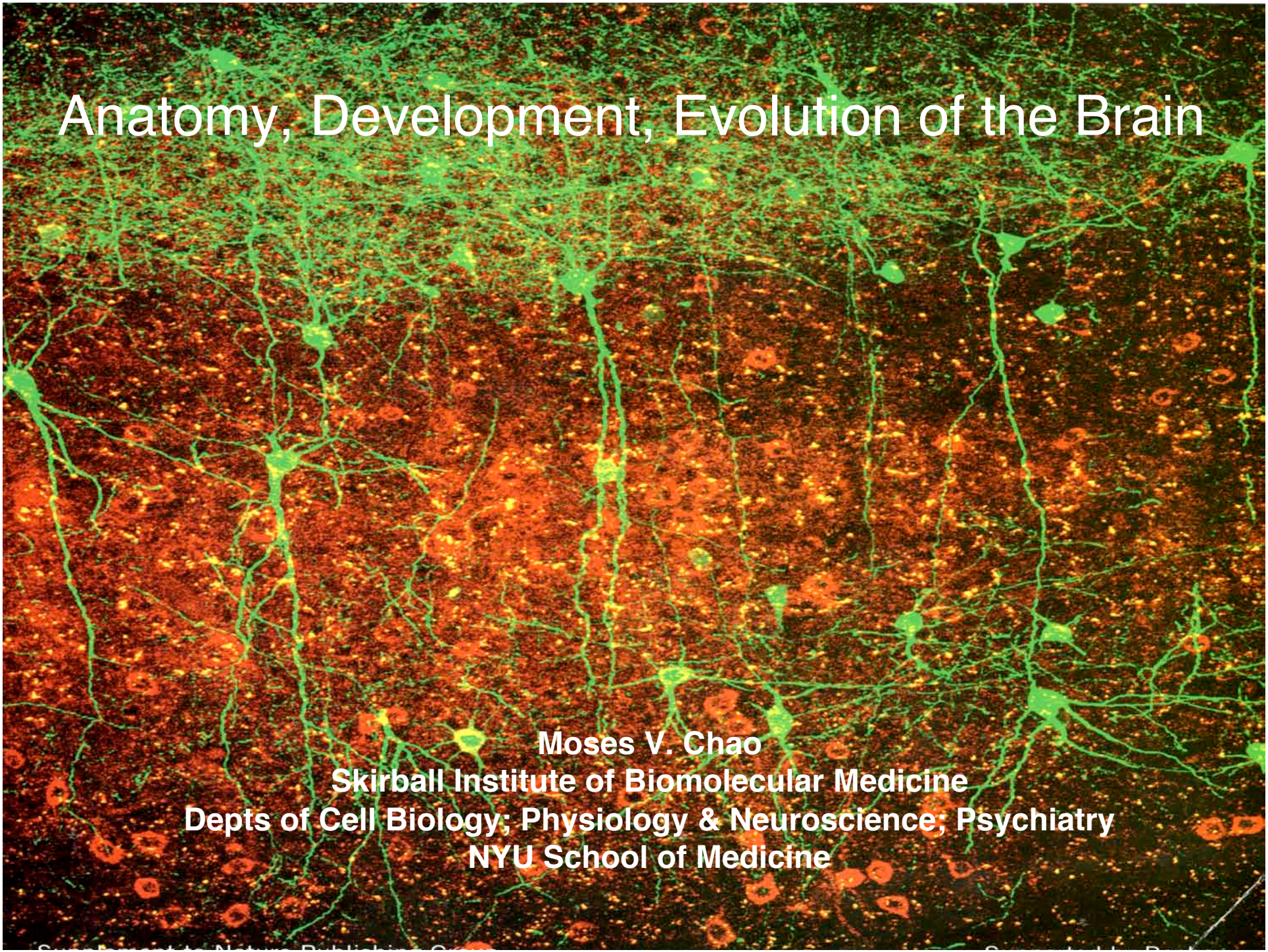
Anatomy, Development, Evolution of the Brain



Moses V. Chao
Skirball Institute of Biomolecular Medicine
Depts of Cell Biology; Physiology & Neuroscience; Psychiatry
NYU School of Medicine

Thomas F. Eagleton, 77, a Running Mate for 18 Days, Dies

By ADAM CLYMER

Thomas F. Eagleton, a former United States senator whose legislative accomplishments were overshadowed by his removal as the Democratic vice presidential candidate in 1972 after revelations of mental illness and electroshock therapy, died yesterday in Richmond Heights, Mo. He was 77 and lived outside St. Louis in Clayton, Mo.

The cause was a combination of heart, respiratory and other ailments, a family spokesman said.

Mr. Eagleton took a leading role on legislative issues like presidential war powers, the bombing of Cambodia and home rule for the District of Columbia. But history will probably remember him primarily as a vice presidential candidate for 18 days.

He was in his first term as a senator from Missouri when the presidential candidate, Senator George McGovern, asked that he join him on the Democratic ticket. Mr. Eagleton was a last-minute selection; Mr. McGovern had been counting on Senator Edward M. Kennedy of Massachusetts to change his mind and become his running mate once Mr. McGovern received the presidential nomination at the Democratic National Convention in Miami Beach. But Mr. Kennedy declined.

After others were considered, the campaign settled on Mr. Eagleton, at 42 a young, Roman Catholic senator with a liberal voting record and the

Associated Press, 1972

Thomas F. Eagleton, left, and George McGovern in Miami Beach.

and electric shocks.

That day Mr. McGovern said, "I think Tom Eagleton is fully qualified in mind, body and spirit to be the vice president of the United States and, if necessary, to take on the presidency on a moment's notice." As objections to Mr. Eagleton mounted, Mr. McGovern insisted that he was "1,000 percent for Tom Eagleton."

But the pressure from party leaders, campaign contributors and members of Mr. McGovern's own staff was unrelenting. On July 31, the candidates met again, this time in

about mental illness. Nobody did."

He said that in recent years he and Mr. Eagleton had been on good terms, and that he regarded Mr. Eagleton as one of the 10 or 12 best senators with whom he had served.

Returning to Congress after he was dropped from the ticket, Mr. Eagleton took a leading role in legislation to halt the United States' bombing of Cambodia in 1973. When, in 1984, he announced that he would not seek a fourth term two years later, he called the Cambodia legislation his top achievement in the Senate.

fice, as prosecutor in St. Louis, in 1956 at the age of 27. It was also in 1956 that he married the former Barbara Ann Smith of St. Louis, who survives him. He is also survived by a son, Terence, of Manhattan; a daughter, Christin Fleming of Greenville, Del.; and two grandchildren.

Mr. Eagleton's early political career was a steady march of quadrennial strides. After four years as prosecutor, he was elected attorney general of Missouri in 1960. In 1964, he was elected lieutenant governor. In 1968, he was elected to the Senate after defeating the incumbent, Edward V. Long, in a Democratic primary. He was re-elected in 1974, benefiting from a widespread feeling in Missouri that he had been ill-treated by Mr. McGovern, and again in 1980.

When he announced his retirement in 1984, he said he had served "a full and complete career," adding, "Public offices should not be held in perpetuity." But he also complained that runaway campaign spending had put "the stench of money" around the Capitol.

After he left the Senate in 1987, he served on the board of the Chicago Mercantile Exchange. He resigned in 1989, saying the decisions it made were "by insiders and for insiders," not the public. He also accused the board of trying to thwart federal fraud investigations.

Mr. Eagleton practiced law in St. Louis, taught at Washington Univer-

The Neurotrophin Hypothesis of Depression

- Reduction in BDNF leads to atrophy and cell loss in the hippocampus and PFC in depressed subjects

- Antidepressants counter these effects by increasing BDNF expression

➢ Stress/Depression-- Decrease in hippocampal [BDNF]

➢ New Activities--Increase in hippocampal [BDNF]

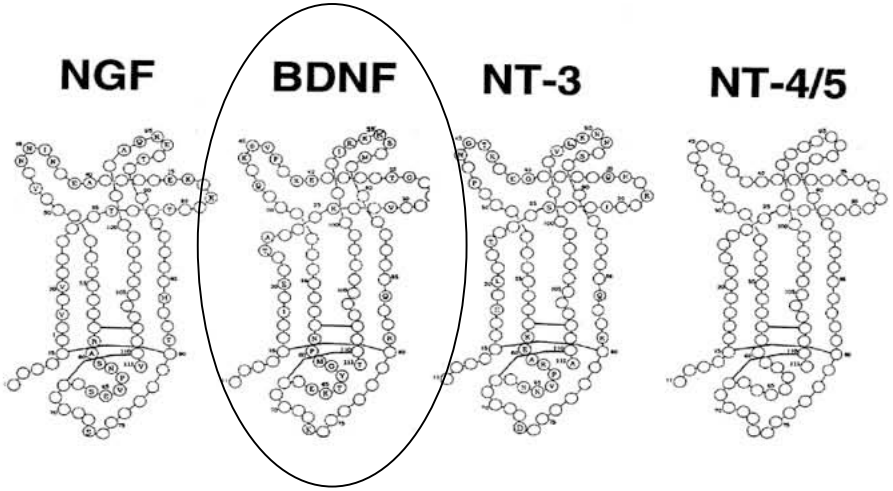
Nature 341, 149-152 (1989)

Molecular cloning and expression of brain-derived neurotrophic factor

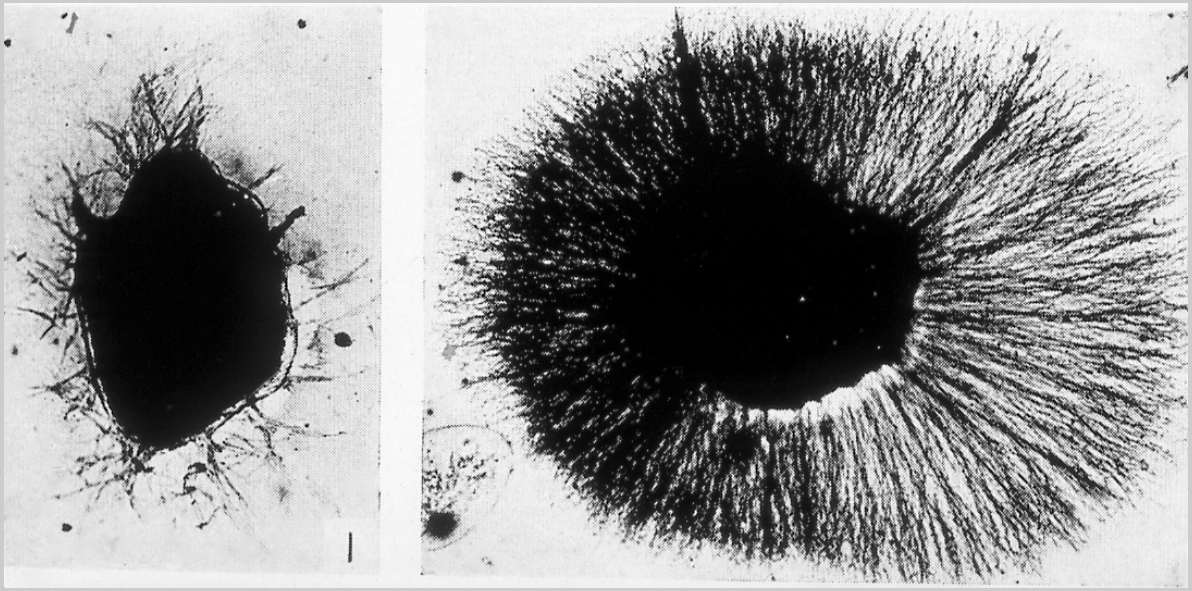
Joachim Leibrock, Friedrich Lottspeich*, Andreas Hohn, Magdalena Hofer, Bastian Hengerer, Piotr Masiakowski†, Hans Thoenen & Yves-Alain Barde‡

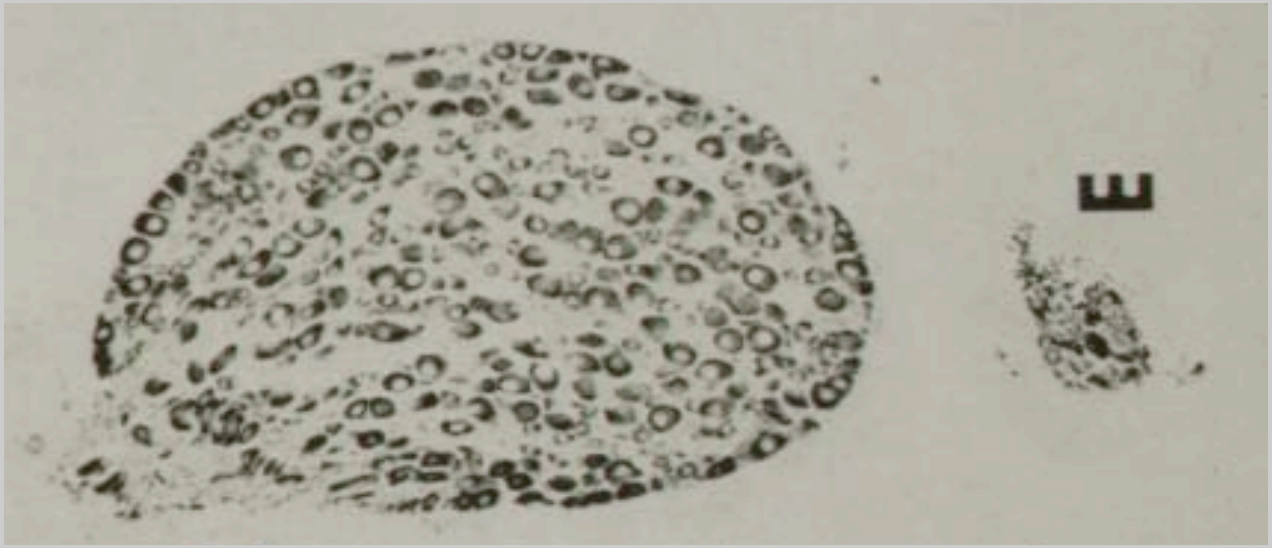
Max-Planck Institute for Psychiatry, Department of Neurochemistry, and *Max-Planck Institute for Biochemistry, Genecenter, Am Klopferspitz 18A, 8033 Planegg-Martinsried, FRG

DURING the development of the vertebrate nervous system, many neurons depend for survival on interactions with their target cells[1]. Specific proteins are thought to be released by the target cells and to play an essential role in these interactions. So far, only one such protein, nerve growth factor, has been fully characterized. This has been possible because of the extraordinarily (and unexplained) large quantities of this protein in some adult tissues that are of no relevance to the developing nervous system[2]. Whereas the dependency of many neurons on their target cells for normal development, and the restricted neuronal specificity of nerve growth factor have long suggested the existence of other such proteins, their low abundance has rendered their characterization difficult. Here we report the full primary structure of brain-derived neurotrophic factor. This very rare protein is known to promote the survival of neuronal populations that are all located either in the central nervous system or directly connected with it[3]. The messenger RNA for brain-derived neurotrophic factor was found predominantly in the central nervous system, and the sequence of the protein indicates that it is structurally related to nerve growth factor. These results establish that these two neurotrophic factors are related both functionally and structurally.



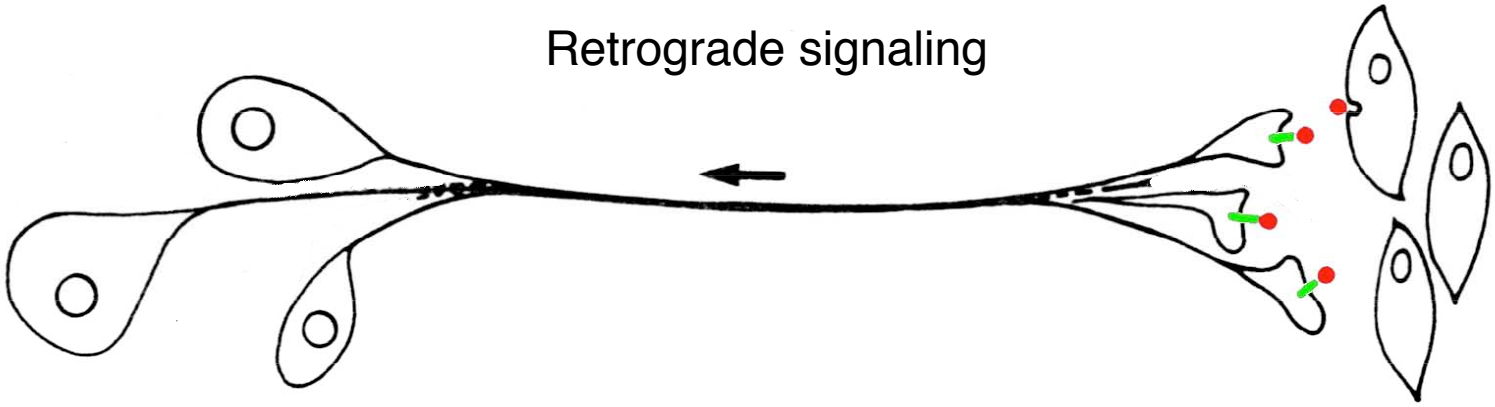
RITA LEVI-MONTALCINI



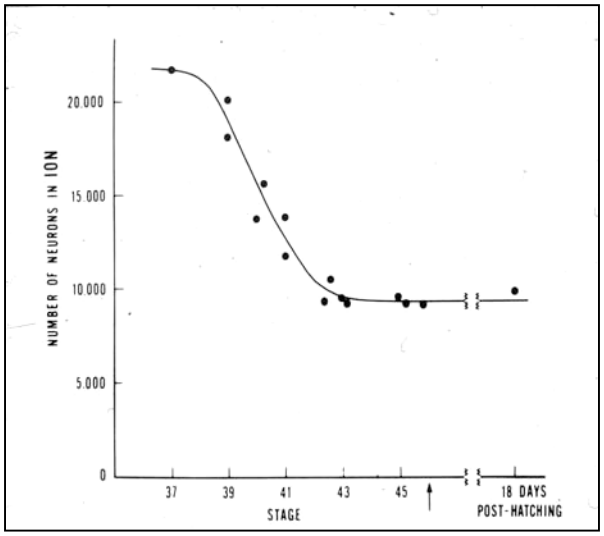


The Classic Hypothesis for Neurotrophic Factors

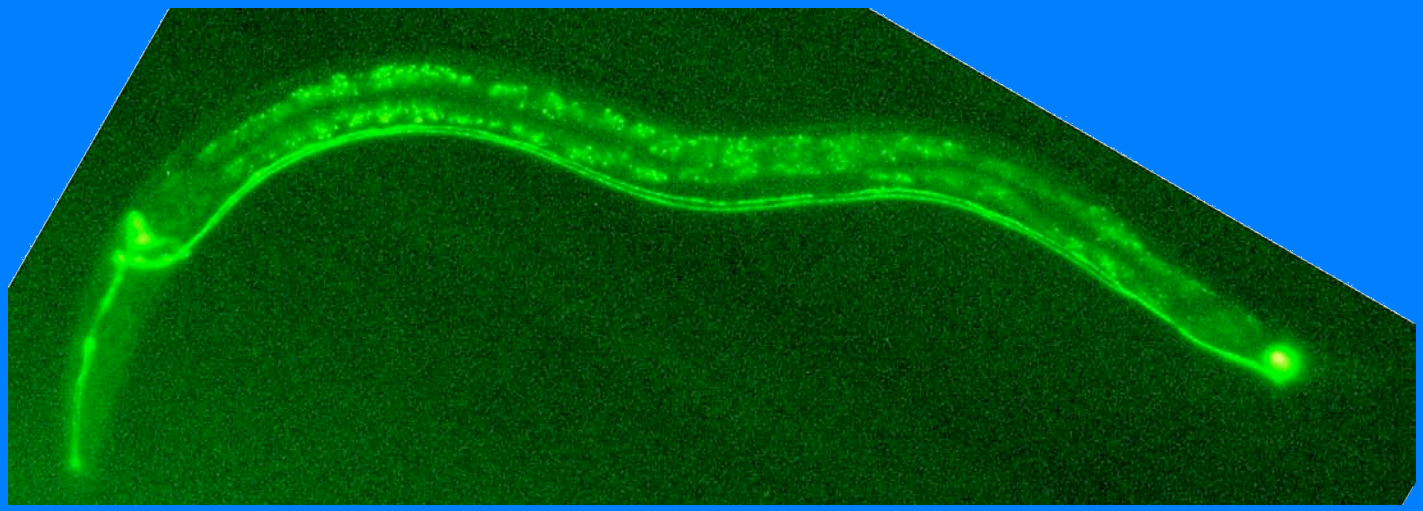
The Classic Hypothesis for Neurotrophic Factors

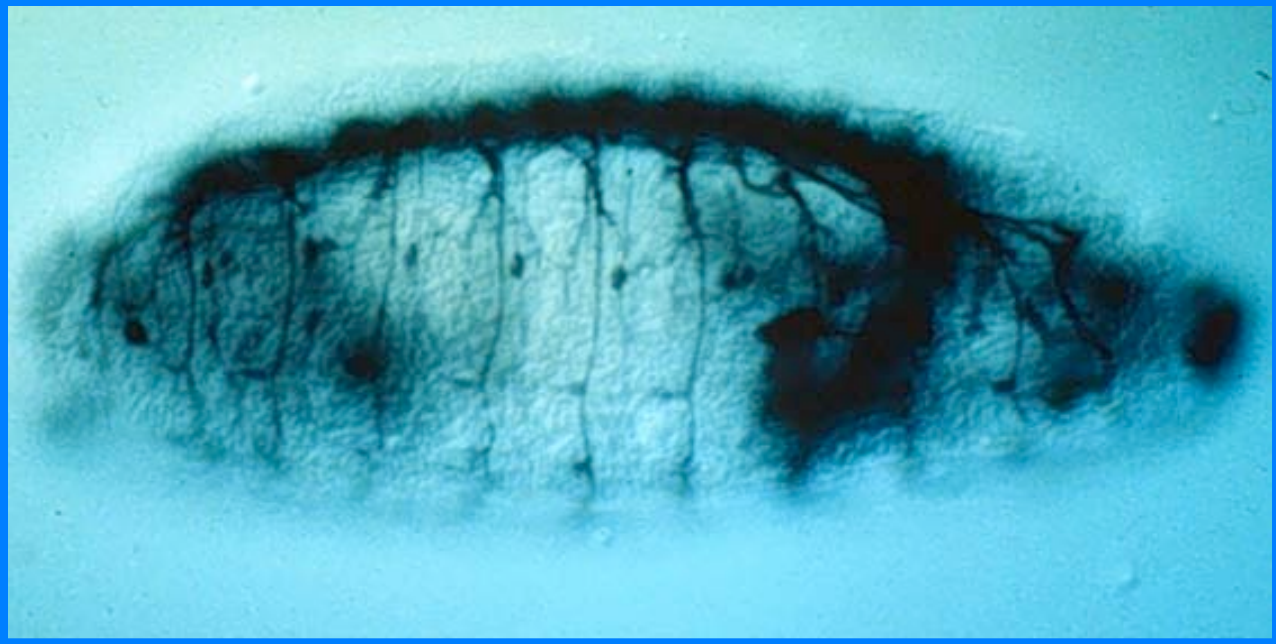


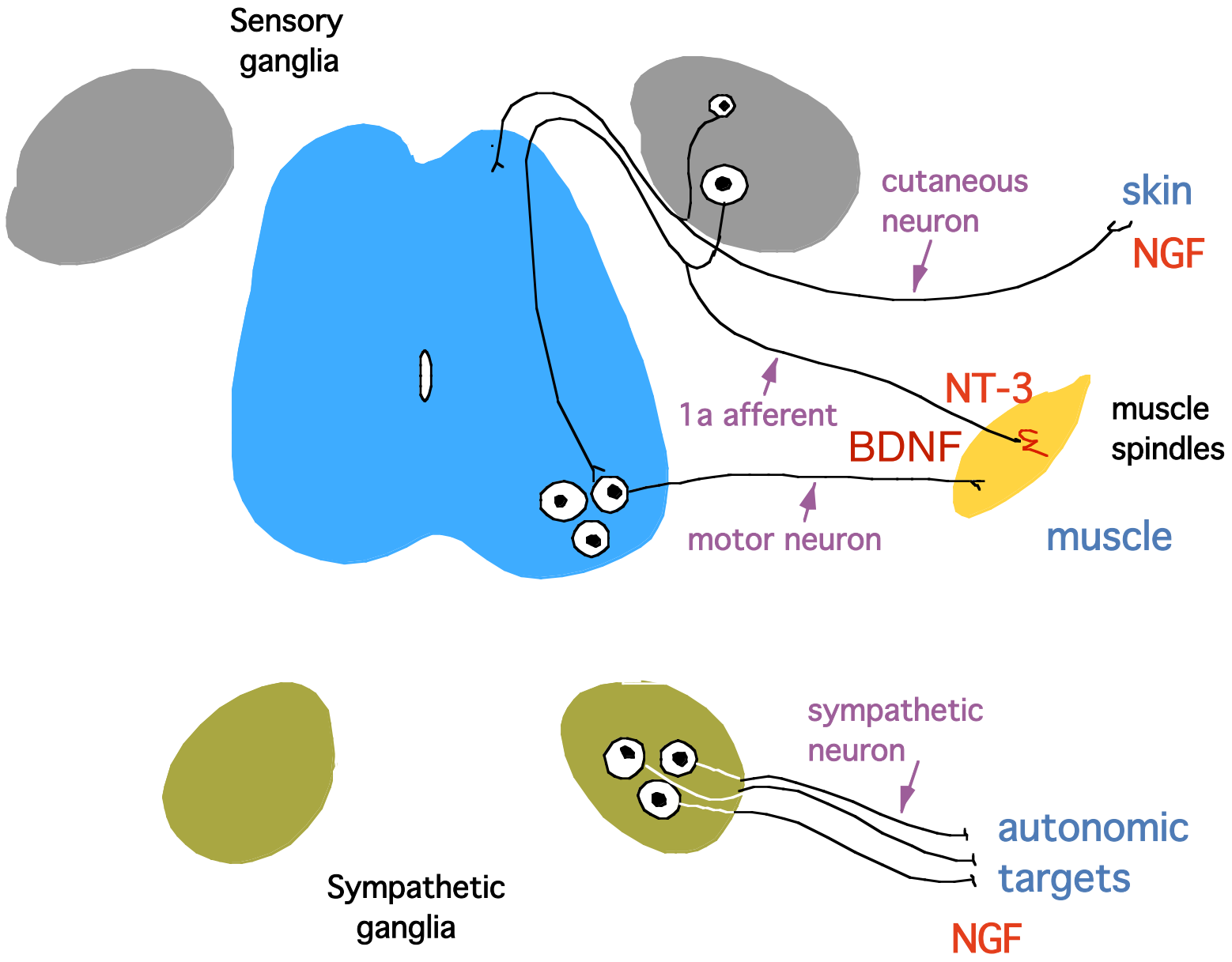
Survival



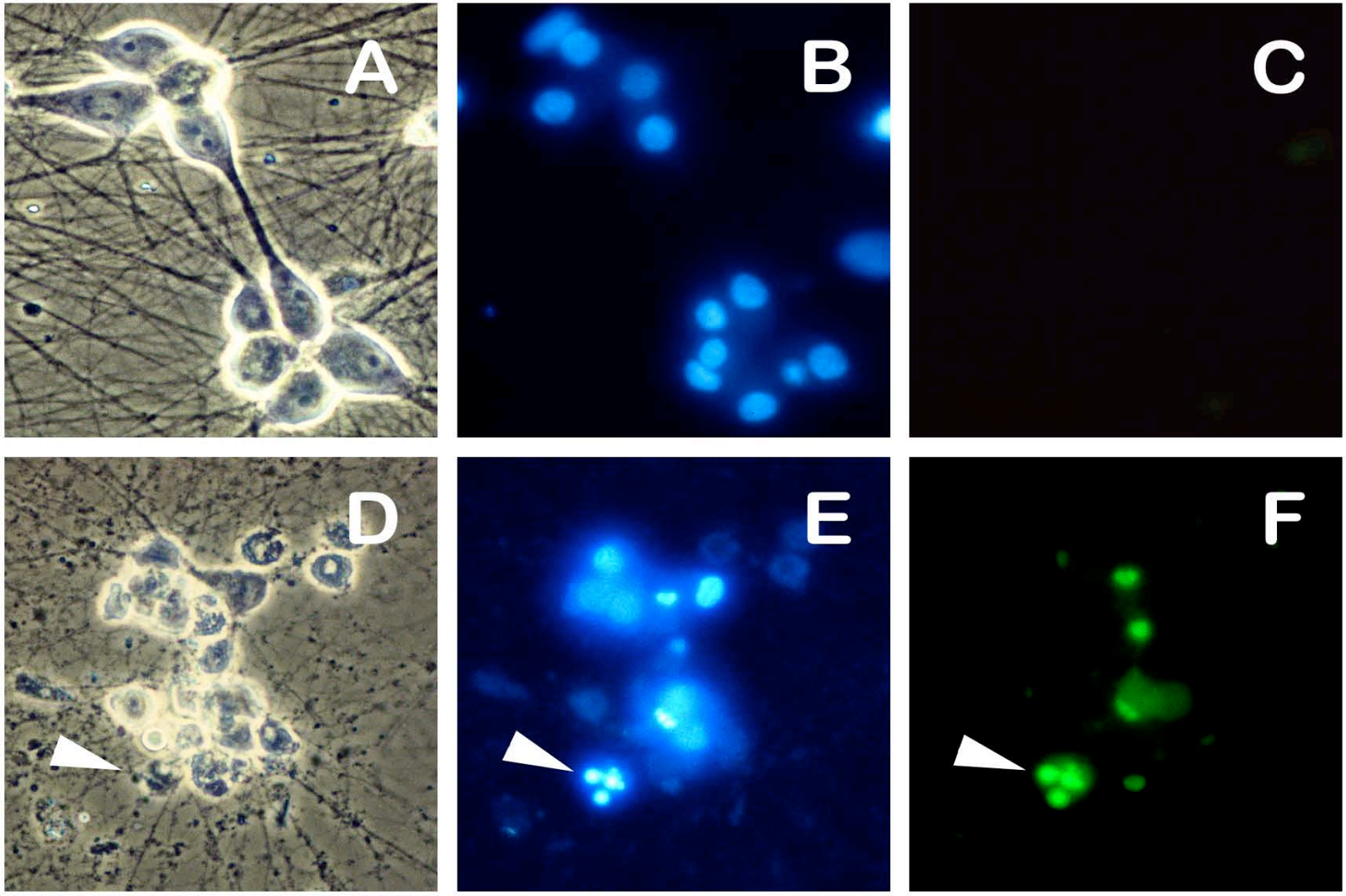
Neurotrophins and their receptors are absent in *C elegans* and *Drosophila melanogaster*



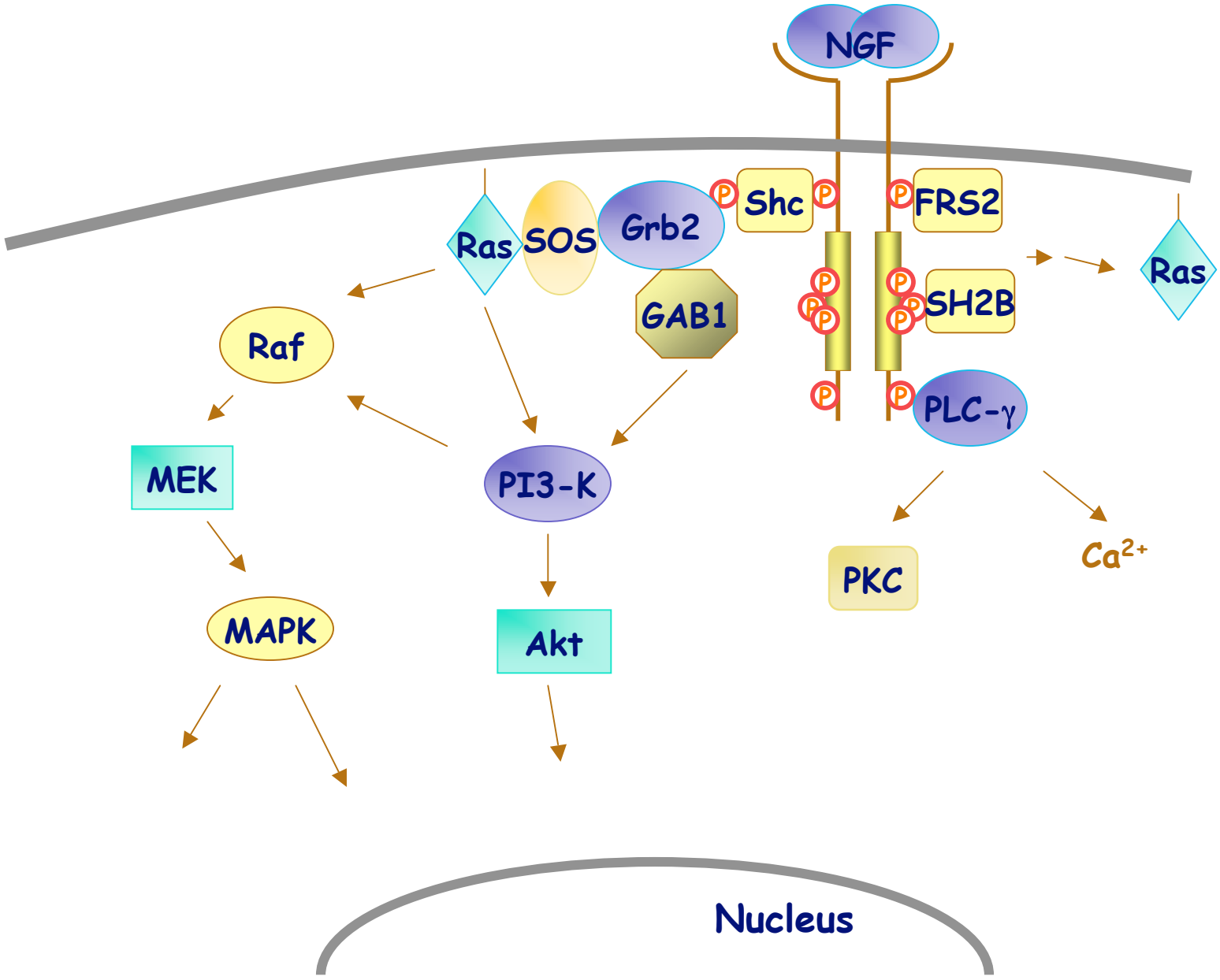



Sensory
ganglia
cutaneous
neuron
skin
NGF
1a afferent
NT-3
BDNF
muscle
spindles
motor neuron
muscle
sympathetic
neuron
autonomic
targets
NGF
Sympathetic
ganglia

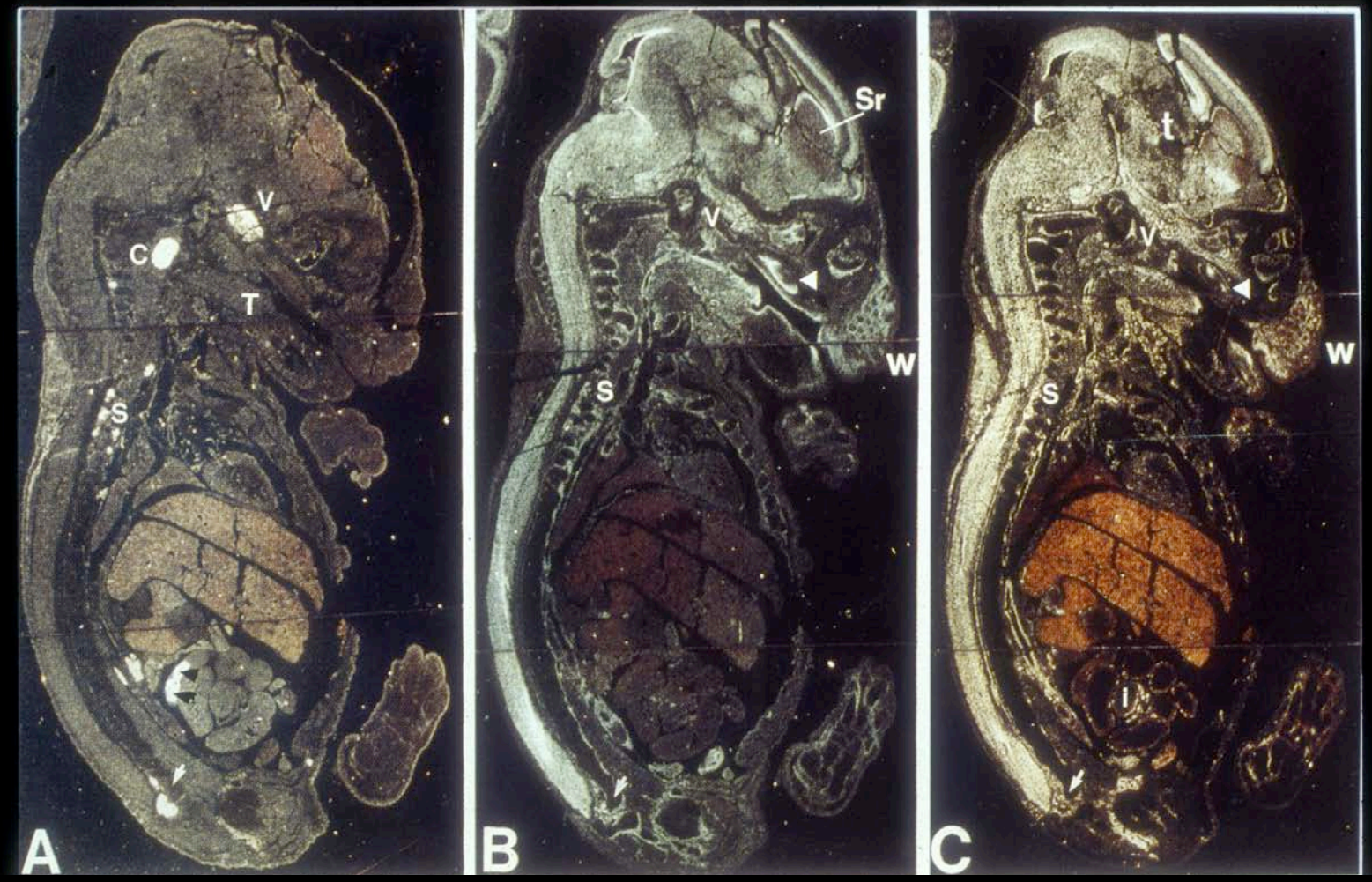
Sympathetic neurons deprived of NGF undergo apoptosis



NGF-Trk Signaling

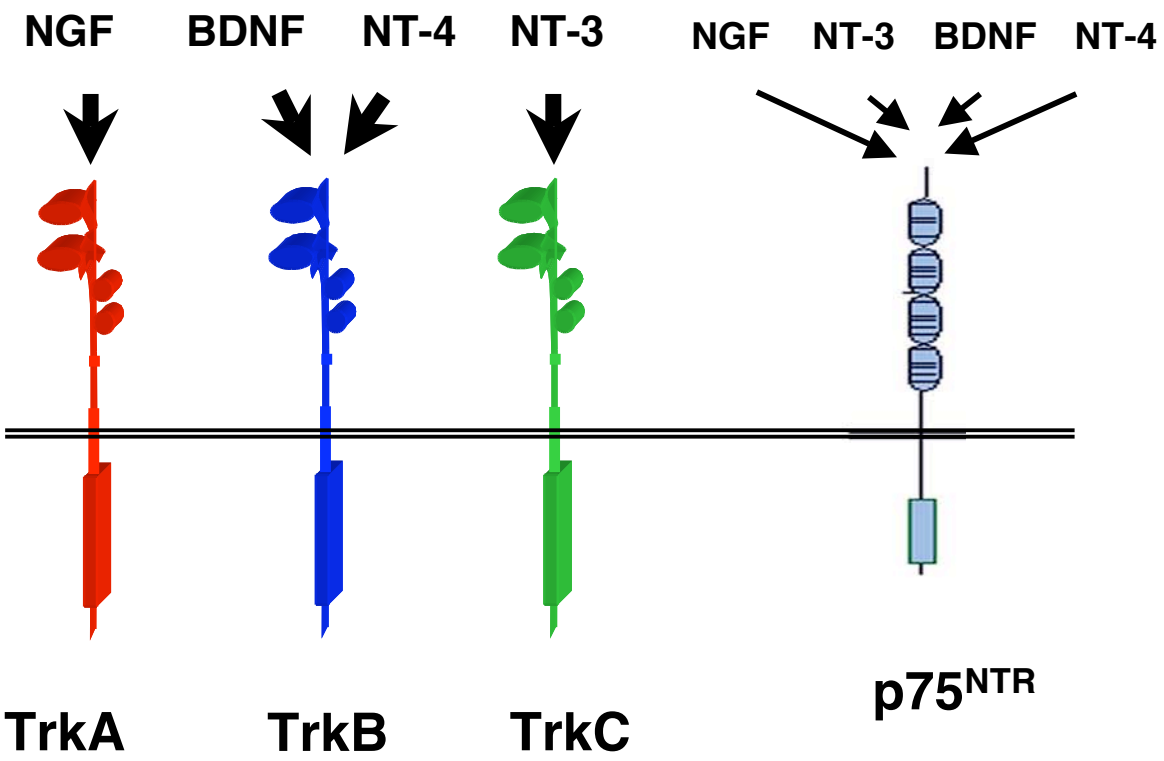


TrkA TrkB TrkC



NGF BDNF NT-4 NT-3

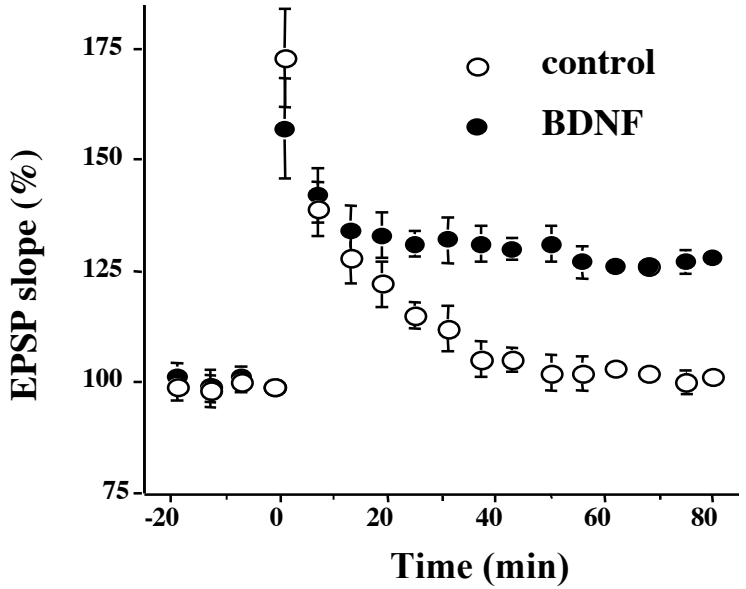
The Neurotrophin Receptors

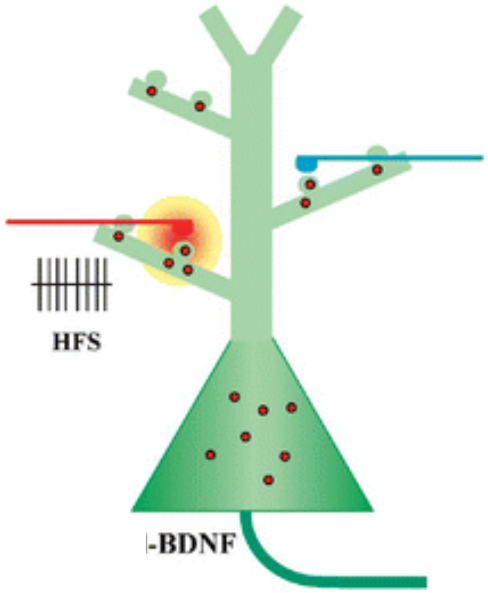


Survival
Differentiation
Synaptic plasticity, LTP
Learning and Memory

Apoptosis
Migration
LTD
Regeneration

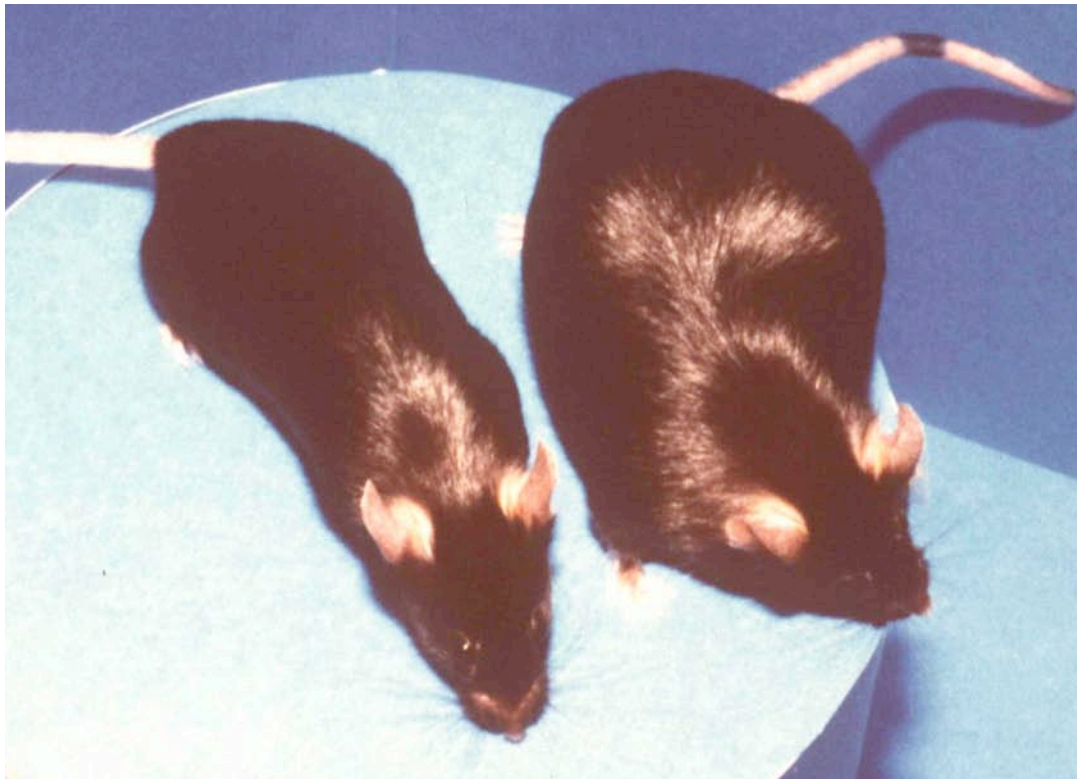
Neurotrophins: Survival factors with a wide range of activities





BDNF and Behavior

↓ BDNF



Intermale aggresssion

Hyperactivity

Hyperphagic

Anxious (light/dark exploration test)

Learning deficit (Morris water maze, contextual fear learning**)**

Increased ETOH intake

Antidepressants that increase BDNF

Serotonin reuptake inhibitors

fluoxetine (Prozac)

sertraline (Zoloft)

paroxetine (Paxil)

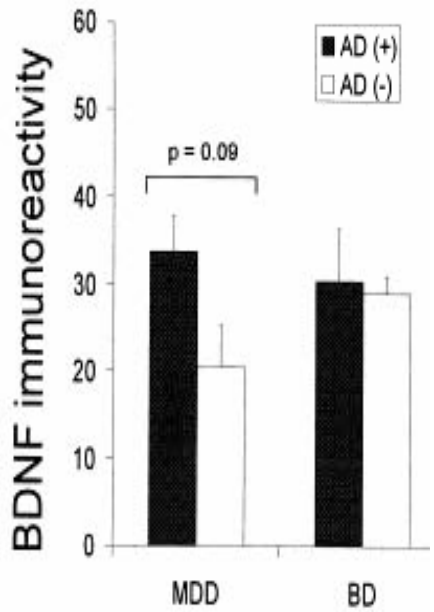
citalopram (Celexa)

Tricyclic antidepressants

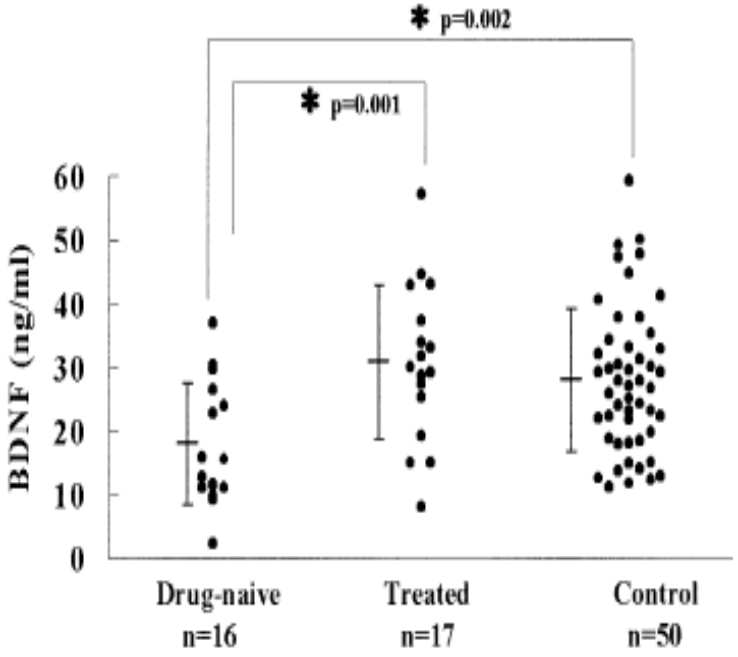
desipramine (Norpramin)

imipramine (Tofranil)

amitriptyline (Elavil)



Chen et al., Biol Psychiatry, 2001



Shimizu et al., Biol. Psychiatry 2003

Exercise and brain neurotrophins

SIR — Physical activity has emerged as a predictor of high mental function in ageing[1]. Exercise has been shown to affect several neurotransmitter systems[2,3], but it remains to be shown whether it can influence other key molecular systems which serve the maintenance and plasticity of the brain. Brain-derived neurotrophic factor (BDNF), a growth factor of the neurotrophin family, supports the function and survival of many neurons[4–6], and may help protect neurons from free-radical damage[7]. Ample evidence indicates that production of BDNF in the brain is regulated by neuronal activity[8–11]. Here we report evidence that physical exercise can increase BDNF gene expression in specific brain regions. These data open the encouraging possibility that exercise may increase the availability of trophic support, and thus resilience against insult, in certain neuronal populations.

neocortex ($P = 0.05$) was significantly increased over control levels after 2 nights with exercise, and remained elevated for 7 nights.

We next examined BDNF mRNA

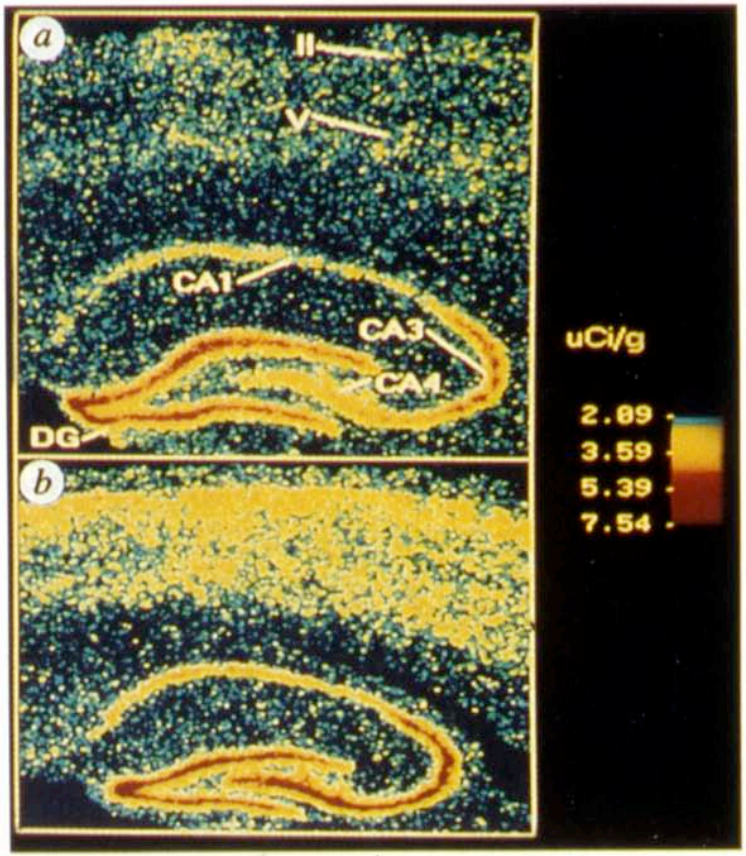
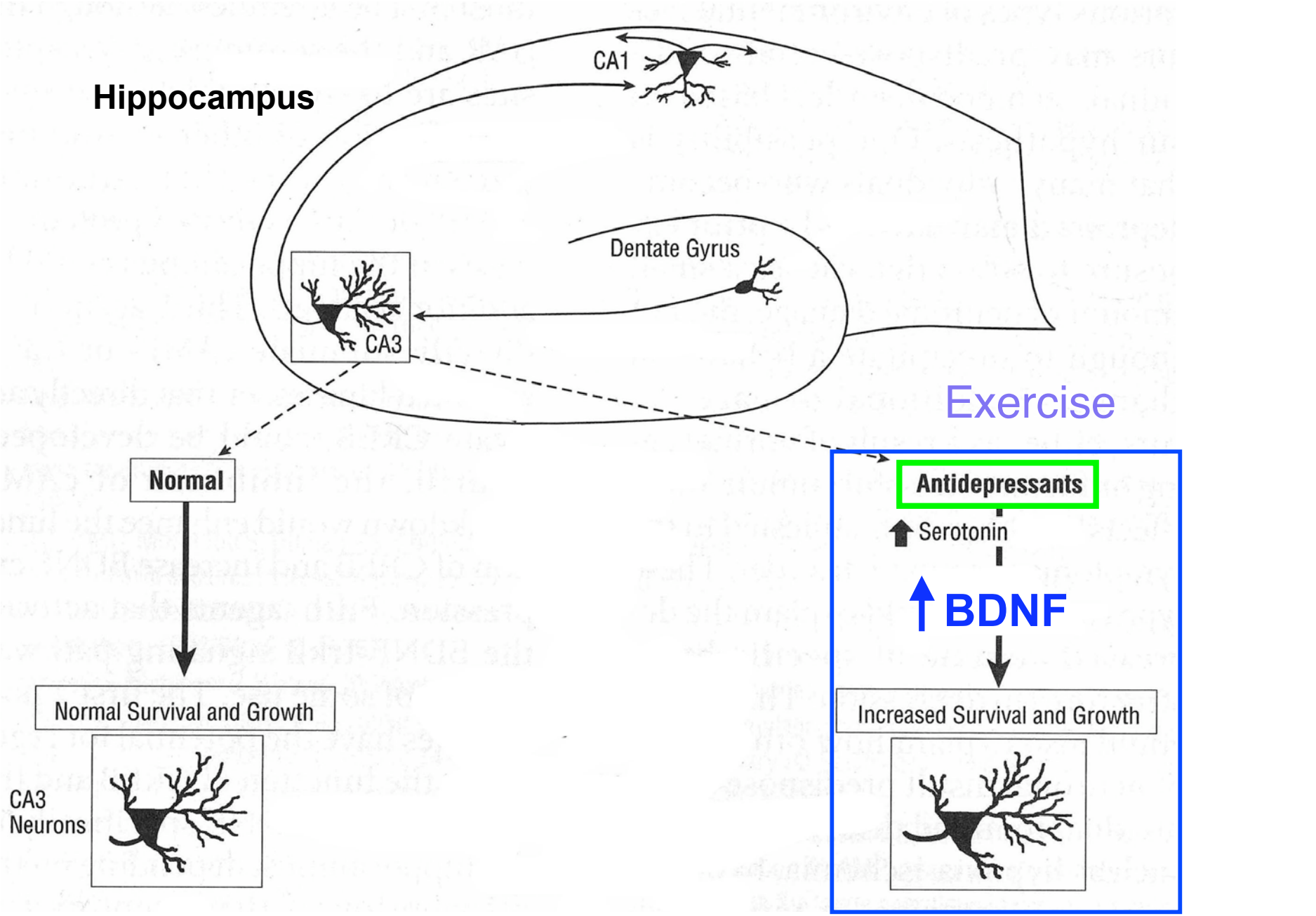


FIG. 1 Colour-enhanced image of autoradiograms from *in situ*

length of exposure to exercise .

Because individual rats in the study maintained different activity levels, we compared BDNF mRNA levels with distance run per night by each rat. We found a significant, positive correlation between mean distance run per night and BDNF mRNA in hippocampus (Fig. 2*a–c*) and caudal neocortex (data not shown) in all exercise groups. One rat in the 2-night group did not run, and had BDNF mRNA measurement (Fig. 2*a*) close to control levels.

Interestingly, the greatest effects of exercise on BDNF occurred in highly plastic, or changeable areas, responsive to environmental stimuli[11–13]. This result supports previous suggestions that BDNF is involved in brain plasticity. A second relevant consideration is BDNF's potential involvement in neuronal survival and functional maintenance. For example, retrograde transport of BDNF from the hippocampus provides vital support to forebrain cholinergic neurons[14,15], a site of Alzheimer's disease and age-related degeneration. Physical activity could increase availability of BDNF to these cells by upregulating its expression in the hippocampus. Exercise-induced upregulation of BDNF could help increase the brain's resistance to damage and degeneration through BDNF's support of neuronal growth, function and survival.



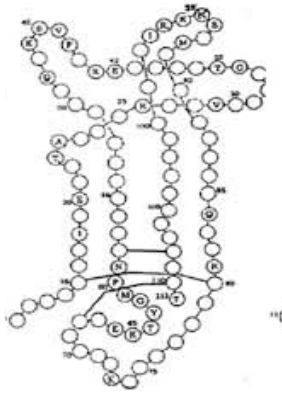
Duman et al., 1998

Family-based association study of 76 candidate genes in bipolar disorder: BDNF is a potential risk locus

P Sklar[1,2,3], SB Gabriel[3], MG McInnis[4], P Bennett[5], Y-M Lim[3], G Tsan[3], S Schaffner[3], G Kirov[6], I Jones[5], M Owen[6], N Craddock[5], JR DePaulo[4] and ES Lander[3]

Molecular Psychiatry (2002) 7, 579-593

BDNF



Evidence for a Relationship Between Genetic Variants at the Brain-Derived Neurotrophic Factor (BDNF) Locus and Major Depression

BIOL PSYCHIATRY 2005;58:307–314

Johannes Schumacher, Rami Abou Jamra, Tim Becker, Stephanie Ohlraun, Norman Klopp, Elisabeth B. Binder, Thomas G. Schulze, Monika Deschner, Christine Schmäl, Susanne Höfels, Astrid Zobel, Thomas Illig, Peter Propping, Florian Holsboer, Marcella Rietschel, Markus M. Nöthen, and Sven Cichon

A BDNF Coding Variant is Associated with the NEO Personality Inventory Domain Neuroticism, a Risk Factor for Depression

Neuropsychopharmacology (2003) 28, 397–401

Sequence Variants of the Brain-Derived Neurotrophic Factor (*BDNF*) Gene Are Strongly Associated with Obsessive-Compulsive Disorder

Am. J. Hum. Genet. 73:370–376, 2003

Diana Hall,[1] Alefiya Dhilla,[2] Anna Charalambous,[1] Joseph A. Gogos,[2] and Maria Karayiorgou[1]

The C270T polymorphism of the brain-derived neurotrophic factor gene is associated with schizophrenia

Schizophrenia Research 65 (2003) 15–18

György Szekeres[a], Anna Juhász[a], Ágnes Rimanóczy[a], Szabolcs Kéri[a,b,c], Zoltán Janka[a,*]

The BDNF val66met polymorphism

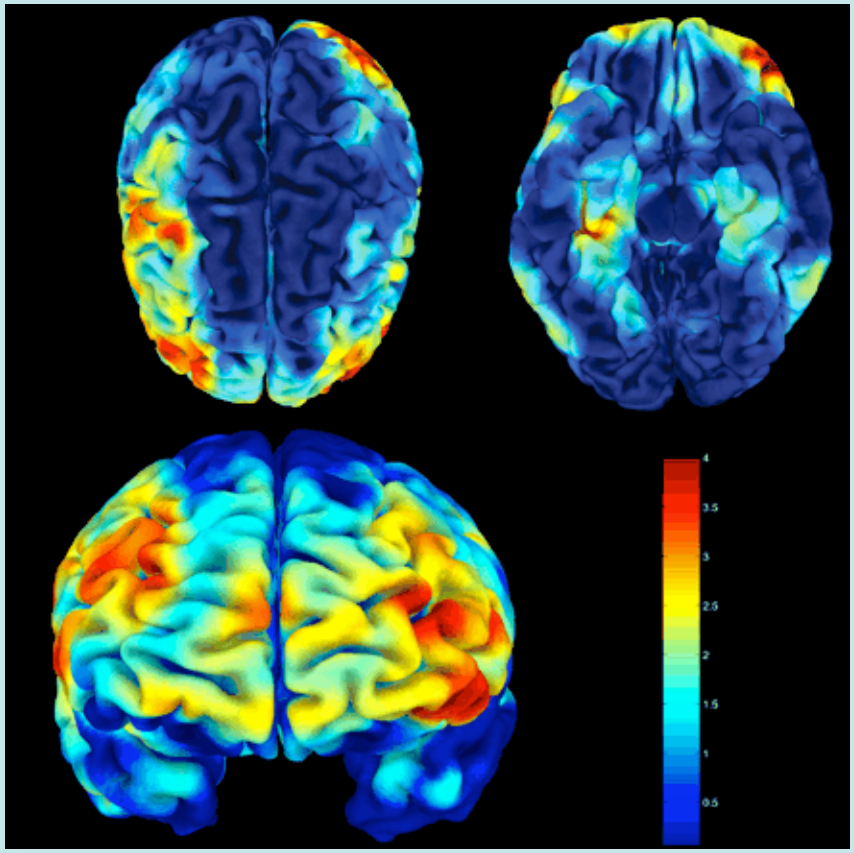
Met allele associated with poor episodic memory (fMRI)

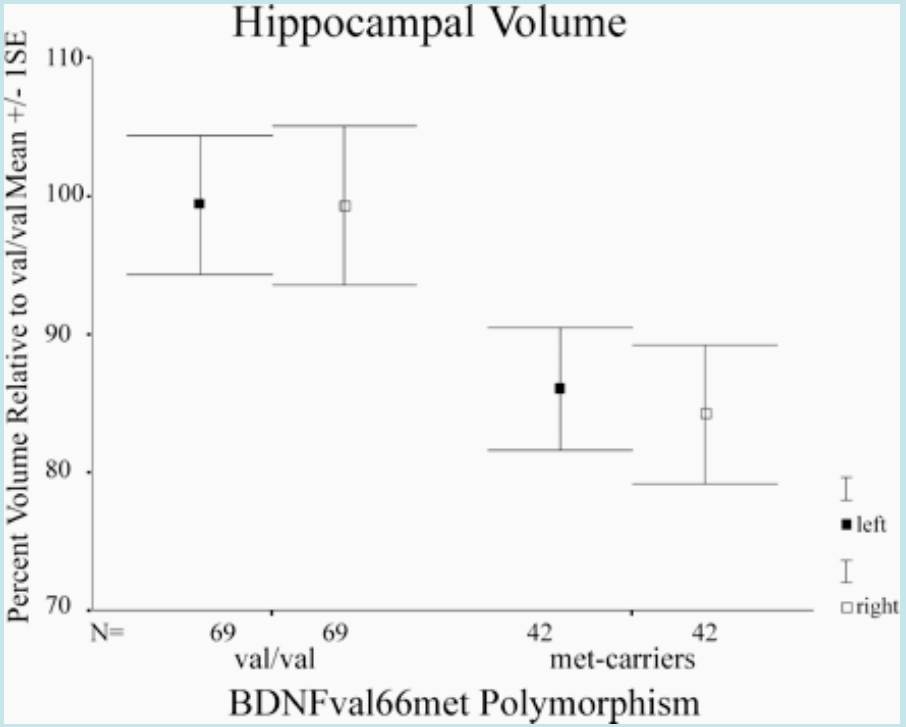
Met-BDNF-GFP failed to localize to secretory granules or synapses

BDNF with Met66 is not processed or secreted normally

Egan *et al Cell* 112, 257 (2003)

Humans heterozygous for $BDNF_{Met}$ display decreased cortical and hippocampal volumes



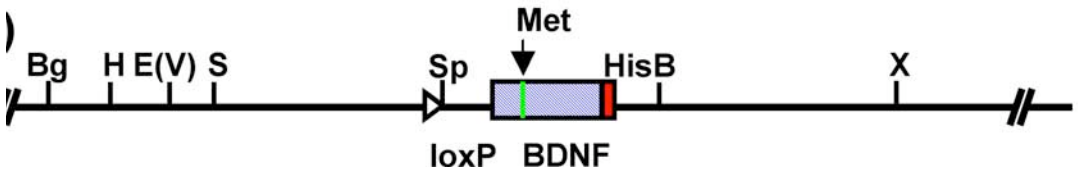


Pezawas et al., 2004

BDNF Val66Met Mice

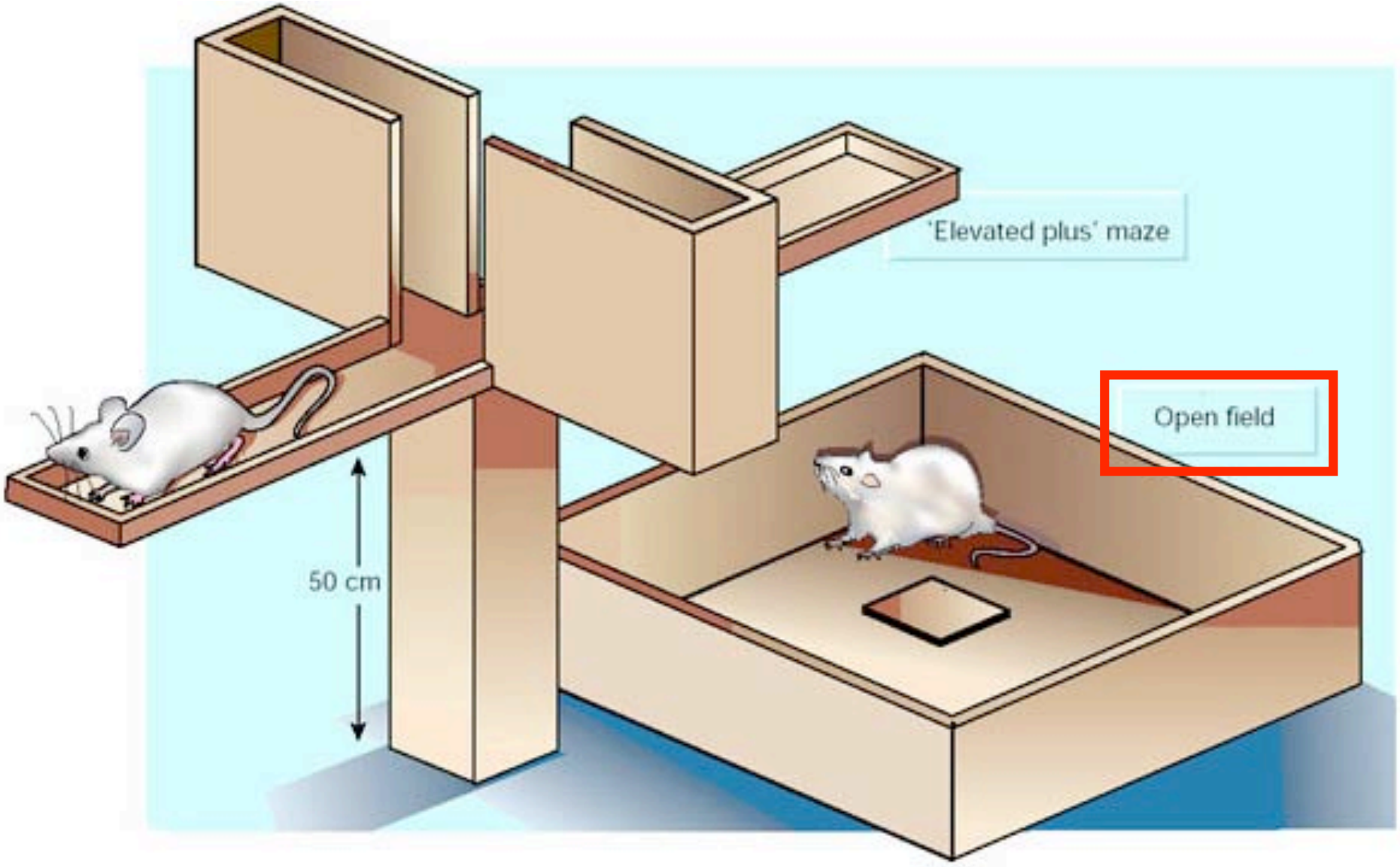
- **Similarity to BDNF +/- mice**
  - Intermale aggressiveness
  - Elevated body weight

Transgenic BDNF$^{Met/Met}$ mouse



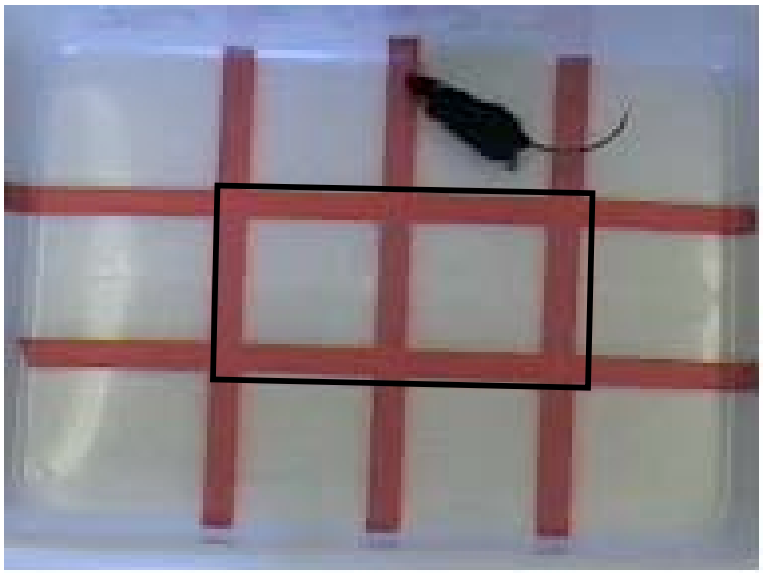
- **Increased anxiety related behaviors**
  - –Open field
  - –Elevated plus maze

Francis Lee

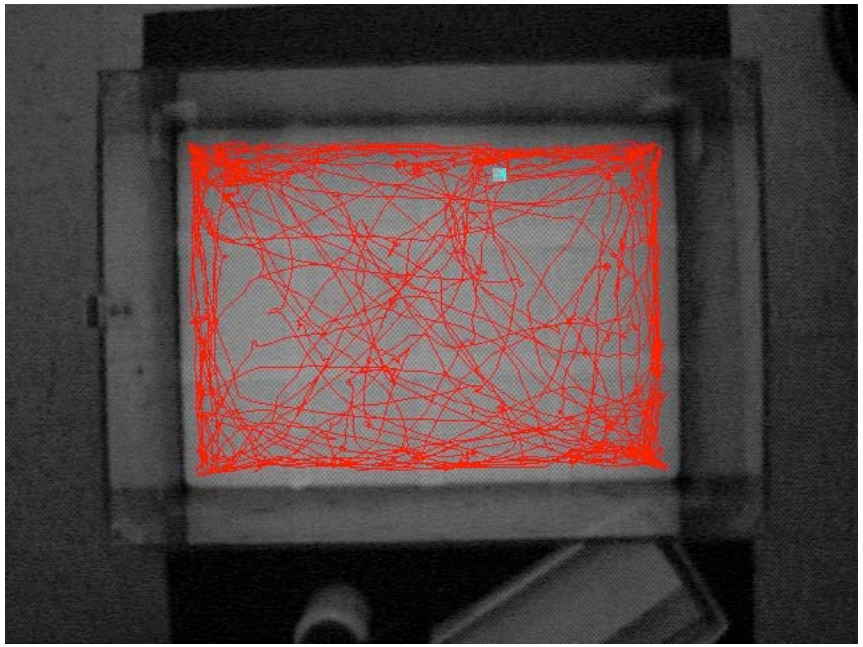


Snyder, 2002

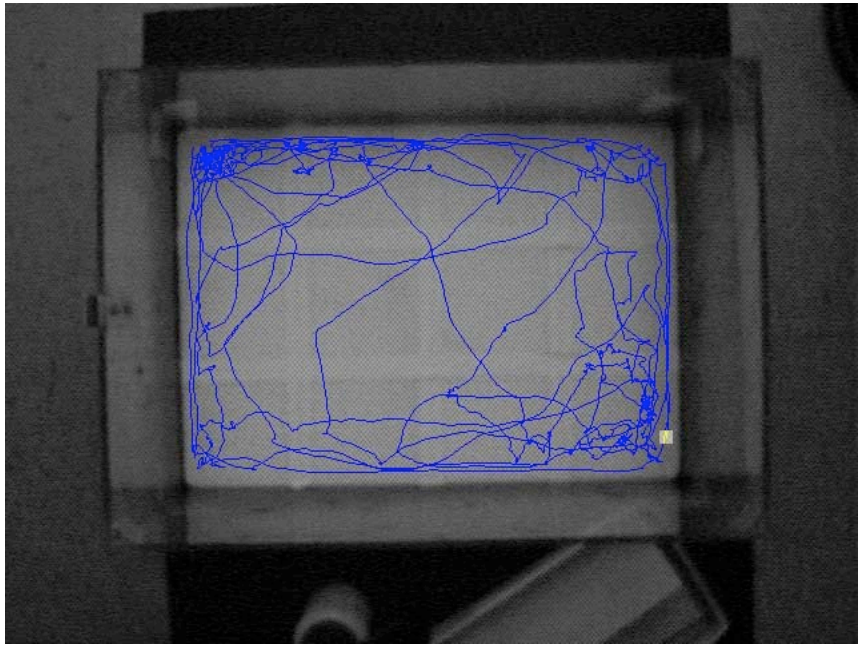
Open Field Test



WT

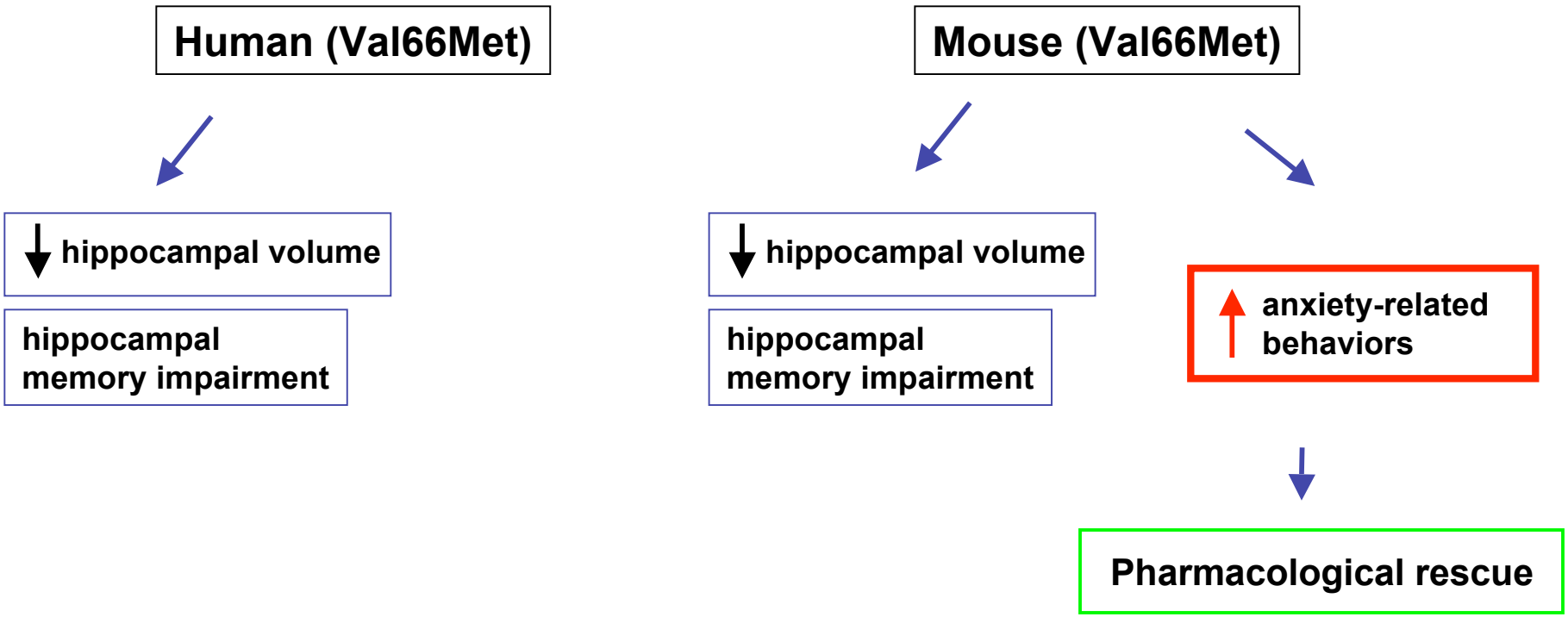


Met/Met

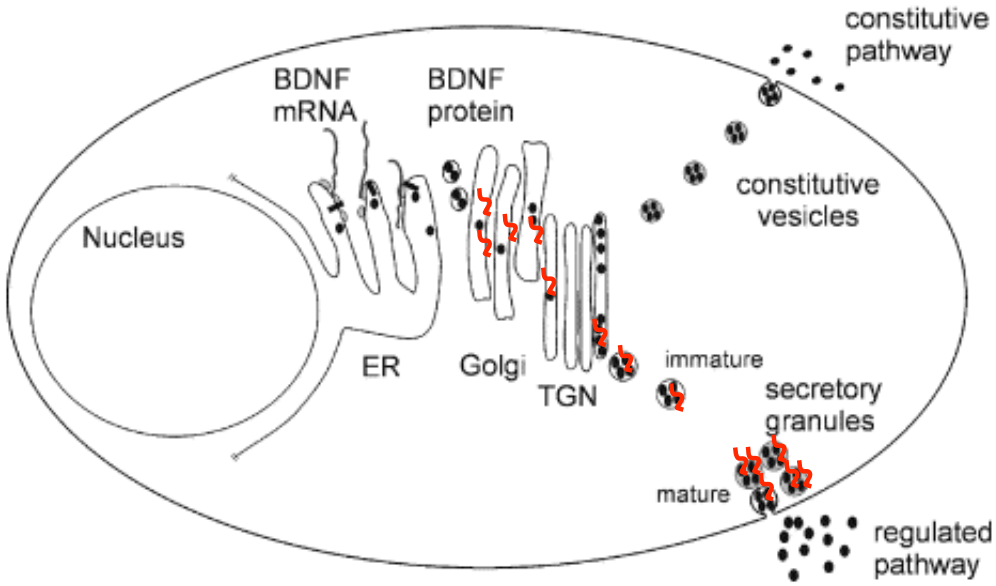


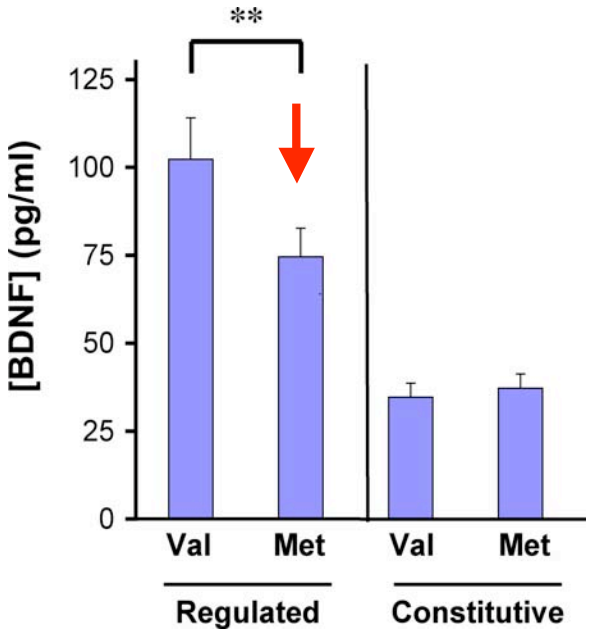
Quantitation of "anxiety-like" behavior

- % time in center
- % entries to center


Human (Val66Met)
hippocampal volume
hippocampal memory impairment
Mouse (Val66Met)
hippocampal volume
hippocampal memory impairment
anxiety-related behaviors
Pharmacological rescue

Val66Met polymorphism affects regulated secretion of BDNF

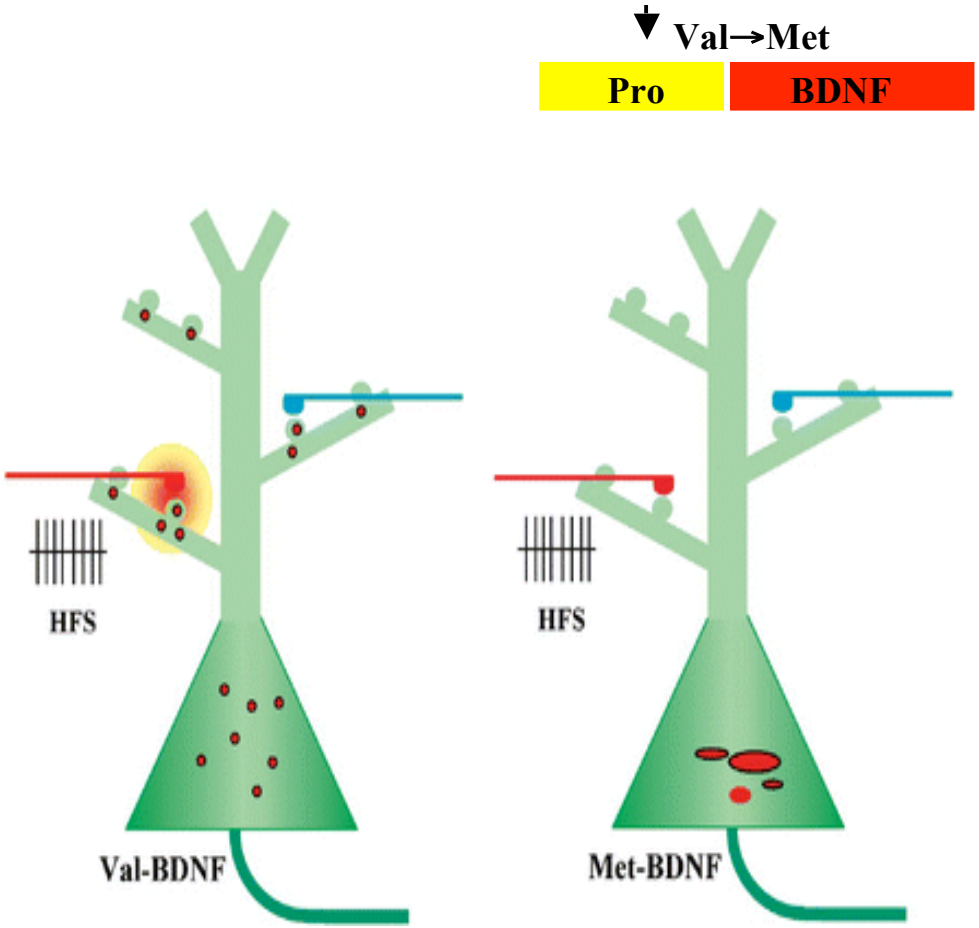


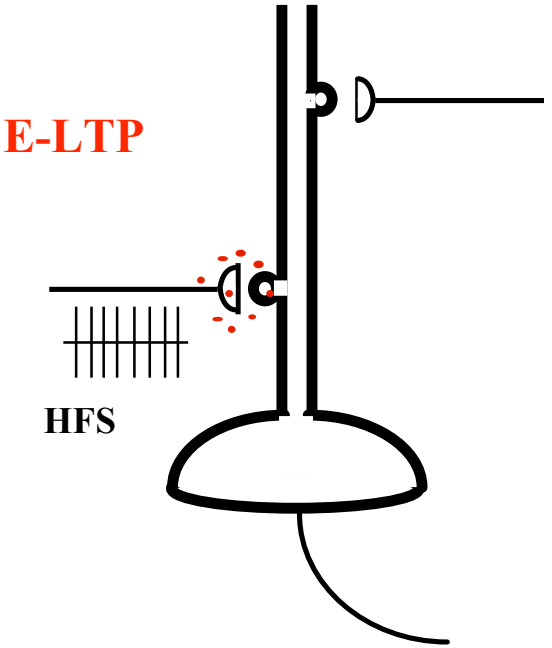


Val/Met

Hippocampal-Cortical Neurons

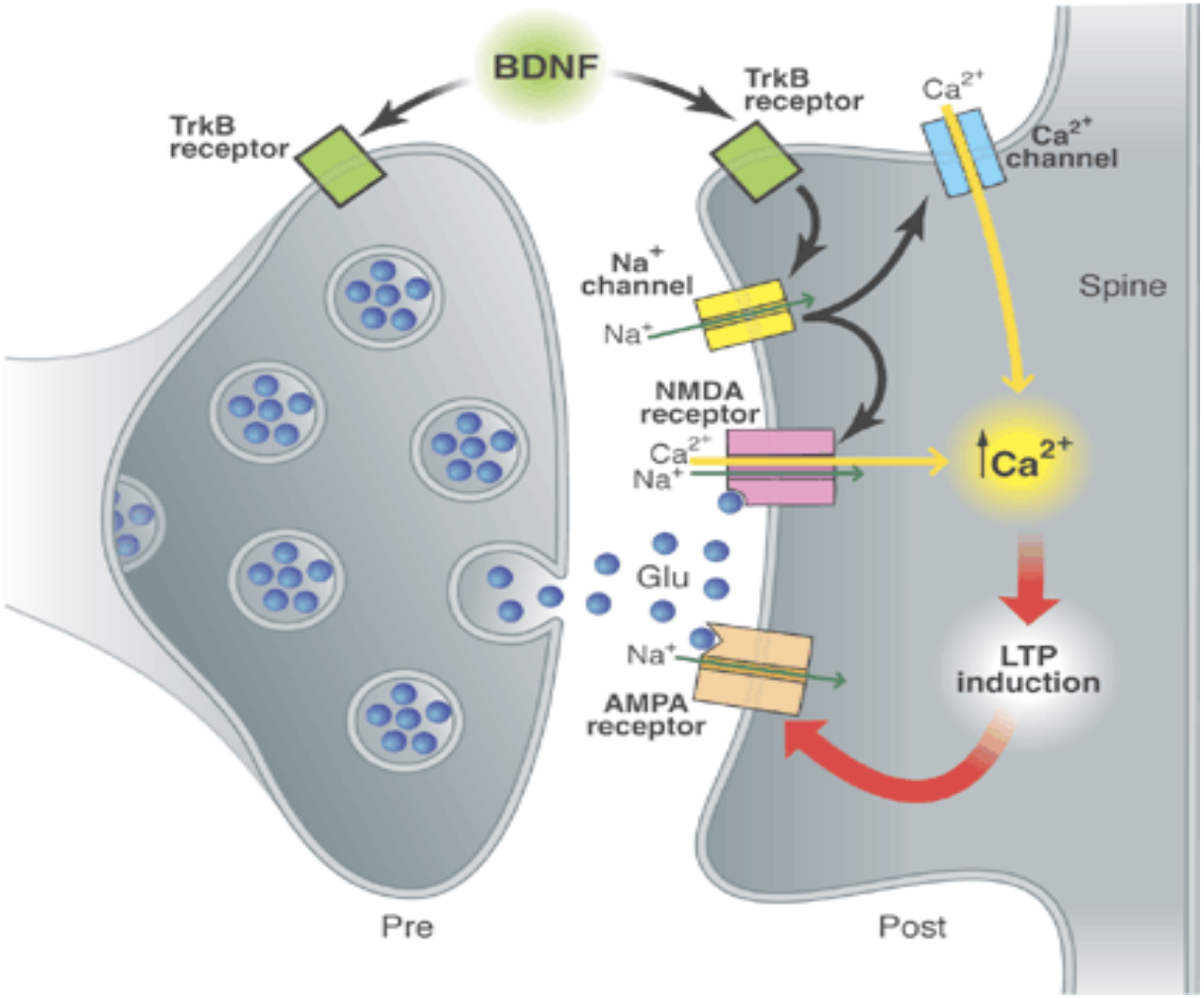
Regulated secretion of BDNF

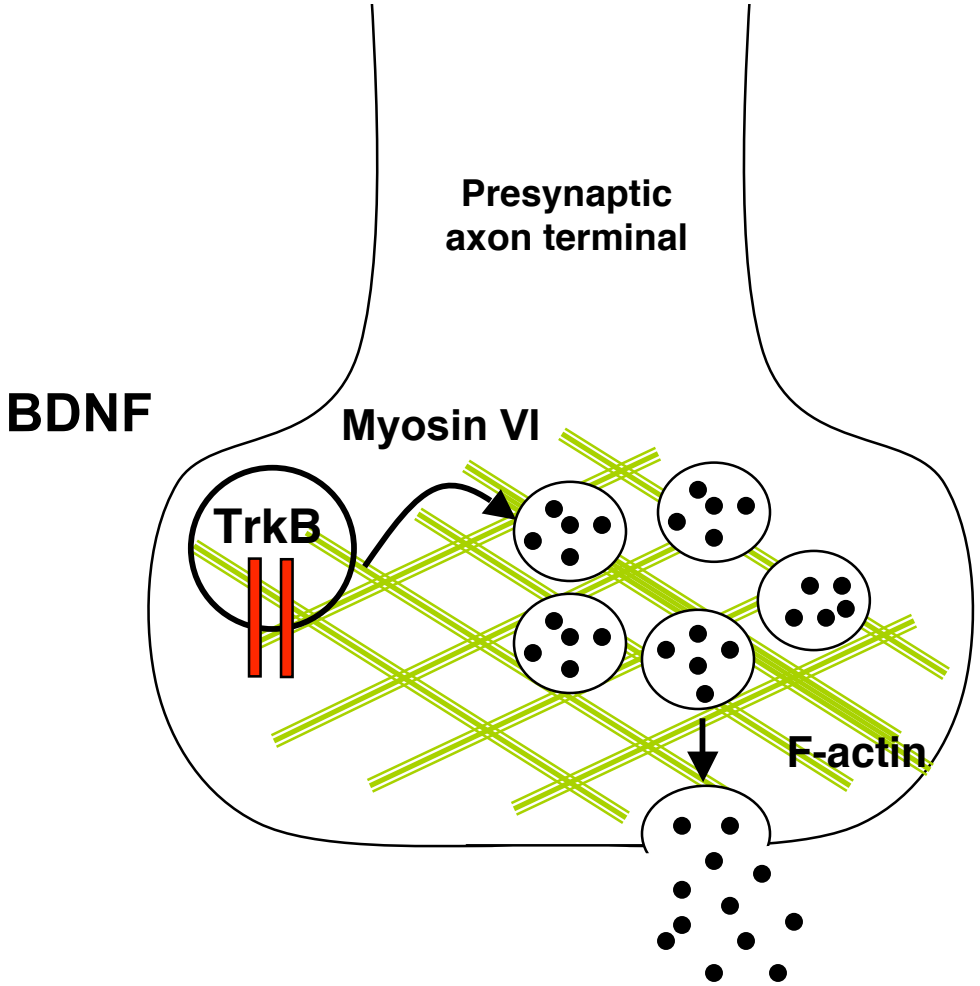




Bai Lu

A main function of BDNF in the adult CNS is synaptic plasticity

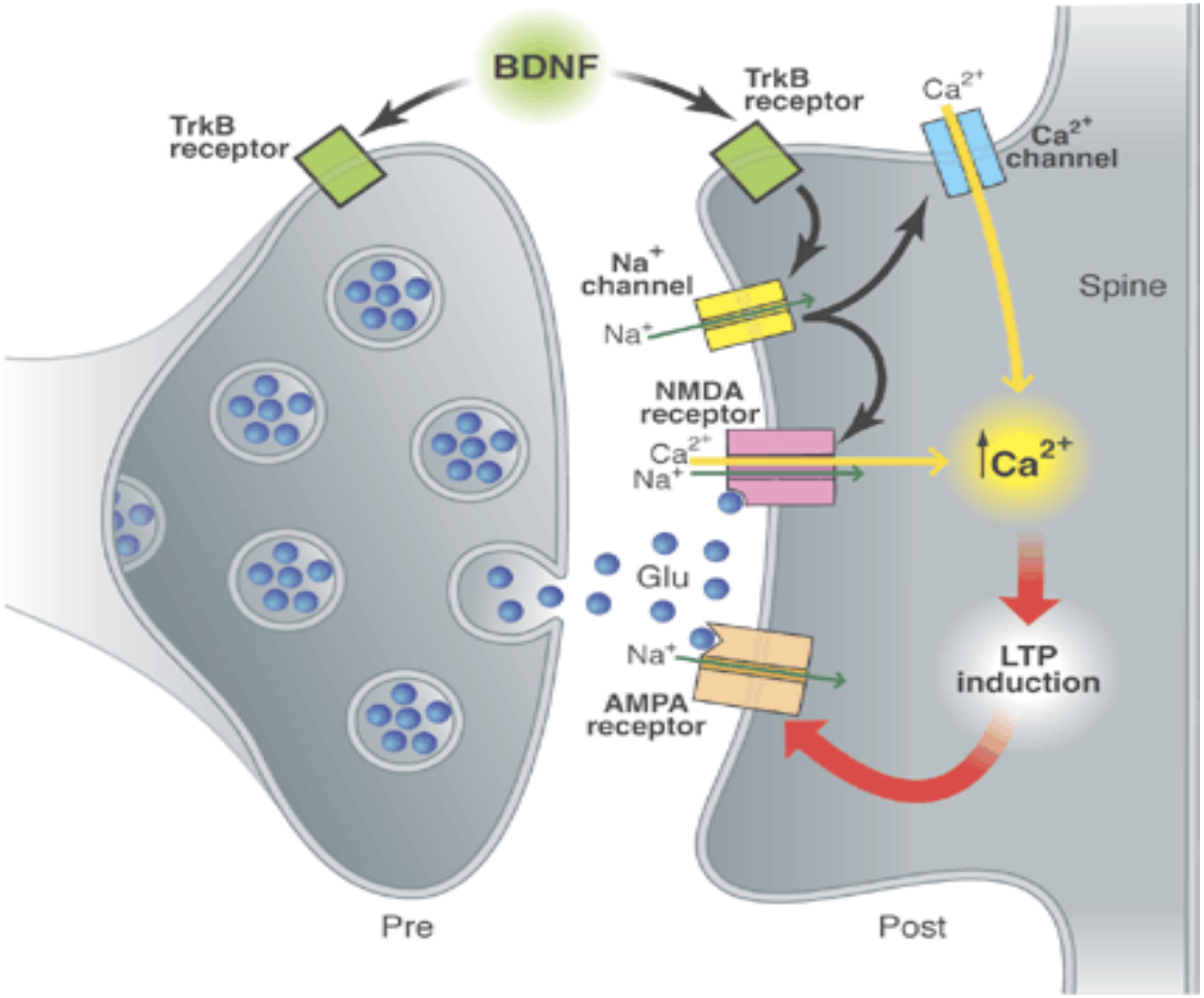




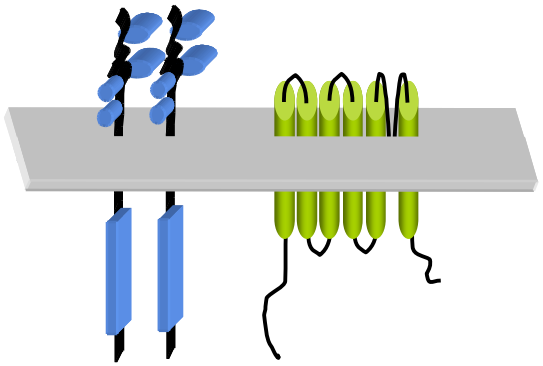
BDNF-induced glutamate release in the hippocampus depends upon TrkB receptor and myosin VI

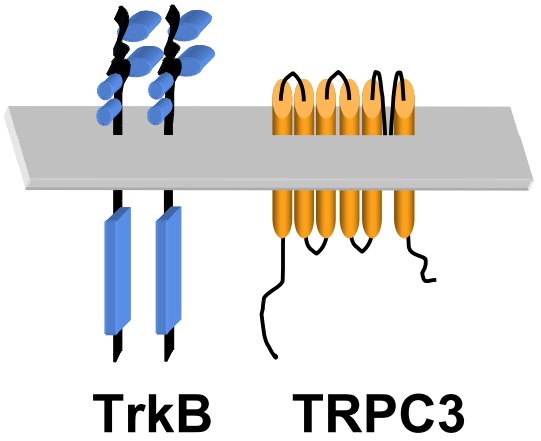
Hiroko Yano
Ipe Ninan
Ottavio Arancio

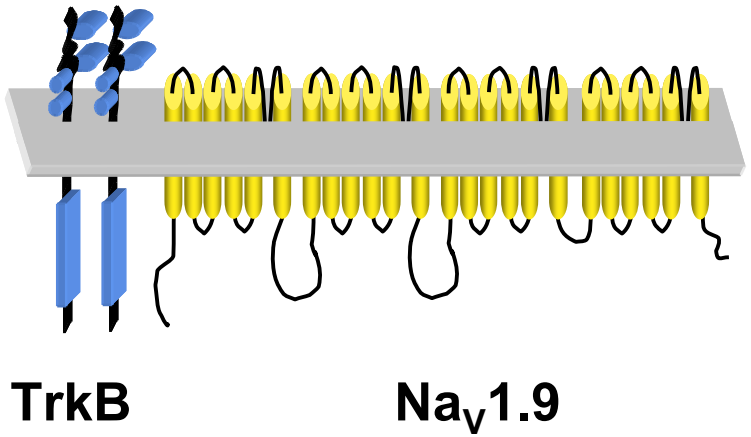
Post-synaptic mechanisms?

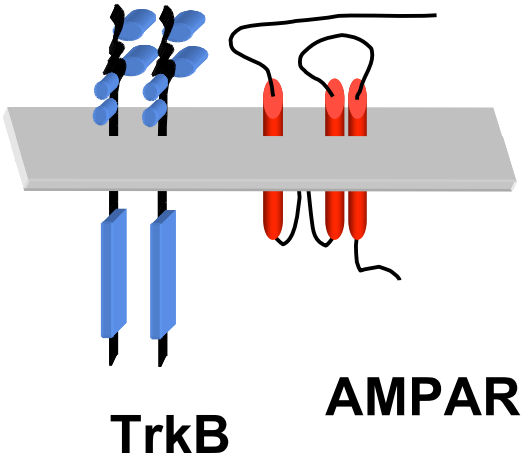


Trk receptors are implicated with multiple ion channels

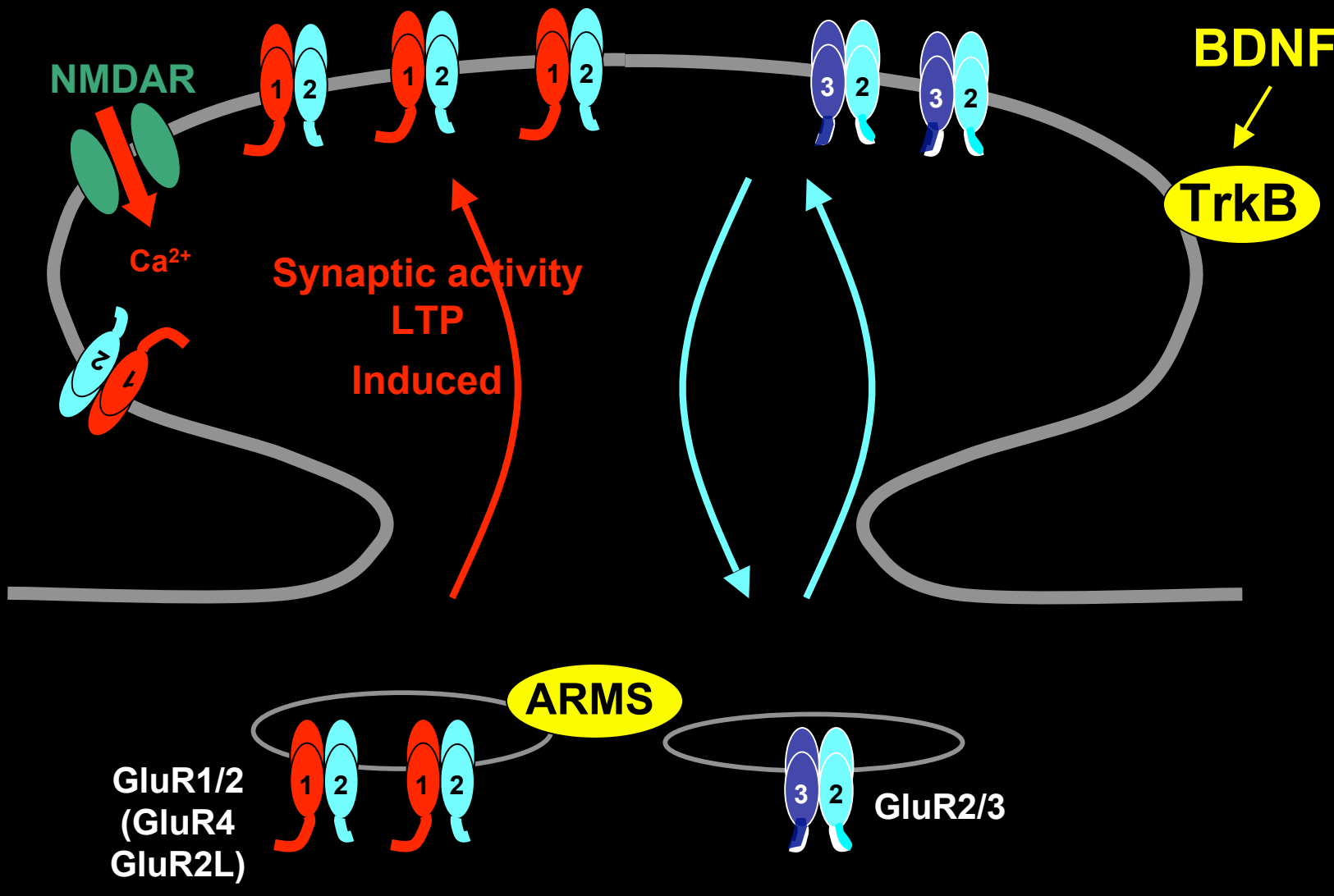




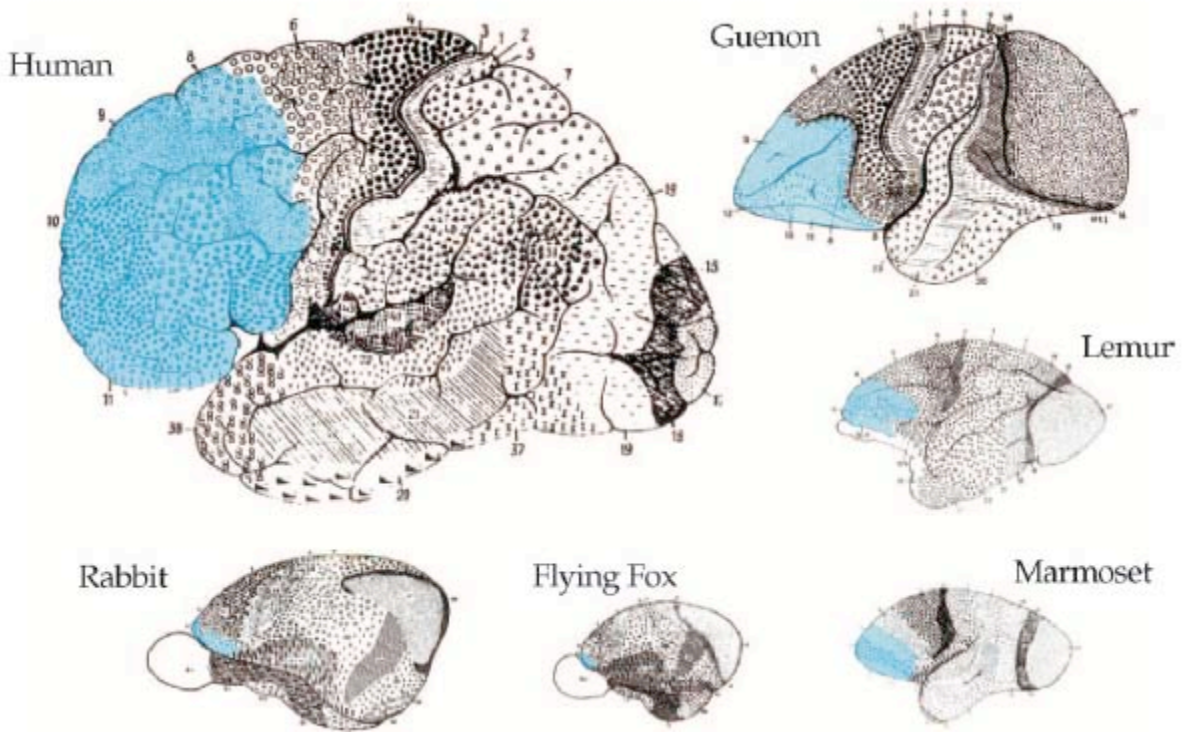




Neurotrophins can regulate synaptic plasticity

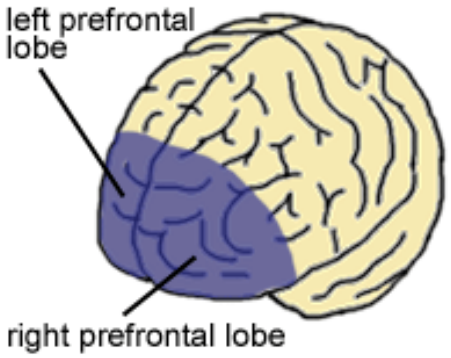


Size = Cognitive function?



Katerina Semendeferi, 2002

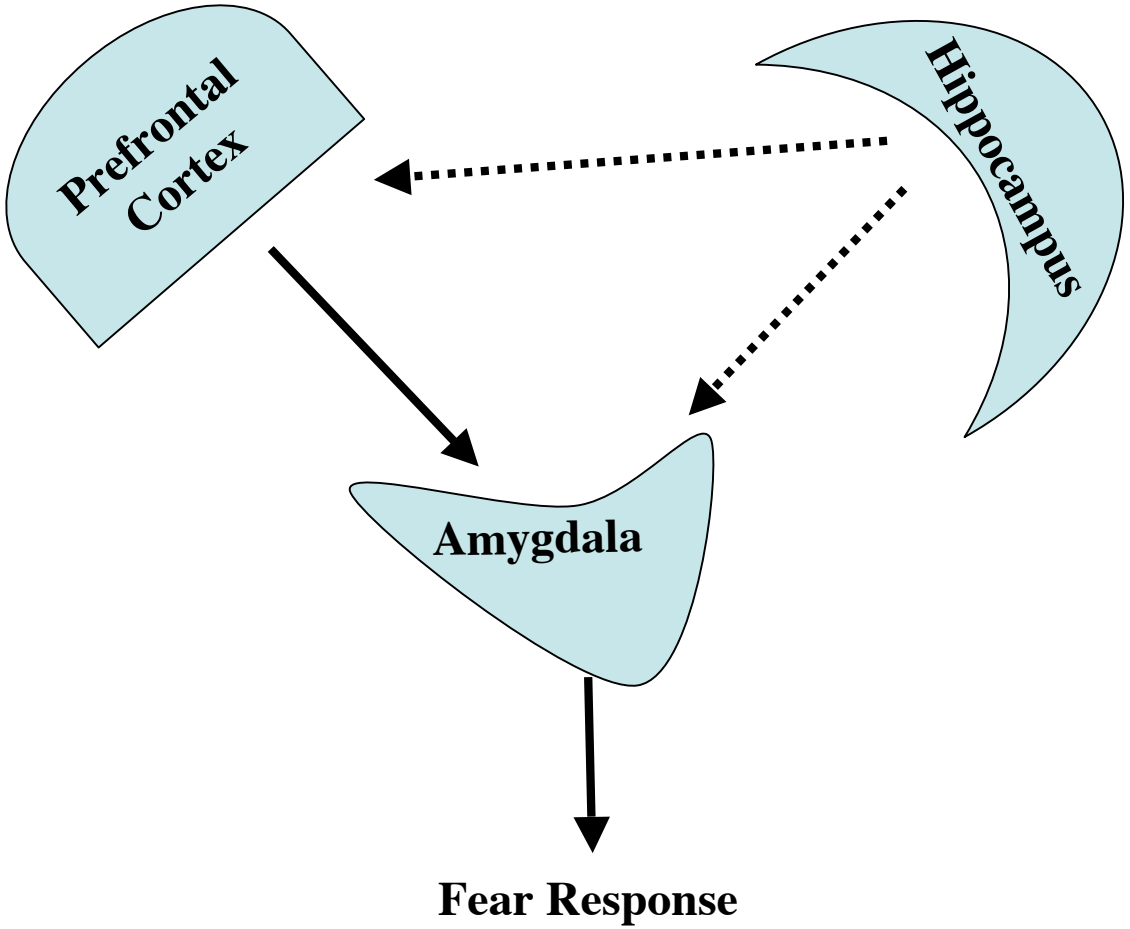
Cytoarchitecture of the prefrontal cortex



Working Memory and Executive Functions

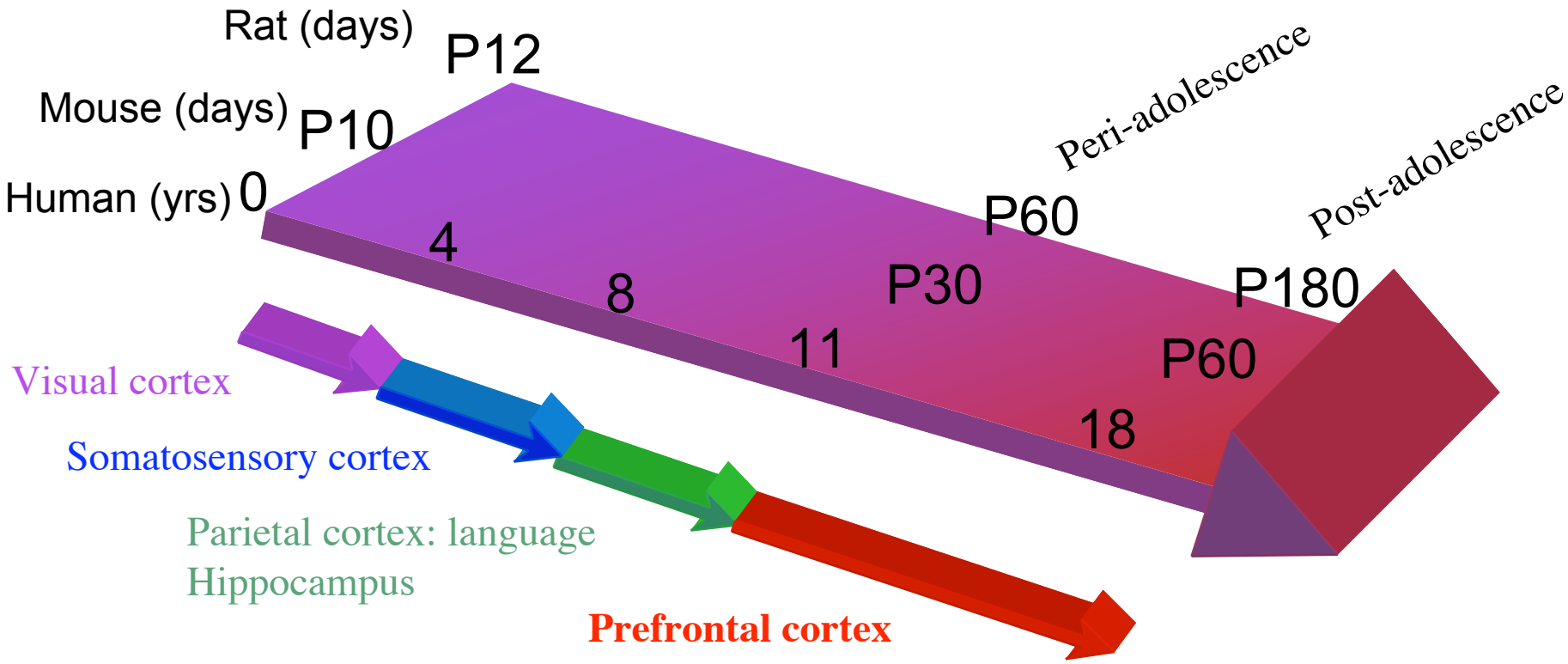
The ability to hold several facts in memory temporarily while performing a task

Prefrontal Cortex Interactions



Matthew & Ho, 2006

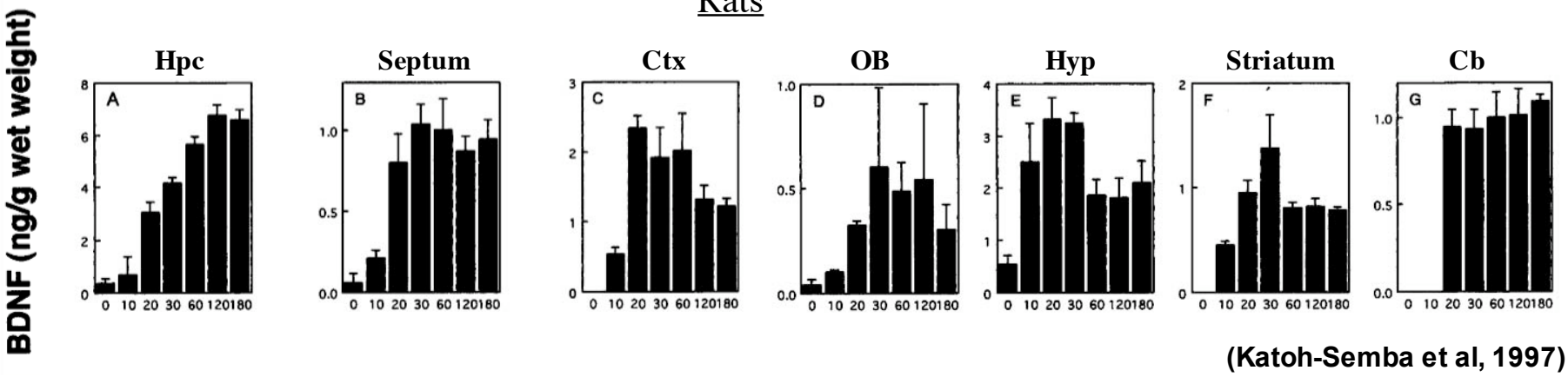
Maturation Trajectories of Different Cortical Areas



Based on Crews et al, 2007

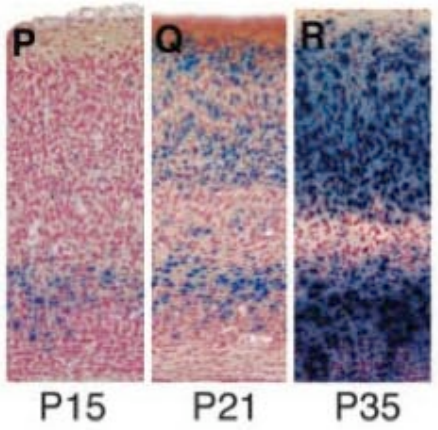
BDNF Levels During Development

Rats



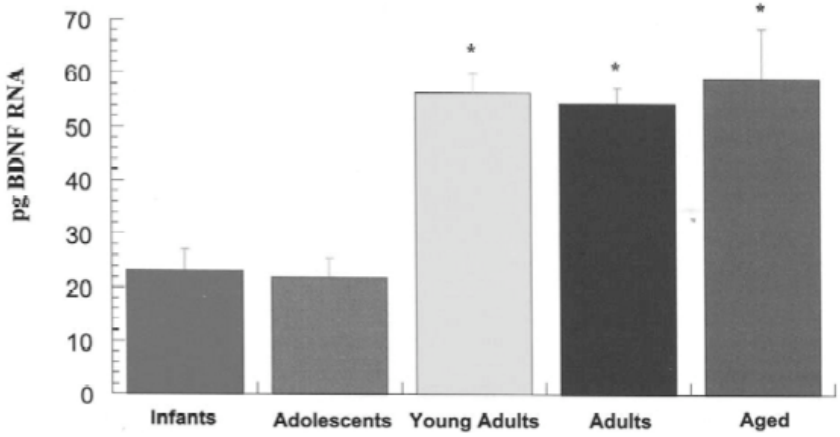
(Katoh-Semba et al, 1997)

Mice - Visual Ctx



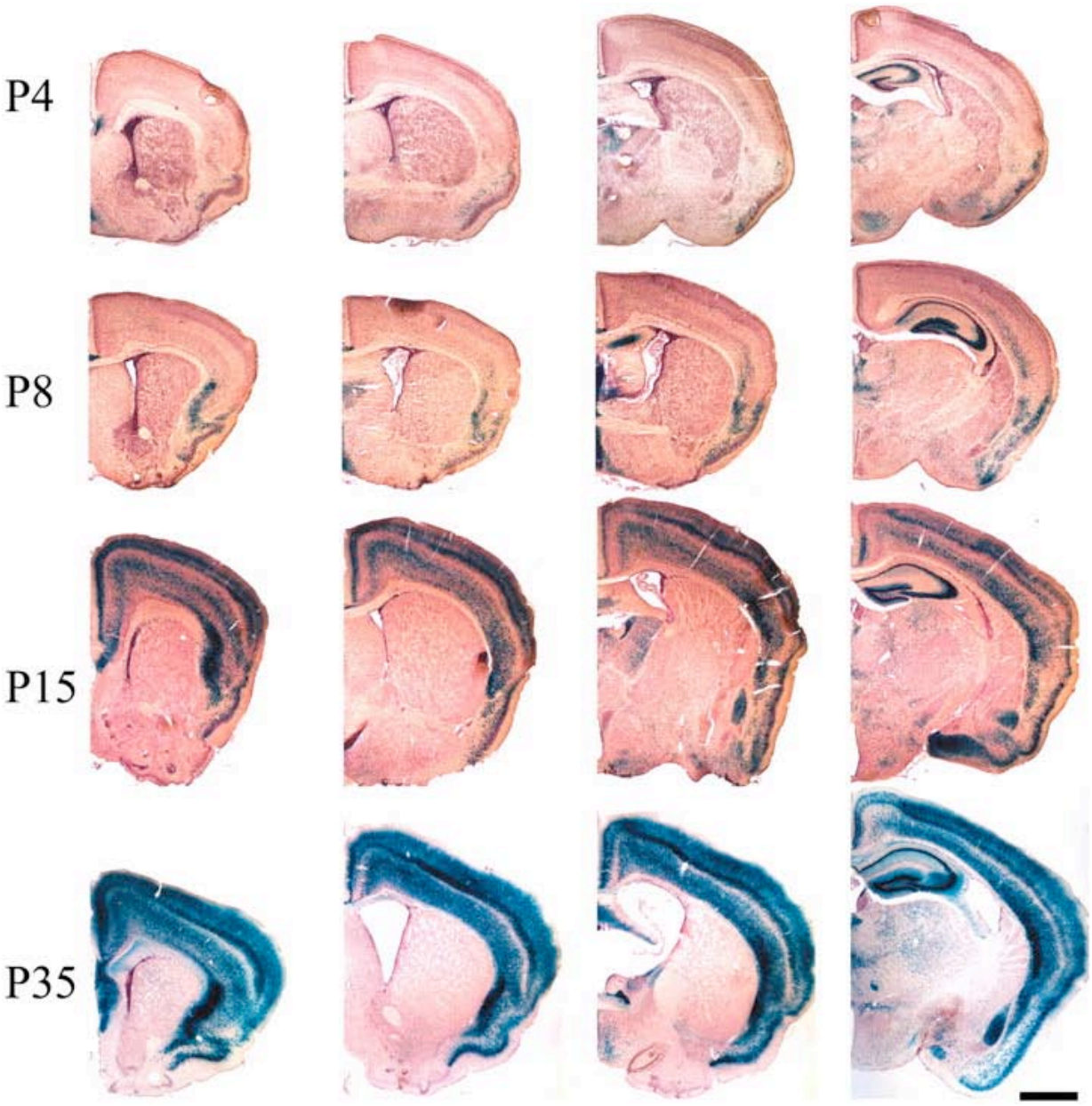
(Gorski et al, 2003)

Humans - Prefrontal Ctx



(Webster et al, 2002)

BDNF expression in postnatal mouse brain



Baquet et al., 2004

BDNF receptors in the PFC

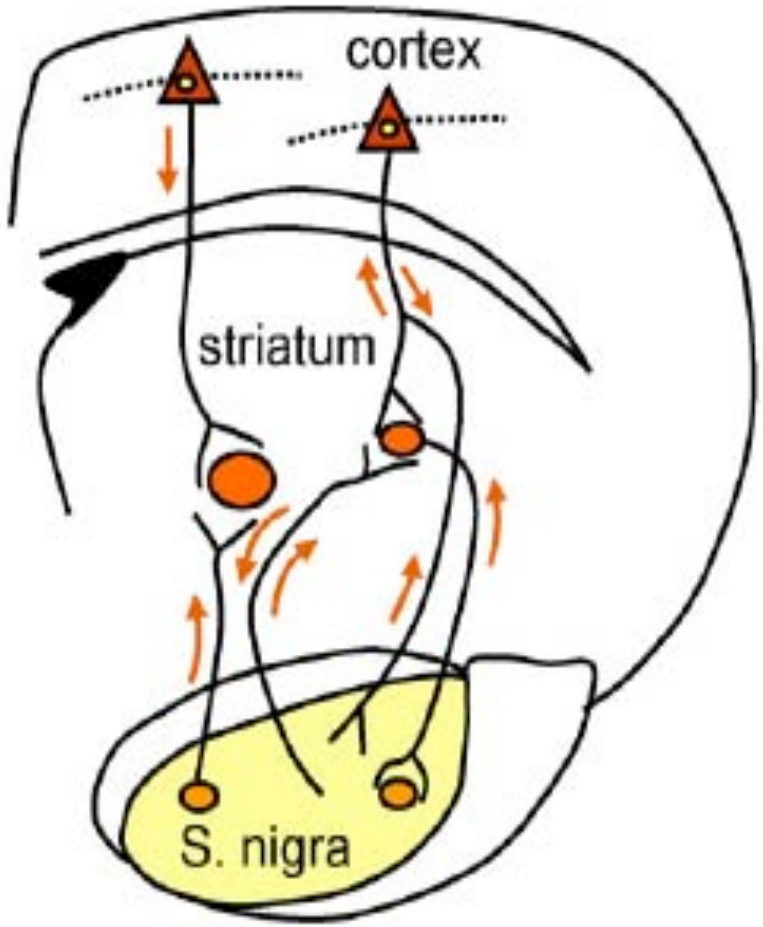
BDNF protein immunoreactivity is preferentially found in pyramidal neurons (Murer et al., 1999)

Decreased **BDNF** and **TrkB** in the PFC of schizophrenics (Hashimoto et al., 2005).

Polymorphisms in the **BDNF** gene in both schizophrenia and ADHD (Krebs et al., 2000; Kent et al., 2005).

Reduced cortical **BDNF** and **TrkB** in Huntington's dementia (Zuccato et al., 2001; Gines et al., 2006).

BDNF is a major factor in the cortex



Huntington's disease

Schizophrenia

ADHD

Huntington's Disease Pathology

-HD is 1 of 15 triplet repeat neurodegenerative disease (CAG)

-Expansion occurs at DNA level in exon 1 of Htt gene.

-Normal 6-34 / Disease 36-121

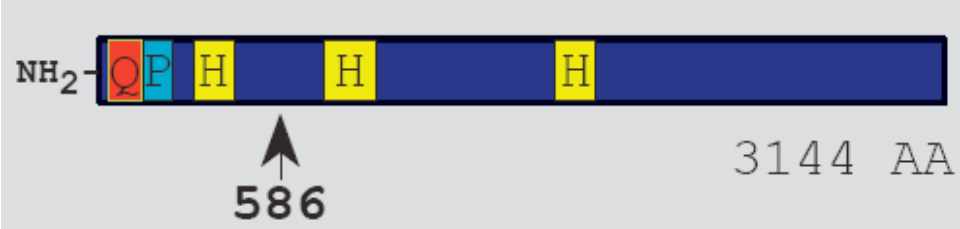
-frequency (European descent) ~ 1/10,000

-Autosomal dominant with complete penetrance

-Late onset: typically 30-50 years of age

-(10-20 years from onset to death)

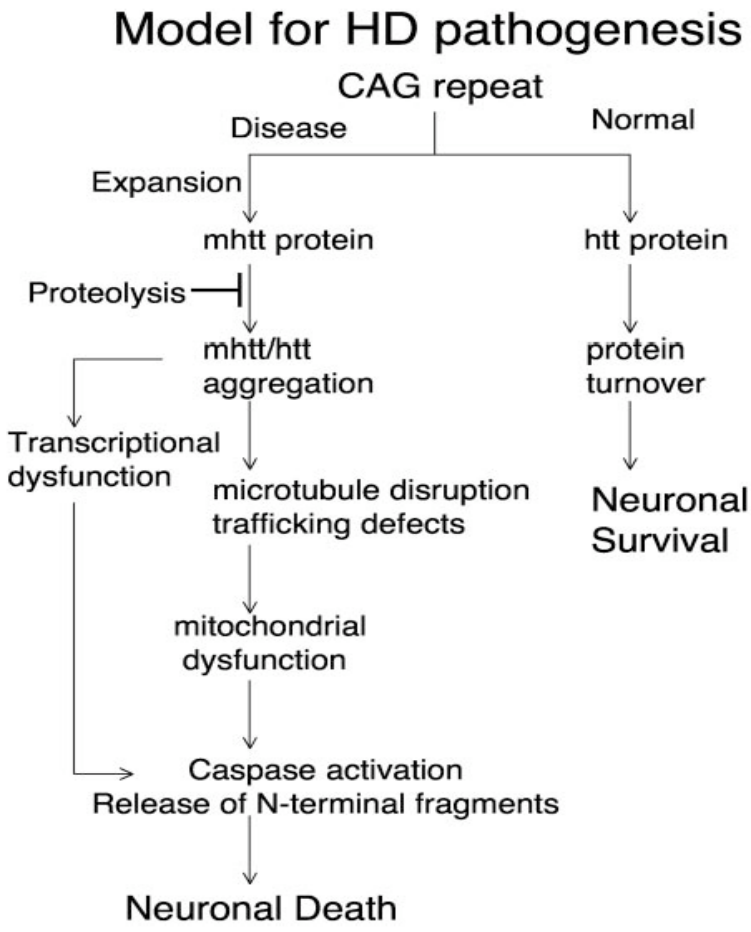
Huntingtin protein (Htt)



Q: poly glutamine (polyQ)

P: proline rich domain (PRD)

H: HEAT repeat



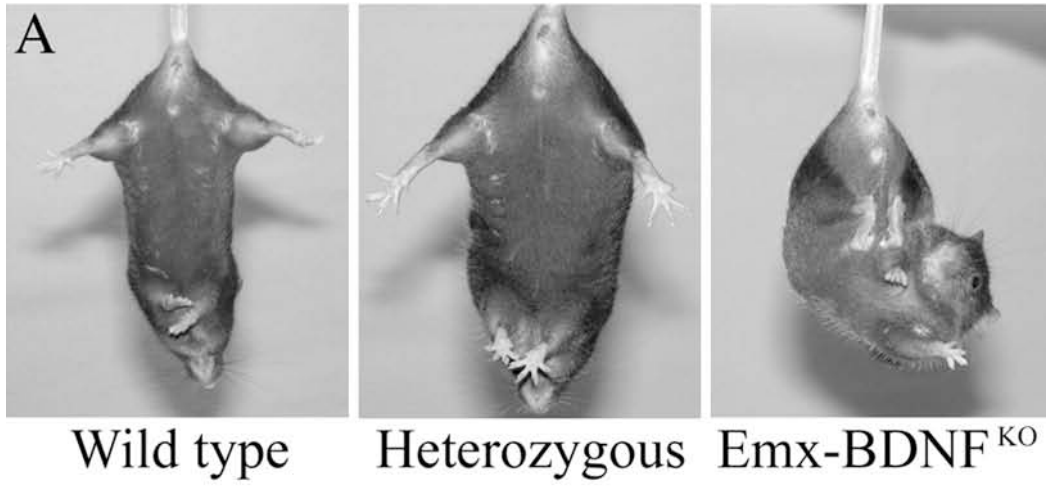
Trushina et. al (2007)

St. Vitus's dance

In East Hampton, it was the name people used for the disease, by the end of the nineteenth century, came to be called "hereditary" or Huntington's chorea after the East Hampton-born physician, George Huntington, who described it in 1872 . . .

Hereditary chorea . . . came on gradually in adulthood, usually beginning in the fourth decade of life. It was characterized by involuntary movements . . . as well as progressive cognitive loss and emotional disturbance.

Alice Wexler, *Chorea and Community in a Nineteenth-Century Town*



Baquet et al *J Neuroscience* 2004

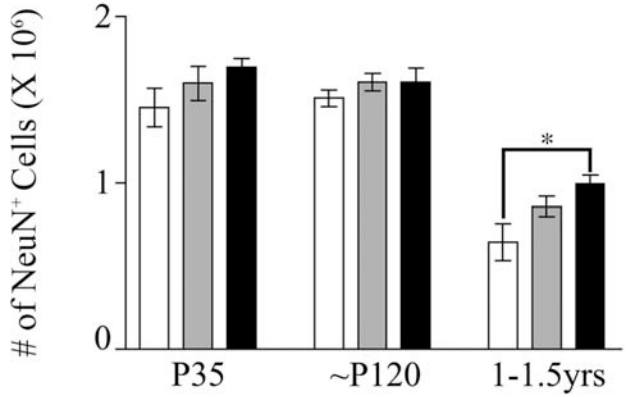
Loss of cortical BDNF--

Decrease in cortical and striatal volumes

Motor dysfunction--limb clasping

Reduction in number dendritic spines of medium spiny neurons

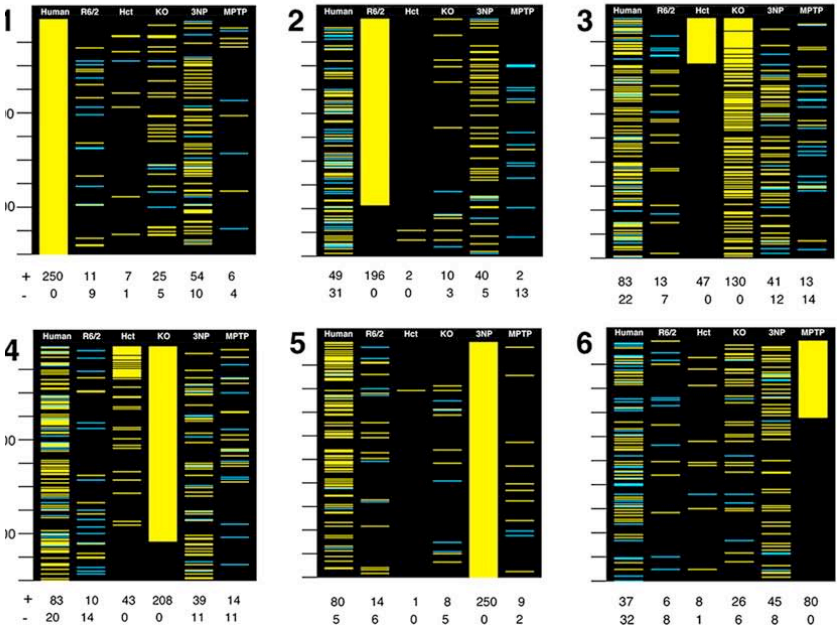
Loss of striatal neurons in old but not young adult Emx-BDNF^{KO} mice



Neurobiology of Disease

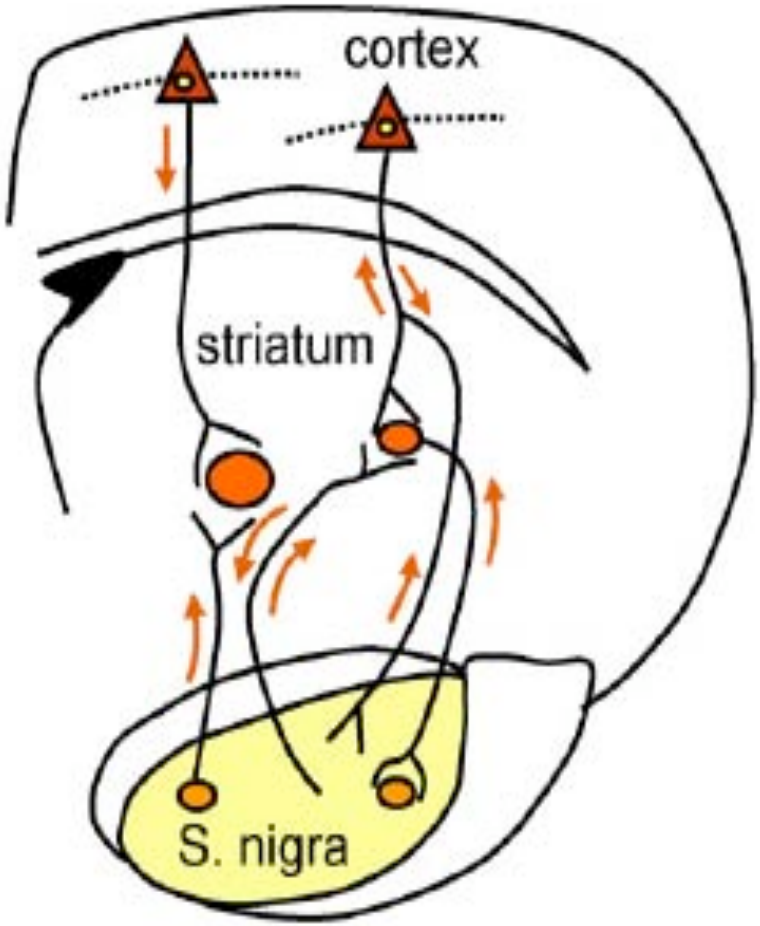
Expression Profiling of Huntington's Disease Models Suggests That Brain-Derived Neurotrophic Factor Depletion Plays a Major Role in Striatal Degeneration

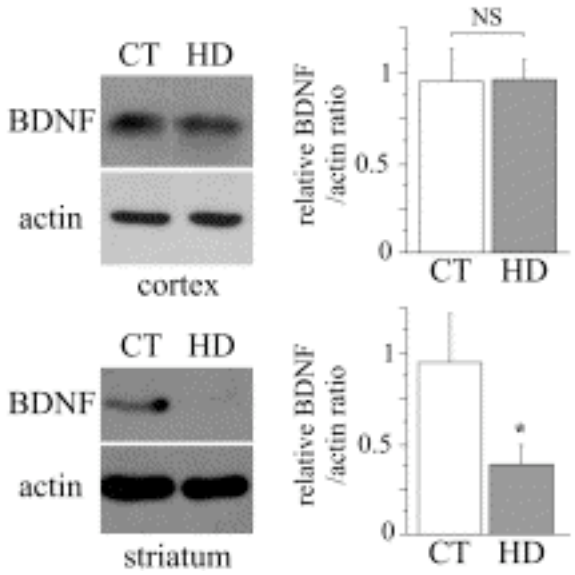
Andrew D. Strand,[1*] Zachary C. Baquet,[2*] Aaron K. Aragaki,[1] Peter Holmans,[3] Lichuan Yang,[5] Carine Cleren,[6] M. Flint Beal,[5] Lesley Jones,[3,4] Charles Kooperberg,[1] James M. Olson,[1‡] and Kevin R. Jones[2‡]



	Up-regulated GO Functions and Processes	*Down-regulated GO Functions and Processes*
Human	hyaluronic acid binding cell-matrix adhesion **nuclear mRNA splicing via spliceosome** thyroid hormone receptor binding transcription regulator activity transcriptional activator activity RNA polymerase II transcription mediator act. cadmium ion binding pos. reg. I-kappaB kinase/NF-kappaB cascade actin filament binding	**ion transport** ATP synthesis coupled proton transport synaptic transmission H-transporting ATP synthase activity rotational mech. H-transporting ATPase activity rotational mechanism **calcium ion transport** proton transport voltage-gated calcium channel activity central nervous system development **NADH dehydrogenase (ubiquinone) activity**
R6/2	**nuclear mRNA splicing via spliceosome** mRNA processing lipoprotein biosynthesis nucleotide binding phospholipid translocation proteasome activator activity protein transport RNAsplicing factor act. transesterification mech. actin filament severing cholesterol transport	calmodulin binding sterol biosynthesis phosphoprotein phosphatase activity cholesterol biosynthesis steroid biosynthesis bone mineralization calcium ion binding protein phosphatase type 1 regulator activity negative regulation of signal transduction regulation of signal transduction
BDNF +/-	actin filament severing structural molecule activity cyclic nucleotide catabolism 2' 3'-cyclic-nucleotide 3'-phosphodiesterase act. axonogenesis GTPase activity intermediate filament-based process intracellular signaling cascade protein kinase C binding barbed-end actin filament capping	transcription factor activity myelination protein binding rhythmic behavior regulation of signal transduction vitamin D binding protein tyrosine phosphatase activity phosphoprotein phosphatase activity microvillus biogenesis transcription
BDNF KO	lipid biosynthesis vesicle-mediated transport structural molecule activity GTPase activity myelination signal transducer activity signal transduction sterol biosynthesis actin filament severing cholesterol biosynthesis	ion channel activity voltage-gated ion channel activity potassium channel activity **ion transport** protein binding calcium ion binding **calcium ion transport** potassium ion binding phosphatidylinositol transporter activity potassium ion transport
3NP	protein biosynthesis immune response ribosome biogenesis RNA binding structural constituent of ribosome GTPase activity response to wounding defense response endopeptidase activity inflammatory response	water homeostasis inorganic diphosphate transporter activity neg. regulator of non-apoptotic programmed cell death water binding inorganic phosphate transporter activity phosphate transporter activity carbonate dehydratase activity
MPTP	NADH dehydrogenase activity **NADH dehydrogenase (ubiquinone) activity** oxidoreductase activity oxygen binding oxygen transport oxygen transporter activity structural constituent of ribosome regulation of NF-kappaB import into nucleus rRNA binding transport	calcium and calmodulin-dependent prot. kinase activity protein binding synaptic vesicle maturation calmodulin binding calcium ion-dependent exocytosis

BDNF support to the striatum

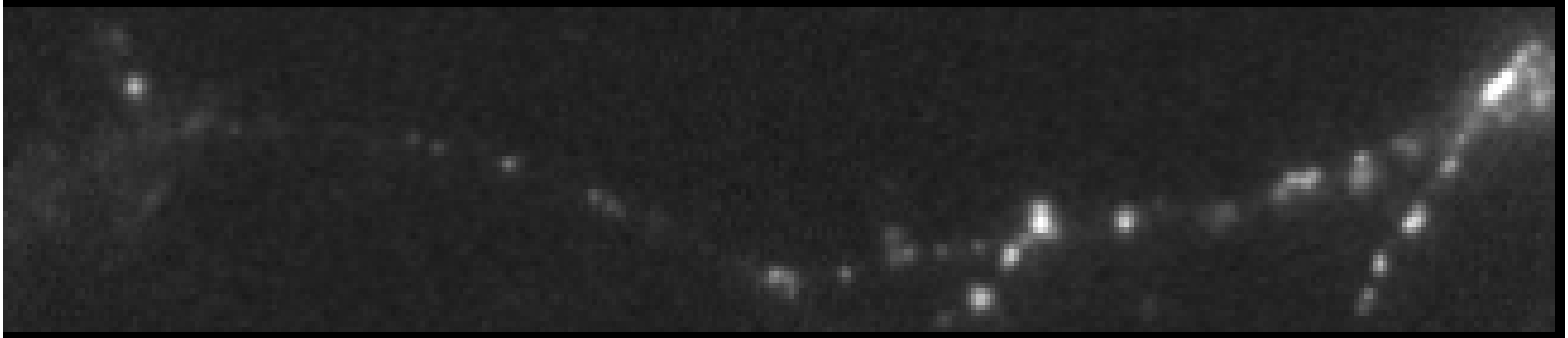




Gauthier L.R. et al Cell. 2004;118:127-138

Altar et al., 1997; Groenewegen and Uylings, 2000; Zuccato and Cattaneo, 2007

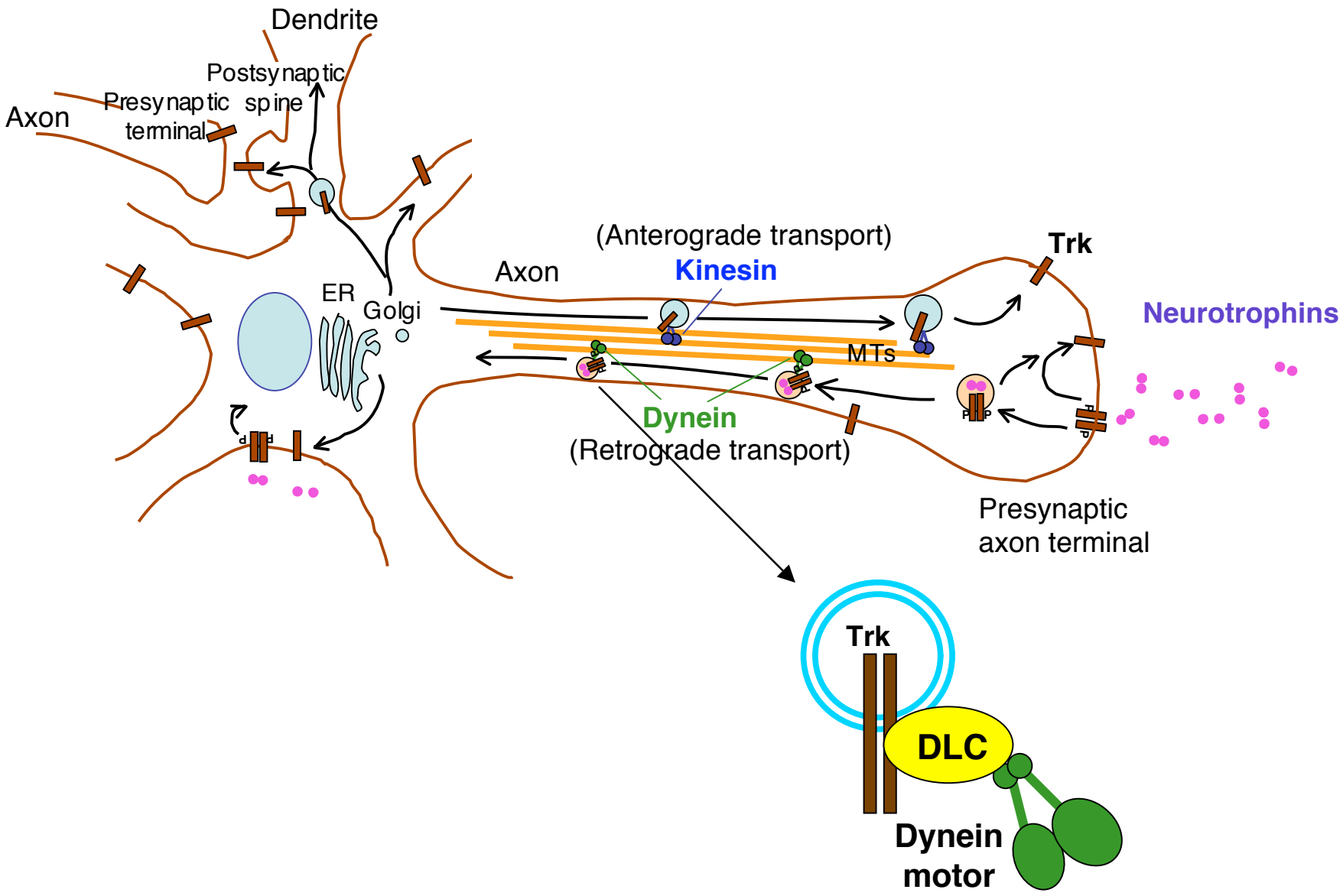
Axonal transport of BDNF-RFP



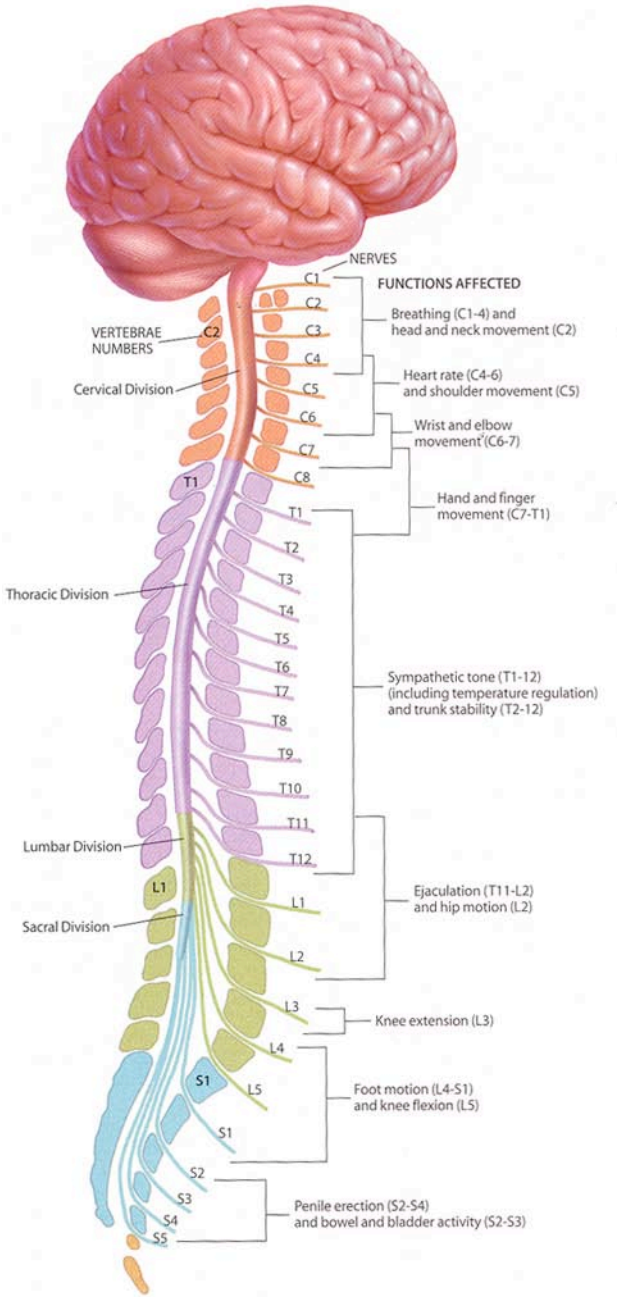
10 μm

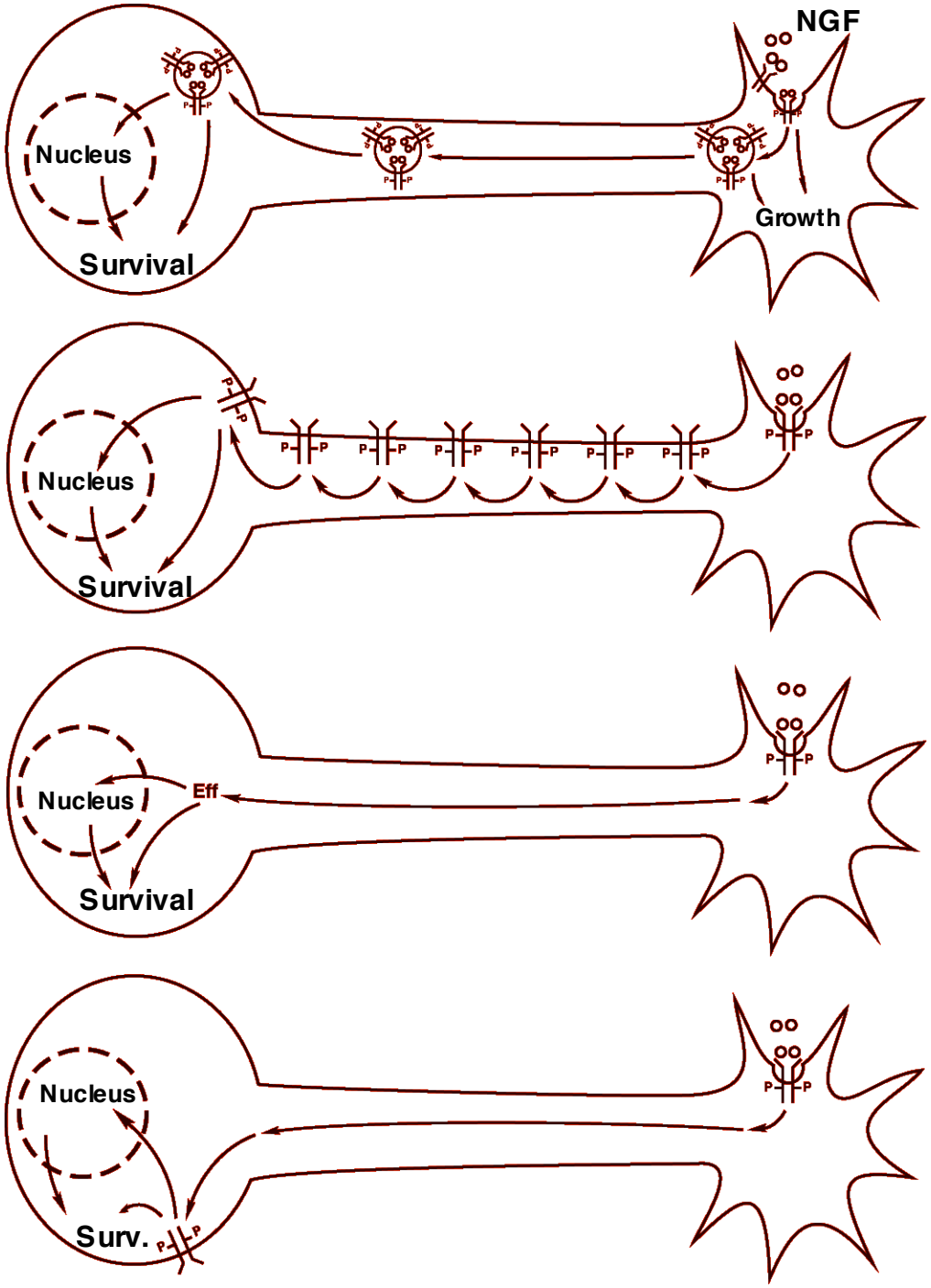
Katrin Deinhardt

How are trophic signals transmitted to different locations?



R. DESCARTES, 1664





Signaling Endosome Model

"Domino" or "Membrane Wave" Model

Retrograde Effector Model

Other Models