3.4 How do we learn about the brain?

- In the above section, I emphasized how little we know about the brain. In this section, I want to talk about how much we do know and how we know it.
- As discussed in the first chapter, the levels to be investigated range from
  studying the **flow of ions through membranes** to studying **cognition**.
- In computational neuroscience, major areas of interest are information, representation, and calculation.
- It is likely that many of the levels of investigation will turn out to be relevant to understanding these areas.
- Other levels may not be relevant to these functional issues but will still be of interest as we try to understand neural dynamics.
- For example, our understanding of epilepsy has benefited greatly from computer models of brain activity.
- Although any and all levels are of potential interest, a few levels get most of the attention.
  These are generally the lower levels, from the gene to the single cell.
- Like the parable of the drunk looking for his keys (under the light rather than where he dropped them), researchers look where they can see.
  Researchers are even more strongly motivated than drunks: they have to get grants.
- The good news is that our light on the brain expands as new techniques are developed.

- The development of physiological probes such as
  positron emission tomography (PET) and **functional magnetic resonance imaging** (fMRI)
  have permitted the viewing of activity in the living, thinking human brain.
- However, there still remains a large gap in the scale at which activity is accessible.
- It is possible to record from a single cell in an animal brain but not usually in a human brain.
- It is generally not possible to record from a neuronal ensemble like mini- and macro-columns (hundreds to hundreds of thousands of neurons).
- An important distinction to be aware of in discussing research methods is the distinction between **anatomy** and **physiology**.
- Anatomical methods provide static measures of structure: classical slice-and-dice man-in-the-pan methods.
- Anatomy does not show activity. Physiological methods do show activity.
- In general, when we are interested in information transfer, we are more interested in physiological measures.
- However, anatomical measures can help us with the wiring and basic layout of the brain.

3.4.1 Anatomical methods and related imaging

- Major anatomical methods involve using some sort of radiations mostly visible light, infrared, radio, x-ray, and electrons.
- Anatomy is the science of figuring out how to look and then figuring out what has been seen.
- The major anatomical tools are: the **microscope** and the **imaging device**.
- This includes **computer tomography** (CT or CAT scan), which uses X-rays, and **magnetic resonance imaging** (MRI), which uses the nuclear magnetic resonance (NMR) that results when radio waves are applied to atoms in a strong magnetic field.
- **Light microscopy** gives a nice view — one can zoom in from the naked eye to about 1000-fold magnification.

  Light microscopy is very convenient since we have an organ that can directly detect and image radiation in this range.
- The limitation to light microscopy is due to the wavelength of light, about half a micron.

  It is impossible to clearly resolve anything much smaller than a micron.
- Cell somas are about 5 to 30 microns across and can be easily seen under a microscope.
- Synapses, however, are tiny structures of about 1 micron and cannot be seen in any detail with light.
- Another problem with most types of microscopy is that the raw brain doesn't provide much contrast — it's mostly white on white with some gray on gray.

- To get contrasting images, various stains are used.
- The Colgi stain is historically important because it was used by Cajal in his turn-of-the-20th-century studies that identified the neuron and its role.
- Ironically, this stain permitted Cajal to see the separation between neurons and correctly counter Golgi's contention that neurons formed a continuous syncytium of tissue.
- The Golgi stain is usually picked up by only a few cells in a slice of tissue and turns these cells black.
- Some modern techniques involve direct injection of dyes though electrodes placed in specific cells.
- Since these electrodes can also be used to measure electrical signals, this offers a nice opportunity to correlate electrical activity with cell shape.
- **Electron microscopy** (EM) works at a shorter wavelength and permits photography of objects down to about 10 nanometers.
- A disadvantage is the inability to zoom in and out so as to identify the connectivity of the structure seen.
- This means that it is not always obvious whether one is looking at a piece of a neuron or a piece of some other cell.
- For example, it took researchers a long time to pick synapses out of the many little circles and lines seen on the black and white images provided by EM.
- Additionally, EM requires difficult staining, embedding, and cutting procedures.

- Imaging methods, CT and MRI, are used to look at macroscopic structures.
- Presently these methods cannot be brought down to microscopic levels except in small pieces of tissue.
- These imaging views can be extremely clear, sometimes better than looking at sliced brain after death.
- Of course, they have the further advantage of not requiring either death or slicing.
- These are in vivo techniques, used in the living organism, to be contrasted with in vitro techniques, used in tissue that has been removed and placed in a dish.
- These techniques are particularly useful clinically since pathology such as brain tumors and stroke can be seen.
- However, since current imaging technology does not permit visualization down to microscopic levels, there remains a large gap between what can be seen in life and what can be seen after death.
- In addition to the neuroanatomical imaging techniques, there are also physiological techniques that give some measure of activity in the brain rather than just recording structure.
- The most prominent of these techniques are PET and fMRI. These can be used to measure ions or metabolites in a living animal or person.

3.5 Neurophysiology — the study of function

- Neuroanatomy is the study of form.
- Neurophysiology would like to be the study of function. Unfortunately, it only occasionally rises to this ideal.
- We are often so clueless as to what's going on that neurophysiology becomes more a description of the dynamics than an explanation of its meaning or intent.
- Physiology measures things that change. In neurophysiology, a major thing that changes is electrical potential; hence, much of neurophysiology is electrophysiology.
- Other things that are measured include the flux of specific ions such as calcium, the uptake of nutrients such as glucose, and the binding of neurotransmitters such as glutamate.
- The techniques of electrophysiology generally involve the use of micro-electrodes that measure either voltage or current.
- The electricity measured in the nervous system is generated by the equivalent of a battery that produces voltage across the cell membrane.
- This battery keeps the inside of the membrane at a negative potential, called the resting membrane potential (RMP).
- Deviations from the RMP are electrical signals in the neuron (Fig. 3.2).
- Signals that make the membrane more negative inside are called hyperpolarizing.

- Hyperpolarization means further polarizing the membrane beyond its already negative polarization.
- These signals are considered inhibitory, although they do not always reduce cell firing (see Fig. 12.9).

  Signals that make the membrane more positive inside are called depolarizing (they relieve some of the negative polarization) and are usually excitatory.
- The action potential or spike is a brief (1 millisecond) duration depolarizing signal that briefly reverses membrane polarity, making the membrane positive inside.
- The action potential can travel along the axon and produce release of chemical (neurotransmitter) at a synapse.
- The most direct way to measure potential is to insert a glass micro-electrode through the membrane and compare the potential inside to the potential of a wire placed outside.
- This is intracellular recording. Electrodes used for intracellular recording are tiny hollow straws of glass called micropipettes.

  The glass itself doesn't conduct electricity but the hollow tube is filled with a salt solution that does.
- Alternatively, metal electrodes are placed near the cell for extracellular recording. Although these electrodes do not directly measure a neuron's intrinsic voltage, they do detect electrical fields that closely reflect this voltage.
- If an extracellular electrode is close enough to a cell, it can record activity from that cell alone. This is called single-unit recording. If you pull the electrode further away, it will pick up signals from multiple cells — multi-unit recording.

- The signals from the different cells will have slightly different shapes that make them distinguishable from one another.
- If you pull the electrode still further away, all of the signals blur into an average field potential. Field potentials can be strong enough to be detected from outside the head. This is the potential measured by electroencephalography (EEG), which detects very small potentials by using electrodes glued to the head.

3.6 Molecular biology

- **Molecular biology** has in recent years been the most rapidly advancing field of biomedicine.
- The capability exists not only to knock out specific genes but in some cases to knock out specific genes in specific brain areas at specific times in development.
- The well-known "central dogma" of molecular biology is that DNA makes RNA makes protein.
- By creating a "knock-out," a particular gene is inactivated, permitting us to evaluate changes in an animal's behavior that reflects the function of that gene.
- The problem with this approach from the modeling perspective is that these behavior changes are unlikely to be a direct and obvious consequence of function.
- By way of a hoary example, if you stick a screwdriver into your radio and it starts making a high-pitched whine, this does not necessarily imply that you have cleverly ablated the "whine-suppressor" for this radio.

3.7 Neuropharmacology

- **Neuropharmacology** is the study of the effects of drugs on the nervous system.
- Neuropharmacology is mostly the study of receptors — figuring out where in the brain different compounds bind and what their binding activates.
- In general there are many different subtypes of receptor for each endogenous ligand and there are usually many different non-endogenous compounds that also bind to specific receptor subtypes.
- Some of these non-endogenous compounds are synthetic, having been developed by drug companies to try to treat disease.
- Many more, however, are natural products that one organism makes in order to kill or disable another organism.

  General examples of this are apple seeds, which contain cyanide, and fungi that make penicillin to kill bacteria.
- Neuroactive compounds are quite common poisons since the nervous system is a particularly vulnerable spot in animals.

  The puffer fish makes tetrodotoxin, a sodium ion channel blocker.

  Bees make apamin, a potassium channel blocker.

  Scorpions produce charybdotoxin, another potassium channel blocker.

  The deadly nightshade plant makes belladonna, deadly at high dose but formerly used at low doses to make a woman beautiful by increasing, the size of her pupils.

3.8 Psychophysics

- Psychophysics uses precisely defined stimuli and then asks how they are perceived by a person, often the investigator himself.
- Early triumphs in this area involved the use of specific colors to probe the way that the eye perceives light.
- Even before detailed molecular and cellular studies could be done, this led to the understanding of the three different types of color receptors in the retina, each tuned to a different frequency.
- The relation between these frequencies explains the effects of color combinations: why blue and yellow appear green.
- More recent psychophysical research has used computer-generated images to probe higher levels of visual function.
- For example, it has been shown that rapid projection of images can lead to breakdown in binding of stimulus attributes such that the color and shape of an object are not correctly correlated.
- For example, rapid presentation of a red square and a blue circle can lead to perceptual error such that a blue square and a red circle are seen (illusory conjunction).

3.9 Clinical neurology and neuropsychology

- Medical study of people with brain disorders has played a central role in our understanding of normal brain function.
- Damage to the brain produces in the victim a very personal experience of the dependence of mind on brain.
- Brain damage can produce peculiar states of depersonalization and derealization.
- Patients with obvious brain pathology are treated by neurology, while those with grossly normal brains are classified as having mental disorders and treated by psychiatry.
- A disease like stroke is easily seen to be a brain disease; if you take the brain out, you find a hole in it.
- In a disease like schizophrenia, abnormalities in brain structure are much more subtle and are only now being discovered.
- Schizophrenia was traditionally viewed as a mind disease, due to having a bad mother rather than a bad brain.
- In addition to the increasing awareness of brain abnormalities in psychiatric disease, there is also increasing appreciation of the changes in personality and thinking that occur in association with brain diseases such as multiple sclerosis and Parkinson disease.
- The object of clinical research is to alleviate illness rather than to understand human function.
- Nonetheless, studies of patients have contributed substantially to our understanding of the brain.

- Disease can be regarded as an experiment of nature that may reveal important insights about neural organization.
- From this perspective, ablative and intrinsic brain diseases represent different kinds of experiments.
- Just as the design of an experiment determines what can be and what is discovered, the kinds of brain diseases that occur have had a large influence on our view of the brain.

3.9.1 Ablative diseases

- An ablation knocks out a piece of brain. Stroke, tumor, and trauma are major ablative disorders. These disorders come from outside of the functioning brain itself. They are imposed on the brain. War injuries were the first brain diseases studied in the early days of neurology, during the Civil War.
- More recently, brain dysfunction after stroke has been heavily studied. A stroke occurs when a blood vessel is blocked off, starving a part of the brain and killing it.
- A stroke of the left middle cerebral artery typically causes an aphasia, a disorder of language.

  Such aphasias have been widely studied to learn how the brain processes language.
- However, the specific patterns of aphasia may have as much to do with the particular patterns of middle cerebral artery organization as with the brain's organization for language production.
- Since ablative diseases are imposed on the brain from outside, these insults can produce idiosyncratic effects that do not reflect attributes of brain organization.

- In general, the modular nature of ablative disease has suggested a modular view of brain function. After a stroke, an area of brain is lost and the patient has a particular dysfunction.
- It is then natural to conclude that the piece of brain that was lost was the "center" for the function that was lost.
- From there, one builds up a view of the brain as a series of these centers that pass information to one another.
- Before the development of brain imaging, such modular brain theories were very useful for the localization of strokes.
- Modular theories continue to be highly influential in brain science as well as in neurology.
- Certainly, the brain is not equipotential: some brain areas are dedicated to vision, while others are used for hearing.
- However, while there is merit to modular theories, they tend to be oversimplified and can tell us only a limited amount about how the brain functions.
- A remarkable set of stroke-related mental disorders are those seen with damage to the right hemisphere.
- Neglect is a neurological syndrome that occurs frequently, albeit often transiently, following large strokes in that area.
- The neglect is of the left side of the world and the left side of the patient's body.

- Patients ignore people and things situated to their left. Most remarkably, they may be unable to identify their own left arm.
- If pressed, they confabulate absurdly, concocting ever more elaborate stories to explain why a strange arm would be found in such close contact with their body.
- One patient, for example, was asked so frequently about his arm that he developed the peculiar habit of throwing one cigarette across his body whenever he smoked.
- When asked, he explained that his brother was sharing the bed with him and he wanted to share the cigarette with him.

  The bright side of ablative diseases is that they are not progressive. They damage the brain and stop. The brain can then start to recover.
- It is remarkable how well the brain can recover. A few months after a stroke, a person may be left with no noticeable deficit, despite having a hole in his brain that can be seen on MRI.
- The process that leads to recovery of function is similar to the process of functional organization during development and to the normal process of cortical reorganization that occurs with learning.
- In all of these cases, modeling has suggested that an initial phase of altered dynamics is followed by synaptic plasticity.
- The brain is a dynamic structure, with functional circuits that are repeatedly organized and reorganized.

3.9.2 Intrinsic diseases

- Diseases caused by alterations in cellular organization, metabolism, neurotransmitters, or electrical conduction are intrinsic diseases.
- Correlation of mental dysfunction in these diseases with underlying cellular or chemical abnormalities will likely provide important insights into how the brain works.
- For example, schizophrenia produces peculiar patterns of thought that are also seen between seizures in some forms of epilepsy.
- These syndromes are likely to involve widespread abnormalities in intercerebral communication.
- Intrinsic diseases are typically progressive, making them degenerative diseases.
- Intrinsic disease are generally harder to study than ablative disease.
- As experiments of nature, they correspond to more recent microscopic experiments that classify various cellular and molecular components of the nervous system.
- Study of these diseases tends to suggest a global inter- connected view of brain function.
- Intrinsic diseases of the brain are caused by disorders of the elements of brain organization: synapses, ion channels, or particular neuronal types.
- The prototypical intrinsic diseases are those involving intoxication with neurotransmitter agonists or antagonists.

- Disorders of mentation associated with various drugs are examples of this.
- Parkinson disease is another example of an intrinsic disease. Loss of a particular type of cell results in a decline in release of dopamine, a neurotransmitter.
- This has profound effects on movement and thinking, causing a marked slowing as well as other problems.

  Giving a dopamine precursor as a drug can restore these functions.
- This finding suggests a diffuse network of interacting units somehow glued together by use of a common neurotransmitter.

3.10 Summary and thoughts

- Even without considering computational neuroscience, one finds many different ways of thinking about the brain.
- These come from the different types of experimental techniques available, the different kinds of training of the people doing the experiments, and even from the varying types of diseases that people get.
- Much of the research that has been done has gone into elucidating the chemical and electrical properties of individual neurons.
- Far less has been done at higher levels. In particular, the technology does not exist to determine detailed neuronal connectivity or to assess the activity in large neuronal ensembles in behaving animals or people.
- Historically, notions about the highest levels of perception and behavior have mostly been deduced from strokes and personal intuition.
- The recent development of functional imaging should give more solid information about brain activity during mentation.
- Now that, techniques for studying most of the levels of organization are becoming available, it is tempting to look forward to the day when we can just look at all levels of neural activity and see how the brain works.

- With the experimental means to identify everything everywhere all the time, we could build the perfect brain model.
- It would do everything that the brain does in just the way the brain does it.
- Even with this, understanding would still elude us. We still wouldn't understand any more about how the brain does what it does.
- Complex systems like the brain show emergent properties, properties that cannot be explained by just knowing the properties of the constituent parts.
- The classic example is the emergence of the laws of thermodynamics from the bulk behavior of very many gas particles, each of which follows Newtonian rules.
- Newton's laws (or quantum mechanical laws) do not directly suggest the thermodynamic laws.
- Similarly, a small ganglion in the lobster runs the lobster stomach with only about 30 neurons.
- These neurons have all been studied thoroughly; their responses mapped.
- Given the simplicity of the network, it would seem that knowledge of the elements would yield understanding of the network dynamics.

  This has not been the case.
- Computer modeling is being done to understand the emergent properties of this simple network.
- There are several Web sites devoted to this thing — look for stomatogastric ganglion.

- Neuroscience subfields like neurophysiology, neuroanatomy, and neurochemistry each cover a particular area of neuroscience understanding.
- Explicit computer models build bridges across the gaps between these fields. Every researcher is a modeler. Without a model, whether held in the head or written out in words, pictures, or equations, data do not confer understanding.
- The brain is a place of myriad wonders and many different models will be needed to explain it.