KING'S College LONDON

INSTITUTE OF PSYCHIATRY,
PSYCHOLOGY & NEUROSCIENCE

Module:
Biological Foundations of Mental Health

Week 4:
Biological basis of learning, memory and cognition

Dr Sam Cooke

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

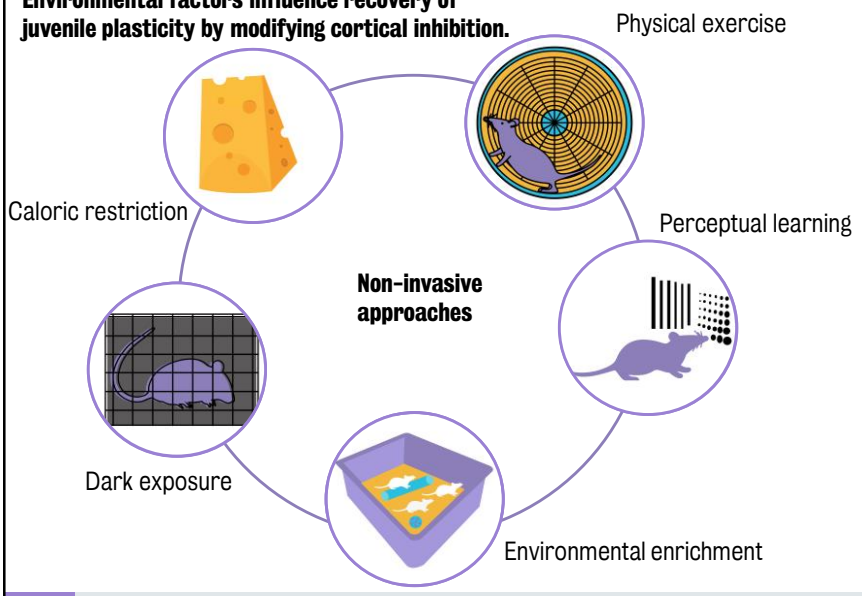
Part 5

Part 5

Re-opening the critical period: therapeutic approaches to recovering function in the deprived nervous system

Environmental factors influencing inhibition

Environmental factors influence recovery of juvenile plasticity by modifying cortical inhibition.

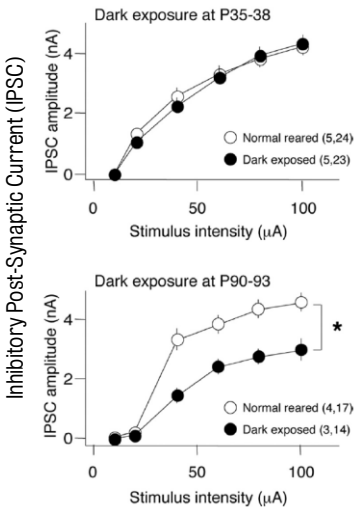


Also, Fluoxetine (Prozac) – which is an SSRI (Selective Serotonin Reuptake Inhibitor) anti-depressant – restores critical period plasticity through reduced inhibition.

Sale et al. 2014

Reducing visual cortical inhibition through dark exposure (DE)

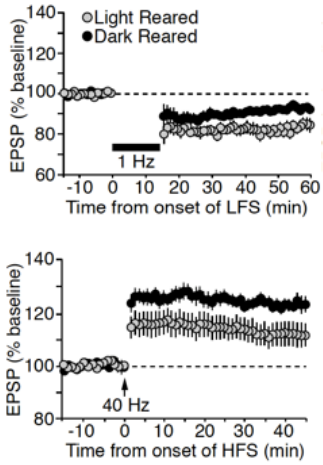
Rodents raised under normal light and exposed to complete darkness for several days



DE during critical period has no effect.

DE after critical period reduces amplitude of IPSCs.

Direction of Hebbian synaptic plasticity in dark-reared animals

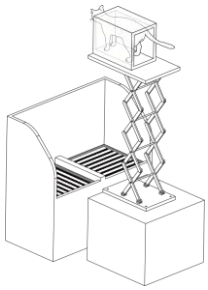


LFS (low frequency stimulation) produces less LTD.

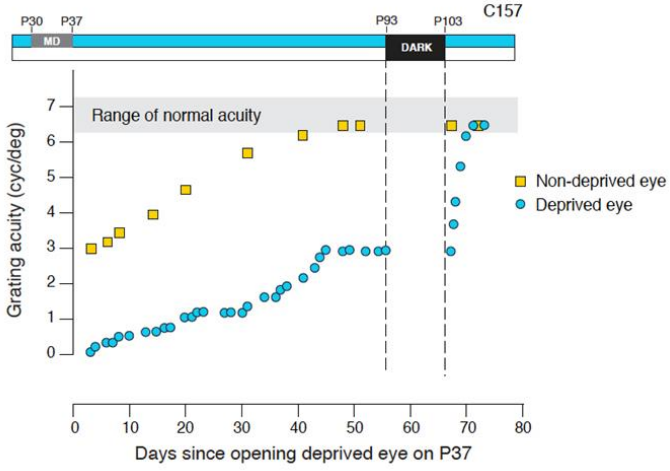
HFS (high frequency stimulation) induces more LTP.

Huang et al., 2010; Philpot et al., 2001

Continuous dark exposure in cats recovers visual function



10 days of continuous dark exposure in the adult cat recovers deprived eye depression that resulted during the critical period.



Dark exposure is a strong candidate for recovery of function in the visual system by modifying inhibition.

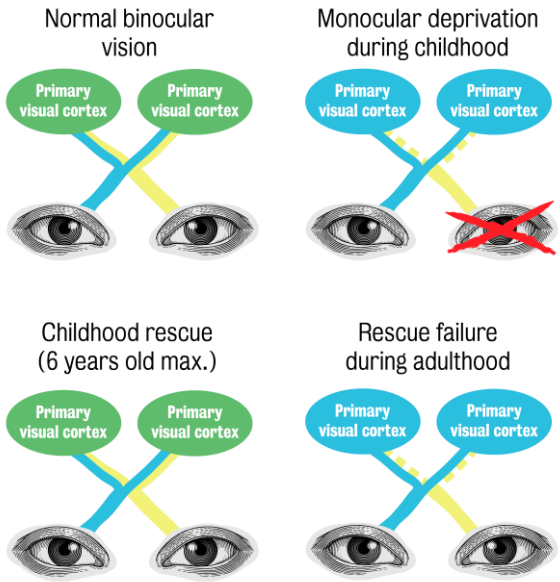
Mitchell et al., 2016

Amblyopia

Amblyopia is a disorder of the brains response to visual input resulting from monocular deprivation occurring during childhood as a result of one of several repairable ocular conditions.

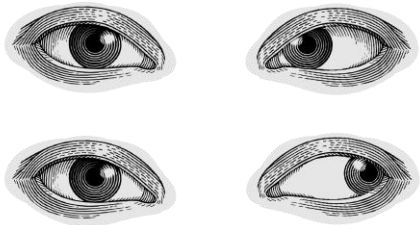
The brain's response to a visual stimulus cannot be fully binocular if visual deprivation that causes amblyopia is not detected before the close of the critical period:

- most common cause of vision loss in children
- reduced visual acuity through an otherwise healthy and properly corrected eye; resulting in almost no depth perception
- affects at least one to two per cent of the UK population
- prevents employment of various sorts
- many more affected in the developing world, where vision and employment are absolutely critical



Causes of amblyopia

Strabismus



Cataracts or corneal scarring

Easy to detect due to obvious physical manifestation; likely to be remedied in the UK but less likely in the developing world

Anisometropia or astigmatism

Subtle defects such as these are less often noticed and therefore often not treated even in countries where treatment is readily available, such as the UK.

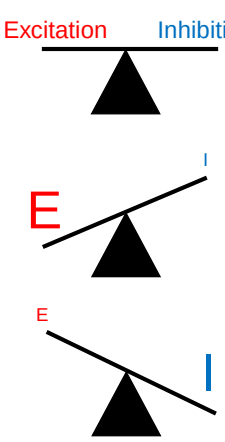
Treating amblyopia

- Best clinical practice is to use surgery to return the 'bad' eye back to normal and then patching or using eyedrops on the good eye.
- Punishing the good eye is not ideal as the visual system is still developing.
- Development of novel treatments for amblyopia would have major societal impact; work on dark exposure and other non-invasive treatments is therefore very important.

Additional therapeutic implications:
research on deprivation in the visual cortex provides insight into the consequences of deprivation in other sensory systems.

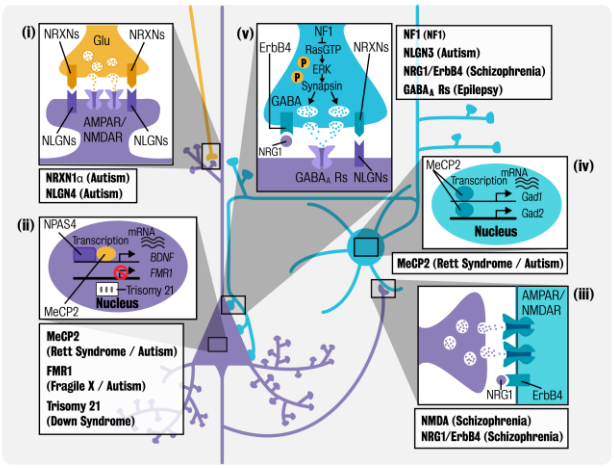
Excitatory-inhibitory imbalance and neurodevelopmental disorders

Highly penetrant **genetic causes** of neurodevelopmental disorders (eg epilepsy, autism spectrum disorders, intellectual disability and schizophrenia**, disrupt excitatory-inhibitory imbalance** by altering synaptic development.



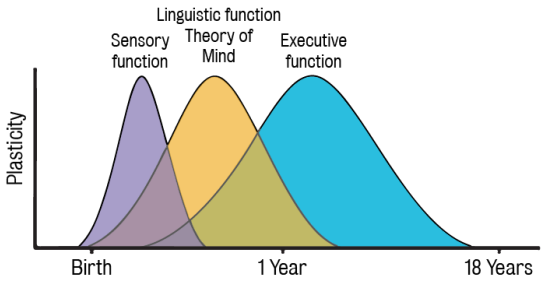
Risk factors for imbalance:

- mutation of the genes that code for neurexins and neuroligins
- critical receptors for Hebbian plasticity (eg NMDA receptor)
- disruption of FMRP (Fragile X Mental Retardation Protein) function (related to Hebbian synaptic plasticity)
- mutations in other highly penetrant genetic causes of neurodevelopmental disorders, including MeCP2; disruption of which causes Rett's syndrome.

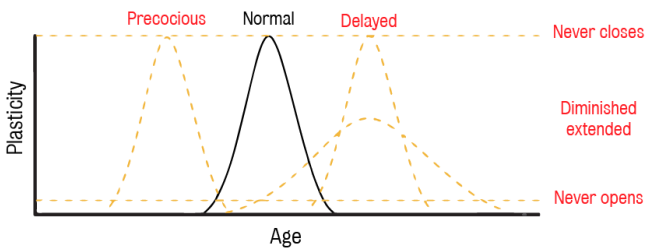


Ramamoorthi & Lin., 2011

Variations in time-course of critical periods



Critical periods **differ by region and function** and can be **disrupted** in various ways.



Disrupted development can contribute to **numerous psychiatric disorders**.

Delayed/exaggerated critical period plasticity, or deprivation/aberrant experience occurring during the critical period may cause **neurodevelopmental disorders.**

Summary

- non-invasive 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 one per cent 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 the 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 disorder and schizophrenia.

References

[1] Huang S. et al. (2010) A refractory period for rejuvenating GABAergic synaptic transmission and ocular dominance plasticity with dark exposure. J Neurosci. 30(49):16636-42.

[2] Mitchell D. et al. (2016) Recovery of visual functions in amblyopic animals following brief exposure to total darkness. J Physiol. 594(1):149-67.

[3] Philpot B. et al. (2001) Visual experience and deprivation bidirectionally modify the composition and function of NMDA receptors in visual cortex. Neuron. 29(1):157-69.

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[5] Sale A. et al. (2014) Environment and brain plasticity: towards an endogenous pharmacotherapy. Physiol Rev. 94(1):189-234.

End of topic