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 5 of 5

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Slide 3:
Now, let's complete our topic by considering the therapeutic possibilities that exist, because of all this fundamental neuroscience work. How might we treat sensory deprivation, and are there further reaching implications for psychiatric disorders? A major focus in this regard is asking whether we could re-open the critical period in mature patients in order to recover developmental disruptions that may have arisen from deprivation during childhood.

Slide 4:
As well as the various invasive treatments that we discussed for reopening the critical period – including genetic modifications in mouse to reduce GABA synthesis and the grafting of inhibitory neurons, precursors into visual cortex – considerable work has been done to develop non-invasive means to influence inhibition and, thereby, extend or re-open the critical period.

These non-invasive approaches would be much more palatable as potential treatments in humans than genetic modifications or surgical grafts – although nothing can be discounted if the condition is severe enough and the patients are willing. Among treatments tested in rodents, that show promise in returning the cortex of adults to critical period levels of plasticity, include environmental enrichment, dark exposure, caloric restriction, physical exercise and perceptual training. In addition, certain drugs that are already available for use in humans, such as Selective Serotonin Reuptake Inhibitors – or 'SSRIs' – which are used as antidepressants, appear to influence cortical inhibition and return it to a critical period-like state.

Slide 5:
Focusing on one of the most promising of these treatments in the visual domain, we can look at some work revealing that dark exposure for several days in rodents alters inhibition within the visual cortex and, as a result, alters the modification threshold for synaptic plasticity.

On the left are direct measurements of cortical inhibition, using intracellular electrophysiological recordings, from slices of visual cortex, taken from rodents that have either been raised under normal lighting conditions, or raised in this manner but, then, briefly exposed to extended dark over several days. The top panel shows that dark exposure has no effect on cortical inhibition if it occurs during the critical period and is compared to critical period mice on a normal light cycle.

However, if the same experiment is conducted in adult animals, in which the critical period is closed and inhibition is fully matured, the dark exposure substantially reduces the amplitude of inhibitory, post-synaptic currents – 'IPSCs' – relative to controls. This effect reveals the capacity of dark exposure to recover cortex to critical period levels of inhibition.

In the right panels, we can see that if animals are raised in the dark, the direction of Hebbian synaptic plasticity can be altered in primary visual cortex, reflecting altered inhibition and a shifted modification threshold. Low frequency stimulation produces less LTD in dark-reared animals than their littermate controls, raised under normal lighting, and higher frequency stimulation, of around 40 Hz, induces more LTP.

Thus, the expectation would be that dark exposure could either reduce the impact of monocular deprivation – remembering the important fact that binocular deprivation does not induce a shift in ocular dominance in the brain – or, more dramatically, recover lost visual function in adult animals after extended monocular deprivation.

Slide 6:
If we return to cats and the behavioural measure of their visual acuity carried out by Donald Mitchell's laboratory, we can see a stunning experimental result that is highly relevant to the treatment of human disorder. Here you can see the kittens that underwent monocular deprivation through the critical period – around one month of age – retain major visual deficits long after that eye is open. These deficits, in visual acuity, are akin to almost complete blindness through the deprived eye for months after the eye has been opened and in contrast to the open eye, which exhibits normal visual acuity. The amazing thing is that exposing the animals to 10 days in the dark, at three months of age, leads to a complete recovery of function through the deprived eye over just a few days of further visual experience. The weight of evidence, therefore, points towards dark exposure as being a strong candidate for recovery of function in the visual system by modifying inhibition.

Slide 7:
Monocular deprivation in animals is, essentially, a model of a not uncommon human condition, known as 'amblyopia' – in which monocular deprivation occurs during childhood as a result of several possible ocular conditions. Sometimes, this deprivation is not detected early enough during childhood and it extends beyond the critical period, to ages eight and upwards. Meaning, that the visual cortex is slowly dedicated to responding to the fully functional eye and cannot be recovered for binocularity even with good treatment of the eye in adulthood.

The condition of amblyopia is colloquially described as 'lazy eye'. Amblyopia reduces visual acuity to varying extents resulting in almost no depth perception, this affects around 2% of the UK population and, even in the subtlest of cases, prevents those people from entering certain professions that require depth perception, such as being a pilot or a fireman or a firewoman. In more extreme cases, it results in complete cortical blindness through that eye and would prevent you from driving. It would also reduce your quality of life in many ways and potentially also lead onto some mental health issues. In the developing world, such as countries in Asia and Africa, the problem is more prevalent – as easily treated ocular problems, such as cataracts, are often not

tended to at all or until it is too late. In these countries, amblyopia also has a more dramatic effect on one's ability to earn a living and can, therefore, be a catastrophic condition.

Slide 8:
Of the causes of amblyopia, some are very easy to detect, such as cataracts or strabismus, due to an obvious physical manifestation. These conditions would likely be remedied early in life, in the UK, and a child can go on to have perfectly normal vision. In the developing world, these dysfunctions may not be attended to, due to a lack of money or facilities.

In countries like the UK, amblyopia can occur due to less noticeable conditions, such as anisometropia – in which the two lenses are of different refractory indices, and one provides a clearer view of the world than the other. It is obviously critical to have good tests of visual function when children are young, to give them the best chance of recovery prior to closure of the critical period.

Slide 9:
The current best clinical practice is to use surgery to return the 'bad' eye back to normal before dealing with residual ocular dominant shift during the critical period. This recovery can be accelerated by performing the equivalent of a reverse suture experiment, either by patching the good eye or by using eye drops of belladonna extracts – or atropine – which prevent muscles in the good eye from working properly. This punishment of vision through the good eye is not ideal, given that the visual system is still developing in numerous other ways.

Development of novel treatments for amblyopia, especially in adults – in which function cannot currently be recovered, would have a major societal impact. The work on dark exposure and related, non-invasive treatments is, therefore, extremely important. The therapeutic implications of the fundamental neuroscience that we have discussed extends way beyond the visual system, however. The work on the effects of visual deprivation on the visual cortex provides deep insight into the likely consequences for deprivation in other sensory systems and in higher order systems.

Slide 10:
Insight into the development of inhibitory systems in the neocortex and how that can influence the effects of experience and deprivation on the nervous system is likely relevant to a slew of conditions, including neurodevelopmental psychiatric disorders: such as epilepsy, intellectual disability, autism spectrum disorders and schizophrenia – where dysfunctions in the postnatal development of balanced excitation and inhibition is heavily implicated.

This so-called 'E-I balance' has been studied in the context of these neurodevelopmental disorders. Highly penetrant genetic causes of these conditions often target synaptic proteins, such as 'neurexins' and 'neuroligins' – which are transsynaptic signalling molecules that are critical for either normal inhibition of excitatory neurons or normal excitation of excitatory neurons.

Mutations in the genes that encode these proteins often result in E-I imbalance and intellectual disability, autism spectrum disorders or schizophrenia. Critical receptors for Hebbian plasticity, such as the NMDA receptors or associated signalling systems, appear to be risk factors for schizophrenia and there is ample evidence, in this condition, that inhibitory neurons in the cortex are reduced in number and in the production of GABA – indicative of E-I imbalance.

Another major risk factor of neurodevelopmental disorder is Fragile X Mental Retardation Protein – 'FMRP' –

which regulates activity-induced protein synthesis required for many synaptic processes, notably including lasting Hebbian synaptic plasticity. Disruption of FMRP function, as its name suggests, results in one of the more common forms of intellectual disability – 'Fragile X Syndrome' – which is often comorbid with epilepsy and autism spectrum disorders and exhibits a clear E-I imbalance at various stages of development.

Other risk genes encode transcription factors, such as MeCP2 – which is the protein that is mutated to cause the debilitating neurodevelopmental disorder known as 'Rhett's syndrome' and which appears to play a critical role in the production of enzymes necessary for GABA production in inhibitory neurons, thereby resulting in major E-I imbalance.

Slide 11:
As we have seen, critical periods reflect the normal development of E-I balance in the cortex, but the time-course of critical periods is very different from region to region of the cortex, reflecting the different functions of these regions. While the sensory critical periods that affect plasticity in primary sensory areas occur early, around and after birth, similar developmental windows are extended much later into life, for language development or socialisation. It's possible that these later critical periods are affected in autism spectrum disorders. Executive function or context/rule-dependent behavioural control, which arises from higher order cortical regions in the frontal lobe may not be fully developed until late into adolescence.

Disrupted development of these faculties may contribute to numerous psychiatric disorders, including schizophrenia. It is a relatively new concept that lost, delayed or exaggerated critical period plasticity – or that deprivation or aberrant experience that occurs during the relevant critical period – may be causal factors in a range of neurodevelopmental disorders. Much further work is now required in this domain.

Slide 12:
To summarise this section, non-invasion means to manipulate inhibition may re-open the critical period, returning the brain to peak plasticity and maximising the therapeutic effects of sensory experience.

Promising methods include environmental enrichment, sensory deprivation, dietary restriction and exercise.

Placing animals in the dark for an extended period greatly reduces the level of inhibition in the visual cortex. Mature cats, that have previously undergone monocular deprivation as kittens and have severe loss of vision through the previously deprived eye, can show dramatic visual recovery after being placed in the dark for 10 days.

This approach holds promise for a debilitating condition, known as 'amblyopia', which results in a visual cortical deficit due to childhood deprivation, that persists even after the eye is rendered fully functional through surgery later in life. Amblyopia affects around 1 to 2% of people in the UK, but many more in the developing world – where treatment of fixable ocular conditions is less likely to occur, in a timely fashion, and where poor vision carries more severe consequences.

Work on the visual system also provides general insight into how cortical function is shaped by deprivation and experience and how altered critical period plasticity may contribute to a wealth of neurodevelopmental disorders, including intellectual disability, autism spectrum disorders and schizophrenia.