Module:
Biological Foundations of Mental Health

Week 4
Biological basis of learning, memory and cognition

Topic 3
The effects of activity, experience and deprivation on the nervous system – Part 2 of 5

Dr Sam Cooke
Lecturer in Neurobiology of Neurodevelopmental Disorders, Basic and Clinical Neuroscience, King's College London

Slide 3:
Now, let's move on to thinking about how Hebbian plasticity could explain the effects of activity on the nervous system during postnatal development.

Slide 4:
The neocortex is a six-layered structure that exists only in mammals. It's highly plastic and is known to be critical for long-term memory. The primary sensory regions of neocortex are by far the best studied and understood regions of the neocortex because, first, they receive relatively unprocessed sensory information, which is relayed from the relevant sensory operators – usually via very few intermediary structures. Second, they potentially provide a general model of neocortical function because they contain all the key circuit and molecular elements that are found in higher-order regions, such as prefrontal cortex. Third, their structure and function are relatively well understood and often exhibits visible specialisations that reflect its topographical organisation as a spatial recapitulation of the sensory world.

For instance, in this slide, you can see a stained surface mount of three primary sensory areas in mouse neocortex. The primary visual cortex, known as 'V1', the primary auditory cortex, known as 'A1', and the primary somatosensory cortex, known as 'S1'. This view reveals particularly striking anatomical specialisations in somatosensory cortex, known as 'whisker barrels', which are columnar organisations that are each dedicated to input from a single whisker. Thus, it's possible to constrain sensory stimulation to a very specific region of interest and study the plasticity that results.

Slide 5:
For this topic, we're going to focus on the visual system and the similar specialisations, known as 'ocular dominance columns', that exist in the primary visual cortex V1 of most mammals – including primates, such as ourselves, and other well-studied species – notably including carnivore species, such as cats and ferrets.

The organisation of ocular dominance layers in the thalamus and columns in the neocortex have been tracked experimentally using radioactive transsynaptic tracers injected into one eye of an animal. This enabled autoradiographic tracing of this functional segregation, which is seen here in a cat brain. On the left, is a section through the primary visual relay nucleus of the thalamus, the 'lateral geniculate nucleus' or 'LGN', revealing layers that are dedicated to the contralateral eye – which is not injected and, therefore, without tracer present in the thalamus – and the ipsilateral eye – which is injected and, therefore, with tracer in the thalamus.

On the right are two views of primary visual cortex. First, a view from above of visual cortex showing the interdigitated zones dedicated to one eye across the visible layer 4. And, second, a transverse section revealing white matter projections up to V1, showing the restriction of these labelled ocular dominance zones to layer 4 of cortex.

Slide 6:
Here's a schematic of the segregation of ocular inputs and the maintenance of this segregation through the cat visual system, up to primary visual cortex. Spatially segregated zones are dedicated to processing visual information provided through the contralateral eye – in blue – or the ipsilateral eye – in yellow.

The segregation is maintained in the optic nerve and the lateral geniculate nucleus all the way up into V1 where ocular dominance columns are maintained in layer 4, which is the first layer of neocortex to receive the thalamic input. If we now look at the laminar organisation in V1, we can see that intracortical connections integrate these two separated inputs in layers 2, 3, and 5 into binocular representations – which are shown in green.

In this topic, we will address both how segregation in ocular dominance columns of layer 4 can be initiated by Hebbian plasticity and how integration into binocular representations can occur in layer 2/3, also through Hebbian plasticity. Let's start with how ocular dominance columns may arise from activity within the nervous system.

Slide 7:
A key question for neuroscientists has been whether this segregation of function arises from genetic programming, that determines the organisation of the developing visual system, or whether the activity of neurons plays a critical role in the development of ocular dominance territories in the brain, as had been hypothesised by British neuroscientist, David Willshaw.

An important observation came from Lamberto Maffei's laboratory, in Italy, that retinal neurons produce spontaneous activity. And this was followed up by Carla Shatz's laboratory, in the US, who used calcium imaging to show that there were, in fact, waves of activity that passed across the retina. This slide shows an example of such a wave which can be recorded in a dish with a calcium imaging dye and reveals the time course of the progression of a wave of activity across the retina, here taken in time snaps over seconds. These retinal waves have subsequently been a major area of investigation. The retinal waves were found to occur long before the eyes of many species open, an event that usually happens a considerable time after birth.

Slide 8:
A first question to address was, what would be the consequence of inactivating the retina and preventing the spontaneous activity from occurring during postnatal development prior to eye opening? To accomplish this, experimenters turned to toxins that are extracted from the animal world. In this case, 'Epibatidine', extracted from the skin of a species of Ecuadorian frog known as 'Anthony's poison arrow frog', and to 'Tetrodotoxin' or 'TTX', which is taken from the puffer fish and is the active ingredient that numbs the lips of those that eat puffer

fish, a delicacy in Japan. These nerve toxins target different molecular mechanisms. Epibatidine is an antagonist of many different acetylcholine receptors and TTX blocks voltage-gated sodium channels but both block neural activity and are commonly used, now, as experimental tools to assess the importance of activity in specific neural populations.

Slide 9:
It had previously been shown by Carla Shatz and Michael Striker, in the US, that application of TTX in the prenatal cat embryo, prevented normal segregation of ocular dominance zones, indicating that spontaneous neural activity must play a major role.

However, blockade of activity in the retina of postnatal ferret pups prior to eye opening, thereby preventing retinal waves, also had a striking effect on the segregation of ocular dominance zones. In the work shown here, from Andrew Huberman and colleagues in the US, you can see that the boundaries between the zones dedicated to ipsilateral and contralateral eyes in the LGN – which are, here, marked with different coloured trans-neuronal dyes delivered to each eye – are significantly blurred if activity is blocked in the retina.

Slide 10:
Similarly, when the retinae are inactivated during postnatal development prior to eye opening, ocular dominance columns in V1 do not segregate at all.

Slide 11:
How does this lack of synchrony between the activity of the two eyes contribute to segregation of ocular dominance layers in the thalamus and ocular dominance columns in layer 4 of the neocortex?

The key factor to note, here, is that while the retinae and other parts of the nervous system are exhibiting a high degree of spontaneous activity at this stage of development, that activity is in no way correlated since the retinae are not receiving shared sensory input. That lack of correlation plays a major role in the ability of Hebbian plasticity to segregate zones of the visual system that are dedicated to input from one eye or the other.

Slide 12:
Remember that Hebbian synaptic weakening, as modelled by LTD, occurs when there is a lack of correlation between activity in the presynaptic neuron and the postsynaptic neuron. Thus, where post-synaptic neurons are having their activity driven by one eye slightly more powerfully than by the other eye, because these two inputs are out of synchrony, the slightly weaker input will be further weakened until it eventually is unable to elicit any activity in the post-synaptic neuron. Thus, the post-synaptic neuron can be said to have a monocular receptive field, more or less dedicated to processing information from one of the two eyes only.

Subsequently, inputs from this favoured eye will be strengthened even further through Hebbian potentiation, as modelled by LTP, given the increasingly reliable coincidence between pre-synaptic activity and post-synaptic response. This overall scenario is depicted in the schematic to explain how highly segregated zones or 'ocular dominance columns' – in blue and yellow – could arise from a population of neurons that initially had a largely binocular response – shown in green.

All that would be required for this to occur is the prior existence of a very slight bias in one direction or another. This bias may arise through chance or it could be that some genetic mechanisms that are not activity-dependent do create some very rough bias before this is hugely refined by activity. This latter scenario would

explain why, for instance, there's some vestige of zones dedicated to input from one eye or the other when the retinas are silenced postnatally.

Slide 13:
A major question posed by this hypothesis is whether segregation requires the NMDA receptor in cortical neurons. Remember, that this ionotropic glutamate receptor acts as a detector of coincidence between pre- and post-synaptic elements and is critical for many forms of Hebbian LTP and LTD. The mouse is the only mammalian species in which genetic engineering can easily be used to ablate, or 'knock out', a gene and, thereby, the expression of the protein encoded by that gene.

Although modern technology is changing that – soon we will be able to knock out or manipulate genes in almost any species. This knock out approach is critical to determine whether Hebbian plasticity is required for functional segregation based on spontaneous activity. This slide shows data from a mouse in which the NMDA receptor has been functionally ablated from glutamatergic neurons of the cortex.

Mice don't exhibit ocular dominance columns, unlike most other mammalian species, but they do have analogous functional segregation in primary somatosensory cortex, known as 'whisker barrels' – as we discussed at the beginning of this section.

On the right, you can see anatomical markers and stains of neural activity that reveal severely ill-defined whisker barrels in the primary somatosensory cortex of mice that do not express NMDA receptors in the neocortex. This requirement, for NMDA receptors to achieve functional segregation in primary sensory areas, is further evidence for a key role played by Hebbian plasticity.

Slide 14:
In summary, 'ocular dominance columns' are zones of cortex that only respond to input through one or another eye. They are present in the primary visual cortex of many species – for example, cats and humans. And functional segregation also exists in the visual thalamus.

In many species, the eyes open sometime after birth, but ocular dominance columns still emerge during this period.

Spontaneous neural activity can be recorded in the retina prior to eye opening and these are known as 'retinal waves'. Similar spontaneous activity can be detected in the visual thalamus. Retinal waves are not correlated between the two eyes.

Inactivation of the retinae to prevent retinal waves prevents the formation of discrete ocular dominance columns. Evidence suggests that blockade of NMDA receptors also prevents segregation of ocular dominance columns and whisker barrels in the somatosensory cortex.

Hebbian synaptic plasticity is hypothesised to progressively sharpen the boundaries between ocular dominance columns by weakening connections between neurons that are uncorrelated in activity – ie responsive to opposite eyes – and strengthen connections between neurons that are correlated– ie those that are responsive to waves in the same retina.