Medical Neuroscience | Tutorial Notes

Modification of Neural Circuits in Early Neonatal Life

MAP TO NEUROSCIENCE CORE CONCEPTS[1]

NCC4. Life experiences change the nervous system.

NCC7. The human brain endows us with a natural curiosity to understand how the world works.

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 significance of genetic specification, self-organization and sensory experience for the construction of neural circuits in the cerebral cortex.
2. Discuss the significance of experience for the plasticity of neural circuits in critical periods of postnatal development.
3. State Hebb's postulate and discuss its relevance for neural plasticity in developing and recovering brains.

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. each of these basic mechanisms is subject to modification due to the consequences of genetic mutation, disease, exposure to environmental and dietary toxins, and normal and abnormal sensorimotor experience

[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. **Sensorimotor experience** in early brain development: "precritical" circuit construction and modification in a critical period

A. subcortical brain circuits and circuits set-up by the topographic mapping of thalamic projections to the cerebral cortex

1. overview

a. such circuits develop in a formative ("*precritical*") phase, under the influence of genetic specification and self-organization, without the need for sensorimotor experience

b. however, in a later ("**critical period**") phase of development, such circuits are plastic for a period of early life

2. evidence for this view has come mainly from studies of **ocular dominance columns** in the visual cortex of animal models

a. ocular dominance columns are alternating patches of monocular inputs from the lateral geniculate nucleus to cortical layer 4 (recall that binocular interactions do not occur until layer 4 signals are passed on to cortical layer 2/3) (see **Figure 12.13**[2] **& 24.4**)

b. ocular dominance column plasticity

i. ocular dominance columns develop early (in utero in primates), even in animals (carnivores) raised in complete darkness

ii. thus, sensory experience (vision) is not needed for the formation of these circuits

iii. however, once established in visual cortical circuitry, ocular dominance columns are plastic in early life (see **Figure 24.4-24.7**)

- a brief period of monocular vision in early life can lead to permanent blindness (amblyopia)
- amblyopia is explained by a dramatic shift in the size of ocular dominance columns in V1 (see **Figures 24.6-24.8**)
  - open-eye columns expand (grow new connections)
  - deprived-eye columns shrink (lose connections)
- these effects are not (usually) seen in adults

iv. ocular dominance column plasticity has been the dominant paradigm for understanding the construction of neural circuits within **critical periods** of early postnatal life; indeed, this paradigm has been the "gold standard" for evaluating mechanisms of neural plasticity for more than 5 decades!

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

v. but does this paradigm—"precritical" period (no plasticity) followed by critical period plasticity—apply to other cortical circuits? (evidently, not universally)

B. intrinsic neural circuits of the cerebral cortex (beyond the input layer, layer 4)

1. more recently, developmental neuroscientists have studied the formation of intrinsic cortical circuits (columnar circuits that compute new functional properties within the middle and upper layers of the visual cortex), and results suggest a more important role for experience in circuit construction

2. two important model circuits for these studies (also in visual cortex)[3]:

a. orientation columns: columnar circuits in the visual cortex that compute the orientation (axis of motion) of contours in visual stimuli (**Figures 12.11 & 12.12**)

b. direction columns: columnar circuits in the visual cortex that compute the direction of motion of visual stimuli

3. studies of orientation columns

a. orientation preference maps in different species share a "common design", with a pinwheel density of π (see Kaschube et al., 2010)

i. this strongly suggests that the neural networks in the visual cortex that compute orientation preference *self-organize*

ii. essential factors are (1) activity-dependent development; and (2) long-range connections across the developing network

b. orientation columns are present at the onset of visual experience in animals reared normally and in animals reared in complete darkness (White et al., 2001), as predicted by models of self-organizing cortical networks

c. *however ...*

i. in animals reared in darkness, orientation selectivity is weak, indicating some benefit of <u>normal</u> sensory experience

ii. in animals reared with <u>abnormal</u> experience (through closed eye-lids), orientation selectivity is so weak that orientation columns are barely discernible (*bad experience is worse than no experience!*)

[3] If you are interested in learning more about this topic, see:

White, L.E., Coppola, D.M. & Fitzpatrick, D. The contribution of sensory experience to the maturation of orientation selectivity in ferret visual cortex. *Nature* **411**, 1049-1052 (2001).

Li, Y., Fitzpatrick, D. & White, L.E. The development of direction selectivity in ferret visual cortex requires early visual experience. *Nature Neuroscience* **9**, 676-681 (2006).

White, L.E. & Fitzpatrick D. (2007) Vision and cortical map development. *Neuron* 56:327-338.

Li Y, VanHooser S, Mazurek M, White LE, Fitzpatrick D (2008) Experience with moving visual stimuli drives the early development of cortical direction selectivity. *Nature* **456**:952-956.

Kaschube M, Schnabel M, Löwel S, Coppola DM, White LE, Wolf F (2010) Universality in the evolution of orientation columns in the visual cortex. *Science* **330**:1113-1116. [see also "Perspectives" article by K.D. Miller published concurrently: *Science* **330**:1059-1060.]

d. *conclusions ...*

i. normally, self-organization operates *synergistically* with sensorimotor experience to promote full functional maturation

ii. when experience is rendered abnormal, this synergy is broken, self-organization goes awry, and the neural circuits are functionally impaired

- in other words, neural circuits self-organize to adapt to the quality of the incoming sensory signals
- not only do neural circuits fail to benefit from normal experience, they are harmed by abnormal experience

4. studies of direction columns

a. direction columns are absent at the onset of visual experience in animals reared normally and emerge after 1-2 weeks of vision

b. direction columns fail to form in complete darkness

c. the critical period for the development of direction columns is remarkably brief: only animals that experience vision in the first 1-2 weeks after eye-opening (neonates) develop direction columns

d. early vision drives the development of direction columns (and neuronal direction selectivity)

i. experience with motion energy is necessary

ii. changes can happen quickly (hours)

iii. for some cells, this requires reversing an initial direction preference

e. *conclusions ...*

i. the neural circuits that underlie direction columns cannot self-organize, but must be instructed (trained) by visual experience with moving stimuli

ii. the window of opportunity for this motion training is very brief, so *early experience is critical!*

C. summary

1. to understand the construction of neural circuits, we must examine multiple circuits in the developing brain (there should be no one "gold standard")

2. the "two-phase" (precritical then critical period) view of brain development in early life is not adequate to account for the role of experience in the development of intrinsic cortical circuits

3. sensorimotor experience may influence the construction of neural circuits as soon as the brain becomes responsive to environmental signals

4. thus, genetic specification, self-organization, and sensorimotor experience interact (concurrently, not necessarily in sequential phases) to shape the ongoing development and refinement of neural circuits in early life

III. Lessons learned and proposed clinical relevance

A. *normal sensorimotor experience has a profound effect on the formation and maturation of neural circuits in the cerebral cortex*

B. *some properties (timing-based properties like direction selectivity) may not develop without normal experience in an early critical period*

C. *abnormal sensorimotor experience in early critical periods may lead to lasting functional impairment*

D. *in sum,* ***normal experience in early postnatal life is critical!***

IV. Neurobiological explanations of how neural activity affects developing circuits

A. remember **Hebb's postulate**

1. coordinated activity of a presynaptic terminal and a postsynaptic cell would strengthen the synaptic connection between them
2. conversely, uncoordinated activity between synaptic partners would weaken their synaptic connections
3. in short, *"neurons that fire together, wire together"*

B. principles of plasticity applied to developing cortical circuits (see **Figures 24.1**)

1. sensorimotor experience is an important source of spatial and temporal structure in evoked patterns of neural activity
2. normal sensorimotor experience provides the conditions for the coordinated synaptic activation of postsynaptic neurons
    a. (presumably) satisfying the requirements for LTP in spike timing-dependent plasticity ("pre" before "post")
    b. such activity is critical for the normal formation and maturation of neural circuits in the cerebral cortex, especially those circuits that must "compute" new functional properties
3. abnormal sensorimotor experience fails to provide for the coordinated activation of pre- and post-synaptic neurons
    a. (presumably) favoring LTD in spike timing-dependent plasticity ("post" before "pre")
    b. this uncoordinated activity fails to promote full functional maturation and may promote the formation of maladapted circuits
4. lasting change in developing cortical circuits is thought to be mediated by *neurotrophins*
    a. the production and release of neurotrophins is activity-dependent

b. neurons that are connected and coordinated will strengthen their interconnections and be nourished via the release and retrograde activity of neurotrophins in presynaptic neurons

c. circuits that are driven by abnormal experience (connected but not functionally coordinated) may weaken their connections; such connections may fail to thrive being deprived of sufficient neurotrophic support

5. in the mature CNS, the regulated secretion of neurotrophin helps to shape neuronal connections in response to injury or adaptation to new patterns of neural activity

   a. several studies of recovering brain (in animal models of stroke or TBI) now link BDNF activity to adaptive circuit plasticity

   b. there are even emerging genomic studies in humans indicating that variations in the BDNF gene render cortical circuits more or less adaptive to challenges in the domains of motor learning and cognition

6. for current and future clinicians, the upshot of this tutorial is … ***what you do with your patients/clients (of any age) with brain injury—the sensorimotor experience you structure and reinforce— will modulate the production of neurotrophins and shape plasticity in their developing/recovering brains!***

STUDY QUESTION

Sadly, it is estimated that congenital cataracts are responsible for 5% to 20% of blindness in children worldwide, and although the incidence varies from country to country, it is reasonable to estimate a rate of 3-4 visually significant cataracts per 10,000 live births.

Q1. For babies born with a cataract in <u>one</u> eye, what is the major neurobiological concern, if left untreated beyond the relevant critical period?

A. impaired formation of the optic nerve in the affected eye
B. exuberant growth of the optic nerve from the unaffected eye
C. cortical blindness (amblyopia) for signals derived from the affected eye
D. exuberant growth of the thalamocortical axons that are driven by the affected eye
E. double vision

Q2. For babies born with cataracts in <u>both</u> eyes, what is the major neurobiological concern, if left untreated beyond the relevant critical period?

A. impaired orientation selectivity in the visual cortex
B. impaired direction selectivity in the visual cortex
C. impaired stereopsis in the visual cortex
D. A, B & C are all significant concerns
E. there are no time-sensitive concerns and successful treatment can be initiated at any age