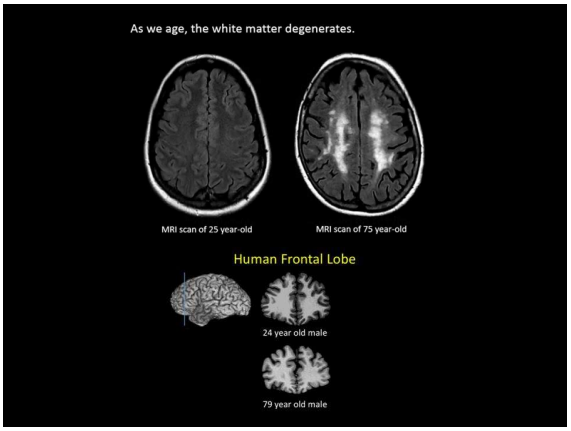
Young people run faster, but seniors know the shortcuts

Cognitive changes and "normal" aging

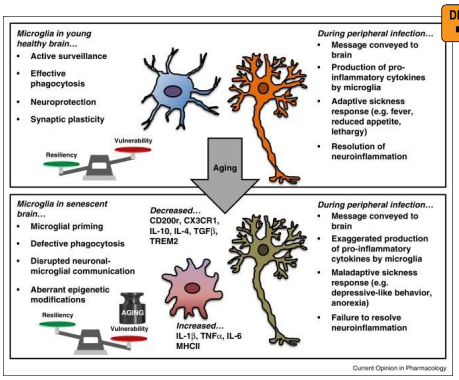
Worse
- Memory: can learn new information well, but slower and less efficient
- Decreased recall (retrieval) ability:
  e.g. remembering people's names, occasional ↓ word-finding … tip of tongue
- Slowing of cognition and motor function
- Difficulty multi-tasking, easier attention lapses

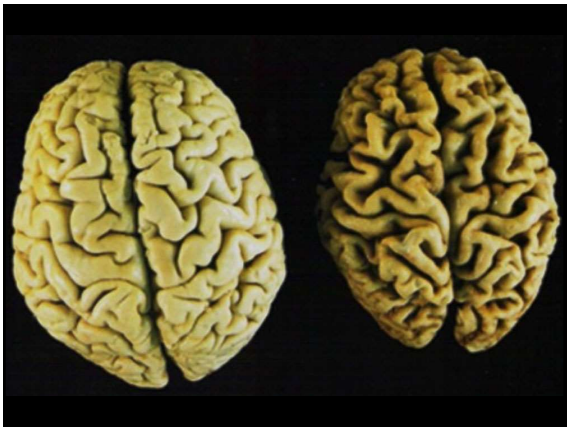
Preserved: verbal IQ, vocabulary, remote memory
Better: wisdom

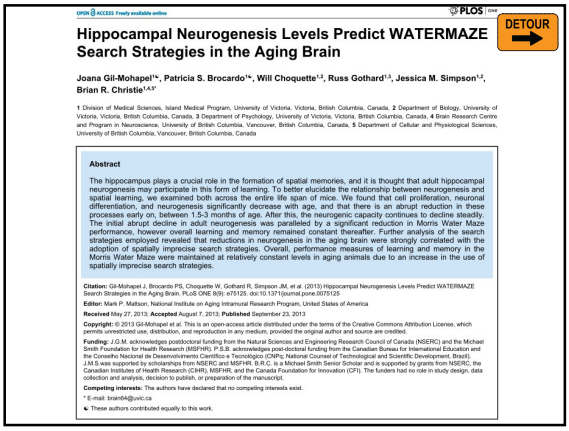




DETOUR







DETOUR

Hippocampal Neurogenesis Levels Predict WATERMAZE Search Strategies in the Aging Brain

Joana Gil-Mohapel[1*], Patricia S. Brocardo[1*], Will Choquette[1,2], Russ Gothard[1,3], Jessica M. Simpson[1,2], Brian R. Christie[1,4,5]

1 Division of Medical Sciences, Island Medical Program, University of Victoria, Victoria, British Columbia, Canada, 2 Department of Biology, University of Victoria, Victoria, British Columbia, Canada, 3 Department of Psychology, University of Victoria, Victoria, British Columbia, Canada, 4 Brain Research Centre and Program in Neuroscience, University of British Columbia, Vancouver, British Columbia, Canada, 5 Department of Cellular and Physiological Sciences, University of British Columbia, Vancouver, British Columbia, Canada

Abstract

The hippocampus plays a crucial role in the formation of spatial memories, and it is thought that adult hippocampal neurogenesis may participate in this form of learning. To better elucidate the relationship between neurogenesis and spatial learning, we examined both across the entire life span of mice. We found that cell proliferation, neuronal differentiation, and neurogenesis significantly decrease with age, and that there is an abrupt reduction in these processes early on, between 1.5-3 months of age. After this, the neurogenic capacity continues to decline steadily. The initial abrupt decline in adult neurogenesis was paralleled by a significant reduction in Morris Water Maze performance, however overall learning and memory remained constant thereafter. Further analysis of the search strategies employed revealed that reductions in neurogenesis in the aging brain were strongly correlated with the adoption of spatially imprecise search strategies. Overall, performance measures of learning and memory in the Morris Water Maze were maintained at relatively constant levels in aging animals due to an increase in the use of spatially imprecise search strategies.

Citation: Gil-Mohapel J, Brocardo PS, Choquette W, Gothard R, Simpson JM, et al. (2013) Hippocampal Neurogenesis Levels Predict WATERMAZE Search Strategies in the Aging Brain. PLoS ONE 8(9): e75125. doi:10.1371/journal.pone.0075125

Editor: Mark P. Mattson, National Institute on Aging Intramural Research Program, United States of America

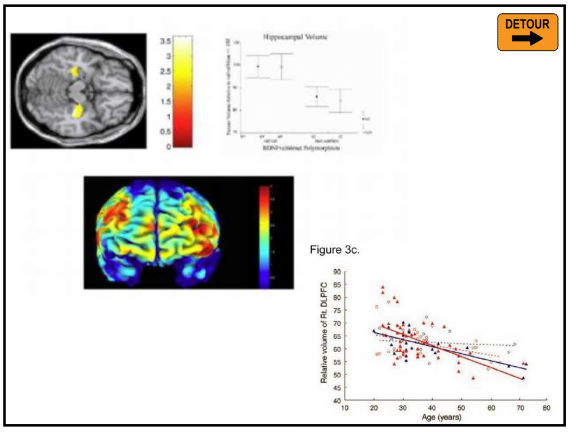
Received May 27, 2013; **Accepted** August 7, 2013; **Published** September 23, 2013

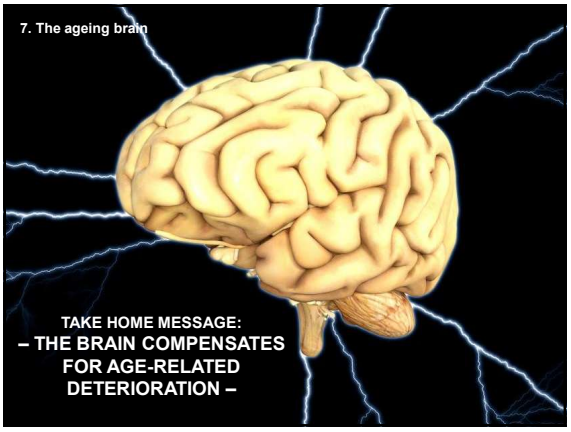
Funding: J.G.M. acknowledges postdoctoral funding from the Natural Sciences and Engineering Research Council of Canada (NSERC) and the Michael Smith Foundation for Health Research (MSFHR). P.S.B. acknowledges post-doctoral funding from the Canadian Bureau for International Education and the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) National Counsel of Technological and Scientific Development, Brazil). J.M.S was supported by scholarships from NSERC and MSFHR. B.R.C. is a Michael Smith Senior Scholar and is supported by grants from NSERC, the Canadian Institutes of Health Research (CIHR), MSFHR, and the Canada Foundation for Innovation (CFI). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

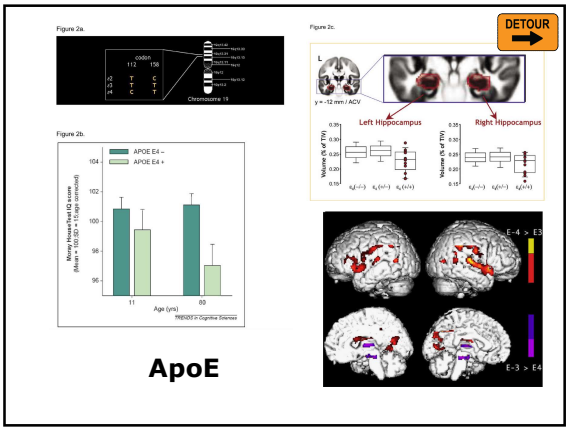
Competing interests: The authors have declared that no competing interests exist.

* E-mail: brain64@uvic.ca

These authors contributed equally to this work.



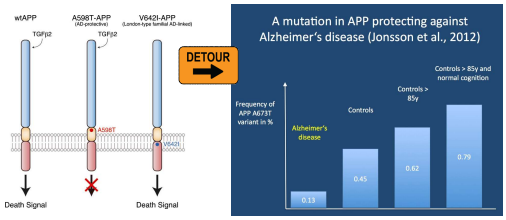




Protective variant for hippocampal atrophy identified by whole exome sequencing

An in-silico predicted missense variant in REST (rs3796529) was found exclusively in subjects with slow hippocampal volume loss and validated using unbiased whole-brain analysis and meta-analysis across 5 independent cohorts. Ann Neurol. 2015 Mar;77(3):547-52.

Amyloid precursor protein (APP) A673T mutation in the elderly Finnish population.



The A673T variant is extremely rare in US cohorts and does not play a substantial role in risk for AD in this population. This variant may be primarily restricted to Icelandic and Scandinavian populations.