Inflammation and Depression

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UNIVERSITY OF CAMBRIDGE

Ed Bullmore
Disclosures

Employment

- **Paid Employment**
  University of Cambridge
  (GSK, 0.5 FTE, 2005-2019)

- **Editorial Roles**
  Biological Psychiatry – Deputy Editor
  Network Neuroscience – Senior Editor

- **National Health Service (HCP) Role**
  Hon Consultant Psychiatrist and Director of R&D, Cambridgeshire & Peterborough NHS Foundation Trust

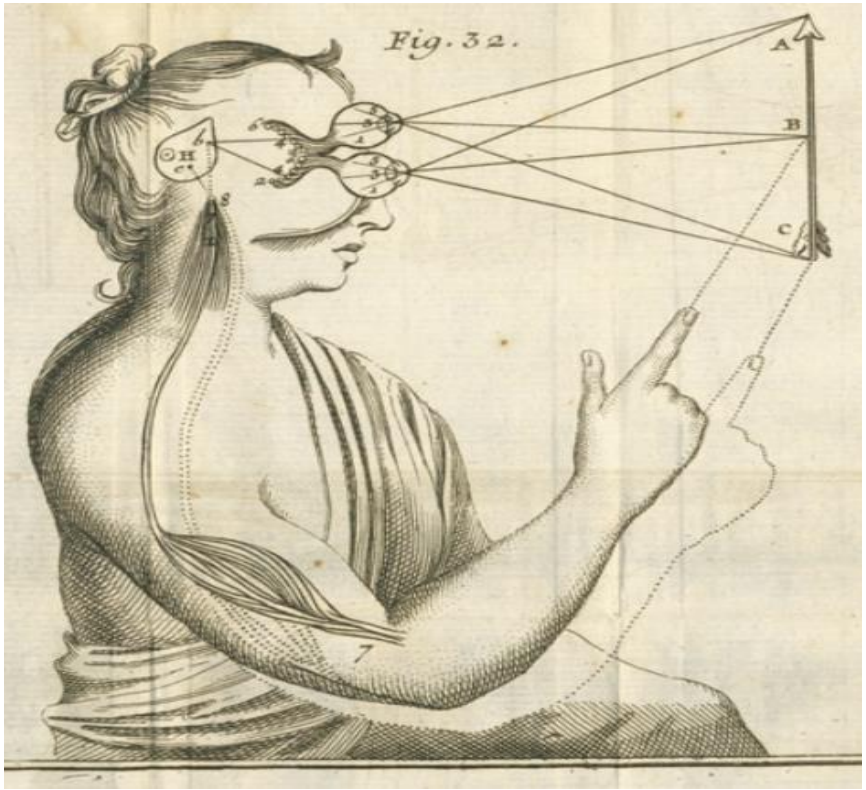
- **Honorary Roles**
  Treasurer, Academy of Medical Sciences

- **Royalties**
  Short Books, London and overseas publishers of "*The Inflamed Mind*"

Sources of Research Support

- Medical Research Council
- Wellcome Trust
- National Institute for Health Research
- National Institutes of Health, Graduate Partnership Program
- GSK, Janssen, Lundbeck, Pfizer

Dualism – the ancient philosophy that still divides us



Descartes (1637) *Treatise on Human Nature*

Dualist sting in the tail of major depressive disorder (MDD)

DSM5 (2013) *American Psychiatric Association*

Inclusion criteria:

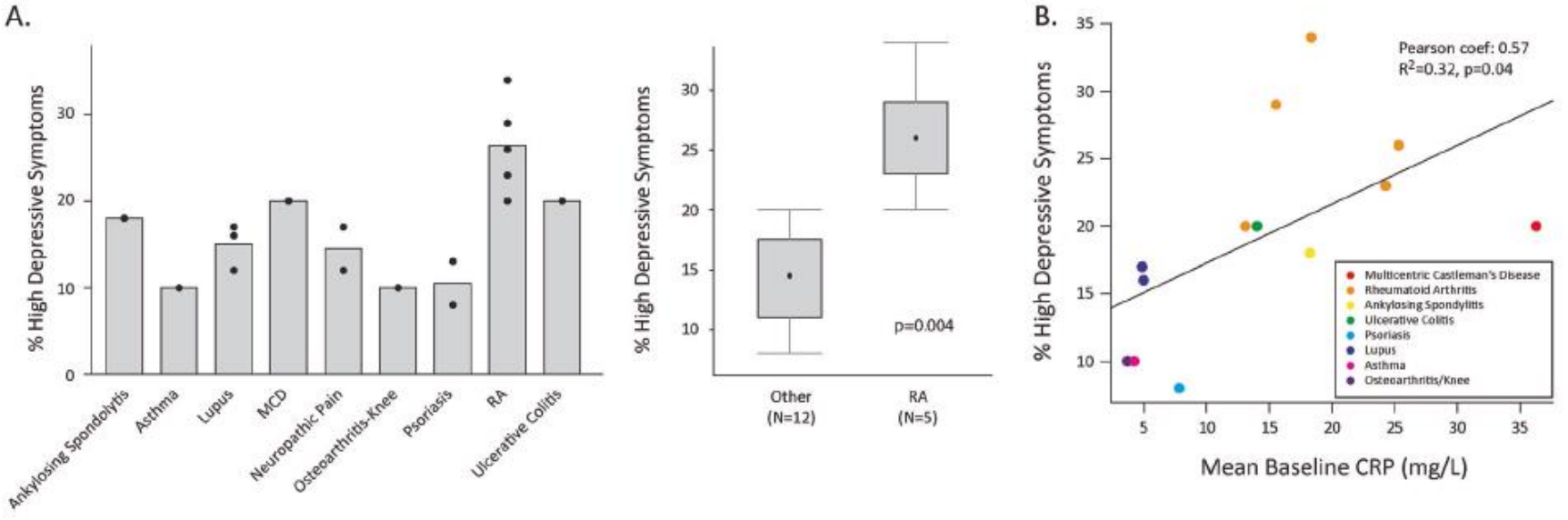
Five or more of nine symptoms, including at least one of two "core" symptoms, representing a change in function, and causing significant distress or impairment, for at least two weeks:

1. ***Depressed mood***
2. ***Loss of pleasure***
3. *Change in weight or appetite (up or down)*
4. *Change in sleep (insomnia or hypersomnia)*
5. *Psychomotor retardation or agitation*
6. *Loss of energy or fatigue*
7. *Worthlessness or guilt*
8. *Impaired concentration or decisiveness*
9. *Suicidal ideation or attempts*

Exclusion criterion:

Symptoms must ***not*** be attributable to a substance or medical condition

Depressive symptoms are commonly "co-morbid" with medical inflammatory disorders



SF-36 mental health questionnaire data on 10,743 patients in anti-inflammatory drug trials for physical health disorders

gsk janssen MRC Medical Research Council

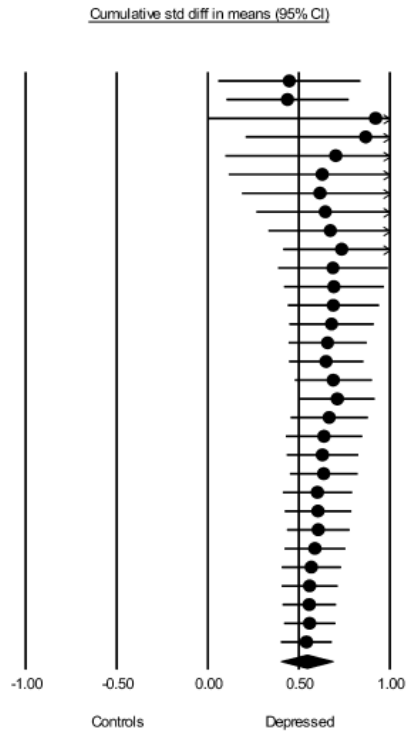
Wittenberg et al (2019) *Molecular Psychiatry*

Case-control studies of MDD replicably demonstrate moderately increased blood concentrations of pro-inflammatory cytokines and C-reactive protein

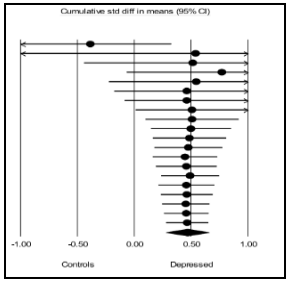
1995

2015

Study name	Subgroup within study	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Depressed	Control
Maes M et al., 1995a	MDD (all)	0.448	0.200	0.040	0.055	0.841	2.236	0.025	77	38
Maes M et al., 1995b	MDD (all)	0.439	0.172	0.030	0.100	0.777	2.542	0.011	90	66
Sluzewska A et al., 1996	MDD (all)	0.923	0.473	0.224	-0.005	1.851	1.949	0.051	139	81
Maes M et al., 1997	MDD (all)	0.868	0.338	0.114	0.206	1.530	2.570	0.010	174	96
Kagaya A 2001	MDD (all)	0.704	0.311	0.097	0.095	1.314	2.264	0.024	183	105
Mkova O et al., 2001	MDD (all)	0.629	0.263	0.069	0.114	1.144	2.392	0.017	211	120
Basterzi AD et al., 2005	MDD (all)	0.617	0.220	0.048	0.186	1.049	2.803	0.005	234	143
Motivala SJ et al., 2005	MDD (all)	0.646	0.194	0.038	0.266	1.026	3.330	0.001	256	161
Fitzgerald P et al., 2006	MDD (all)	0.674	0.175	0.031	0.331	1.016	3.855	0.000	275	180
Leo R et al., 2006	MDD (all)	0.736	0.165	0.027	0.412	1.061	4.449	0.000	321	226
Pavon L et al., 2006	MDD (all)	0.688	0.155	0.024	0.384	0.992	4.439	0.000	354	259
Pike JL and Irwin MR 2006	MDD (all)	0.693	0.141	0.020	0.416	0.970	4.904	0.000	379	284
OBrien S et al., 2007	MDD (all)	0.690	0.130	0.017	0.436	0.944	5.324	0.000	407	308
Yang K et al., 2007	MDD (all)	0.680	0.120	0.014	0.445	0.915	5.680	0.000	440	331
Simon NM et al., 2008	MDD (all)	0.659	0.111	0.012	0.442	0.875	5.958	0.000	489	380
Dhabhar FS et al., 2009	MDD (all)	0.650	0.106	0.011	0.443	0.858	6.144	0.000	501	391
Weinstein, AA et al., 2010	MDD (all)	0.690	0.109	0.012	0.476	0.905	6.307	0.000	515	405
Yoshimura R et al., 2010	MDD (all)	0.712	0.106	0.011	0.504	0.921	6.697	0.000	535	425
Euteneuer F et al., 2011	MDD (all)	0.667	0.110	0.012	0.453	0.882	6.092	0.000	572	473
Fornaro, Met al., 2011	MDD (all)	0.638	0.108	0.012	0.427	0.850	5.911	0.000	588	489
Hughes MM et al., 2012	Combined	0.630	0.102	0.010	0.431	0.829	6.202	0.000	627	528
Karlovic D et al., 2012	Combined	0.637	0.096	0.009	0.449	0.825	6.634	0.000	682	564
Voderholzer U et al., 2012	MDD (all)	0.603	0.099	0.010	0.410	0.796	6.117	0.000	695	579
Carvalho LA et al., 2013	MDD (all)	0.605	0.095	0.009	0.420	0.791	6.385	0.000	714	600
Dunjic-Kostic B et al., 2013	Combined	0.607	0.089	0.008	0.433	0.782	6.813	0.000	761	678
Frodl T et al., 2013	MDD (all)	0.589	0.087	0.007	0.419	0.758	6.799	0.000	801	721
Hennings, A et al., 2013	MDD (all)	0.569	0.085	0.007	0.403	0.735	6.725	0.000	839	769
ODonovan A et al., 2013	Combined	0.560	0.080	0.006	0.404	0.716	7.020	0.000	913	865
Dahl J et al., 2014	MDD (all)	0.558	0.076	0.006	0.408	0.708	7.298	0.000	963	899
Kéri S et al., 2014	MDD (all)	0.560	0.074	0.005	0.416	0.704	7.612	0.000	1013	929
Rudolf S et al., 2014	Combined	0.542	0.073	0.005	0.399	0.685	7.430	0.000	1045	977
		0.542	0.073	0.005	0.399	0.685	7.430	0.000		



IL6, d ~ 0.5



CRP, d ~ 0.5

Happakoski et al (2015) *Brain Behavior & Immunity*

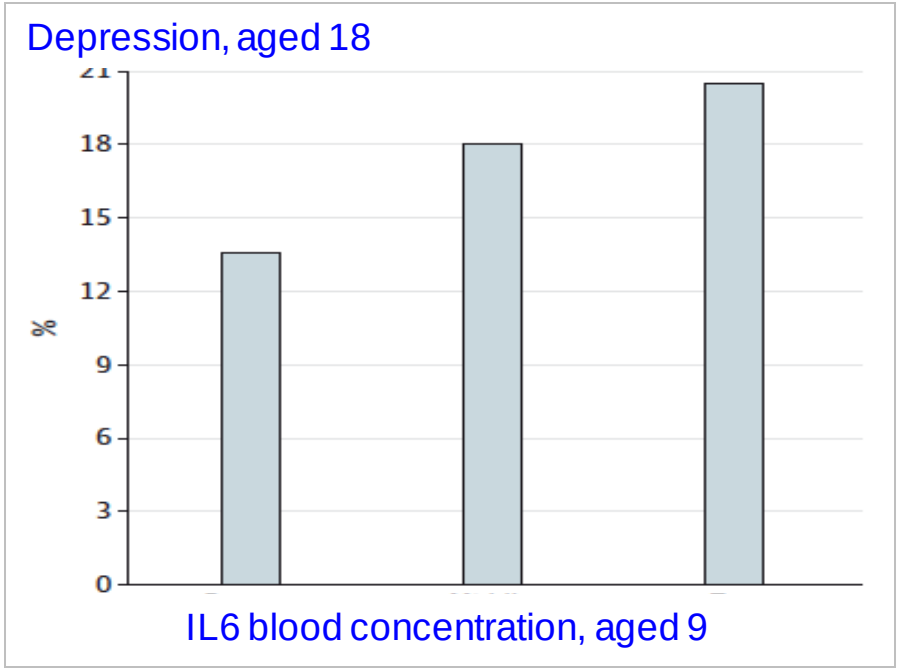
Some questions about causality

- Causes precede effects: does inflammation precede or anticipate depression?
- Causes are mechanistically linked to effects: can inflammation of the body be mechanistically linked to the brain and mind?
- Causes have causes: what are causes of inflammation that are also known risk factors for depression?
- In biology, natural selection of DNA is ultimately causal: is there an evolutionary theory of inflamed depression – and is there any genetic evidence for it?
- In medicine, causality implies therapeutic tractability: can anti-inflammatory drugs be effective as anti-depressants, at least for some patients?

Inflammation can precede depression, so could be causal…

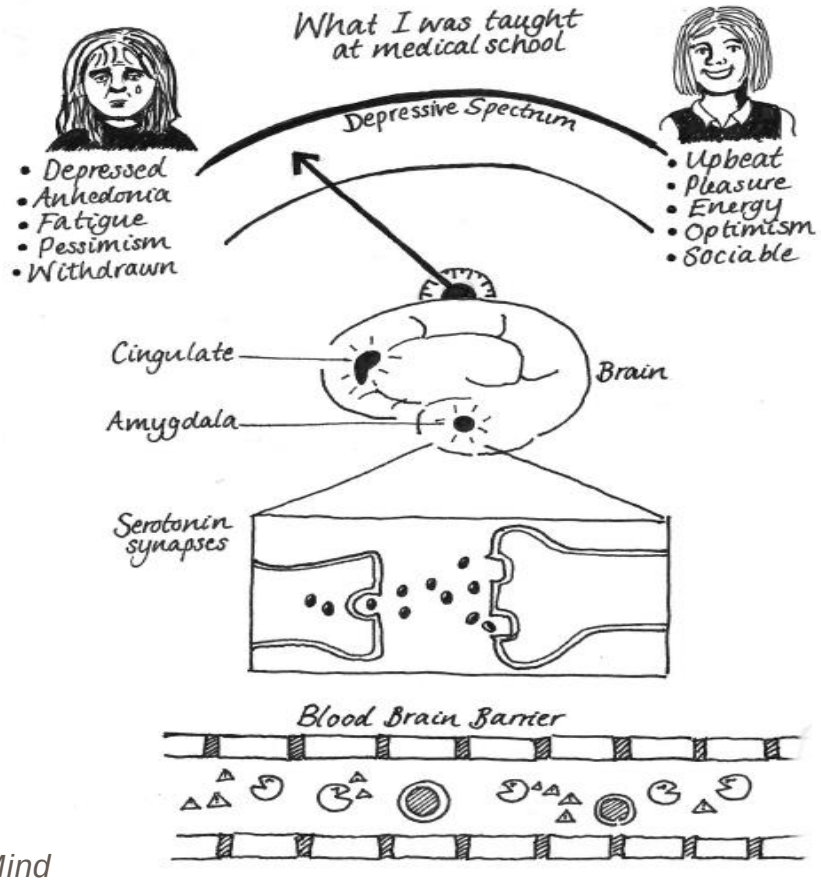
First inflammation then depression, over a range of time scales:

- ***Days**: typhoid vaccination induces 24-48 hours of "feeling down" for many people*
- ***Weeks:** interferon treatment for hepatitis is followed by depression several weeks later in about 40% of patients*
- ***Years**: low grade inflammation in a birth cohort predicts greater risk of depression 10 years later*



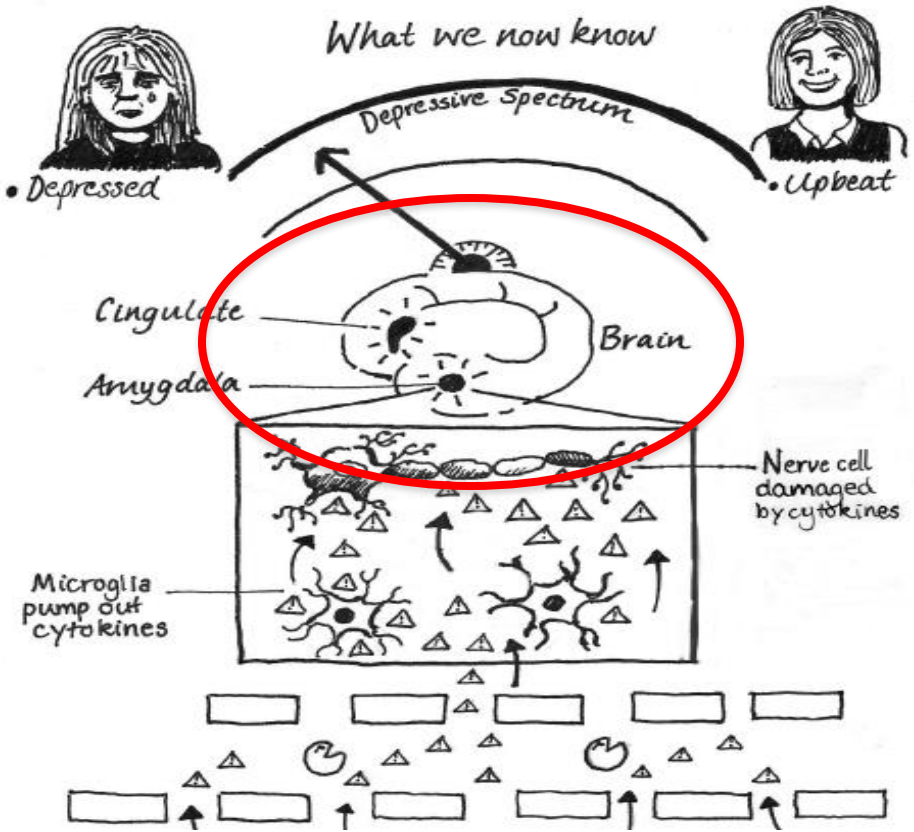
Harrison et al (2009) *Biological Psychiatry*
Pariante et al (1999) *The Lancet*
Khandaker et al (2013) *JAMA Psychiatry*

The blood brain barrier – BBB – like a Berlin wall in the brain?



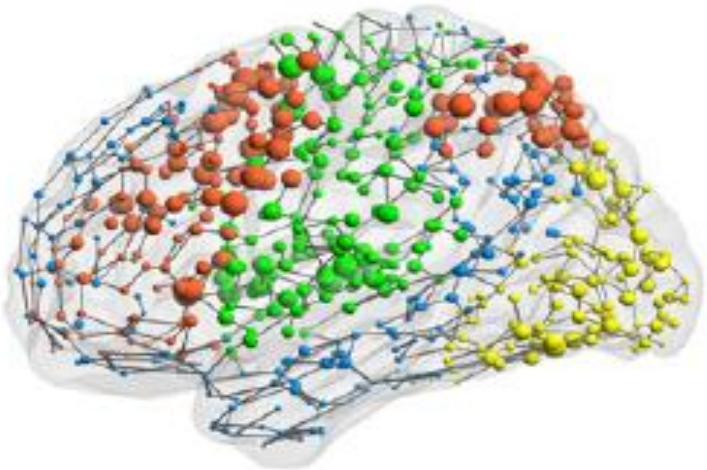
Bullmore (2018) *The Inflamed Mind*

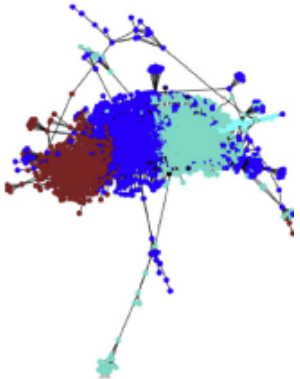
The BBB - like the Berlin wall – is not what it was in the 1980s



Bullmore (2018) *The Inflamed Mind*

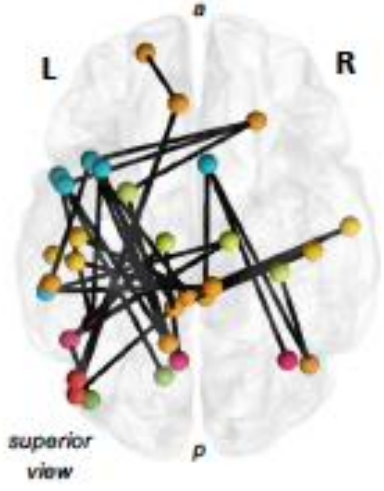
Brain networks are topologically complex – like gene transcriptional networks, the global airline network, etc





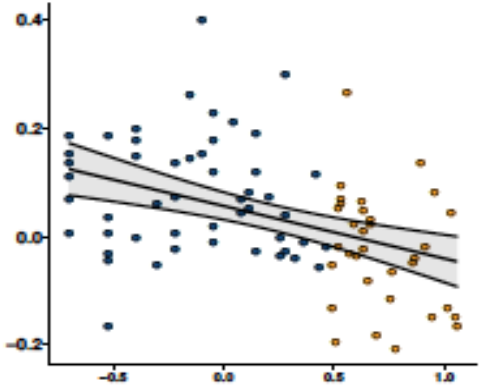
Haber et al (2021) *Neuropsychopharmacology*
Fornito, Zalesky, Bullmore (2016) *Fundamentals of Brain Network Analysis*

Inflammation (CRP and immune cell counts) associated with decreased functional connectivity of an interoceptive brain network



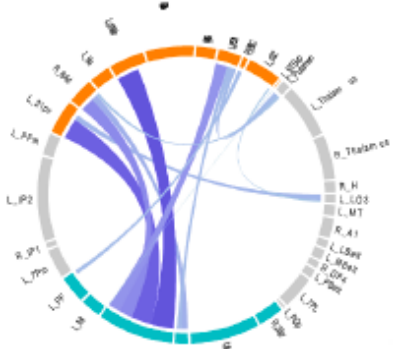
Default mode network
Ventral attention network

Interoceptive network connectivity

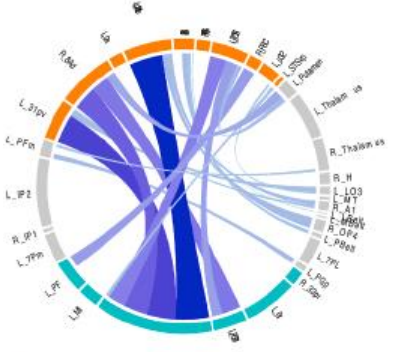


CRP blood concentration

Low-cell count

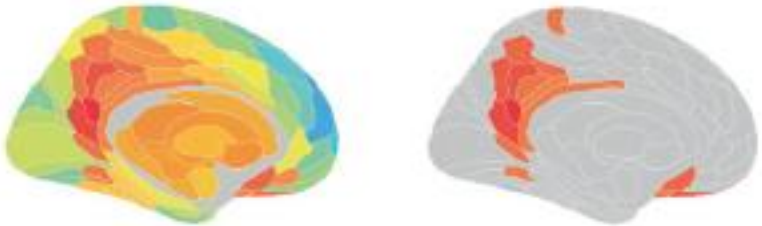


High-cell count

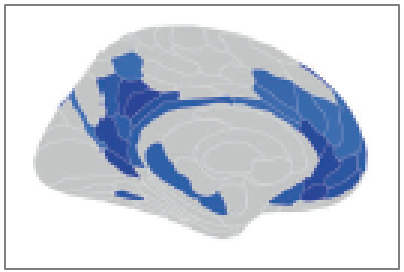


Aruldass et al (2021) *Brain Behavior & Immunity*

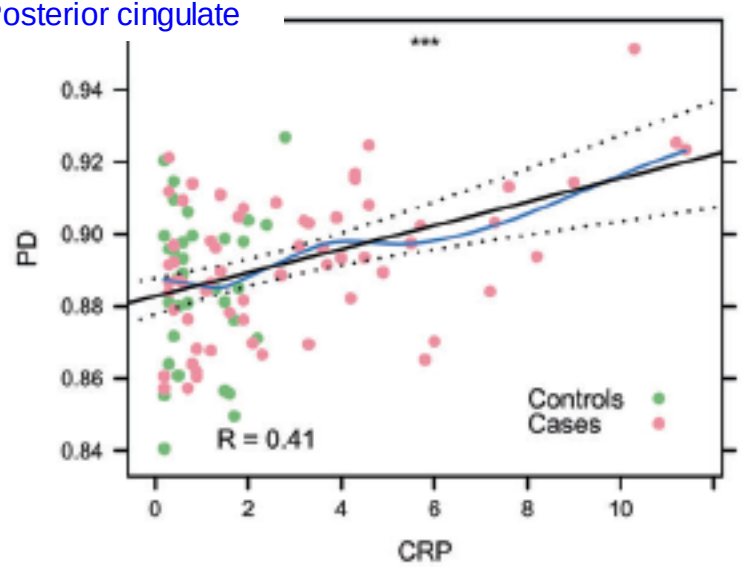
Inflammation (CRP) scales with proton density – a micro-structural MRI marker of oedema – in default mode nodes



Map of depression-related loss of fMRI connectivity in DMN nodes

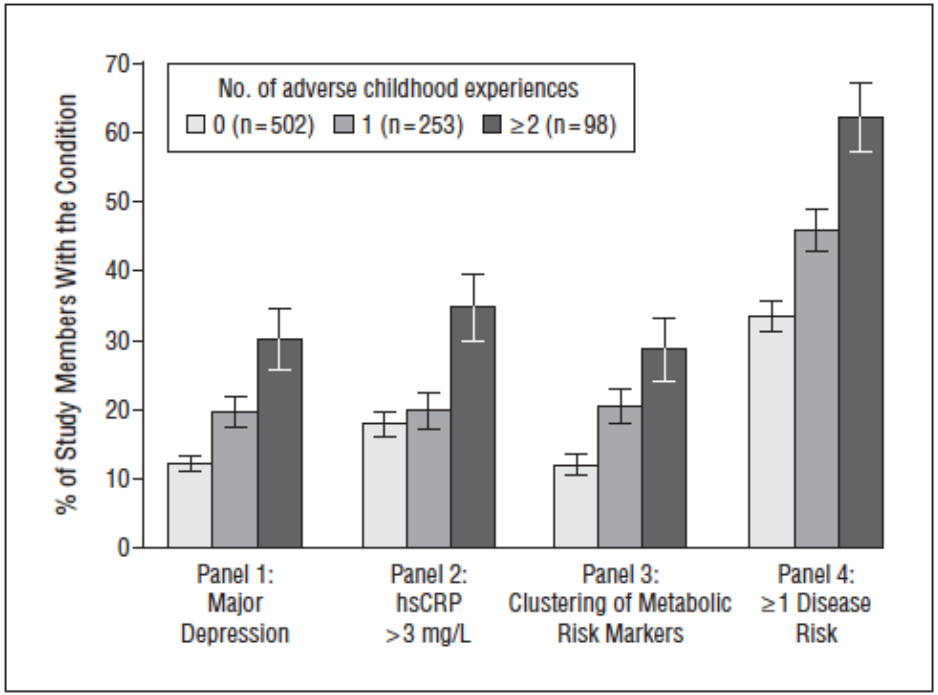


Posterior cingulate



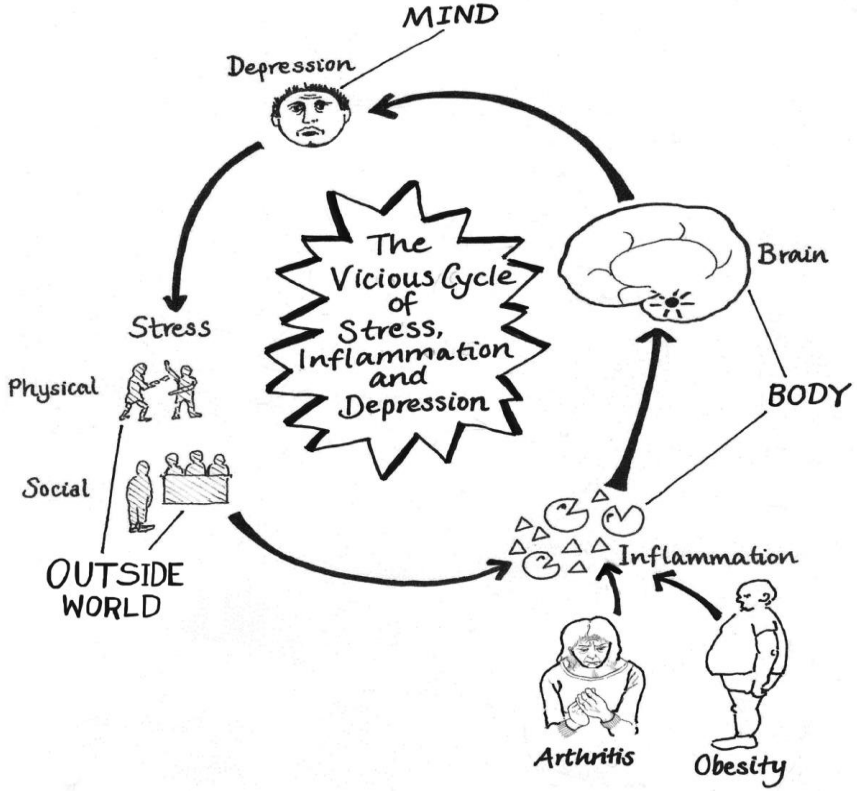
Kitzbichler et al (2021) *Molecular Psychiatry*

Adverse childhood experiences predispose to inflammation, metabolic risk and depression



Danese et al (2012) *Archives of Pediatric & Adolescent Medicine*

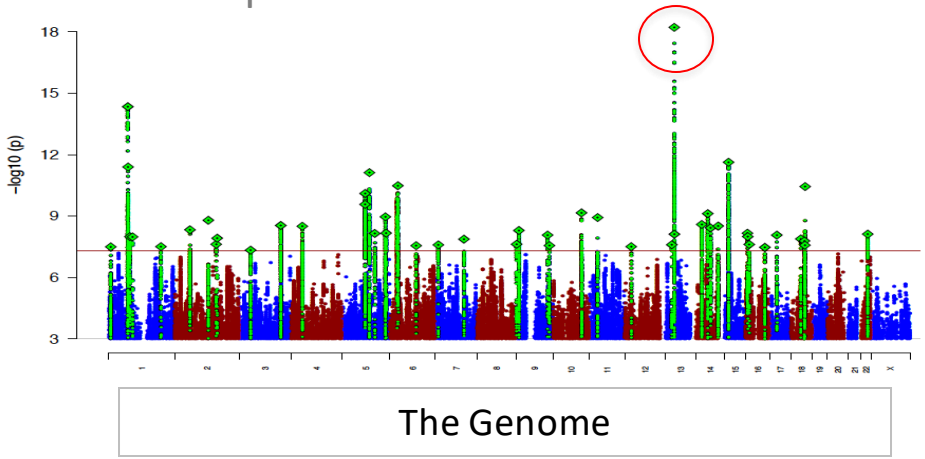
Stress, inflammation and depression
an artist's impression



Bullmore (2018) *The Inflamed Mind*

Why does inflammation cause depression?

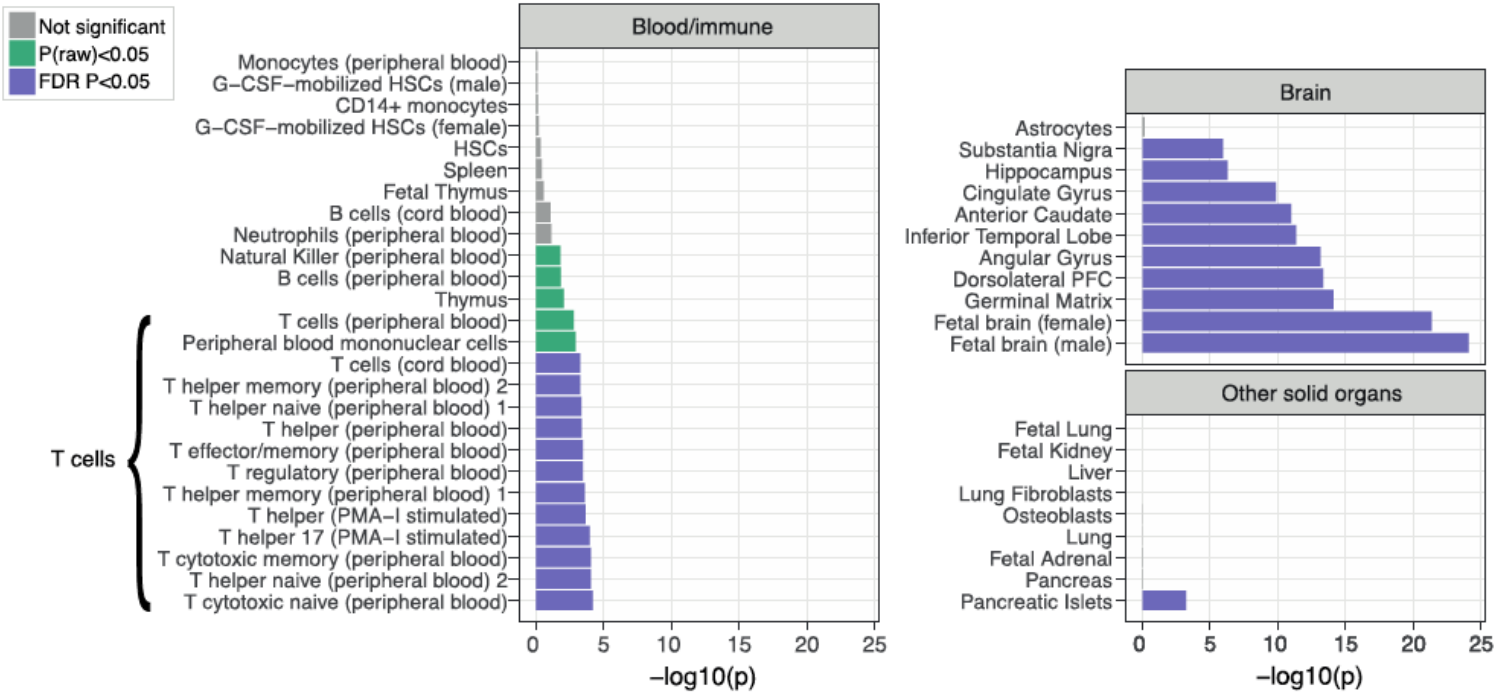
Olfactomedin 4 – moderates gastric inflammatory response in animals



The Genome

Miller & Raison (2016) *Nature Reviews Immunology*
Wray et al (2018) *Nature Genetics*

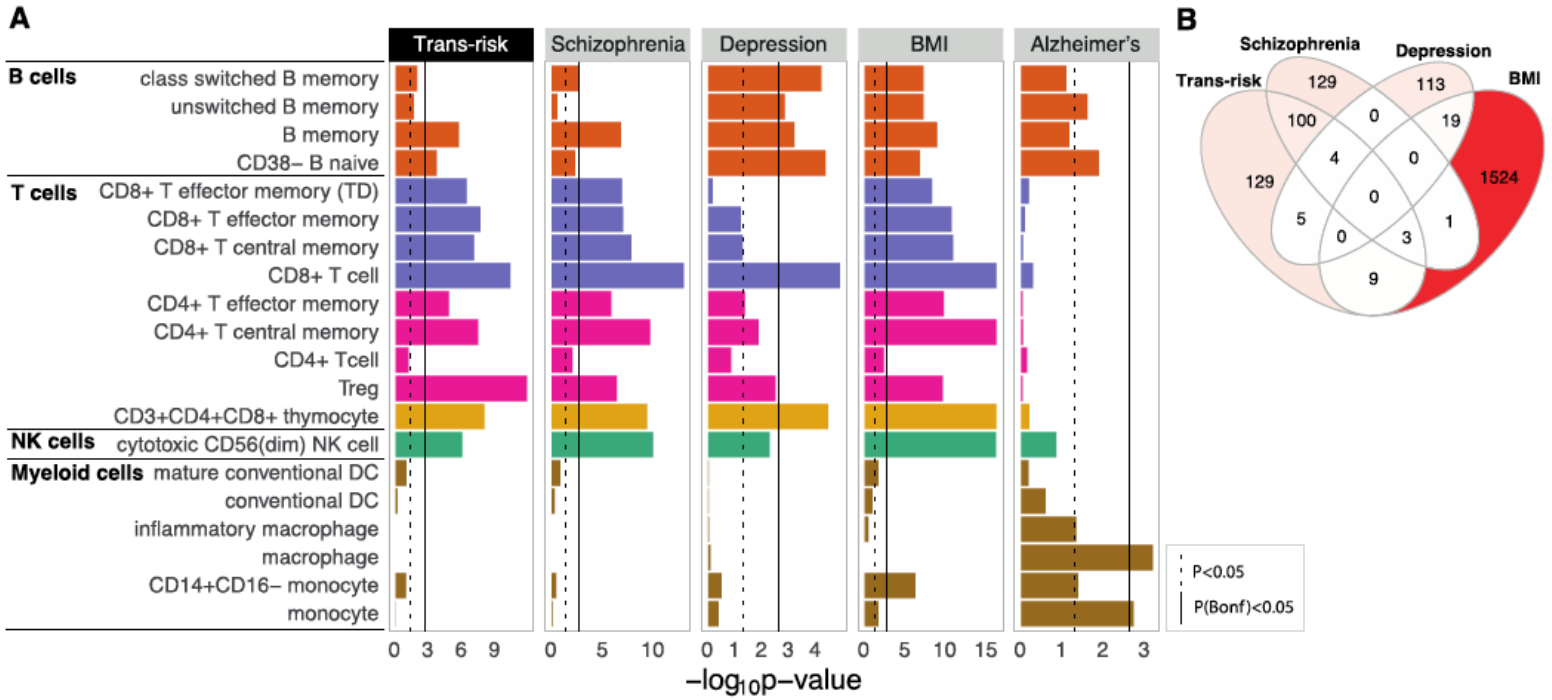
Trans-diagnostic risk variants from GWAS are enriched at epigenetically activated sites in CNS and immune (T) cells



Roadmap data on 88 tissue types, tested for enrichment of epigenetically active sites by GWAS trans-diagnostic variants, using s-LDSC regression

Lynall et al (2021) *medRxiv*

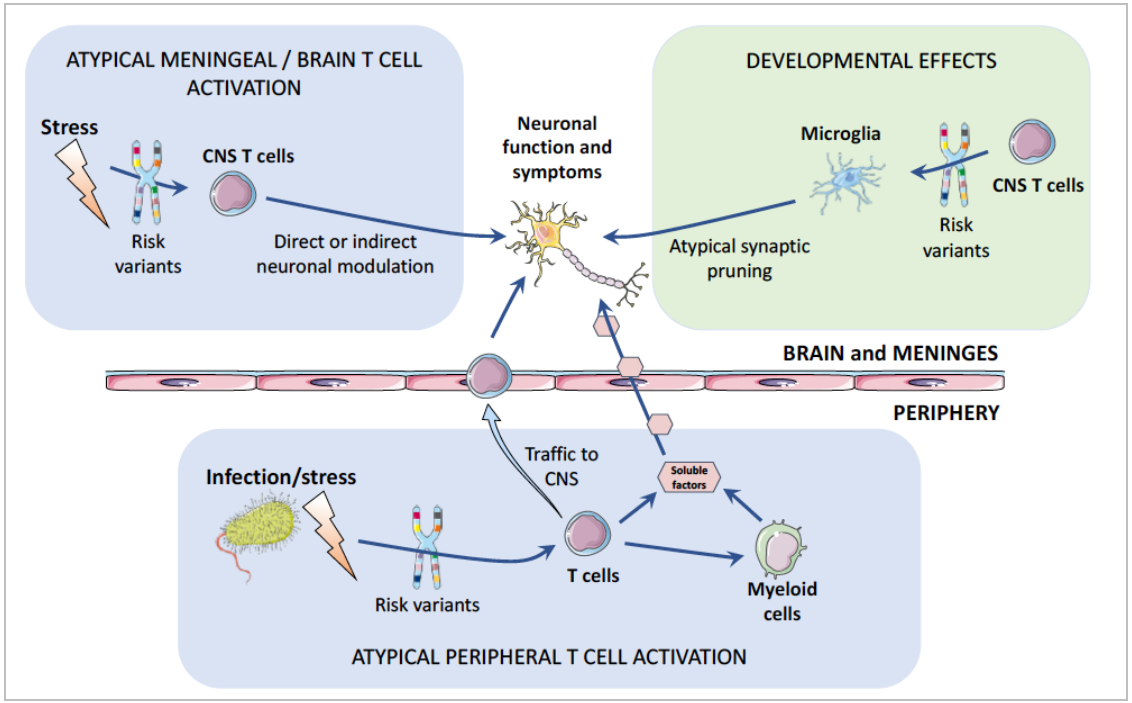
Trans- and cis-diagnostic risk variants from GWAS are enriched at epigenetically activated sites in lymphoid cells



Lynall et al (2021) *medRxiv*

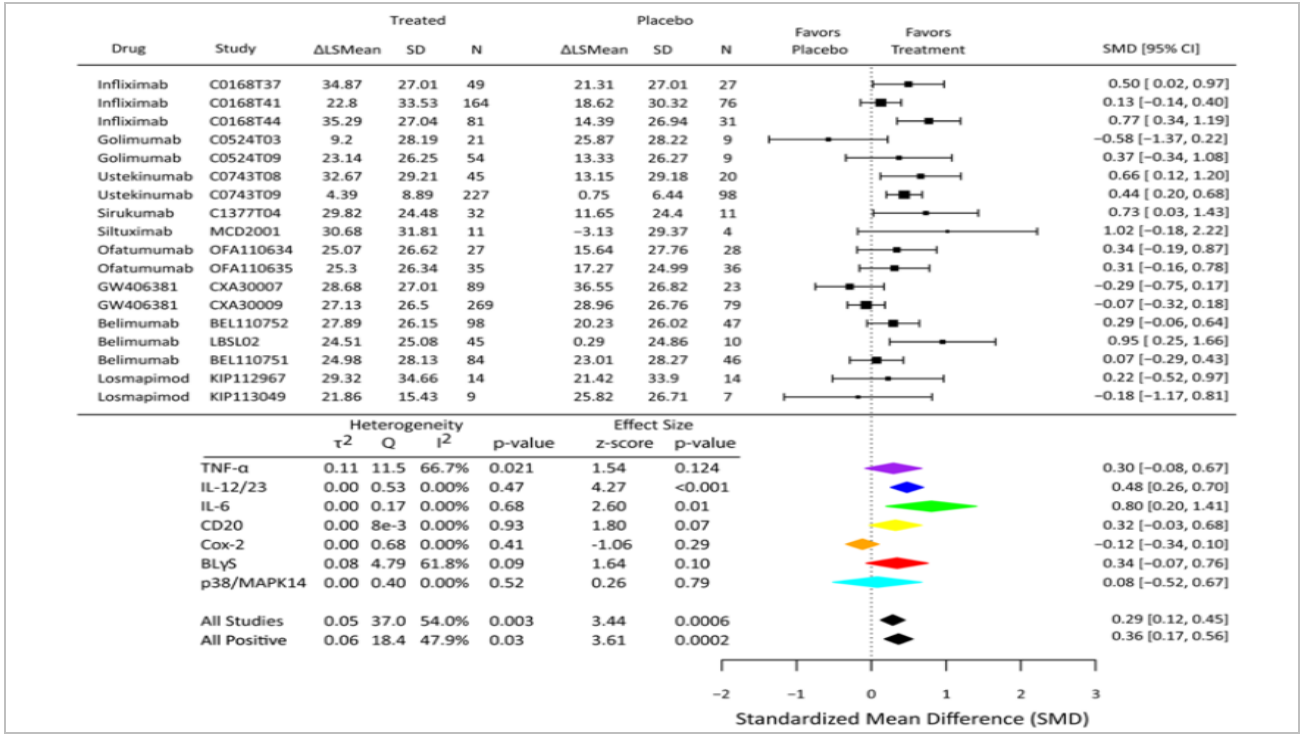
BLUEPRINT data tested for enrichment of histone-acetylated marks by GWAS trans-diagnostic and disorder-specific variants, using CHEERS

Environmental stress *may* lead to development of psychiatric disorders by epigenetic modification of risk variants in immune cells



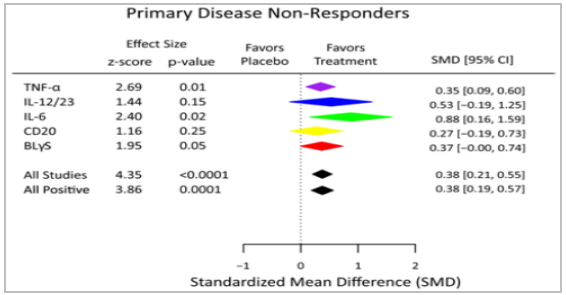
Lynall et al (2021) *medRxiv*

Anti-inflammatory drugs often have anti-depressant effects for “co-morbid” depression



Drug	Study	Treated ΔLSMean	Treated SD	Treated N	Placebo ΔLSMean	Placebo SD	Placebo N	SMD [95% CI]
Infliximab	C0168T37	34.87	27.01	49	21.31	27.01	27	0.50 [0.02, 0.97]
Infliximab	C0168T41	22.8	33.53	164	18.62	30.32	76	0.13 [−0.14, 0.40]
Infliximab	C0168T44	35.29	27.04	81	14.39	26.94	31	0.77 [0.34, 1.19]
Golimumab	C0524T03	9.2	28.19	21	25.87	28.22	9	−0.58 [−1.37, 0.22]
Golimumab	C0524T09	23.14	26.25	54	13.33	26.27	9	0.37 [−0.34, 1.08]
Ustekinumab	C0743T08	32.67	29.21	45	13.15	29.18	20	0.66 [0.12, 1.20]
Ustekinumab	C0743T09	4.39	8.89	227	0.75	6.44	98	0.44 [0.20, 0.68]
Sirukumab	C1377T04	29.82	24.48	32	11.65	24.4	11	0.73 [0.03, 1.43]
Siltuximab	MCD2001	30.68	31.81	11	−3.13	29.37	4	1.02 [−0.18, 2.22]
Ofatumumab	OFA110634	25.07	26.62	27	15.64	27.76	28	0.34 [−0.19, 0.87]
Ofatumumab	OFA110635	25.3	26.34	35	17.27	24.99	36	0.31 [−0.16, 0.78]
GW406381	CXA30007	28.68	27.01	89	36.55	26.82	23	−0.29 [−0.75, 0.17]
GW406381	CXA30009	27.13	26.5	269	28.96	26.76	79	−0.07 [−0.32, 0.18]
Belimumab	BEL110752	27.89	26.15	98	20.23	26.02	47	0.29 [−0.06, 0.64]
Belimumab	LBSL02	24.51	25.08	45	0.29	24.86	10	0.95 [0.25, 1.66]
Belimumab	BEL110751	24.98	28.13	84	23.01	28.27	46	0.07 [−0.29, 0.43]
Losmapimod	KIP112967	29.32	34.66	14	21.42	33.9	14	0.22 [−0.52, 0.97]
Losmapimod	KIP113049	21.86	15.43	9	25.82	26.71	7	−0.18 [−1.17, 0.81]

	Heterogeneity τ^2	Q	I^2	p-value	Effect Size z-score	p-value	
TNF-α	0.11	11.5	66.7%	0.021	1.54	0.124	0.30 [−0.08, 0.67]
IL-12/23	0.00	0.53	0.00%	0.47	4.27	<0.001	0.48 [0.26, 0.70]
IL-6	0.00	0.17	0.00%	0.68	2.60	0.01	0.80 [0.20, 1.41]
CD20	0.00	8e-3	0.00%	0.93	1.80	0.07	0.32 [−0.03, 0.68]
Cox-2	0.00	0.68	0.00%	0.41	-1.06	0.29	−0.12 [−0.34, 0.10]
BLyS	0.08	4.79	61.8%	0.09	1.64	0.10	0.34 [−0.07, 0.76]
p38/MAPK14	0.00	0.40	0.00%	0.52	0.26	0.79	0.08 [−0.52, 0.67]
All Studies	0.05	37.0	54.0%	0.003	3.44	0.0006	0.29 [0.12, 0.45]
All Positive	0.06	18.4	47.9%	0.03	3.61	0.0002	0.36 [0.17, 0.56]



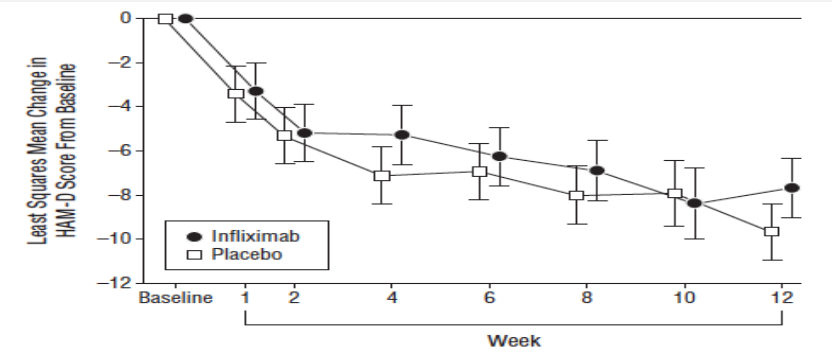
Overall (7 mechanisms of action) d ~ 0.29

Anti- IL-6 (sirukumab and siltuximab) d ~ 0.80

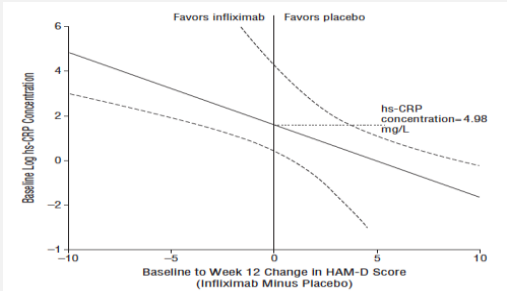
Anti-IL-12/23 (ustekinumab) d ~ 0.74

Wittenberg, Stylianou, Khan et al (2019) *Molecular Psychiatry*

Anti-inflammatory drug treatment for MDD will need biomarkers



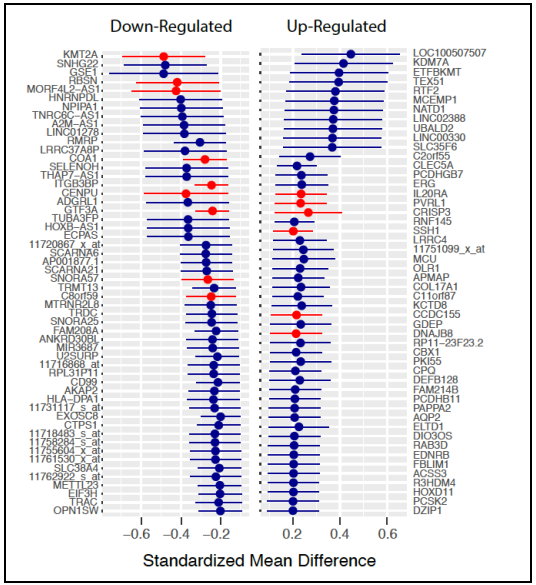
Higher blood CRP level at baseline



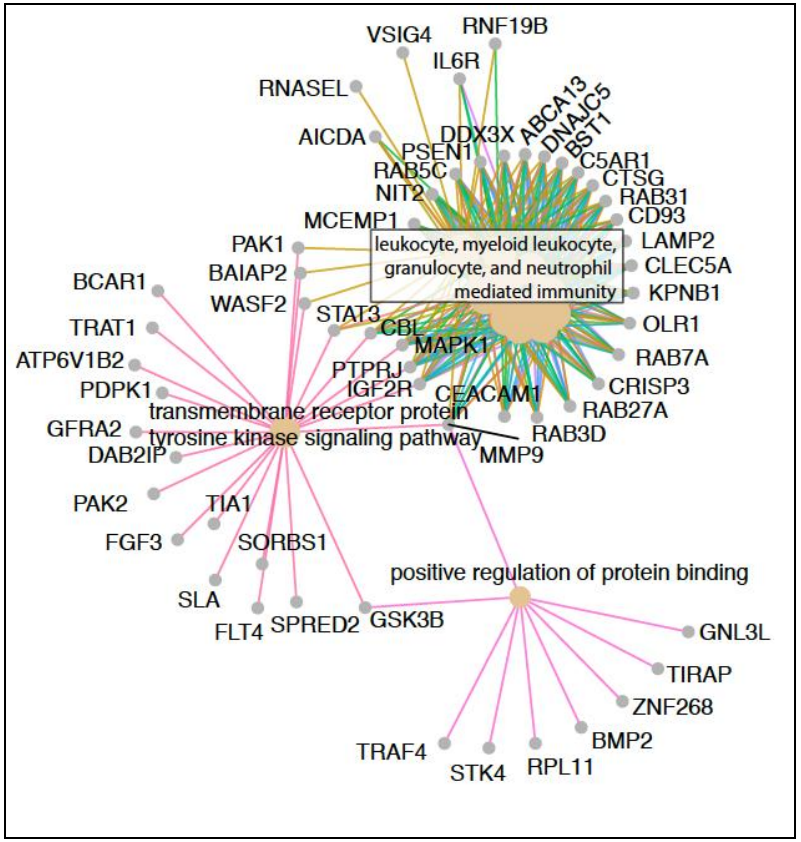
Greater anti-depressant effect of anti-TNF antibody

Raison et al (2013) *JAMA Psychiatry*

Whole genome transcriptional biomarkers of MDD in whole blood

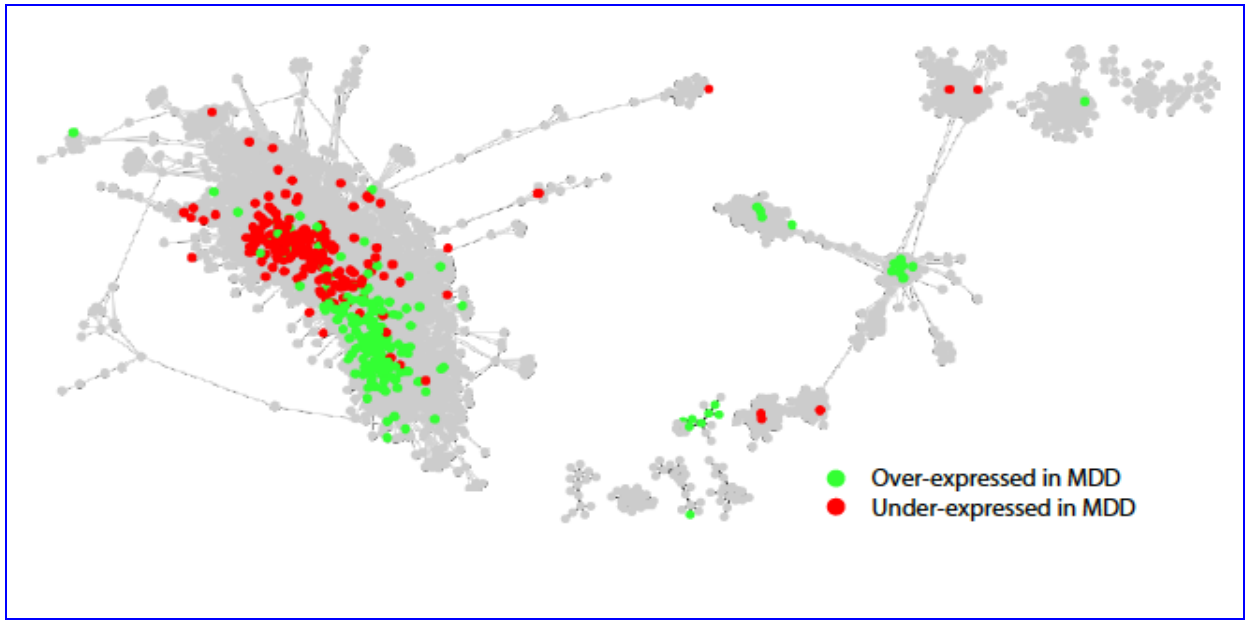


- 4 independent primary studies
- N = 1,552 MDD cases and 947 healthy controls
- 325 genes differentially expressed with FDR 5%
- Genes coded for a significantly interactive protein network and were enriched for myeloid leukocyte functions



Wittenberg et al (2020) *Biological Psychiatry*

Genes over-expressed (or under-expressed) in MDD are concentrated in transcriptional network modules specialised for innate (or adaptive) immunity



Wittenberg et al (2020) *Biological Psychiatry*

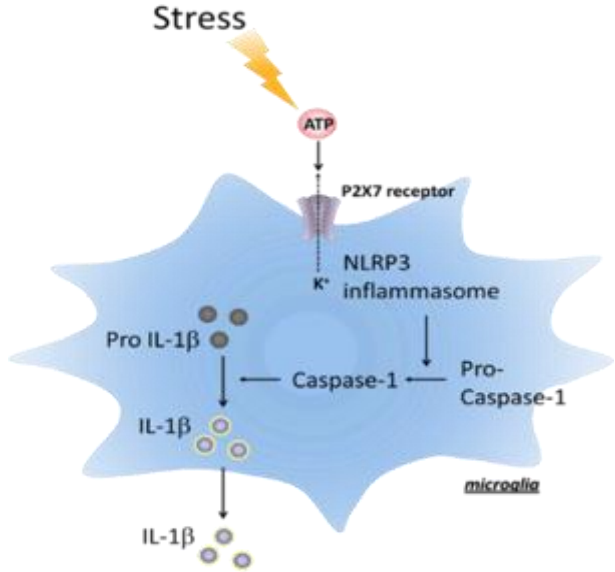
ATP: a phase 2 trial of a P2X7 antagonist for treatment of depression

The Target

- P2X7 is a ligand-gated ion channel, expressed on the surface of microglia, that is activated by supra-physiological levels of ATP
- In CNS, P2X7 signaling mediates neuroinflammation; antagonism of P2X7 produces efficacy in models of anhedonia (Bhattacharya et al., 2018)
- P2X7 antagonism could have anti-depressant efficacy by uncoupling stress from adverse brain changes caused by microglial release of IL1-β

The Drug

- JNJ-54175446 is a novel P2X7 antagonist with high selectivity, high CNS penetration and good safety and tolerability profile from previous clinical trials (Letavic et al., 2017; Timmers et al., accepted)



IL1β release from microglia has neurotoxic effects on local neurons

NIMA
The Neuroimmunology Consortium

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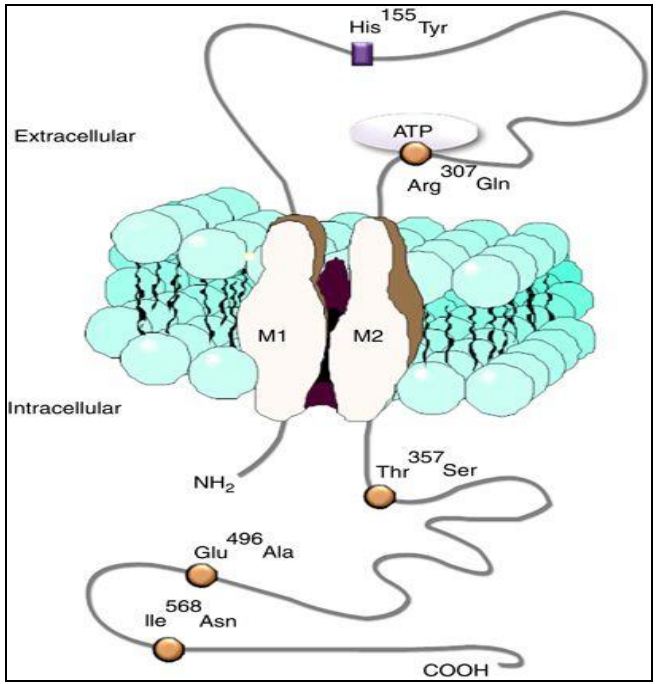
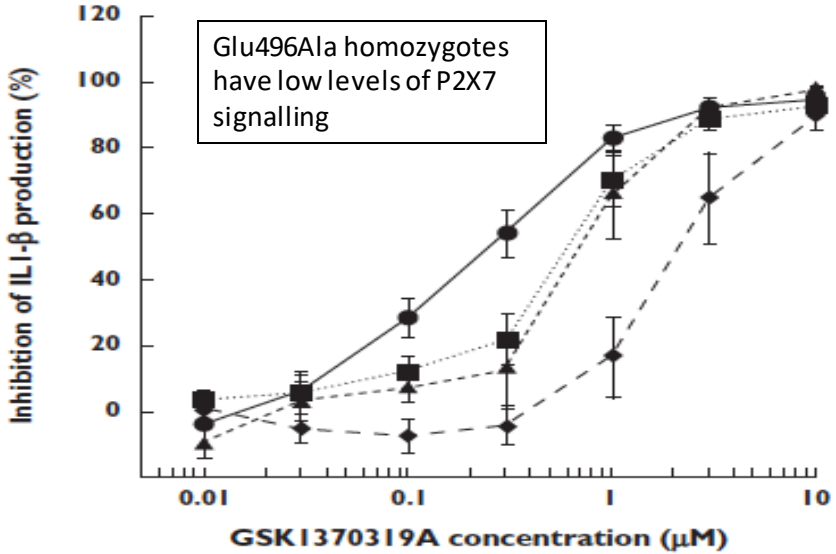
janssen

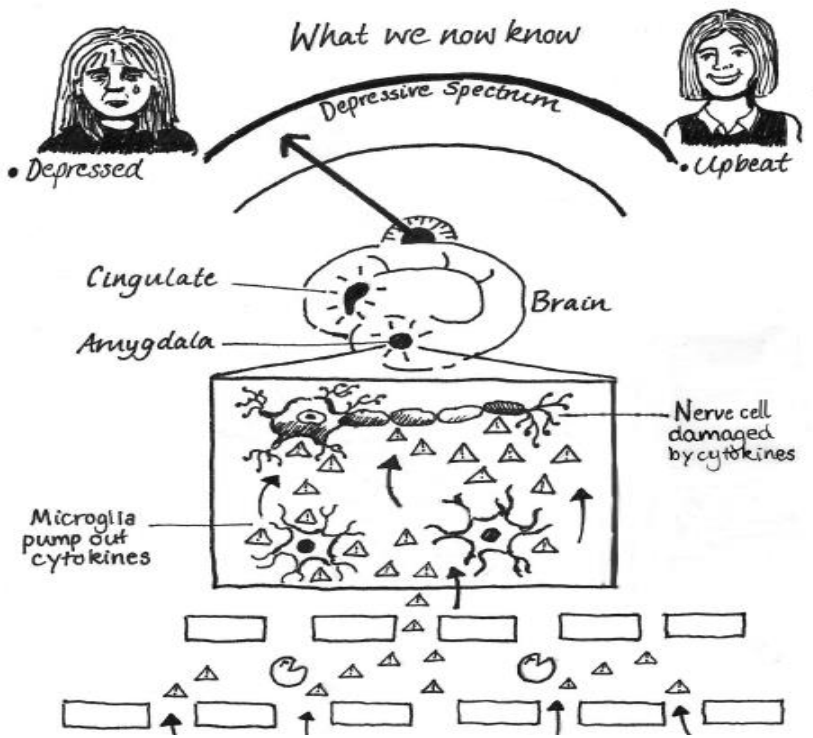
Functional polymorphism of *P2RX7* as a biomarker of anti-inflammatory response to P2X7 antagonist

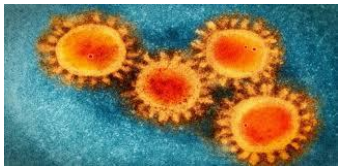




McHugh et al (2012) *British Journal of Clinical Pharmacology*
Gartland et al (2012) *Eur J Human Genetics*

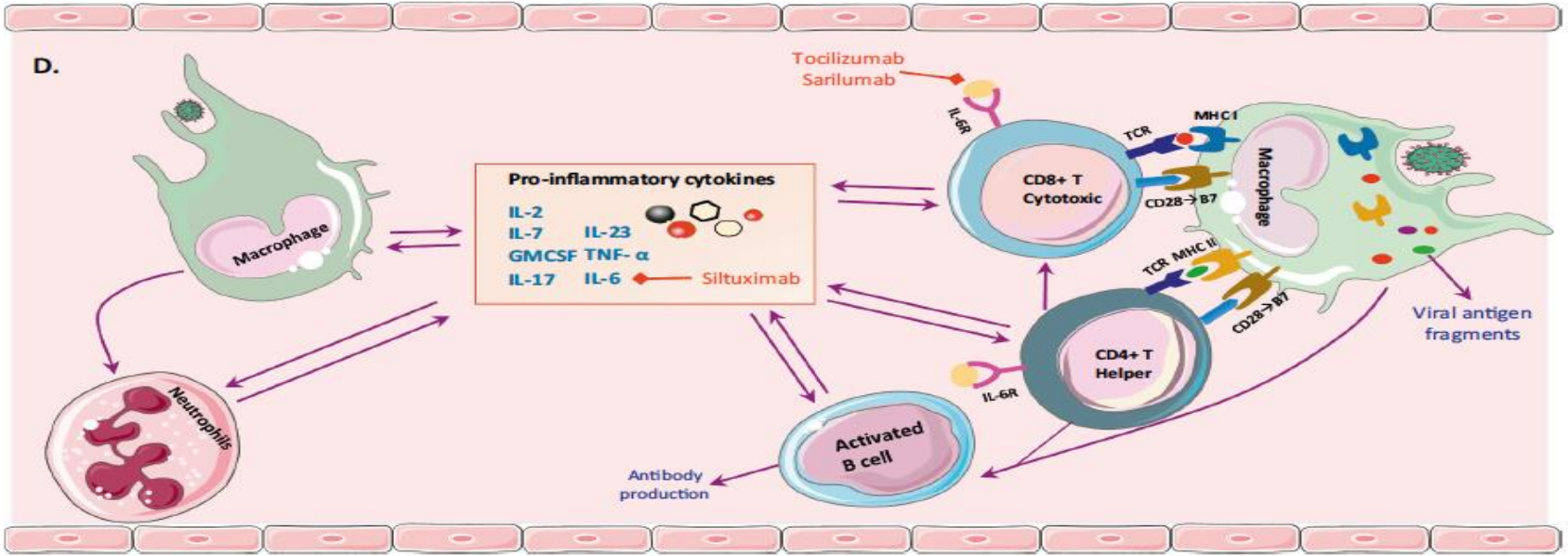
Implications for treatment of post-COVID depressive symptoms?





Bullmore (2018) *The Inflamed Mind*

SARS-CoV2 can elicit a pro-inflammatory "cytokine storm", with myeloid cell hyper-activation and lymphopenia

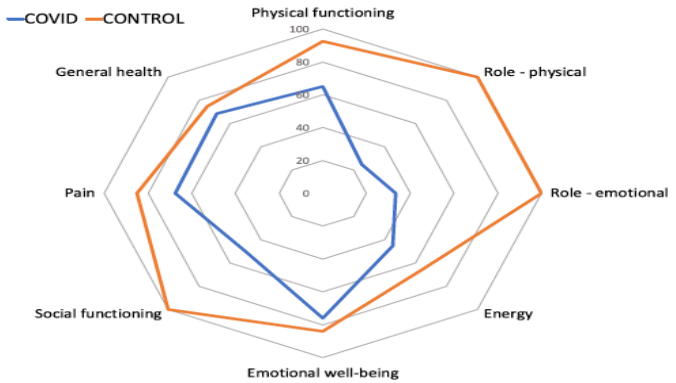


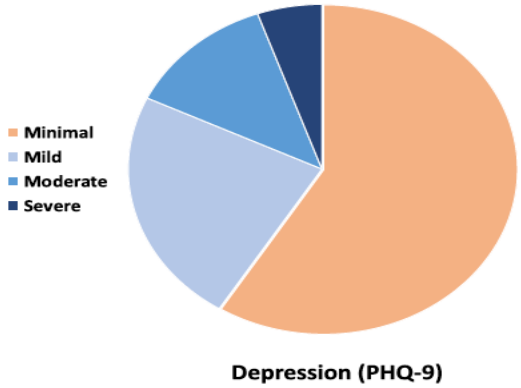
Innate immune response

Adaptive immune response

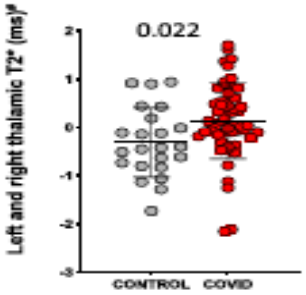
Keyhanian et al (2021) *J Neuroimmunology*

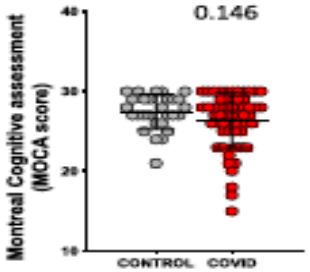
Brain MRI changes in post-hospitalised COVID patients correlated with increased blood inflammatory markers

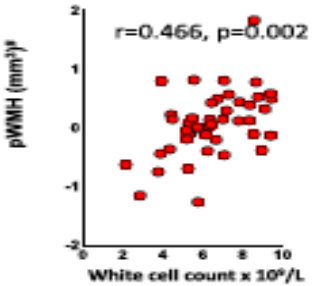




Depression (PHQ-9)







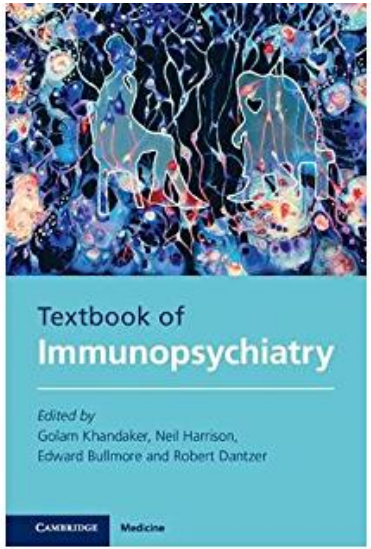
Raman et al (2021) *EClinicalMedicine*

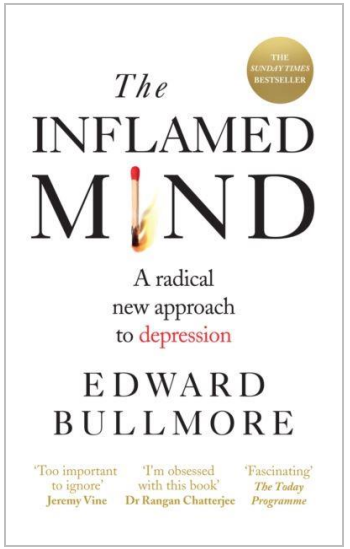
Conclusions

- **Association between depression and inflammation is beyond reasonable doubt and there is growing evidence for causality**
  - Peripheral inflammation is linked with reduced functional connectivity and increased water (oedema) in interoceptive and depression-related brain networks
  - Risk variants for depression and other psychiatric disorders are enriched for epigenetic activation in brain and immune cells, compatible with gene-by-environment interaction
- **Anti-inflammatory drugs might have anti-depressant efficacy but it won't be "one size fits all"**
  - Meta-analyses indicate anti-depressant effects of anti-inflammatory drugs in "co-morbid" depression
  - Biomarkers will likely be important for stratifying MDD patients most likely to respond to anti-inflammatory drugs
- **In future, maybe, depression will be diagnosed by causal factors rather than categorised dualistically**

Thanks!

- Athina Aruldass
- Wayne Drevets
- Neil Harrison
- Golam Khandaker
- Manfred Kitzbichler
- Mary-Ellen Lynall
- Husseini Manji
- Carmine Pariante
- Gayle Wittenberg





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