Module:
Biological Foundations of Mental Health

Week 4
Biological basis of learning, memory and cognition

Topic 2
From the dynamic synapse to synaptopathies – Part 4 of 4

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Slide 3:
In the final part of this lecture, I would like to explore synaptic deficits in schizophrenia and one way we can study genetic mutations and link them with abnormal dendritic spine function.

Slide 4:
I would like to now focus on how we believe dysfunction of dendritic spines may contribute to mental illnesses. In order to explore this question, I want to focus on schizophrenia. This mental illness is a highly complex disorder. Indeed, schizophrenia is a chronic disease that significantly impacts the psychological and the social and cognitive functioning. It affects approximately 1% of the population.

At the clinical level, it is described as having positive symptoms – such as hallucinations and delusion, negative symptoms – blunted affect, avolition, asociability – as well as thought disorders. Working memory deficits or other cognitive deficits seem to be incorporated into these thought disorders. Most importantly, schizophrenia is a heterogeneous disorder. That is, the symptoms that one patient displays may be very different to what another patient experiences.

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Current treatments for schizophrenia rely on the use of antipsychotic drugs such as haloperidol, olanzapine and clozapine. These drugs are particularly good at addressing the positive symptoms that are associated with schizophrenia in the majority of patients. However, about a fourth of patients are non-responsive to this type of drug treatment. In addition to this, antipsychotics have little impact on the negative symptoms seen in schizophrenia as well as on the thought disorders for cognitive deficits associated with this disorder. This has major implications, in terms of the functional recovery of the patient, as it seems that the severity of the negative and cognitive symptoms of schizophrenia that seem to be most associated with the functional recovery of the patient. Furthermore, there are a number of severe side effects including sedation and weight gain as well as even motor deficits, which, again, seem to have a negative impact on patient functional recovery.

There are a number of other approaches to treating schizophrenia, such as behavioural treatments, including cognitive behavioural therapy. This is an approach that has been used as an adjunct to antipsychotic drug treatment and can be effective in reducing relapse and resistant symptoms. However, these behavioural therapies have little impact on the negative and cognitive symptoms that are associated with schizophrenia and, therefore, they have little impact on the patient's functional recovery.

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So, how do we go about trying to understand what may be causing the negative and cognitive deficits in this disorder? And how can we make more effective and safer therapies for this disorder?

Well, one thing we can do is to start looking at the neuropathology of the disorder. So, what do we know about the neuropathology of the disorder? Well, actually, we don't know very much, mostly because there are many inconsistencies between studies. However, what is agreed upon by many is that there are reductions in the grey matter or patients compared to unaffected individuals.

Here we have structural MRI images of brains of healthy individuals or those who are suffering from schizophrenia. And we can see that there seems to be a difference in the overall volume of the brain of schizophrenic patients as compared to the healthy individuals. In addition to this, EEG and MEG studies have suggested that there is a dysfunction in neuronal network function in schizophrenic patients. And, as we've seen already before, post mortem human studies suggest that there may be a reduction in the number of dendritic spines in patients with schizophrenia as those compared to healthy individuals.

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The cause or causes of schizophrenia is likely to be multifaceted and likely involves a range of genetic as well as environmental factors. Each of these factors are unlikely to cause the disease by itself. But, a combination of both genetic and environmental factors would likely increase the chance of an individual developing the disease. While a number of environmentals have been linked with an increased risk of developing schizophrenia, there is also a very strong genetic component to this disease. This topic will be covered in more detail elsewhere in this course. But for now, what I would like to highlight is that the genetic landscape of schizophrenia is highly complex.

Genetic studies indicate that there are a large number of mutations that are associated with schizophrenia. Some of these mutations are very rare, only occurring in fewer than 1% of patients with schizophrenia, but they have a strong effect. That is, if you have this mutation, you are more likely to have the disease. Conversely, there are a large number of genetic variants that have a weak effect. That is, they only slightly increase your chance of developing the disease. Taken together, we believe that it is a combination of environmental and genetic factors, both rare and common variants, that combine to underlie schizophrenia.

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So, how do we go about testing this theory that mutations in genes associated with schizophrenia can result in altered synaptic structure or function and, therefore, impact brain wiring? Well, the two most commonly used approaches are to either use animal models – where the gene of interest has been knocked out or mutated – or to use primary neuronal cell cultures – where cells are grown in a dish and we, again, manipulate the expression of genes to try and understand the role that the protein may play in controlling synaptic structure or function.

Both of these experimental approaches have their benefits as well as their caveats. For example, using an animal model, we can not only look at the overall morphology of the cell, but we can also examine how altering the expression of specific genes may impact the behaviour of an animal. But you may also argue, that how can you model the behaviour of an animal with schizophrenia? Whereas, on the other hand, looking at primary neuronal cell cultures, it is a very easy way to manipulate gene expression and also allows you to examine dendritic spines in quite a bit of detail.

Slide 9:
Let's take the approach of growing neurons in a dish and explore how we can use this experimental approach to examine or model synaptic deficits in schizophrenia. What we can do in this approach is to grow neurons on a glass coverslip. And, then, using some clever molecular biology, we manipulate the expression of our target gene. After this, we can use a microscope to image the morphology of the neuron and then to perform detailed analysis of the dendritic spines.

Slide 10:
Let's take a real-life example of this approach. In this experiment, we have chosen to target the DISC1 or 'disrupted in schizophrenia one' gene. This gene encodes for a protein that is found in dendritic spines and is involved in a number of processes at the synapse. The mutation in this gene has been linked with a range of psychiatric disorders, including schizophrenia, autism spectrum disorders, depression as well as a number of other disorders. It was first identified in a Scottish family where a number of individuals were found to have mutations in this gene and to also have schizophrenia or bipolar disorder. Mutations of the DISC1 gene often seem to result in a reduction in the expression of the protein or in a dominant negative effect.

So, in order to test whether this one protein is important for regulating dendritic spine number – and, therefore, wiring within the brain – we decided to try and reduce the expression of DISC1 in cultured neuronal cells – or cells grown in a dish – and to compare them with a control cell. Hopefully, you can see here a control cell and, if we zoom in on the dendrite, you can see the dendritic spines that are shown here with the red arrows. However, in cells where there's a reduction in the levels of DISC1, you can see that there are fewer dendritic spines – as shown with the red arrows.

These data are consistent with a number of previous studies that have shown the same effect using a wide range of different approaches. And, simply put, this experiment allows us to say that by reducing DISC1 levels, we can negatively impact the number of dendritic spines. This allows us, therefore, to suggest that DISC1 plays an important role in, at least, the maintenance of dendritic spines. And, therefore, alterations in the expression of DISC1 protein, as seen in patients with various psychiatric disorders, may impact the synaptic connectivity within their brain.

Slide 11:
In this lecture, we have covered what the basic function of dendritic spines are, what their overall structure is and what they contain. We have explored how dendritic spines are the site for where the majority of excitatory synapses occur and discussed the model whereby dendritic spines can form new synaptic connections.

We then went on to investigate in more depth, the idea that dendritic spine structure is strongly linked with synaptic function and that changing these two parameters are coordinated in response to different stimuli. We then went on to examine the evidence that dysfunction in dendritic spine function – and, therefore, altered synaptic connectivity – was linked with a number of neurodevelopmental and psychiatric disorders.

In particular, we focused on evidence coming from genetic studies that implicate these structures in the pathogenesis of disease. Finally, we touched on some of the approaches whereby we can test the hypothesis that dendritic spine dysfunction may contribute to a complex disorder, like schizophrenia. Moreover, I have tried to show you that we could test the idea that altering the expression of proteins associated with disease, allows us to see how these proteins may contribute to the pathophysiology of disorders, such as schizophrenia.