Can we recruit the brain's immune cells to help treat Parkinson's disease ?

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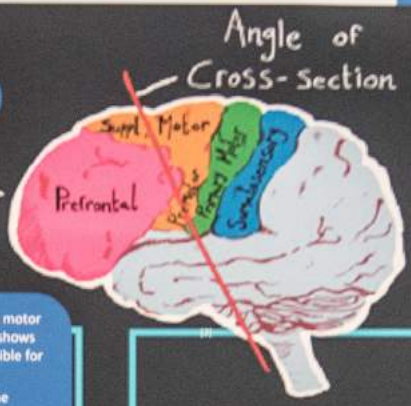
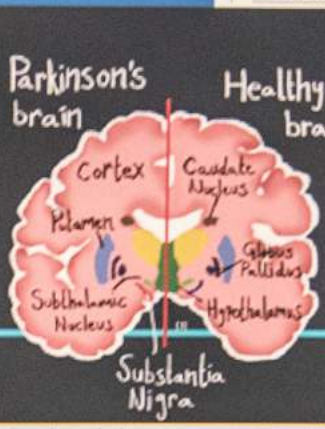
Parkinson's disease is a highly distressing neurodegenerative disorder that affects movement, mood, and digestion.
Symptoms may include; trembling hands, a shuffling short-stepped walk, stooped posture, rigidity/'freezing', some memory problems, and a change in behaviour.

- A slice (cross section) through the motor co-ordination centre of the brain shows the basal ganglia: regions responsible for initiating movement.
- Parkinson's patients lose dopamine neurons in the substantia nigra.
- It is not known why this occurs...
- But, look below: recent evidence suggests inappropriate inflammation may exacerbate or even cause this loss of cells.



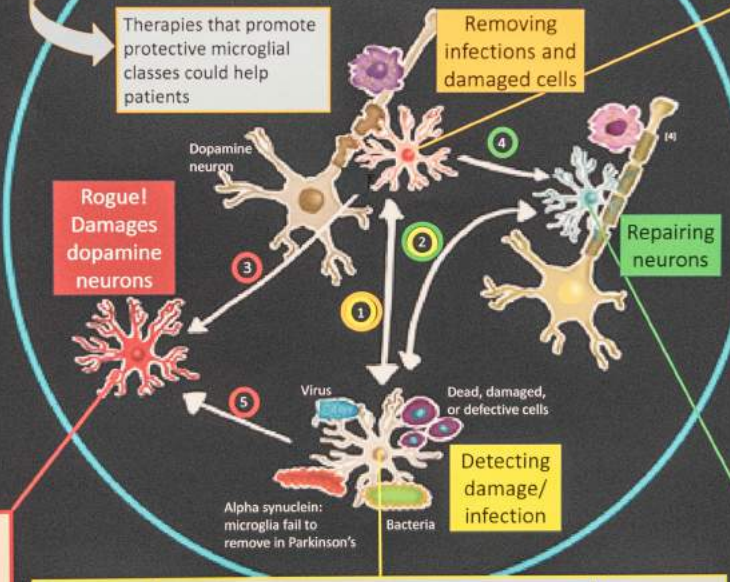


A cross section through the motor cortex shows the basal ganglia. The left hand side shows the basal ganglia of a patient with Parkinson's disease. The substantia nigra is shaded red here to indicate death of dopamine neurons.

Dopamine neurons are sometimes damaged by microglia, making Parkinson's symptoms worse. But, microglia can sometimes protect these neurons, depending on their 'class'.

Microglia can transform into three classes, each with their own unique appearance and functions. 'Security', 'Fighter', and 'Engineer' classes

Therapies that promote protective microglial classes could help patients



Fighter Class

Functions:
- Eats infectious agents and damaged/ dead cells
- Marks targets for destruction and alerts cells of the immune system
- Releases molecular 'grenades' to destroy infections
- Reverts to security class (1) or becomes engineer (4)

Weakness:
- Collateral damage to bystander cells such as neurons
- Can become irreversibly rogue (3) (thought to be leading to dopamine neuron cell death)

Rogue Actor

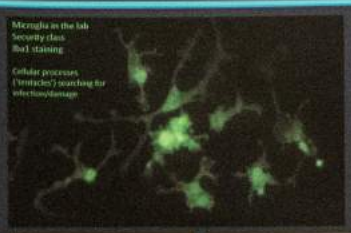
Characteristics:
- Loses ability to stop inflammation
- Permanently trapped in Fighter mode (does not switch to Security or Engineer class)
- Damages healthy tissue, particularly by releasing molecular 'grenades'

Security Class (dominant in healthy brain)

Functions:
- Highly active 'tentacles' constantly monitor brain tissue for infection or dead/damaged cells
- (1) Transform into fighter class in response to inflammatory cues: viruses, bacteria, alpha synuclein aggregates, dead cells
- (2) Transform into engineer class in response to damaged/defective cells

Engineer Class

Functions:
- Calm the fighter cells thereby reducing collateral damage
- Recruit new cells to move into damaged areas and repopulate
- Produce signals that prevent neuron death, and promote repair
- (2) Can revert back to security class



Concluding remarks

- Treatments that reduce numbers of Fighter class microglia can reduce loss of dopamine neurons, slowing Parkinson's progression
- Whilst, producing more Engineer class microglia may additionally promote *repair* of dopamine neurons, restoring some function
- Both, reducing the number of Fighter class and producing more Engineer class, is an approach that is not only of interest to Parkinson's disease treatment but also other disorders including Alzheimer's, Huntington's, and stroke
- My research focuses on modulating microglial activity, promoting the presence of the engineer class, for restorative and preventative therapies

References
[1] Matt_Lankie_F_art
[2] [3] drouilb.faculty.mjc.edu
[4] Prinz, M. & Priller, J. Microglia and brain macrophages in the molecular age: from origin to neuropsychiatric disease. Nat. Rev. Neurosci. 15, 300–12 (2014).