9.01
Review for the first half of the semester

See also: flashCube definition file, classes 1-21.

[Bracketed items below were not discussed in lectures, or will be discussed after the midterm more extensively.]

Goals of scientists trying to explain mind and behavior in brain terms:
(Exact dates are not essential; see the flashCube items)

Stimulus→Response models from Descartes onward: Pursuing the first type of goal of explaining behavior in terms of underlying circuits.

Descartes (1662): reflex arc

LaMettrie (1748): The soul is an enlightened machine. Human is unique species only in complexity of reflex connections.

Bell (1811), Magendie (1822): the "law of roots".

Sechenov (1866): reflexology as a philosophy of human and animal nature.

Pavlov (1900): conditional (conditioned) reflexes; influenced development of American S-R psychology, with emphasis on learning.

Ramon y Cajal: Used Golgi stain to study anatomy of CNS; the neuron is the basic unit of the nervous system; showed connections between neurons from input to output.

Sherrington: synapses (named by him), excitatory and inhibitory; spinal reflex integration.

Donald MacKay: "The logical indeterminacy of free choice"; even with the assumption of physiological cause-effect relationships underlying all behavior, a person's responsibility for choices remains.

Second type of goal (localization of function):

Phrenology's extremes: Franz Joseph Gall (1825); collecting anecdotal stories as method.

Paul Broca (1861): 2 cases of disturbed speech (aphasia), with lesions in lower part of left frontal lobe. This region became known as Broca's area.

Fritsch and Hitzig (1870): Defined "motor cortex" with electrical stimulation of dog brain, as the region where movements could be elicited with the weakest currents..

Betz (1874): Discovered giant pyramidal cells in layer 5 of motor cortex, using Nissl stain for cell bodies.

Carl Wernicke (1874): Discovered a second area for language, located in temporal lobe; proposed a model for speech generation involving connections from this area (now called Wernicke's area) and Broca's area, later promoted by Boston behavioral neurologist Norman Geschwind in 1960's – 1980's.

Pierre Flourens (1824): Experimenter who found evidence for general localization of function but not for the modular subdivisions claimed by phrenologists. (Experiments on pigeon brain described in class: defined general functions of hindbrain, cerebellum, optic lobes, forebrain.)

Goltz (1876): Experiments on dogs; conclusions similar to those of Flourens (considered "anti-localization" in nature). Critique: Inadequate analysis of behavior.

Karl Lashley (1920s, 1930s): tried to localize the engram (the physical changes underlying a memory) for maze learning in rats. Presented evidence for "equipotentiality" and "mass action" of neocortex, no longer generally accepted after more recent studies.

What is specifically localized in brain? Not psychological functions, but only physiological processes in a structural substrate.

D.M. MacKay: Do brains think? This is a poor question; "...if we want to use language consistently, we cannot say that brains think or decide. Brains do those physical things appropriate in their own logical dimensions as correlates of what people do when deciding, thinking, feeling, hoping, fearing, believing, and so forth." (from "A mind's eye view of the brain.")

The third type of goal: finding mere correlations of brain and behavioral events.

Example 1: Using EEG to define states of sleep and arousal, in terms of brain states rather than localized functions.
Example 2: Modern studies of human brain using functional imaging, to define brain modules for specific functions. (Dangers: Temptation to return to phrenology-like maps; sophisticated knowledge of both anatomy and of information flow underlying behavioral functions will be needed.)

Modern "subsystems" analysis:

Use of information flow logic, and considering the brain as a "massively parallel" computer.
Difficult for such models to take account of 1) modulating influence of diffuse connections and changes in chemical environment; 2) the complexity of single neurons, with generation of spontaneous rhythmic changes.

Properties of neurons:

Primitive cellular mechanisms: irritability, conduction, movement (contractions via contractile proteins), secretion, membrane specializations for irritability (transducer mechanisms), endogenous activity.
Receptor potential in specialized epithelial cells (receptor cells) $\rightarrow$ generator potential in primary sensory neurons
Graded response
Decremental conduction
Regions of a neuron for reception, conduction, and transmission.
Dendrites *vs.* axon and axon telodendria
All-or-none response, non-decremental conduction (action potential)
Boutons (boutons termineaux = end buttons, or endfeet)
EPSP *vs.* IPSP
Spatial summation, temporal summation
Axon hillock
Resting potential
Semipermeable membrane
Sodium-potassium pump
Three types of transducer mechanism (chemo-, mechano-, and photoreceptors)
Myelin: role of oligodendrocytes (CNS) and Schwann cells (PNS) (these are two types of glial cells, or glia)
Nodes of Ranvier
Saltatory conduction
Synapse and bouton (not the same concept)
Oxytocin and the milk ejection reflex (a neuro-humoral reflex)
Axo-axonal synapses and presynaptic inhibition or facilitation.
Reciprocal synapses
Serial synapses
Primary sensory neurons of the nasal epithelium
[Primary sensory neurons of the taste system]
Primary sensory neurons of the dorsal root ganglia

Endogenous activity and pacemaker loci in cell membranes
[Entrainment of an endogenous rhythm (oscillator)]

Evolution of Nervous Systems:

Major types of neurons: primary sensory, secondary sensory, interneuron, motor neuron.
Peripheral ganglia (dorsal root *vs*. autonomic)
Notochord
Amphioxus *vs*. other chordates: the shape of the neural tube
Cranial nerves *vs* spinal nerves
Head receptors and expansion of regions of the neural tube in evolution:
   What probably caused the earliest expansion of the endbrain (telencephalon)? Can you
   give examples of what probably caused later expansions?

Introduction to CNS as a system of interconnected cells:

Dermatome
Segmental conduction *vs*. intersegmental and suprasegmental conduction
Channels of conduction: local reflex, cerebellar, paleolemniscal, neolemniscal
Spinothalamic tract
Dorsal column - medial lemniscus pathway
Interpreting effects of decerebration (or of other large lesions): diaschisis effects.
   Diaschisis = deafferentation depression of function. Deafferentation = removal of /
   loss of inputs to neurons
Basic functions of nervous system: maintenance of stability of internal milieu, stability in
   space, stability in time.
Limbic forebrain defined anatomically by connections to hypothalamus, and functionally
   by control of visceromotor mechanisms and of motivational states serving basic
   needs.
"Nothing escapes the influence of the neocortex": Neocortex sends projections (axons)
   down to all levels of the CNS. Regions that expand (in evolution and in development)
   most strikingly with expansion of neocortex: thalamus (reciprocally connected to the
   neocortex), corpus striatum (gets inputs from all cortical regions, including limbic
   components), the pons (the cells of the pontine gray at the base of the upper hindbrain
   which get input from neocortex, and project to cerebellar cortex), and the cerebellar
   hemispheres.

Spinal cord and autonomic nervous system:

Embryonic spinal cord: ectoderm, neural plate, neural tube and neural crest, ventricular
   zone (= matrix layer), intermediate zone (= mantle layer), marginal zone (marginal
   layer); alar and basal plates, sulcus limitans, roof and floor plates. (See figures used
   in classes.)
Adult spinal cord: differences in white and gray matter at different levels (why?), origins
   of major lemniscal channels, corticospinal fibers, propriospinal fibers. (Other fibers:
   see later notes on motor systems.)
Autonomic nervous system: Contrasting functions of its two major divisions.
   Sympathetic ganglia of the thoracicolumbar system (paravertebral chain of ganglia,
   prevertebral ganglia), dual innervation of smooth muscle and glands, parasympathetic
   system (cranio-sacral). (In addition: the "enteric" nervous system" controlling the
   intestines is partially independent of autonomic n.s., and can function without those
   connections.)
Chemical mediation at synapses: Otto Loewi's (1921) discovery with frog heart.

Development of neurons and nervous system:

Induction as a developmental event: [Hans Spemann and Hilde Mangold (1924) discovered induction of CNS by notochord region.] Tom Jessell et al.: recent discovery of inducing molecules: sonic hedgehog (SHH, the ventralizing factor), BMP-4 and 7 (dorsalizing factors) (BMP = bone morphogenetic protein).

Proliferation and migration

Two types of neuronal migration: 1) involving nuclear translocation (as in spinal cord and in midbrain tectum, discovered by Morest), and 2) involving guidance by radial glia (as in neocortex, discovered by Rakic).

Inside-out pattern of migration in neocortex (discovered, e,g., by tritium labeling of DNA by injection of tritiated thymidine at varying embryonic ages of rats, and doing autoradiography on sections of mature brain).

Subventricular layer in developing neocortex: where cells undergo mitosis although not at ventricular surface. The external granular layer of developing cerebellum is not "subventricular" as in neocortex, but it has a similar function.

Growth cone and its filopodia.

CAMs: cell adhesion molecules, like N-CAM (N = neuronal)

Two modes of axonal growth: 1) during elongation and 2) during arborization (differences in rate, in fasciculation, and in branching, as well as in intracellular proteins which play roles in these events)

Developmental pruning of axons as focalization of the end arbor commences (Programmed Axon Pruning). See illustration showing developmental stages in optic tract axon growth.

Programmed cell death (= apoptosis)

Growth factors: NGF (nerve growth factor), the first in the family of diffusable factors called neurotrophins. Dual role: cell survival, axon growth and guidance.

Formation of topographic maps, promoted by chemoaffinity and selective repulsion phenomena. Role of chemical gradients. See also: the growth-promoting (and repelling) effects of netrins in developing spinal cord (role in elongation of spinothalamic tract axons)

Chemoaffinity idea of Roger Sperry (1963) has been supported by discoveries of specific growth factors, and selective adhesion and selective repulsion of growing axons. There are gradients of receptor tyrosine kinases ("Eph" family) in retinal ganglion cells and their axons, and gradients of their ligands in the optic tectum (superior colliculus of mammals). These appear to determine the matching of the naso-temporal axis of the retina with the rostro-caudal axis of the tectum (superior colliculus). [More recently, similar gradients have been discovered for the medio-lateral axis of the tectum and the superior-inferior axis of the retina.]

Plasticity in axonal arbor formation: effects of lesions on regional specificity (e.g., lesions of developing midbrain tectum plus auditory pathways to thalamus can cause collateral sprouting of optic-tract axons into the auditory thalamus (medial geniculate body).

Plasticity in axonal arbor formation: e.g., effects of lesions on map formation (phenomena of map compression and expansion).

These plasticity phenomena occur only during critical periods, with a cut-off at a critical age. However, collateral sprouting does occur in the mature CNS in some axons, e.g., as discovered by Raisman (1969) in the septal area of the limbic forebrain; also there is sprouting of the dorsal root axons in the spinal cord after destruction of descending connections [first reported in 1958].

Selective repulsion of growing axons: midline barriers formed by radial glia cells, with surface molecules that block retinal axon growth (believed to be proteoglycans)

General (less selective) repulsion of growing axons: by proteins in the membranes of oligodendrocytes (oligodendroglia).

Regeneration and regenerative failure in developing mammalian brain. [Role of intracellular protein Bcl-2 in promoting axonal elongation; it also inhibits apoptosis.]

Competition for terminal space

Axon-axon interactions: retraction reactions which often involve a collapse of the growth cone followed by its reformation; discovery of "collapsin" molecules.

Intrinsic growth vigor of axons, modulated by chemical factors (growth factors), by electrical activity levels, and by "pruning" effects.

Motor control: reflexes

Withdrawal reflex, a cutaneous reflex involving at least 2 synapses. Effects of intensity of stimulation: spread of effect within spinal cord. Subliminal fringe, where neurons are facilitated but below threshold.

Synaptic delay (How was this first measured, in the spinal cord?)

Relationship between fiber size, conduction rate, and threshold for eliciting action potentials by mechanical or electrical stimulation. (See early lectures, and readings)

Reciprocal inhibition.

Crossed extension reflex.

Alpha *vs*. gamma efferents (axons of motor neurons).

Muscle spindles.

Muscle stiffness (tone); spring-like properties of muscle.

Golgi tendon organ, and tendon reflexes.

[Renshaw cells: inhibitory interneurons which receive collaterals of alpha motor neuron axons.]

"Alpha-gamma linkage" and alpha-gamma co-activation

Plasticity of reflex connections:

Post-tetanic potentiation of monosynaptic reflexes.

[Long-term potentiation.]

Low-frequency depression.

Crossing of flexor and extensor nerves in rat *vs*. monkey.

Collateral sprouting and reflex spasticity.

Conditioning of withdrawal reflex in spinal rats.

Motor systems: higher control. **(see lecture notes)**

Unique role of corticospinal connections to motor neurons.

Pathways for axial muscle control and whole-body movements: location and examples

Pathways for distal muscle control, e.g., in reaching and grasping movements

Brain lesions indicated in histological sections: by demyelination and by gliosis

Parkinson's Disease

Huntington's Disease (Huntington's Chorea)

Tremor at rest in Parkinson's Disease

Intention tremor after cerebellar lesions

Implicit learning