

# Why neuroscience is important for mental health

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# THE CREATION OF DEPRESSION

## DEPRESSION CAUSES MORE DISABILITY THAN ANY OTHER DISORDER. A SPECIAL ISSUE EXPLORES HOW SCIENCE CAN HELP.

A few months after the world went grey, Sue Wright checked into a hospital. A social slight had flipped a switch in her mind, draining life of colour and joy. Blue skies became dull; laughter was unthinkable. Often, the depression left her bedridden. "I had prided myself on being able to get through anything," says Wright, now a social worker in Germantown, Maryland. "Suddenly, I couldn't."

Wright's story is familiar to too many people. Depression is not just the most common mental health disorder; it is responsible for a greater burden of disability than any other cause. In this special issue, *Nature* asks why that burden is so great, how science is helping and where research is running aground.

A graphic tour on page 180 shows that depression is far from a Western blight, and that many of the countries most afflicted by it are those with the least resources to help. Some mental-health experts say that the high levels of undiagnosed or untreated depression would not be tolerated for a disease such as cancer, and a News Feature (page 182) examines this claim. It

finds that the absence of a crisp diagnosis and a lack of tools to understand the brain's complexities have held back therapy and research.

The urgent question is how to overcome those barriers, and scientists are exploring several routes. Some argue that there is much to be learned from studying the mechanisms of existing antidepressants; others that there is most promise in teasing apart the affected brain circuits (see page 200) or gleaned information on common medicines that might have unexpected benefits for brain disorders (see page 165). Identifying the genes associated with depression has been a thankless task, but ambitious studies involving many thousands of patients are now called for (see page 189).

There is also plenty to be done to refine existing treatments, such as cognitive behavioural therapy, and to tailor them to groups who might benefit most (page 183).

Medication, counselling and electroshock therapy did not work for Wright. After trawling through medical journals, she found a psychiatrist prescribing drug combinations that may boost the effect of antidepressants. After weeks of one such combination plus therapy, Wright realized that the sky was blue again. It took months for her to find a way out; the hope is that research will find a faster route to relief. ■

### DEPRESSION

A *Nature* special issue  
[nature.com/depression](http://nature.com/depression)

- 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

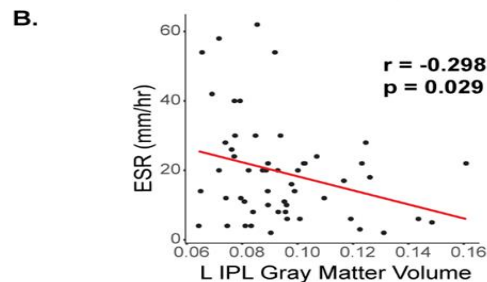
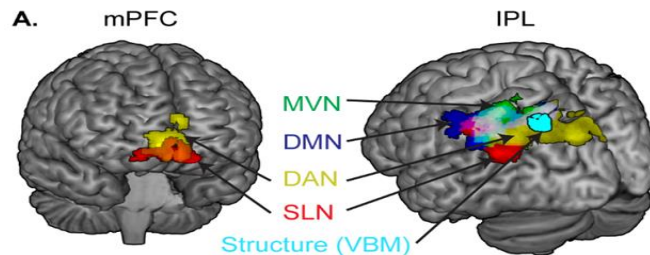
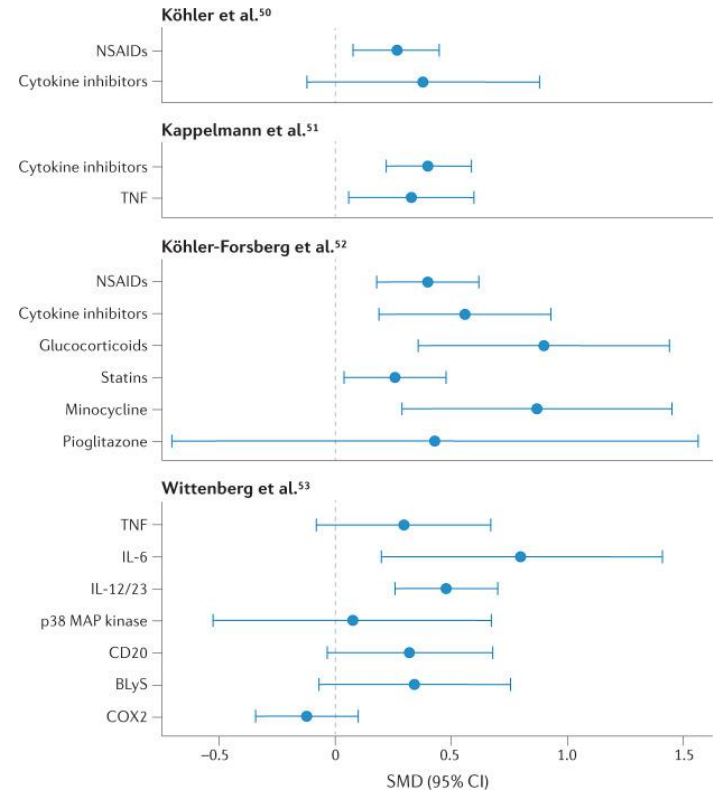
- Risk of lost generation of therapeutic development
- Lack of mechanistically specific human biomarkers
- Paucity of novel tractable molecular targets
- Poorly predictive preclinical models

## Why is neuroscience important?

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

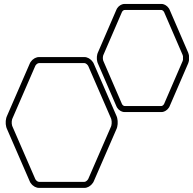
# Immune mediated inflammation

- *Inflammation can induce depression symptoms:*
  - IFN- $\alpha$  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 antidepressants*
- *Anti-inflammatory drugs may have antidepressant effects*
  - Infliximab effects correlated with baseline CRP levels in MDD – greater benefit in more inflamed patients



Drevets ...Bullmore Nat Drug Disc 2022

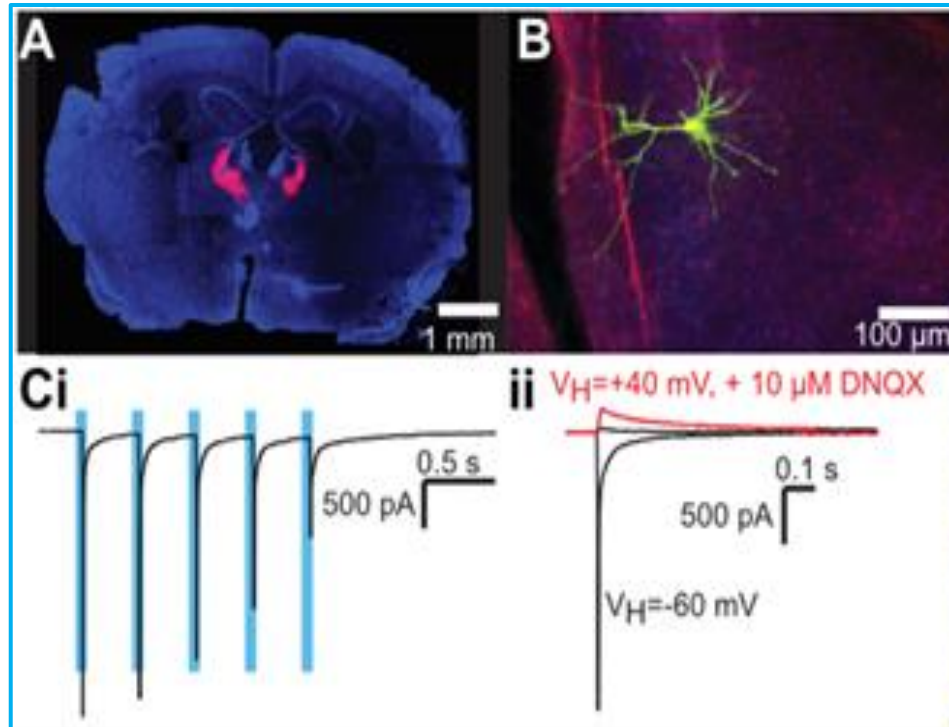
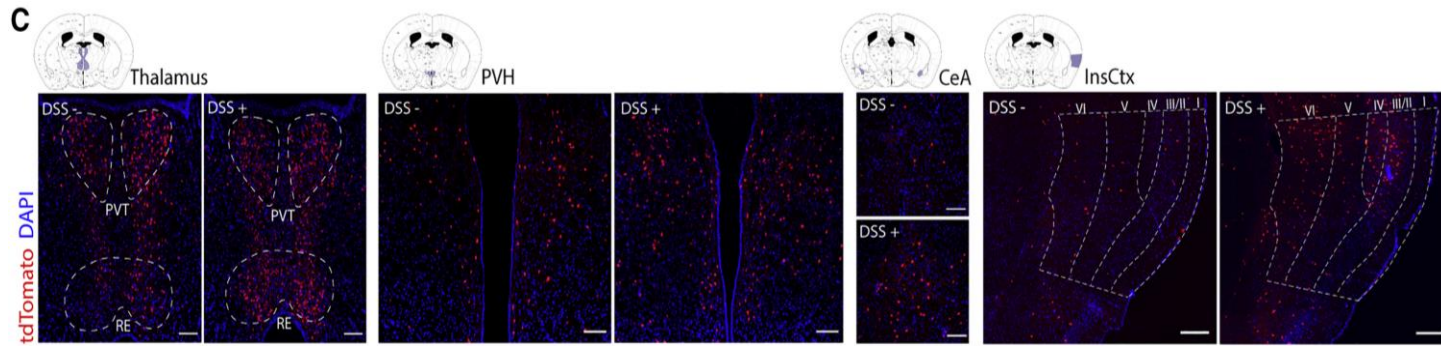
Schrepf et al Nat Comms 2018



# Connectivity

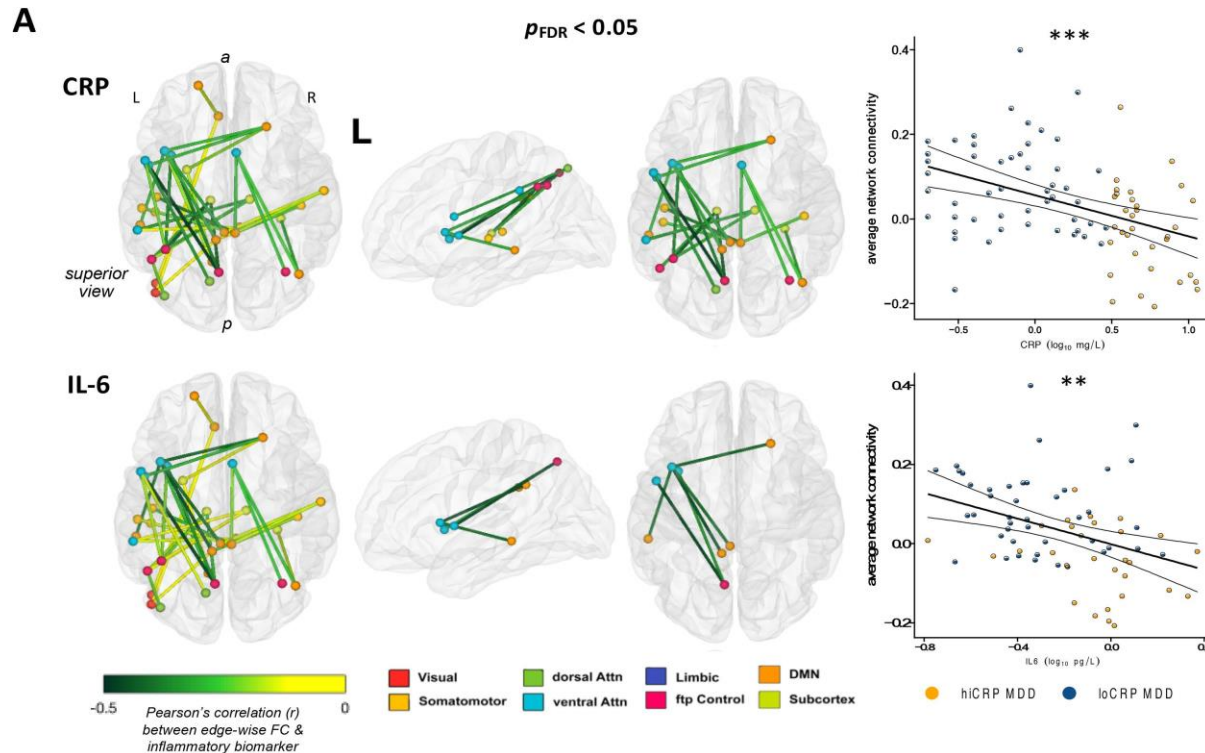
- Which neuronal ensembles are important?  
**FOSTRAP**

- 
- What's the connectivity?  
**OPTOGENETICS and EPHYS**



# Human neuroimaging

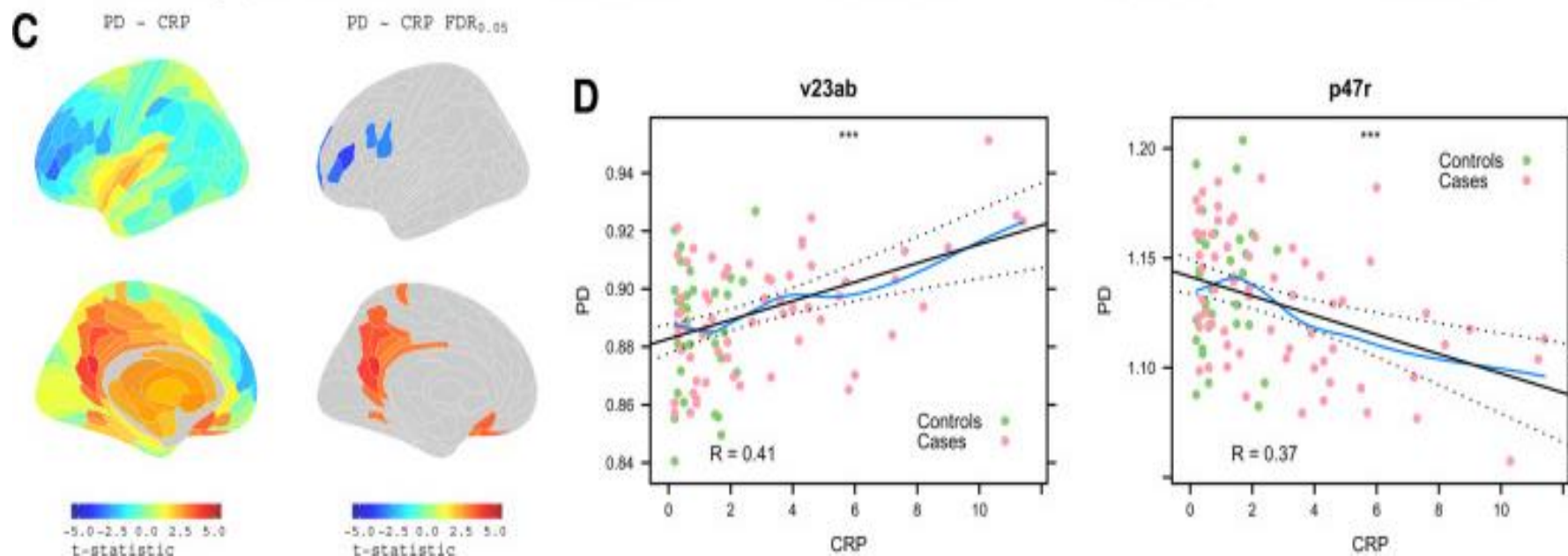
# Functional connectivity associations with inflammatory proteins in depression



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

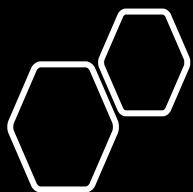
## Microstructure changes as proxy of inflammation

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



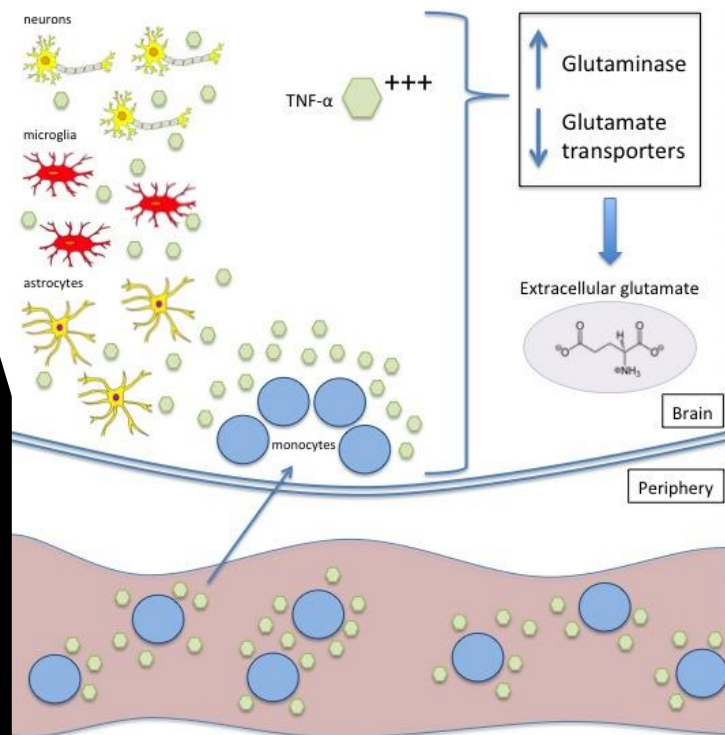
CRP-related increases in proton density—  
 a plausible marker of extracellular oedema—and changes in functional connectivity were anatomically co-localised with DMN nodes effects of peripheral inflammation on DMN node micro-structure and connectivity may mediate inflammatory effects on depression.





## *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).



### Sickness behaviours

- Low mood
- Decreased cognitive function
- Fatigue
- Increased pain sensitivity

MRC

Medical  
Research  
Council

# Potential molecular targets

## Group Members

### Post Docs

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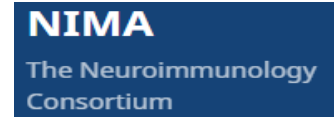
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*Prof Ed Bullmore, Prof Charlotte Summers and colleagues, University of Cambridge*



*Inger M. Lilya and George  
Simpson Biological Psychiatry  
Scholarships*

