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 4 of 5

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Slide 3:
Now, let's turn our attention to a related developmental process that introduces a major permissive factor to this deprivation-induced plasticity – the critical period.

Slide 4:
Another Nobel laureate, who really crystallised the concept of the critical period, was the Austrian ethologist, Conrad Lorenz. Lorenz conducted many fascinating experiments on the phenomenon of imprinting, in which he became the major parental figure to numerous different bird species.

If he served as the primary provider and carer for chicks, goslings or cygnets during a critical period of post-natal development, they formed a powerful, unbreakable attachment to him that could not be superseded by a member of their own species. Importantly, this attachment persisted if he took on this role during and beyond the close of the defined period, which was termed a critical period.

This concept of the critical period – a relatively brief window during which defining plasticity was permitted – has become influential throughout education, psychology, psychiatry and neuroscience and it's highly relevant to the effects of visual experience in deprivation on the neocortex of mammals.

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This is illustrated by a series of experiments in kittens and cats of various ages. The first key observation is that the effects of monocular deprivation are highly reversible if the deprivation occurred during an early critical period. In five-week-old kittens, monocular deprivation would not only result in the ocular dominance shift in the response of layer 2/3 neurons, as we've discussed already, but after un-suturing the deprived eye, a reverse suture of the opposite eye would result in an equivalent shift in the opposite direction.

Slide 6:
If this experiment were carried out in the same way with monocular deprivation during the critical period of 5 weeks of age, but then un-suturing and reverse suturing occurred much later, at 14 weeks of age, then not only did the reversal of ocular dominance in Layer 2/3 not happen, but recovery from the initial shift did not occur.

Slide 7:
Similarly, the ocular dominance plasticity does not occur at all if eyelid suture occurs in the adult animal, demonstrating very clearly that the capacity of the cortex for plasticity is lost after the critical period.

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A key question, of course, is whether this permanent shift not only compromises response in layer 2/3 of visual cortical neurons but also actually impairs vision itself.

In humans, we would test vision with a Snellen chart, which many of you may be familiar with. The Snellen chart is a test of visual acuity, and it asks you to resolve lines that are different distances apart and this is known as varying spatial frequency. At some point, a threshold can be found beyond which you cannot differentiate the letters 'M', 'W', 'E' and the number '3', which is the determinant of your visual acuity. 20/20 vision just means that your vision at 20 feet matches normal vision at 20 feet.

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One classic test of vision teaches a cat to associate a specific orientation of lines with a reward – say vertical stripes but not horizontal stripes. Once this association is formed then one can just assess vision by changing the spatial frequency and determining how often the cat chooses to jump to the rewarding orientation.

If one eye or other is covered during this test, then vision can be tested independently through each eye. Here you can see work from Canadian vision scientists Donald Mitchell and Kevin Duffy, in which monocularly deprived kittens show normal binocular vision a week or so after the eye is open post-critical period.

However, vision limited to the deprived eye never recovers and the animals remain functionally blind through this eye even though the eye, itself, is fully operational. Thus, if visual experience does not return to normal until after closure of the critical period, then there is no functional recovery.

Slide 10:
The visual cortical critical period varies in time and longevity from one species to another. Rather conveniently, this roughly lines up in weeks for cats, months for monkeys and years for humans, as shown in this graph, with closure of the critical period occurring around eight to nine weeks, months or years depending on the species.

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Much work has now been done by several laboratories, notably including those of Mark Bear and Takao Hensch in the US, to demonstrate that a key determinant of both the opening and the closing of the critical period is the degree of cortical inhibition.

Inhibition develops late in the cortex, relative to excitation circuits, and we now know that the critical period really represents a sweet spot between too little and too much inhibition.

Slide 12:
So, how can inhibition be a key determinant in whether Hebbian plasticity occurs or does not?

Here, we can see a schematic of how a simple feed-forward circuit in the visual cortex looks, with tick marks representing action potentials. As the schematic shows, cortical inhibition after the eyes open, but before the critical period opens, is too low to really impact the activity of cortical circuits resulting from visual input.

This means that Hebbian plasticity cannot operate to integrate signals because there's too much noise in the system. After inhibition has started to develop, during the critical period, conditions are optimised so that only the strongest visual inputs will drive enough cortical activation to modify synaptic strength through Hebbian plasticity. It is during this period that the cortex is primed to be modified by visual experience and deprivation. The closure of the critical period appears to arise once inhibition is so powerful that it suppresses the propagation of activity through cortical circuits for all but the very strongest sensory input.

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Thus, the critical period is closed once inhibition in the cortex is matured. However, it is important to note that the capacity for change still exists in cortical circuits if inhibition can be modified. The opening of the critical period can be advanced by positively modulating GABA receptors with benzodiazepines. The critical period can be reopened with treatments that reduce inhibition, such as a genetic knockdown of the key enzyme for synthesising GABA or, interestingly, by grafting immature inhibitory neurons into the visual cortex of mature mice. In the next section, we will consider some of the therapeutic implications that this work gives rise to.

Slide 14:
So, in summary for this section on critical periods:

Critical periods define the time window during which the effects of sensory experience or deprivation on the nervous system are most pronounced, usually occurring quite early in post-natal development.

Critical periods vary for brain regions and sensory modalities, for example, the critical period for plasticity in somatosensory cortex opens and closes earlier than for visual cortex. Higher order regions of cortex, such as prefrontal cortex, have even later critical periods.

Critical periods vary from species to species, for example, the critical period for ocular dominance plasticity closes much earlier for mice than cats, and earlier for cats than primates.

Several lines of evidence indicate that inhibitory neurons play a key role in critical period duration, with development of inhibition opening the critical period of maturation and maturation of cortical inhibition closing it. Increasing inhibition can prematurely open the critical period and reducing inhibition can re-open the critical period after it has closed.

Inhibition is believed to serve as a permissive factor for Hebbian plasticity by reducing overall activity at the opening of the critical period, thereby reducing 'noise' and allowing differentiation of correlated and uncorrelated activity. However, too much inhibition can prevent enough post-synaptic activity to allow Hebbian plasticity to occur, thereby closing the critical period.