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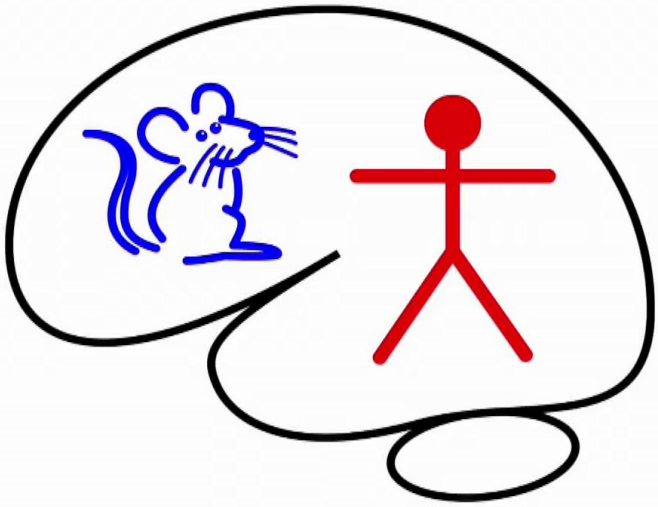
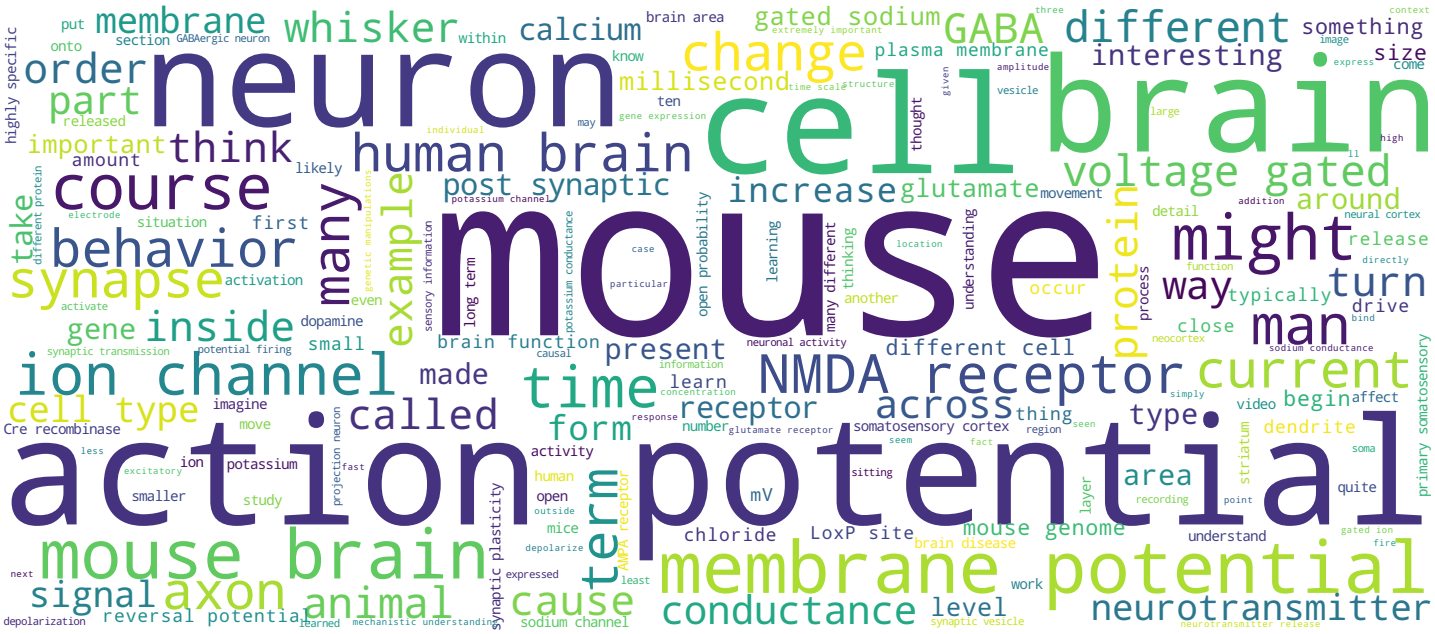


6.2 Man and mouse

Cellular Mechanisms of Brain Function

Prof. Carl Petersen



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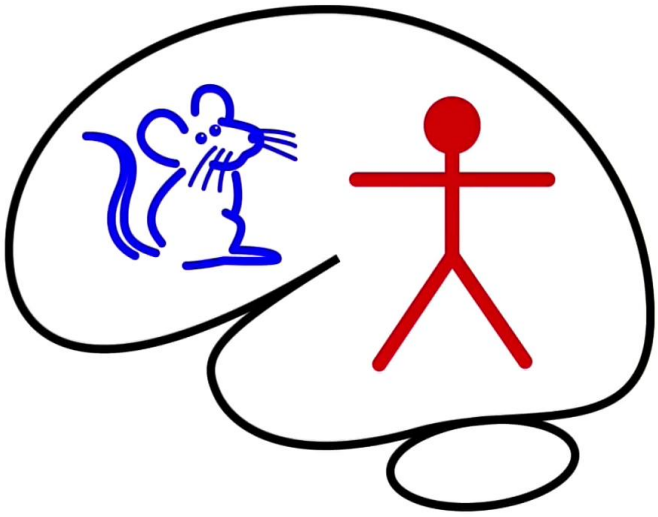
Video

EPFL

Man and mouse



Cellular Mechanisms of Brain Function

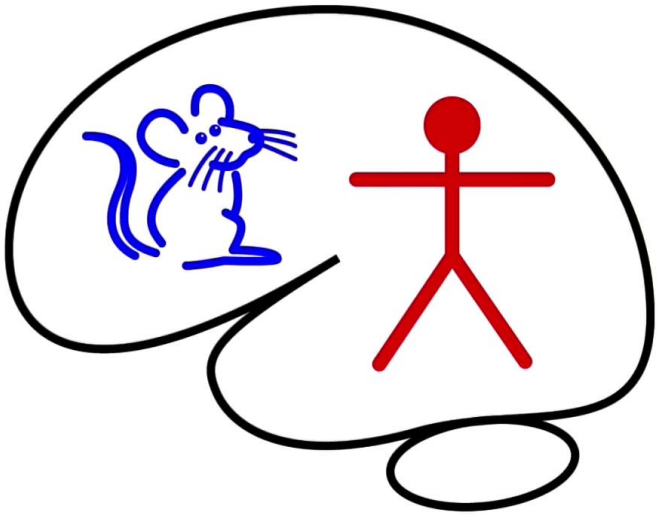
In the last video, we set an important goal for modern neuroscience: to determine the causal mechanisms through which brain function drives mammalian behavior. We thought that there were three key aspects that needed to be done. We need to measure neuronal activity and the synaptic connections between neurons during behavior. We need to be able to manipulate those neurons and monitor the impact upon other neurons in the brain and also, of course, see what impact that has upon behavior. And if we can combine that measurement and manipulation of neuronal activity with sufficient resolution in time and space, then it would be important to quantitatively see to what extent we've really understood how event A causes event B that then finally causes the animal to move, driving a behavior. So how are we going to do that? Many of us, of course, dream of understanding the thought processes of the human brain. We have obvious questions: How do we perceive the world? How do we remember? How do we do the things we like to do? And of course, we're also interested in curing the many brain diseases that affect large populations. Now, it's likely that it'll take a long time before we understand the details of how the human brain works.

Notes

Summary

0m 05s

Man and mouse



Cellular Mechanisms of Brain Function

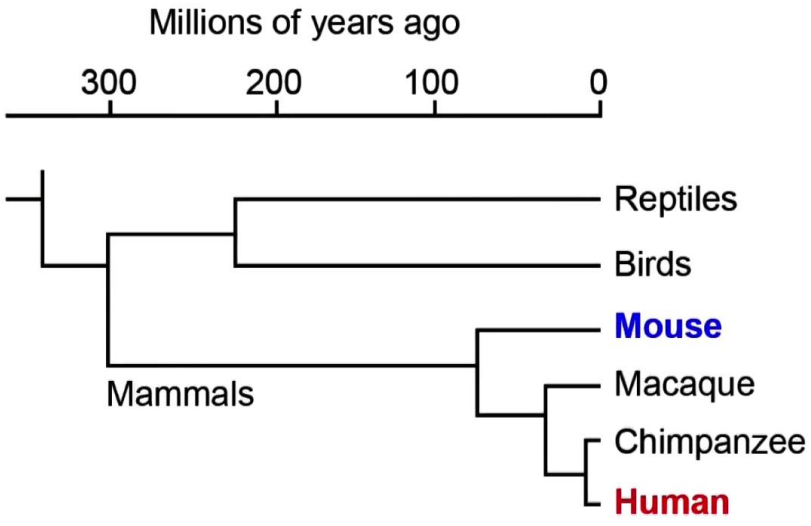
On the other hand, neuroscientists have high hopes that we'll get a detailed causal and mechanistic understanding of how the mouse brain works, perhaps in our lifetimes, and likely within the 21st century. So let's have a look and see how close the mouse brain is to the human brain, and how likely it is that we'll be able to learn from the mouse and translate that into anything that relates to what goes on in the human brain.

Notes

Summary

1m 39s

Evolution



The closest common ancestor between man and mouse is thought to have lived ~80 million years ago.

~99 % of genes coding for proteins have homologs comparing man and mouse.

Cellular Mechanisms of Brain Function

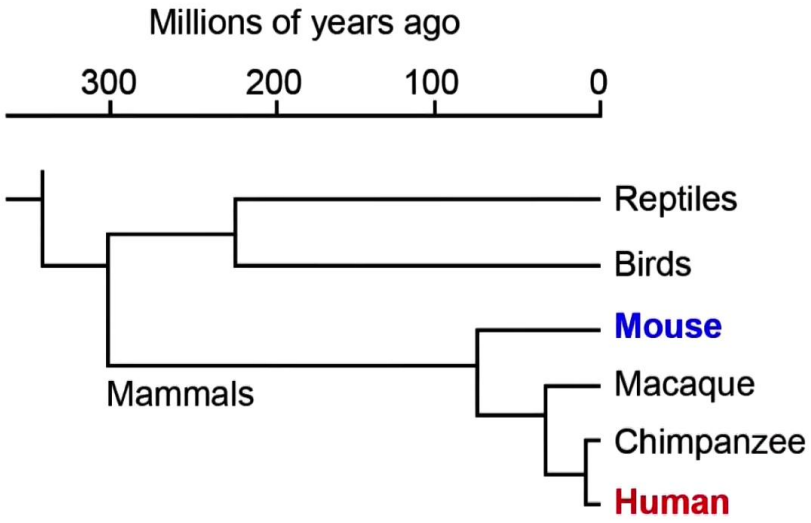
A good starting point, in terms of thinking about man in the context of other animals is to think about evolution. So here we have man that diverged from its common ancestor with the apes, the chimpanzee, for example, some tens of millions of years ago. If we go back some further tens of millions of years ago, we diverge from the monkeys, and here we have within the primates, of course, our closest relatives, and of course, it's extremely interesting to understand the behavior of monkeys and apes and of course, in the context of their brain activity. But, of course, detailed mechanistic investigations into brain function in monkeys and apes is extremely difficult to do. The mouse, on the other hand, diverged some 80 million years ago from man. That's when we had our last common ancestor, and within at least the context of evolution, mouse and man are close to each other compared, for example, to birds and reptiles where the mammals diverge from the rest of the vertebrates some 300 million years ago. So on an evolutionary timescale, mouse and man are relatively close to each other. If we look in terms of the genes that code for the various proteins that carry out functional roles inside our cells, about 99 percent of the genes that are found in man have homologues in mouse.

Notes

Summary

2m 07s

Evolution



The closest common ancestor between man and mouse is thought to have lived ~80 million years ago.

~99 % of genes coding for proteins have homologs comparing man and mouse.

Cellular Mechanisms of Brain Function

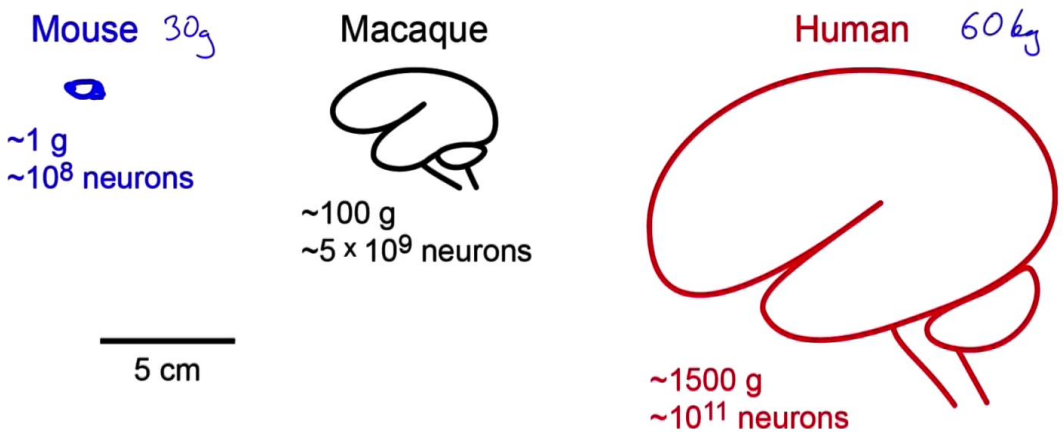
So if there's a given genetic mutation in man that's linked to some disease, there's a 99 percent chance that we can find a homologous protein in a mouse and because of its strong homology in terms of the genetic sequence, it's likely that it's going to be carrying out a related function. So at least from a genetic perspective, mouse and man are very close to each other and we may be able to learn a lot at that level of detail comparing mouse and man.

Notes

Summary

3m 42s

Mammalian brain size



There are big differences in brain size and neuron numbers.
However, many of the organising principles are very similar.

Cellular Mechanisms of Brain Function

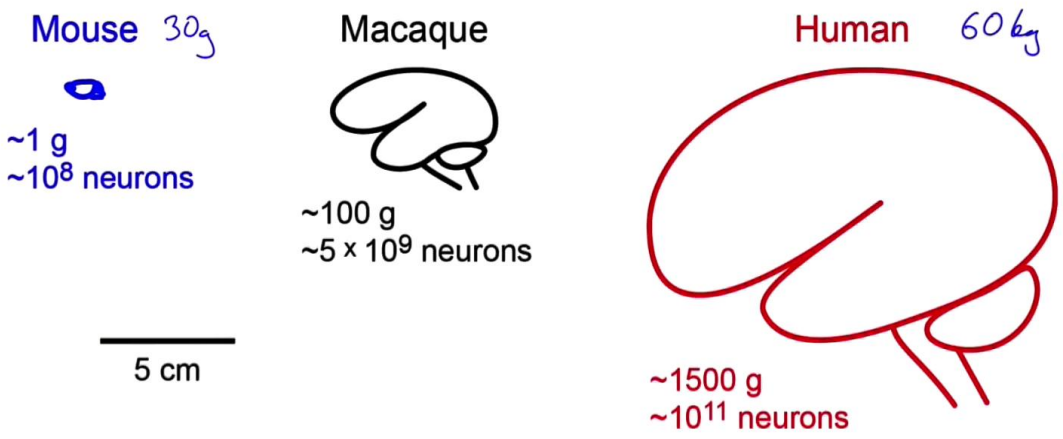
The mouse brain is, of course, different from the human brain. The most obvious difference is in its size. So very much like the overall size of the mouse is much smaller than man's. So mouse typically has a weight of around 30 grams, and a human might have a weight of around 60 kg so there's about three orders of magnitude in terms of the difference in their size of man and mouse. There's also about three orders of magnitude difference in the size of brain, and so the human brain is about 1.5 kg in weight, has some ten to the power of 11 neurons, whereas the mouse brain is much smaller. It's about one centimeter in length dimensions, weighs about one gram, and has some ten to the eighth neurons present in it. So there's about three orders of magnitude difference comparing mouse and man brains, and in the midst of this is the monkey brain that's also used in neurophysiological experiments, and of course, is much closer to the human brain in both size and number of neurons. So there are big differences in the size of the mouse brain, and that scales more or less with the size of the body of the animals.

Notes

Summary

4m 12s

Mammalian brain size



There are big differences in brain size and neuron numbers.
However, many of the organising principles are very similar.

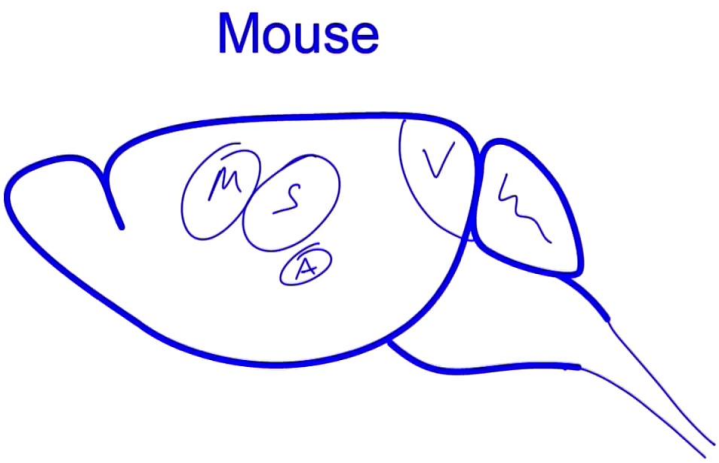
Now in the same way that there's a strong homology in terms of the overall layout of the human body and the mouse body, we have four limbs, we have lungs, heart, kidneys, livers, the internal organs are all the same. There's also strong similarities in terms of the organizing principles of the human brain compared to the mouse brain.

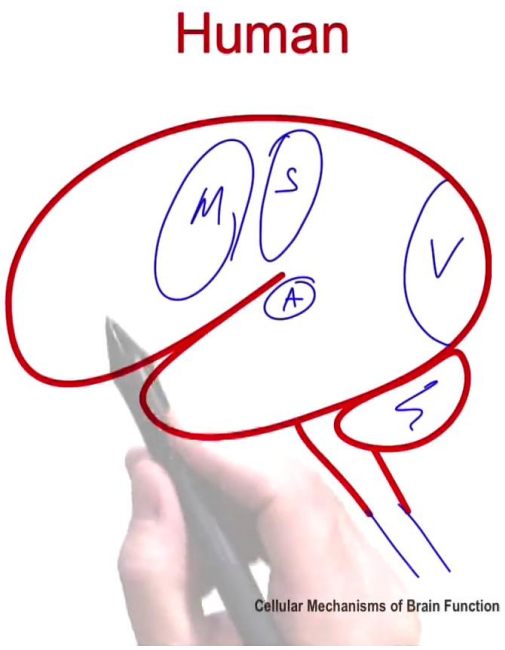
Notes

Summary

5m 28s

Organisation of the mammalian brain





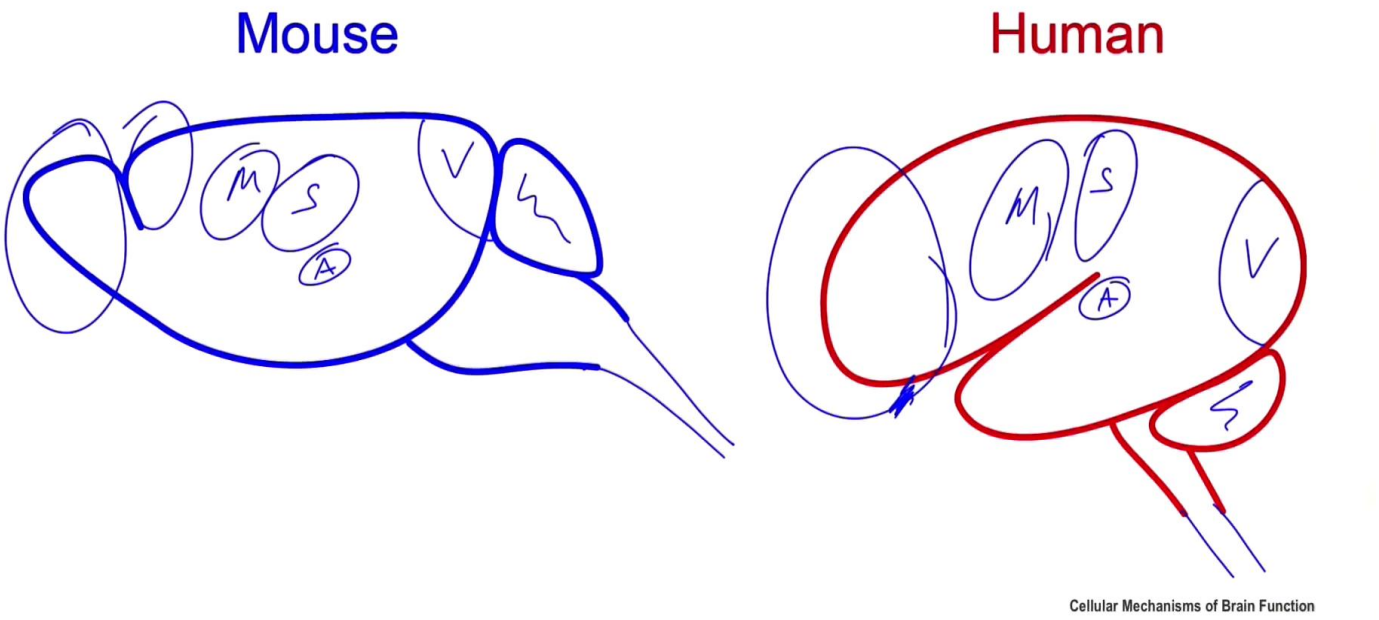
So if we now expand the mouse brain and make it look like it's the same size as the human brain, we'll see that many of the parts are the same. So here we have the spinal cord and of course the human brain sits here on top of the spinal cord also. We have the brain stem and the brain stem, we have the cerebellum of the mouse and the cerebellum of man, and here with a large cerebral hemisphere of human, that also is there in the mouse in the form of a large neural cortex. If we now look at the different subdivisions of the neural cortex, we also see that the organization there is strikingly similar. At the posterior pole of the human brain we have the visual cortex, and that's also where the visual cortex of the mouse is. Our feeling of touch, somatosensation, is located around here in the human brain, and it's also somewhere centrally placed here in the mouse brain. Hearing, the auditory cortex is located somewhere around here, in similarly displaced locations in mouse and man, and the motor areas of the human and the mouse are also similar, with their motor areas being in front of the somatosensory areas in both cases. The human brain has a vastly expanded prefrontal cortex that's relatively small in the mouse.

Notes

Summary

5m 50s

Organisation of the mammalian brain



Cellular Mechanisms of Brain Function

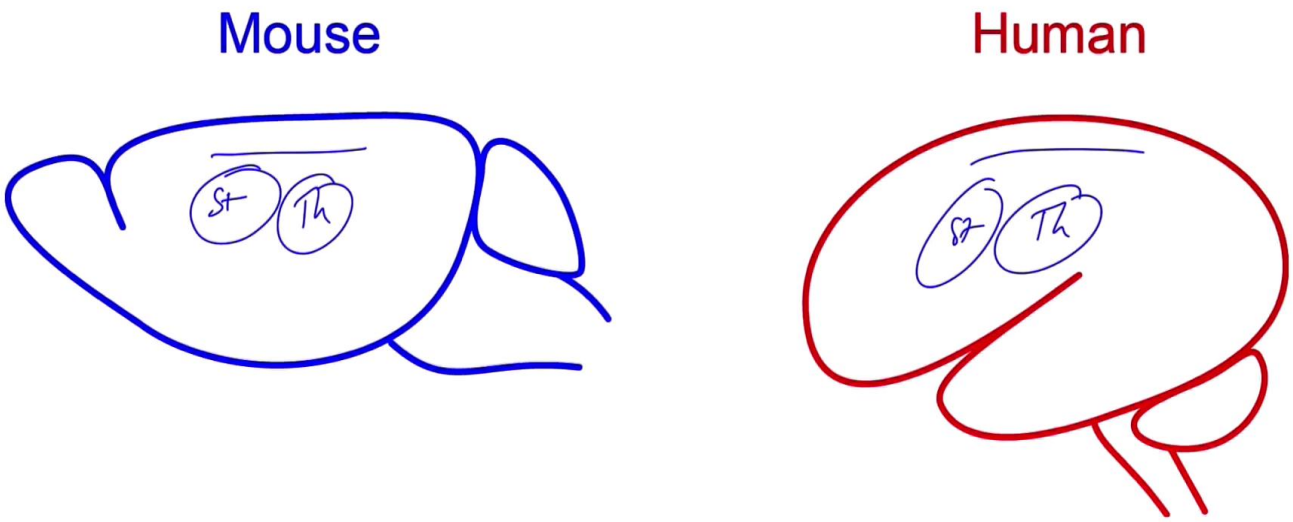
On the other hand, the mouse has a relatively large olfactory bulb that's only much smaller in the man, and only just drawn in here, sketched in this particular diagram now by me. So the overall organization of the brain is extremely similar, even at the level of where different brain areas are processing different forms of sensory information.

Notes

Summary

7m 12s

Organisation of the mammalian brain



Cellular Mechanisms of Brain Function

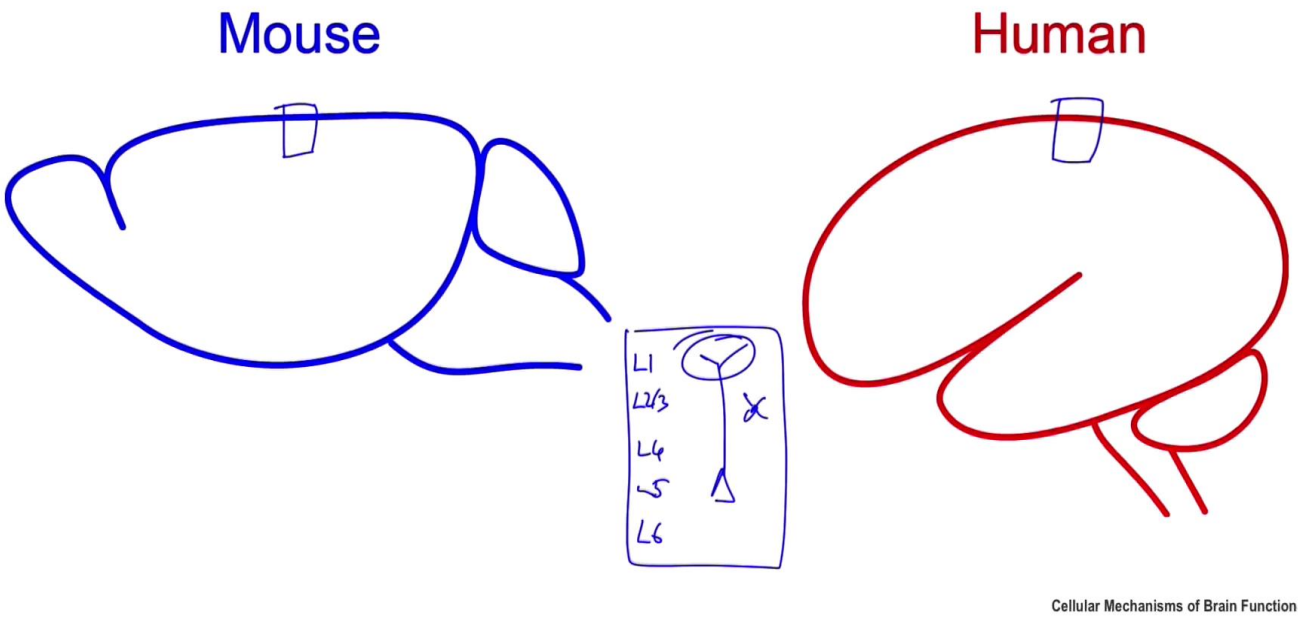
If we look at the subcortical areas. So here we have the outer layers of the mouse brain, the neural cortex, and that's also how it is in the man. The outer layers forming the neural cortex. Below that we have the striatum, we have the thalamus in the mouse, and similarly in man we have the striatum and we have the thalamus located here and there are many other subcortical nuclei that are organized in similar locations, express similar genes, have the same receptors, and apparently, play highly homologous roles comparing mouse and man.

Notes

Summary

7m 35s

Organisation of the mammalian brain



Cellular Mechanisms of Brain Function

So the large scale organization of man and mouse brain is very similar. But even if we look at the details, if we say, zoom in on a patch of neural cortex, we find that there are very similar features. So there are different layers, so the mouse brain is divided into layers that are very obviously different from each other, and you see the same layers in the human brain and the cells that are present there have a very similar structure. So there are large pyramidal cells in layer five in both mouse and man, with big apical dendrites and big dendrites here, tufts, in layer one. Equally, there's GABAergic interneurons present in both man and mouse and there are strong similarities in the organization then, both of cells and at the large scale comparing man and mouse. So by studying the mouse brain, it's likely that we'll learn a lot about how the human brain is organized.

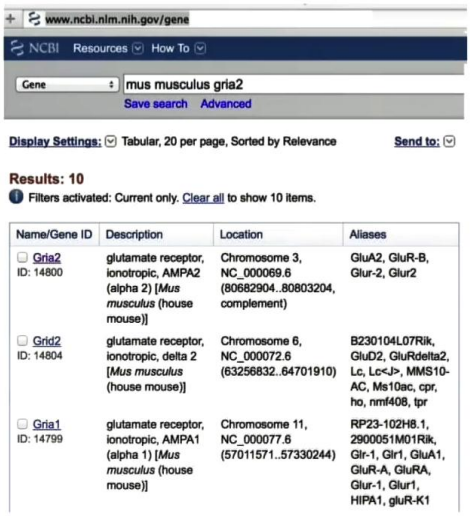
Notes

Summary

8m 08s

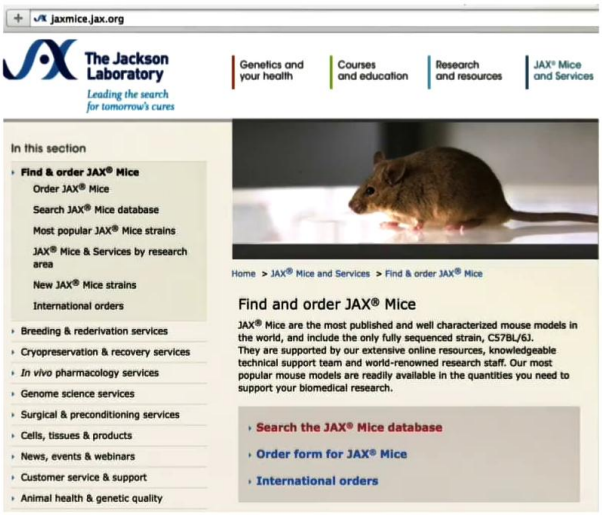
Mouse genetics

www.ncbi.nlm.nih.gov



NCBI - National Center for Biotechnology Information

www.jax.org



Studying the mouse has been greatly helped by a number of large-scale projects that have been undertaken. The Mouse Genome Sequencing Consortium published the mouse genome in 2002 and the entire mouse genome is freely available on a variety of internet websites. And so here from the NCBI, the National Center for Biotechnology Information, you can, for example, search for your favorite gene, perhaps the AMPA Type II receptor is what I've searched for here, and if you do that search you find out that this glutamate receptor is located on chromosome three of the mouse genome. You can click on this and you get the entire DNA sequence for the coding region, as well as the surrounding introns that then gives the promoter sequences for this gene and determine where it's expressed in the mouse brain. So we've learned a lot about the genome sequence of the mouse, and of course, molecular biologists are being able to use that sequence in order to introduce mutations and transgenes into the mouse genome, and so, we can also change that mouse genome. So, for example, if we know of a mutation in a human that's linked to a genetic disease, we can insert that mutation into the mouse genome and study the effects of it.

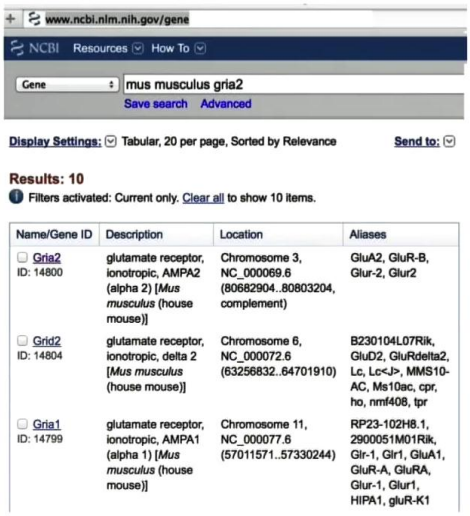
Notes

Summary

9m 06s

Mouse genetics

www.ncbi.nlm.nih.gov



NCBI - National Center for Biotechnology Information

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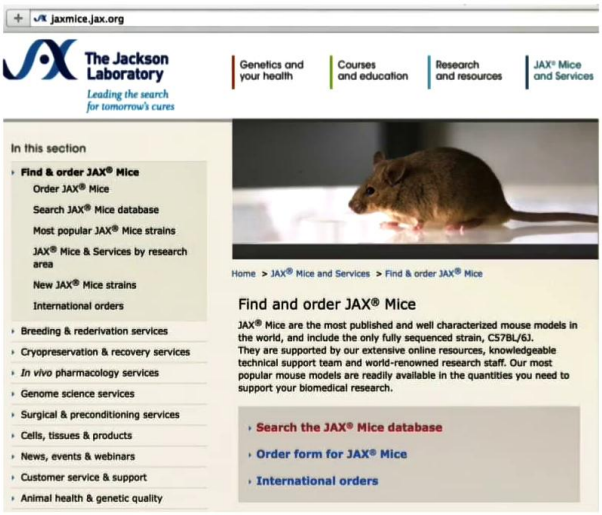


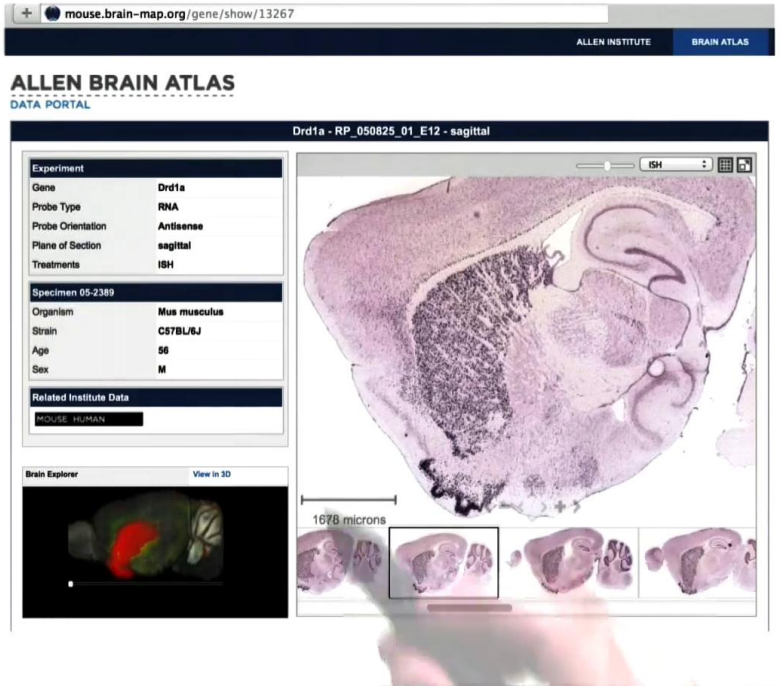
There are of course, many different mouse mutants that have been made for many different purposes to try and help the advances in medical research. Typically, when investigators make mutant mice, they then donate those mice to different repositories which then serve as mouse libraries, and one of the most important ones is the Jackson Laboratory in America, Jax, and if you go to this website you'll be able to see a complete list of the mice that they have. You can search by different genetic mutations or insertions that have been made, and these mice are then a good way in which different researchers can share their resources. So typically when a mutant mouse is made, it's deposited here, and then other investigators can take those mutant mice and investigate them for their own particular purposes. So that's a way in which resources are being shared amongst mouse investigators and that then helps advance research dramatically.

Notes

Summary

10m 26s

Gene-expression maps of the mouse brain



www.brain-map.org

Allen Brain Atlas

Complete gene expression atlas of the mouse brain.

Cellular Mechanisms of Brain Function

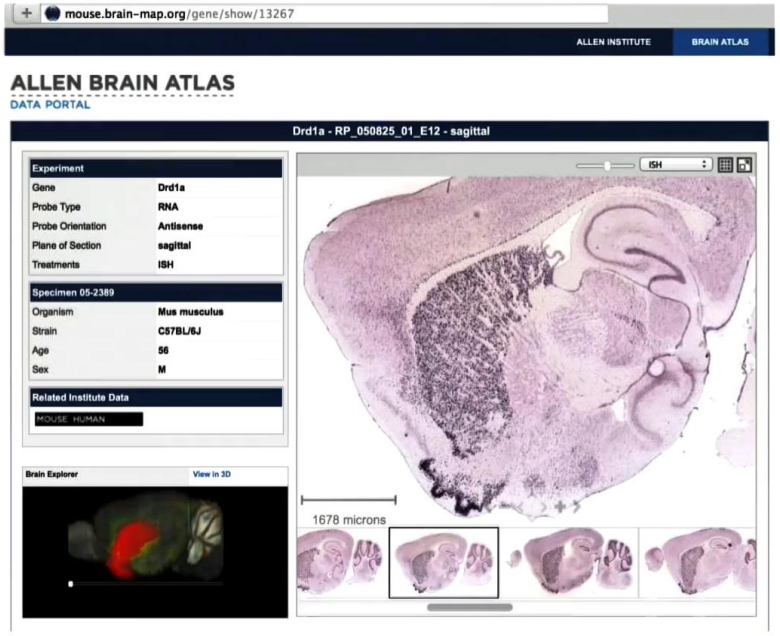
One of the key ways in which we can differentiate different parts of the brain is through gene expression. So in early development as the fertilized egg divides and gradually forms the different specializations of the body, our different organs, our different tissues, that is accompanied by differential gene expression so that's one of the things that differentiates a cell in the kidney from muscle, from brain, is that they express different proteins. They need to do different jobs, and so they express different proteins. And within the brain, there are many different cell types and in part, they can be differentiated through their expression of different proteins and an important advance and tool for investigators looking at the mouse brain has been the Gene Expression Atlas carried out through the Allen Brain Institute and again, freely available on the internet. You can go to this address, you can search for your favorite gene, and you will then see throughout the entire mouse brain where that gene is expressed. So here I've searched for the dopamine type I receptor gene it's stained here through in-situ hyperization of saggital sections of the mouse brain.

Notes

Summary

11m 24s

Gene-expression maps of the mouse brain



www.brain-map.org

Allen Brain Atlas

Complete gene expression atlas of the mouse brain.

I'm showing you one particular section here, and you'll see that these black dots here correspond to individual cells that express the dopamine I receptor. That turns out to be largely restricted to the striatum, something that we already discussed last week with the GABAergic projection neurons located here in the striatum. This, of course, is just one section of the brain. You can look at many other sections and they have the entire 3D structure reconstructed quantitatively in terms of the density of the in-situ hyperdization signal and if you go to the internet you'll be able to spin this around and get a very good feel for the expression pattern of this particular gene. That's, of course, extremely important in terms of understanding the anatomy of the mouse brain, and in terms of thinking about interventions, treatments and molecules that will affect brain function. It's extremely important to know what different proteins are actually expressed, so this Mouse Gene Expression Atlas is serving an extremely important role for neuroscience research.

Notes

Summary

12m 37s

Genetically-defined cell-types

Transgenic or knock-in of GFP, Cre-recombinase, …
Cre-LoxP system for precise genetic manipulation
LoxP = **ATAACTTCGTATA**GCA**TA**CAT**TATACGAAGTTAT**

Highly-specific genetic manipulation in well-defined cell-types.
Essential for causal and mechanistic understanding of brain function.
Cre-LoxP system is part of a family of recombinases e.g. Flp-FRT

Cellular Mechanisms of Brain Function

The expression of different proteins and different cell types of the brain is clearly extremely important in order to understand the function of these different cell types. So one thing that we can do through mouse genetics is to label these different cells through expressing different types of proteins. So for example, we can take green fluorescent protein and put it next to the dopamine Type I receptor in the mouse genome and then the cells that express green fluorescent protein are the same ones that express the Type I dopamine receptor. So we can then cut brain sections and study their electrophysiology and the synaptic inputs onto these D1 expressing neurons. That's an extremely important thing in terms of understanding the role of different cell types in the mouse brain. Even more interesting is the possibility to express other proteins that might be functional reporters, or perhaps enzymes that might act upon other genetic elements, and a great deal of advances have been made through the expression of recombinases that combine different DNA elements and then you can make different genetic manipulations in a highly targeted way.

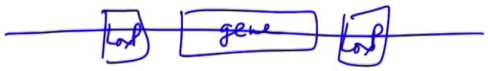
Notes

Summary

13m 42s

Genetically-defined cell-types

Transgenic or knock-in of GFP, Cre-recombinase, …
Cre-LoxP system for precise genetic manipulation
LoxP = **ATAACTTCGTATA**GCATACAT**TATACGAAGTTAT** 34 nt



Highly-specific genetic manipulation in well-defined cell-types.
Essential for causal and mechanistic understanding of brain function.
Cre-LoxP system is part of a family of recombinases e.g. Flp-FRT

Cellular Mechanisms of Brain Function

So I'll briefly describe the so-called Cre-LoxP system that has become extremely powerful for making precise genetic manipulations in the mouse genome. This is something that was first developed from bacteriophage P1 but it doesn't have an endogenous counterpart in the mammalian genome. So we can exogenously insert LoxP sites which are simply DNA sequences of 34 nucleotides long, highly specific sequences, you can insert those into, say, intron sequences that surround a genome. Intra-serve, this is the genome, and we have a gene of interest located here. We can, in intron regions, put LoxP sites surrounding that gene, so that's simply inserting these 34 nucleotide sequences in surrounding elements around where the gene is normally expressed, and doing that, hopefully wouldn't affect the expression pattern of that gene. So the mouse by itself would be wild type and the only thing we've done is to introduce these small genetic elements into regions that flank our gene of interest. Now, what Cre-recombinase will do is to recombine between these two LoxP sites and then remove the gene of interest, creating a knockout.

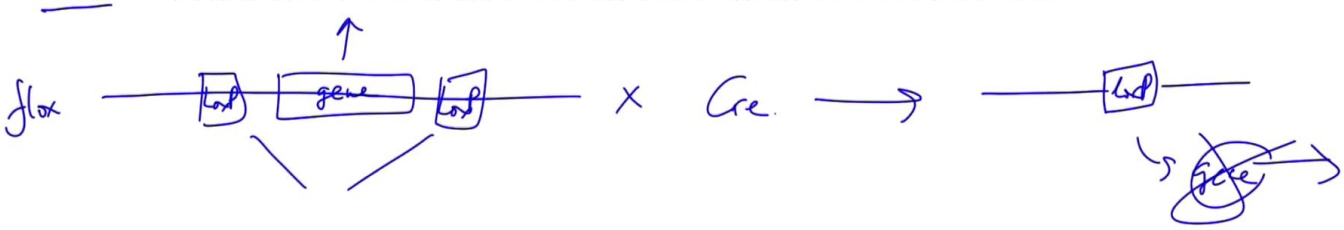
Notes

Summary

14m 57s

Genetically-defined cell-types

Transgenic or knock-in of GFP, Cre-recombinase, …
Cre-LoxP system for precise genetic manipulation
LoxP = **ATAACTTCGTATA**GCATACAT**TATACGAAGTTAT**



Highly-specific genetic manipulation in well-defined cell-types.
Essential for causal and mechanistic understanding of brain function.
Cre-LoxP system is part of a family of recombinases e.g. Flp-FRT

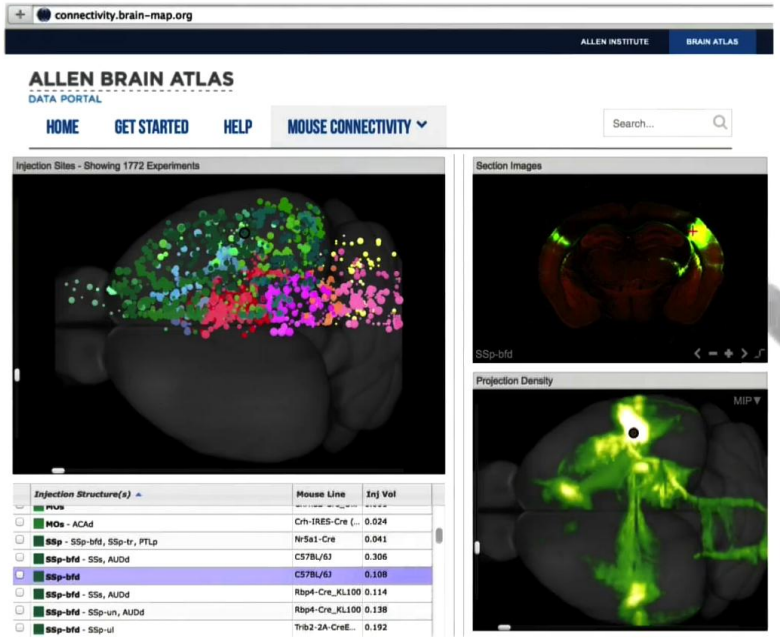
We can do that in specific cells because we can express Cre-recombinase under promoters that express in specific cell types, for example, like in the D1 receptor expressing cells. So we can cross one mouse that has these so-called floxed genes flanked by LoxP sites, we can cross that by another mouse that expresses Cre-recombinase in specific cell types, and in those cell types, but not in the other cell types of that mouse, we'll then create a situation where the LoxP sites recombine and the gene sitting in between those is removed and degraded and knocked out. So we can make very precise, highly specific genetic manipulations in well-defined cell types, and that's something that's really essential for causal and mechanistic understanding of brain function. One of the interesting things is that the Cre-LoxP system isn't the only one, but rather there are many. So for example this Flp-FRT system which is very similar, but acting on different genetic elements and one can then combine the different types of genetic manipulations to get that combinatorial specificity in which one can make multiple independent genetic manipulations, perhaps even in different cell types.

Notes

Summary

16m 22s

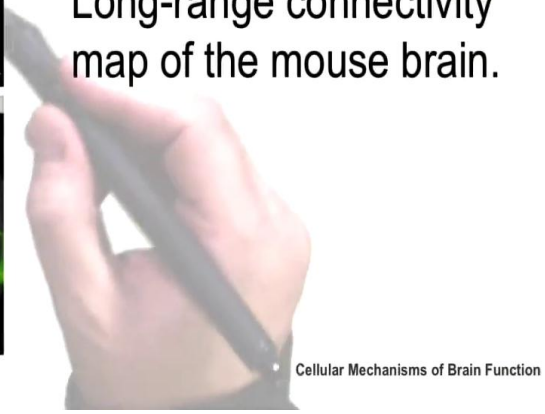
Projection maps of the mouse brain



www.brain-map.org

Allen Brain Atlas

Long-range connectivity map of the mouse brain.



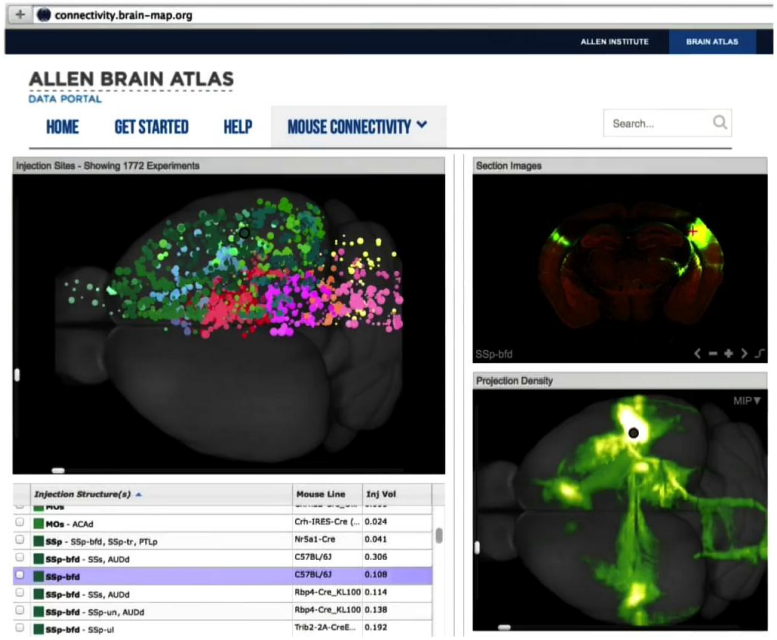
In addition to these interesting advances in the genome manipulation of the mouse, there's also increasing data relating to the connectivity of different brain areas inside the mouse. Again, the Allen Brain Atlas has take the lead here in providing online data for where different cells project in the mouse brain. Here I'm showing you one particular example, where they're looking at the injection site here in the primary somatosensory cortex and injecting their tracer, they then see where axons from neurons located in this particular area of the brain, where they project to, in terms of other parts of the brain. They've made injections of many different parts of the mouse brain. Each one of these dots here corresponds to an injection site from where they're mapping where the axons go from that brain area. And I've selected the primary somatosensory cortex, that barrel field, the whisker representation that we've already thought a bit about in previous weeks. So here's what the data looks like.

Notes

Summary

17m 44s

Projection maps of the mouse brain



www.brain-map.org

Allen Brain Atlas

Long-range connectivity map of the mouse brain.

Cellular Mechanisms of Brain Function

They've made an injection of their tracer into this area here, the primary somatosensory cortex of the mouse, and in this cornal section of the mouse, you see that the axons go to the striatum, they go to the thalamus, they go to the contralateral somatosensory cortex, and if we now look at some of the whole brain view, and again, if you go to the website you'll be able to spin this around in three dimensions and get really quite a good impression of where these axons are going, you'll see that the primary somatosensory cortex projects to motor cortex, contralateral cortex, striatum, thalamus, and also there are descending projections down here to brain stem. So we're beginning to get quite a good idea about which brain areas are connected to which other brain areas, and that's obviously of key importance to get a causal and mechanistic understanding about how the mouse brain processes sensory information and how that might lead to behavior.

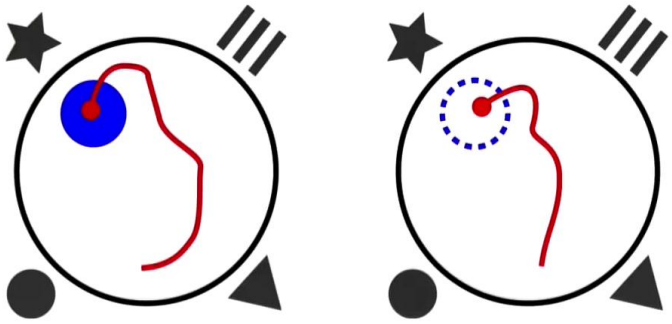
Notes

Summary

18m 47s

Mouse behavior

Morris water maze



CA1 knockout of NMDA receptors

CA1-Cre
x
Flox-NR1

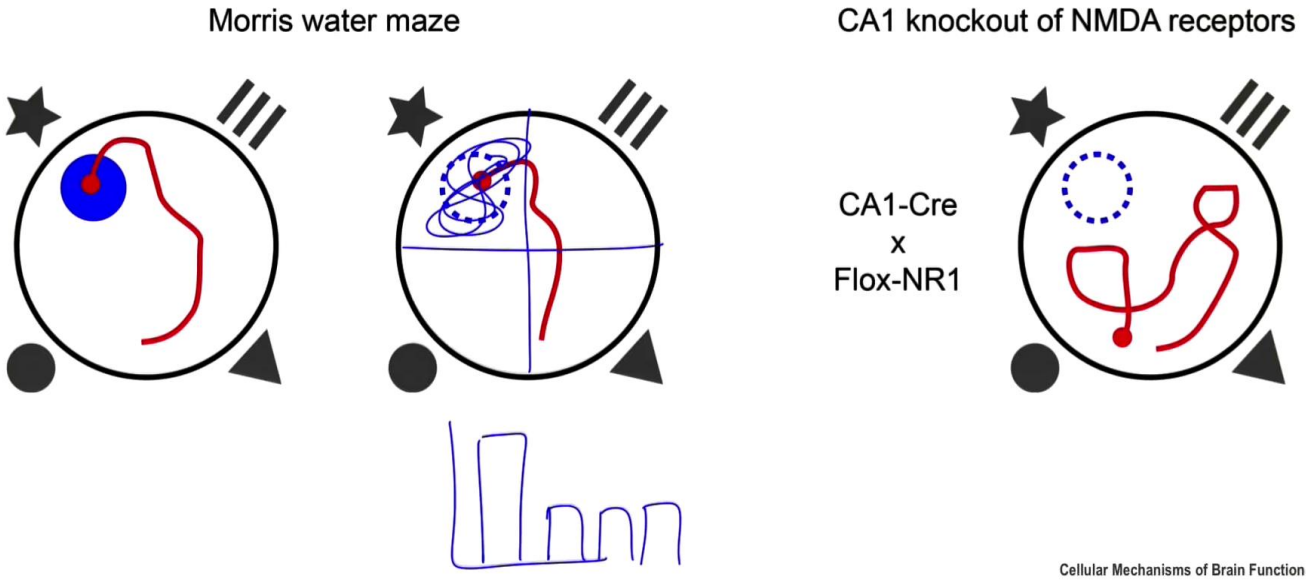
Cellular Mechanisms of Brain Function

So in order to link what we've learned about the mouse brain with behavior, we clearly need to study mouse behavior in quite some detail. One of the more interesting things that the brain can do is to learn and remember things, and an important behavioral paradigm, then, tests learning and memory, and one of them is the Morris Water Maze. In the Morris Water Maze experiments, a mouse is put inside a swimming pool that's been filled with opaque water. The mouse will then swim around and eventually it finds that there's actually a hidden platform where it can stand on, and swimming is a rather exhausting task for a mouse, so it's rather happy when it gets here to the submerged platform where it can then stand and relax, and gradually, over days, as the mouse is put in it learns to swim more and more directly to this hidden platform guided by visual cues that are placed around it. So in this example, it'll learn to swim more and more directly towards the star, and that's how it'll locate the hidden platform. On a transfer test day, the platform's removed and the mouse is again placed inside the swimming pool and it swims around, and if it's learned correctly that the platform's located here, in this environment around the star, it'll swim around in this area here searching for where that platform might be.

Notes

Summary

19m 40s



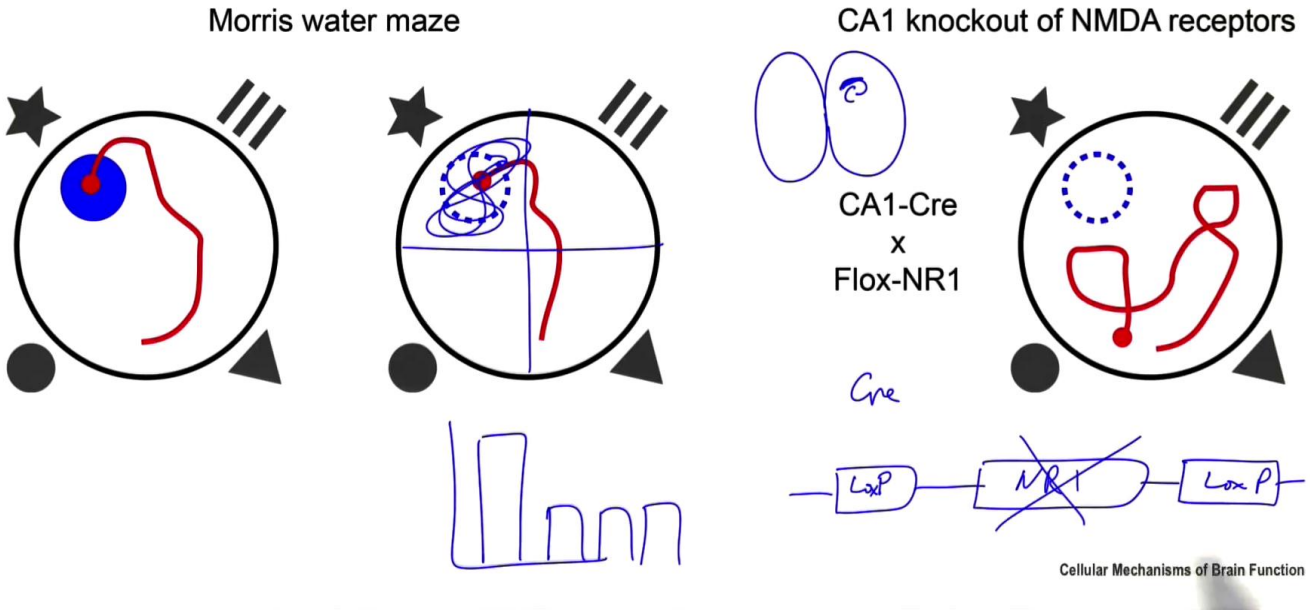
So one can then quantify the amount of time that the animal spends in this target platform relative to the other quadrants, so you see okay, it might spend a lot of time here in the target quadrant and much less time in the three other quadrants, and then we can quantify to what degree the mouse has learned the behavior and remembered it. So that's a way in which we can test learning and memory in mice. Now, we can connect that to the specificity of the genetics that we've been talking about and in 1996 Susumo Tonogawa and his laboratory created a rather interesting mouse that tested some of the things that we've been discussing. When we were discussing glutamate receptors, we had time to think about long term synaptic plasticity and at that time we said that probably was the basis for learning and memory. One of the key experiments that supported that has been this experiment here, where genetic knockouts, deletions of NMDA receptors have being carried out in highly specific brain areas. So we discussed that the NMDA receptor during the concomitant activity of presynaptic release of glutamate and postsynaptic depolarization, the magnesium popped off the NMDA receptor allowing calcium to enter, and that would then start off plasticity processes that might then encode memories.

Notes

Summary

21m 05s

Mouse behavior



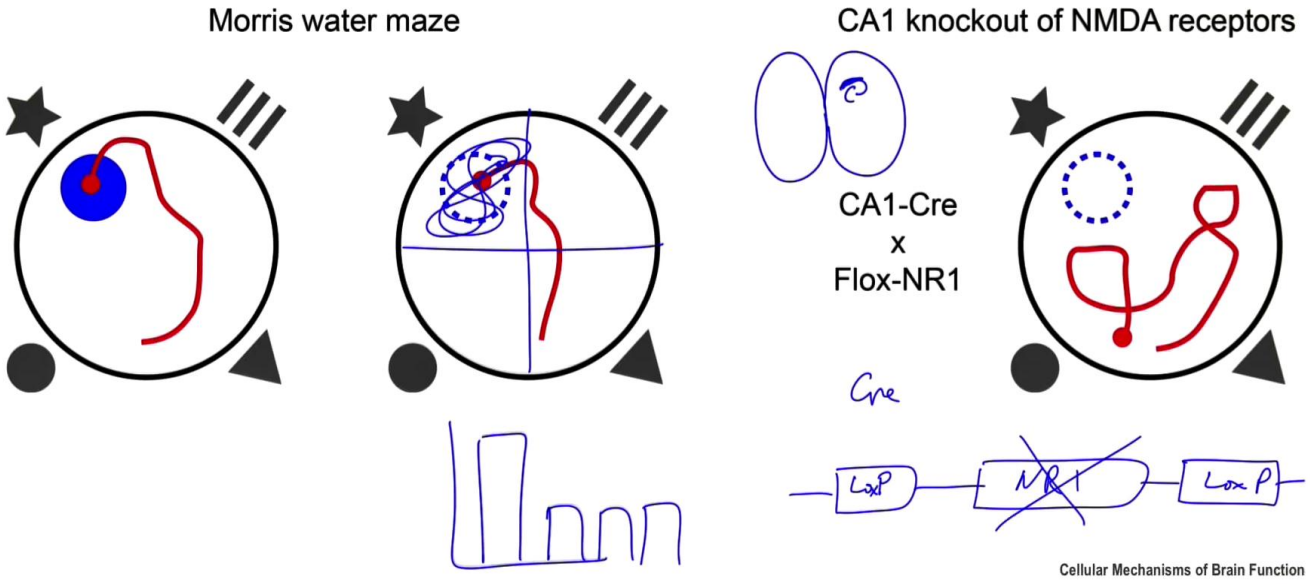
In this particular experiment, the Tonagawa lab created mice where the LoxP sites were surrounding the NMDA receptor type I gene. So this is the one that's absolutely critical for NMDA receptor function. They put LoxP sites surrounding the NR1 gene, in the presence of Cre-recombinase that would then knock out the NMDA receptor but in other cells that were not expressing Cre-recombinase, this would be wild type because the LoxP site is in introns, and doesn't affect the expression of the native NMDA receptor. The Cre-recombinase was expressed in a highly specific way inside the brain. It was expressed post-natally and only in a small part of the brain called the hippocampus, so there's a so-called CA1 region of the hippocampus that's located around here, and cells in this area are known to encode space. So they are so-called play cells that were discovered by the 2014 Nobel Prize winner, John O'Keefe, that encoded the location of where the animal is in space, and it's thought that the reason that the animal learns these place representations is through long-term synaptic plasticity. They can then use that spatial information to navigate and find where it is in terms of carrying out this spatial memory task.

Notes

Summary

22m 26s

Mouse behavior



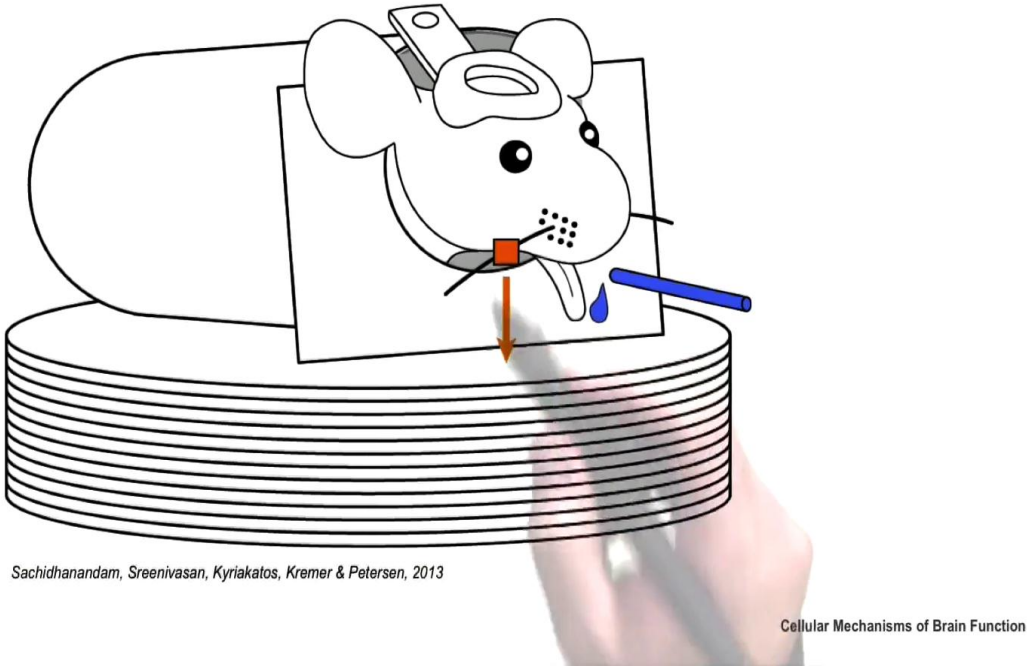
So when the Tonagawa lab made these CA1 specific NMDA receptor knockout animals, they put them through the Morris Water Maze learning and on the transfer test day, the animal would swim around and have no recollection that the platform would be near its supposed location here, in this example, by the star. So learning and memory was disrupted by knocking out NMDA receptors in this highly specific area of the mouse brain thought to encode the spatial location and that then gives us strong genetic evidence for the role of synaptic plasticity in NMDA receptor function in forming memories. So that's one interesting behavior that's been studied in some detail in the mouse, and begins to give us confidence that we are on the right tracks in terms of understanding simple aspects of mouse learning and behavior.

Notes

Summary

23m 49s

Head-restrained mouse behavior



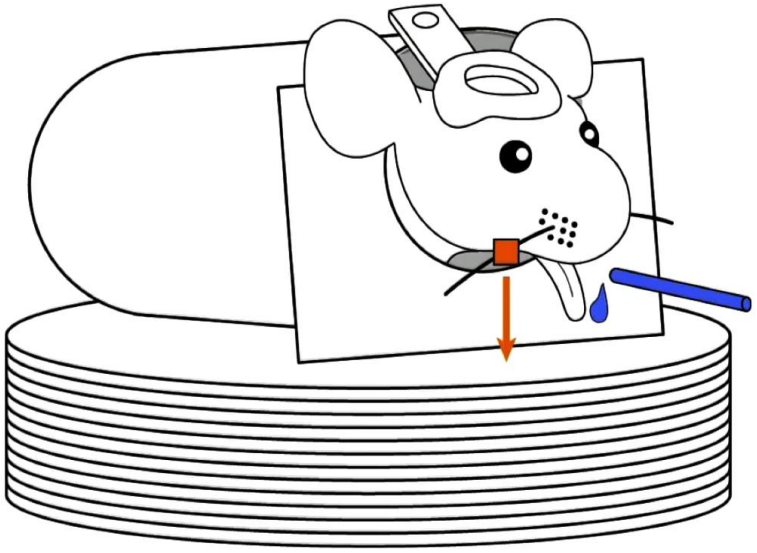
Making neurophysiological measurements while mice are swimming in the Morris Water Maze is relatively difficult, so investigators have also been working on simplifying the behavioral tasks and also providing a more highly-controlled environment in terms of the sensory inputs that the mouse will receive. One of the key steps has been to develop head restraint mouse behavior where metal implants are placed on the head of the mouse and that then stabilizes the mouse brain to the level that there are only microsecond level movements of individual nerve cells. So we can make high quality neurophysiological measurements, electrophysiology and imaging of the mouse brain and the mice rapidly adapt to this head restraint behavior and they show no obvious signs of discomfort. So in one particular paradigm we've investigated sensory perception through these whiskers. So we put small pieces of metal on the whisker. The animal is placed on top of an electromagnetic coil, and we can give one second pulses onto this whisker, and the animal learns that those one millisecond deflections of the whisker predict reward availability if the animal licks a reward spout.

Notes

Summary

24m 42s

Head-restrained mouse behavior



Sachidhanandam, Sreenivasan, Kyriakatos, Kremer & Petersen, 2013

Cellular Mechanisms of Brain Function

So here we can begin to study mechanisms of motivation, reward based learning, and sensory perception in a highly controlled manner. And we can get to that causal and mechanistic understanding of simple behaviors in a head restrained mouse. Other laboratories are making more sophisticated head restraint mouse behaviors where an animal might be running on a floating trackball and navigating a virtual visual environment. So there's a great deal of excitement in the neuroscience community right now about the head restrained mouse as a way of linking genes' behavior and neurophysiology at that level where we might get a causal mechanistic insight as to how the brain really works.

Notes

Summary

25m 53s

Brain dysfunction

Brain diseases make a big impact upon the world,
both at the level of individuals and for society as a whole.

A key goal for neuroscience is therefore to develop better treatments for brain diseases. In order to improve our ability to repair the brain it would be helpful to understand more about it.

Challenge: can we develop *rational* therapies for brain diseases?
Translational neuroscience research: mouse ➔ monkey ➔ man

Cellular Mechanisms of Brain Function

So there's a great deal of interest in understanding the mouse brain from a purely scientific point of view where we're really addressing one of the main frontiers of human knowledge. Another major reason for studying the mouse brain, of course, is to try and understand the mechanisms of brain dysfunction with the hopes that we might be able to provide cures or at least new treatments, so brain diseases make a big impact on the world, both at the level of individuals and for society as a whole. So a key goal for neuroscientists is to develop better treatments for brain diseases, and clearly, in order to improve our ability to repair the brain, it's really helpful to understand what's going on inside the brain. So a challenge for many neuroscientists is to see if we can develop rational therapies for brain diseases. So in the field of so-called translational neuroscience research we might have a genetic mutation that is linked to a human brain disease and you put that genetic mutation inside the mouse. There we can study the causal impact of that genetic lesion and see what difference it makes to the brain cells, their connectivity, and also their function during behavior.

Notes

Summary

26m 37s

Brain dysfunction

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Cellular Mechanisms of Brain Function

One can then begin to develop therapies that in the first instance work for that mouse model of the disease, and if that works in the mouse, one might then think of seeing whether that also works as a therapy in monkey models of the same disease, and if we have these two scales over which that treatment works, then, of course, it becomes extremely interesting to try and see if we can translate that to humans and the hope, of course, is then that we provide rational therapies for the large number of brain diseases that cause such trouble for mankind.

Notes

Summary

27m 50s

Cellular mechanisms of mouse brain function

- Understanding the mouse brain will likely provide clues about the workings of the human brain.
- Large-scale efforts in mouse genetics and brain mapping are helping to accelerate research.
- The mouse is well-suited for detailed causal and mechanistic study of brain function during simple behaviors.

Cellular Mechanisms of Brain Function

And so in this video we've seen that understanding the mouse brain might provide clues as to how the human brain works. Investigating the mouse brain has been helped by large scale efforts in terms of molecular biology, gene expression patterns, also in terms of connectivity and general organization of the mouse brain. And so, research in the mouse is developing at a rapid rate and there's now growing excitement about the ability to connect that basic fundamental knowledge about proteins, molecules, cells, wiring diagrams, with the behavior of the mouse. We're now beginning to see the causal and mechanistic underpinnings of behavior at the level of cells and synapses by studying the mouse. Over the next videos we'll look at more of the details about how, technically, we make measurements from the mouse brain during behavior and how we can also manipulate and control the neurons in the mouse during behavior.

Notes

Summary

28m 28s