Medical Neuroscience | Tutorial Notes

The Changing Brain Across the Lifespan: Development, Repair & Regeneration

Map to Neuroscience Core Concepts[1]

NCC4. Life experiences change the nervous system.

NCC8. Fundamental discoveries promote healthy living and treatment of disease.

Learning Objectives

After study of the assigned learning materials, the student will:

1. Discuss the neurobiological basis for changes in gray matter and while matter volume in the developing human brain throughout childhood.
2. Discuss the mechanisms of regeneration of peripheral nerves following injury.
3. Discuss the mechanisms of plasticity in adult sensorimotor maps following peripheral injury.
4. Discuss the mechanisms of plasticity in adult neural circuits following central injury.
5. Discuss the evidence regarding neurogenesis in the adult CNS.

Tutorial Outline

I. Introduction

- A. mechanisms of neural development
  1. **genetic specification**: phenotypes produced by spatial and temporal patterns of gene expression in cells derived from common precursors
  2. **self-organization**: phenotypes produced by cell-cell interactions mediated by endogenous patterns of activity in neural networks
  3. **sensorimotor experience**: the modulation of endogenous neural activity by the activation of sensory receptors during environmental interactions
- B. as development proceeds across the lifespan, these fundamental forces continue to shape the structure of function of neural circuits—albeit with limited capacity to learn, repair and regenerate outside of the critical periods that characterize early life

[1] Visit **BrainFacts.org** for *Neuroscience Core Concepts* (©2012 Society for Neuroscience) that offer fundamental principles about the brain and nervous system, the most complex living structure known in the universe.

II. Ongoing development of the human brain throughout childhood

A. commensurate with the onset and duration of many known critical periods in early life, there is an explosive increase in **synaptogenesis** across the cortical mantle (see **Figure 24.12**[2])

1. in rhesus monkey (and presumably in humans):

a. there is an explosive increase in synapse formation (synaptogenesis) in the neonatal period that continues through early childhood

b. although there is likely both synapse construction AND synapse pruning occurring concurrently, the major developmental theme of early life is the *construction of neural circuits* with a several-fold increase in the total numbers of synaptic connections in most gray matter structures

2. presumably, the capacity to build new synaptic connections is an important component to critical period plasticity and the rapid learning that occurs in early life (see **Figure 24.11**)

3. however, the rate of synaptogenesis and/or the proper construction of functional, adaptive neural circuits may be altered in disorders of cognition and behavior, such as autism spectrum disorders, schizophrenia, and attention deficit-hyperactivity disorder (ADHD)

a. autism spectrum disorder

i. there appears to be an accelerated rate of synaptogenesis in the frontal and temporal lobes, and in the amygdala and cerebellum, resulting in an overgrowth of neural circuits and an early increase in overall brain size

ii. by adolescence, differences in gray matter trend toward normal volumes

iii. however, aberrant wiring patterns of cortical and subcortical networks are likely to persist, especially in networks subserving social cognition and verbal and non-verbal communication

b. attention deficit-hyperactivity disorder (ADHD)

i. there appears to be decreased rate of synaptogenesis resulting in a developmental delay in circuit construction and an overall decrease in the thickness of cortical gray matter, especially in the frontal and temporal lobes

B. beginning in later childhood (pre-adolescent), there is a *net reduction* in the numbers of synapses in the cerebral cortex (see **Figure 24.12**)

1. in most cortical areas, there is 20-50% reduction in the numbers of synaptic connections from the peak in early childhood to a stable plateau in young adulthood

[2] Figure references to Purves et al., *Neuroscience, 5th Ed.*, Sinauer Assoc., Inc., 2012. [click here]

2. this reduction in synaptic connections is the major factor responsible for a reduction in the volume of gray matter in the cerebral cortex observed in the same time frame (recall that synapses are localized to gray matter) (see **Figure 24.13**)
    a. in ADHD, there appears to be a modest increase in the rate of gray matter thickness reduction (see **Figure 24.14**)
    b. consequently, cortical gray matter volumes are (on average) reduced in adults with ADHD

C. throughout childhood and into adulthood, there is an increase in white matter volume (see **Figure 24.13B**)
    1. this increase likely reflects an increase in myelination of axonal pathways in the brain; and it could also reflect an increase in the numbers of axons within pathways

D. thereafter, overall brain size gradually decreases throughout adulthood, presumably reflected the loss of synaptic connections, axons and myelin (see **Figure 31.18**)
    1. however, a loss of neurons is not typical in adult aging, unless neurodegenerative disease is manifest

III. Plasticity in sensory and motor maps

A. the organization of sensory and motor maps may be altered by damage to peripheral nerves and/or changes in ongoing patterns of neural activity

B. the degree of plasticity is much greater during early critical periods, but some plasticity in map structure persists into adulthood

C. in the somatic sensory cortex
    1. when peripheral nerves are lesioned, central representations reorganize (see **Figures 9.14**; consider also phantom limb sensations – **Box 10D**)
        a. in the short-term, newly deafferented cortical zones become unresponsive
        b. however, over time, deafferented cortical zones become responsive to sensory stimuli that drive adjacent regions of cortex
    2. reorganization may also be seen in an intact system when patterns of neural activity are habitually reinforced (e.g., with extensive practice or non-use) ((see **Figures 9.15**)

D. in the motor cortex
    1. "over training" can induce an expansion of the motor representation of the practiced movements in the primary motor cortex
    2. similar plasticity has been observed in animals recovering from brain injury (e.g., stroke) who were rehabilitated using specific motor sequences

E. mechanisms of circuit plasticity in the cerebral cortex

1. plasticity may occur at multiple stations along a sensory or motor pathway
2. however, plasticity is understood best at the level of the cerebral cortex where intrinsic cortical circuits are modified by experience
3. **long-range horizontal connections** are a likely mediator of cortical plasticity in sensory and motor maps
    a. horizontal connections span many cortical columns and interconnect different parts of maps that are functionally synergistic
        (i) normally, effects of horizontal connections are weak (or maybe even "silent" – see **Box8B**)
        (ii) in response to deafferentation (see below), disuse or overuse, the synapses made by horizontal connections may become strengthened and more effective at driving neuronal responses; they may mediate at least the early phases of cortical reorganization
        (iii) long term consequences may involve growth of new connections that reinforce longer lasting effects on the structure of cortical maps

IV. Peripheral nerve regeneration

A. following damage (severing, evulsing or crushing a nerve), a sequence of events plays out that results in partial restoration of sensory and motor function (see **Figure 25.6**)

1. macrophages rapidly remove myelin and axonal debris as the distal portion of the axon degenerates
2. Schwann cells proliferate, express adhesion molecules and other growth-promoting signals
3. the neuronal cell body expresses genes that reactivate growth programs that allow for the formation of a growth cone and the transduction machinery that is necessary to respond to factors produced by Schwann cells
4. regenerating axons elongate as growth cones migrate along extracellular matrix and the relatively orderly array of Scwhann cells that guide growth cones to their peripheral targets
5. for motor axons and some sensory afferents (e.g., Merkel cell-neurite complexes), synapses form on target tissues using similar mechanisms that established synaptic connectivity in development

B. however, the fidelity of regeneration is limited and full functional recovery may not be achieved

V. Plasticity of neural circuits in response to brain injury

A. in response to brain injury (following trauma, hypoxia or the onset of neurodegenerative disease), neuronal loss is often exacerbated by programmed cell death and the inability to restore long axonal projections

1. fatally injured neurons die acutely or undergo **apoptosis** (see **Figure 25.9**)

a. cell death may be triggered by over-activation of glutamatergic synaptic inputs ("excitotoxicity" – see **Box 6C**)

b. cell death may be triggered by inflammatory mediators (cytokines), DNA damage, loss of neurotrophic support, and other means of cellular stress

c. whatever the trigger, lost neurons cannot be replaced via mitosis and differentiation of neuroblasts (with few exceptions – see below)

2. in compact white matter structures, damage to long pathways in the CNS have *limited capacity to regenerate*

a. glial cells respond to signals produced by damaged tissues and immune cells that infiltrate the region of damage, and proliferate forming scars that congest the local volume of brain tissue (see **Figure 25.3B**)

b. glial reactions create an environment that is "non-permissive" for the regrowth of long axonal projections (see **Figure 25.11**)

c. oligodendrocytes produce signaling molecules (myelin associated proteins) that inhibit axonal growth and elongation

B. however, in gray matter, surviving circuit elements may undergo functional and structural plasticity; the key to recovery is the capacity of these elements to reorganize and reshape the strength and distribution of their synaptic connections

1. cortical (and subcortical) connections may be modified by central injury; e.g., following stroke

a. injury to brain tissue surrounding the core of infarction will undergo a sequence of activity-dependent changes in:

i. patterns of neural activity

ii. patterns of gene expression

iii. patterns of synapse formation and axonal outgrowth

b. changes in the patterns of gene expression (and their consequences) often involve expression of the same genes (i.e., encoding tropic molecules, trophic molecules, and their receptors) that were initially induced in the early construction of neural circuits

c. thus, the *plastic response of injured neural tissue likely involves the reactivation of developmental programs*

C. the capacity for neuronal regeneration (i.e., mitosis and production of new neurons) is *limited* to special populations of neural stem cells close to the lateral wall of the lateral ventricle (in the so-called "subventricular zone") (see **Figure 25.13** & **25.14**)

1. these new neurons provide interneurons for local circuits in the dentate gyrus (a component of the hippocampus)

2. despite some recent controversy, it now appears clear that few if any new neurons contribute to neural circuits in the neocortex (see **Box 25C**)

3. nevertheless, the addition and integration of new neurons in the dentate gyrus may be important for neuropsychiatric disease and treatment

STUDY QUESTIONS

Q1. At roughly what age would you expect that highest density of synapses in the human cerebral cortex?

A. third trimester of gestation
B. first 6 (postnatal) months of infancy
C. near the middle of the first decade of life
D. near the middle of the second decade of life
E. after the second decade of life

Q2. What factors contribute to the limited regenerative capacity of corticospinal tract axons following spinal cord injury?

A. glial scar formation in damaged white matter (e.g., in the lateral column of the spinal cord)
B. the suppression of growth promoting genes in the cell bodies of corticospinal tract neurons
C. the expression by astrocytes of semaphorins, ephrins and slits that promote growth cone collapse
D. the expression by oligodendrocytes of integral membrane proteins, such as NogoA, myelin associated protein, and oligodendrocyte myelin glycoprotein, that inhibit axon growth
E. all of the above factors contribute to the limited regenerative capacity of corticospinal tract axons following spinal cord injury