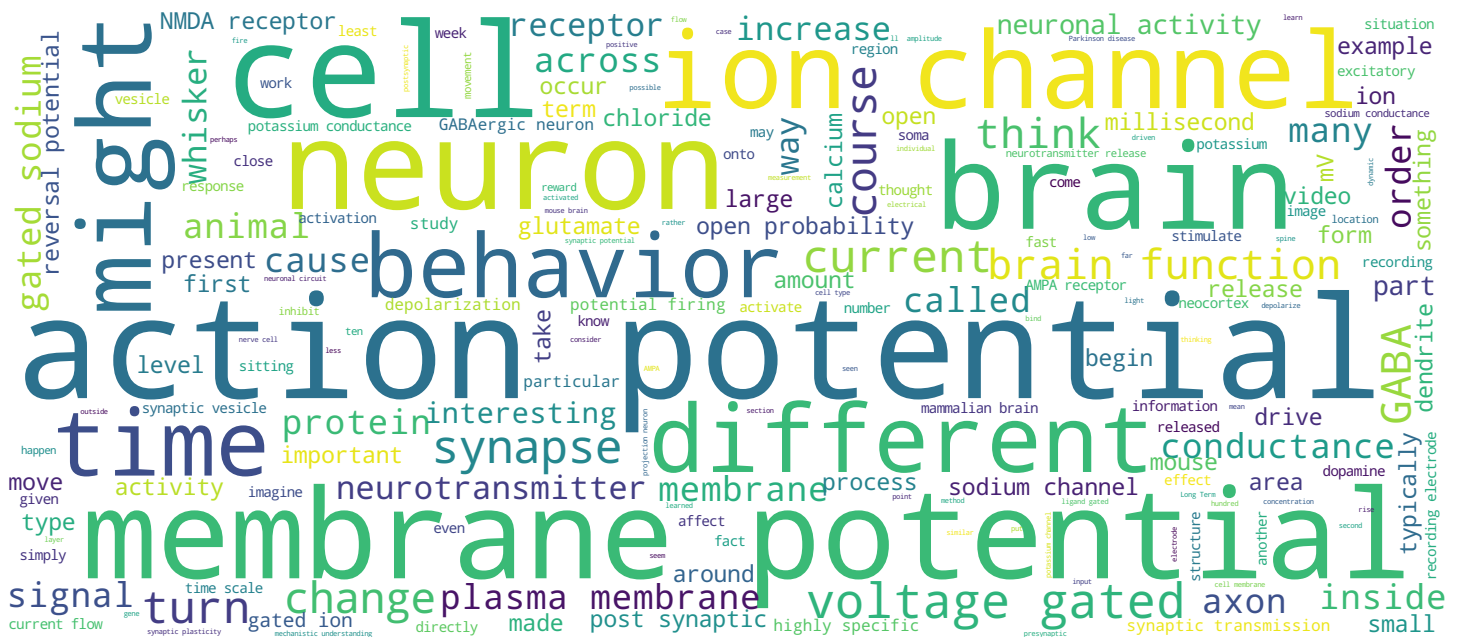
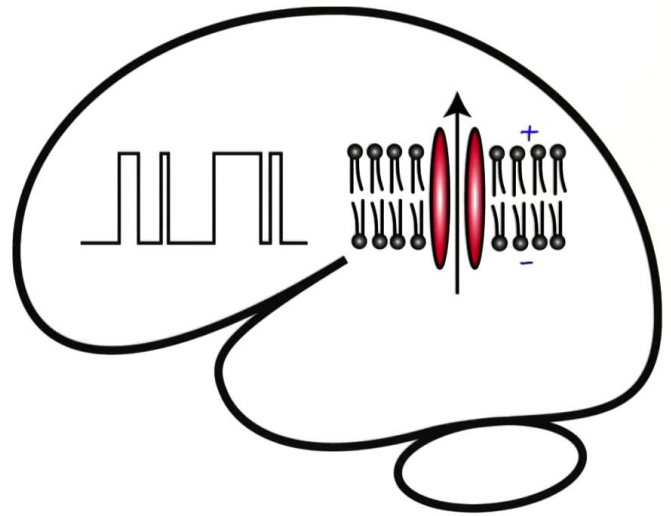


## Cellular Mechanisms of Brain Function

Prof. Carl Petersen



# Cellular mechanisms of brain function



Cellular Mechanisms of Brain Function

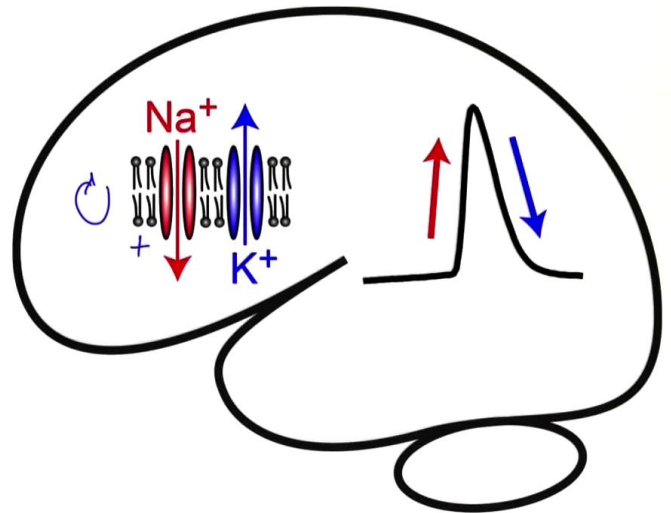
We've now reached a turning point in our studies of the cellular mechanisms of brain function. The purpose of brain function is to govern behavior. We must now see to what extent the biophysical mechanisms that we've studied over the last five weeks are able to account for behavior. Let's begin by briefly reviewing what we've learned. The brain is made of cells, each delimited by a phospholipid bilayer. The cell membrane is impermeable to ions and so we can have charge separation across the plasma membrane. The plasma membrane is about five nanometers thick and so there can be strong electric fields across this plasma membrane. That gives rise to membrane potential and the electrical signals that we know underlie brain function. Charge movement across the plasma membrane is mediated by ion channel proteins that are inserted into the plasma membrane and they can have highly specific conductances for one species of ion, for example. These ion channels are not always open, but rather, they are tightly regulated, and they have a certain open probability. Sometimes they're closed — no current flow — and then they open and close again.

Notes

Summary



0m 05s



Cellular Mechanisms of Brain Function

That open probability of these ion channels determines the net flux of ions and therefore the change in potential across the plasma membrane. The tight regulation of ion channels underlies the ability of electrical signals to occur across the plasma membrane. In particular, we considered a class of voltage-gated ion channels that's particularly useful in terms of making the brief action potential signals that are an important way of coding information in the brain. The voltage-gated sodium channel increases its open probability steeply as the membrane potential depolarizes more positive to around -40 millivolts. As the membrane potential depolarizes, the open probability of the voltage-gated sodium channel increases — that in turn causes more depolarization and that in turn then increases the open probability of the voltage-gated sodium channel, generating the explosive depolarization of the cell towards the sodium reversal potential. The brief opening of the sodium channel, its fast inactivation, and the delayed activation of the potassium conductance drives repolarization and we're left with a brief all-or-none unitary signal, the action potential, lasting about one millisecond.

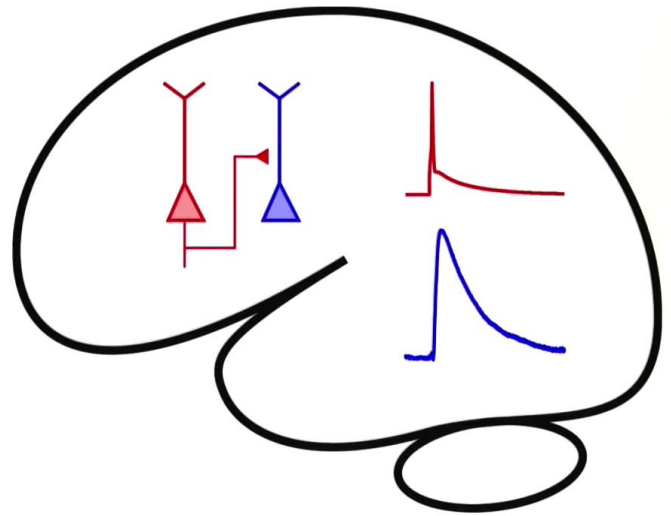
Notes

Summary



1m 37s

# Cellular mechanisms of brain function



Cellular Mechanisms of Brain Function

Nerve cells don't operate on their own; they communicate with each other. Through the action potential that propagates down the axon, invades specializations, boutons, there's a release of a neurotransmitter substance that binds onto ligand-gated ion channels in the postsynaptic neuron, in turn causing a change in the membrane potential of that downstream neuron. So the action potential in one cell, lasting about one millisecond, conveys a longer-lasting signal, sub-threshold depolarization or hyperpolarization lasting some tens of milliseconds interconnected downstream neurons. The process of synaptic transmission is highly plastic. It depends on the previous history of activity of that neuron and also depends upon the overall experience of the animal. So there's that interesting synaptic plasticity that occurs, and that in turn appears to be the mechanism underlying learning and memory.

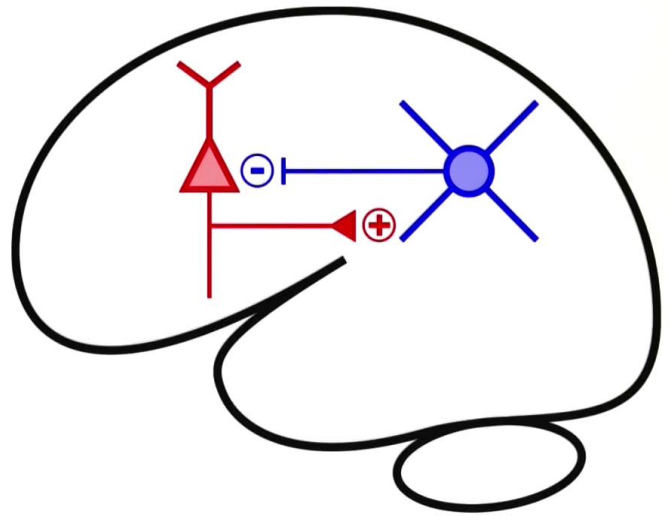
Notes

Summary



3m 10s

# Cellular mechanisms of brain function



Cellular Mechanisms of Brain Function

So the individual neurons communicate with each other and each neuron receives inputs from many hundreds of neurons and in turn also delivers messages to hundreds of neurons, some of which are widely distributed across the neuronal circuits of the brain. We thus need to begin to divide the neurons and the types of neurons. We know that there are excitatory glutamatergic neurons that release glutamate and try to excite their postsynaptic targets. There are inhibitory GABAergic neurons that release GABA and try to inhibit their targets. There are neuromodulatory neurons that release neuromodulators that affect the dynamics and interactions of the system as well as the plasticity of these neuronal circuits, and we need to deal then with a great deal of complexity as to where and how these neurons communicate in highly specific patterns and how they do so during behavior.

Notes

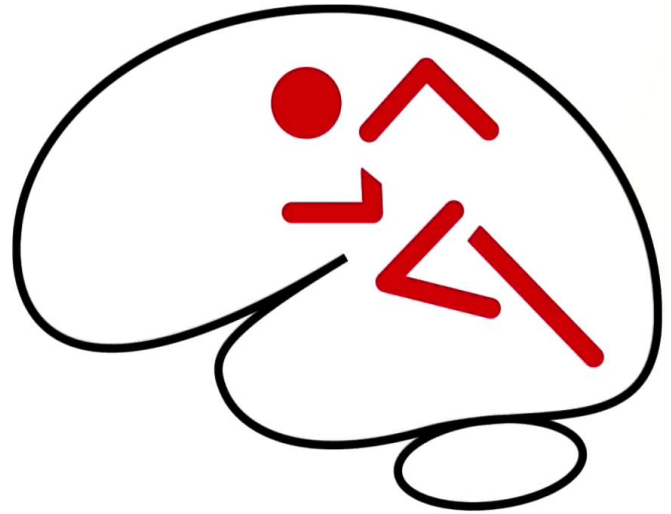
Summary



4m 19s

# Causal mechanisms of behavior

Our goal is to obtain a causal understanding of behavior, so we need to investigate brain function at the level of individual neurons and their synaptic interactions within the complex neuronal networks of the living mammalian brain.



Cellular Mechanisms of Brain Function

So if our goal is to obtain a causal understanding of behavior, we need to investigate brain function at the level of individual neurons and their synaptic interactions — that's how we're going to get a causal, mechanistic understanding — and we need to do that within the complex neuronal networks of the living mammalian brain during behavior. We need to see the action of the brain during action.

Notes

Summary



5m 20s



# Cellular measurements of brain function *in vivo*

Measure neuronal activity in the living brain and correlate with behavior.

## 1. Electrophysiology

Whole-cell patch-clamp recordings of membrane potential

Extracellular recordings of action potentials

## 2. Optical imaging

Fluorescence microscopy

High resolution structural and functional measurements

Cellular Mechanisms of Brain Function

So how are we going to do that? The first thing we need to be able to do is to measure neuronal activity in the living brain and to correlate it directly with ongoing behavior. At the level of cells and synapses, there are two methods that so far have proved to be extremely useful. One is the electrophysiological approach, where we introduce recording electrodes into the brain. We've already seen the whole-cell patch-clamp recording of membrane potential and currents that has been applied *in vitro* in brain slices. It turns out that this method can also be applied with small modifications to study the brain in action — *in vivo*, during behavior. It also turns out to be possible to make extracellular recordings of action potential firing. To date we've thought of the extracellular solution as being at zero millivolts isopotential and invariant. In fact, that turns out not to be completely true, and there are small changes in the extracellular potentials that can be recorded, and they can be recorded relatively easily. The inference of which cell is firing action potentials can also be made.

Notes

Summary



5m 47s

# Cellular measurements of brain function *in vivo*

Measure neuronal activity in the living brain and correlate with behavior.

## 1. Electrophysiology 6.3

Whole-cell patch-clamp recordings of membrane potential

Extracellular recordings of action potentials

## 2. Optical imaging 6.4

Fluorescence microscopy

High resolution structural and functional measurements

Cellular Mechanisms of Brain Function

The extracellular recordings are technically easier than the intracellular recordings, and so one can in parallel record from many neurons at the same time and study network function using extracellular recordings. Electrophysiological measurements are certainly proving useful in correlating neuronal activity with behavior. However, in the electrophysiology, we need to introduce recording electrodes into the brain. These recording electrodes must have some size, and that in turn perturbs the brain. It's interesting to think about other techniques that might be less invasive, and introducing photons into the brain is one of the most interesting techniques that is being developed at the moment for studying brain function at high resolution. So optical imaging techniques, and in particular fluorescence microscopy, is turning out to be extremely interesting in terms of getting high-resolution structural and functional measurements of the brain, and at this time this is possible to do in the living brain and correlate it with behavior. In later videos of this week, we'll study how we can apply electrophysiological measurements in video 6.3 and how we can apply optical methods for investigating neuronal activity in video 6.4.

Notes

Summary



7m 05s



# Perturbations of brain function

Measurement and correlation of neuronal activity with behavior is essential, but correlations do not necessarily imply causality.

In order to investigate the causal impact of a specific neuronal activity, we need to specifically perturb that activity.

Optogenetics – offers combinatorial specificity through:

- i) Optical control - spatiotemporal resolution
- ii) Genetics - cell-type specificity

Cellular Mechanisms of Brain Function

So we're beginning to have methods for measuring and correlating neuronal activity with behavior. That's absolutely essential as a starting point. But correlations don't necessarily imply causality, and so if we want to investigate the causal impact of a specific neuronal activity, we need to specifically perturb that activity. We need to be able to take control of the neurons and the neuronal circuits and see what effect that has upon behavior. That's turned out to be an extremely difficult problem to have highly specific interventions in the brain. So typically, one has relied upon lesions, brain damages, diseases, stimulation or pharmacological manipulations, and all of these lack specificity in space and time. So it's been difficult to get a real detailed information about the causal impact of specific types of neuronal activity. Over the last years, there's been a revolution in neuroscience that's been driven by *optogenetics*, a way in which we can control neuronal activity by light. This occurs through expressing specific light-sensitive proteins that can then affect the activity of specific nerve cells, we can use genetics to put these optogenetic actuators in specific cell types, and we can then shine light on specific neurons or parts of neurons gaining high spatiotemporal resolution.

Notes

Summary



8m 33s

# Perturbations of brain function

Measurement and correlation of neuronal activity with behavior is essential, but correlations do not necessarily imply causality.

In order to investigate the causal impact of a specific neuronal activity, we need to specifically perturb that activity.

Optogenetics – offers combinatorial specificity through:

- i) Optical control - spatiotemporal resolution
- ii) Genetics - cell-type specificity

Cellular Mechanisms of Brain Function

So there's a great deal of hope now that we'll be able to make highly specific perturbations during behavior, and then we'll be able to study the impact of that.

Notes

Summary



10m 05s

# Quantitative modelling of brain function

Having made measurements and perturbations of specific neuronal activities, it is essential to quantitatively model the phenomena in order to gain causal mechanistic insight and to test specific hypotheses.

We currently have a very incomplete understanding of neuronal circuits in the mammalian brain and we are far from having a quantitative mechanistic understanding of even the simplest behaviors.

Although many brain regions are highly interconnected there is also a high degree of modularity, through so-called *small world networks*. Detailed cellular and synaptic modelling of selected subnetworks of the brain is now becoming feasible with increases in computing power.

Cellular Mechanisms of Brain Function

So if we're able to make measurements and perturbations of highly specific neuronal activities, the next step is to try and see how those measurements and perturbations fit together. In order to do that, we need to quantitatively model the phenomenon and that then will give us causal mechanistic insight and allow us to test specific hypotheses. Unfortunately, we currently have a very incomplete understanding of neuronal circuits in the mammalian brain. We're very far from having a quantitative mechanistic understanding of even the very simplest behaviors. So the starting point is far from where we want to be. Of course, the brain is highly interconnected, so it's an extremely complex question as to how we can quantitatively model the neuronal networks of the brain. There's a simplification that we might be able to make. Although many brain regions are highly interconnected, there's also a high degree of modularity. So there are so-called small world networks where neurons near to each other might be highly interconnected with each other but they will only have sparse connections to another part of the brain.

Notes

Summary



10m 17s

# Quantitative modelling of brain function

Having made measurements and perturbations of specific neuronal activities, it is essential to quantitatively model the phenomena in order to gain causal mechanistic insight and to test specific hypotheses.

We currently have a very incomplete understanding of neuronal circuits in the mammalian brain and we are far from having a quantitative mechanistic understanding of even the simplest behaviors.

Although many brain regions are highly interconnected there is also a high degree of modularity, through so-called *small world networks*. Detailed cellular and synaptic modelling of selected subnetworks of the brain is now becoming feasible with increases in computing power.

Cellular Mechanisms of Brain Function

So we can think about local subnetworks and it may be that we can get detailed cellular and synaptic modeling of these selected subnetworks and model that, and that is now becoming feasible with the increases in computing power. So there's some hope that over the next decades — perhaps in our lifetimes — we might be able to get quantitative, causal, mechanistic understanding of at least very simple forms of brain function and their link to behavior.

Notes

Summary



11m 36s

Karl Popper (1934) *The logic of scientific discovery*.

We can falsify hypotheses, but we cannot not prove them.

Cellular Mechanisms of Brain Function

As a cautionary note, I think it's important to consider the limitations of the scientific method. These were clearly stated by Karl Popper in his famous treatise of 1934, *The logic of scientific discovery*. He pointed out that we can falsify hypotheses, but we cannot prove them, and so scientific progress is at best a continual refinement of our ideas as we make more and more detailed measurements and perturbations.

Notes

Summary



12m 10s

# Causal mechanisms of brain function and behavior



- Correlate the activity of specific cells with behavior.
- Perturb the activity of specific cells during behavior.
- Quantitatively model the causal interactions driving brain function and behavior.

Cellular Mechanisms of Brain Function

Here we've begun to think about how we might put together our biophysical knowledge of how the components of the brain work in the context of behavior, and most of the videos of this week will deal with methods as to how we might approach the problem of linking the biophysics of brain function with animal behavior. We've come across three important steps that we need to make. First we need to measure brain function, and we need to do so at the level of cells and synapses and how the membrane potential changes drives further action potential activity in those neurons that we've been recording from. So we need to make detailed measurements of brain function at the level of cells and synapses. These measurements will allow us to correlate neuronal activity with behavior. But in order to reach causality, we need to perturb brain function and see what types of effects that causes. We need to take control of the brain and see what happens if we stimulate and inhibit specific neurons within the brain in a highly controlled spatiotemporal pattern.

Notes

Summary



12m 46s



# Causal mechanisms of brain function and behavior



- Correlate the activity of specific cells with behavior.
- Perturb the activity of specific cells during behavior.
- Quantitatively model the causal interactions driving brain function and behavior.

Cellular Mechanisms of Brain Function

If we can take control of these neurons and measure the effects of the brain and at the same time see the behavioral consequences, then we're getting to a position where it becomes extremely interesting to try to quantitatively model and see to what extent we've really got the right variables and that we've made the correct measurements and that we really have a causal and mechanistic understanding of brain function, including its link to behavior. So in this week's videos, we're going to take a look at the methodology as to how one might obtain a causal and mechanistic insight into brain function during behavior.

Notes

Summary



14m 06s