Biomarkers, Inflammation, and the New Mind-Body Science of Depression

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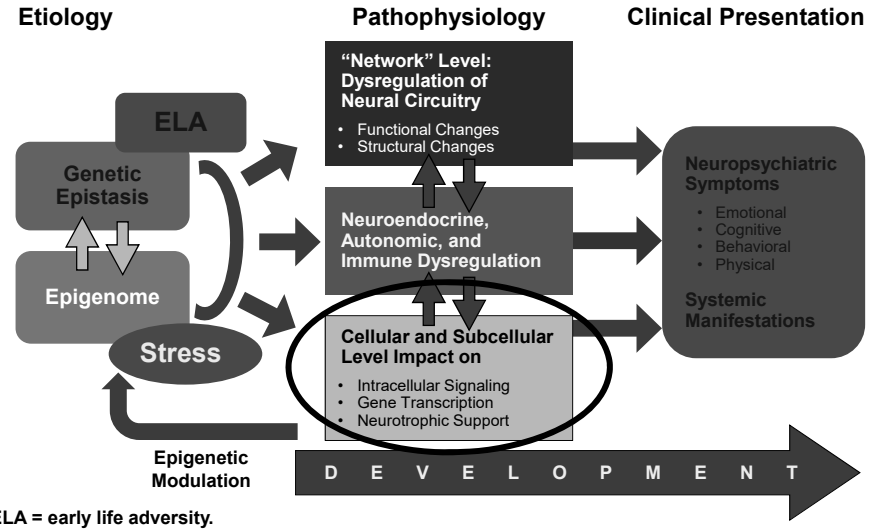
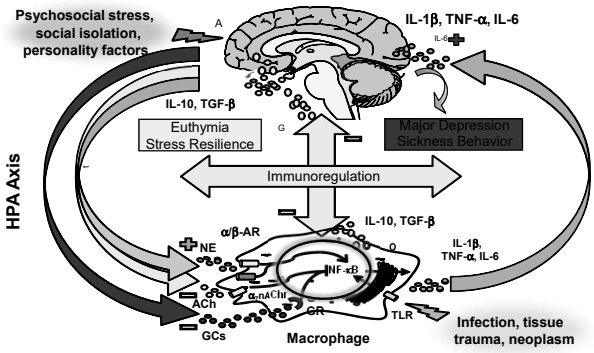
Neurobiology of Mood Disorders



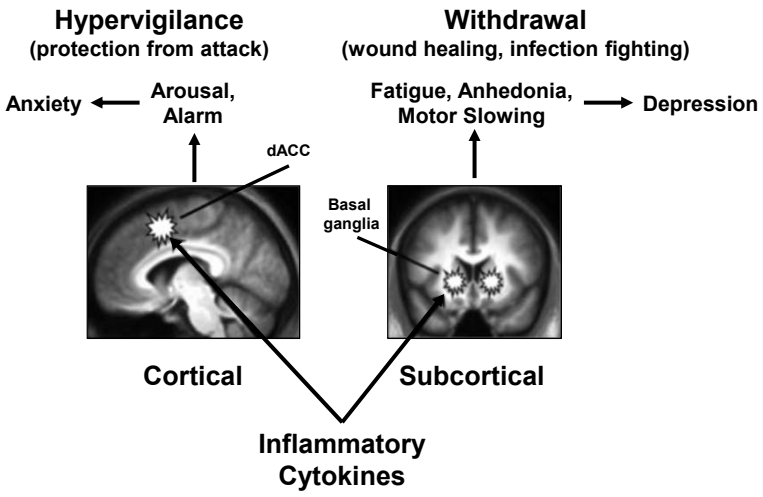
ELA = early life adversity.
Maletic V, et al. *Front Biosci*. 2009;14:5291-5338.

Stress and Inflammation in MDD



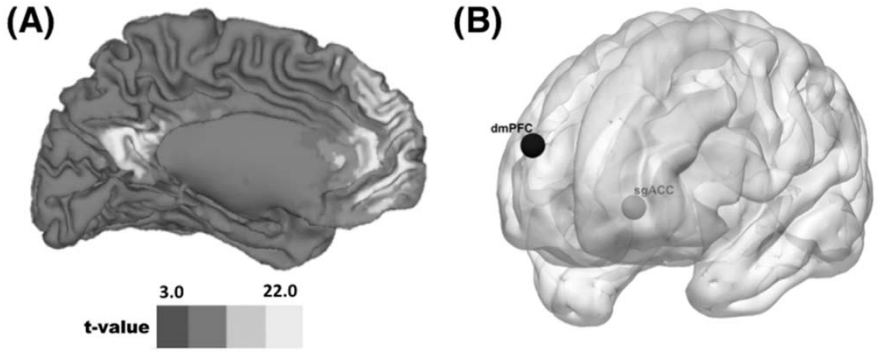
Ach = acetylcholine; α/β-AR = α- or β-adrenoreceptor; GC = glucocorticoid; HPA = hypothalamic–pituitary–adrenal; IL = interleukin; NE = norepinephrine; NF-κβ = nuclear factor-κβ; TGF = transforming growth factor; TLR = toll-like receptor; TNF = tumor necrosis factor.
Raison CL, et al. *Arch Gen Psychiatry*. 2010;67(12):1211-1224.

Impact of Inflammatory Cytokines on Brain Circuitry



dACC = dorsal anterior cingulate cortex.
Miller AH, et al. *Depress Anxiety*. 2013;30(4):297-306.

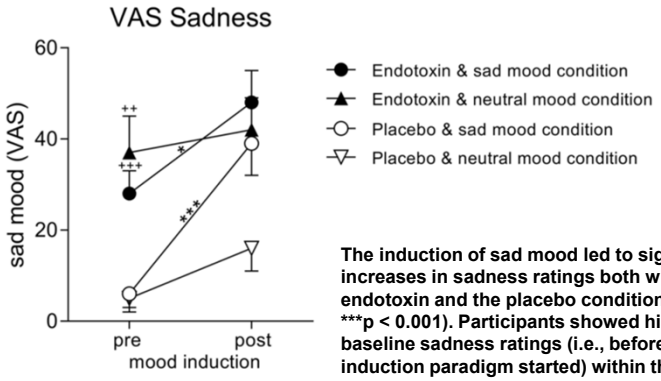
Peripheral inflammation alters DMN connectivity



Within default mode network (DMN), Circulating levels of IL- 6 correlated positively with resting state connectivity of subgenual anterior cingulate cortex (sgACC) and negatively with dorsal medial prefrontal cortex; (dmPFC). 98 adults aged 30–54 (39% male; 81% Caucasian).

Marsland et al, 2017, Brain, Behavior, and Immunity 62: 162–170

Inflammation amplifies sad mood

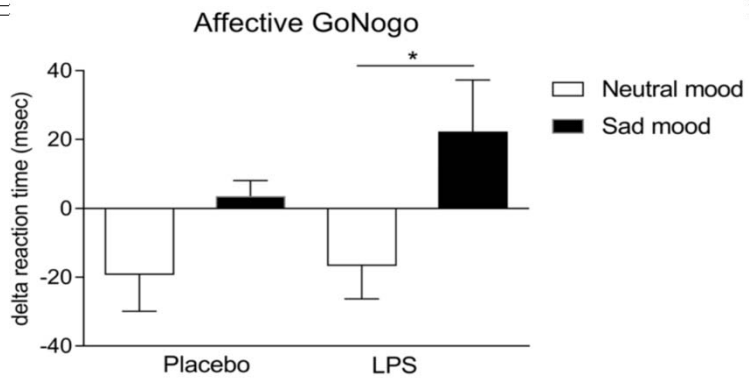


The induction of sad mood led to significant increases in sadness ratings both within the endotoxin and the placebo condition (*p < 0.05, ***p < 0.001). Participants showed higher baseline sadness ratings (i.e., before the mood induction paradigm started) within the endotoxin condition (++p < 0.01, +++p < 0.001, results of Bonferroni-corrected post-hoc paired t-tests)

N = 15 healthy males received endotoxin (0.8 ng/kg lipopolysaccharide iv).

Benson et al. Translational Psychiatry (2017)7:1281

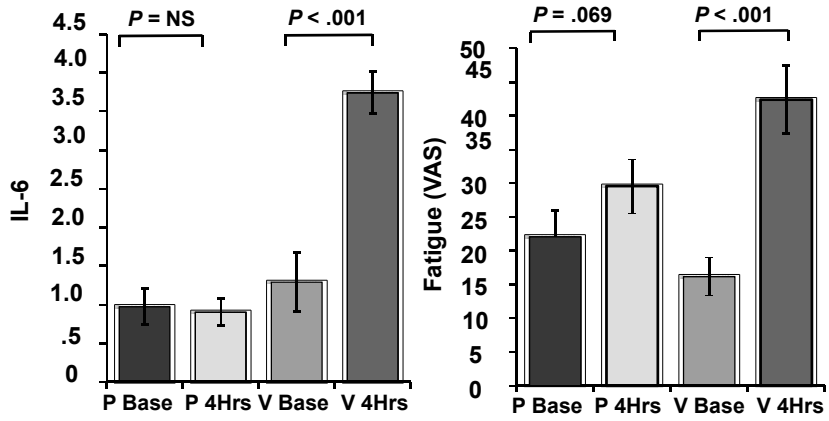
Inflammation and negative mood interfere with affective cognition



Positive scores indicate a tendency to respond slower and negative scores indicating a tendency to respond faster to sad targets. Differences in delta reaction time between the sad and neutral mood condition were significant only in the LPS condition (*p < 0.05, result of post-hoc paired t-test). Valence × mood interaction (p < 0.05),
N = 15 healthy males received endotoxin (0.8 ng/kg lipopolysaccharide iv).

Benson et al. Translational Psychiatry (2017)7:1281

Inflammatory and Fatigue Level Changes after an Immune Stimulus

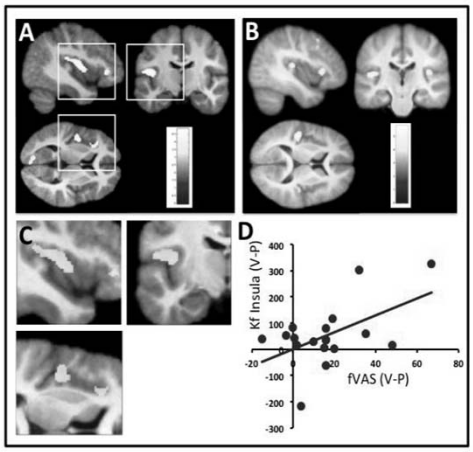


A) Change in circulating IL-6 pre- and post-vaccine (V base and V 4Hrs) and placebo injection (P base and P 4Hrs). **B)** Change in fatigue pre- and post-typhoid vaccination and placebo saline injection.

Harrison NA, et al. *Biol Psychiatry*. 2015;78(1):49-57.

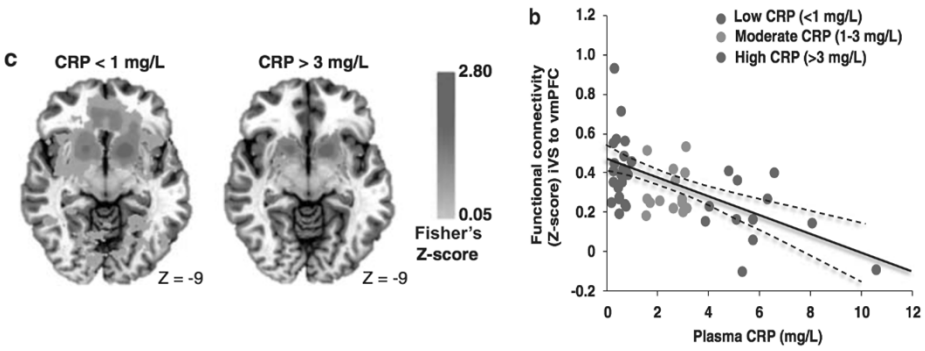
Peripheral Inflammatory Response is Associated with Increased Insula Activity and Fatigue

B) 18FDG PET imaging study: Brain regions showing a significant increase in 18FDG uptake 3 to 4 hours after Typhoid vaccine induced inflammation; exclusively masked by changes in 18FDG uptake 3 to 4 hours after placebo (mask threshold $P < .005$). Data displayed at a whole brain corrected threshold of $P < .05$. **C)** Left insula voxels showing a significant increase in kf 3 to 4 hours after experimentally induced inflammation (yellow) overlaid with voxels (green) additionally predicting inflammation-induced fatigue (fVAS, $P < .05$). **D)** Correlation of fVAS scores 4 hours after typhoid vaccine minus placebo (x-axis) with inflammation induced changes in kf of all 1196 voxels within the posterior insula cluster (illustrated in yellow in C) on the y-axis, $R^2 = .2$, $P < .05$.



fVAS = fatigue visual analog scale;
kf = magnetization transfer exchange rate constant.
Harrison NA, et al. *Biol Psychiatry*. 2015;78(1):49-57.

Peripheral inflammation in MDD is associated with diminished connectivity in reward circuitry

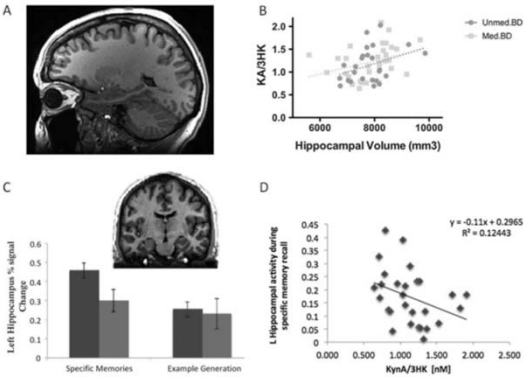


In 48 medically stable, unmedicated outpatients with major depression plasma C-reactive protein (CRP) was negatively associated with functional connectivity between left inferior ventral striatum (iVS) and ventromedial prefrontal cortex (vmPFC; BA32).

Felger et al, Molecular Psychiatry (2016) 21, 1358–1365;

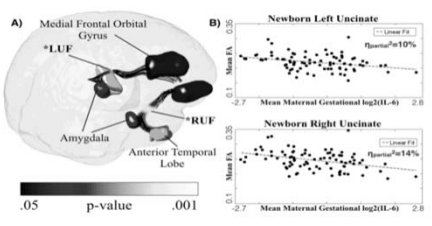
Inflammation Alters Hippocampal, Structural, Functional, and Cognitive Performance

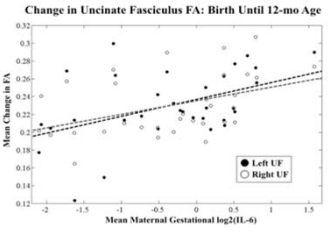
Coronal anatomical MRI slice showing the left hippocampal mask overlay and the percent signal change in the left hippocampus during specific autobiographical memory recall and example generation in the MDD (blue) and healthy control (green) groups. Scatterplot showing the correlation between KYNA/3HK and activity of the left hippocampus during specific autobiographical memory recall in the MDD group. KYNA vs 3HK and its derivatives is central to the pathogenesis of depressive illness.



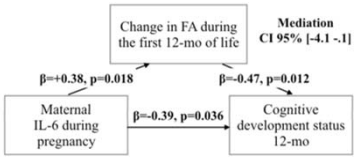
Savitz J. *Curr Top Behav Neurosci.* 2017;31:249-267.

Maternal Inflammation during Pregnancy Influences Infant White Matter Connectivity and Cognition at 12 Months





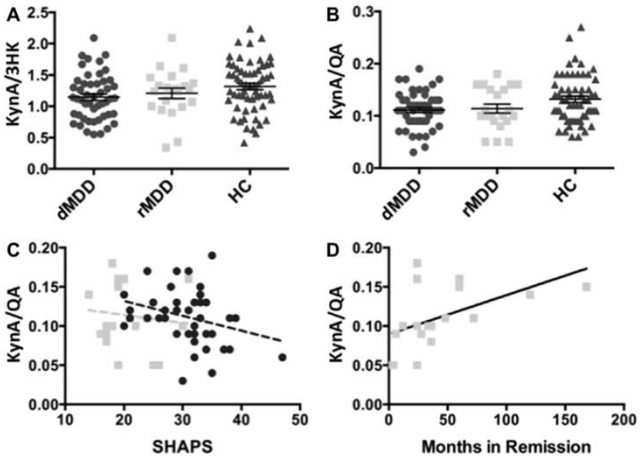
Diffusion tensor imaging was used to characterize FA along the left and right UF, representing the main frontolimbic fiber tract. N=30 infants.



FA = fractional anisotropy; UF = uncinate fasciculus; LUF = left UF; RUF = right UF.
Rasmussen JM, et al. *Neuroimage.* 2018 Apr 11;[Epub ahead of print].

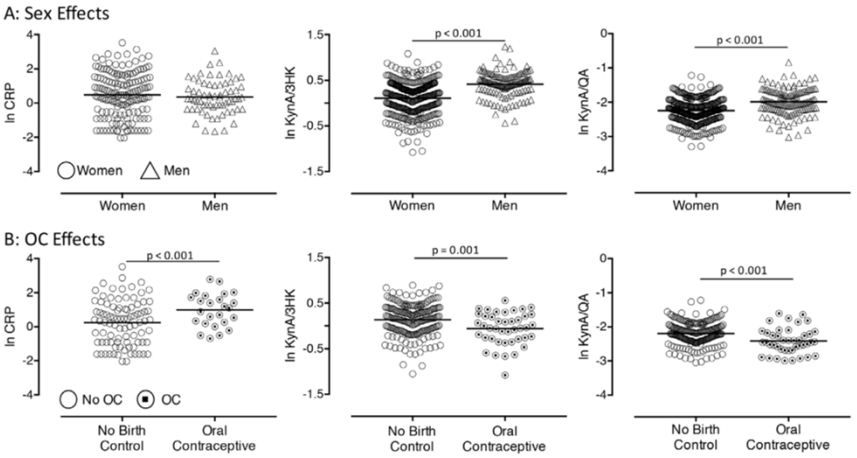
Disrupted neuroprotective/neurotoxic balance in MDD and anhedonia

The depressed dMDD subjects (n=49) are represented by blue circles and the remitted rMDD subjects (n=21) are represented by green squares. KynA/QA was inversely correlated with anhedonia measured by by SHAPS = Snaith–Hamilton Pleasure Scale.



Savitz et al, 2015, Brain, Behavior, and Immunity 46: 55–59

Sex difference in inflammatory signaling as a vulnerability for MDD



Sex differences in a priori measures of inflammation and the kynurenine pathway. Scatter plots show natural log transformed (ln) levels of C-reactive protein (CRP), the ratio of kynurenic acid to 3-hydroxykynurenine (KynA/3HK), and the ratio of kynurenic acid to quinolinic acid (KynA/QA) broken down by sex (A) and oral contraceptive use (B).

Meier at al, 2018, Brain, Behavior, and Immunity 67:59–64

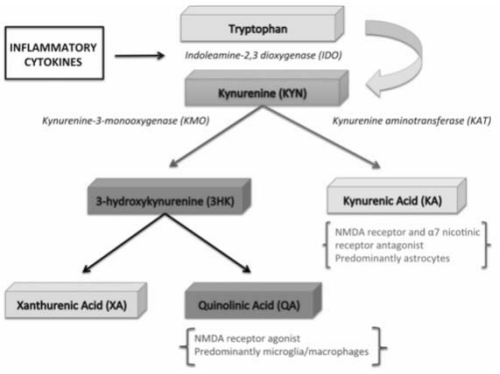
Clinical pearls.
Peripheral and Neuro-inflammation May Cause:

- **Fatigue and psychomotor retardation**
- **Anhedonia, compromised reward signaling**
- **Anxiety, hypervigilance and depression**
- **Sleep disturbance and circadian regulation**
- **Suicidality**

Maletic and Raison, 2017, *The New Mind-Body Science of Depression*, Norton

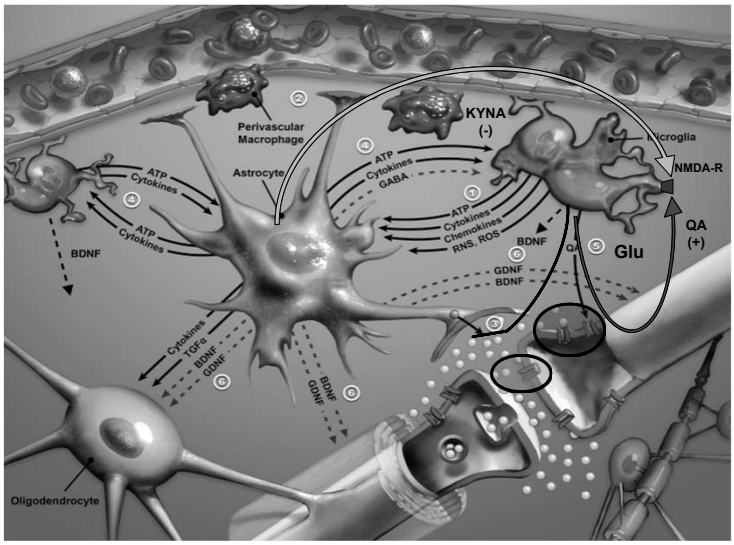
Neuroinflammation Alters Tryptophan Metabolism in MDD

The enzyme IDO, which converts tryptophan to KYN, is upregulated by pro-inflammatory cytokines. Each box represents a metabolite resulting from the oxidation of tryptophan.



NMDA = N-methyl-D-aspartate.
Mechawar N, et al. *Transl Psychiatry.* 2016;6(11):e946.

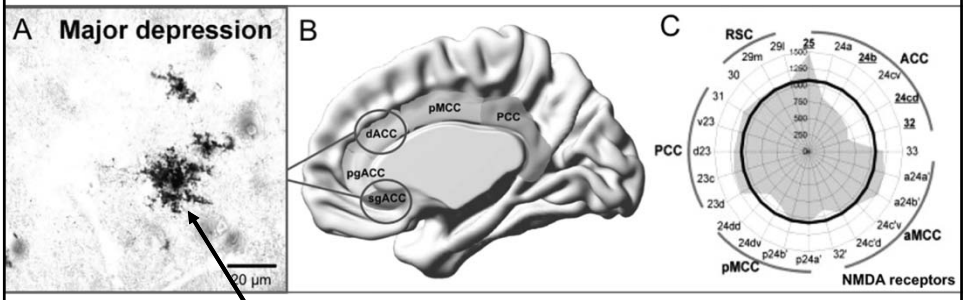
Interactions at the Glia–Synaptic Junction



NMDA-R - N-methyl-D-aspartate receptor (glutamate); QA – quinolinic acid; KA – kynurenic acid

Modified from: Maletic and Raison, 2014, Frontiers in Psychiatry, 5, (98): 1-24

Localization of microglia and NMDA receptors in MDD patients

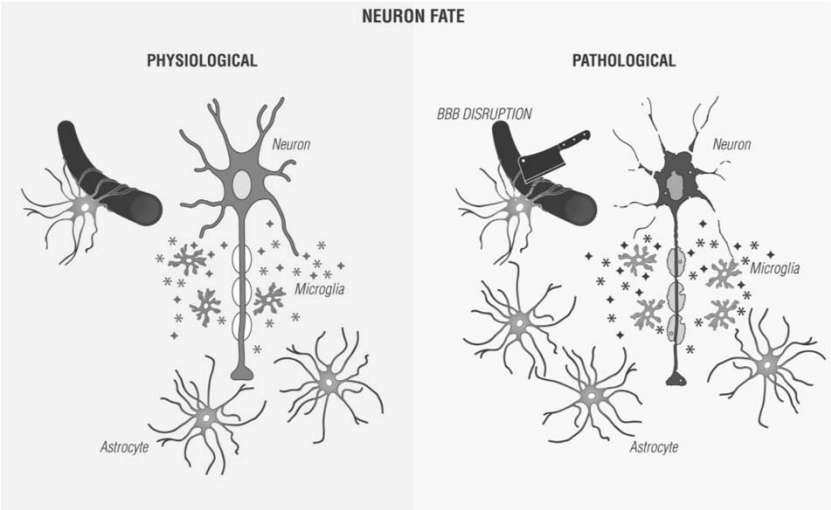


QUIN-expressing microglia

Region specificity in anterior cingulate cortex (ACC) overlaps with NMDA receptor expression and quinolinic acid (QUIN) expressing microglia distribution. (A) Picture shows a representative immunohistochemistry staining for QUIN expressing cells, which are mainly detected within the dACC but not in the pgACC.

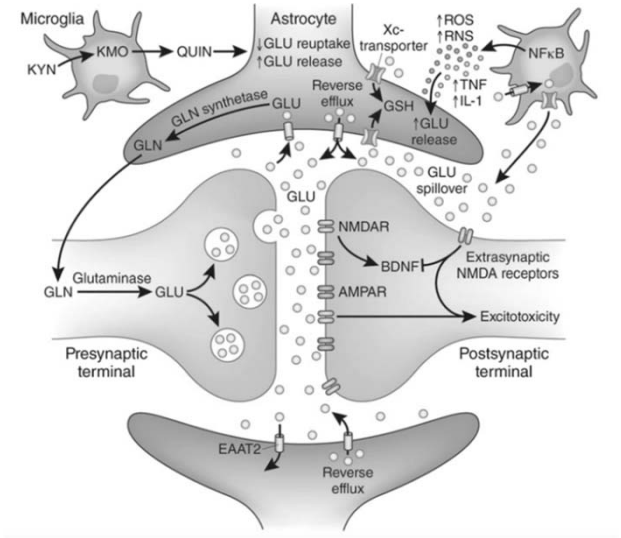
Woelfer et al, 2018, Neuroscience, aop

Shift in astroglia/microglia balance may contribute to MDD



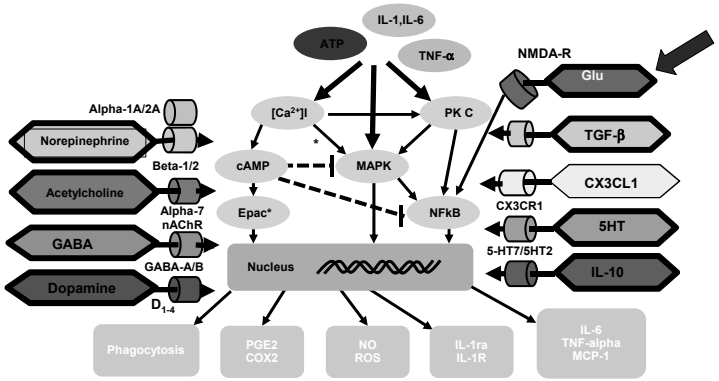
Skaper et al, 2018, *Front. Cell. Neurosci. 12:72.*

Inflammation=glutamate dysregulation?



Haroon, Miller, 2017, Curr Topics Behav Neurosci. 31: 173–198

Regulation of Microglial Activation



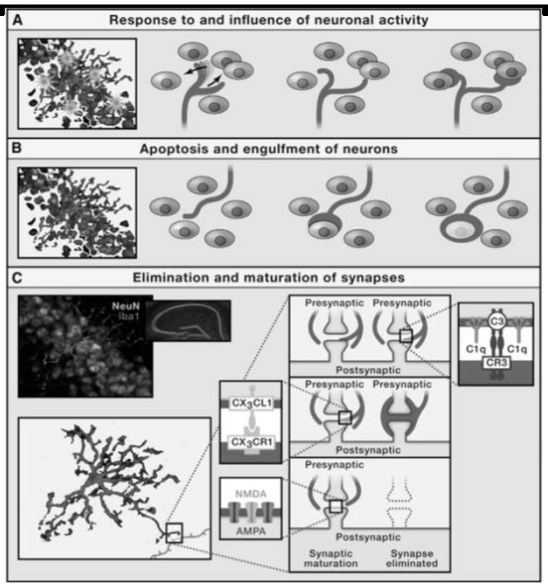
Microglia are activated by proinflammatory cytokines (eg, IL-1β), endogenous antigens (eg, Aβ), exogenous antigens (eg, LPS), or ATP. Norepinephrine has properties to inhibit microglial inflammatory reactions through the activation of cAMP and suppression of downstream MAPK and/or NFkB.

Adapted from: Maletic and Raison, 2017, *The New Mind-Body Science of Depression*, Norton; Liu H, et al. Stroke and Vascular Neurology 2016;1:e000012

The role of microglia in synaptic plasticity

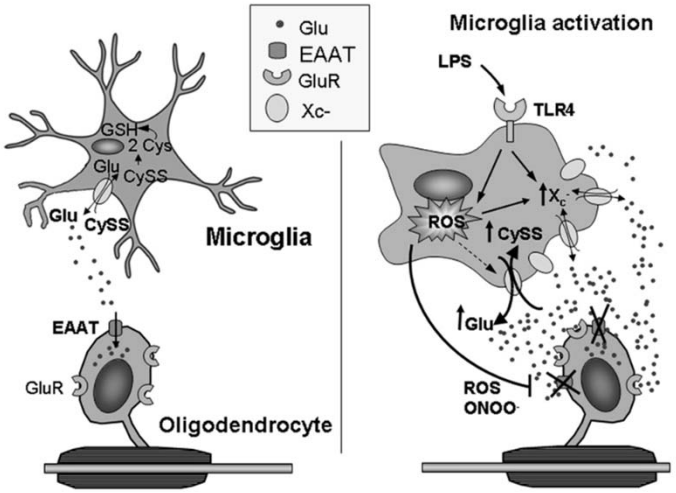
Microglial processes are highly motile in surveillance mode and are instructed and directed by local neuronal activity to the most highly active neurons. Microglia interact with adjacent neurons through neuronally released signaling molecules, monitoring and directing their activity. Microglial processes (red) engage with the soma of highly active neurons (orange), after which there is a decrease in both spontaneous and evoked neuronal firing. Accumulation of C1q at targeted synapses leads to neuronal C3-microglial CR3 signaling and subsequent synaptic engulfment of both pre- and postsynaptic structures (green) by microglia (red). Other appropriate synapses can be strengthened by a CX3CR1-dependent mechanism and subsequent maturation through postsynaptic NMDAR subunit changes and AMPAR insertion.

Salter,Beggs, 2014, Cell, 158:15-24



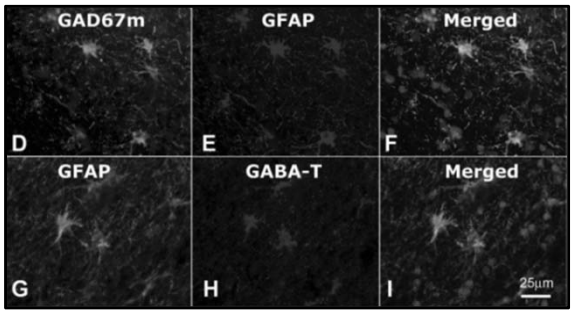
Who dun it? Microglia! Activated microglia may destroy oligodendrocytes

CySS, cystine; GSH, glutathione; EAAT, excitatory amino-acid transporter; Glu, glutamate; LPS, lipopolysaccharide ; ONOO, peroxynitrate, reactive nitrogen species; ROS, reactive oxygen species; TLR4, Toll-like receptor.

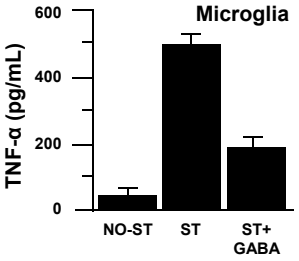


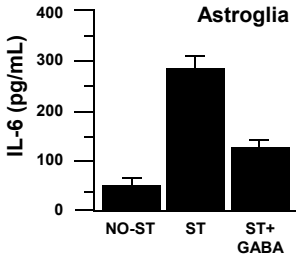
Domercq et al, 2013, Frontiers in Cellular Neuroscience, Volume 7, Article 49: 1-17

Are Astrocytes GABAergic Cells?



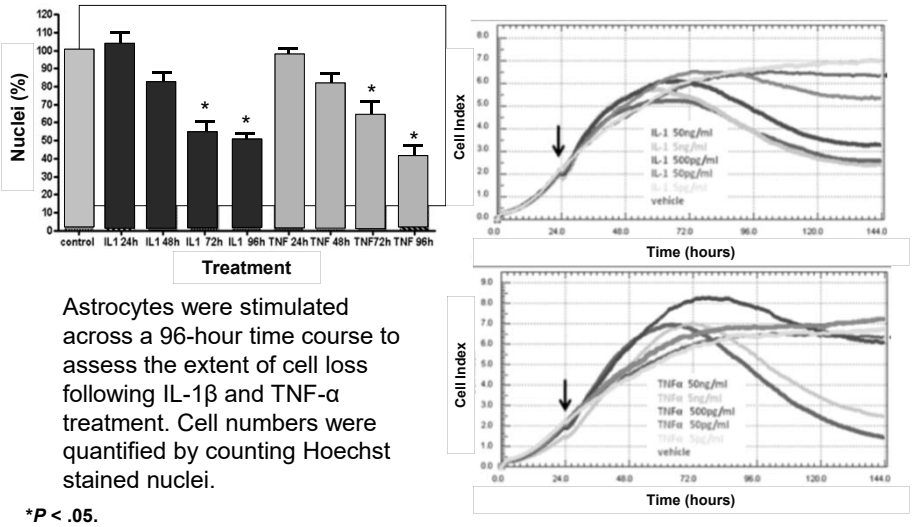
In immunohistochemical studies of the adult human brain, astrocytes expressed GAD 67 and GABA-T at a comparable or greater intensity level to known GABAergic neurons.





GAD = glutamic acid decarboxylase; GFAP = glial fibrillary acidic protein; GABA-T = GABA transaminase; ST = stimulated.
Lee M, et al. *Glia*. 2011;59(1):152-165.

Inflammatory Cytokines Induce the Death of Astrocytes

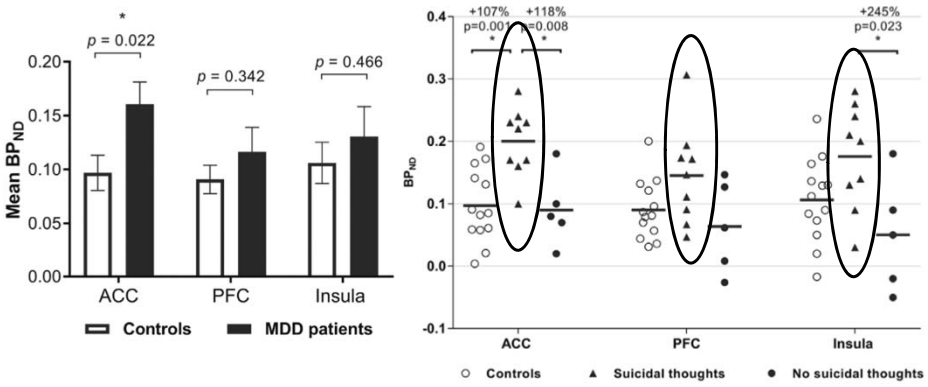


Astrocytes were stimulated across a 96-hour time course to assess the extent of cell loss following IL-1β and TNF-α treatment. Cell numbers were quantified by counting Hoechst stained nuclei.

***$P < .05$.**

van Kralingen C, et al. *PLoS One*. 2013;8(12):e84269.

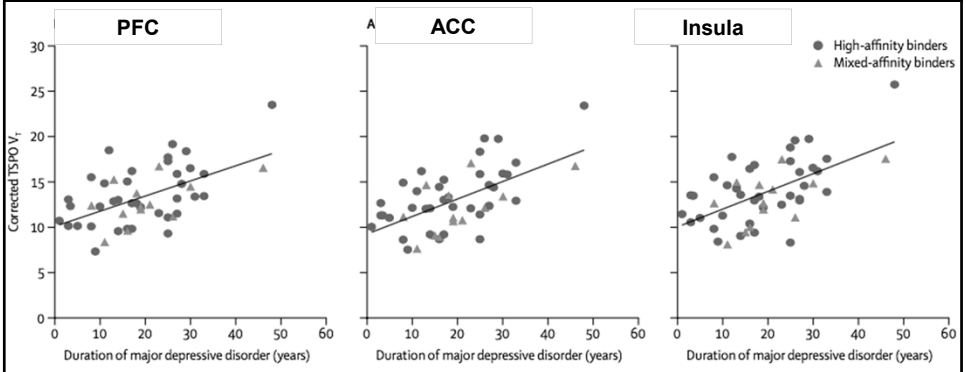
Role of inflammation in suicidal ideation in MDD?



N= 14 medication-free patients in a major depressive episode of at least moderate severity and 13 matched healthy controls. Translocator protein (TSPO), which is upregulated in activated glia (predominantly microglia), can be measured as an indication of neuroinflammation in vivo using positron emission tomography and TSPO-specific radioligands.

Holmes et al, 2018, Biol Psychiatry, 83(1):61-69

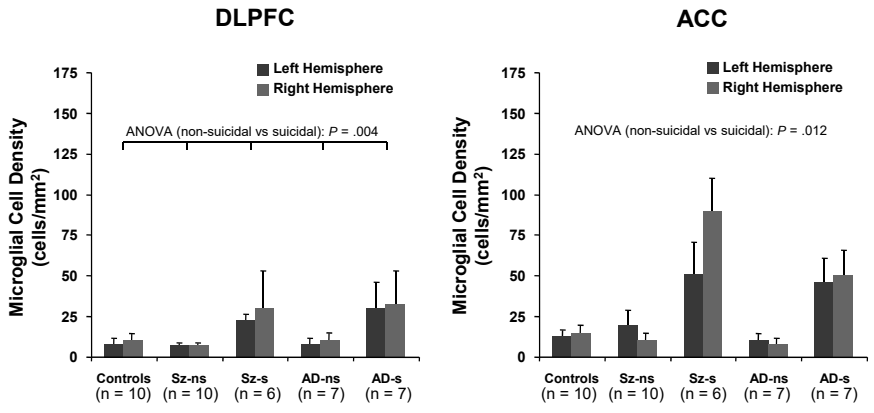
Duration of depression is associated with microglial activation



Translocator protein (TSPO), upregulated in activated microglia. In participants who had untreated major depressive disorder for 10 years or longer, TSPO V_T (total binding volume) was 29–33% greater in the prefrontal cortex, anterior cingulate cortex, and insula than in participants who were untreated for 9 years or less. Total illness duration was a strong predictor of TSPO V_T (p=0·0021). Current major depressive episode n=51, healthy n=30).

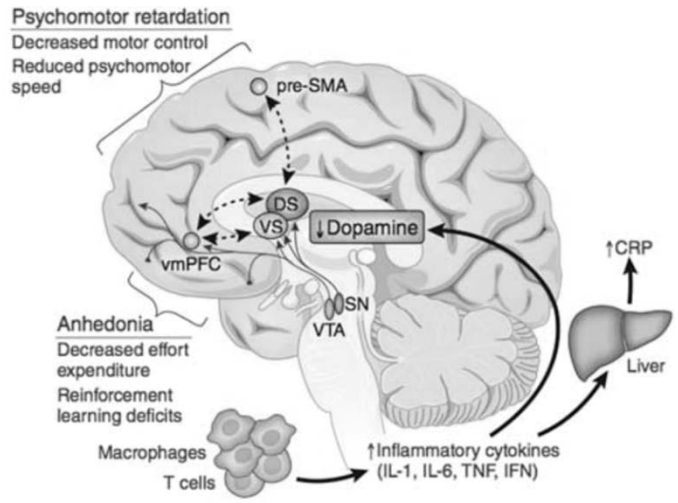
Setiawan et al, 2018, Lancet Psychiatry, aop

Microglial Density in the Brains of Patients with Schizophrenia and Mood Disorders was Associated with Suicidal Ideation



DLPFC = dorsolateral prefrontal cortex; AD-ns = nonsuicidal patients with affective disorder; AD-s = suicidal patients with affective disorder; Sz-ns = nonsuicidal individuals with schizophrenia; Sz-s = suicidal individuals with schizophrenia.
Steiner J, et al. *J Psychiatr Res.* 2008;42(2):151-157.

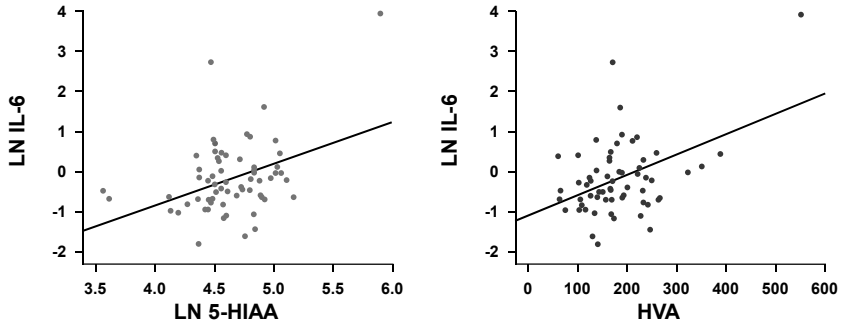
Central Inflammation disrupts DA transmission and reward signaling



Felger, Treadway, Neuropsychopharmacology Rev (2017) 42: 216–241

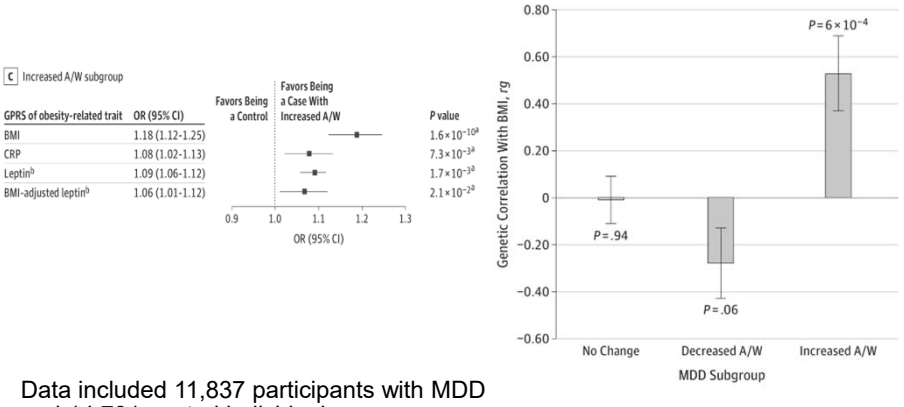
Elevation of Inflammatory Cytokines in CSF May Alter 5-HT and Dopamine Metabolism

- Inflammatory cytokines and monoamine metabolites were compared in 63 suicide attempters and 47 healthy controls
- MADRS scores correlated significantly with CSF IL-6 levels
- IL-6 and TNF-α correlated with CSF 5-HIAA and HVA
- Higher cytokine levels were associated with increased suicidality



CSF = cerebrospinal fluid; 5-HT = 5-hydroxytryptamine; IL = interleukin; TNF = tumor necrosis factor; HIAA = hydroxyindoleacetic acid; HVA = homovanillic acid; LN = natural log.
Lindqvist D et al. *Biol Psychiatry*. 2009;66(3):287-292.

Is there a genetically-based MDD biotype associated with increased inflammation and appetite/weight gain?

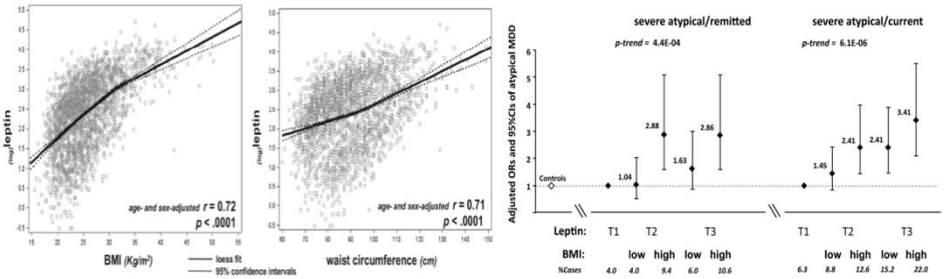


Data included 11,837 participants with MDD and 14,791 control individuals.

A/W = appetite and/or weight symptoms; GPRS = genomic profile risk scores.
Milaneschi Y, et al. *JAMA Psychiatry*. 2017;74(12):1214-1225.

Yes! It is also known as atypical depression.

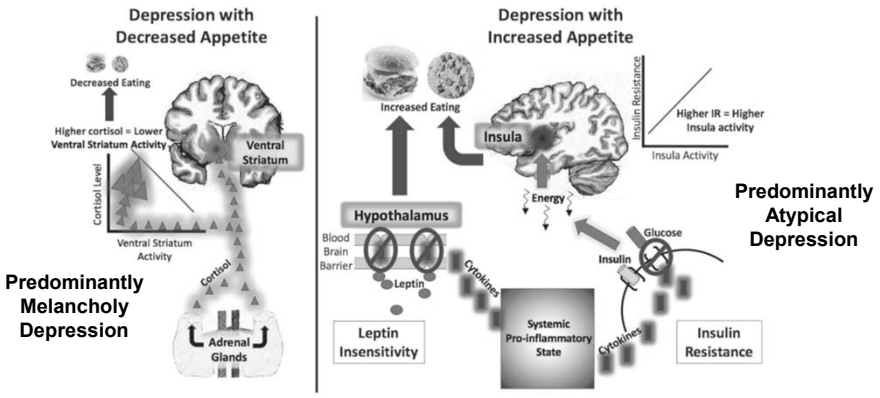
Leptin levels correlate with BMI and waist circumference



The sample consisted of participants (aged 18 to 65 years) from the Netherlands Study of Depression and Anxiety with current (n=1062) or remitted (n=711) MDD and healthy control participants (n=497). Diagnoses of MDD and subtypes were based on *DSM-IV* symptoms. Compared to control participants, higher leptin was associated with the atypical MDD subtype both for remitted (n=144, odds ratio = 1.53, 95% confidence interval = 1.16–2.03, *P*=.003) and current (n=270, odds ratio = 1.90, 95% confidence interval = 1.51–2.93, *P*=5.3e–8) cases.

Milaneschi Y, et al. *Biol Psychiatry*. 2017;81(9):807-814.

Appetite changes reveal 2 distinct biotypes of MDD?



Simmons WK, et al. *Mol Psychiatry*. 2018 Jun 13;[Epub ahead of print].

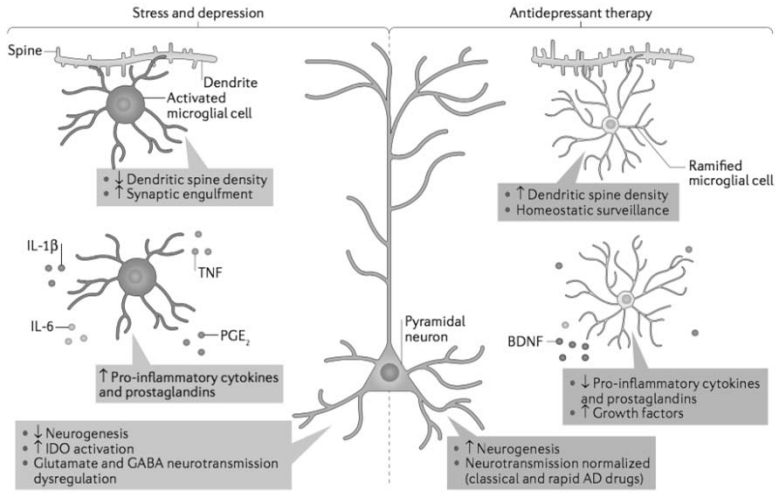
Clinical pearls. Consequences of Neuroinflammation

- **Acutely increased glutamate signaling, in chronic and recurrent episodes, decreased glutamate signaling**
- **Disturbance of glutamate/GABA balance**
- **Dysregulated release of inflammatory molecules, ROS, RNS from microglia and astrocytes**
- **Excitotoxicity, damage to astrocytes and oligodendrocytes**
- **Disruption in white matter tracts and neural network function**
- **Decreased neurotrophic signaling and neuroplasticity**
- **Abnormal, NA, 5HT and NE turnover/signaling**

Maletic and Raison, 2017, *The New Mind-Body Science of Depression*, Norton

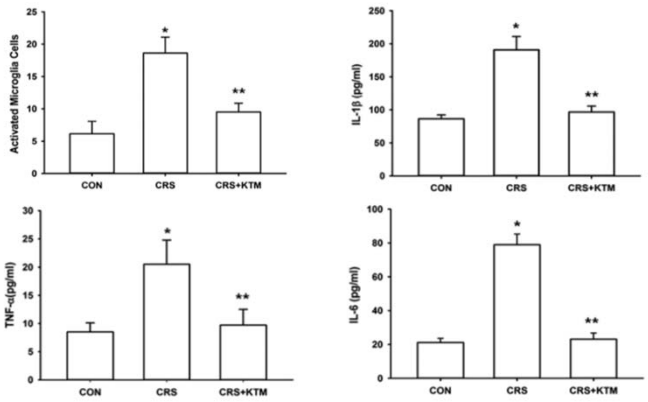
Treatment Implications

Impact of antidepressants on microglia and dendritic spines



Wohleb et al, 2016, Nature Rev Neurosci, 17: 497- 511

Ketamine modulates microglia and inflammation in a rodent CRS model

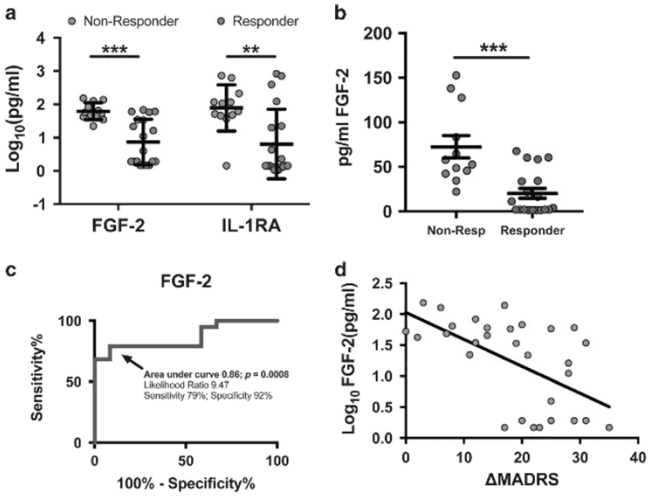


Chronic restraint stress (CRS) exposure caused depressive-like behaviors in mice, which was associated with increased pro-inflammatory cytokines (interleukin (IL)-1*β*, tumor necrosis factor (TNF)-*α* and IL-6) levels, reactive microglia numbers. Such neurobehavioral and biochemical abnormalities were normalized by ketamine treatment.

Tan et al, 2017, *Biol. Pharm. Bull.* 40:1260–7

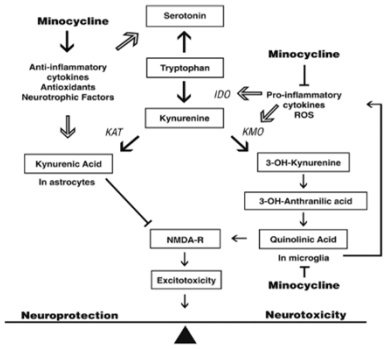
Elevated peripheral inflammation predicts lower response to ketamine

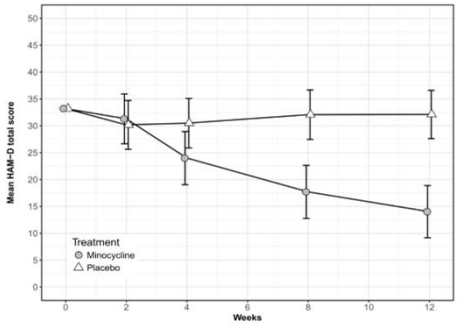
Low serum levels of FGF-2 predict treatment response to ketamine. Analysis of serum levels of all factors was examined in all patients by treatment response (⩾50% reduction in MADRS at 24 h) versus non-response. These analyses showed that lower serum levels of FGF-2 (P = 0.0001) and IL-1ra (P = 0.0035) were seen in treatment responders.



Kiraly et al, 2017, Translational Psychiatry; 7: e1065

Minocycline: Mechanism of action and adjunctive use in MDD



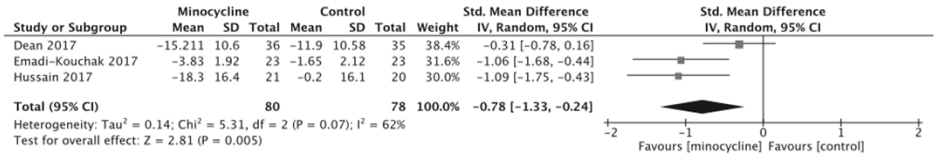


A total of 41 participants were randomised, with 21 in the minocycline group and 20 in the placebo group. Patients have previously failed at least 2 antidepressants.

J.K. Soczynska et al.2012 , Behavioural Brain Research *235 : 302–317; Husain et al, 2017, J Psychopharmacology,* 31(9) 1166–1175

5M solution: Minocycline-midiatated microglia modulation in MDD

Minocycline is a tetracycline antibiotic with potent anti-inflammatory and neuroprotective effects

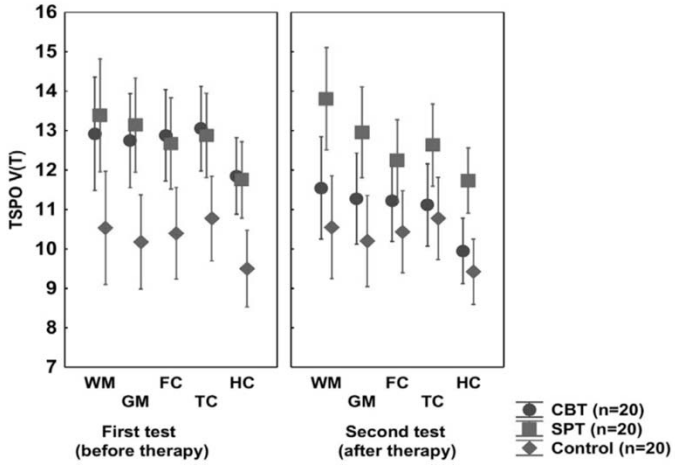


18 clinical studies (including published and unpublished RCTs, open label studies, ongoing clinical trials and a case report) were identified for inclusion in the qualitative synthesis. Only three RCTs (n = 158) met inclusion criteria for quantitative synthesis. The overall antidepressant effect size of minocycline compared to placebo was − 0.78 [95% confidence interval − 0.4 to − 1.33 (P = 0.005)], indicative of a large and statistically significant antidepressant effect.

J.D. Rosenblat, R.S. McIntyre, 2017 *Journal of Affective Disorders 227 : 219–225*

CBT reduces microglia activation in MDD

Participants were newly diagnosed patients with MDD receiving CBT (n = 20) or SPT (n = 20) who were compared with 20 healthy control subjects. Participants received 16 individual sessions (1 session/week, duration: 1.5 h) of CBT or SPT.



[18F]-FEPPA positron emission tomography (PET) was used to examine translocator protein total distribution volume (TSPO VT), a marker of microglial density and inflammation.

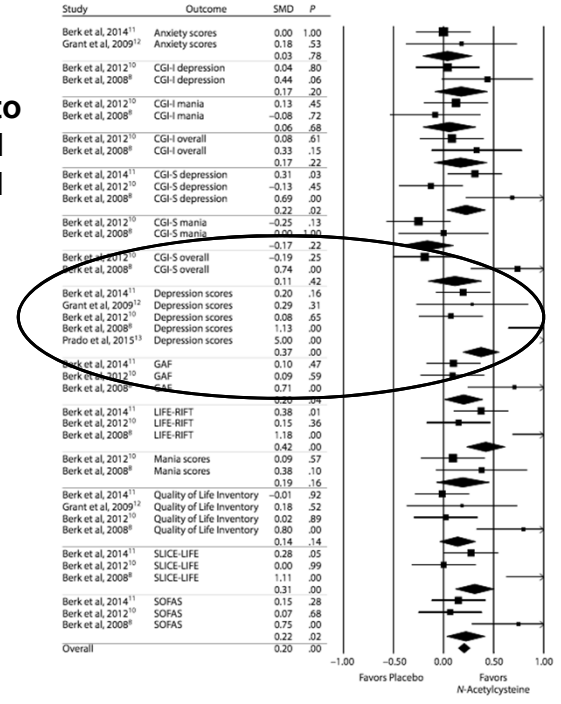
Li et al, 2018, *Progress in Neuropsychopharmacology & Biological Psychiatry 83,aop*

N-Acetylcysteine for Depressive Symptoms for Outcomes Related to Depressive, Manic, and Anxiety Symptoms and for Functionality and Quality of Life

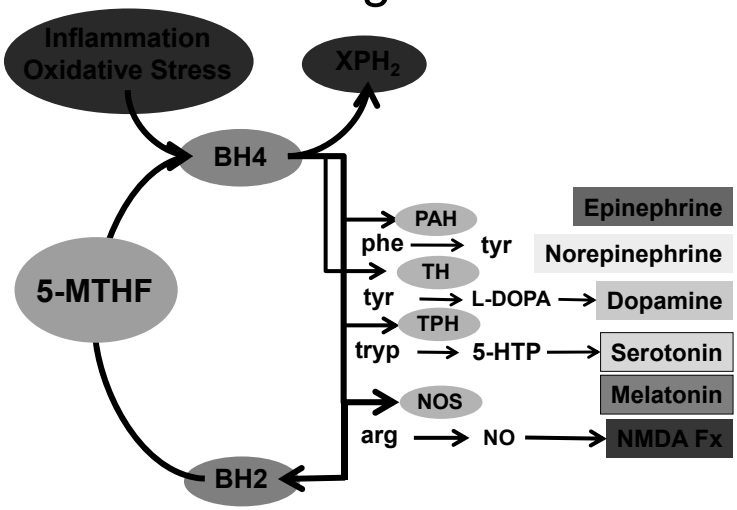
Treatment with *N*-acetylcysteine improved depressive symptoms as assessed by Montgomery-Asberg Depression Rating Scale and Hamilton Depression Rating Scale when compared to placebo (SMD = 0.37; 95% CI = 0.19 to 0.55; *P* < .001).

CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, GAF = Global Assessment of Functioning, LIFE-RIFT = Longitudinal Interval Follow-Up Evaluation-Range of Impaired Functioning, SLICE-LIFE = Streamlined Longitudinal Interview Clinical Evaluation from the Longitudinal Interview Follow-up Evaluation, SMD = standardized mean difference, SOFAS = Social and Occupational Functioning Assessment Scale.

Fernandes et al, 2016, *J Clin Psychiatry;77(4):e457–e466*

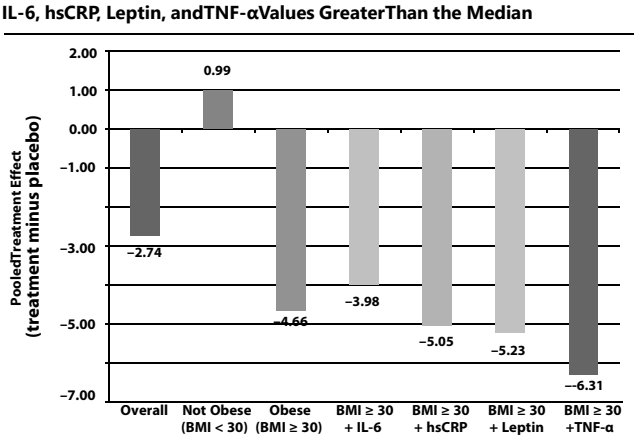


BH4 is a Cofactor for Monoamine Synthesis and a Target of Inflammation



BH4, tetrahydrobiopterin; XPH2, dihydroxanthopterin; PAH, phenylalanine hydroxylase; TH, tyrosine hydroxylase; TPH, tryptophan hydroxylase; NOS, nitric oxide synthetase; phe, phenylalanine; tyr, tyrosine; tryp, tryptophan; 5-HTP, 5-hydroxytryptophan; arg, arginine; NO, nitric oxide.
Haroon E et al. *Neuropsychopharmacology*. 2012;37(1):137-162.

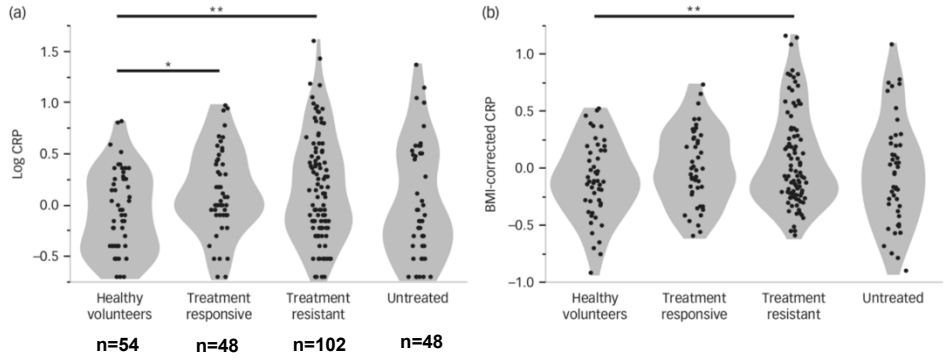
Response to adjunct L-methylfolate in MDD patients with previous inadequate SSRI response



Adults with *DSM-IV* MDD and an inadequate response to a selective serotonin reuptake inhibitor (SSRI) were eligible. N=69 participants were randomized to an SSRI plus placebo versus an SSRI plus L-methylfolate calcium (15 mg/d). Pooled Treatment Effect (change with placebo minus change with L-methylfolate calcium) on the HDRS-17 for the Total Population

Shelton et al, 2015, *J Clin Psychiatry , in press*

Is inflammatory depression a clinical phenotype (resistant subtype)?

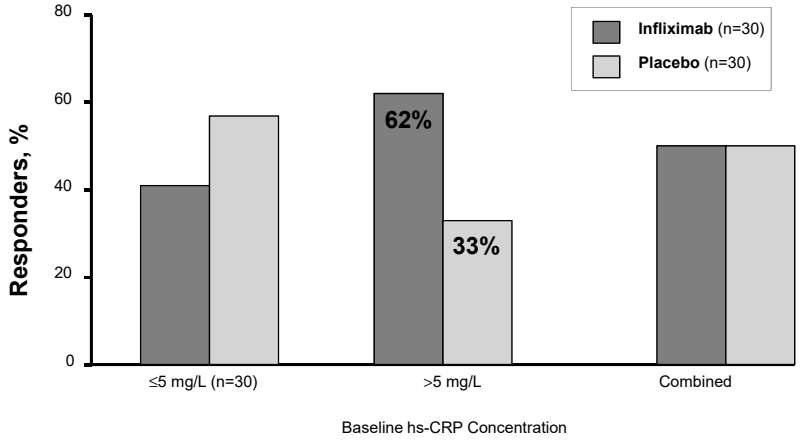


F = 3.57, p = 0.015; F = 2.67, p = 0.048). *p < 0.05, **p < 0.01 significant pairwise difference.

Clinical phenotypes most strongly associated with CRP were not feeling calm, psychomotor retardation, middle insomnia, not being able to work, BMI, state anxiety and feeling unloved as a child or wishing for a different childhood.

Chamberlain et al, 2018, The British Journal of Psychiatry (aop)

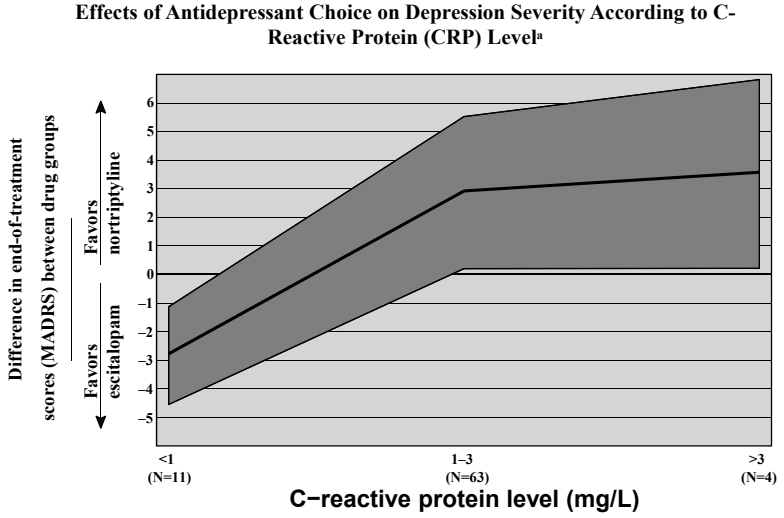
Anti-inflammatory treatment in TRD



The percentage of treatment responders, which was defined by a 50% or more decrease in the 17-item Hamilton Scale for Depression at any time during treatment, was compared between infliximab- and placebo-treated patients with TRD.

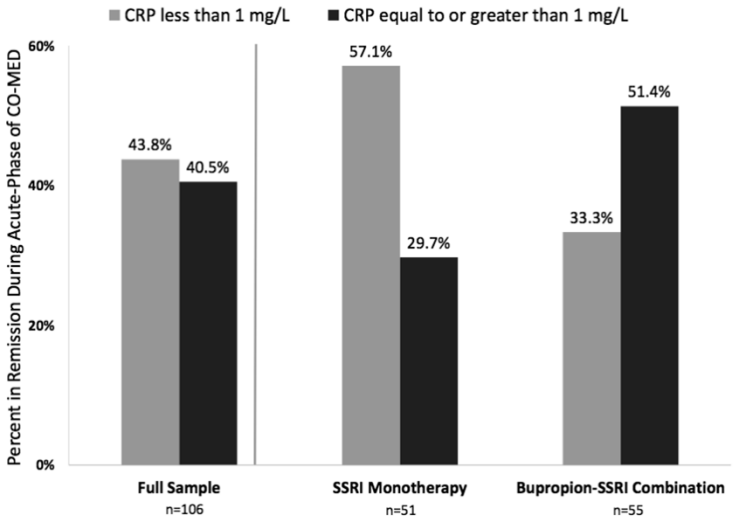
Raison et al, 2013, JAMA Psychiatry, 70(1): 31-41

CRP level may predict a response to a class of antidepressants in MDD



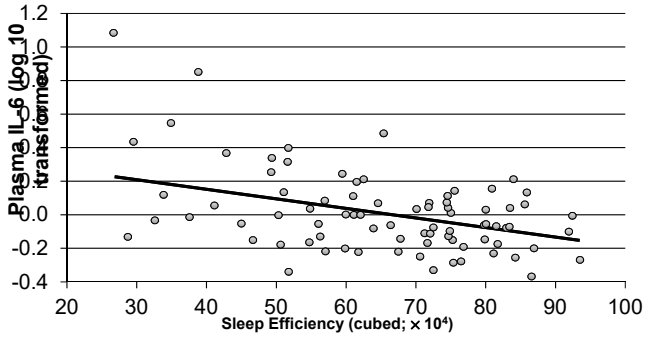
Uher et al, 2014, Am J Psychiatry, aop

Bupropion/SSRI combination in depressed patients with higher CRP



Jha et al, 2017, Psychoneuroendocrinology, in press

Good Sleep Benefits the Inflammatory Response

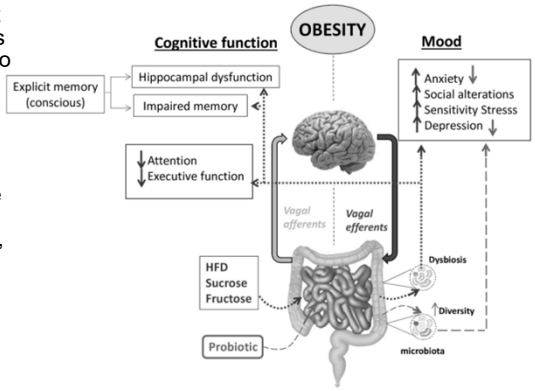


Study examined the interplay of social engagement, sleep quality, and plasma levels of IL-6 in a sample of aging women (N=74, aged 61–90 years, mean age = 73.4). Sleep was assessed by using the NightCap in-home sleep monitoring system. The interaction significantly predicted plasma IL-6 levels (β = 1.19, *P*<.05).

Friedman EM, et al. *Proc Natl Acad Sci U S A*. 2005;102(51):18757-18762.

Unhealthy Diet May Contribute to Obesity Gut Dysbiosis, Inflammation, and Cognitive Impairment

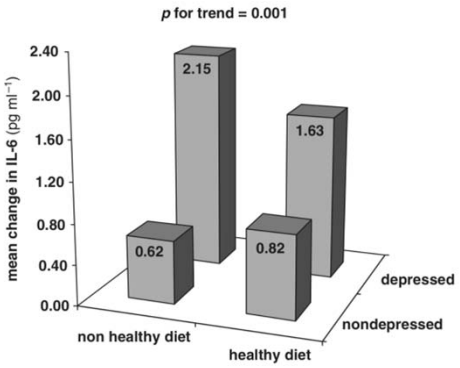
The diversity and stability of the gut microbiota can be affected by HFDs or high carbohydrate diets leading to dysbiosis, which is a typical alteration observed in obesity. A dysbiotic microbiota is thought to alter the communication between the gut and the brain axis contributing to mood alterations like anxiety, depression, sensitivity to stress, social behavioral alterations, and cognitive alterations like hippocampal dysfunction, impaired memory and reduction of attention or the executive function.



HFD = high-fat diet.
Agustí A, et al. *Front Neurosci*. 2018;12:155.

Healthy Diet May Mitigate Inflammation in Patients with MDD

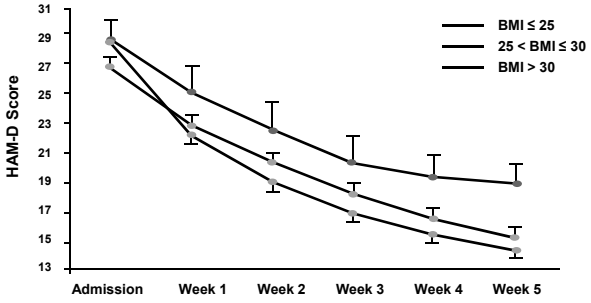
793 participants aged ≥ 65 years were evaluated at enrollment (1998–1999) and again at 3- and 6-year follow-up visits. Depressive symptoms were assessed at baseline with the CES-D. Adherence to the Mediterranean diet was assessed at baseline by a well-validated dietary questionnaire and a Mediterranean Diet Score. Mediterranean diet score was dichotomized around the median. Depressed mood: CES-D ≥ 20. Healthy diet: Mediterranean diet score ≥ 5.



CES-D = Center for Epidemiologic Studies-Depression scale.
Milaneschi Y, et al. *Mol Psychiatry*. 2011;16(6):589-590.

BMI Impacts Antidepressant Response

- Response to antidepressant treatment according to weight status
- Mean HAM-D rating scores and SEMs for 5 weeks after hospitalization

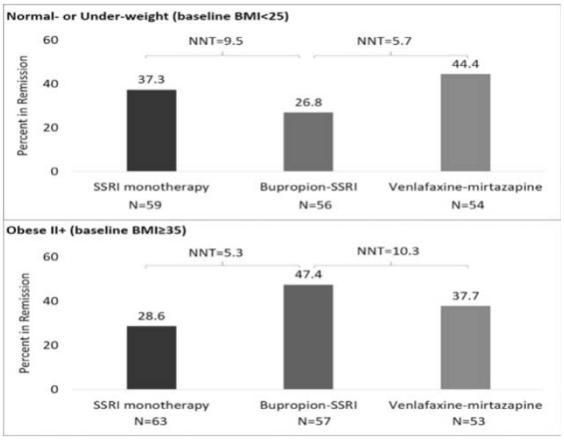


Kloiber S, et al. *Biol Psychiatry*. 2007;62(4):321-326.

BMI may influence the response and remission related to different classes of antidepressants

Remission rates in normal- or under-weight and obese II+ participants of CO-MED trial. BMI is body mass index, SSRI is selective serotonin reuptake inhibitor

Jha et al, Journal of Affective Disorders 234 (2018) 34–37



Take-Aways

- Depression, sleep disturbance, weight gain, and cognitive impairment share pathophysiologic mechanisms
- Immune disturbances underpin depressive disorders, insomnia, weight gain, and cognitive dysfunction
- Thoughtful selection of pharmacologic agents for treatment of depression is important not only because of comprehensive benefits but also relative to their adverse reactions, especially associated sleep disturbance, weight gain, and cognitive impairment
- Nonpharmacologic interventions for depression may successfully ameliorate cognitive difficulties, sleep disturbances, and weight gain