

# Strategies for Repairing the Injured Brain

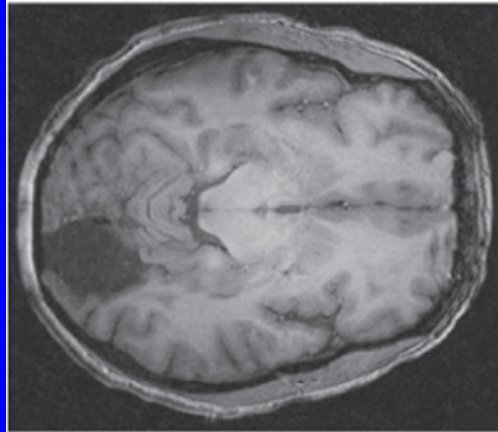


**Bryan Kolb**

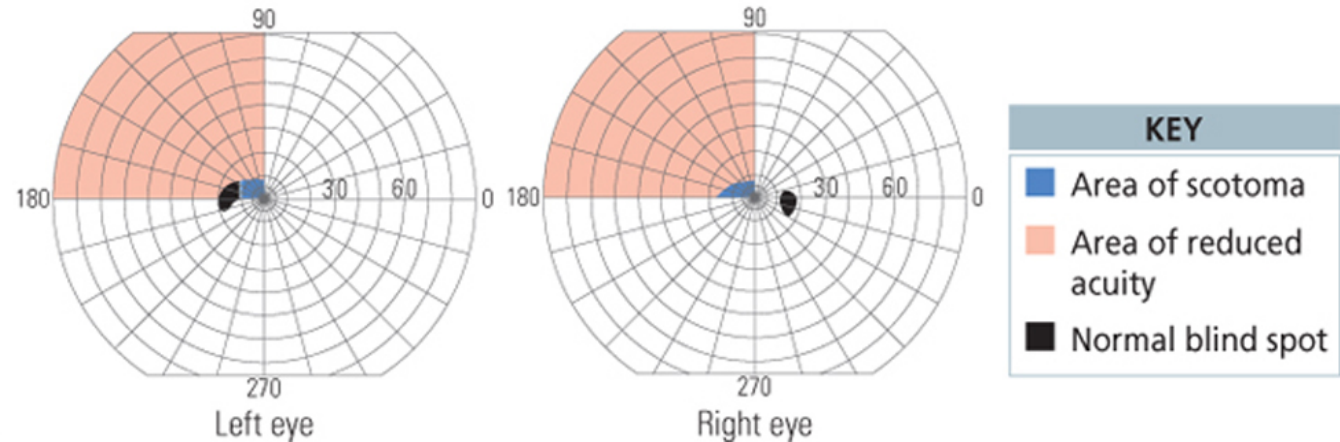
**Canadian Centre for Behavioural Neuroscience  
University of Lethbridge  
Canada**

# A January 1985 surprise!

(A) MRI scan of B.K.'s brain



(B) B.K.'s left and right visual fields



**My thoughts:**

**That is a BIG hole...**

**What is the treatment???**

**I am on the wrong side of the table here!**

# Obstacles to Translation

1. What constitutes recovery? (e.g., 3-legged cat)

# The problem of the 3-legged cat.



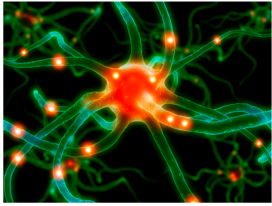
# Obstacles to Translation

1. What constitutes recovery? (e.g., 3-legged cat)
2. What is the right model for preclinical trials?
3. The problem of grey-white matter ratio in the cortex of rodents versus humans.
4. The choice of subjects for human clinical trials...

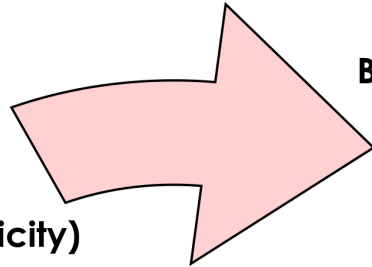
# What happens during recovery?

1. Synaptic reorganization
2. Neuro/glio/angiogenesis
3. Altered gene expression

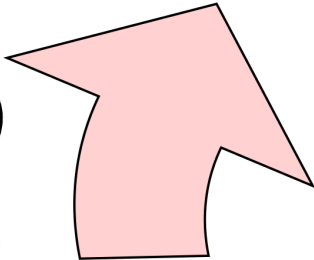
I will return to these shortly.



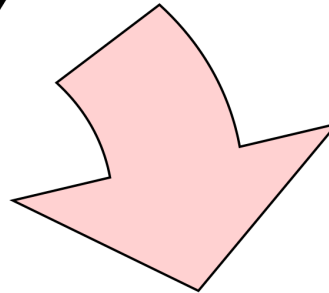
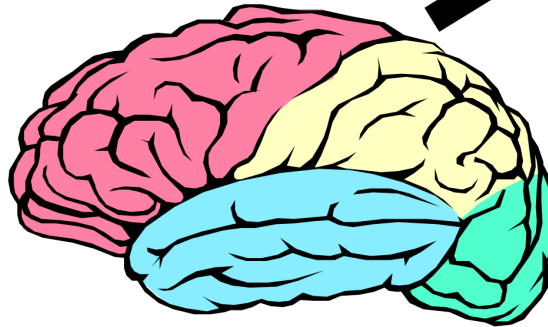
Neurons (Neuroplasticity)



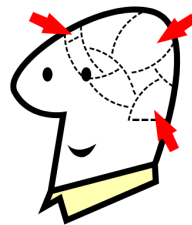
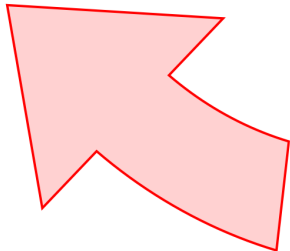
Brain (behavior-related neural activity)



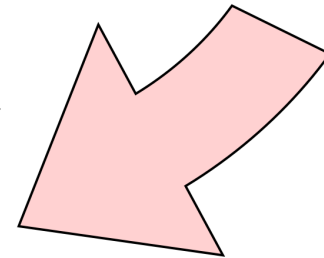
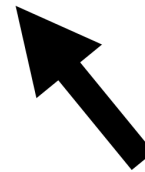
Genes (expression changes)



Behavior/Environmental Interaction



Brain (experience-related neural activity)



**What does this lead to?**

**1. Compensation (positive plasticity)**



## **What does this lead to?**

- 1. Compensation (positive plasticity)**
- 2. Maladaptation (negative plasticity)**

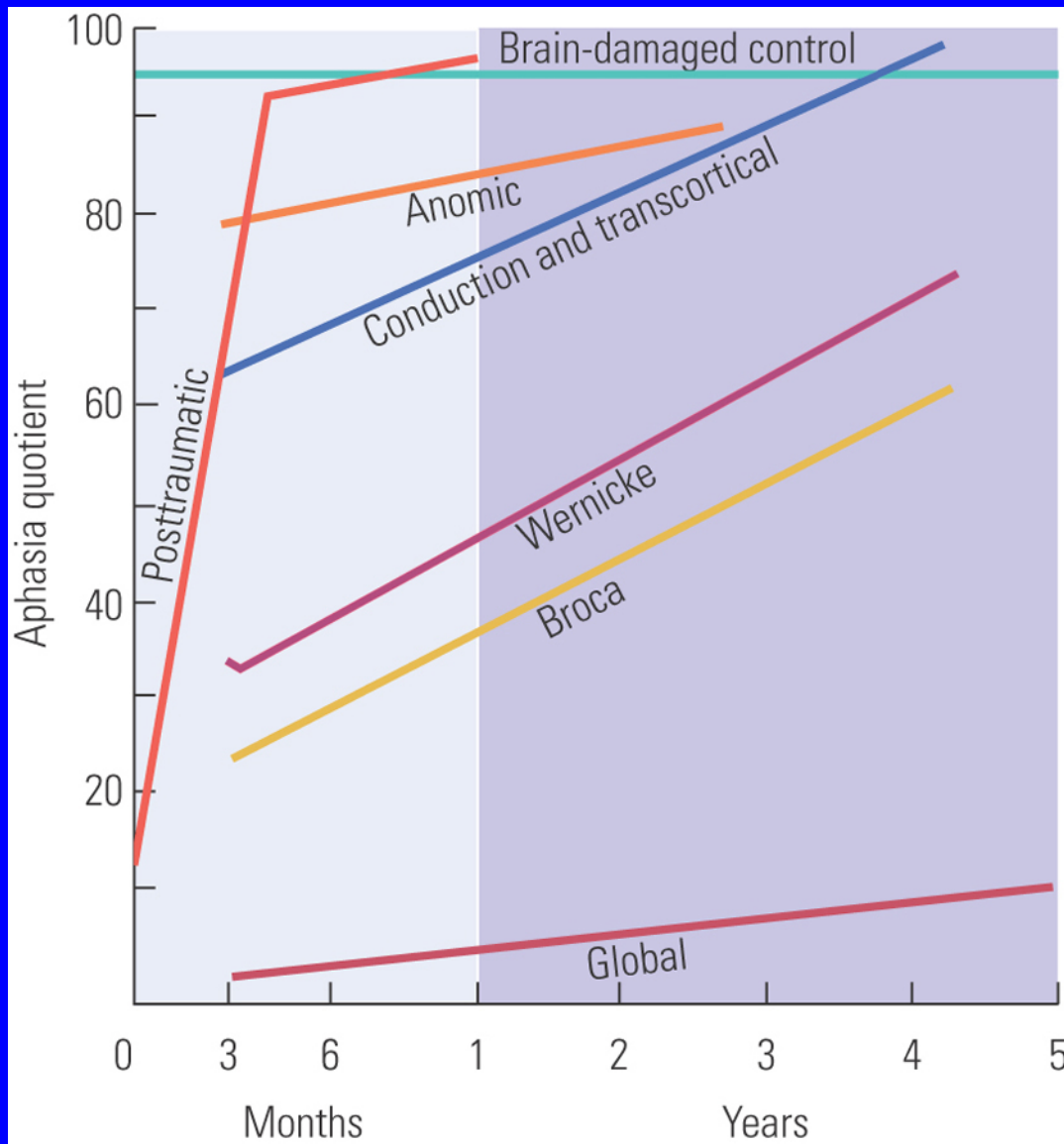
**The idea of “learned non-use” of both motor and cognitive functions...**

# **Is there spontaneous 'recovery' after injury?**

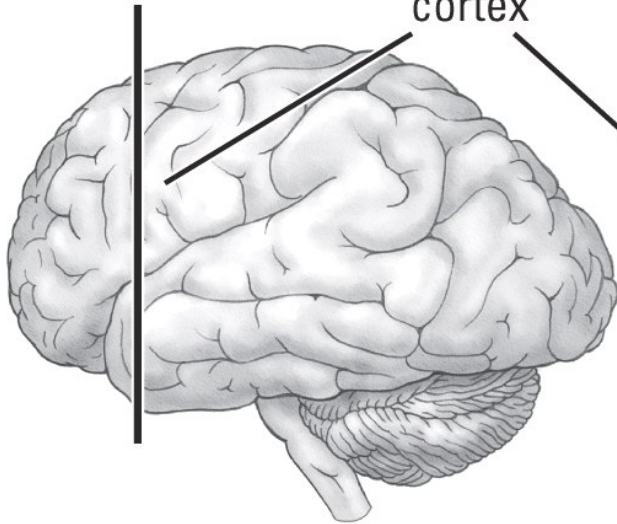
**Yes, although it is dependent on a variety of factors including:**

- nature of the injury (stroke, TBI, etc)**
- location and size of injury**
- white versus gray matter involvement**
- age at injury**
- pre-injury factors**  
**(e.g., SES, stress, age, prenatal events)**

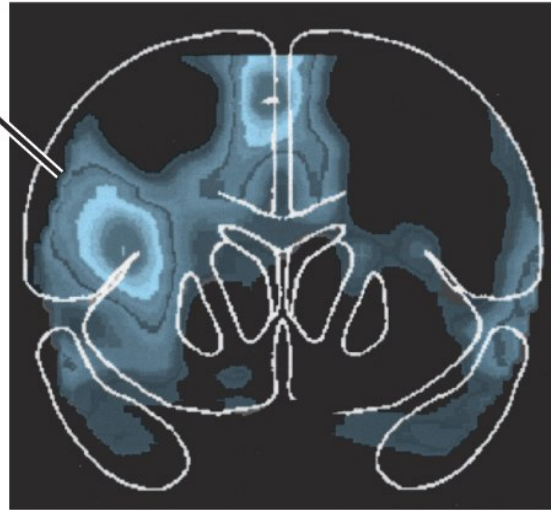
# "Recovery" over time



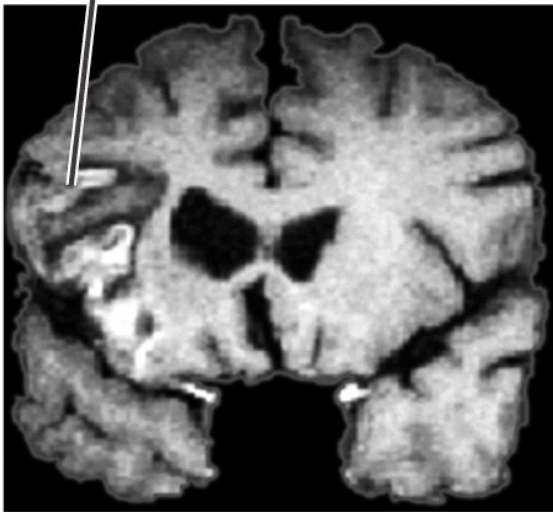
Plane of sections Left prefrontal cortex



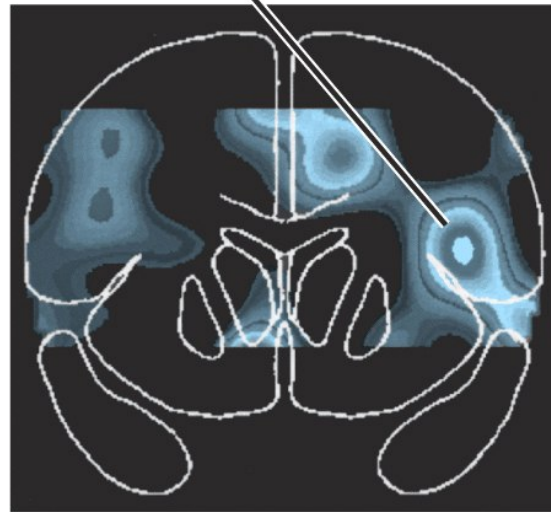
Controls



LF1's stroke



LF1's recovery

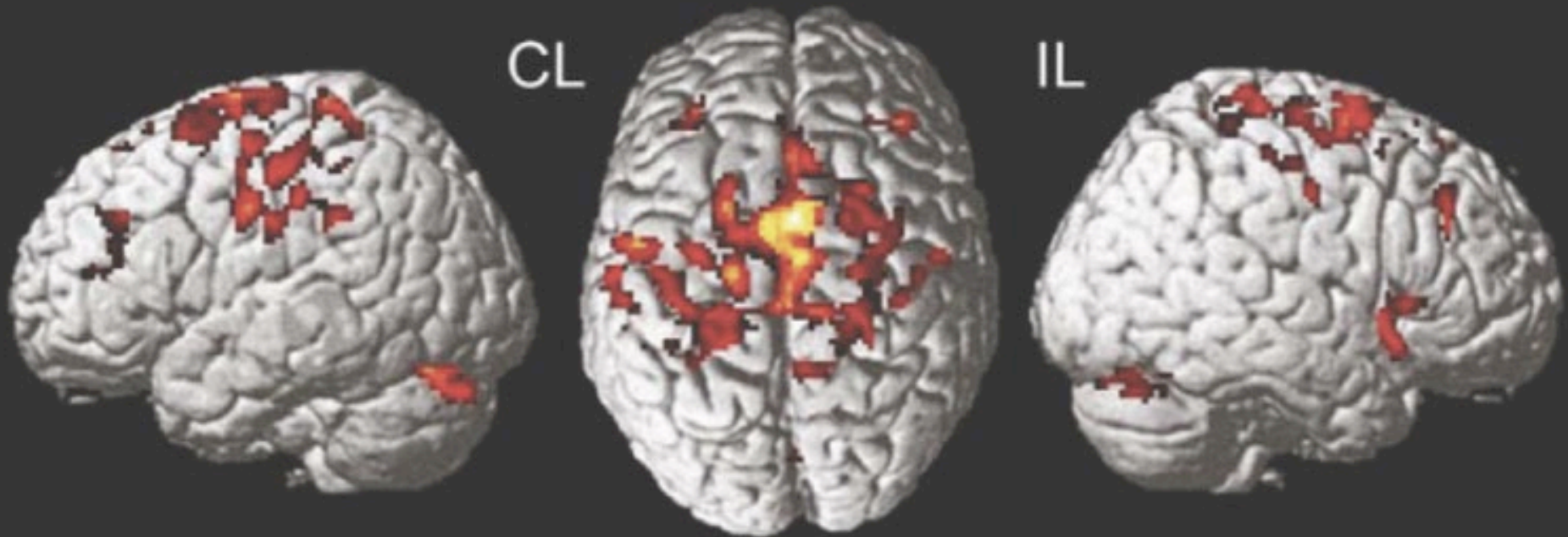


**Spontaneous Compensation**

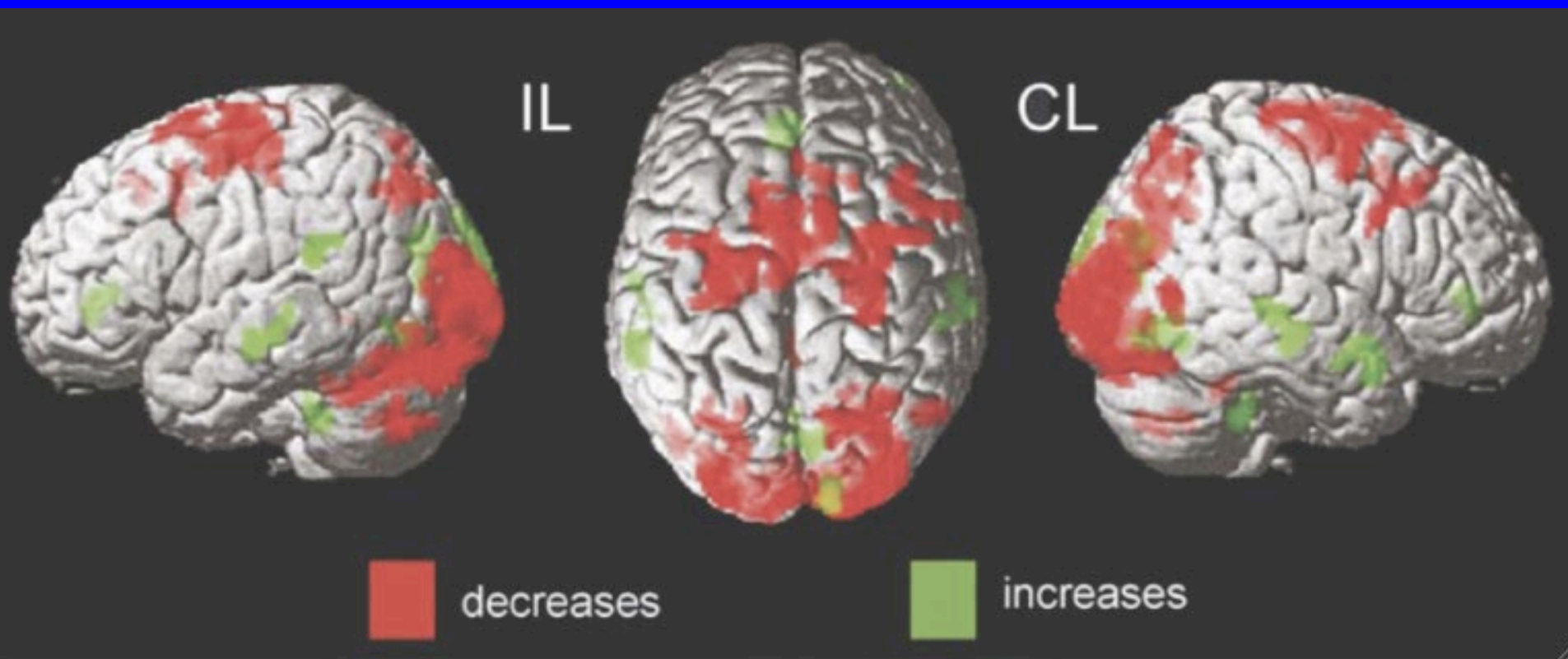
**This may reflect normalization of activity or re-organized activity**

**Ward & Frackowiak, J Physiol, 2006**

**Hand grip activated broad regions of both hemispheres  
BUT, there was an inverse correlation between recovery and  
amount of activation – see below**



One subject scanned over time. As performance improved activation decreased.



# What do we know about treatments for brain injury in people?

It is clear that some people improve after injury and some get treatments, but what is not clear is what the relationship might be between improvement and treatment.



# Evidence-Based Review of Stroke Rehabilitation

Prepared for the  
Ministry of Health & Long-Term C  
and the  
Heart and Stroke Foundation of O

**Robert Teasell MD**  
**Norine Foley BAsc**  
**Sanjit K. Bhogal BA (Hon)**  
**Jeffrey Jutai PhD**  
**Mark Speechley PhD**



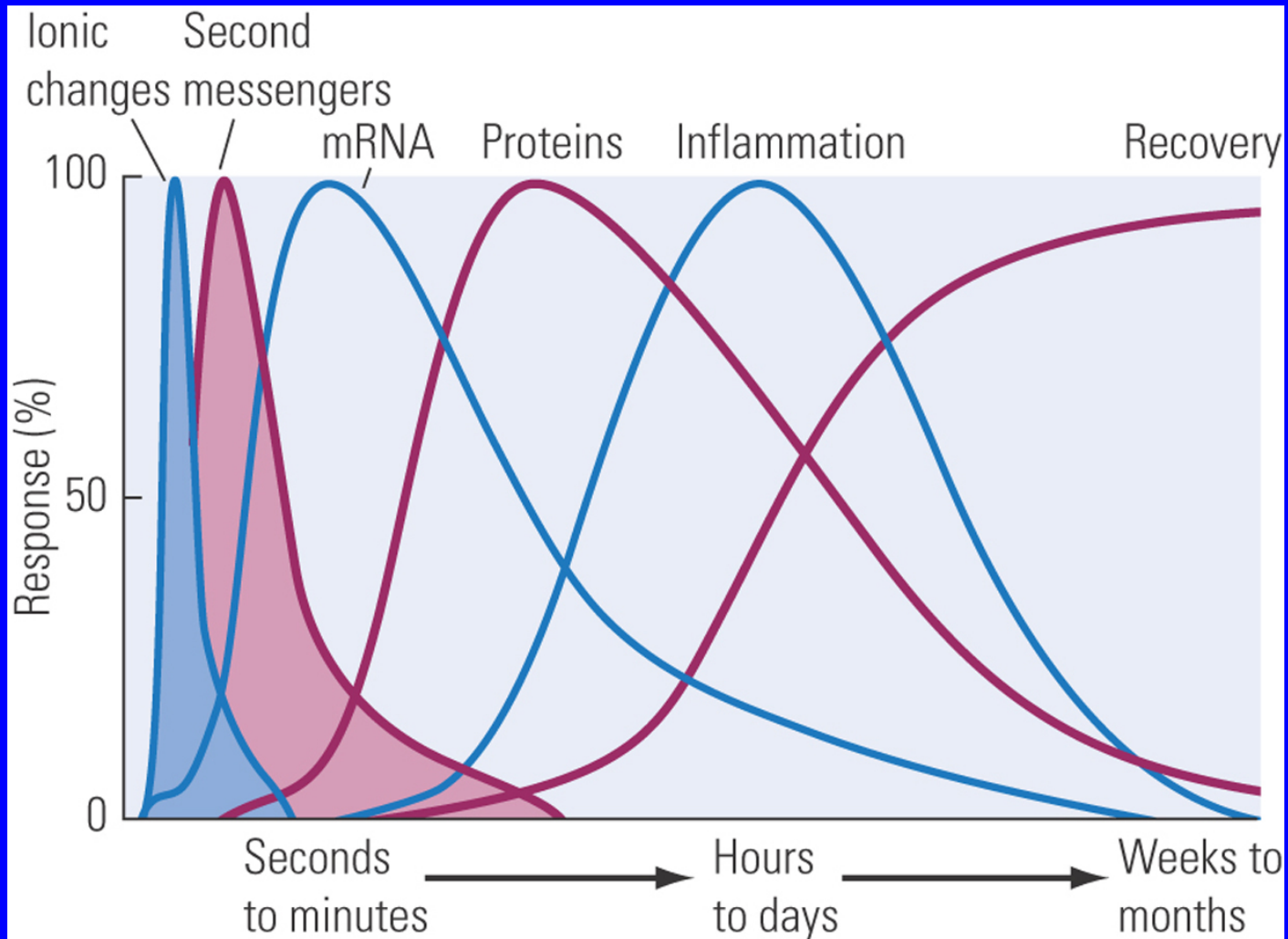
# Major Findings

1. **Interdisciplinary rehabilitation is beneficial over spontaneous recovery.**
2. **Rehabilitation has no effect on mortality.**
3. **Conflicting evidence regarding which therapies are beneficial. Use of therapies largely based on hunch and habit. Many appear to have little direct benefit.**
4. **Strong evidence that greater intensity is beneficial over the short run.**
5. **No evidence about timing and duration of therapy.**

# Considerations

1. The evolution of brain injury

# What happens in response to injury?



# Key Features of the injury

1. Ionic changes leading to toxic levels of glutamate & calcium.
2. Development of edema and inflammation related in part to the cell death related to ion changes.
3. Stimulation of stem cells in the SVZ.

Thus, treatments must be related to the timing

# Early Post-injury Treatments

1. tPA to unblock vessels in ischemic stroke.
2. Neuroprotectants – sad history
  - new treatments related to transient receptor potential channels (trps) that can stabilize ion channels
3. Hypothermia

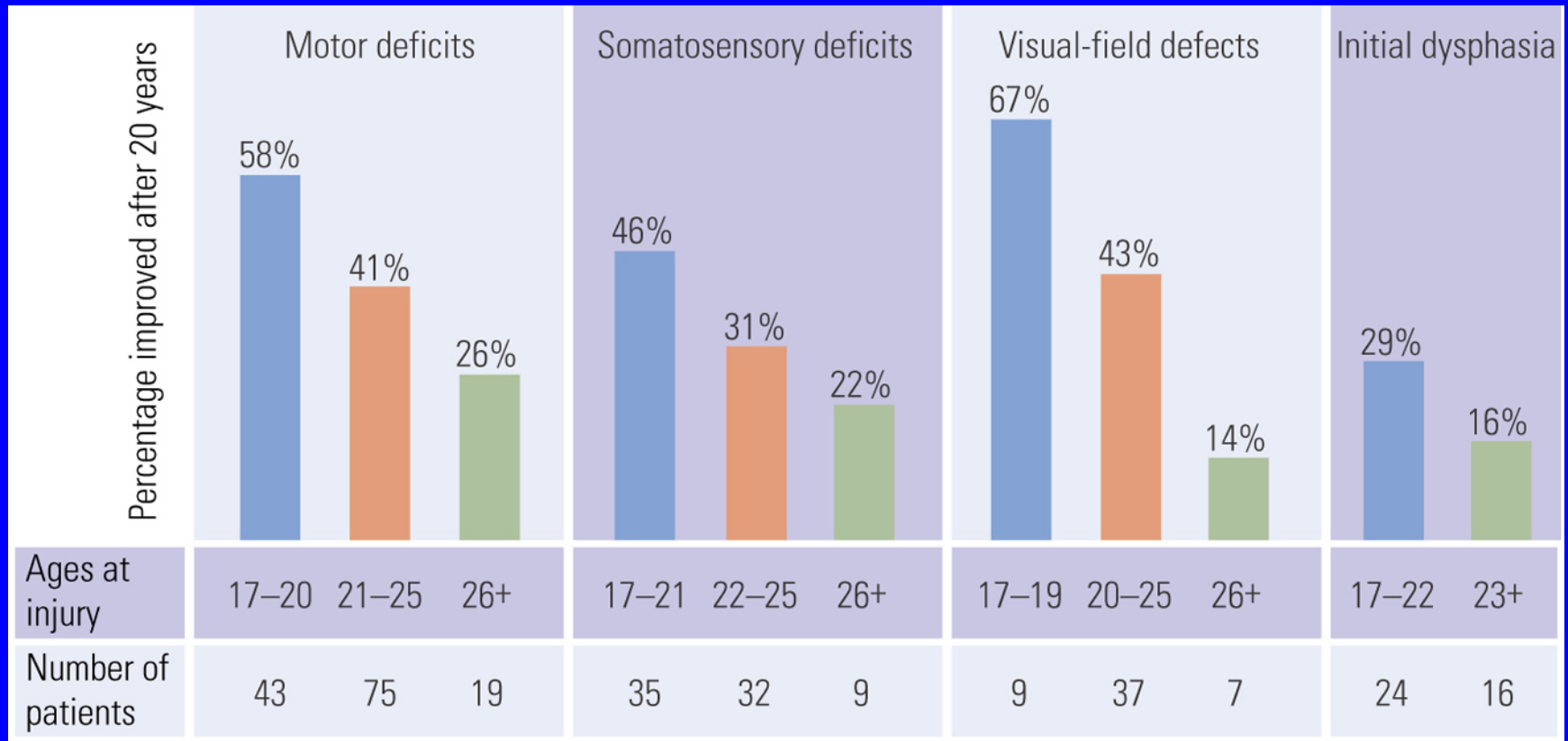
# Considerations

2. **Timing and Intensity of Interventions**
  - vast area of ignorance
  - too much too soon may be bad (think of injury evolution)

# Considerations

## 3. Age

# Recovery from head injury in soldiers





# Considerations

## 3. Age

But age includes very young to very old...

~25% of asymptomatic vaginal births have bleeds...

-importance of comorbid factors here including  
intrauterine insufficiency, intrauterine  
subclinical infection, prenatal stress, etc

# Considerations

## 3. Age

**Kennard Principle: If you are going to have brain injury, have it early.**

**Problem: many factors involved including**

- 1. behavior(s) in question**
- 2. focal vs diffuse injury**
- 3. precise developmental stage**

## **TABLE 7-1** Stages of Brain Development

1. Cell birth (neurogenesis; gliogenesis)
2. Cell migration
3. Cell differentiation
4. Cell maturation (dendrite and axon growth)
5. Synaptogenesis (formation of synapses)
6. Cell death and synaptic pruning
7. Myelogenesis (formation of myelin)

**worst time for injury: during cell migration (3<sup>rd</sup> trimester +)**

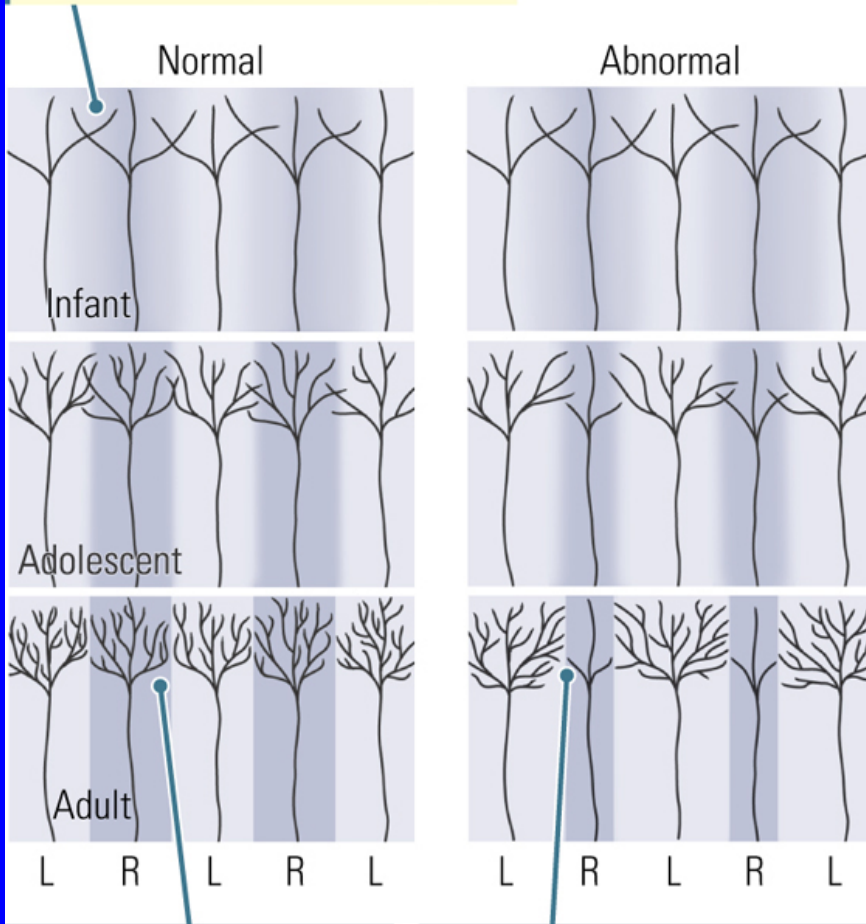
**best time for injury: during synaptogenesis and pruning (3-6 yr)**

# **A Surprising Idea.....**

**Hemiplegic Cerebral Palsy May be Equivalent to Amblyopia of the Corticospinal System**

**See: Eyre et al., Ann Neurol 2007, 62, 493–503**

In infancy, the projections from both eyes overlap.

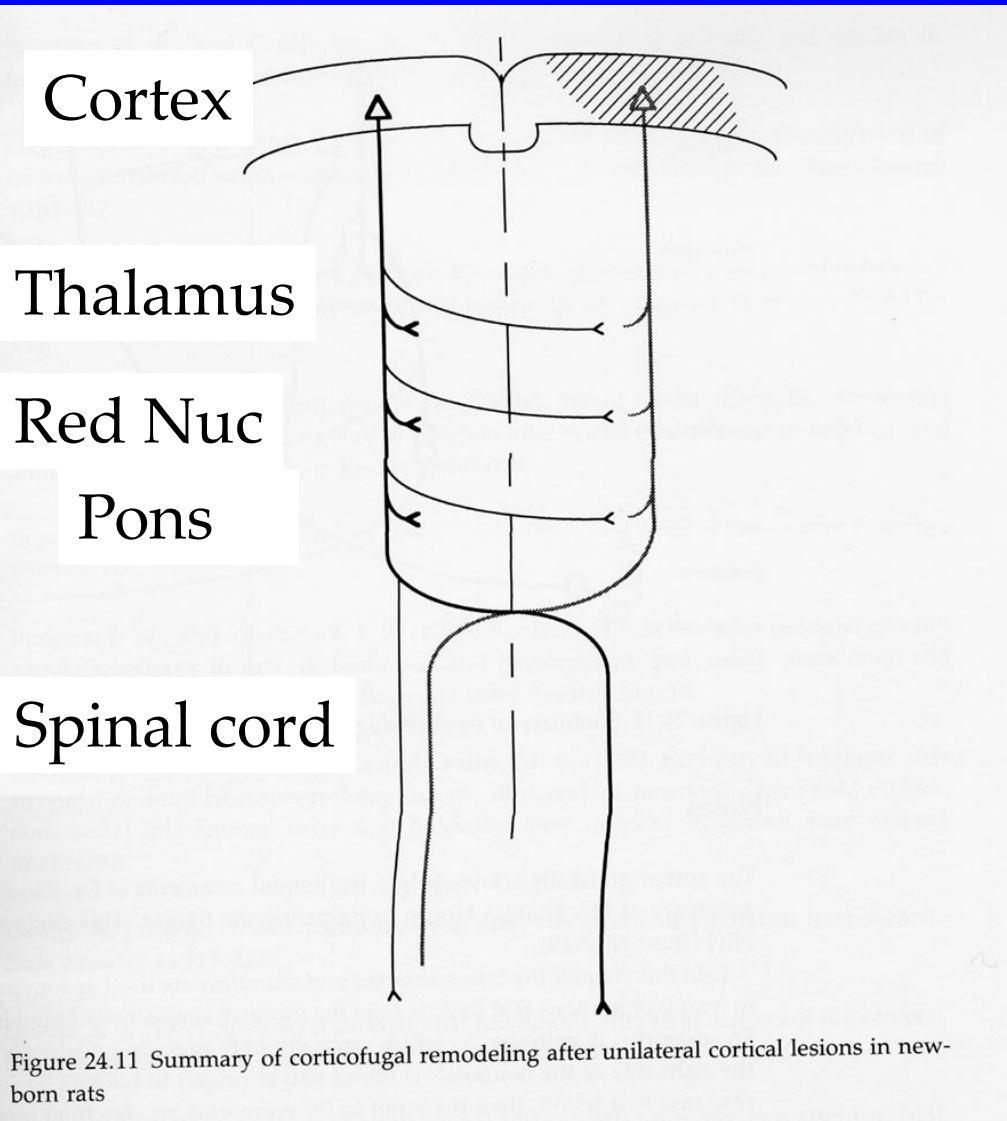


In adulthood, a nonoverlapping pattern of terminal arborizations from each eye is normal.

If one eyelid of a kitten is sewn shut during a critical week of development, the terminations from that eye retract and those from the open eye expand.

## The amblyopia story

# Rebuilding the motor system of the infant rat or cat

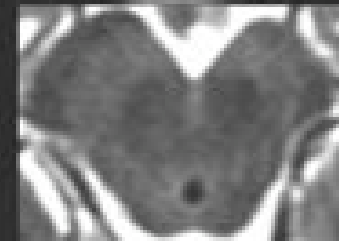
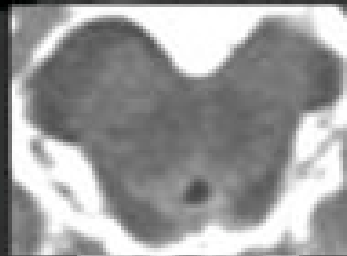
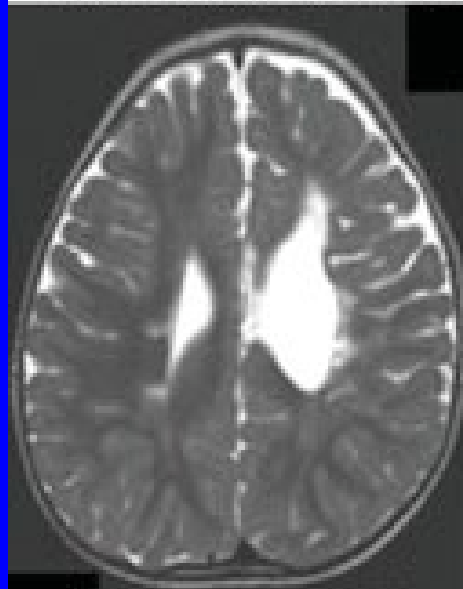


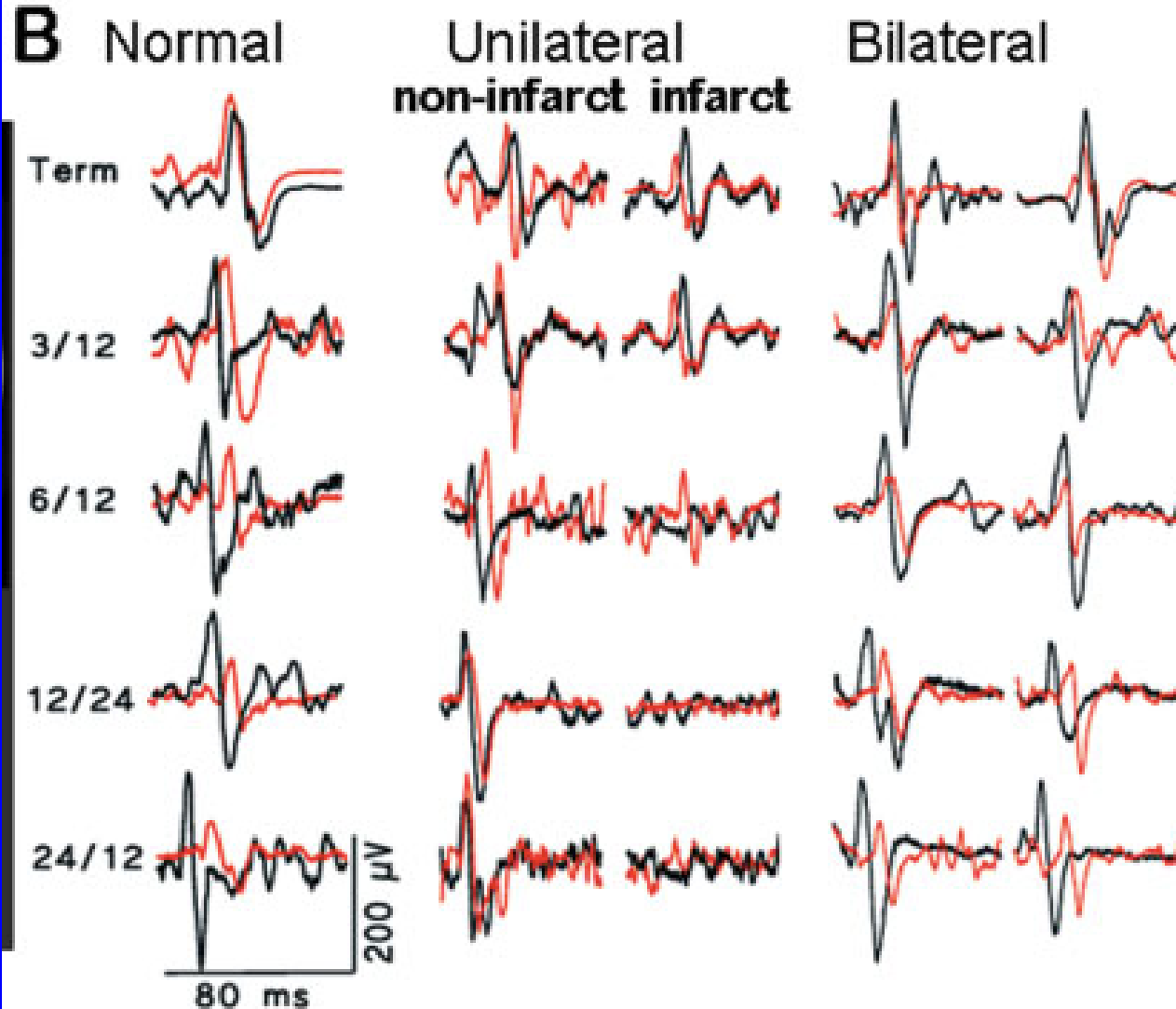
**A**

**Unilateral  
venous infarct**

**arterial infarct**

**Bilateral**





**TMS-induced movement**

**The infarcted hemisphere can initially control movement but loses this ability BUT only in the unilateral injury.**



# Considerations

## 4. Comorbid conditions:

a. other medical conditions (atherosclerosis, coronary disease, diabetes, hypertension)

b. medications – problem of SSRIs

c. seizures – a double edged sword

prolonged = increased lesion size & poor outcome

brief = release of NTFs

seizure medication blocks plasticity

# Considerations

## 5. Sex and hormone status

estrogen VS progesterone

## Hormones alter neuronal and glial structure in the adult *neocortex*

1. Removing estrogen stimulates synaptic growth.
2. Adding estrogen inhibits synaptic growth.
3. Tamoxifen (an estrogen antagonist used in the treatment of breast cancer) stimulates synaptic growth and reverses memory loss in aged female rats.

Note that this is different than the hippocampus...

# Considerations

## 6. Measurement Issues

What is recovery?

Who decides?

Endpoint measures VS more refined measures

# Considerations

**7. Lesion etiology makes a difference to both outcome and neural response.**

**e.g., diffuse versus focal  
different causes of focal**

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# A comparison of different models of stroke on behaviour and brain morphology

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C.L.R. Gonzalez and B. Kolb

**Three types of lesions to motor cortex: suction, MCA, transient ischemia**

**Different behavioral effects**

**Different changes (atrophy or hypertrophy) and specific to region (forelimb cortex, cingulate cortex, striatum) in the injured and intact hemisphere.**

# How do we go about finding and evaluating treatments for brain injury?

1. Identify those factors that produce plastic changes in the normal brain.
2. Develop animal models of injury.
3. Use the plasticity factors in the animal models.

**O. Stewart, June 4, 2010**

**“The key task is to increase intrinsic growth potential.”**





# Background

Once seen as a static organ, the brain is now understood to be a dynamic organ that undergoes both acute and chronic changes. These changes are referred to as plasticity.

The challenge is to identify principles that may control these changes.

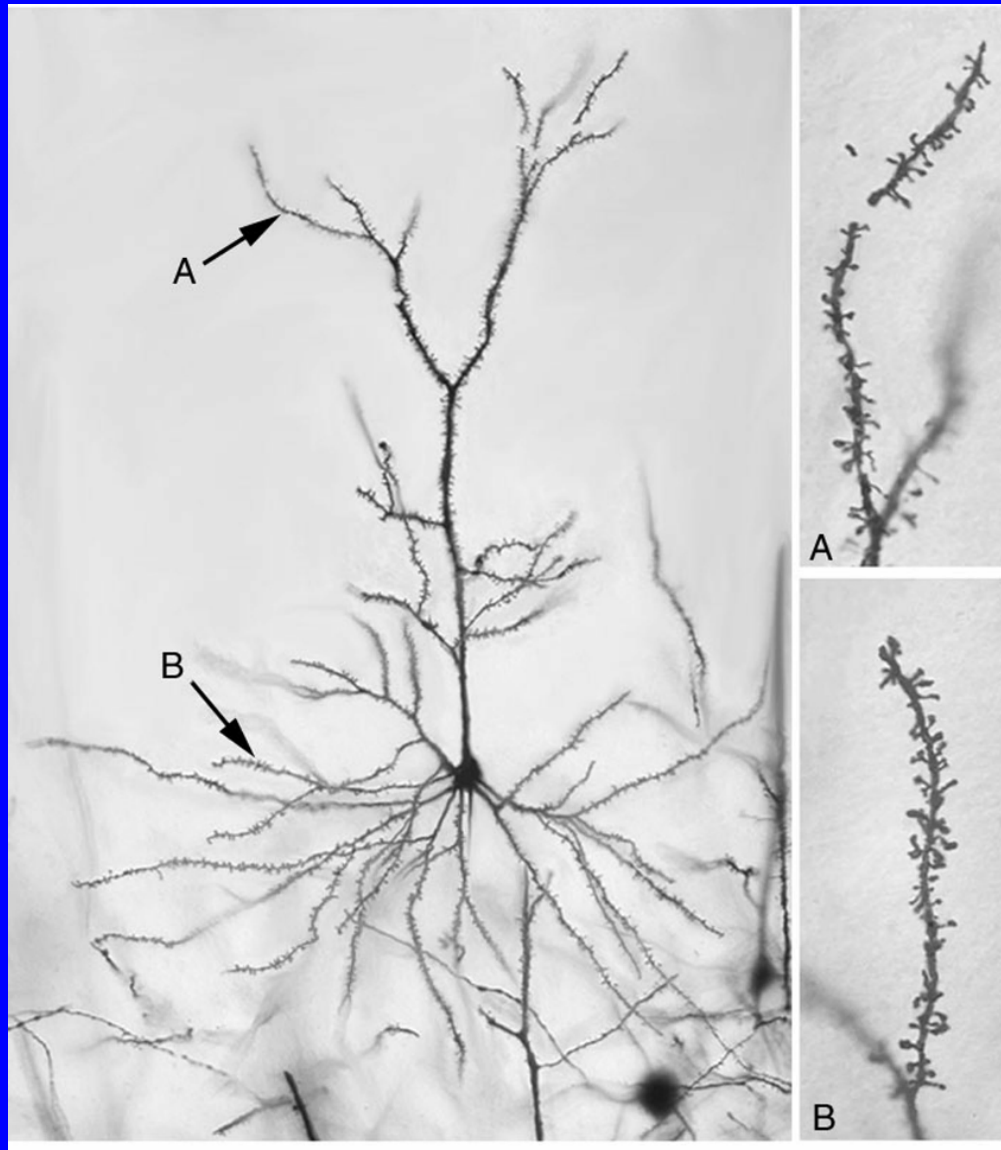
# Principle 1

Plasticity can be seen a many levels of analysis

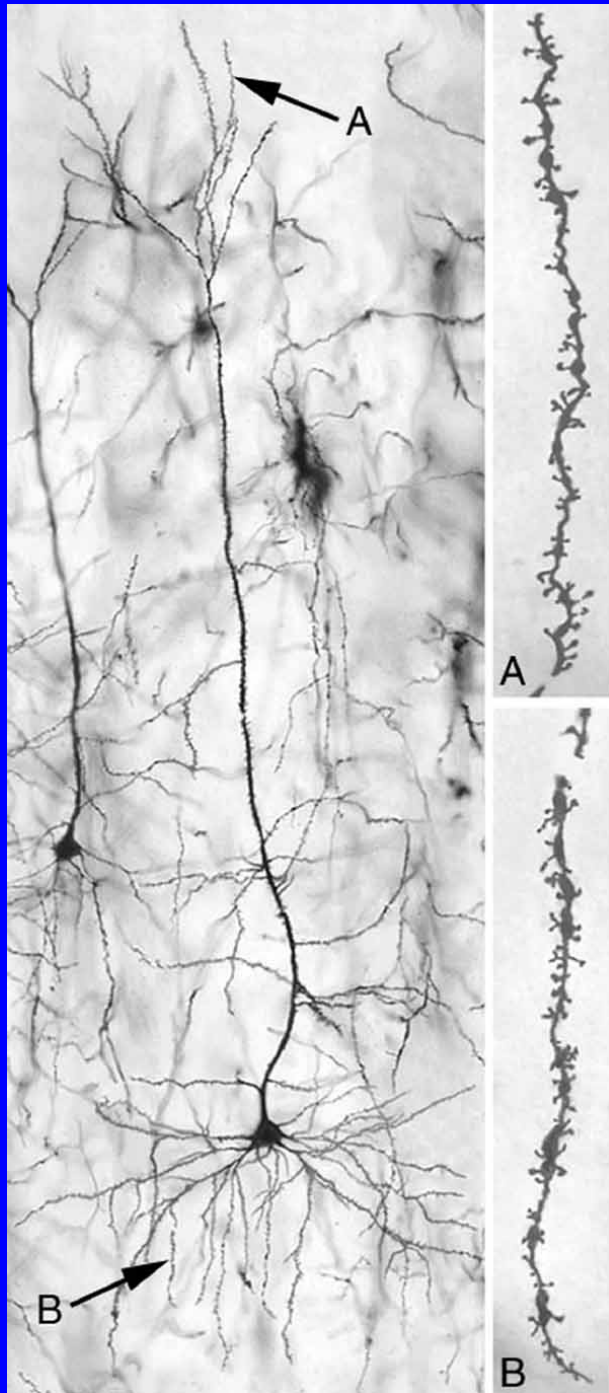
# Levels of Analysis

1. Behaviour
2. Maps – noninvasive and invasive
3. Physiology (e.g., LTP, unit recording)
4. Neuronal morphology
5. Genetics and epigenetics
6. Proteins and other molecules

# Neurons 'R Us



# Measuring connections



Connection numbers can be estimated by knowing the length of the cell branches.

The number of connections can go up or down with experience - more is not always better.

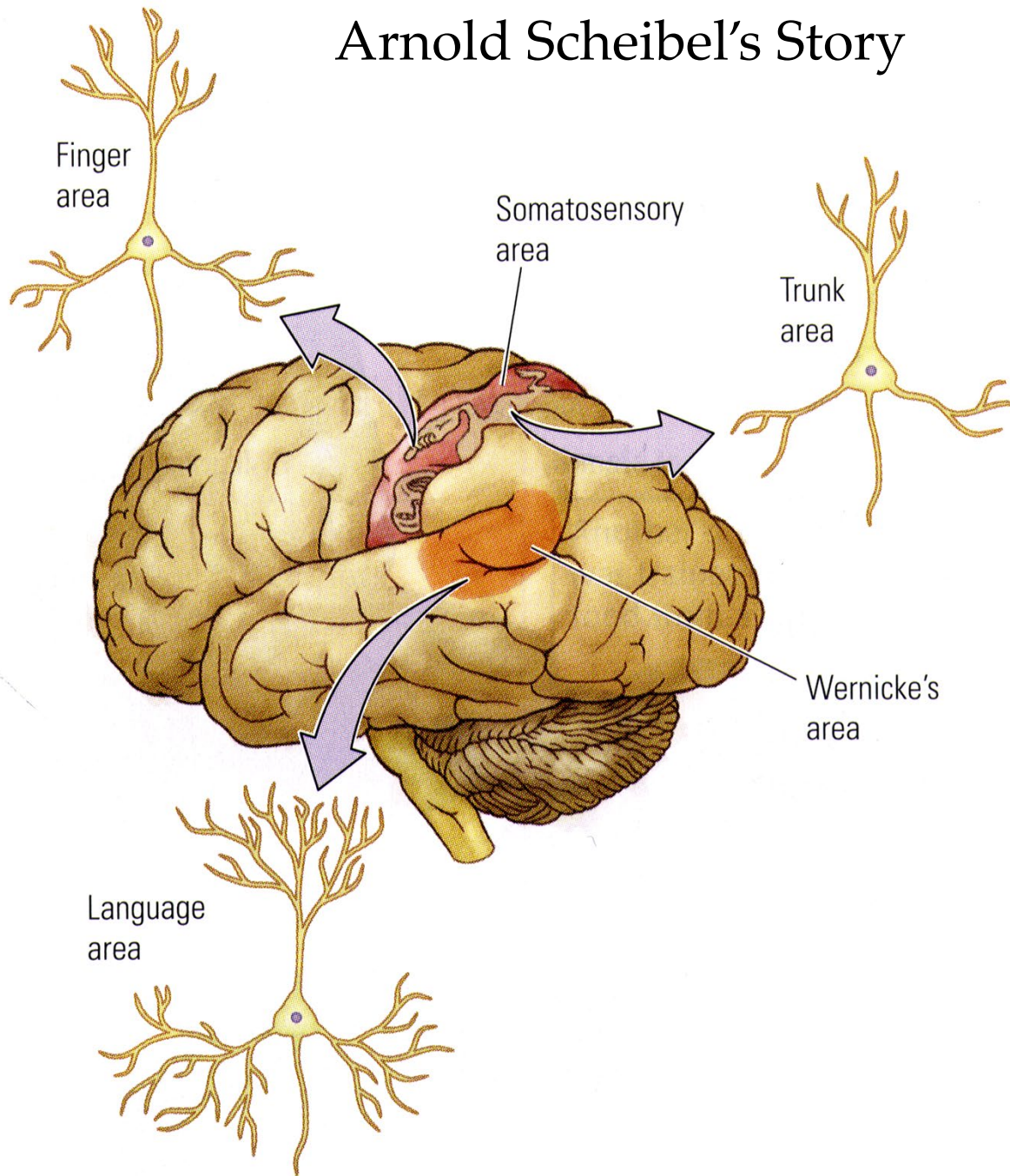
The same experience can produce opposite changes in different places...

## Principle 2

When the brain changes, this is reflected in behavioural change.

This change is known by names such as learning, memory, addiction, maturation, ageing, recovery, etc.

# Arnold Scheibel's Story



## Cell Structure

1. Complexity of computations
2. Education
3. Occupation
4. Sex Effect



## Principle 3

The brain can be changed by an amazingly rich variety of experiences.

# Factors that alter normal cortex

1. sensory & motor experience
2. task learning
3. gonadal hormones
4. psychoactive drugs (e.g., stimulants, THC)
5. neurotrophic factors (e.g., NGF, FGF-2)
6. natural rewards (e.g., social interaction, sex)
7. stress (social; fear)
8. anti-inflammatories (e.g., COX-2 inhibitors)
9. diet (e.g., choline)
10. cortical stimulation

# Results

All of the factors produce BOTH behavioural change and morphological change, although the latter are site-specific.

They all likely produce changes in gene expression although we have only studied a subset to date.

# Some Examples

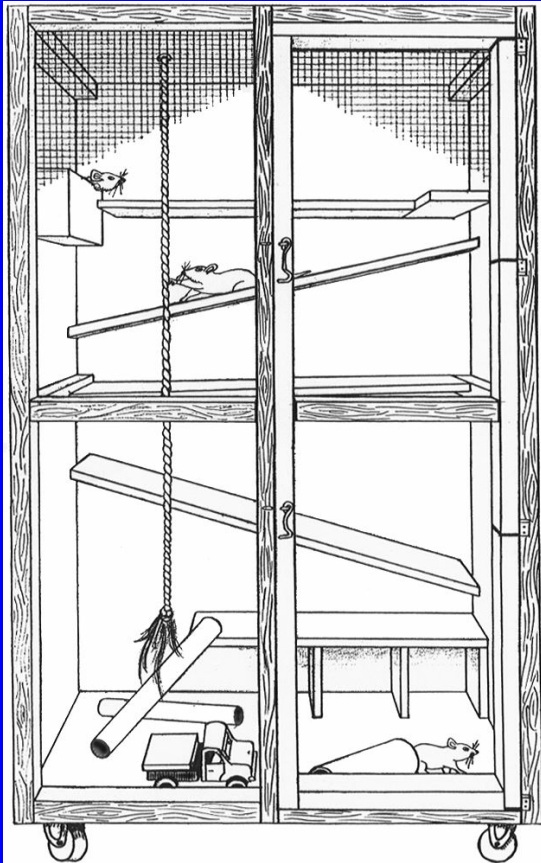
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# Experiential Treatments

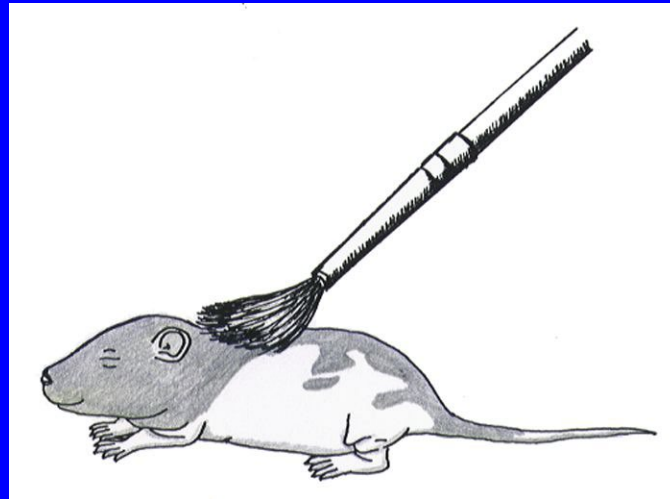
## Complex Housing

All ages



## Tactile Stimulation

Infant



Adult



# How can this happen?

Experience alters brain activity, expression of genes, brain chemistry, behaviour, and so on.

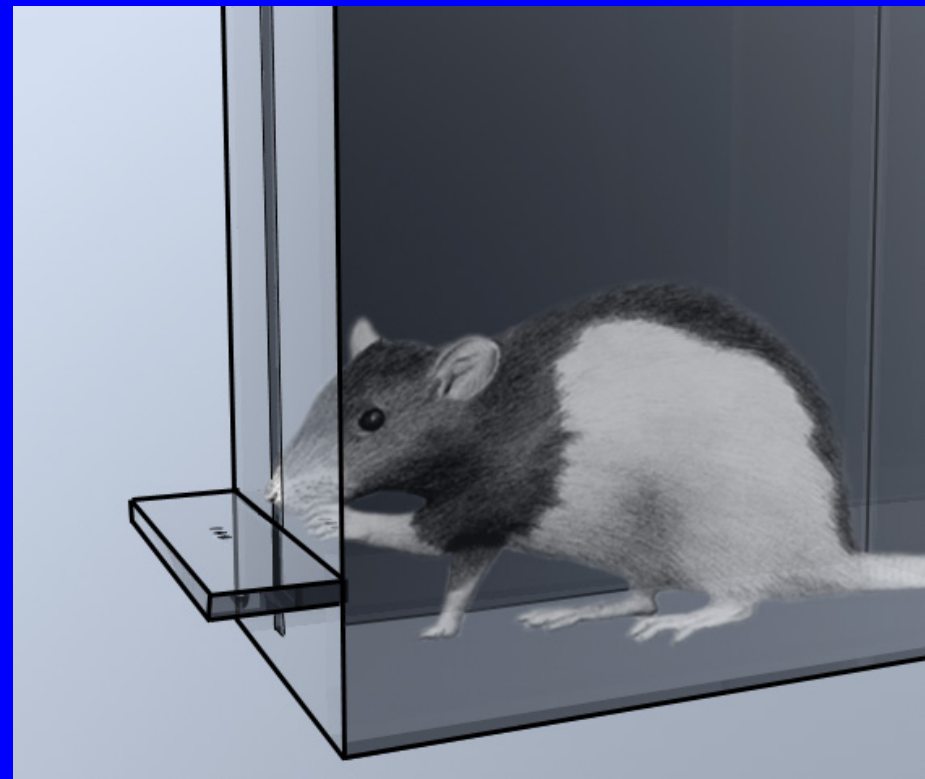
Any one of these can alter connectivity and thus function.

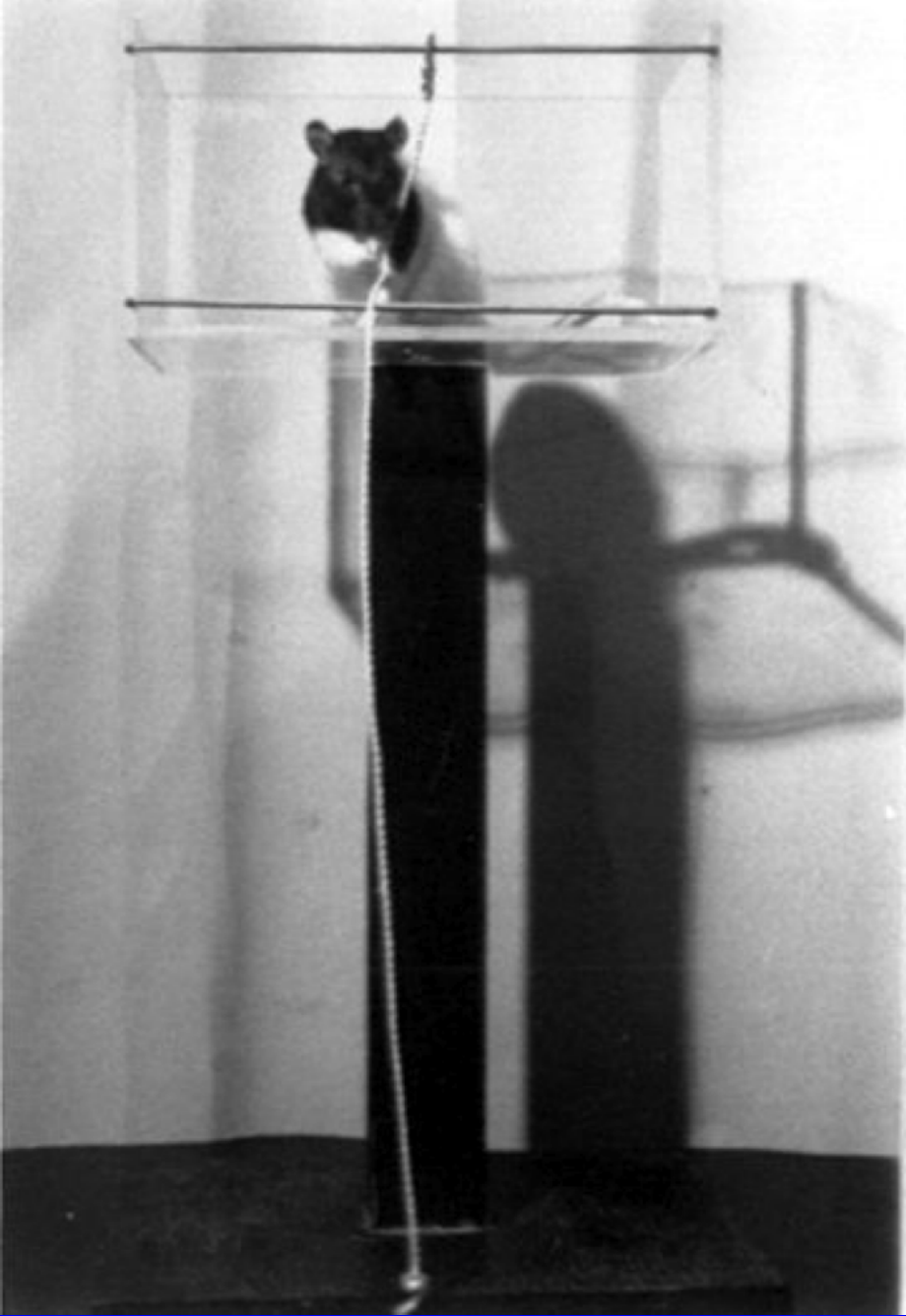
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# Performance on motor and cognitive tasks

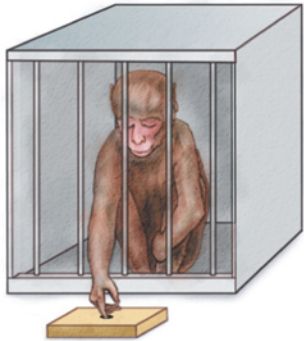




(A)

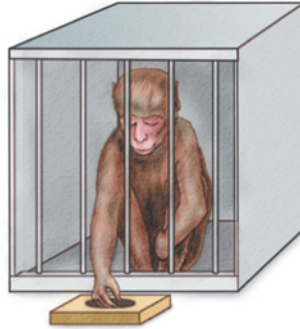
**Difficult task**

One group of monkeys was trained to retrieve food from a small well.



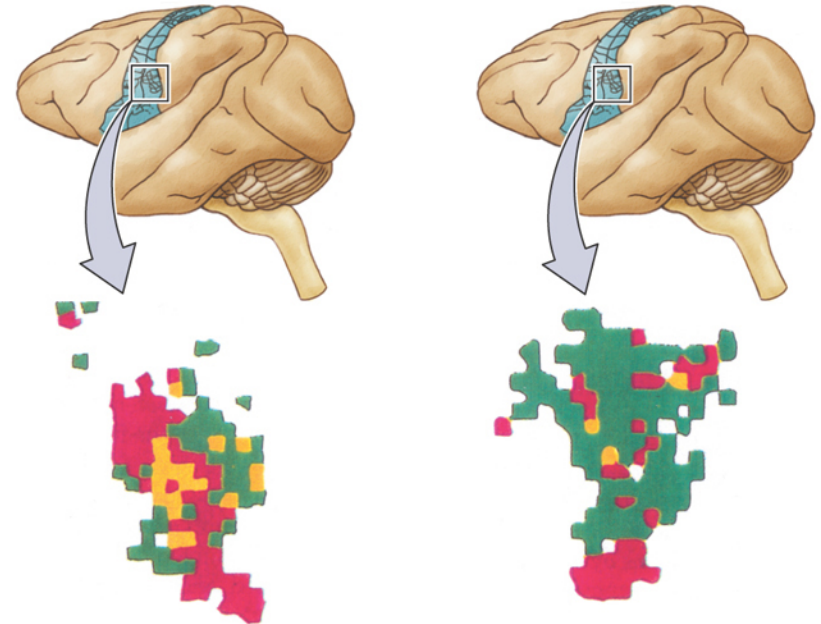
**Simple task**

Another group of monkeys was trained to retrieve food from a large well.



(B)

The motor representation of digit, wrist, and arm was mapped.



**KEY**

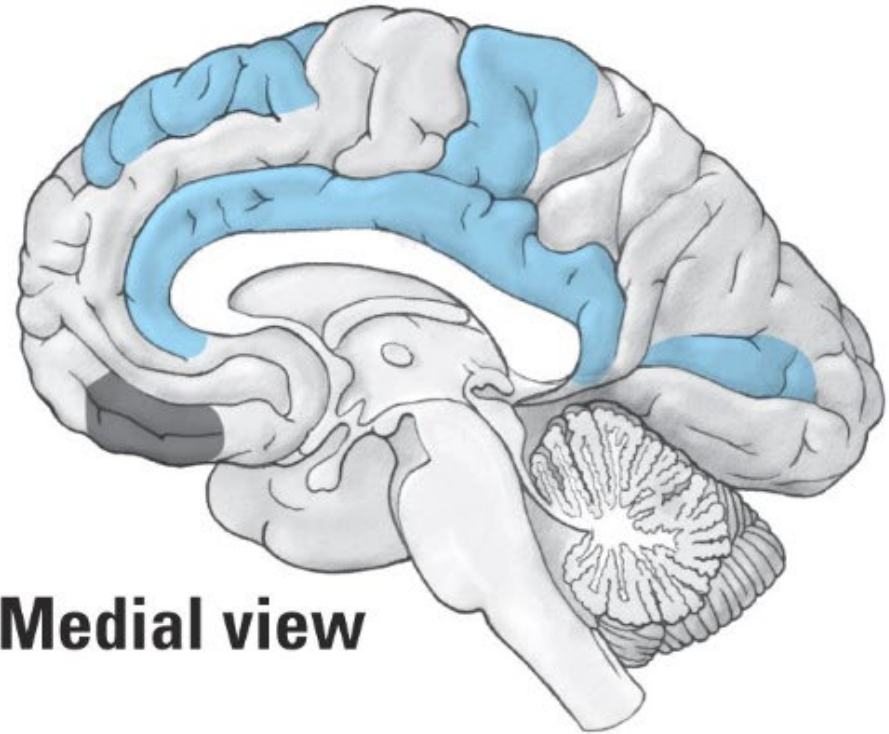
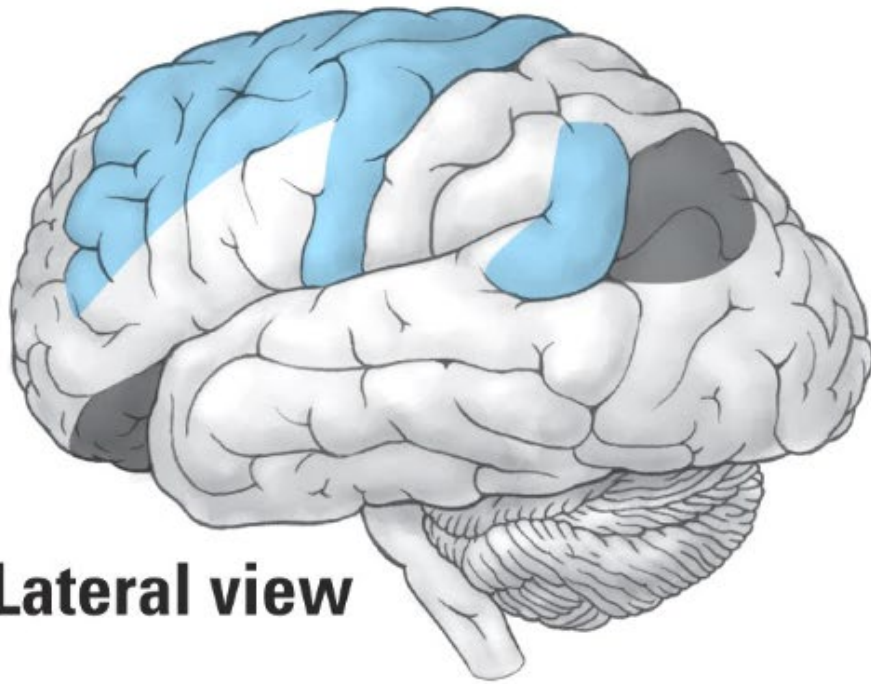
■ Digit   ■ Wrist/forearm   ■ Digit, wrist, and forearm

The digit representation in the brain of the animal with the more difficult task is larger, corresponding to the neuronal changes necessary for the acquired skill.

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# Relative differences in the volume of different cortical areas

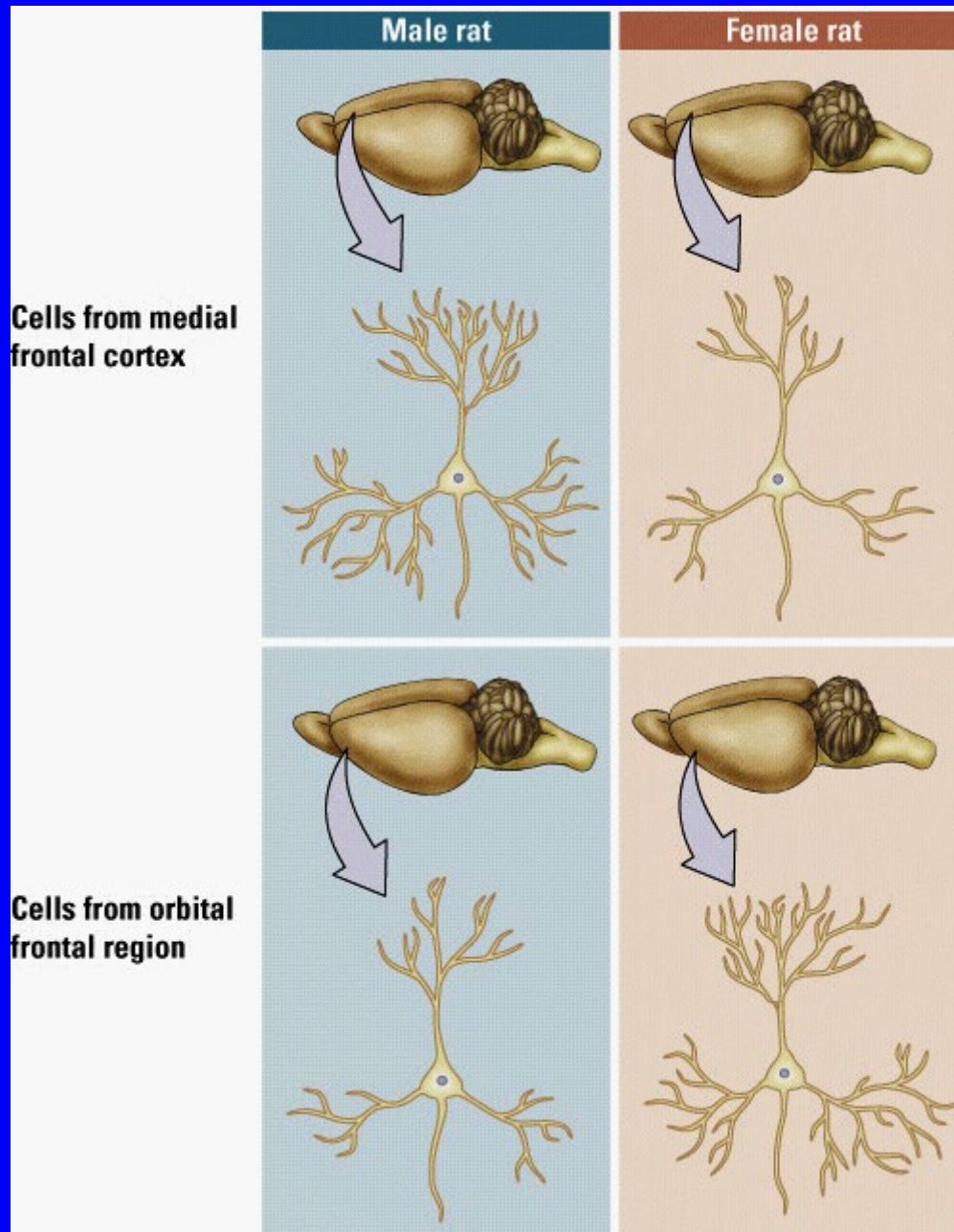


Female=blue

Male=gray

The "same" injury can have very different effects...

# Gonadal hormones have organizing effects on PFC



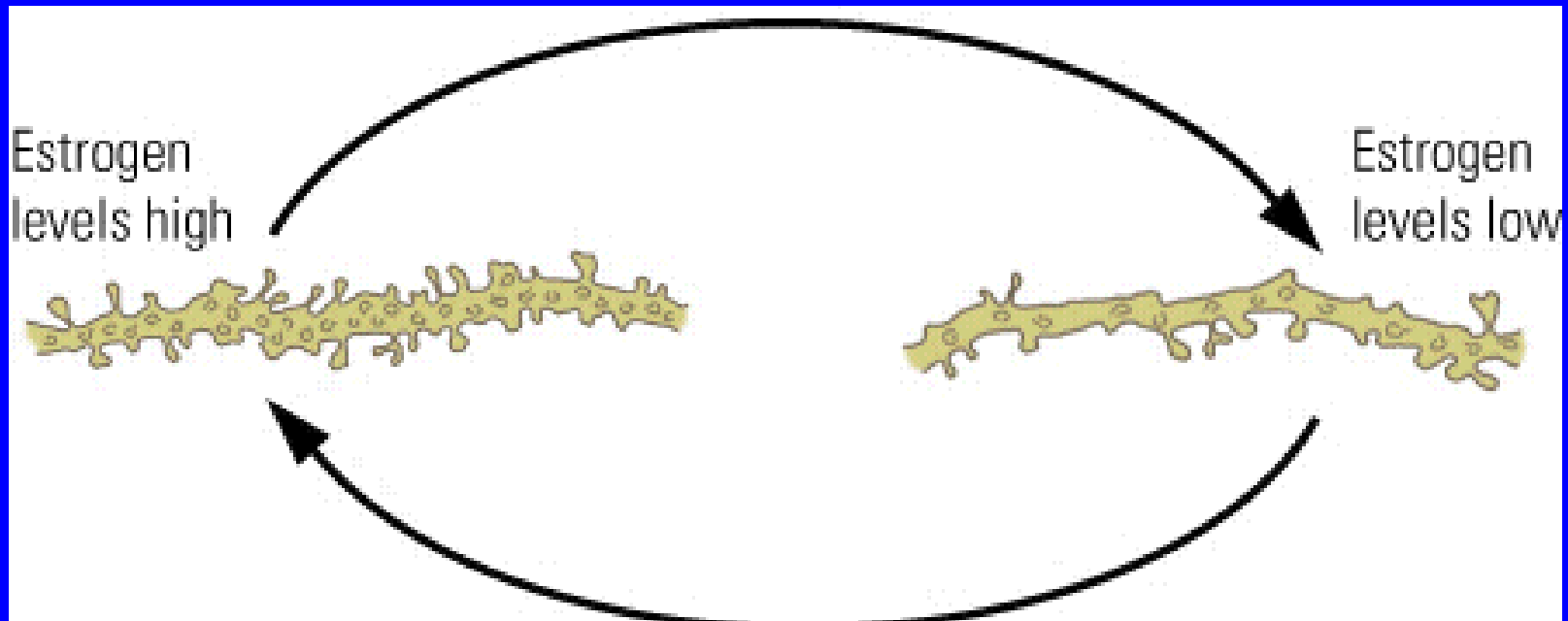
**Kolb & Stewart, 1991,  
J. Neuroendocrinology**

**Males have more synapses  
in MF**

**Females have more synapses  
in OF**

**The effects are hormone-  
dependent.**

# Gonadal hormones have effects throughout life in hippocampus



BUT, the neocortex appears to be opposite

(see review by Cooke & Woolley, *J Neurobiol*, 2005, 64, 34-46)

## Hormones alter neuronal and glial structure in the adult *neocortex*

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# Drug-induced behavioural sensitization

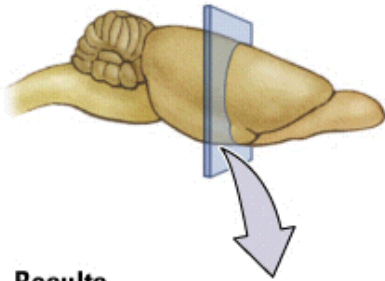


The phenomenon whereby there is an escalating behavioral response to repeated administration of a constant dose of a psychomotor stimulant such as amphetamine, cocaine, or nicotine.

## EXPERIMENT

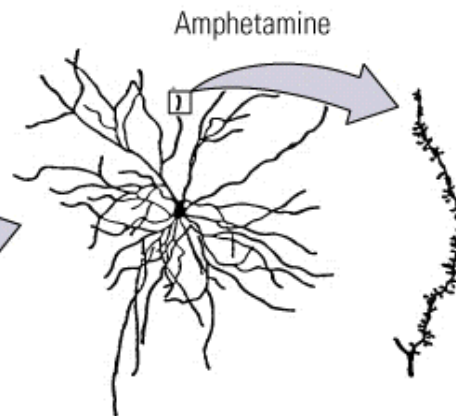
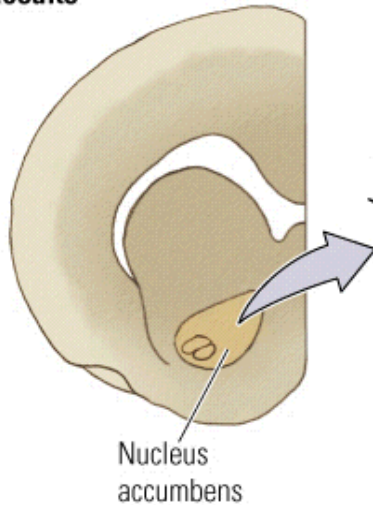
**Question:** What effect do repeated doses of amphetamine, a psychomotor stimulant, have on neurons?

### Procedure

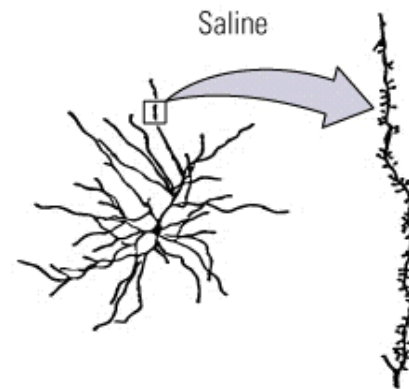


Animals received multiple doses of amphetamine. Neurons were drawn from nucleus accumbens.

### Results



Rats that show sensitization to amphetamine have increased dendritic growth and spine density...

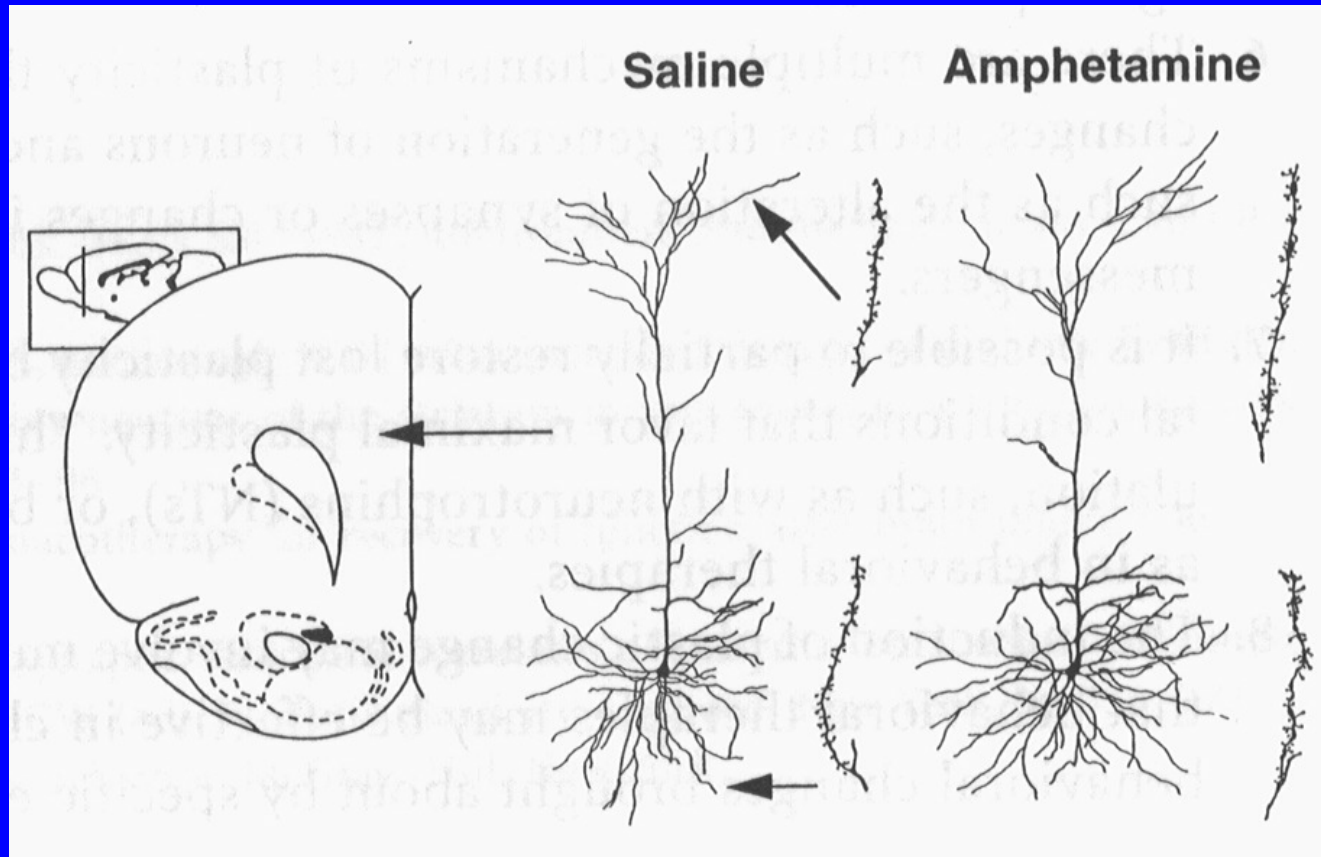


...relative to saline-treated rats.

### Conclusion

The sensitization induced by repeated exposure to amphetamine changes the structure of neurons in certain brain areas.

Similar Results are seen in Prefrontal Cortex but not other cortical areas



Nicotine produces more widespread changes that include the motor cortex.

# Frontal lobe Plasticity is area-dependent

Psychomotor stimulants all have the opposite effect in the orbital cortex.

i.e., there is a decrease in dendritic length and/or spine density in response to psychomotor stimulants.

Thus, the same drug can alter differently the function of different regions, much like hormones and stress do.

The drug-induced changes are not trivial:

NAcc = 37% increase in total synapses per neuron

PFC = 19% increase in total synapses per pyramidal neuron

OFC = 20% decrease in total synapses per pyramidal neuron

## Other drugs also alter synaptic organization of the PFC/NAcc system

- morphine -- mPFC & NAcc show atrophy
  - OFC shows hypertrophyI.E. OPPOSITE of stimulants
- THC acts like stimulants but no change in N.Acc
  - probably why it is relatively nonaddicting
- SSRIs alter hippocampus in 2 ways (e.g., Prozac)
- Ritalin is much like THC

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# Neurotrophic Factors

Neurotrophic factors act to stimulate mitosis, cell survival, differentiation, and synaptogenesis.

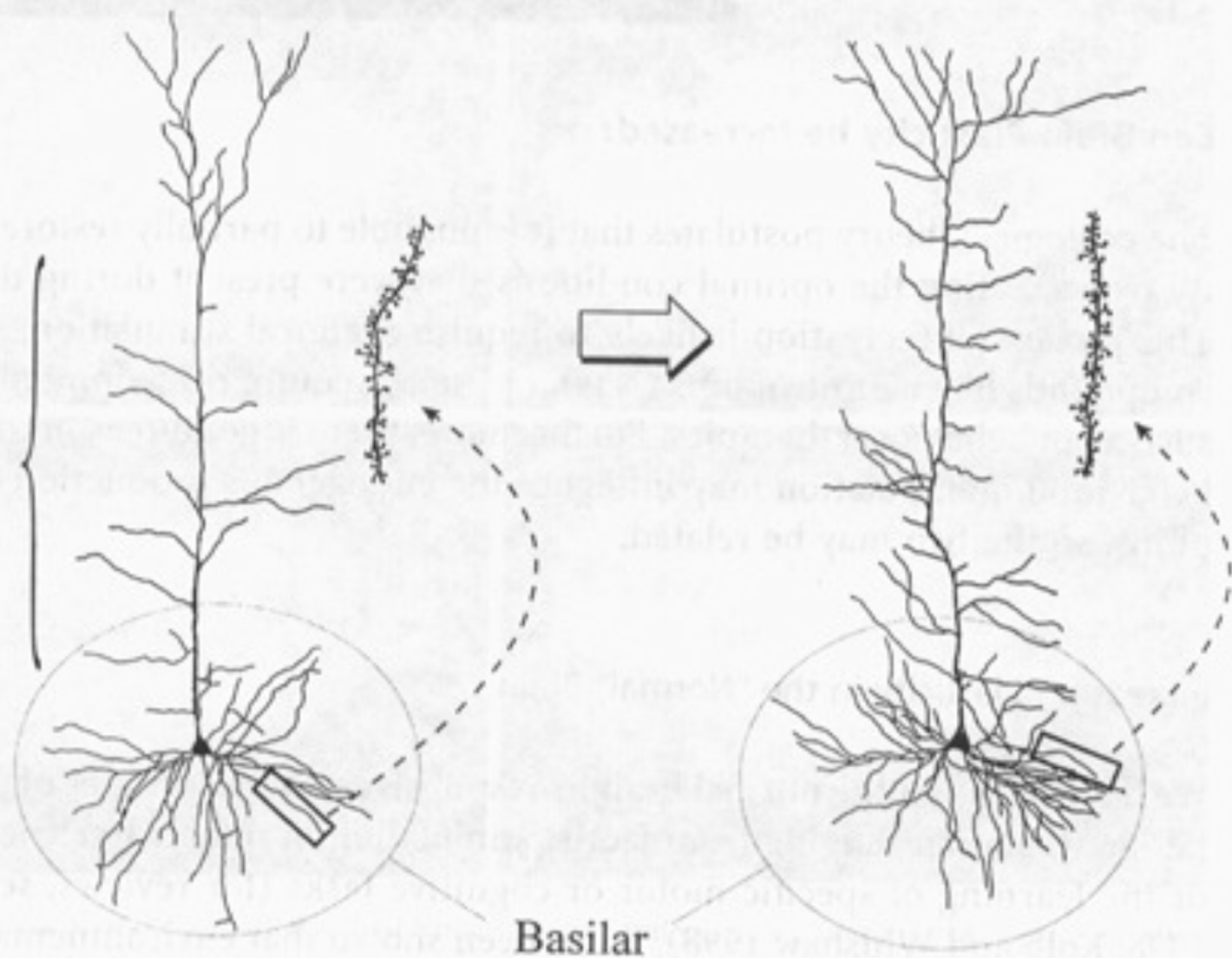
Neurotrophic factors are produced naturally in the brain.

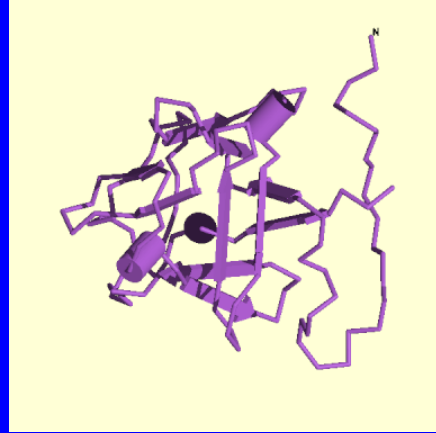
NTFs are modulated by experience & psychoactive drugs.

NTFs also change in development and ageing.

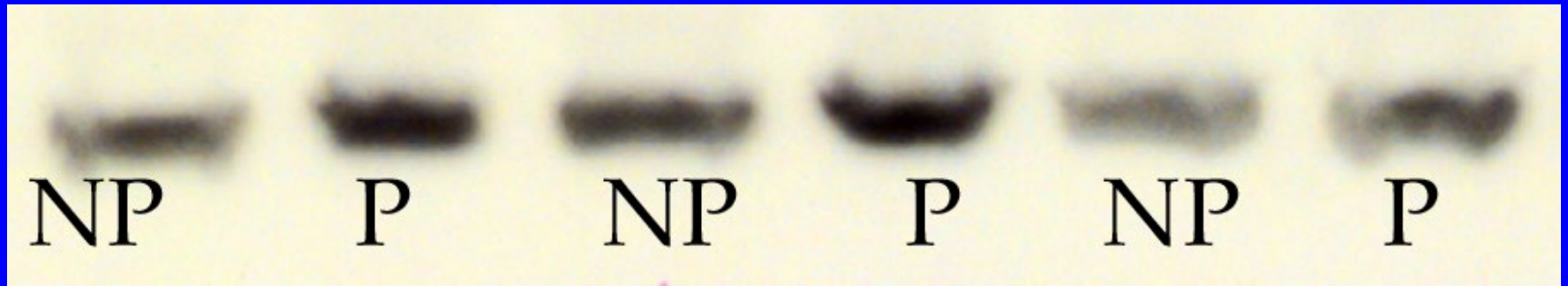
**Control**

**NGF**





## FGF-2



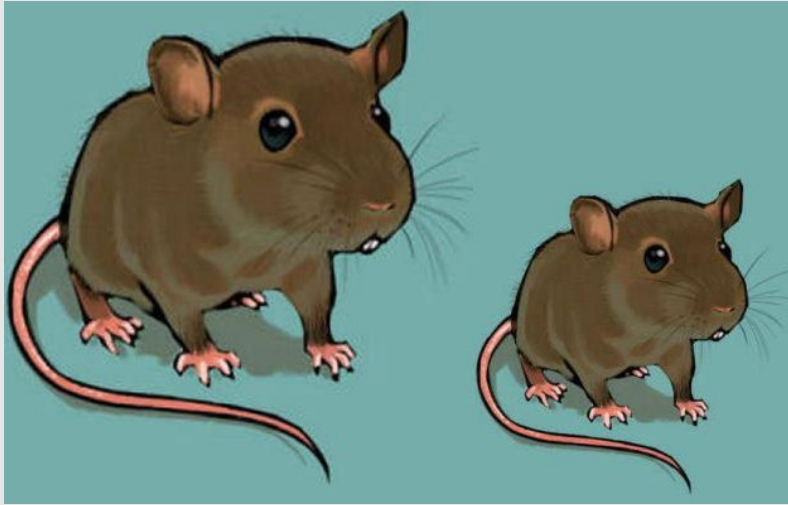
Tactile stimulation (P) increases FGF-2 receptor & protein expression in skin and cortex.

# Factors that alter normal cortex

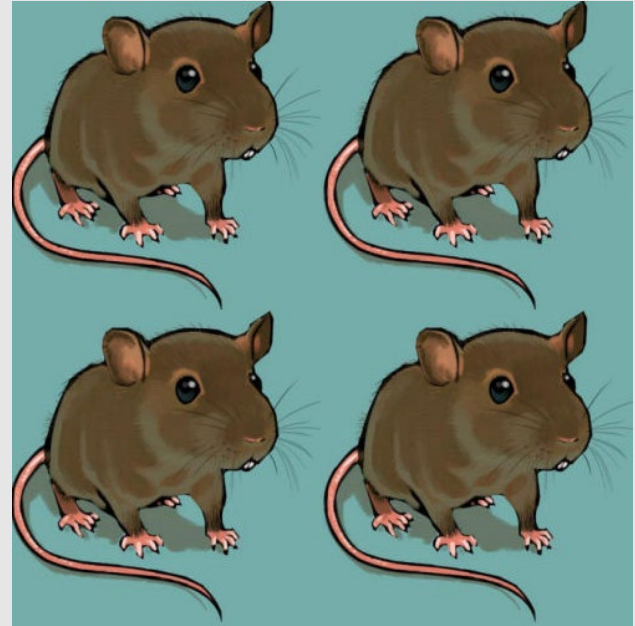
1. **sensory & motor experience**
2. **task learning**
3. **gonadal hormones**
4. **psychoactive drugs (e.g., stimulants, THC)**
5. **neurotrophic factors (e.g., NGF, FGF-2)**
6. **natural rewards (e.g., social interaction, sex)**
7. **stress (social; fear)**
8. **anti-inflammatories (e.g., COX-2 inhibitors)**
9. **diet (e.g., choline)**
10. **cortical stimulation**

*All mammals have play  
behaviour with rules*





Little Play: Adult + Juvenile

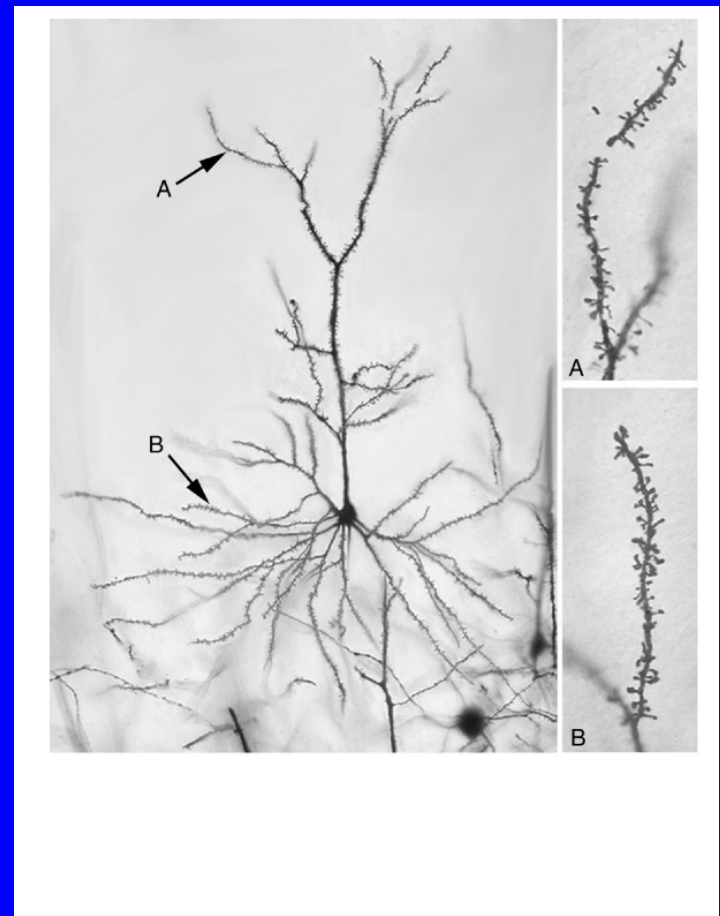
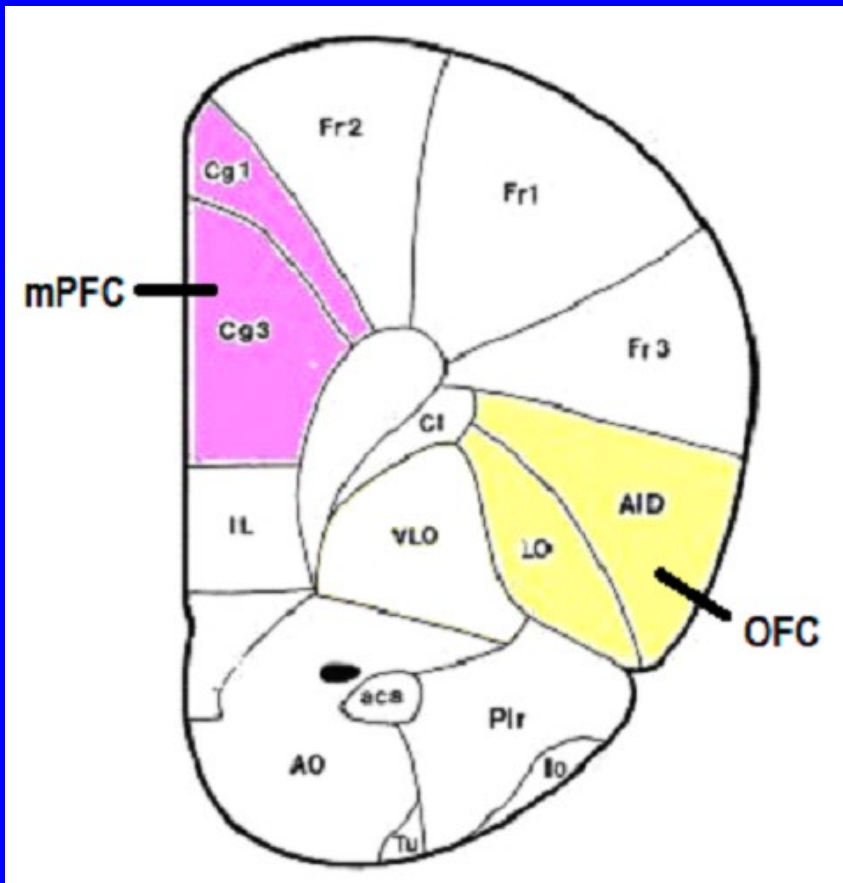


Enriched Play: 4 Juveniles



Limited Play: 2 Juveniles

Bell, Pellis & Kolb, BBR, 2010



Sibling play = more pruning of mPFC

Conspecific number = more complex OFC

# Factors that alter normal cortex

1. **sensory & motor experience**
2. **task learning**
3. **gonadal hormones**
4. **psychoactive drugs (e.g., stimulants, THC)**
5. **neurotrophic factors (e.g., NGF, FGF-2)**
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# Stress Effects are Area-Specific

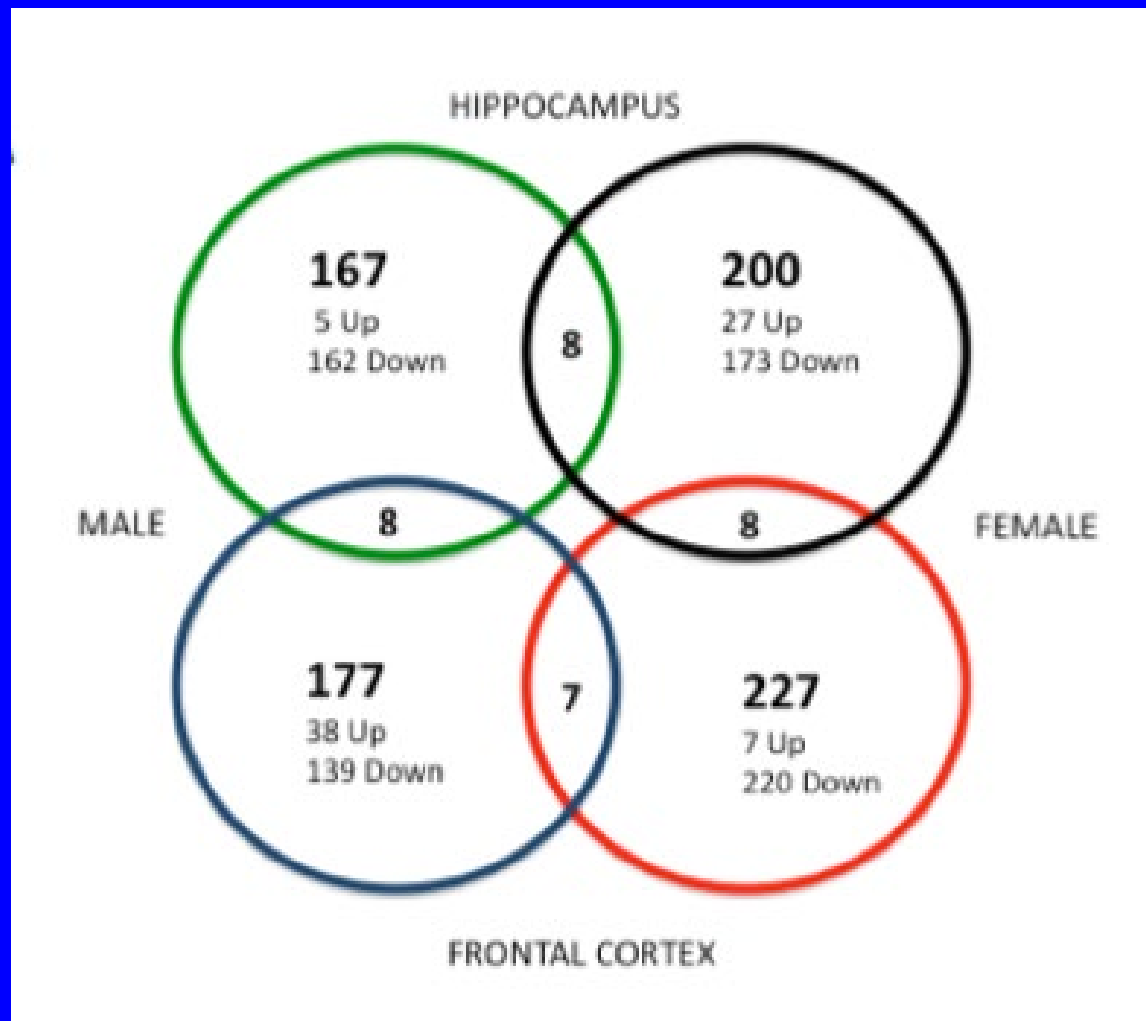
Hippocampus: loss of cells in dentate gyrus

Medial PFC: loss of synapses

Orbital PFC: increase in synapses

(e.g., Liston et al., J Neuroscience, 2006, 26, 7870-4)

# Gene expression changes are areal and sex specific



# Stress Effects are Area-Specific

fMRI studies show similar results in humans  
(e.g., Liston, McEwen & Casey, PNAS, 2009)

# Factors that alter normal cortex

1. **sensory & motor experience**
2. **task learning**
3. **gonadal hormones**
4. **psychoactive drugs (e.g., stimulants, THC)**
5. **neurotrophic factors (e.g., NGF, FGF-2)**
6. **natural rewards (e.g., social interaction, sex)**
7. **stress (social; fear)**
8. **anti-inflammatories (e.g., COX-2 inhibitors)**
9. **diet (e.g., choline)**
10. **aging**

# Other Factors That Affect Brain and Behavioural Development

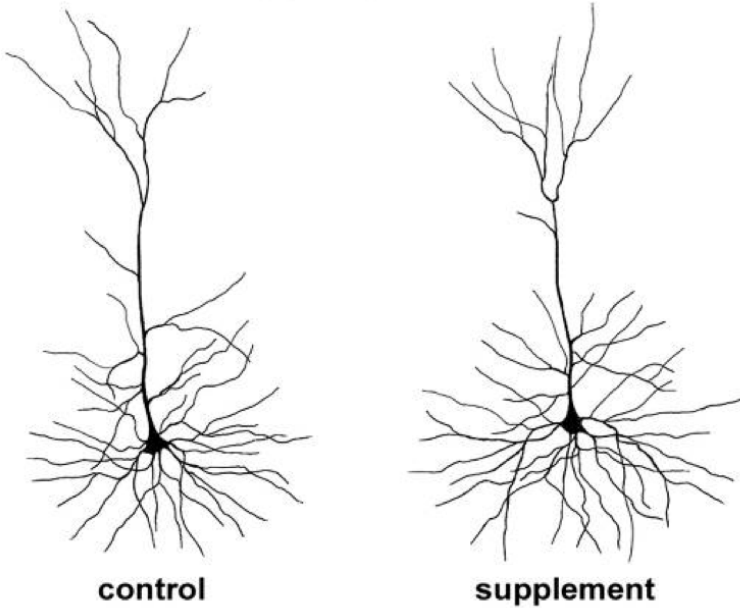
Diet:

- Choline
- vitamin/mineral supplements

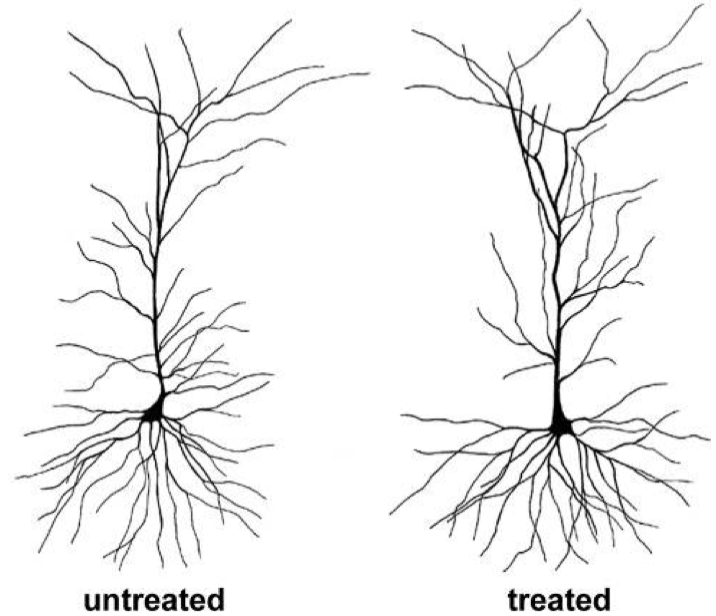
Cox-2 inhibitors

Both act to increase synapse formation and facilitate behaviour

Area Par 1 L.III



Hippocampus area CA 1



Enhanced vitamin/mineral diet increases synaptic space in the basilar fields and enhances both motor and cognitive behaviours

Enhanced choline diet has similar effects in development

# Factors that alter normal cortex

1. **sensory & motor experience**
2. **task learning**
3. **gonadal hormones**
4. **psychoactive drugs (e.g., stimulants, THC)**
5. **neurotrophic factors (e.g., NGF, FGF-2)**
6. **natural rewards (e.g., social interaction, sex)**
7. **stress (social; fear)**
8. **anti-inflammatories (e.g., COX-2 inhibitors)**
9. **diet (e.g., choline)**
10. **aging**

# How does the ageing brain change?

Three types of change:

1. Cell death and reduced regeneration
2. Atrophy of cells
3. Hypertrophy of cells

These changes can be expected to interact with treatment-induced changes.



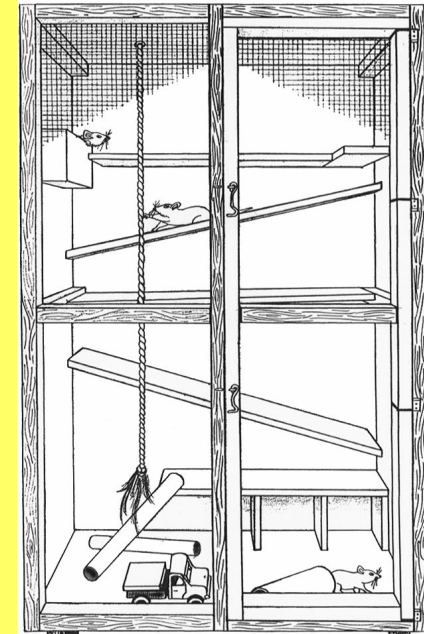
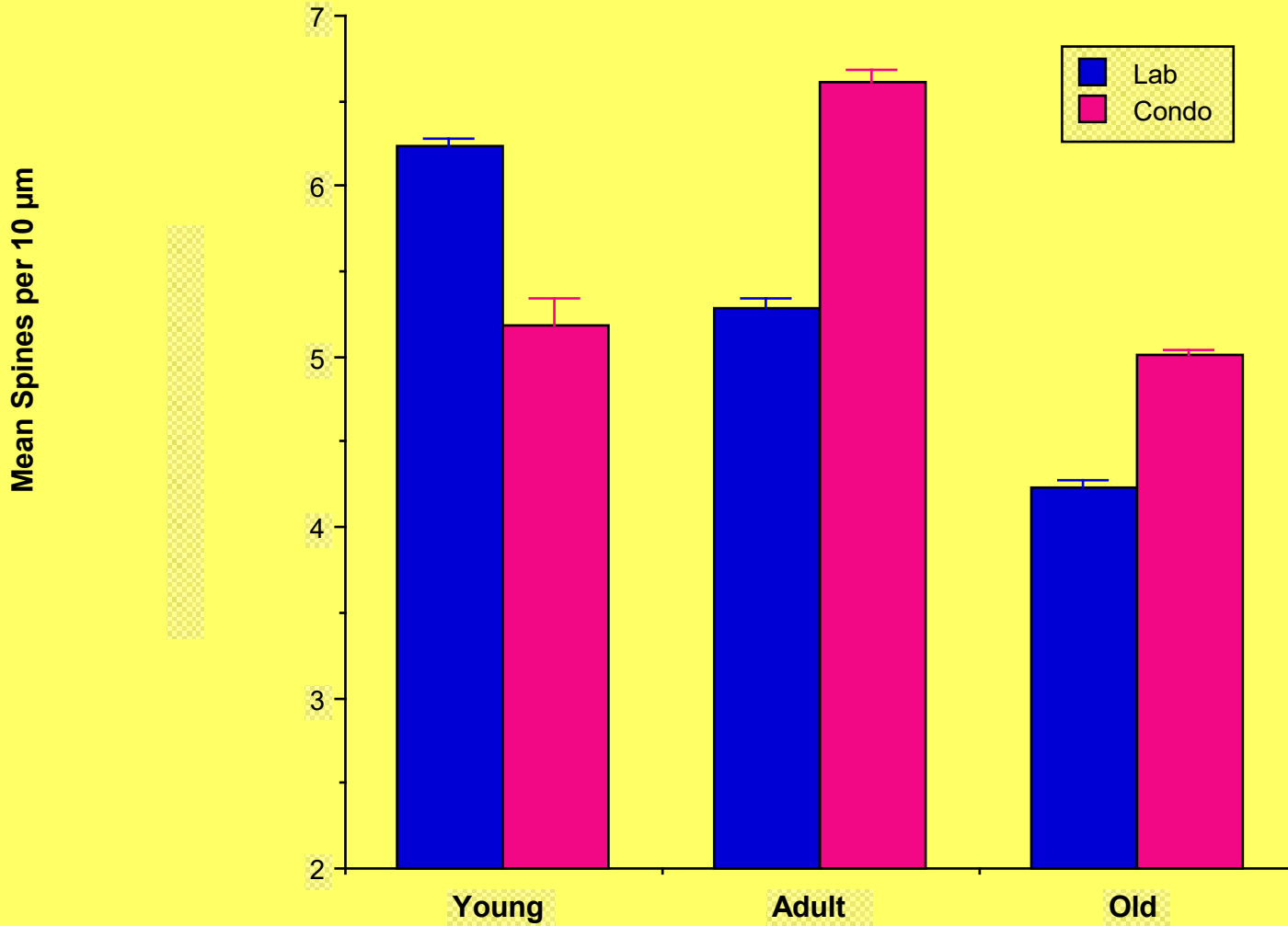
In sum...

All of the factors produce BOTH behavioural change and morphological change, although the latter are site-specific.

## Principle 4

Changes are age-specific and can occur in response to both pre and postnatal experiences

# Complex housing alters spine density differently in young rats

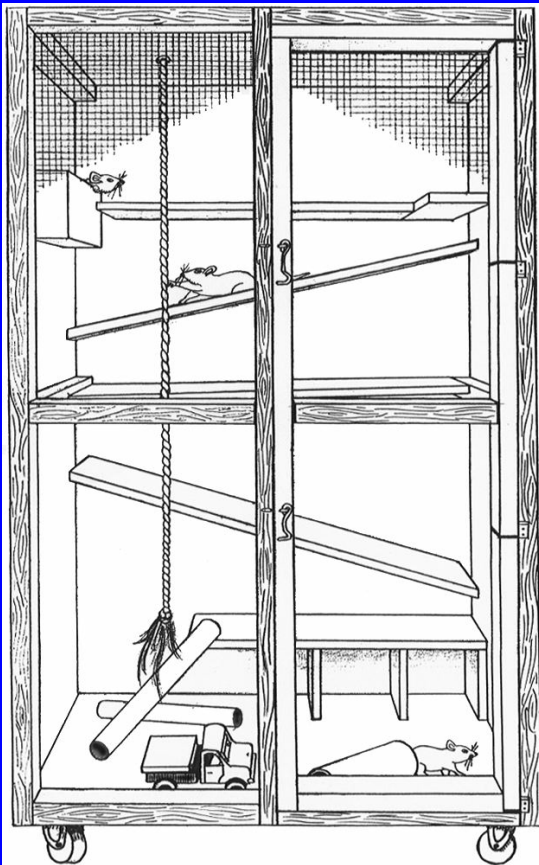


Same story with tactile stimulation

# Prenatal Experiential Treatments

## Complex Housing

Dad or Pregnant mom



## Tactile Stimulation

Pregnant mom



# Other Prenatal Treatments

## Prescription Drugs

Antidepressants  
Anxiolytics

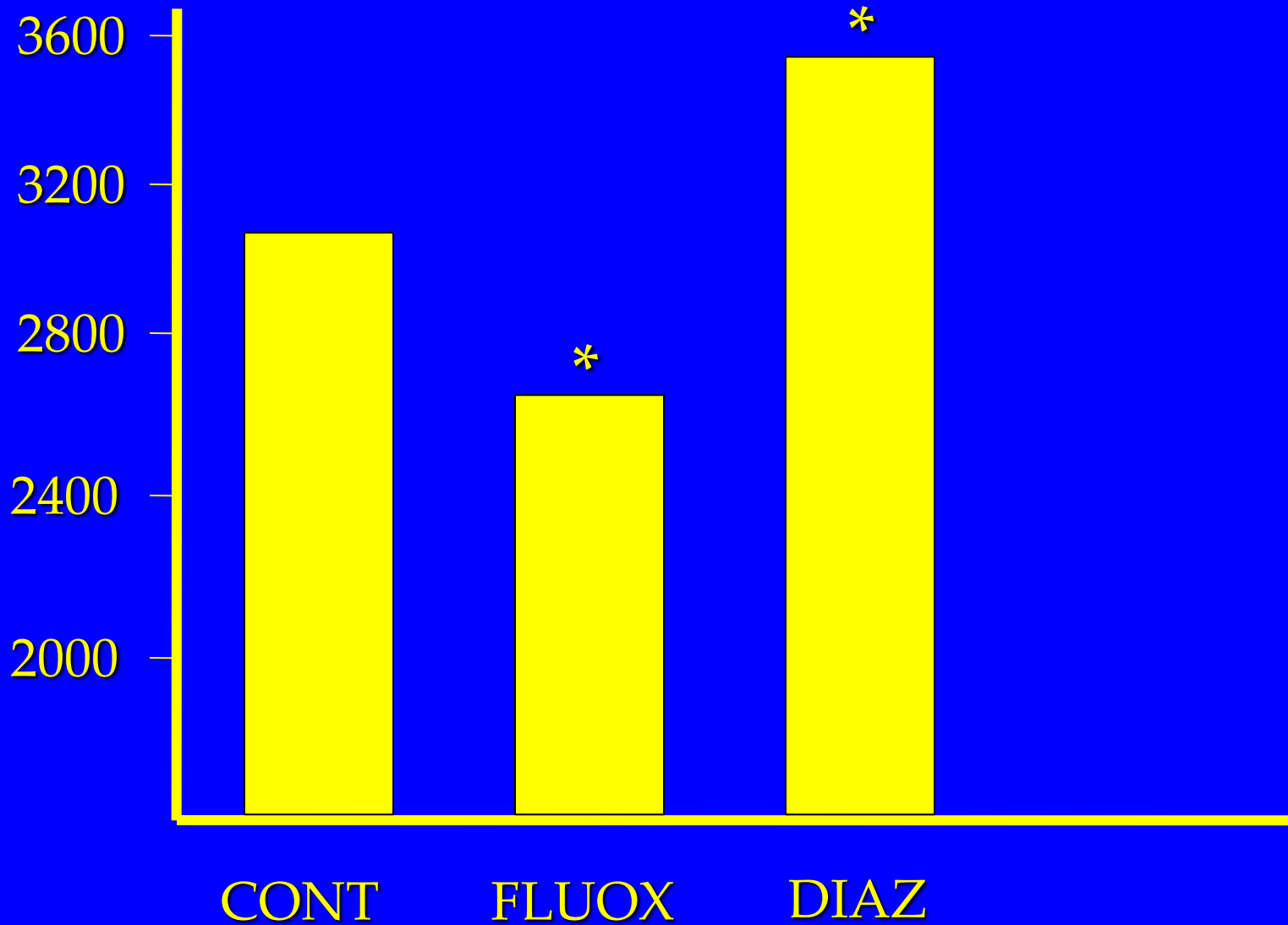
## Social interactions

Parent-infant  
Stress

## Other Drugs

Stimulants  
Alcohol  
& likely all other  
'recreational' drugs

# Par 1 Layer III DENDRITIC LENGTH



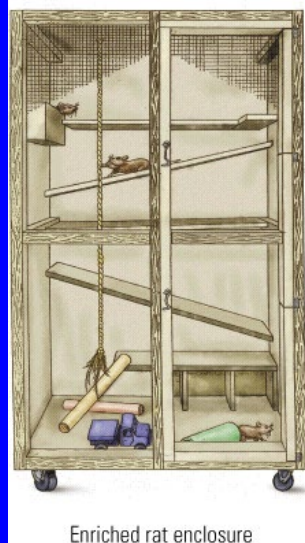
## Principle 5

Experiences interact – “metaplasticity”

# Drug exposure reduces the capacity for further change



Drug Treatment +



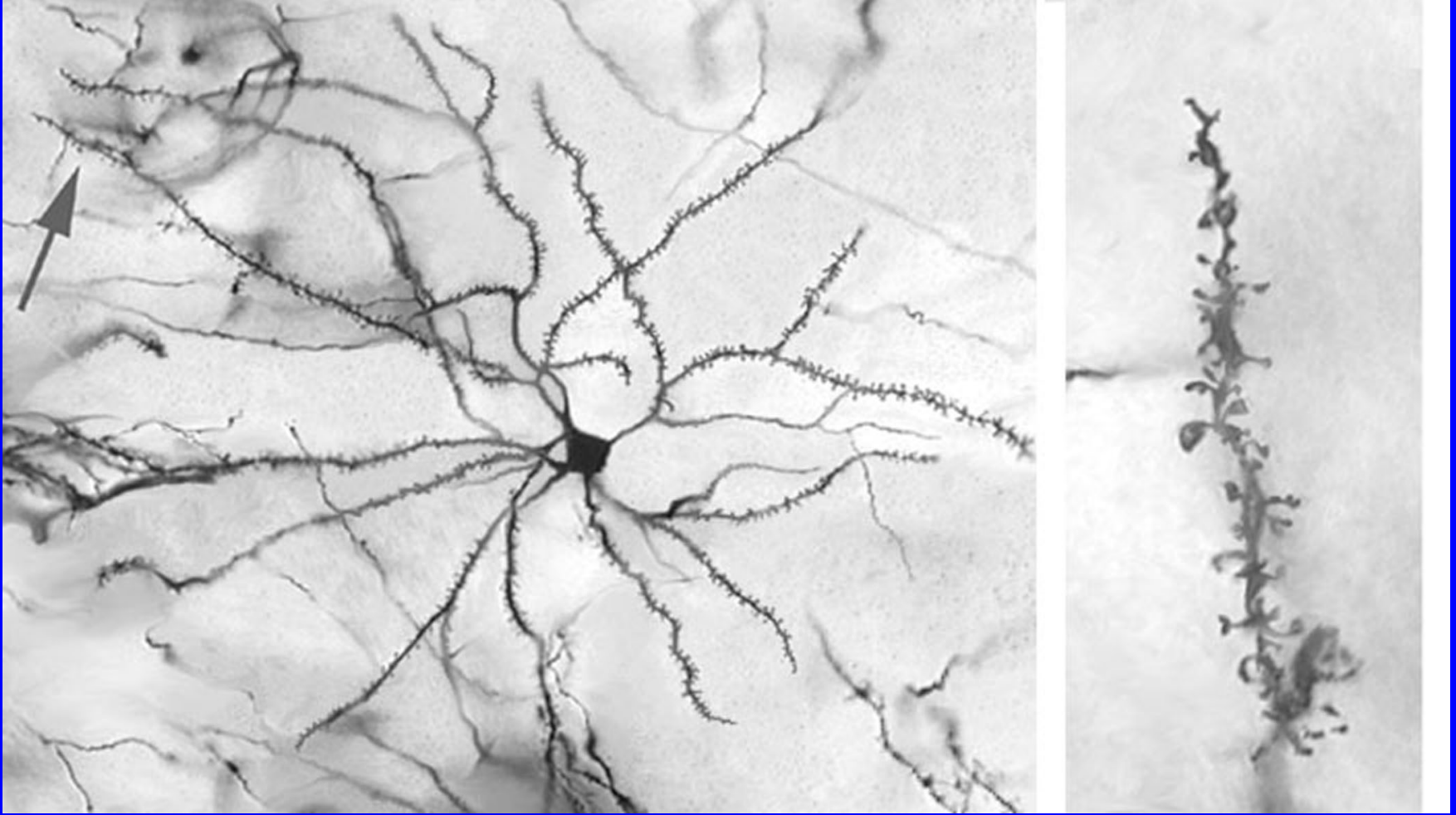
= ?

LTP



# Predictions

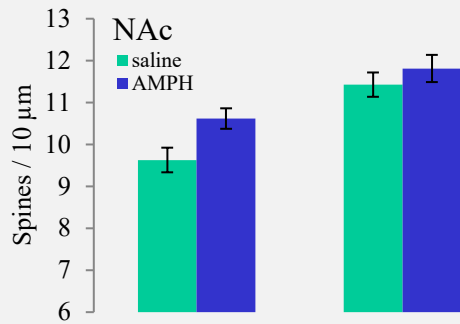
1. Makes no difference
2. Blocks the effect of experience in the regions altered by the drug
3. Alters the effect of experience
4. Blocks the effect of experience all over.



The drugs either *block or alter* the later experience-dependent changes throughout the cerebrum – NOT just in drug-affected regions.

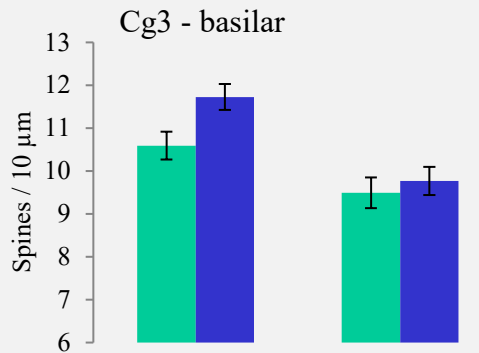
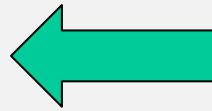
What about the reverse?

Mild prenatal stress alters adult drug effects

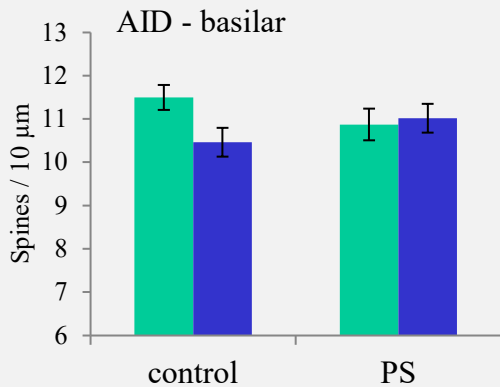
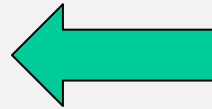


1. Mild prenatal stress has area-dependent effects on spine density.

Up in NAcc



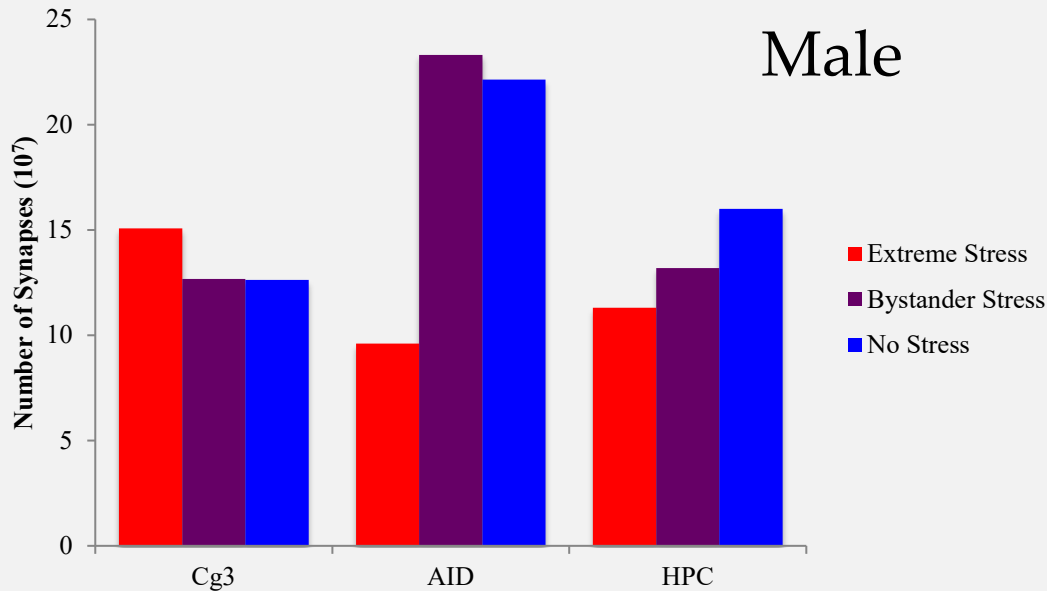
Down in Cg3



2. Prenatal stress blocks the effect of amphetamine in all 3 regions

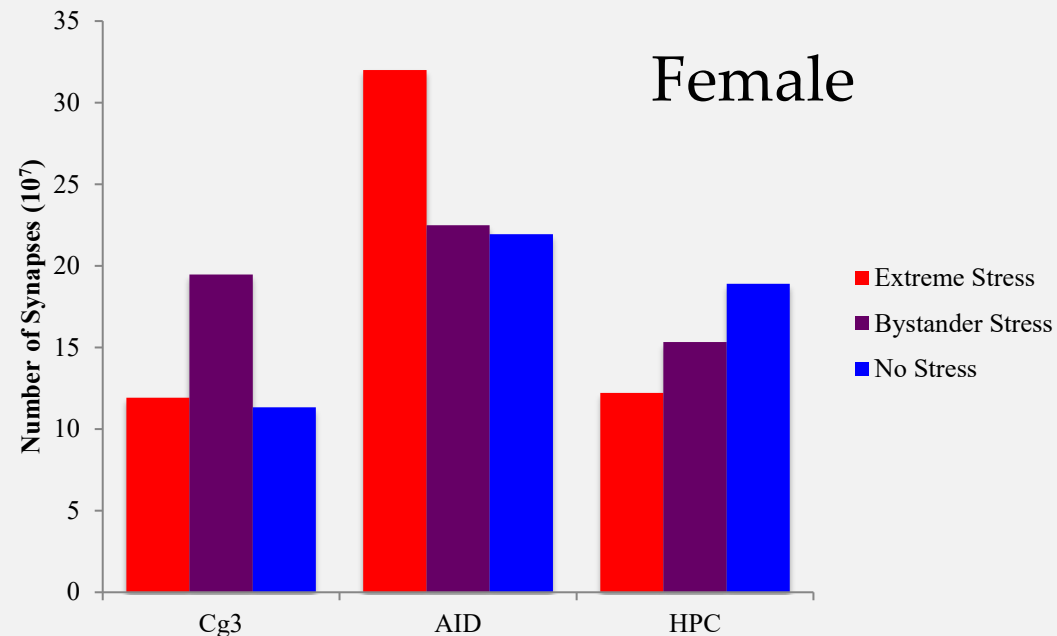
(Muhammad & Kolb, 2011)

# Sex interacts with virtually everything!



For Example...

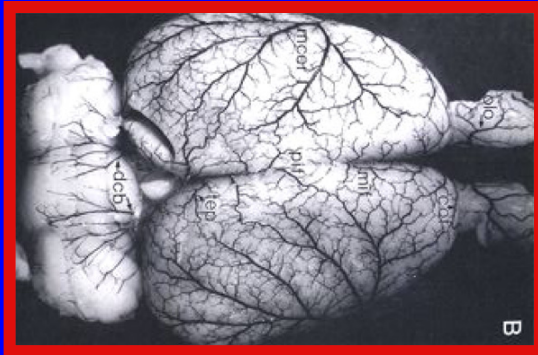
The pattern of synaptic change is completely different in the PFC in the 2 sexes



# How do we go about finding and evaluating treatments for brain injury?

1. Identify those factors that produce plastic changes in the normal brain.
2. Develop animal models of injury.
3. Use the plasticity factors in the animal models.

# Some Adult Models



## 1. Suction removals:

Long history

## 2. Devascularization of the motor cortex:

Provides a consistent set of behavioral & anatomical effects

## 3. MCA occlusions:

More variable lesions and deficits

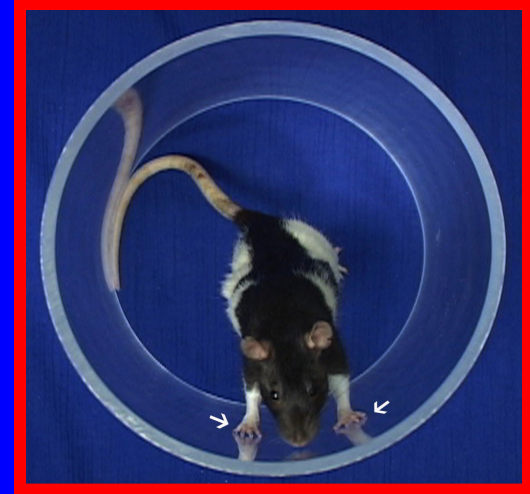
## 3. TBI

# Motor Measures

## Forepaw Inhibition



## Forepaw Asymmetry



## Tray Reaching



## Single Pellet Reaching



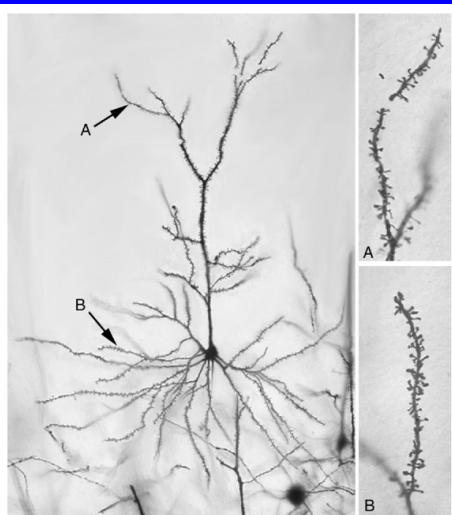
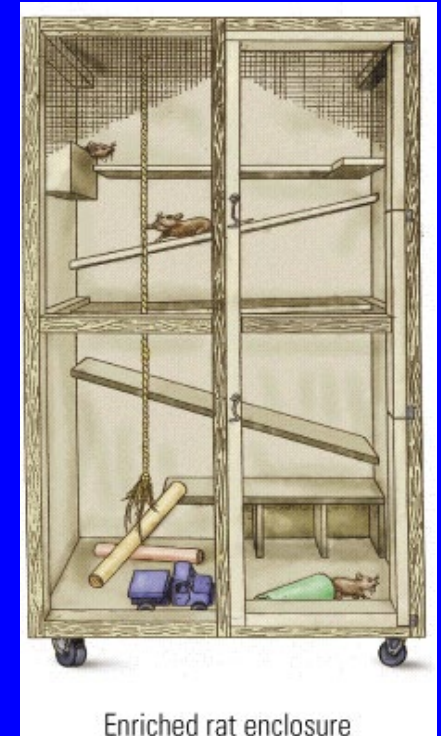
# **General Types of Treatments**

- 1. Postinjury experience**
- 2. Pharmacotherapy**
- 3. Cell-based therapy**
- 4. Cortical stimulation**
- 5. Combinations of treatments**

**Lets break and return to see what treatments work...**

# Postinjury Experience

Tactile/Olfactory stim  
Complex housing  
Rehab Training  
Social stimulation  
Diet

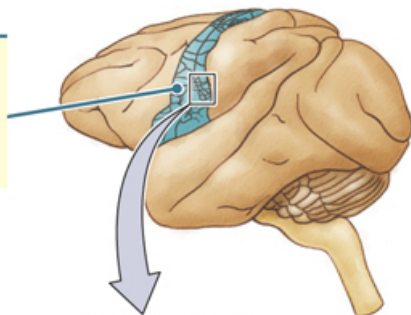


# The Logic

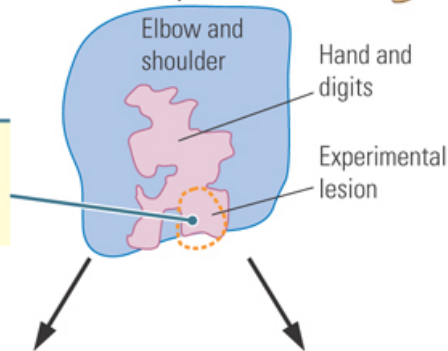
- 1. Multisensory/motor/social experience induces widespread synaptic changes in the normal brain.**
- 2. Thus, such experience should enhance synaptogenesis that will reverse stroke-induced atrophy AND induce synaptic growth in residual motor areas.**

## Procedure

Areas of motor cortex that produce digit, wrist, and forearm movement.

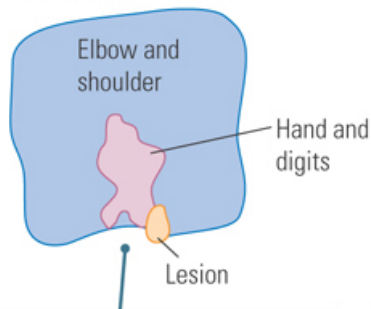


Small lesion is made with electrical current.



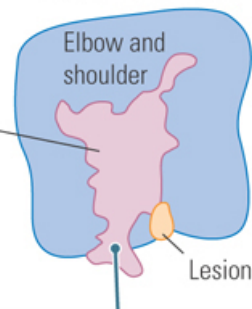
## Results

3 months postlesion with no rehabilitation



Without rehabilitation, the area regulating the hand becomes smaller and the area regulating the elbow and shoulder becomes larger.

3 months postlesion with rehabilitation



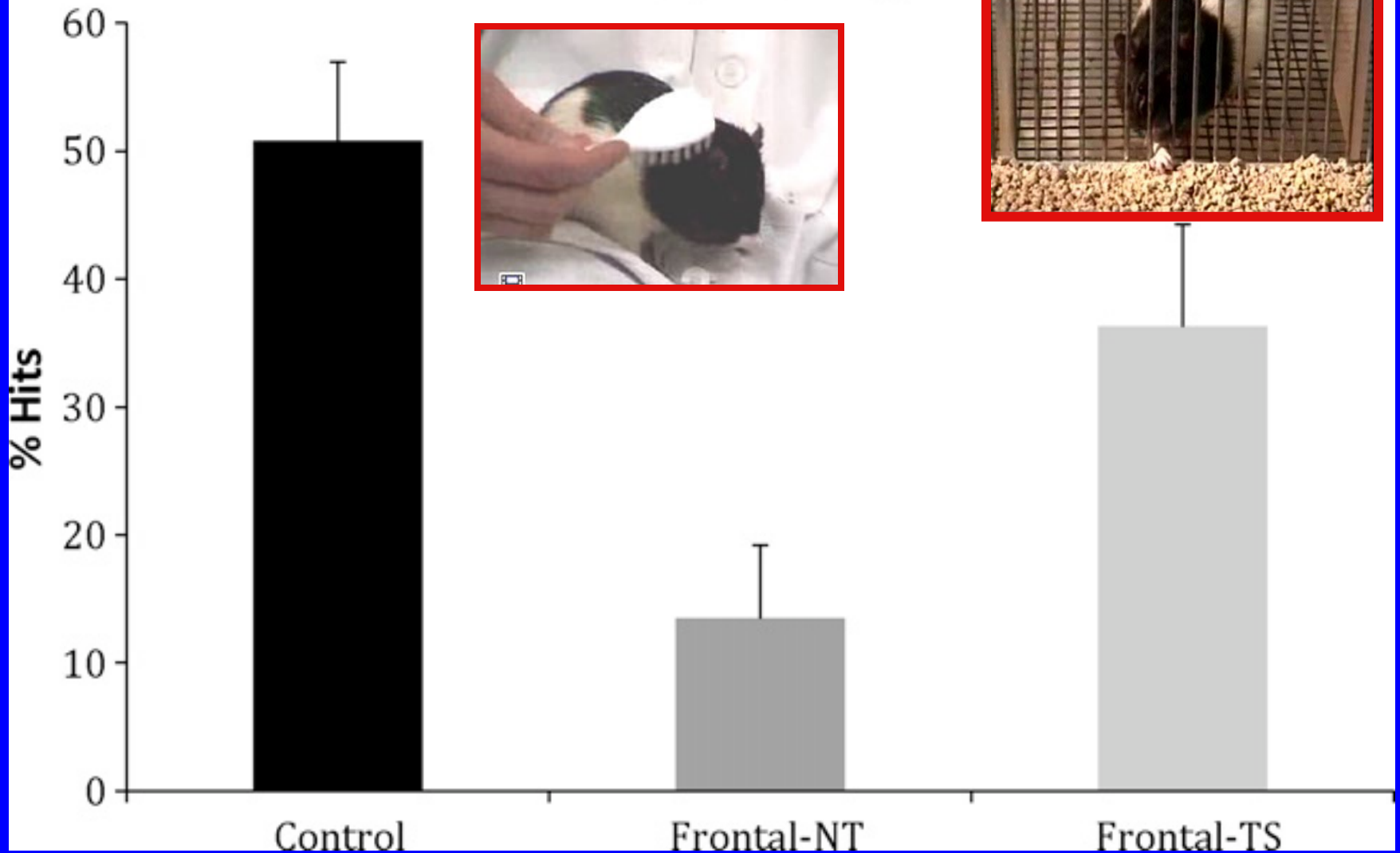
With rehabilitation, the area regulating the hand retains its large cortical representation.

## Conclusion

Rehabilitation prevents both a loss of movement in the hand and a decrease in the hand's cortical representation.

Treatment not only improves outcome but also can help deficits from getting worse

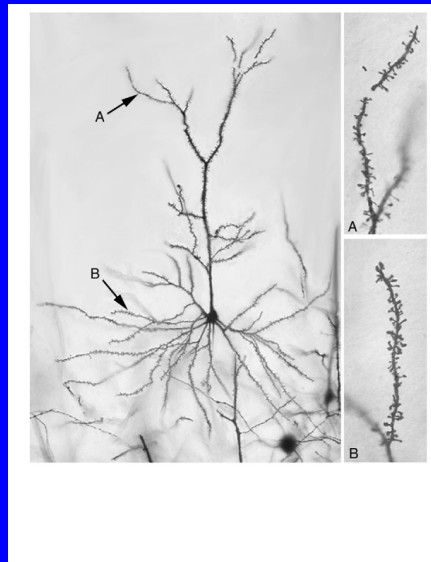
## Tray Reaching



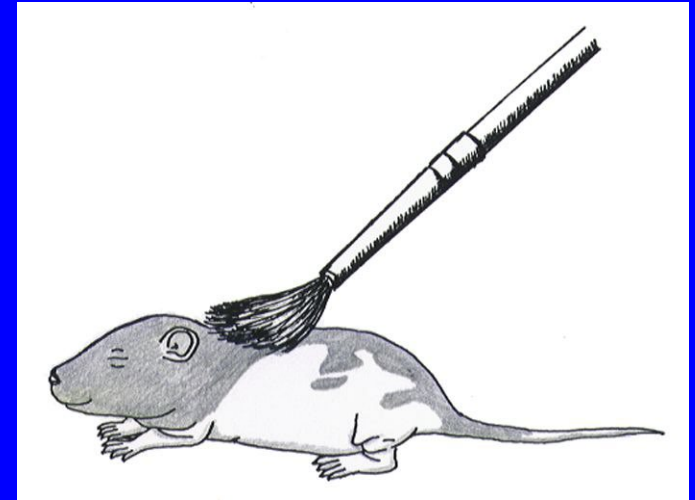
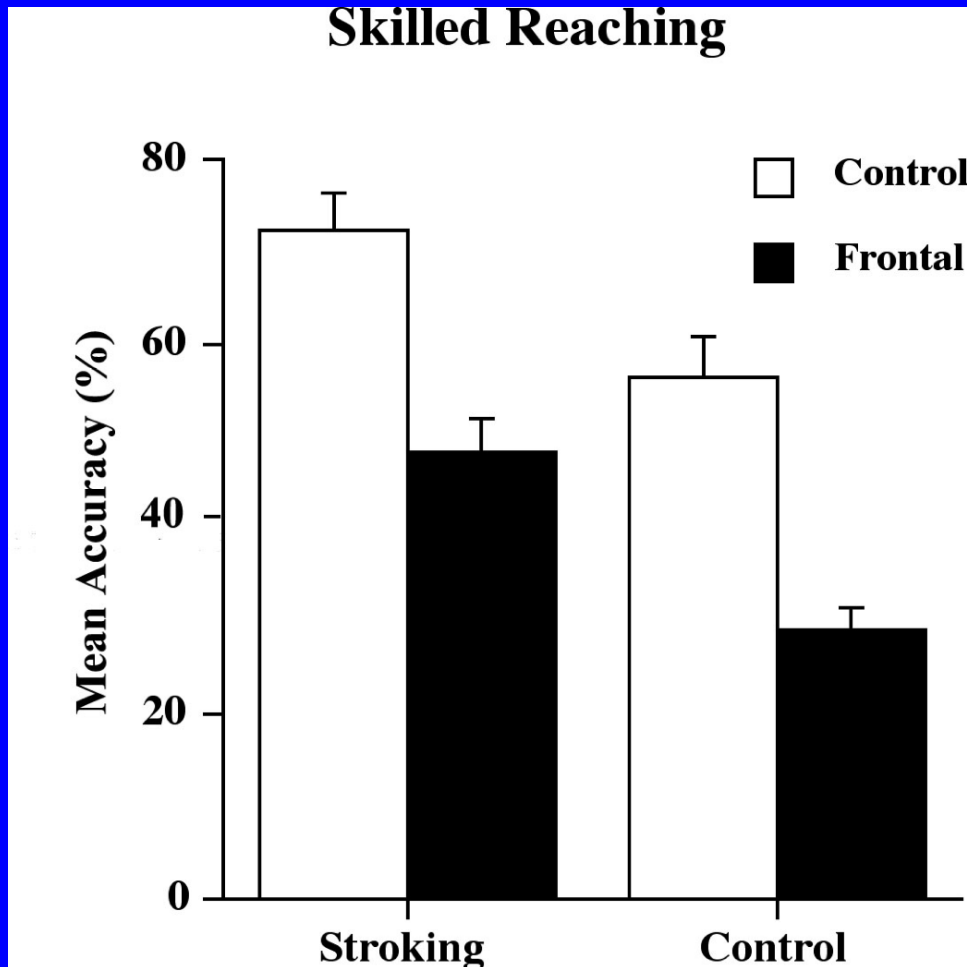
Gibb et al., Behav Brain Research, 2010, in press

# Synaptic Changes??

1. Increased dendritic length and complexity in the pyramidal cells in the *contralateral* forelimb area.
2. Ditto in the perilesional parietal cortex.



# Tactile Stimulation in Infants

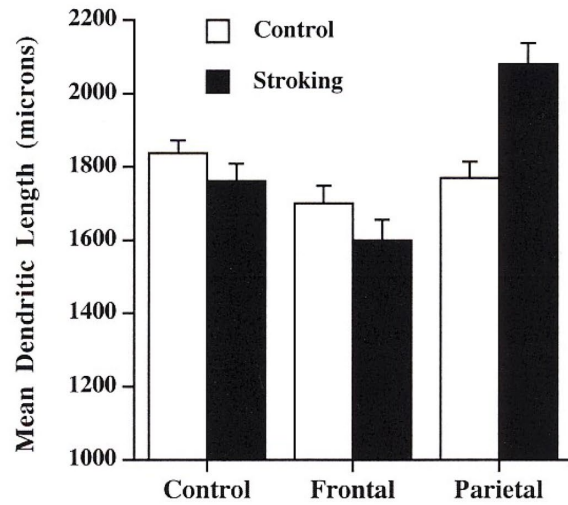


**Again correlated with synaptogenesis.**

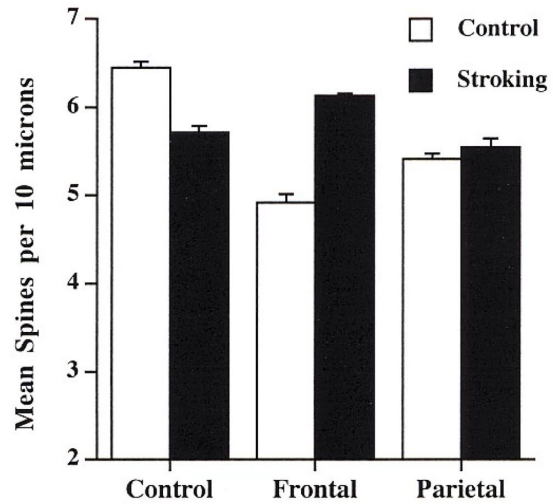
**Kolb & Gibb, BBR, 2010  
in press**



### A. Basilar Dendritic Length



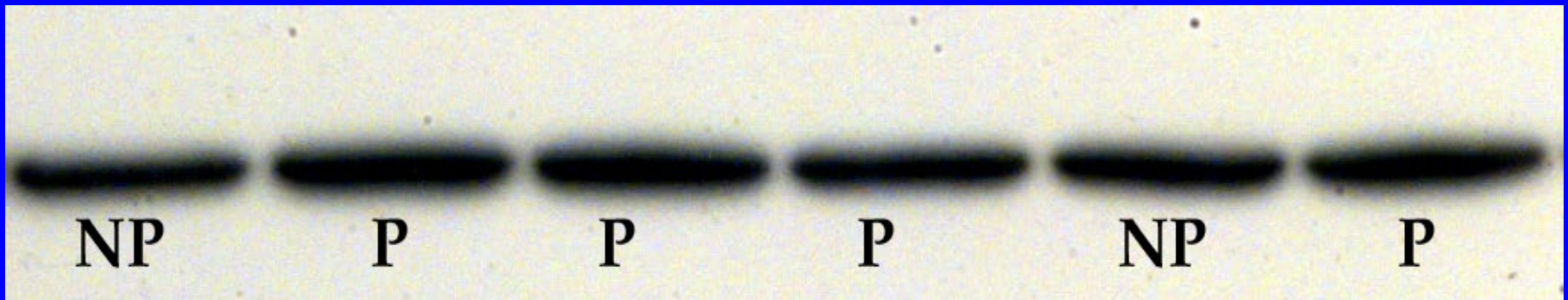
### B. Apical Spine Density



**Experience increases FGF-2 expression**

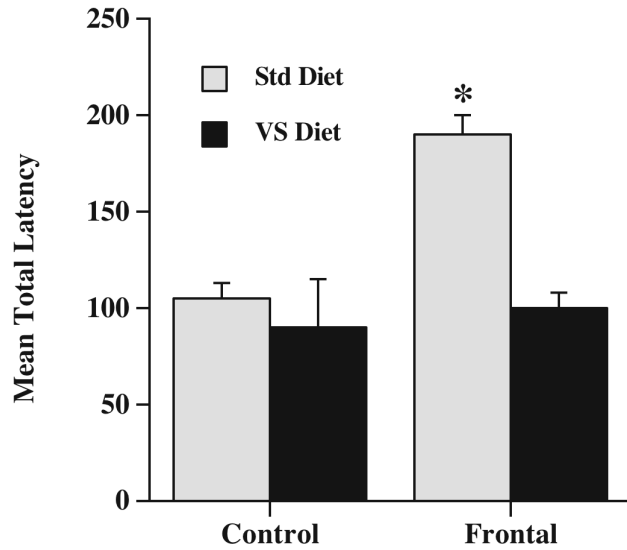


**SKIN**



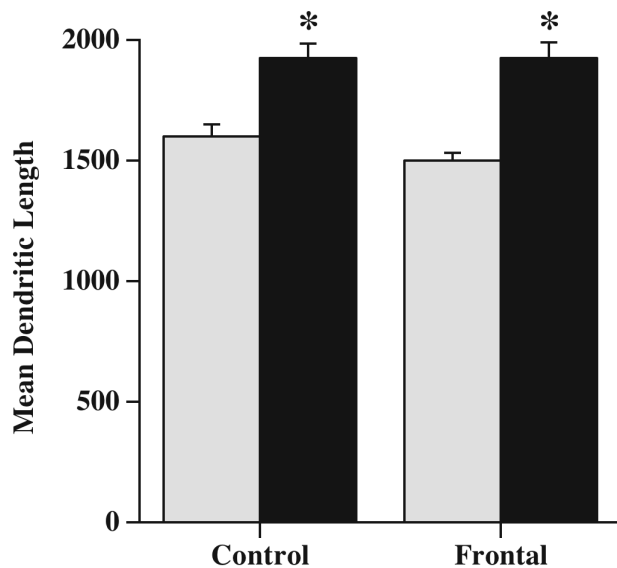
**FR. CTX.**

### A. Morris Water Task



**Enhanced diet from birth to testing enhances recovery and stimulates dendritic growth**

### B. Par 1 Basilar Dendrite Length



**Diet facilitates recovery in human infants as well as in the lab**

# What Human Treatments Work?

1. Constraint-induced therapy
2. Treadmill training
3. Virtual environments
4. Robotic devices
5. Behavioral shaping
6. Task-oriented physical therapy

**BUT:** the more complex treatments (2,3,4) are no more effective than the simpler ones.

**AND:** the treatments work better in combination and with pharmacological therapy.

# Pharmacotherapy

**Stimulants (amphetamine, nicotine, methylphenidate)**

**Inosine**

**Antibodies to NoGo-A**

**Neurotrophic Factors (NGF; FGF-2)**

# The Logic of Stimulants

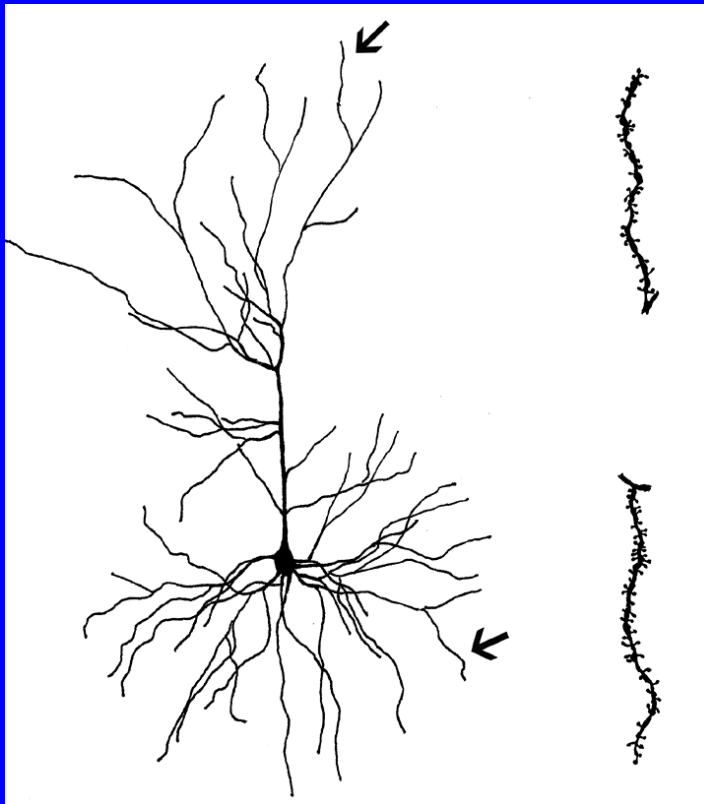
- 1. Psychomotor stimulants induce synaptic change in the normal brain. Nicotine produces more widespread changes than amphetamine.**
- 2. Thus, the drugs should enhance synaptogenesis that will reverse stroke-induced atrophy AND induce synaptic growth in residual motor areas.**
- 3. Behaviours controlled by regions unaffected by the drugs should not show functional improvement.**

# RESULT

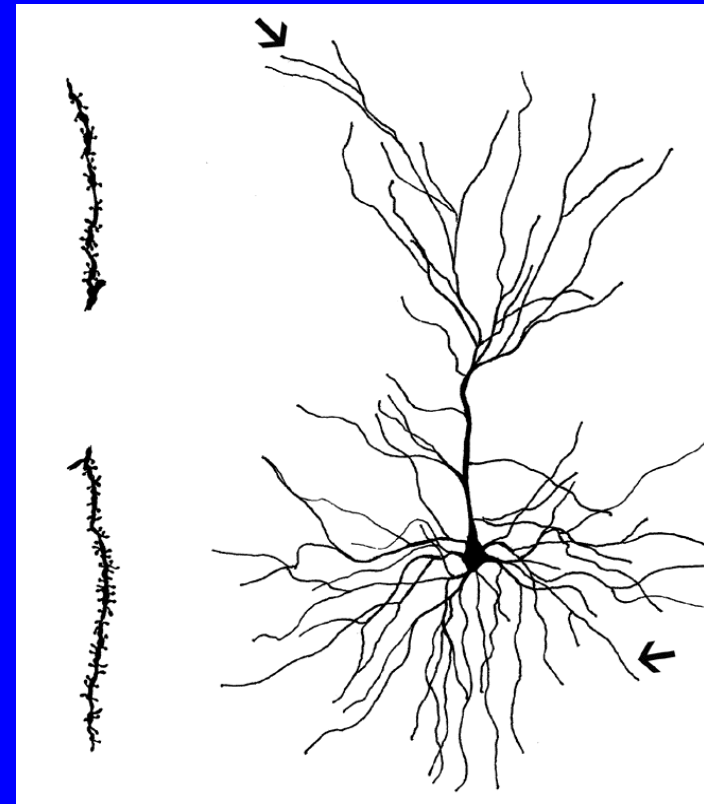
- 1. Nicotine improves performance on all of the motor tests.**
- 2. Amphetamine improves performance only on reaching and only with small infarcts.**
- 3. Both drugs induce synaptogenesis in anterior cingulate corticospinal region. Nicotine also induces changes in perilesional motor cortex.**

# Nicotine stimulates dendritic hypertrophy in remaining motor cortex

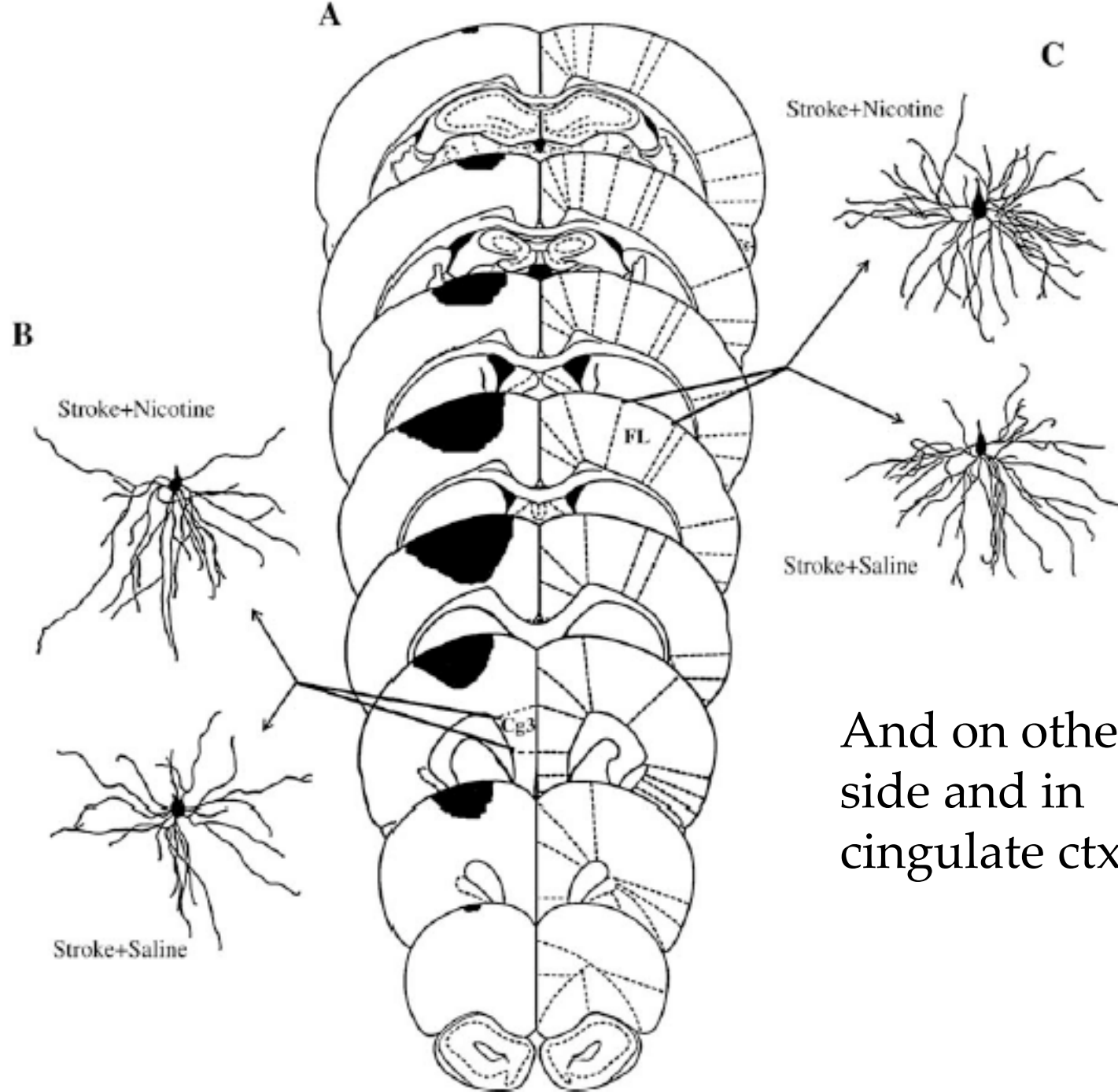
No Treatment



Nicotine





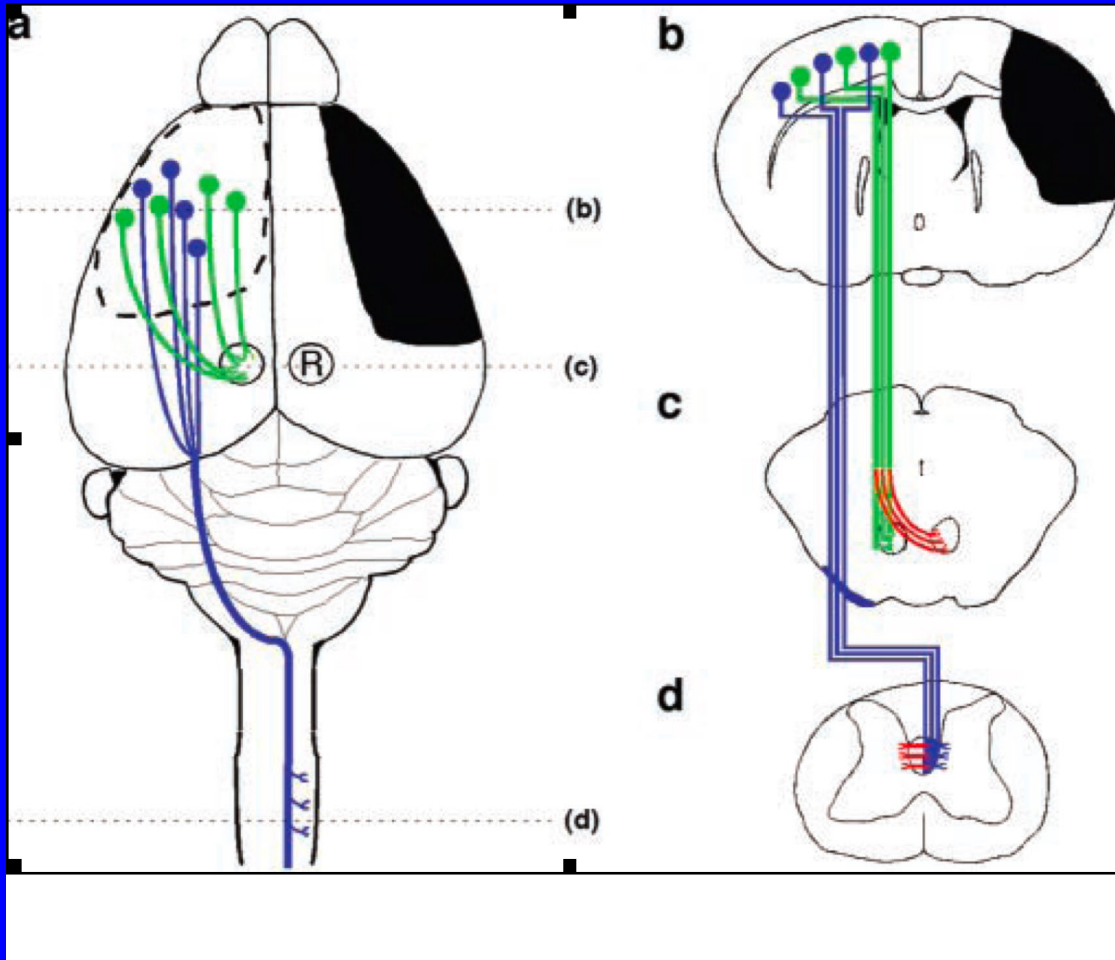


And on other  
side and in  
cingulate ctx

# Ritalin?

1. Ritalin produces neural changes much like amphetamine
2. Attentional effects?

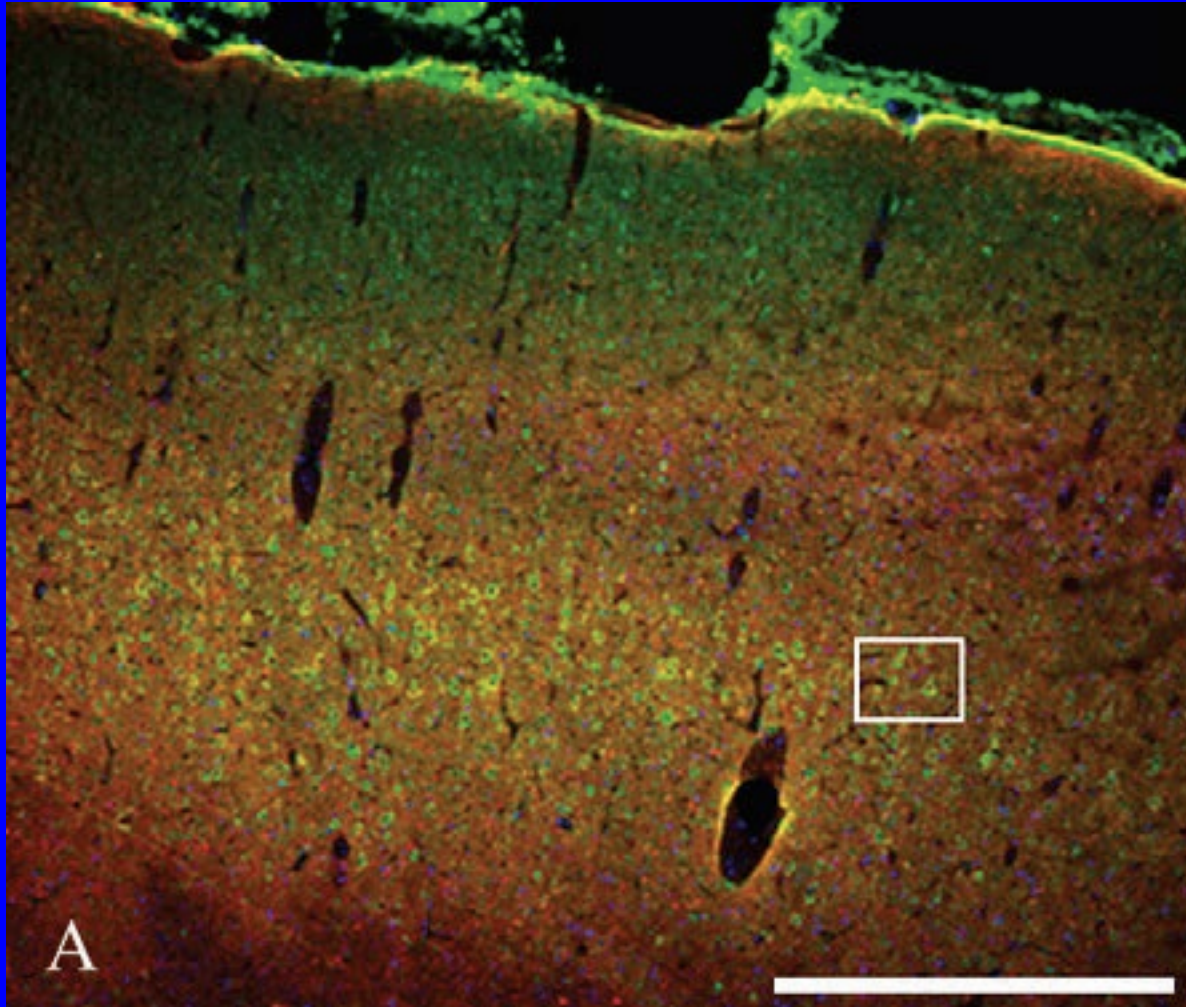
# Inosine



**A purine nucleoside that can activate an intracellular signaling pathway that regulates the expression of multiple genes involved in axon outgrowth.**

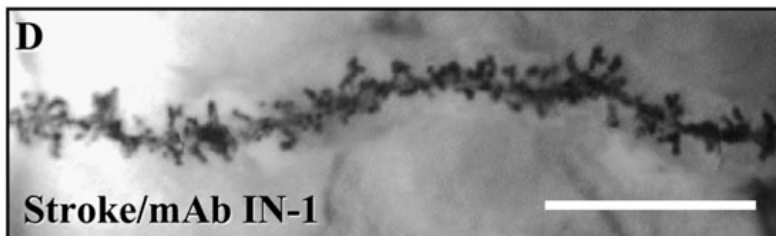
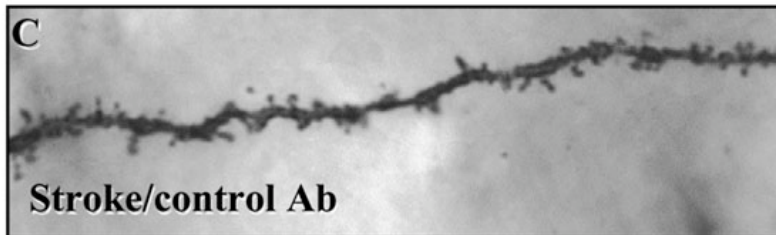
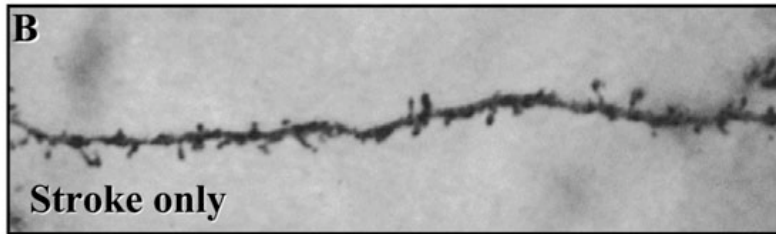
**Functional recovery correlated with axonal sprouting.  
Chen et al., PNAS, 99, 9031-9036.**

# Antibodies to NoGo-A



**Pyramidal cells  
in FL are + for  
NoGo-A (green)**

# Antibodies to NoGo-A



**Both dendritic length and spine density in contralateral FL cortex enhanced by the antibodies. Correlated with functional recovery of skilled reaching.**

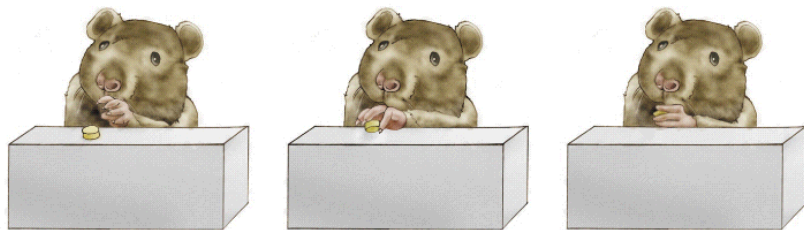
**Papadopoulos et al.,  
Cerebral Cortex, 2006,  
16:529--536**

## EXPERIMENT

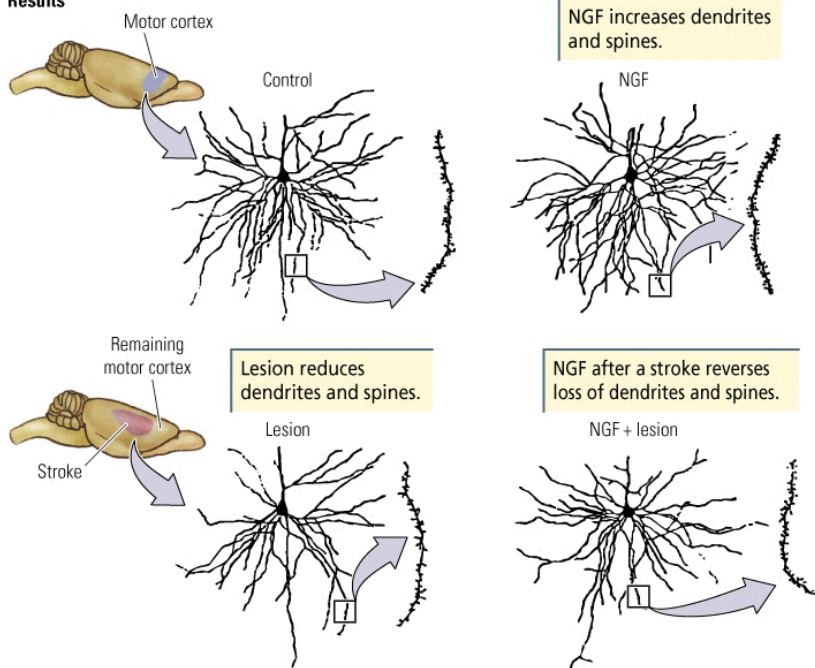
**Question:** Does nerve growth factor stimulate recovery from stroke and/or influence neural structure?

### Procedure

Animals received a cortical stroke. Some were treated with NGF; others were not. Skilled reaching was assessed.



### Results



### Conclusion

Nerve growth factor stimulates dendritic growth and increased spine density in both normal and injured brains. These neuronal changes are correlated with improved motor function after stroke.

# NGF

**Dendritic and spine changes correlate with behavioural recovery**

**Problem of BBB**

**Kolb et al., Neuroscience, 1997, 76, 1139-1151**

# Neurotrophic Treatments

**Fibroblast Growth Factor-2 (FGF-2) enhances synaptogenesis and functional recovery.**

**BUT, FGF-2 only works in combination with behavioural therapy**

**Note: both NGF and FGF-2 are increased by most of the other treatments...**

# FGF-2 alone or in combination with behavioural therapy

<u>TESTS</u>	Reach	Complex	bFGF	Rch+ bFGF	Cx+ bFGF
Reaching Tasks		+		+	+
Cylinder Task		+			+
Forepaw Inhib			+		+
Tongue					+
Claw Cutting					+

1. Behavioural therapy was ineffective.
2. The combination of FGF-2 and experience was far more effective than any other treatment(s).



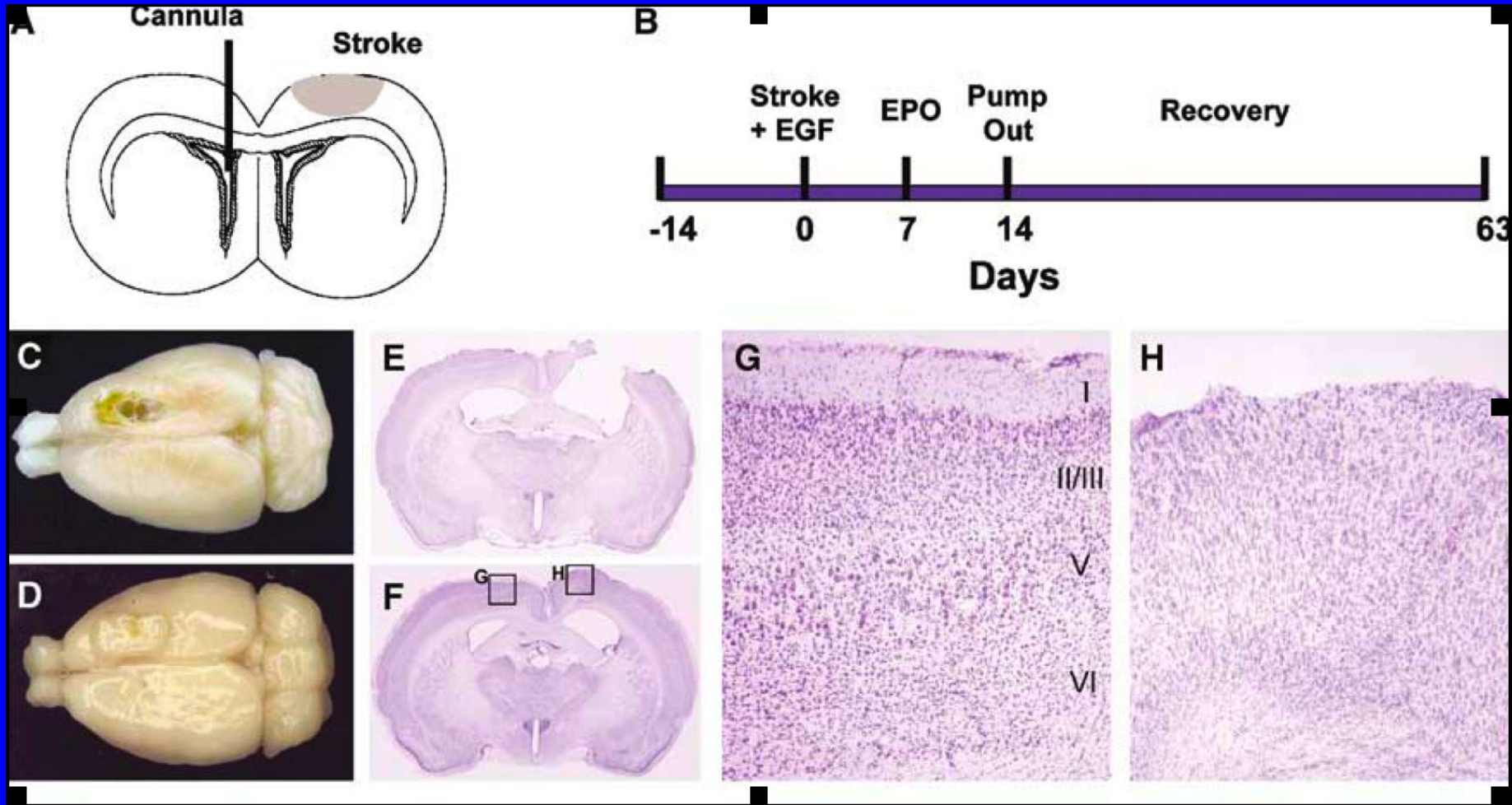
# Endogenous stem cells

Stem cells can be recruited to induce plasticity and behavioural changes.

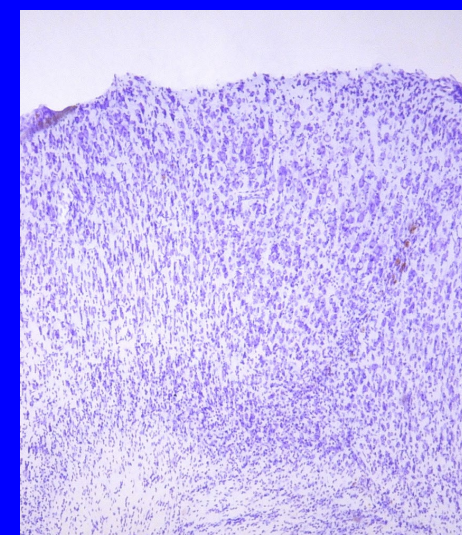
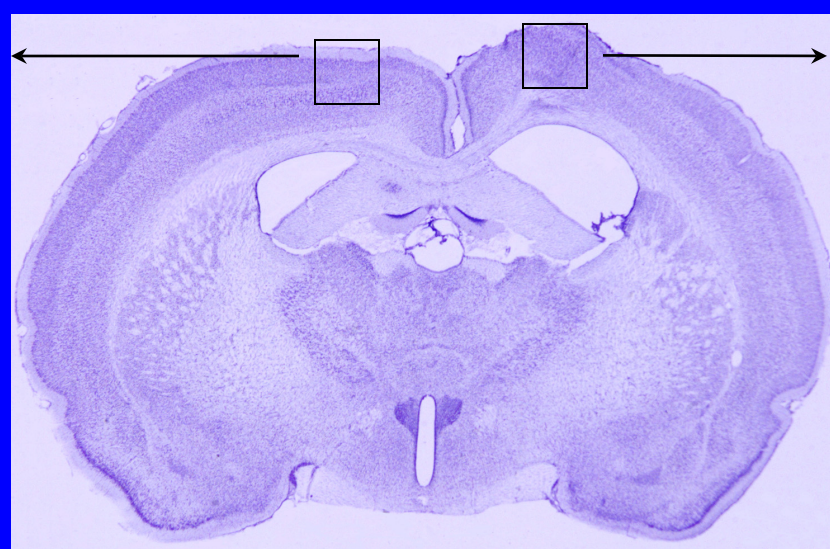
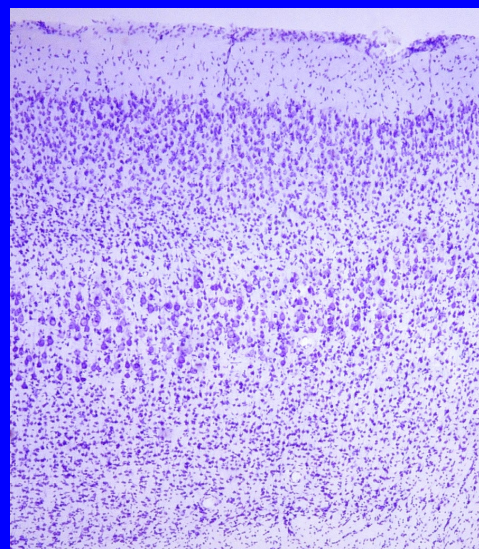
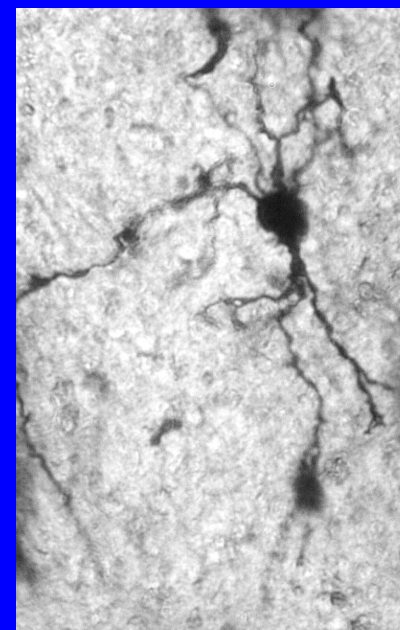
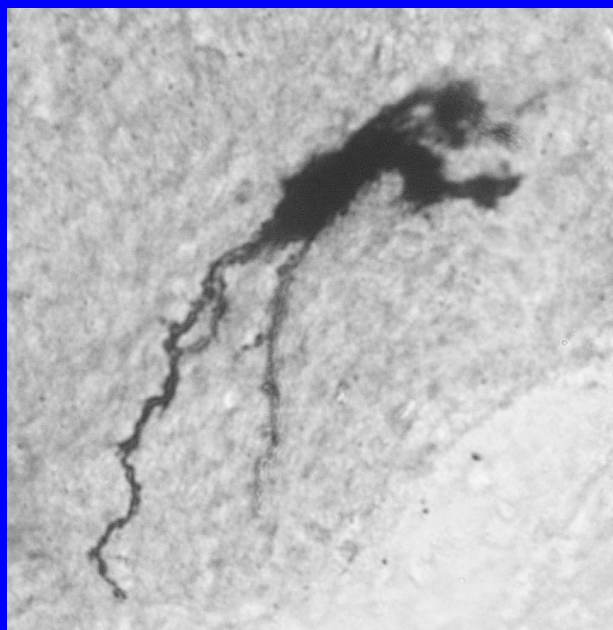
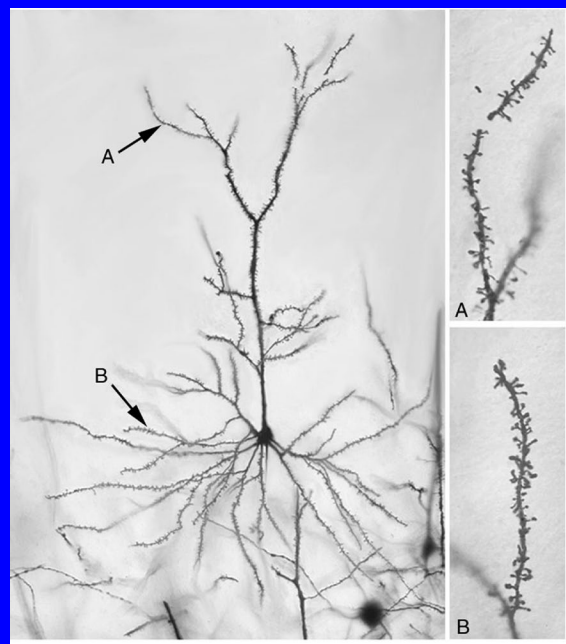
# Cell-Based Treatments

- 1. Use Neurotrophic factors to induce stem cell proliferation.**
- 2. Use EPO to induce neuronal differentiation, if needed.**
- 3. Block stem cell activity OR remove new cells to demonstrate role in function.**

# Cell-Based Treatments

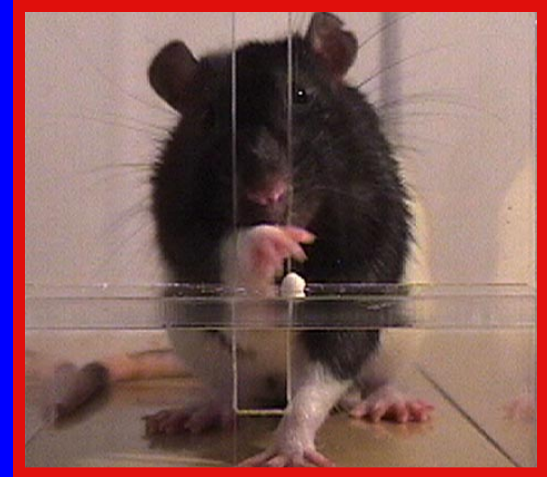


# Golgi and cresyl violet staining reveals neurons with immature morphologies and a lack of normal cortical layer formation



# Function?

1. Yes. There is a gradual return of postural symmetry and forelimb inhibition.
2. There is partial return of reaching.



# Pre-Lesion



## 3 Days Post-Lesion



# 6 Weeks Post-Lesion - EGF+EPO





**Why is there functional improvement?**

**What happens when the plug is removed?**

**What predictions would you make?**

# Function?

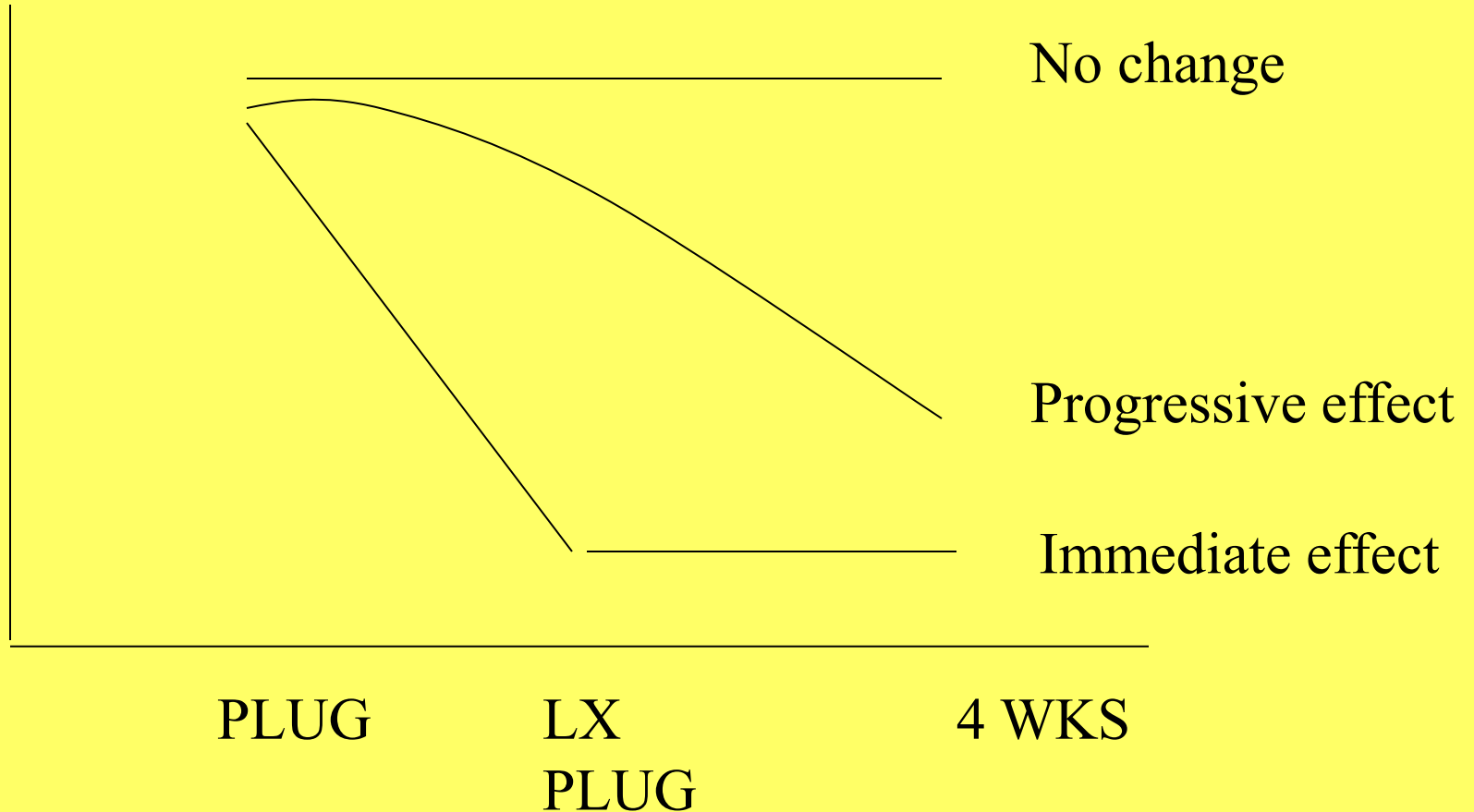
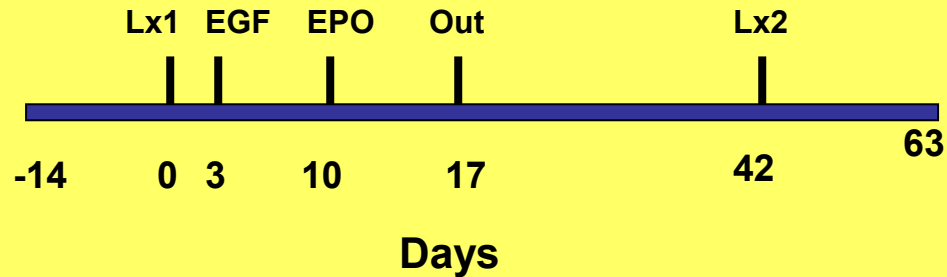
1. Yes. There is a gradual return of postural symmetry and forelimb inhibition.
2. There is partial return of reaching.



Why is there functional improvement?

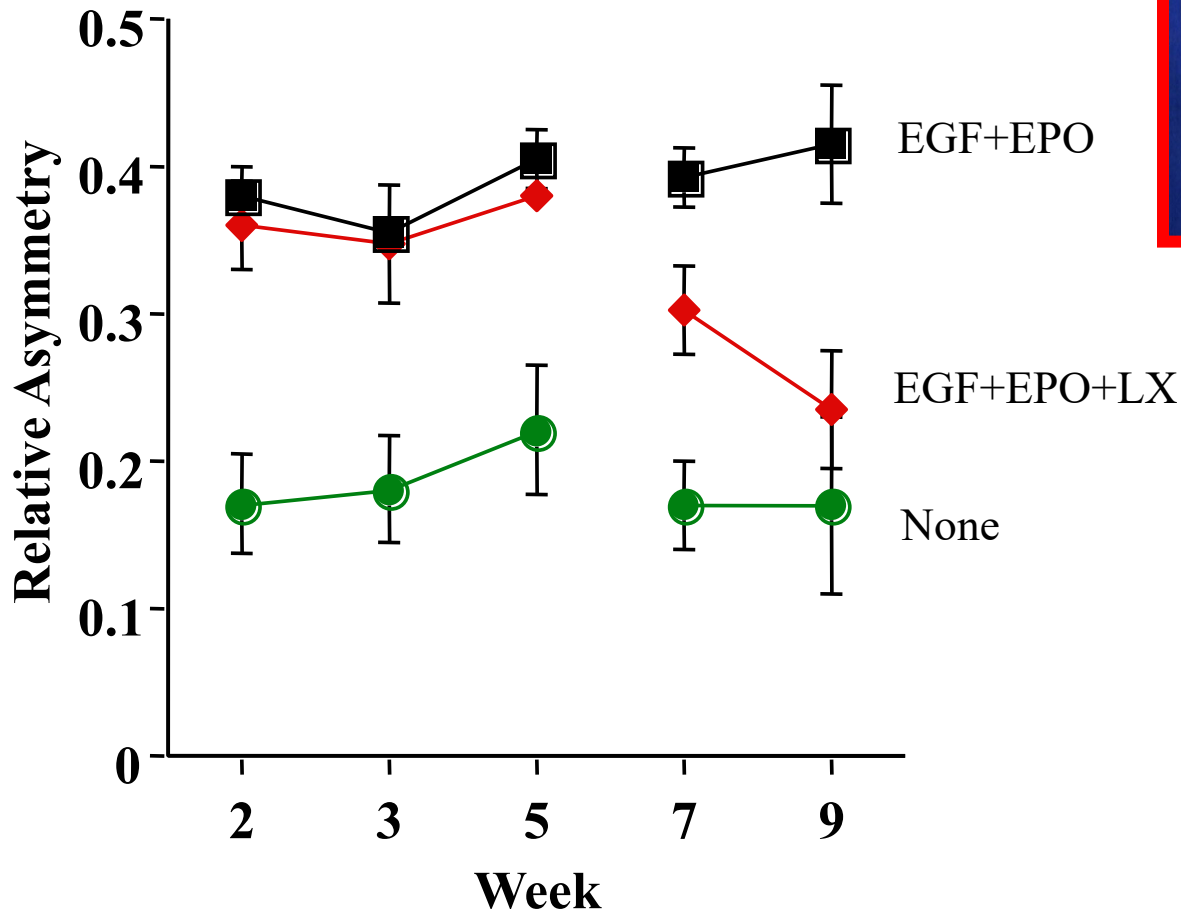
Direct VS indirect effects of the treatments

# Does the newly-generated cortical tissue matter?



# Removing the plug

## Forelimb Asymmetry



## **Current Status in the clinic?**

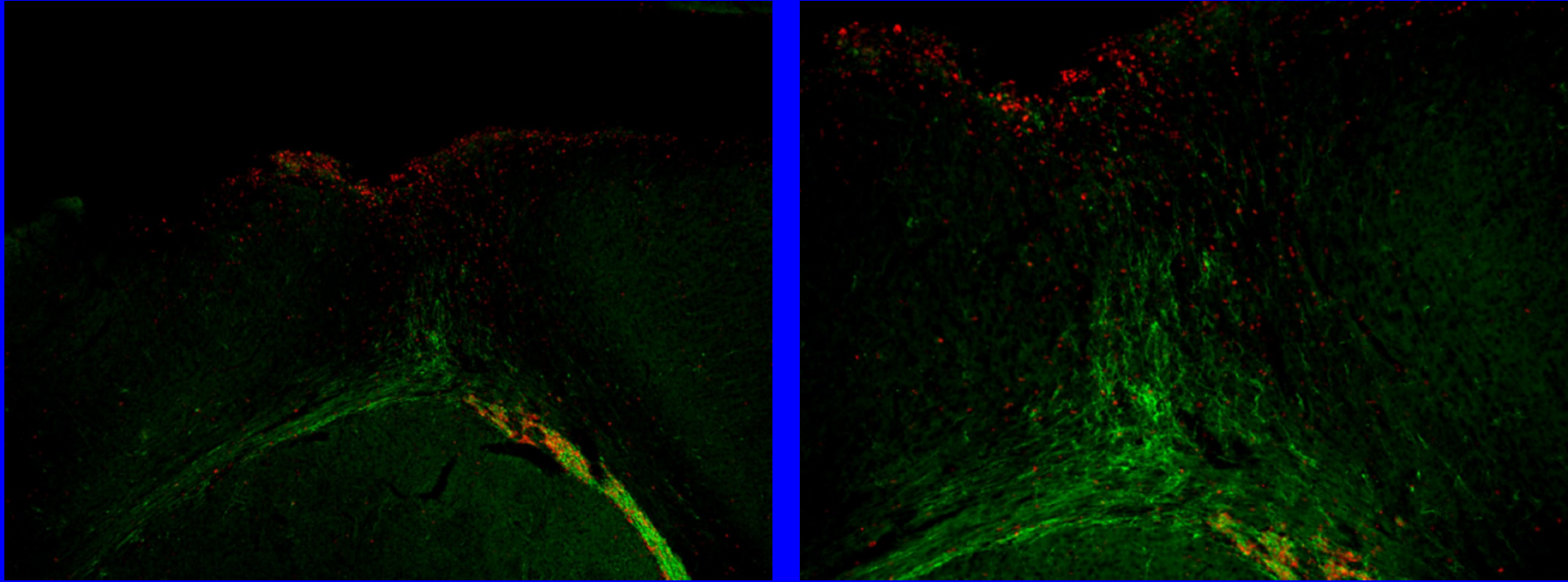
**Currently in Phase II clinical trials with plans to move Phase III.**

**Instead of EGF it is a derivative of GH.**

## **FGF-2 and neurogenesis**

**FGF-2 stimulates neurogenesis and functional recovery after motor cortex injury at P10 but not in adulthood.**

## FGF-2 induces neurogenesis after P10 Motor Ctx Lesion



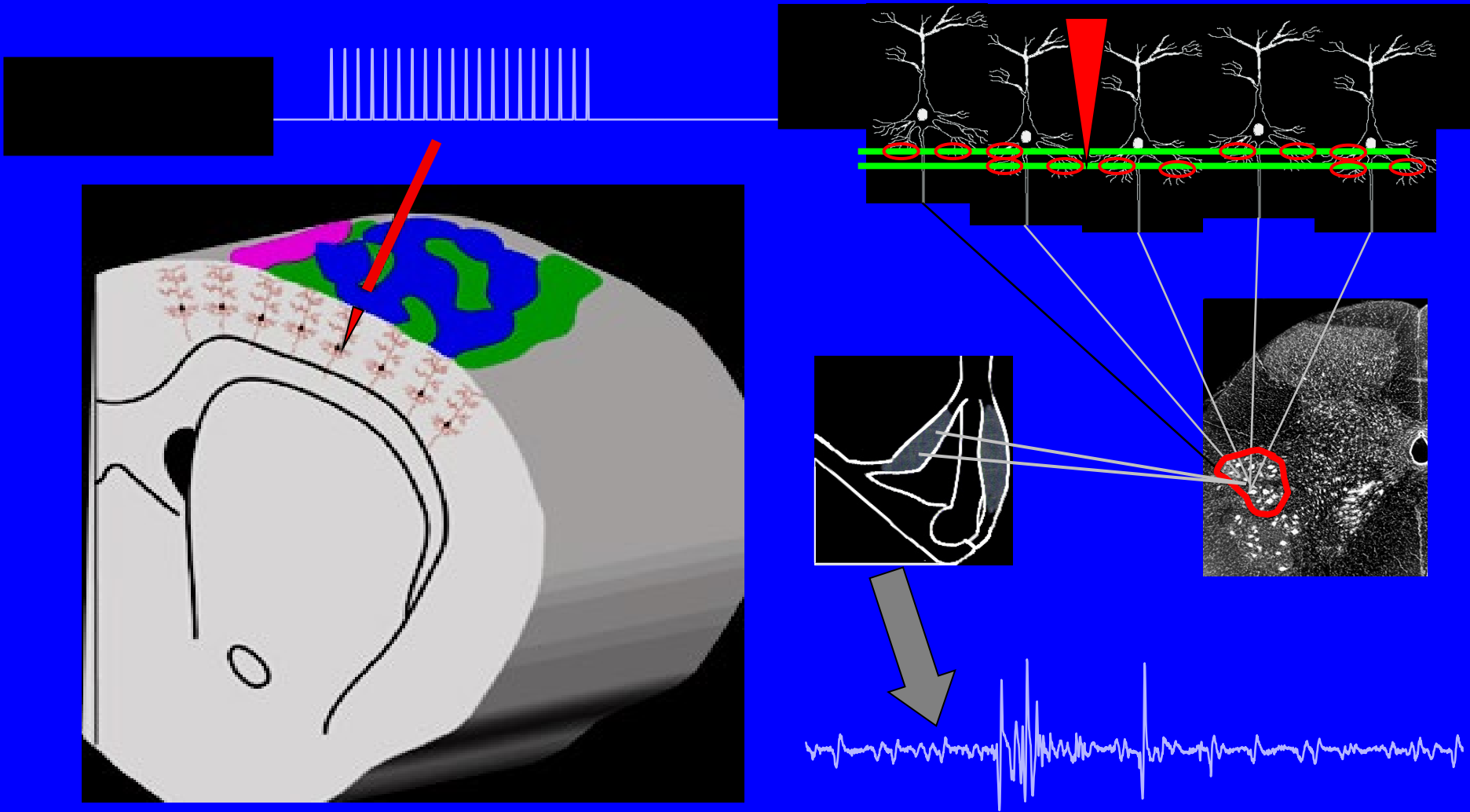
**Doublecortin (green- migrating, differentiating neurons)  
and Ki67 (red- proliferating cells) from a lesion+FGF-2 rat  
(Monfils et al., 2005, 2006, 2008)**



# Function?

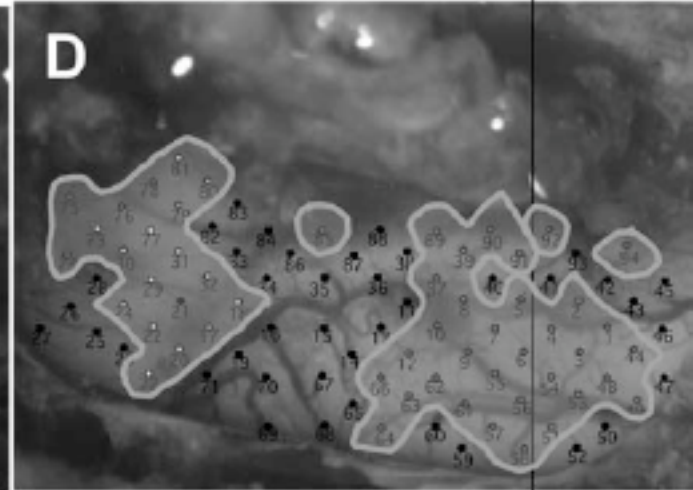
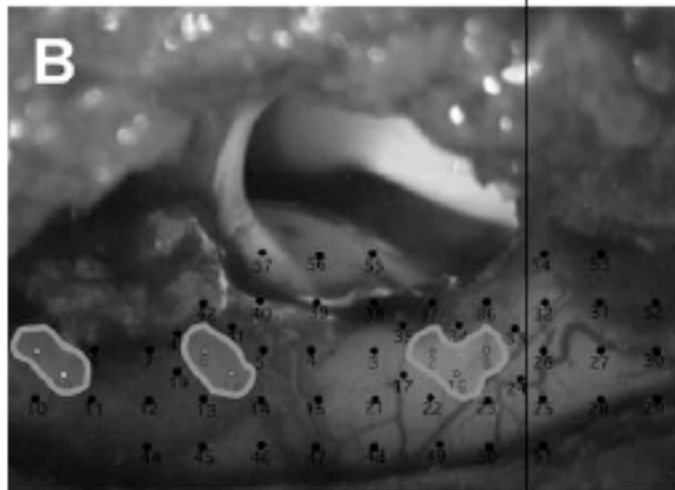
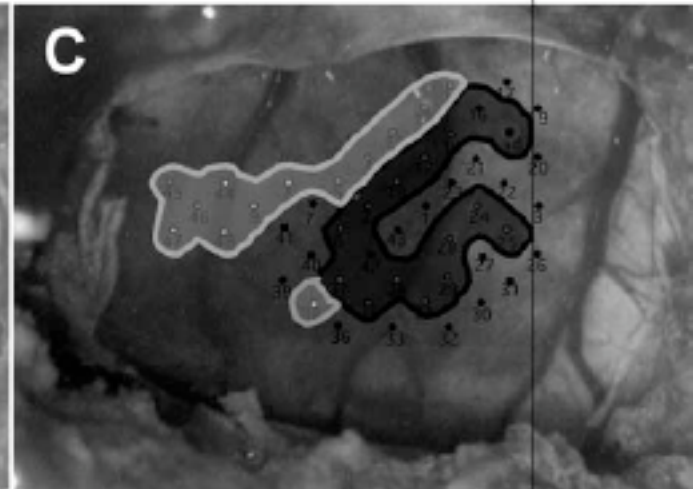
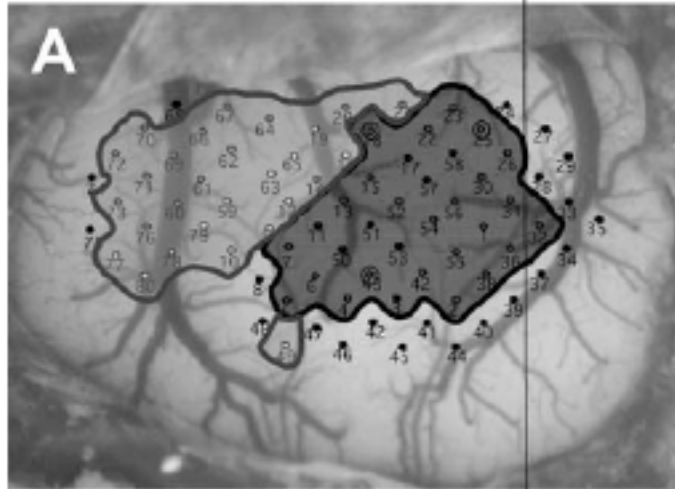
1. **Nearly completely normal motor functions.**
2. **Corticospinal connections from the plug.**
3. **EMG activity from stimulation.**

# Cortical stimulation identifies motor maps



**Control**

**Lesion + FGF-2**



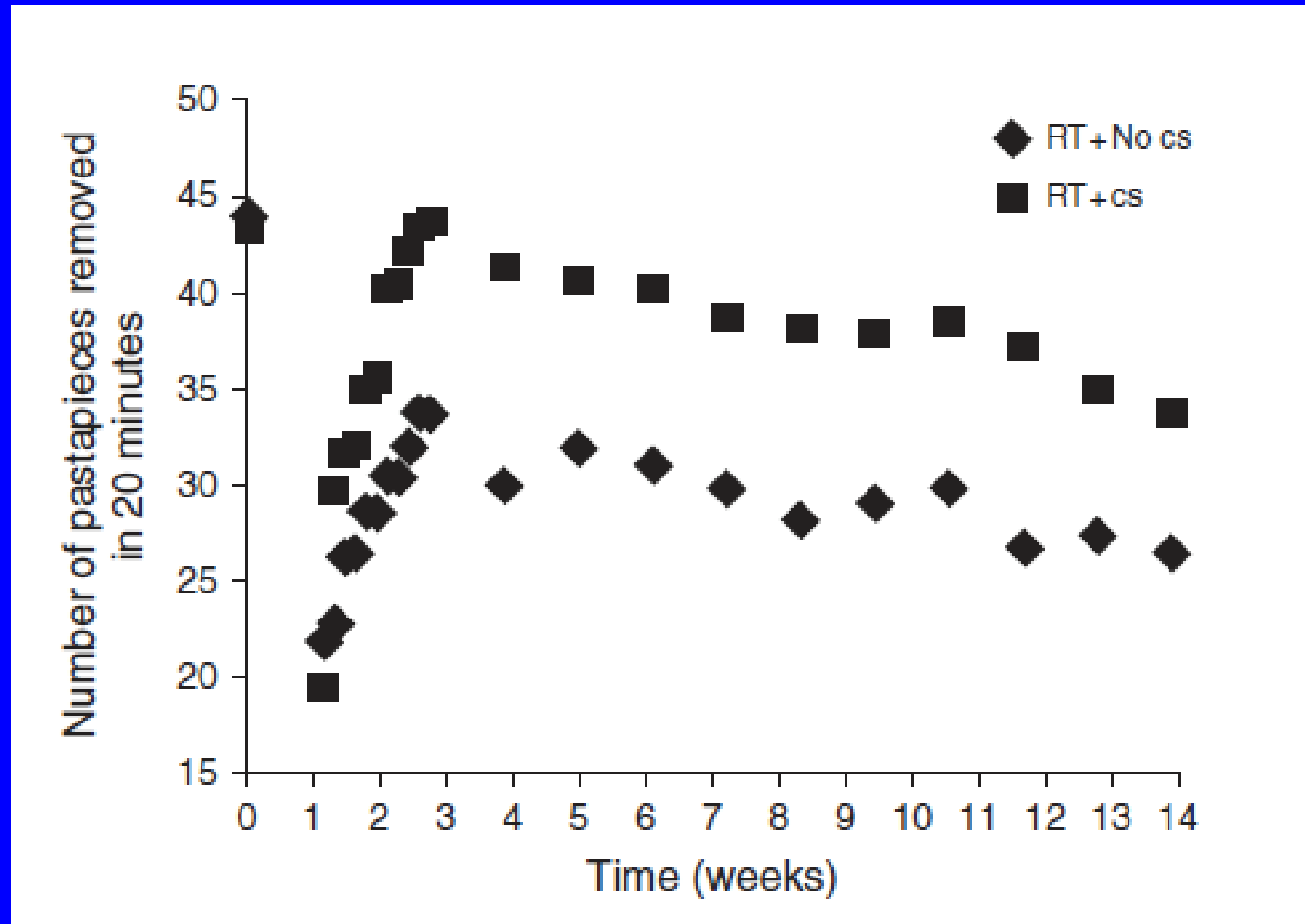
**Lesion**

**Lesion + FGF-2**

# Cortical Stimulation

**The logic is to use either direct electrical stimulation of the cortex, deep brain stimulation of thalamus or other regions, or Trans Cortical Magnetic Stimulation.**

# Cortical Stimulation



Teskey et al., 2003, 25, 794-800.

# Cortical Stimulation: A case history of translation

A Clinical trial not successful

**BUT**, the stimulation parameters were not identical  
**AND**, the patients had large infarcts...

# Combined Treatments

**Many treatments are most effective in combination with behavioral therapies.**

# Summary of 'Repair' Treatments

## 1. Treatments that *improve* functions:

**Nicotine; amphetamine (conditionally)**

**Olfactory or tactile stimulation**

**Complex housing**

**Exercise**

**Electrical brain stimulation**

**NTEs**

**Inosine**

**Antibodies to NoGo**



# What is most effective?

**Complex housing...but not if only for short periods each day.**

**What is equivalent in humans?**

**Best guess is *intense*, multidisciplinary treatments.**

# Summary of 'Repair' Treatments

## 2. Treatments that *do not improve* functions:

**Diet (but...)**

**COX-2 inhibitors**

**Repetitive practice (may be infarct size issue)**

# Summary of 'Repair' Treatments

3. Treatments that make functions worse:
  - Fluoxetine (ie., Prozac)
  - social change (stress??)

# Anatomical Correlates

**Each of the effective treatments is associated with changes in synaptic organization, although the details vary from treatment to treatment.**

**As a rule of thumb, the more synaptogenesis, the better the outcome.**

# **New Directions**

## **1. Training in Executive functions**

**The general idea is that training patients in frontal lobe functions will allow them to develop more effective strategies for developing compensatory strategies.**

# **New Directions**

## **2. Targeting microRNAs**

**These are the noncoding part of the gene. They are altered by injury and effective treatments produce enhanced alterations (e.g., EGF+EPO; nicotine).**

**The logic is to try to target the most effective ones.**

# **New Directions**

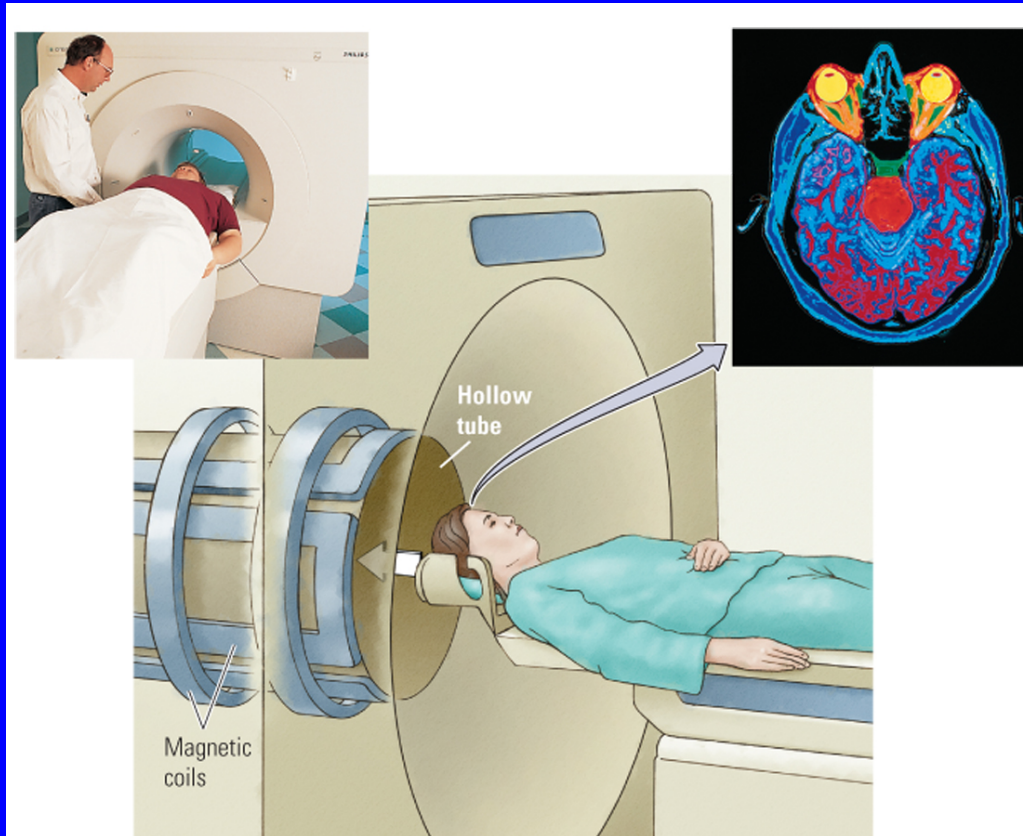
## **3. Understanding gene methylation**

**Injuries can increase or decrease it in brain.**

**Strokes also alter it in peripheral tissues such as liver and kidney!**

# New Directions

## 4. Using real-time fMRI (rtfMRI)



Has been shown to work for pain management and anxiety disorders (with CBT). Next is to apply to ABI.



# Mechanisms?

1. **Epigenetic changes (e.g., gene methylation)**
2. **Growth Factors (e.g, FGF-2, NGF, BDNF)**
3. **Stem Cells**
4. **Metabolic changes (e.g., PET)**
5. **Hemodynamic changes (e.g, fMRI)**
6. **Altered stress reactivity**
7. **And no doubt many more...**

# Principle 7

Plastic changes are areal-dependent

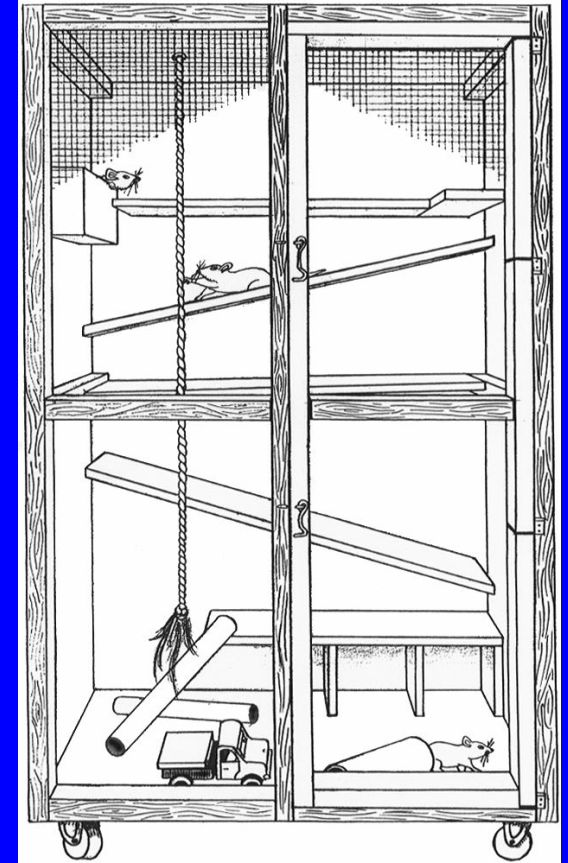
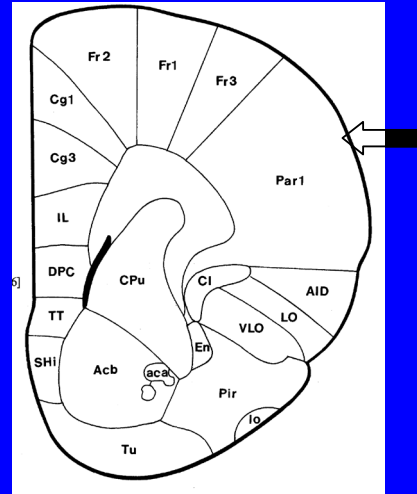
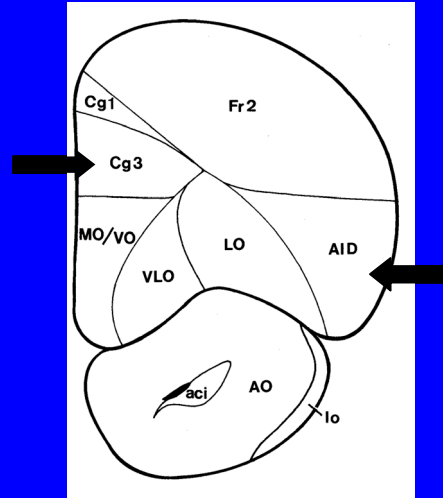
The same experience can differentially affect different cerebral regions

E.G., drugs, stress, gonadal hormones all have different effects on different cerebral regions

## Principle 8

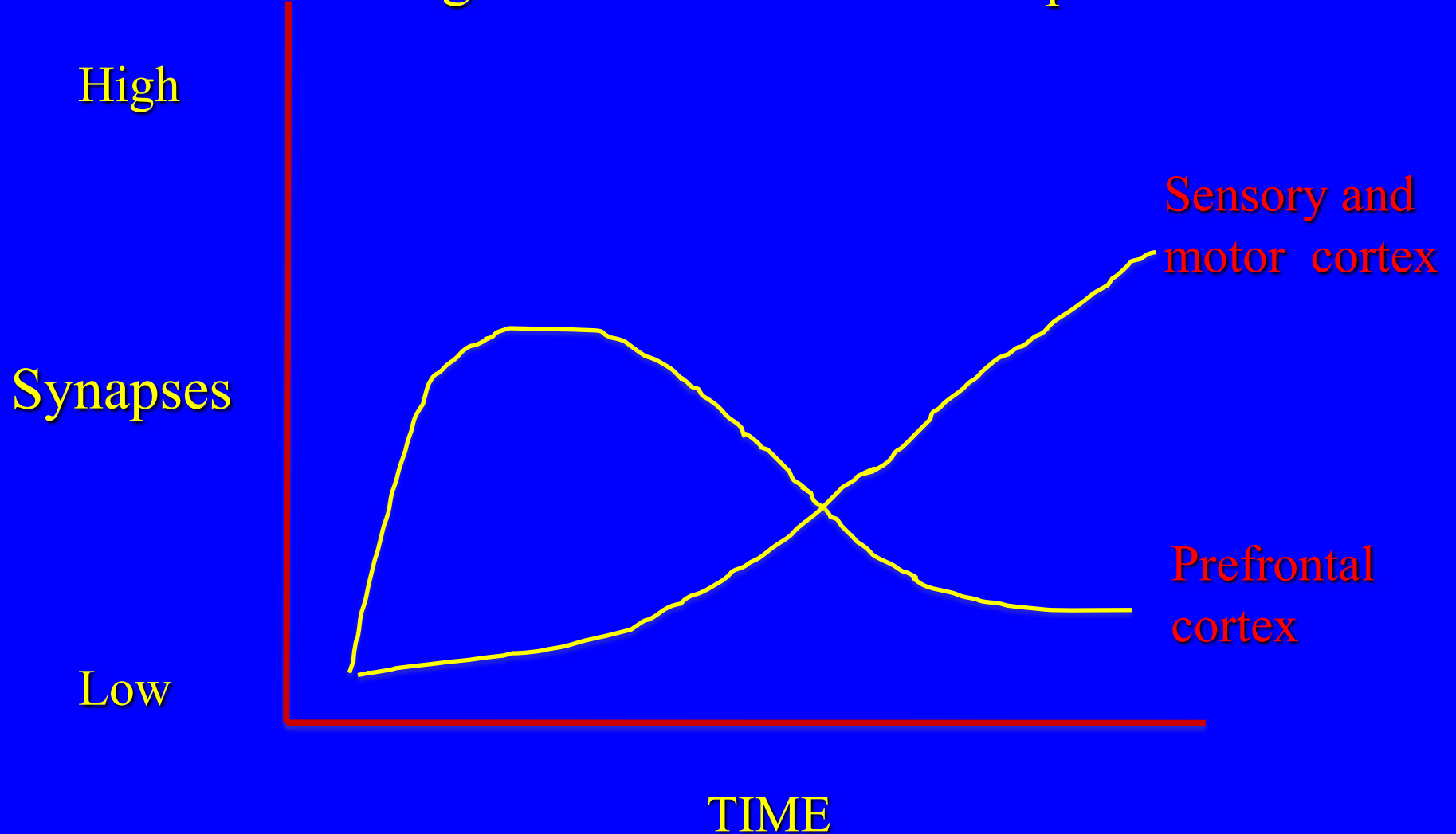
Plastic changes are time-dependent

The same experience can differentially affect different cerebral regions at different times. This is especially important for designing rehabilitation programs.



Compare medial PFC, OFC, and Parietal Cortex

# Changes are time and areal dependent



(Comeau, McDonald, & Kolb, BBR, 2010)

# Principle 9

There is something different about frontal lobe plasticity

The frontal lobe responds to drugs and hormones but shows only transient changes with many experiences.

The two main prefrontal regions show opposite effects of drugs, hormones, & experience. This may reflect some type of opponent-process functioning.

# Principle 10

Not all plasticity is good:

Behavioural disorders reflect abnormalities in brain organization and/or functioning

Examples: schizophrenia; depression; PTSD, anxiety, drug addiction, pathological pain

In recovery, it could be learned non-use or the learning of poor habits.

# Conclusions

- 1. Plastic changes in synaptic organization can support functional improvement after cerebral injury.**
- 2. A wide range of factors can influence outcome from adult injury.**
- 3. Factors appear to work via altered gene expression, microRNAs expression & neurotrophic release, leading to synaptic re-organization.**
- 4. There are synergistic interactions between behavioural and pharmacological treatments. Future work should focus on the nature and advantages of such interactions.**



