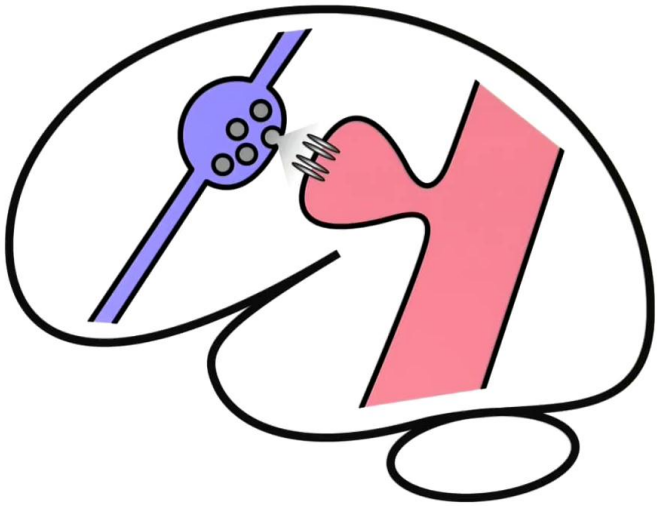
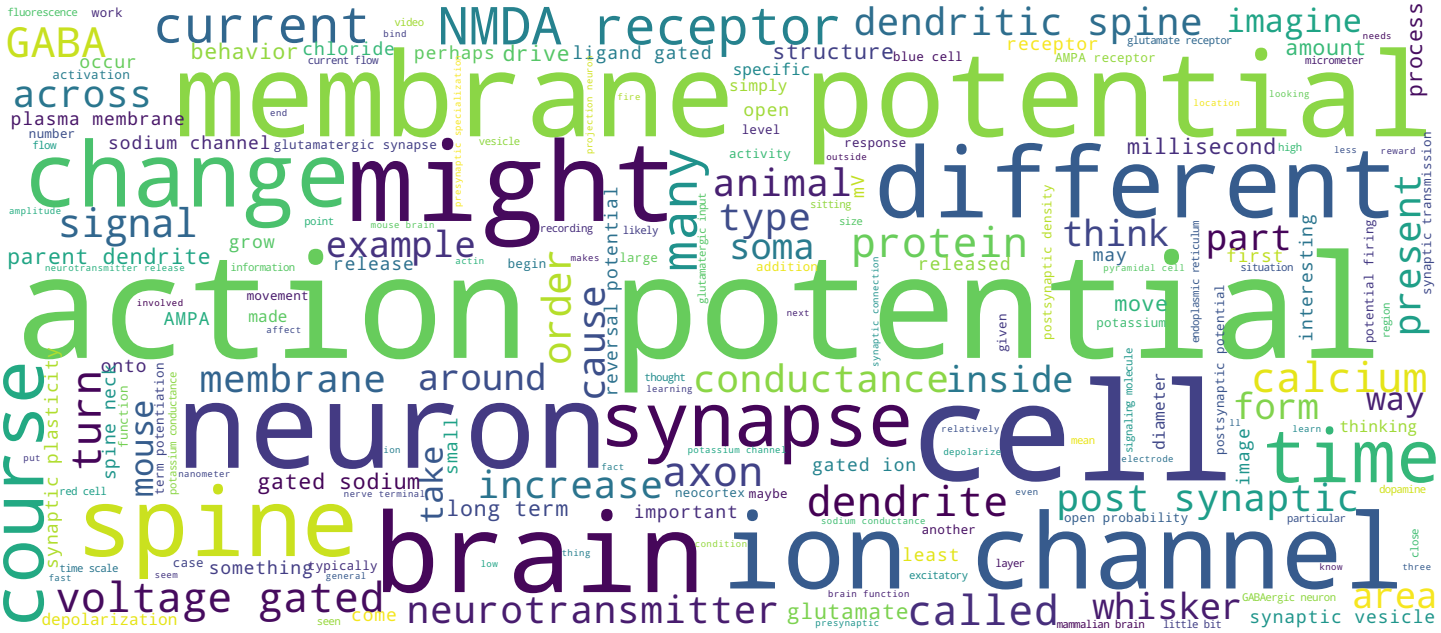


4.5 Dendritic spines

Cellular Mechanisms of Brain Function

Prof. Carl Petersen

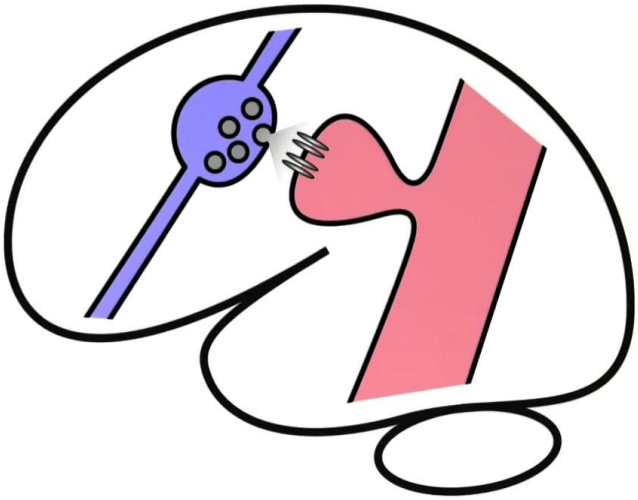


Search MOOC

Video

EPFL

Excitatory synapses on dendritic spines



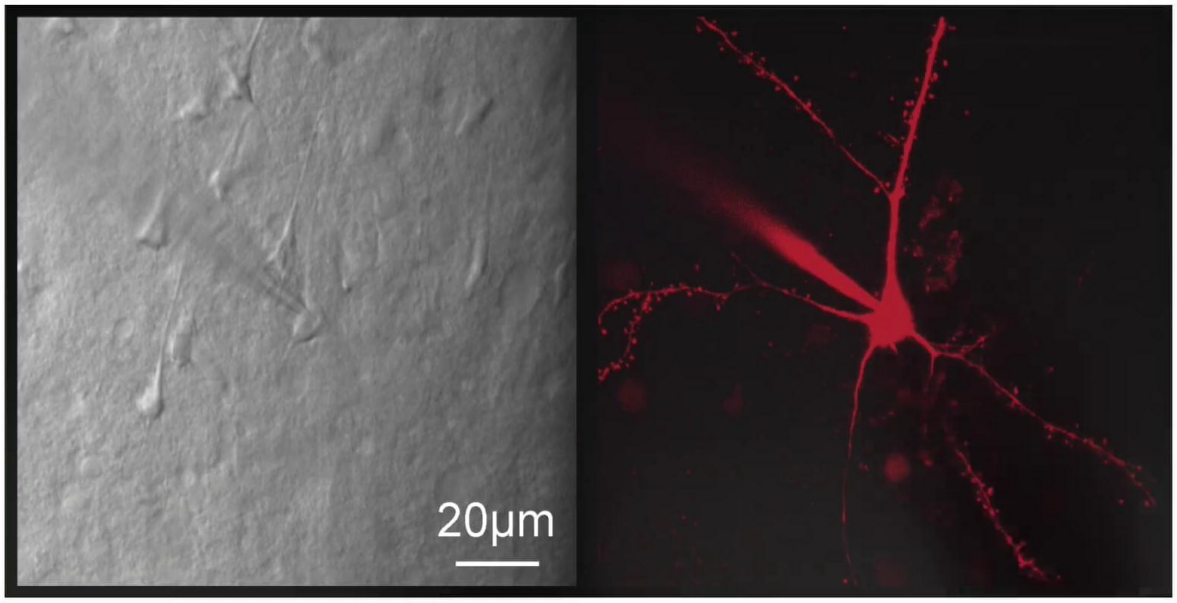
As we've discussed over the last weeks, neurons have extensive dendritic arborizations. They grow these protrusions from the cell body, extending out, reaching out to try to make synapses and receive information from presynaptic neurons. This means that there are local and complicated electrical and presumably also biochemical interactions occurring at some distance from the soma. In this lesson, we'll learn that there's a further level of specialization that occurs on the dendrites, where small protrusions grow from those dendrites in order to make excitatory synapses. Those protrusions are called *dendritic spines*. For most cells, the excitatory glutamatergic inputs that arrive across the dendritic arborization don't come directly in onto the main parent dendrites. The main place where glutamatergic synapses are found is on these small protrusions, about one micrometer in size or so, that grow from the parent dendrite, reach out and make contacts with presynaptic specializations. These one-micrometer structures are the main sites of where excitatory glutamatergic inputs arrive onto most types of cells in the brain. They're likely to have a variety of important functions, and that's what we'll discuss in this video.

Notes

Summary

0m 06s

Dendrites are often decorated with spines



Aronoff & Petersen, 2007

Cellular Mechanisms of Brain Function

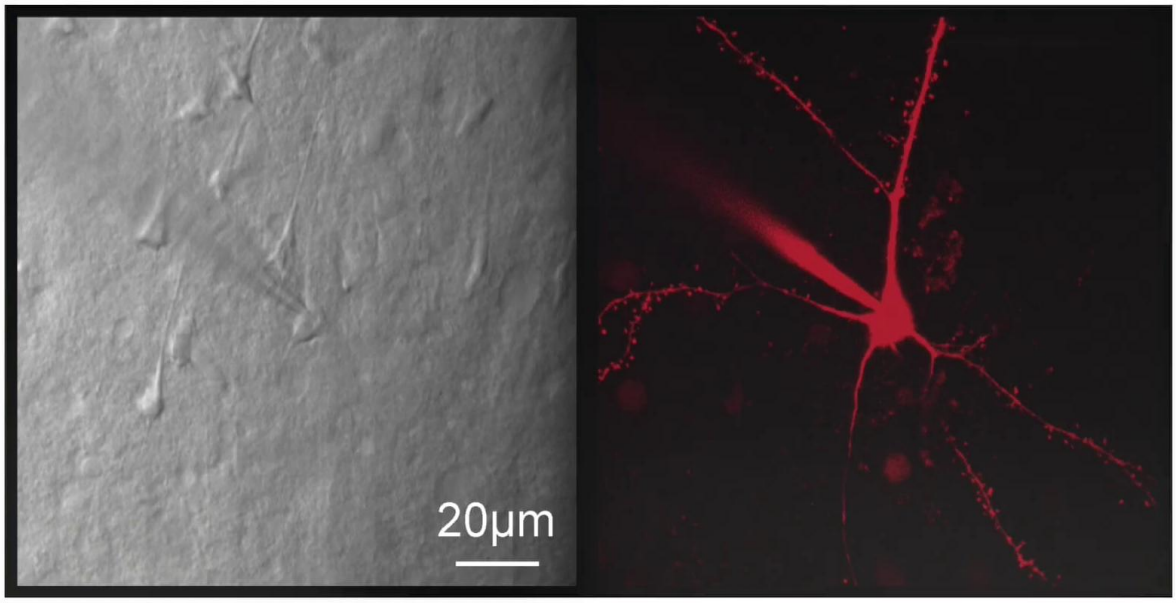
First, to get an impression of what the structure of neurons looks like, here we have a recording from a brain slice, very much like what you saw in previous weeks. A whole-cell recording electrode has been introduced onto a layer-II free pyramidal cell. Here you see the soma of that cell. This glass electrode makes an intracellular recording of the structure and electrophysiological properties of that neuron. Because there's a fluorescent dye inside the electrode, we can take a fluorescence image of that cell — you see the cell body, the pipette, as you did here, in the video image of that cell. Here in addition, through the high contrast that's given by the fluorescence, you also see the dendritic structure of the cell where these dendrites are reaching out, trying to get synaptic input. If you would now look more carefully at these dendrites, you'll see that there are little red spots that are decorating the side of all of these dendrites. These, then, are the dendritic spines, the outgrowths that come and grow out of the main dendrite, reaching out yet further to make a synaptic contact with a presynaptic bouton that releases glutamate. Each one of these spines receives at least one glutamatergic input.

Notes

Summary

1m 52s

Dendrites are often decorated with spines



Aronoff & Petersen, 2007

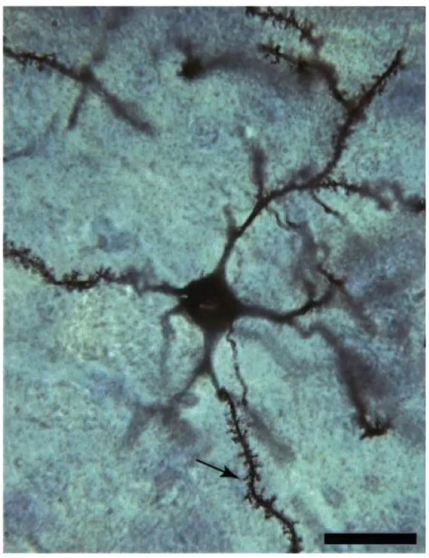
In mature pyramidal cells, no glutamatergic synapses arrive on the main dendrite. All glutamatergic synapses arrive on these spines. So as a first-order approximation to see how many glutamatergic inputs arrive on one of these excitatory pyramidal cells one can simply go and count the number of spines, and that amounts to some thousand or so for a typical nerve cell.

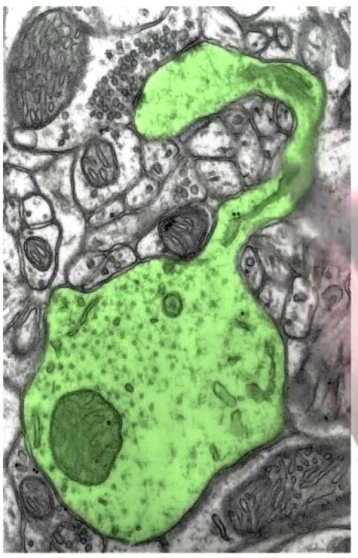
Notes

Summary

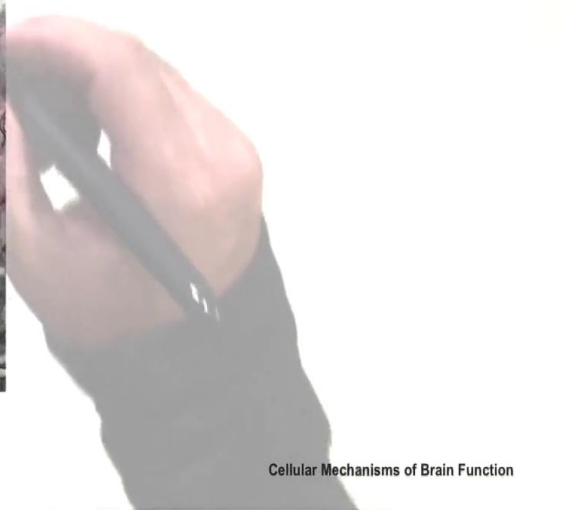
3m 25s

Structure of dendritic spines





Graham Knott



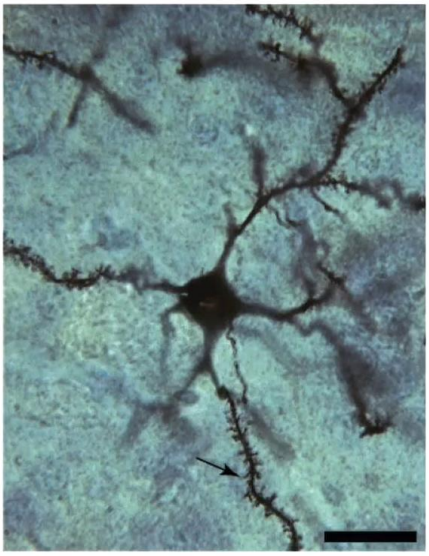
If we now want to look a bit more carefully at the structure of dendritic spines, because of their small size, we can't use light microscopy. Light microscopy gives you an image like this, where on this 20-micrometer scale, we see the cell body, about ten microns in diameter, we see the dendrites, which are maybe one or two micrometers in diameter, and we also see, just about, these fuzzy protrusions, but we are unable to resolve their structure fully, because light microscopy has a resolution limit that's set largely by the wavelength of light. In order to see at higher resolution the structure of these dendritic spines, we must turn to electron microscopy, that you've already heard about from Graham Knott. Here is one of the images that Graham Knott has taken of a dendritic spine. In this particular plane, we see the main dendrite that has about a one-micrometer diameter and growing out, emanating from that parent dendrite is the dendritic spine. That's much narrower, it has something, a so-called spine neck, on the size of around 100 or 200 nanometers, so about a tenth the size of a dendrite, and it might grow for a micron or so, reaching out, and here it contacts a glutamatergic presynaptic specialization filled with synaptic vesicles.

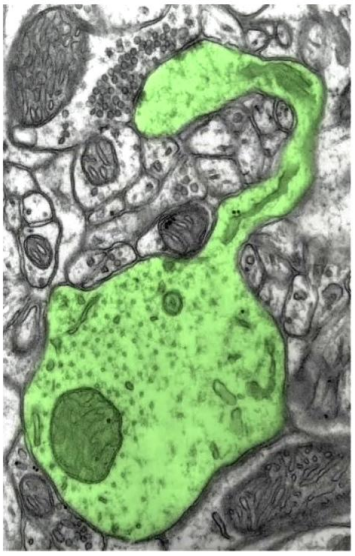
Notes

Summary

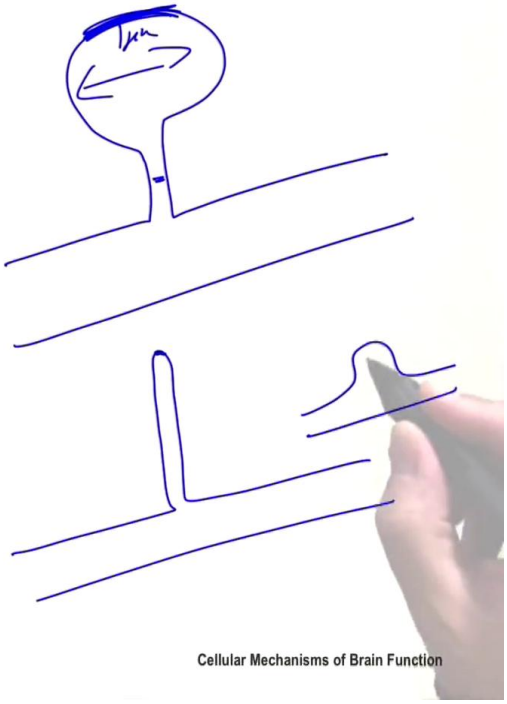
3m 56s

Structure of dendritic spines





Graham Knott



When an action potential invades this presynaptic nerve terminal, it will release glutamate and it will then affect the AMPA and NMDA receptors that are present here on the postsynaptic density at the tip of the spine that will then communicate those electrical currents through to the parent dendrite that then in turn signals through to the soma, where an action potential might be initiated. Now, dendritic spines come in many shapes and forms. There are the so-called large mushroom spines, where there's a large dendritic head that sticks off the dendrite — here, this is an example of this. The head is perhaps a little bit small, but the heads here of these mushroom spines can maybe be a micrometer in diameter. The spine neck here that has a diameter of around 100 to 200 nanometers can be one or two micrometers long. There are, however, other types of dendritic spines. There's a continuum of these, and so others just have thin protrusions like that and maybe just have a very small synapse sitting on the end. These large mushroom spines might have very large synapses sitting on them. In between, there are other small, stubby spines.

Notes

Summary

5m 30s

Structure of dendritic spines

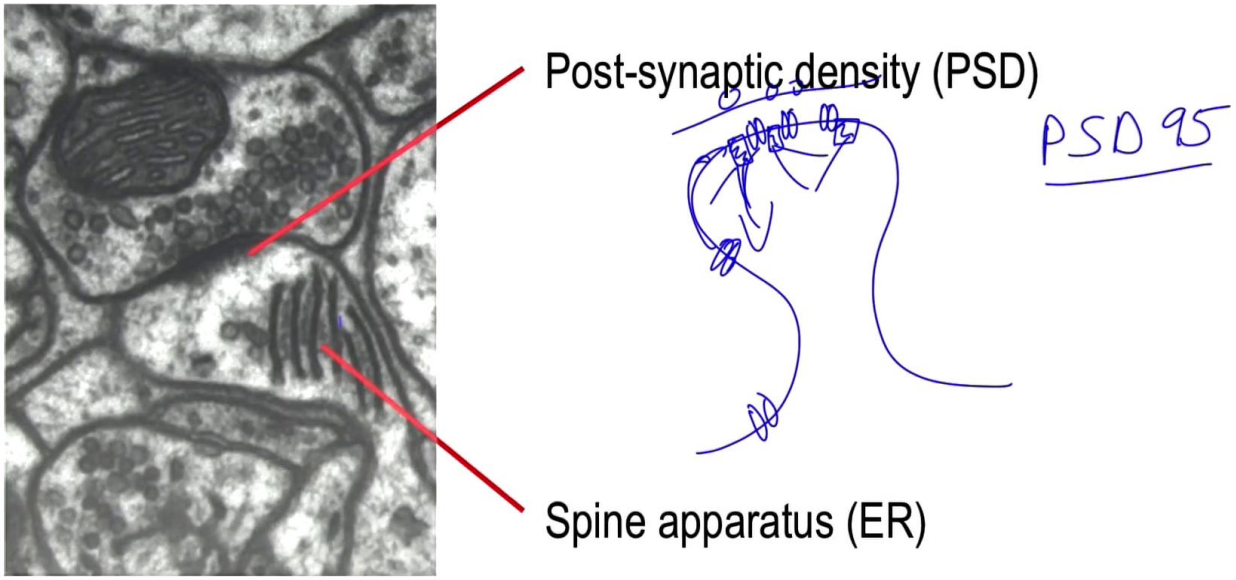
If we now zoom in a bit further one one of these electron micrographs, we can begin to see further structural specializations inside the dendritic spine. Just to orient you again, here is a presynaptic nerve terminal filled with synaptic vesicles. Each one of these contains a high concentration of glutamate and will be released upon action potential invasion of the presynaptic bouton. Postsynaptically, we find that there's a darker region here that shows up in the electron-dense staining of the electron micrograph. This is the so-called post-synaptic density. What this indicates is that there's an area here that contains a very dense matrix of proteins that are present here on the postsynaptic density. So of course, we already know that the postsynaptic membrane must contain ligand-gated ion channels, the glutamate receptors, the AMPA, and the NMDA receptors. In addition, they also have other molecules that are in part used to anchor these molecules, the AMPA and NMDA receptors, in position. So some of these, and perhaps one of the most important ones, is called PSD95, postsynaptic density molecule with 95 kilodaltons. This is one of the most highly expressed proteins that are present here in the postsynaptic density.

Notes

Summary

6m 56s

Structure of dendritic spines



Graham Knott

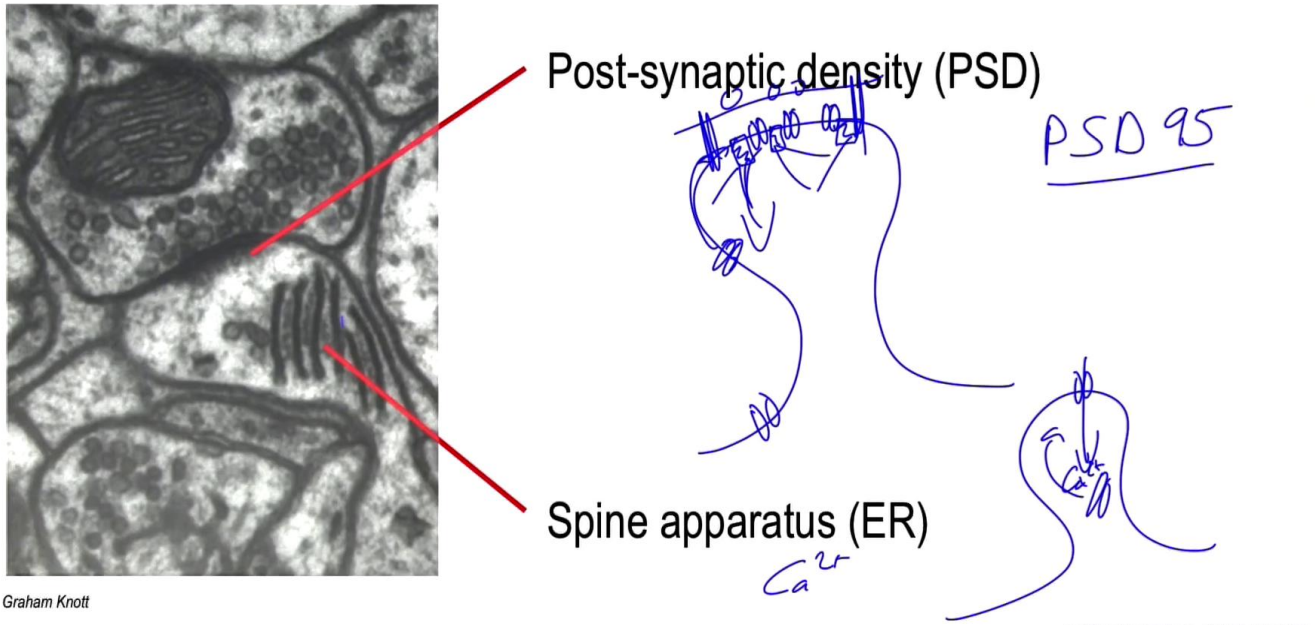
This probably provides a scaffolding molecule which can link in to the ligand-gated ion channels, together with a host of other signaling molecules that help keep the ligand-gated ion channels in the right place, right next to the presynaptic specialization where glutamate is going to get released from. These molecules are of course also involved in signaling cascades. We've just heard in the last lesson about the process of synaptic plasticity, where we need to be able to recruit receptors that are diffusing on the plasma membrane into the synapse if it's going to be a long-term potentiation or we need to be able to get rid of these receptors if it's a question of long-term depression. So there are many signaling molecules that are also present and many of them are present right here at the postsynaptic density where they're being held in place exactly where they need to be, next to the AMPA and NMDA receptors. If we look a little bit deeper inside the spine that we can outline here — here's the spine neck, the parent dendrite begins somewhere down here — there's another interesting and prominent feature called the spine apparatus. Not all spines have a spine apparatus, but many do.

Notes

Summary

8m 32s

Structure of dendritic spines



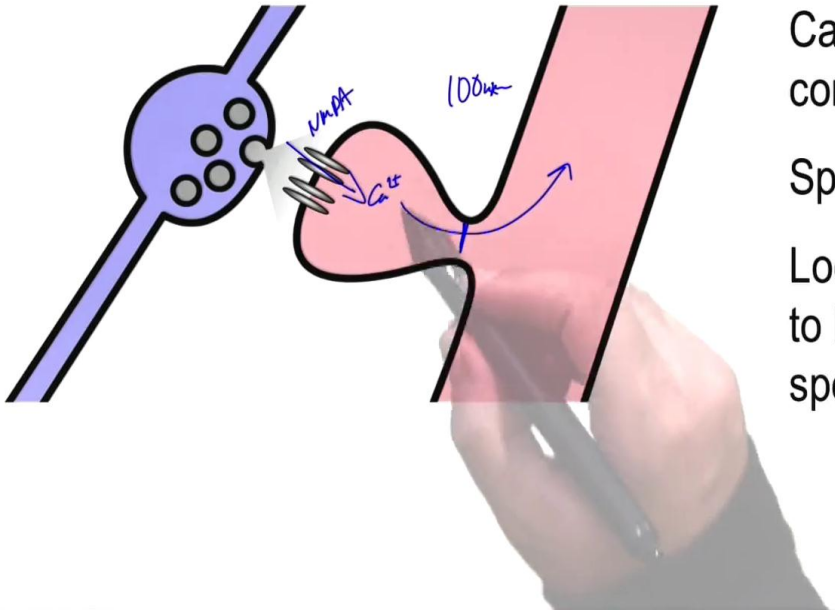
This turns out to be a part of the endoplasmic reticulum or a specialization of endoplasmic reticulum that's present inside spines. So it's quite likely that proteins are being made in some cases, and so there's local protein synthesis that might occur inside spines. The other thing that the endoplasmic reticulum does is to handle calcium. So this is likely to be an intracellular calcium store that's likely to contribute to what happens downstream of, say, NMDA receptor activation, which causes a calcium influx, and that might then be buffered or handled by the endoplasmic reticulum here in the spine apparatus, and that might contribute to releasing calcium in some cases, or sucking calcium up in other cases, and that might contribute to regulating synaptic plasticity. So within even these small, one-micron dendritic spines, there's an enormous complexity, a scaffold of signaling molecules linking up to the ligand-gated receptors, also proteins that stretch across there from presynaptic to postsynaptic densities, and there's also interesting endoplasmic reticulum for perhaps manufacturing new proteins and also for dealing with calcium signals.

Notes

Summary

9m 53s

Localised biochemical reactions in spines



Calcium signals can be confined to a single spine.

Spine neck limits diffusion.

Localised signalling is likely to be important for synapse specific plasticity.

Cellular Mechanisms of Brain Function

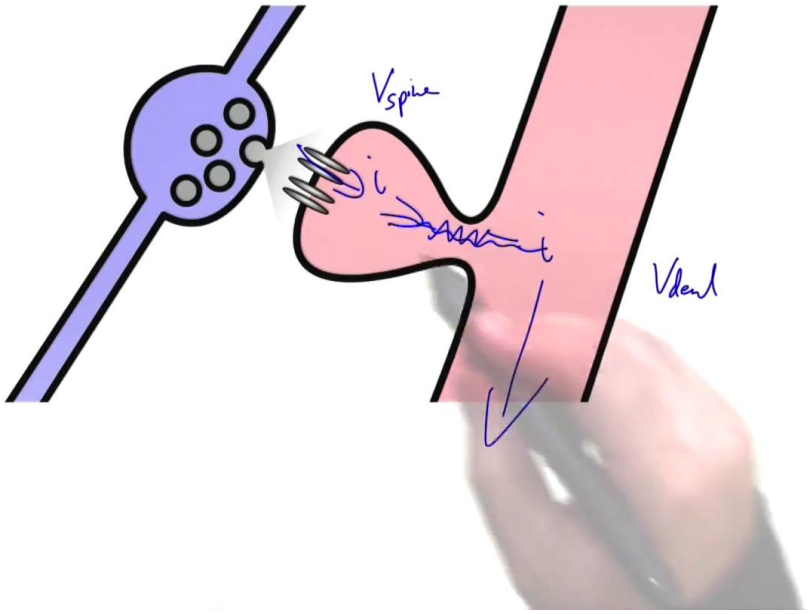
What might the function of these spines be? At one level, the narrow constriction of the spine neck provides a diffusional barrier where we can imagine having biochemical reactions taking place in this one-micron spine head that might be localized and it might be difficult for those proteins or other signaling molecules to diffuse out of the spine. There's simply a very narrow spine neck of say 100 nanometers that will then restrict the diffusion of various different signaling molecules. Perhaps the first signaling molecule we might think of, coming through the NMDA receptor and thinking about synaptic plasticity, is calcium. Calcium will enter during spike-timing-dependent plasticity or long term potentiation, the postsynaptic neuron is depolarized, the magnesium comes out of the NMDA receptor, gluatamate is released, and now calcium can flood into the post-synaptic spine. The local concentration inside this spine can rise quite strongly because it's a small volume and so only a few calcium ions are needed in order to increase the calcium concentration quite dramatically in this small volume.

Notes

Summary

11m 21s

Electrical resistance of spine necks



In some spines, the neck might offer high electrical resistance (~1 GΩ).

Spine V_m might differ from V_m of parent dendrite.

Regulation:
Spine neck diameter ?
GABAergic synapse ?

Cellular Mechanisms of Brain Function

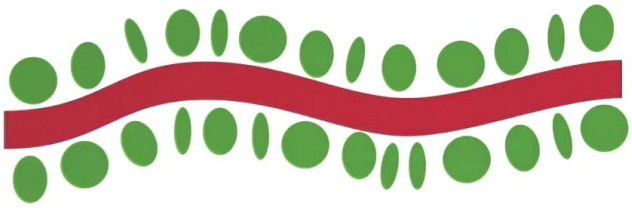
It's difficult for the calcium to leave because the spine neck is restricted in diameter and so diffusion of the calcium out is rather difficult and indeed there are many calcium-binding molecules and it may be that the spine apparatus, the endoplasmic reticulum, further restricts the diffusion of calcium out of spine heads. This then means that we can have calcium signals that are entirely localized to a single dendritic spine — to a single synapse. That, then, might help synaptic plasticity remain synapse-specific. In addition, it's possible, and there's some discussion of this point in research at the moment, that there's some resistance for the currents flowing in here through the ligand-gated ion channels. In order for them to get to the soma and signal through, there must of course be some current flow. If there's a strong resistance here, then it's more difficult for that synaptic current to flow to the parent dendrite and of course subsequently to reach the soma. There are measurements that suggest that, at least at some synapses, the spine neck resistance might be on the order of 1 gigaohm. That's the type of resistance that makes it relatively difficult for currents to flow from the spine head to the parent dendrite. So it may be that the potential here at the spine head might be quite different from the potential at the parent dendrite.

Notes

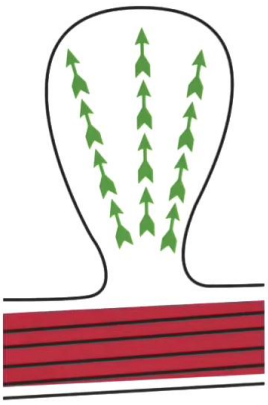
Summary

12m 42s

Actin filaments in spines



Actin - dendritic spines
MAP2 - microtubules



Cellular Mechanisms of Brain Function

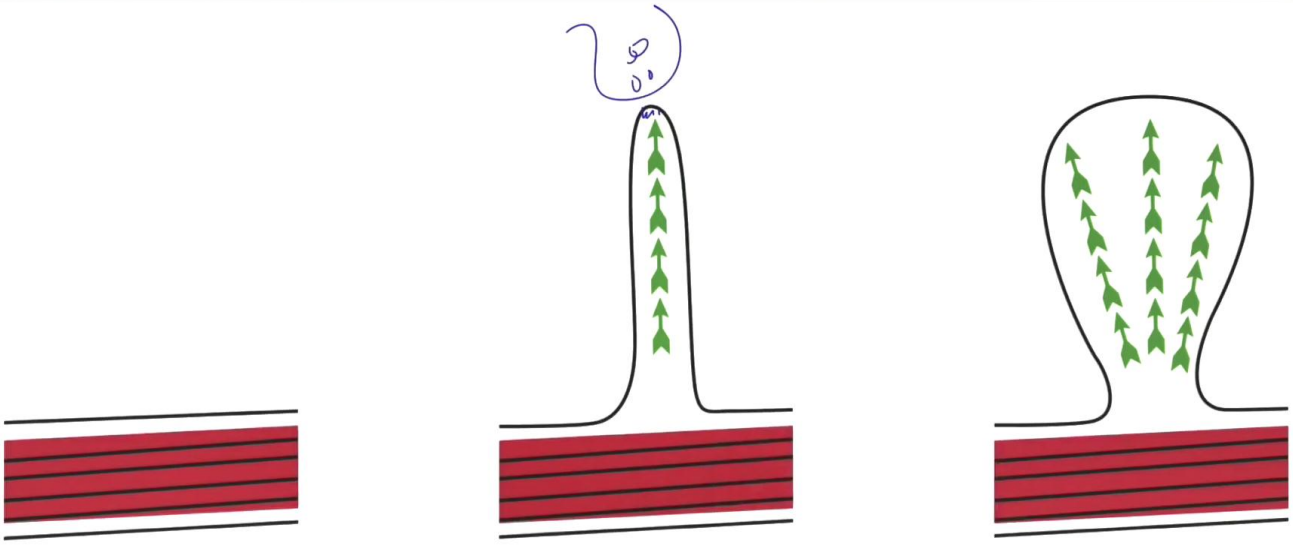
The final point that I'd like to make about spines is that they are highly motile — they move around. The reason that they move is because of actin. If we now look at a piece of dendrite that's schematically drawn here and we imagine it's stained for microtubules — MAP2 — or for actin, then we see that the main parent dendrite is full of microtubules, stained here with MAP2. But the spines that decorate this are full of actin, and actin is an extremely interesting substance. It's a protein that readily polymerizes and depolymerizes and it's the reason that cells — all types of cells across biology — can move. They do so by extending — in a treadmill-type fashion, they can get rid of actin at one end of a filament and they can add additional actin molecules to grow and thus they can push the membrane around in interesting ways.

Notes

Summary

14m 25s

Spine motility



Cellular Mechanisms of Brain Function

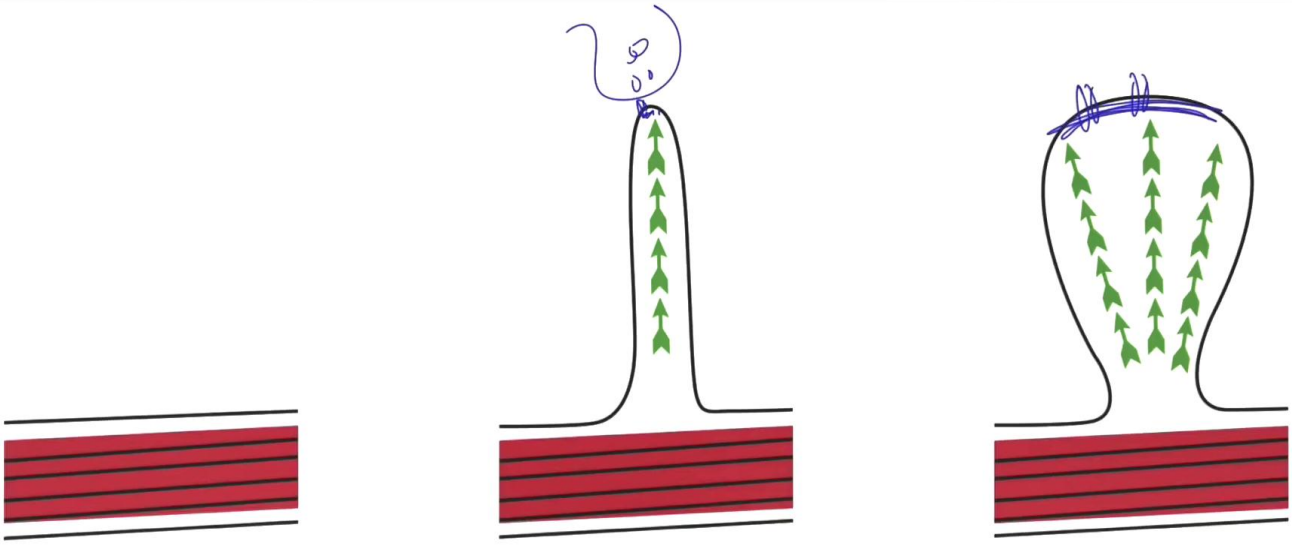
Now this is particularly interesting because this also underlies, or at least is thought to underlie, the formation of the dendritic spine. *De novo*, under conditions, for example, of where one tries to induce long-term potentiation, there are conditions where new spines can appear where there used to not be any. Here we are looking at a piece of dendrite — some manipulation has been done, there may be a change in sensory experience to the animal, or we might be thinking about a brain-slice dish experiment where some glutamate has been released in this area, and that then induces a signaling process where a spine might grow. So the polymerization of actin will then push out a membrane here and would then begin the process of forming a synapse which may be reaching out to the presynaptic nerve terminal. If that synapse turns out to be successful and useful and is perhaps further strengthened by additional long-term potentiation, there would then be a spine growth process, where more actin polymerization would induce an enlargement of that spine.

Notes

Summary

15m 34s

Spine motility



Cellular Mechanisms of Brain Function

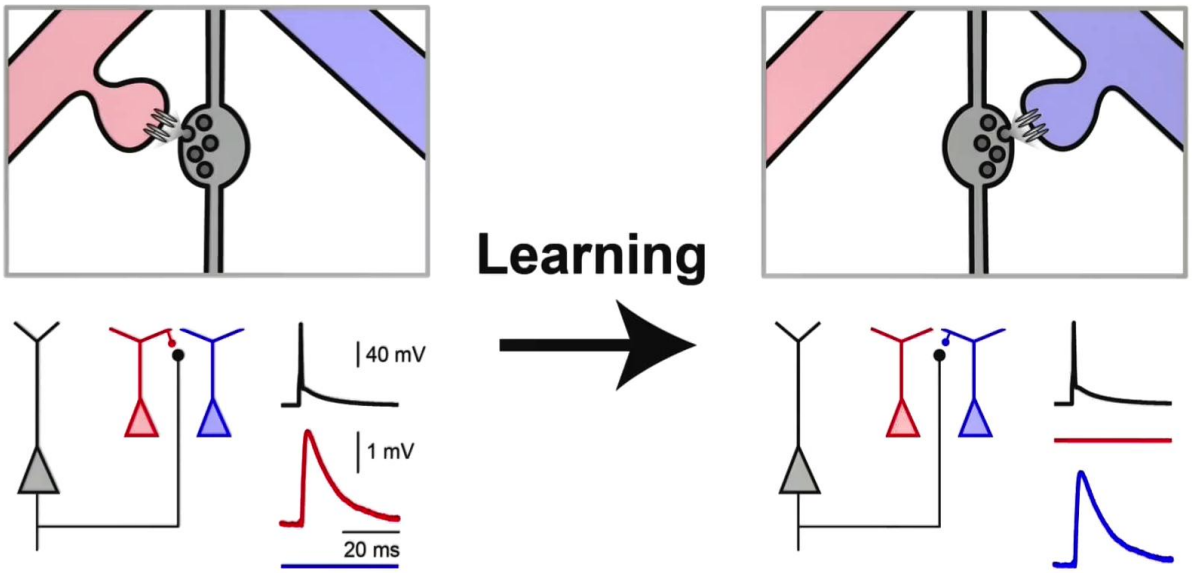
So we move from the thin, filamentous type of spines, to the mushroom, large type of spine here, where we can have a large postsynaptic density with very many glutamate receptors sitting here, and a major important impact of this synapse, whereas this one might just have one or two ligand-gated glutamate receptors and so this might just be more an exploratory type of synapse that has a relatively small impact upon the soma.

Notes

Summary

16m 45s

Dendritic spines for rewiring neuronal networks



Cellular Mechanisms of Brain Function

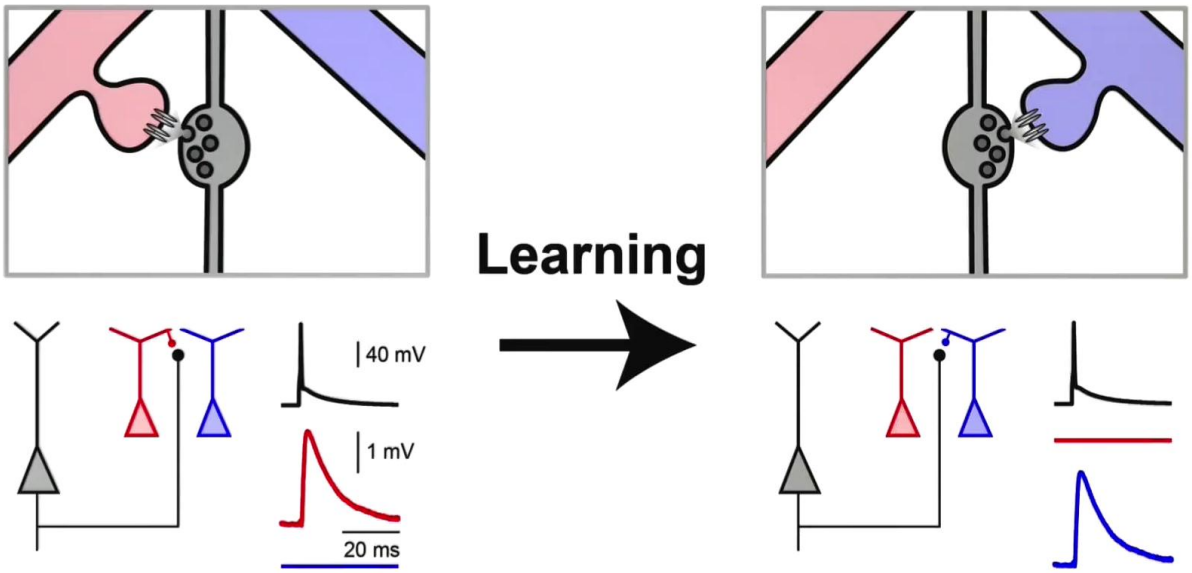
This type of *de novo* spine growth is extremely interesting because it implies that one might be able to rewire neuronal networks through sensory experience. This is the type of theory that people are thinking about. We imagine that there's a presynaptic neuron that sends off its axon into an area here where there are dendrites from two other postsynaptic neurons. The axon has a bouton and in the basal state there's a synapse that's been formed here onto the red postsynaptic cell. It has a spine that grows out here and makes a synapse with the gray axon. So the action potentials release glutamate, activate AMPA and NMDA receptors, causing postsynaptic potentials in the red neuron. That's what you see here: An action potential in the gray cell — here's the action potential — releases glutamate onto the red cell. Then we have a postsynaptic potential in the red cell and the blue cell. There's no synaptic connection so there's obviously no depolarization in response to that action potential. So there's a synaptic connection from the black to the red cell and there's no synaptic connection from the black to the blue cell. Then we envisage some sort of learning experience.

Notes

Summary

17m 16s

Dendritic spines for rewiring neuronal networks



Cellular Mechanisms of Brain Function

The animal has learned something, and something in the brain must change. In this example we imagine that there's a change in the wiring. The black cell now needs to talk to the blue cell. The synapse from the red cell may not be useful anymore. It may retract and disappear. So spines can both appear *de novo* and they can also disappear. In general, there's a turnover where spines are appearing and disappearing at a certain rate, and during learning experiences the rate of change of synapses, or at least of spines, changes dramatically. So we can increase the amount of turnover of spines during learning experiences. Here we imagine that the black cell needs to communicate now with the blue cell, so the blue cell grows the spine, perhaps even to the same bouton as was there already, senses the glutamate, and forms a synapse. Now the black cell, when an action potential is fired, causes a postsynaptic potential in the blue cell, and the red cell — where it used to be connected to — is now unconnected. So we've changed the wiring diagram of the brain in an experience-dependent manner during learning.

Notes

Summary

18m 39s

Dendritic spines

- Dendrites are often decorated with a high density of spines, which are postsynaptic specialisations of excitatory glutamatergic synapses.
- Spines are localised compartments for biochemical signalling, allowing synapse specific plasticity.
- Spine growth and disappearance may be important for rewiring neuronal networks during learning.

Cellular Mechanisms of Brain Function

So we've seen that dendrites of many cells in the mammalian brain are decorated with spines at a very high density. These spines grow one, maybe two micrometers out from the parent dendrite and they form specializations where glutamatergic synapses are made. The spines likely have several important functional roles. One important role is that they may form isolated biochemical compartments where signaling can occur in a synapse-specific way so that signals that result from, say, synaptic plasticity, can be confined to that individual synapse, and we don't change all the nearby synapses on the dendrite, but just that one specific synapse that wants to be altered. So the spine neck provides an important diffusional barrier where signalling can be confined to the dendritic spine of interest. The other important aspect about dendritic spines is that they provide us enormous flexibility in terms of rewiring. There are many axons in the immediate one-to-two-micron vicinity of every dendrite, and by simply growing out a small dendritic protrusion, the spine, you can rewire and get signals from different axons from many different cells, and that can then reconfigure how a neuronal network functions.

Notes

Summary

19m 57s