Why neuroscience is important for mental health

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- Depression (MDD) is common, disabling and costly
- Biggest share of the global burden of disease (YLD)
- Increased mortality
- Very common in physical illness

Mood disorders, psychotic disorders and the dementias are major areas of unmet need

- Risk of lost generation of therapeutic development
- Lack of mechanistically specific human biomarkers
- Paucity of novel tractable molecular targets
- Poorly predictive preclinical models

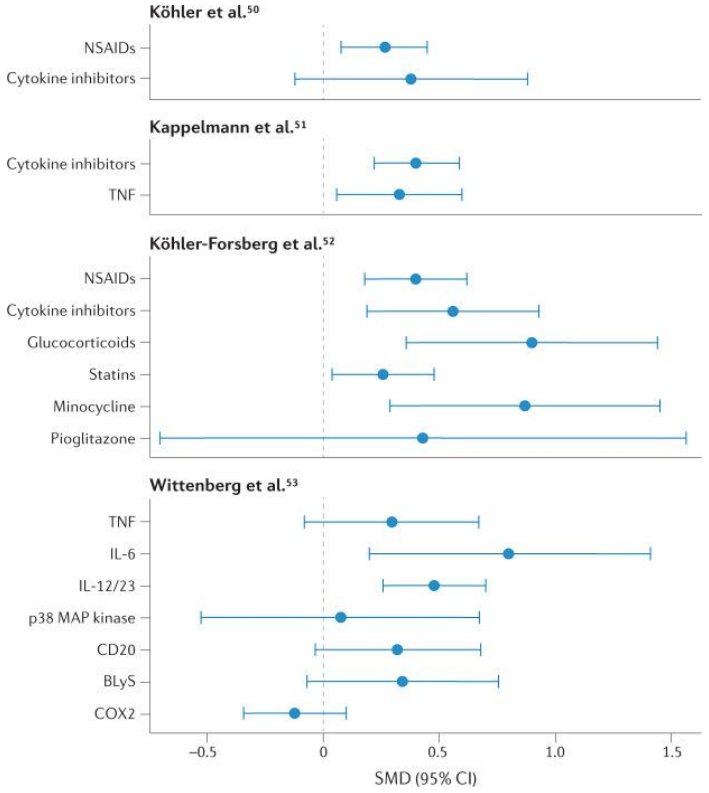
Challenges

Why is neuroscience important?

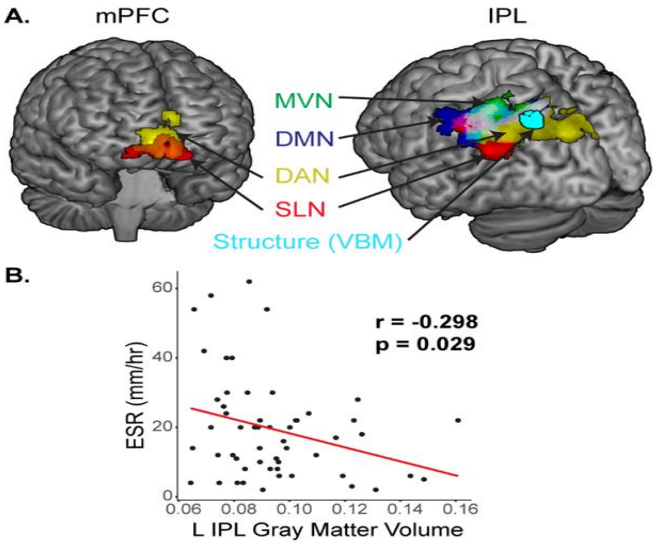
- Allows interrogation of neural systems
- Allows exploration and testing of mechanisms
- Allows identification of new molecular targets……

Immune mediated inflammation

- *Inflammation can induce depression symptoms:*
  - IFN-α and endotoxin can cause depression in hepatitis patients and illness behaviour in pre-clinical models
- *Elevated cytokines in psychiatric patients*
  - e.g., IL-1b and TNFa
- *Inflammation may cause treatment resistance for monoaminergic anti-depressants*
- *Anti-inflammatory drugs may have anti-depressant effects*
  - Infliximab effects correlated with baseline CRP levels in MDD – greater benefit in more inflamed patients



Drevets ...Bullmore Nat Drug Disc 2022



Schrepf et al Nat Comms 2018

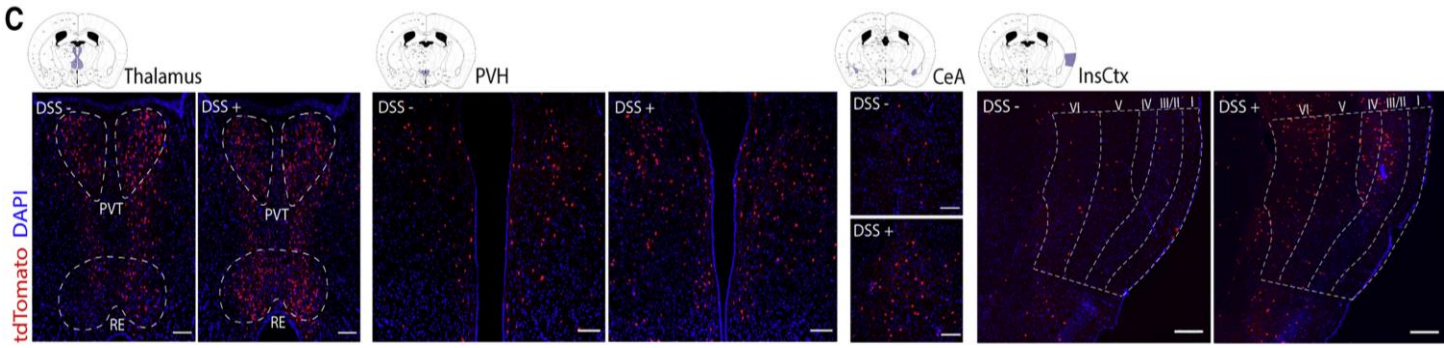
Connectivity

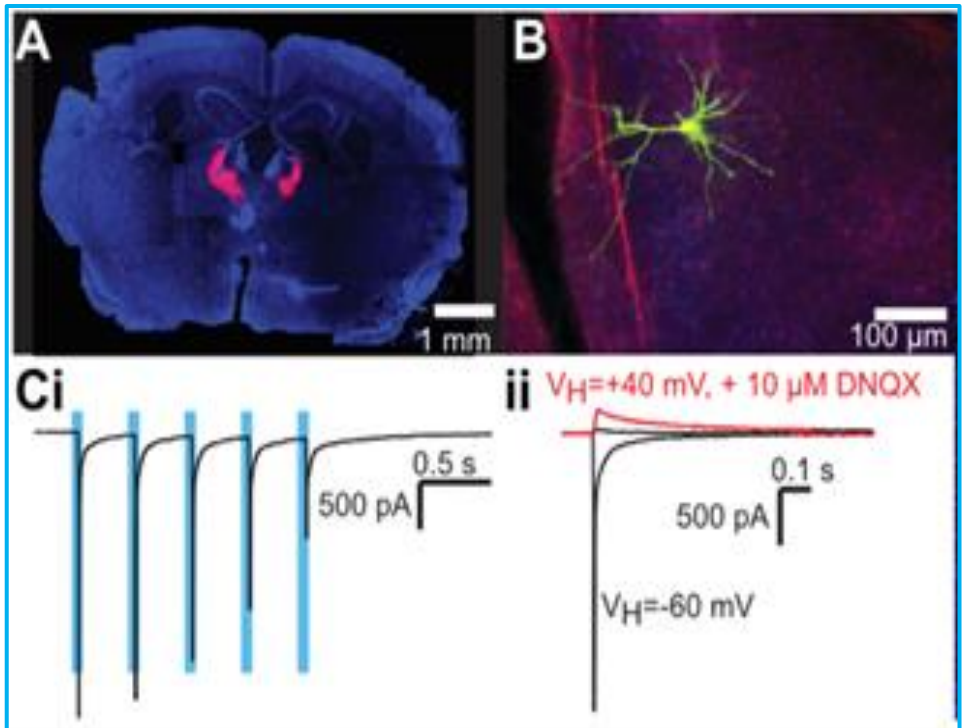
- Which neuronal ensembles are important ?
FOSTRAP

-

- What's the connectivity?

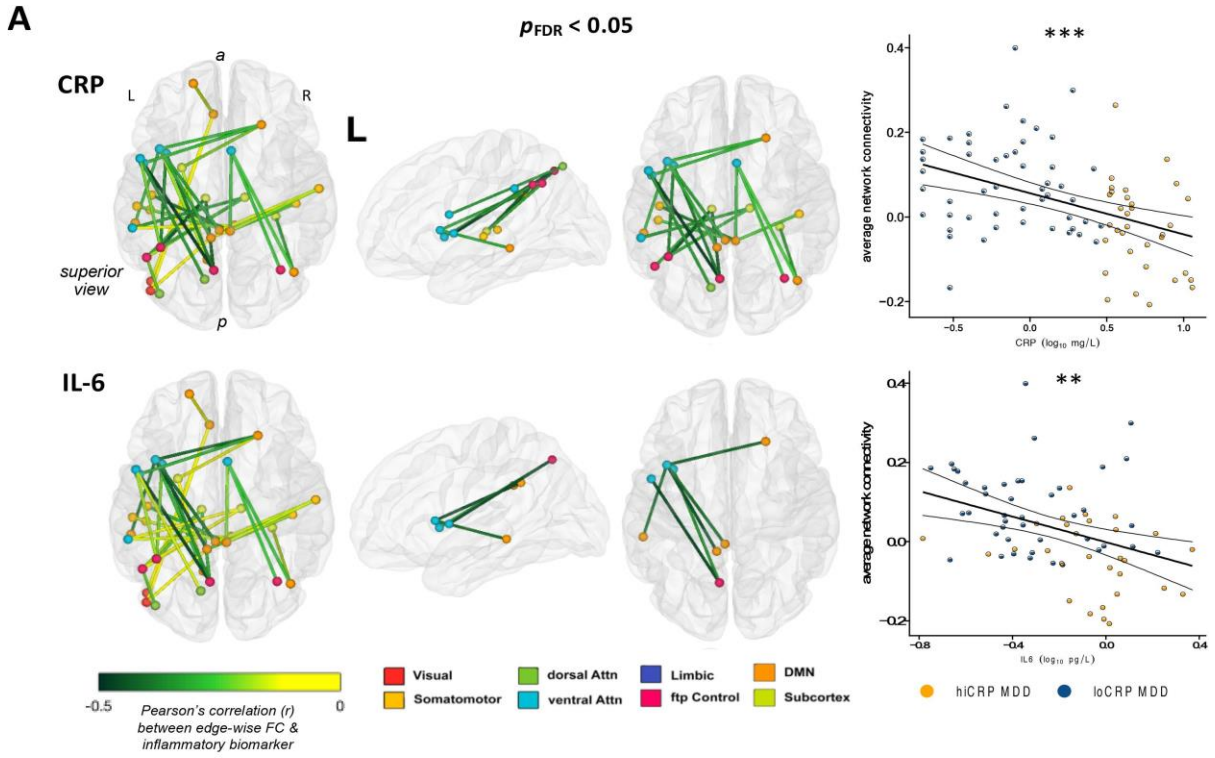
OPTOGENETICS and EPHYS





Human neuroimaging

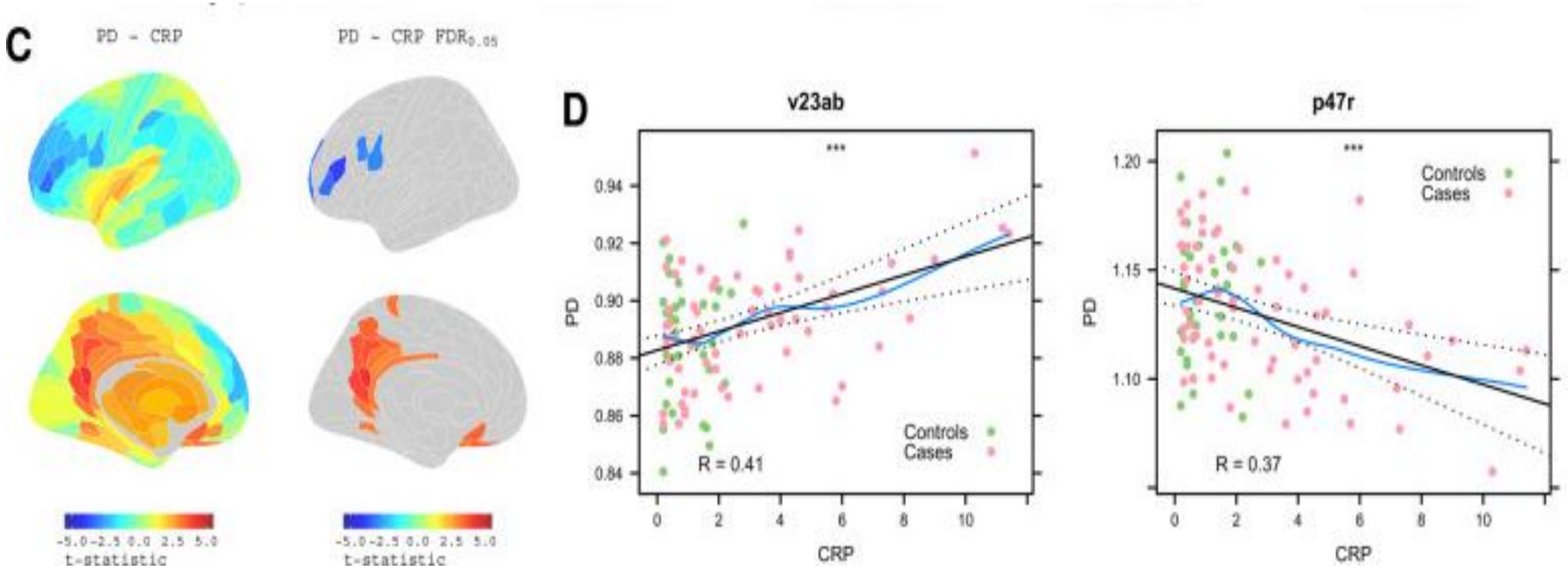
Functional connectivity associations with inflammatory proteins in depression



Scatterplots of the continuous (negative) relationships between average network connectivity and blood concentrations of CRP and IL-6

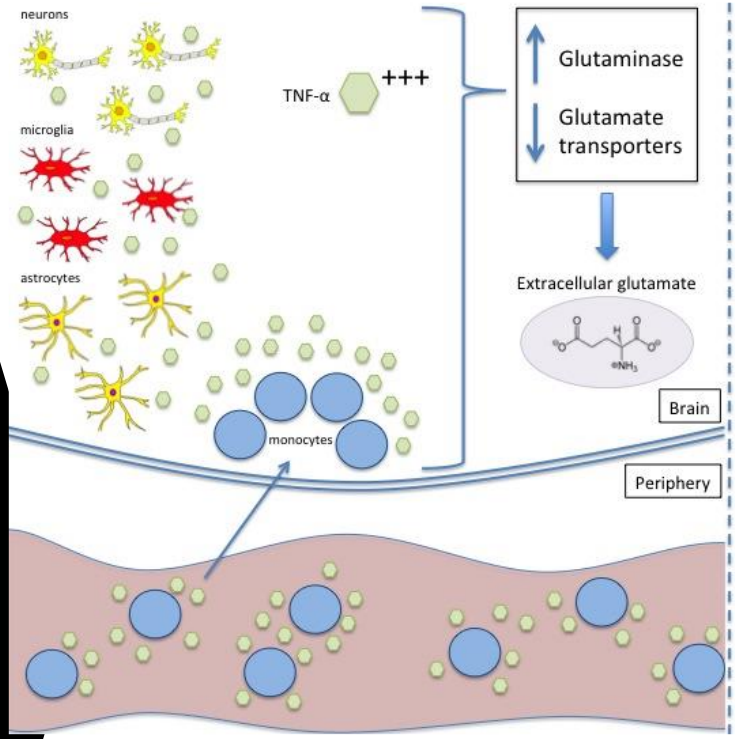
Microstructure changes as proxy of inflammation

Positive correlation between CRP and Post cingulate PD and
negative correlation between CRP and and dorsolateral prefrontal cortex PD



CRP-related increases in proton density—
a plausible marker of extracellular oedema—and changes in functional connectivity were anatomically co-localised with DMN nodes effects of peripheral inflammation on DMN node micro-structure and connectivity
may mediate inflammatory effects on depression.

Experimental medicine approach linking brain and peripheral immune mechanisms mediating sickness behaviours in people with rheumatoid arthritis



- **Our objectives are to**:

- Determine the effects of TNF antagonism on brain networks and glutamate quantification in RA.

- Examine and detail the relationship between sickness behaviour, brain network connectivity and glutamate quantification (using 7T MRI and MRS).

- Evaluate, for the first time, peripheral monocyte circulation into the brain in RA and whether such monocyte recruitment correlates with sickness behaviour (using SPECT).

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Potential molecular targets

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