

## Bear: Neuroscience: Exploring the Brain 3e

### ◆ Chapter 23: Wiring the Brain

THE CHANGING BRAIN  
WHEN DOES IT END???

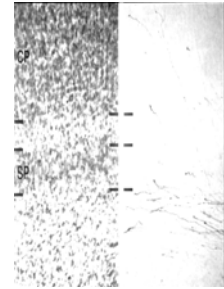
IS IT **GENETICS OR ENVIRONMENT??**

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## Introduction

- ◆ Operation of the brain
  - ◆ Precise interconnections among 100 billion neurons
- ◆ Brain development
  - ◆ Connections formed and modified
- ◆ Wiring in brain
  - ◆ Correct pathways and targets
  - ◆ Fine tuning

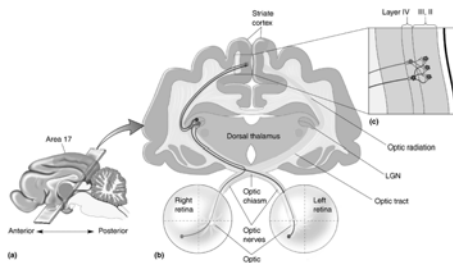


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## The Genesis of Neurons

- ◆ Example: Development of Striate Cortex
  - ◆ Cortical layers (I through VI)



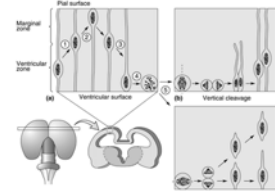
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## The Genesis of Neurons

- ◆ Development of neuronal structure
  - ◆ Cell proliferation; Cell migration; Cell differentiation
- ◆ Cell Proliferation

250,000/min



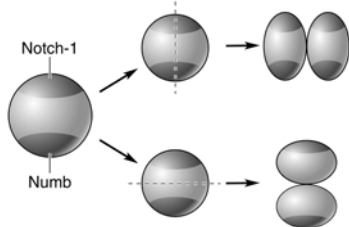
neurogenesis (birthday)

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## The Genesis of Neurons

- ◆ Cleavage plane during cell division

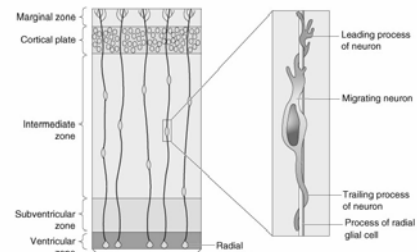


follows vertical cleavage (symmetric) and horizontal cleavage (asymmetric)

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## migration of "neuroblasts" extracellular molecular factors & radial glia



BUT ALSO MOVE LATERAL

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## The Genesis of Neurons

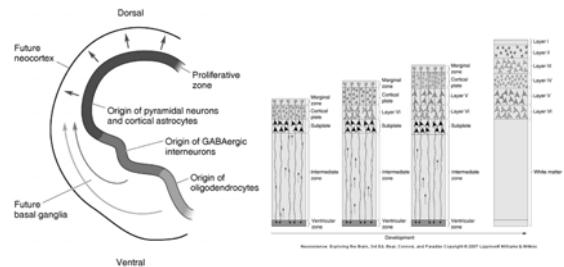
- ◆ Cell Migration
  - ◆ Daughter cells
    - ◆ Migrate by moving along thin fibers
  - ◆ Radial Glial cells: Provide scaffold on which cortex is built
  - ◆ Neuroblasts: Immature neurons
  - ◆ Migration paths: Radial glial guides
  - ◆ Neuroblasts cross the subplate to arrive in the cortical plate (first cells become layer VI neurons)
  - ◆ Inside-out development of the cortex
  - ◆ Experimental analyses: Gene mutations (e.g., reeler mouse)

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## The Genesis of Neurons

- ◆ Cortex: Cell sources and Inside-Out Development



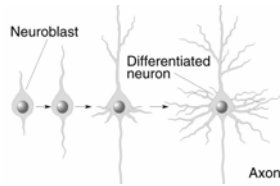
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## differentiation of neuroblasts into neurons

- ◆ may actually begin as cells divide
- ◆ somewhat sealed upon arrival in brain region
- ◆ also requires environmental factors

we now know some  
“undifferentiated” cells  
remain in ventricular zones  
OF ADULTS!!!



Axon slide 9

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## new adult neurons

- ◆ song-learning centers of canaries
- ◆ hippocampus of rats
- ◆ lateral ventricle (ventricular zone) in monkeys

- ◆ hippocampus of humans??!!

- ◆ why do we care???????

## new adult glial cells??

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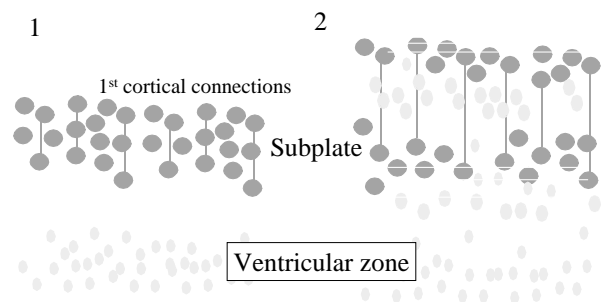
## The Genesis of Neurons

- ◆ Differentiation of Cortical Areas
  - ◆ Neocortex and Cortex
  - ◆ Cortical neurons
  - ◆ Cortical “protomap”
  - ◆ Radial migration
  - ◆ Contribution of thalamic input to differentiation of cortical areas

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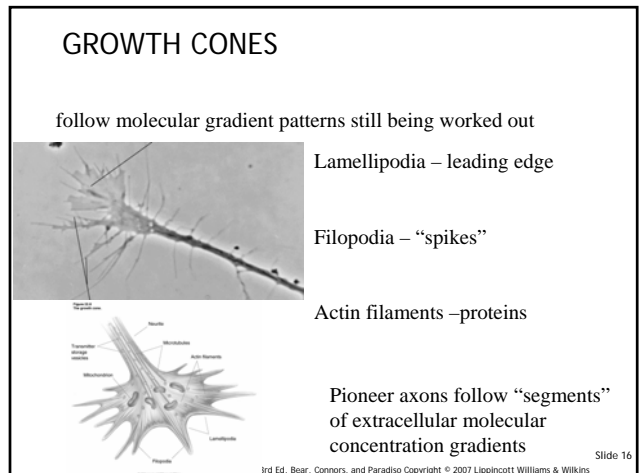
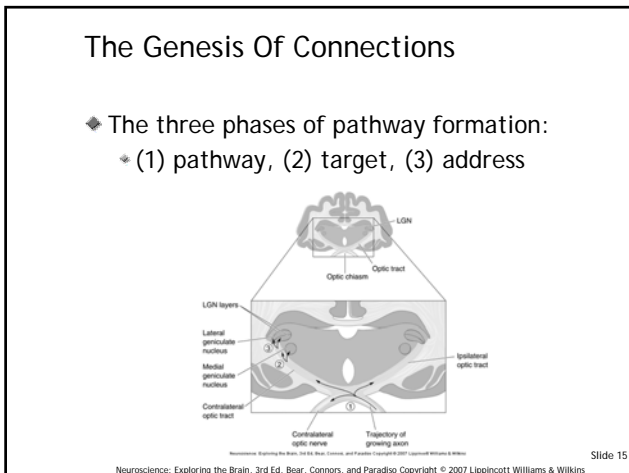
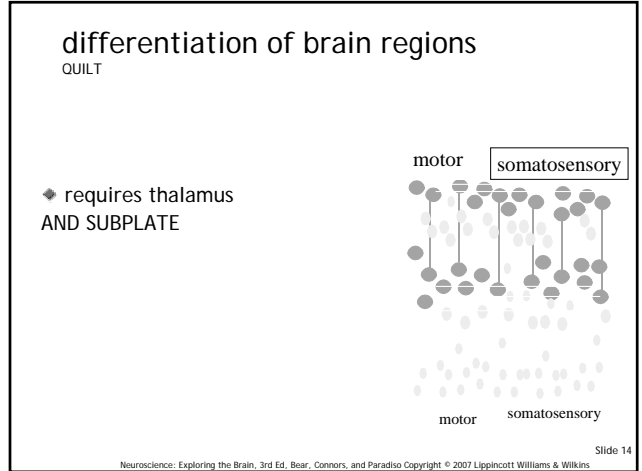
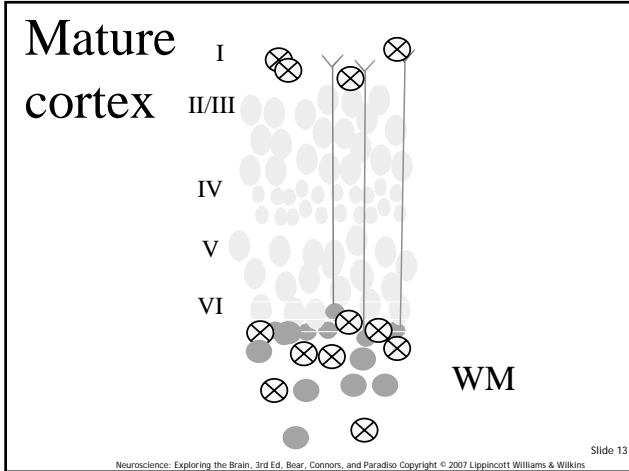
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## how does cortex develop?



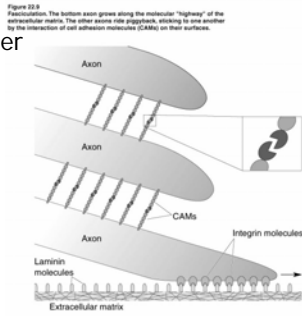
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other axons stick together  
**FASCICULATION**

- ◆ CAMs sticking together

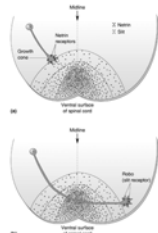


**The Genesis Of Connections**

- ◆ Axon Guidance
  - ◆ Challenge in wiring the brain
    - \* Distances between connected structures
    - \* Mature nervous system
  - ◆ Early stages
    - \* Nervous system a few centimeters long
  - ◆ Pioneer axons
    - \* Axons stretch
    - \* Guide neighbor axons to same targets
  - ◆ Growth in the correct direction

**The Genesis Of Connections**

- ◆ Axon Guidance
  - ◆ Guidance Cues; Growth cones
  - ◆ Chemoattractant; Chemorepellent

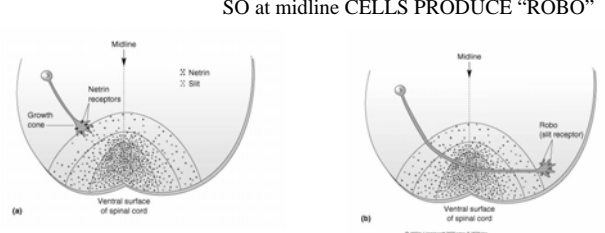


not sticking together

**CHEMOATTRACTION  
CHEMOREPULSION**

**how to solve the midline crisis?**

Netrin and netrin receptors slit – but slit requires RECEPTORS ROBO SO at midline CELLS PRODUCE “ROBO”



## The Genesis Of Connections

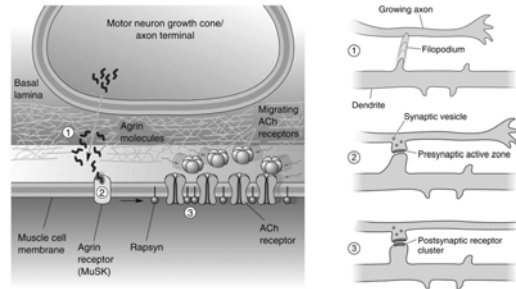
- ◆ Axon Guidance
  - ◆ Establishing Topographic Maps
    - \* Choice point; Retinal axons innervate targets of LGN and superior colliculus
  - \* CNS axons regenerate in amphibians, not in mammals
  - \* Factors guiding retinal axons to tectum
    - ◆ Ephrins/ *eph* (repulsive signal)

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## The Genesis Of Connections

### ◆ Synapse Formation



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## how do synapses form?

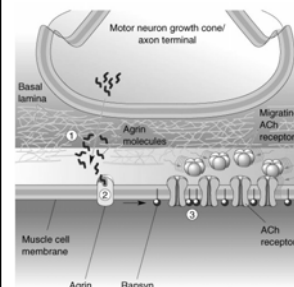
- ◆ motor neuron and a muscle fiber
- ◆ BOTH PRE AND POST PARTICIPATE

### KEY PLAYERS:

1. agrin
2. basal lamina
3. Muscle-specific kinase (MuSK)
4. rapsyn
5. ACh receptors

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1. agrin is released from motor neuron (yes, PREsynaptic) into basal lamina

2. agrin binds to MuSK receptor on muscle cell (Postsynaptic)- MuSK activates rapsyn

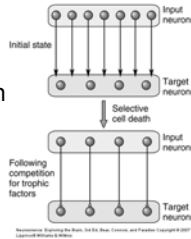
3. rapsyn "gathers" ACh receptors (postsynaptic)

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## The Elimination Of Cells And Synapses

- ◆ The mechanisms of pathway formation
  - ◆ Large-scale reduction in neurons and synapses
- ◆ Development of brain function
  - ◆ Balance between genesis & elimination of cells and synapses
- ◆ Cell Death

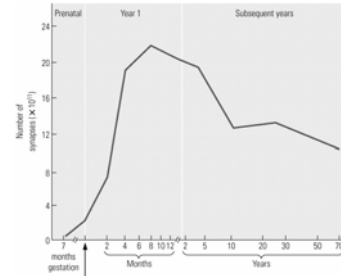


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## HOW SYNAPSES DIE

pruning – up to 5000 per second!!!!



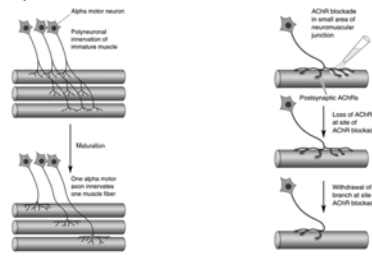
BUT WHY? very EXPENSIVE strategy!!!  
needed for experience-based activity

Competition sometimes determines which cells and connections grow and which die. 26

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## The Elimination Of Cells And Synapses

- ◆ Changes in Synaptic Capacity
  - ◆ Synapse elimination



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## HOW DO CELLS DIE - apoptosis

Is this neural Darwinism?

Cell death begins in ventricular zone

WHY??? CELL DEATH GENES?

Genes can determine which grow and which die

Also may be competition for trophic factors (kinase receptors)  
Nerve growth factors (NGF), BDNF

remember genes and environment interact

NOTE: death from necrosis and excitotoxins DIFFERENT (?)

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## WHY DO CELLS DIE

normal apoptosis?

1/2 MOTOR NEURONS

Most SUBPLATE

abnormal?

AD – neurons die , ACh

ALS – alpha motor neurons die

alpha – directly innervates muscles

gamma – keeps motor muscles “spindles” active

SOMEHOW INDUCE CELLS TO DIE?

SUBSTANCE P NEURONS

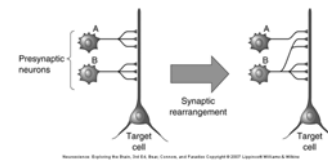
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## Activity-dependent Synaptic Rearrangement

◆ Synaptic rearrangement

- ✦ Change from one pattern to another
- ✦ Consequence of neural activity/synaptic transmission before and after birth
- ✦ Critical Period



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## Activity-dependent Synaptic Rearrangement

- ◆ Synaptic segregation
  - ✦ Refinement of synaptic connections
- ◆ Segregation of Retinal Inputs to the LGN
  - ✦ Retinal waves (*in utero*) (Carla Shatz)
    - ✦ Uncorrelated between the 2 eyes
  - ✦ Depends on process of synaptic stabilization
  - ✦ Hebb synapse (Donald Hebb)
    - ✦ Hebbian modifications

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## WAVES

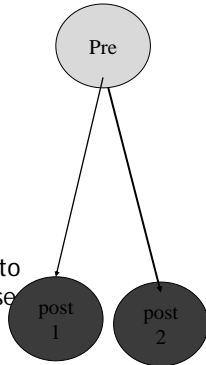
- ◆ synchronous waves of electrical activity
- ◆ BEGINS BEFORE BIRTH
- retinal waves help segregate visual input
- neurons that fire together have a relationship

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## HEBB

- ◆ connectivity strengthened by USE
- ◆ basis for computer models
- ◆ but not all!
  - \* some circuits need to be ready to respond even when not often use

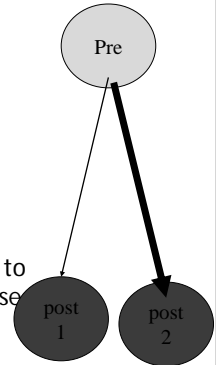


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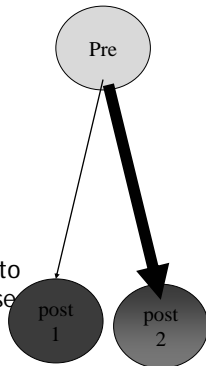


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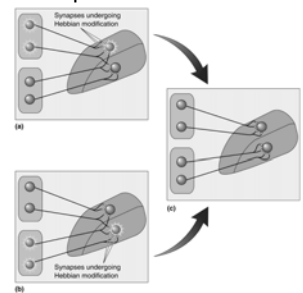
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## Activity-dependent Synaptic Rearrangement

- ◆ Segregation of Retinal Inputs to the LGN (Cont'd)

- ◆ Plasticity at Hebb synapses
- ◆ "Winner-takes-all"



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## Activity-dependent Synaptic Rearrangement

- ◆ Segregation of LGN Inputs in the Striate Cortex
  - Visual cortex
    - Ocular dominance columns (cat, monkey)
    - Synaptic rearrangement
      - Activity-dependent
      - Molecular cues

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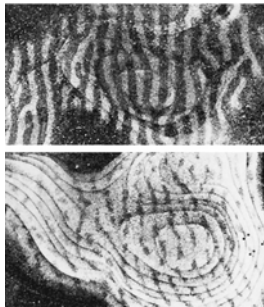
## Activity-dependent Synaptic Rearrangement

- ◆ Segregation of LGN Inputs in the Striate Cortex (Cont'd)
  - Plasticity of OD columns
    - Experience-dependent
      - Monocular deprivation
      - Reversed-occlusion
    - Development:
      - "critical period"

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WHEN INPUTS FROM ONE EYE ARE STRONGER  
look what can happen!



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## Activity-dependent Synaptic Rearrangement

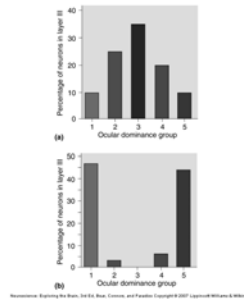
- ◆ Synaptic Convergence
  - Binocular vision
  - Anatomical basis
  - Establishment of binocular receptive fields
  - Ocular dominance shift
  - Features of ocular dominance shifts
  - Plasticity of binocular connections

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## Activity-dependent Synaptic Rearrangement

### ◆ Synaptic Competition



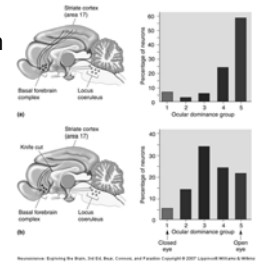
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## Activity-dependent Synaptic Rearrangement

### ◆ Modulatory Influences

- ◆ Increasing age
- ◆ Before and after birth
- ◆ Enabling factors



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## Elementary Mechanisms Of Cortical Synaptic Plasticity

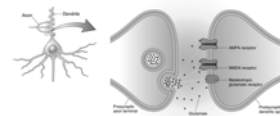
- ◆ Two rules for synaptic modification
  - ◆ Wire together fire together (Hebbian modifications)
  - ◆ Out of sync lose their link
  - ◆ Correlation: heard and validated

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## Elementary Mechanisms of Cortical Synaptic Plasticity

- ◆ Excitatory Synaptic Transmission in the Immature Visual System
  - ◆ Focus on 2 glutamate receptors (Rs):
    - ◆ AMPARs: glutamate-gated ion channels
    - ◆ NMDARs: Unique properties

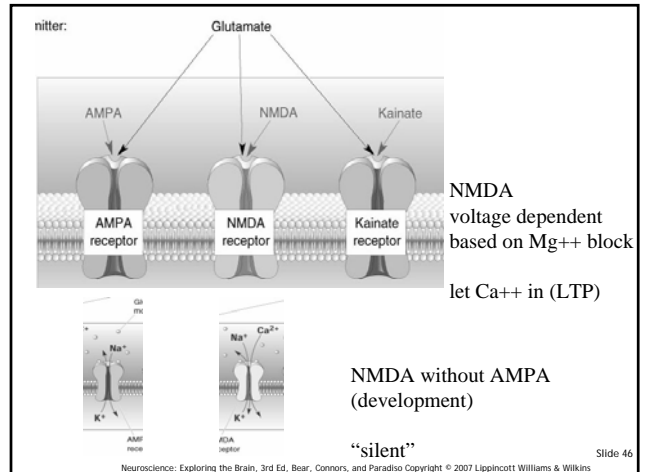


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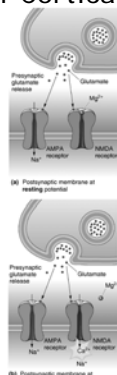
another kind of plasticity  
LTP

- ◆ strengthening of synaptic transmission
- ◆ glutamate synapses
- ◆ strong NMDA receptor activation



Elementary Mechanisms Of Cortical Synaptic Plasticity

- ◆ Long-Term Synaptic Potentiation (LTP)
  - ◆ Role of the NMDAR
    - ◆ Unique properties
      - ◆ Voltage-gated ion channel
      - ◆ Calcium-permeable

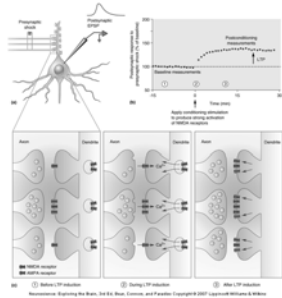


Elementary Mechanisms Of Cortical Synaptic Plasticity

- ◆ Long-Term Synaptic Potentiation (cont'd)
  - ◆ Experimental tests
    - ◆ Monitor synaptic strength before and after episodes of strong NMDAR activation
  - ◆ Accounting for LTP
    - ◆ AMPAR insertion (“AMPAfication”)
    - ◆ Splitting synapses (doubling)

## Elementary Mechanisms Of Cortical Synaptic Plasticity

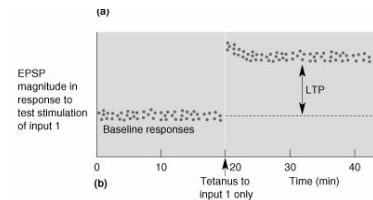
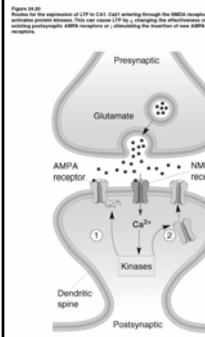
### ◆ Long-Term Synaptic Potentiation (cont'd)



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## LTP



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## Elementary Mechanisms Of Cortical Synaptic Plasticity

### ◆ Long-Term Synaptic Depression (LTD) (cont'd)

- ◆ Neurons fire out of sync
- ◆ Synaptic plasticity mechanism
  - \* Opposite of LTP
  - \* Loss of synaptic AMPARs
  - \* Loss of synapses? (unknown)
- ◆ Mechanism for consequences of monocular deprivation

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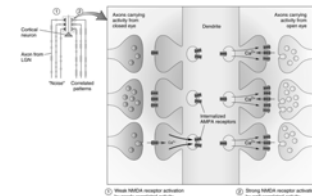
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## Elementary Mechanisms of Cortical Synaptic Plasticity

### ◆ Long-Term Synaptic Depression (LTD) (cont'd)

### ◆ Presynaptic and postsynaptic connections

- \* Both depend on retinal activity, NMDAR activation, postsynaptic calcium



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## Critical periods

### striate cortex

- ◆ activity-dependent synaptic rearrangement
- ◆ strabismus must be corrected early
- ◆ HUMANS CPS END BY ABOUT AGE 10 (?)

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## Why Critical Periods End

- ◆ Hypotheses for the end of critical period
  - ◆ Plasticity diminishes:
    - \* When axon growth ceases
    - \* When synaptic transmission matures
    - \* When cortical activation is constrained
  - ◆ Intrinsic inhibitory circuitry
    - \* Late maturity in striate cortex
  - ◆ Understanding developmental regulation of plasticity → Recovery from CNS damage

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## when are we finished??

- ◆ plasticity until death - particularly in frontal and temporal lobes

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