Inflammation, the Brain and N-3 Fatty Acids

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COI and Recent Support

- **2021-2025** NIMH R01MH123451 “Latino Ancestry Genomic Psychiatry Cohort (AAGPC)” (PI: Pato, Site PI: Rapaport) $90,000 subcontract annual direct
- **2021-2023** NCI R21CA263453-01 “Massage for Prostate Cancer-Related Fatigue” (PI: Rapaport) $150,000 annual direct
- **2020-2021** NIDA UG3DA48502 **“**Non-Invasive Vagal Nerve Stimulation in Patients with Opioid Use Disorders” (PI: Bremner, Co-I: Rapaport) $76,865 annual direct
- **2015-2020** NCCIH UG3 AT008857-01 “Omega-3 Fatty Acids for MDD with High Inflammation: A Personalized Approach” (PI: Rapaport) $1,029,613 annual direct
- **2015-2021** NIH R01 “African American Genomic Psychiatry Cohort” (PI: Pato, Site PI: Rapaport), $130,000 annual direct
- **2015-2019** NCCIH 1R01AT009169-01 “Mechanism of Action for n-3 PUFA Antidepressant Properties” (PI: Rasenick, Site PI: Rapaport) $250,000 annual direct
- **2014-2019** NIMH 1R25MH101079-01:”Emory Psychiatry Clinical Scientist Training Program (CSTP)” (PI: Ressler/Miller, Mentor: Rapaport), $968,142
- **2012-2015** NIMH HHS-NIH-MH-2010-024 “Double-Blind, Proof-of-Concept (POC) Trial of Low Field Magnetic Stimulation (LFMS),” (PI: Fava, Site PI: Rapaport), Total costs $358,045.
- **2012-2017** NIMH 1K23MH098014-01: “A Potential State and Relapse Predictive Marker in Schizophrenia (PI: B Miller, Mentor: Rapaport), Total costs $170,600
- **2013-2018** NIMH MH100023-01: “Silvio O. Conte Center for Oxytocin and Social Cognition,” (PI: L Young, Co-I: Rapaport), Total costs $1,161,874

COLLABORATORS

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Inflammation: A Common Mechanism of Disease - Insight of the Decade (*Science*, 2010)

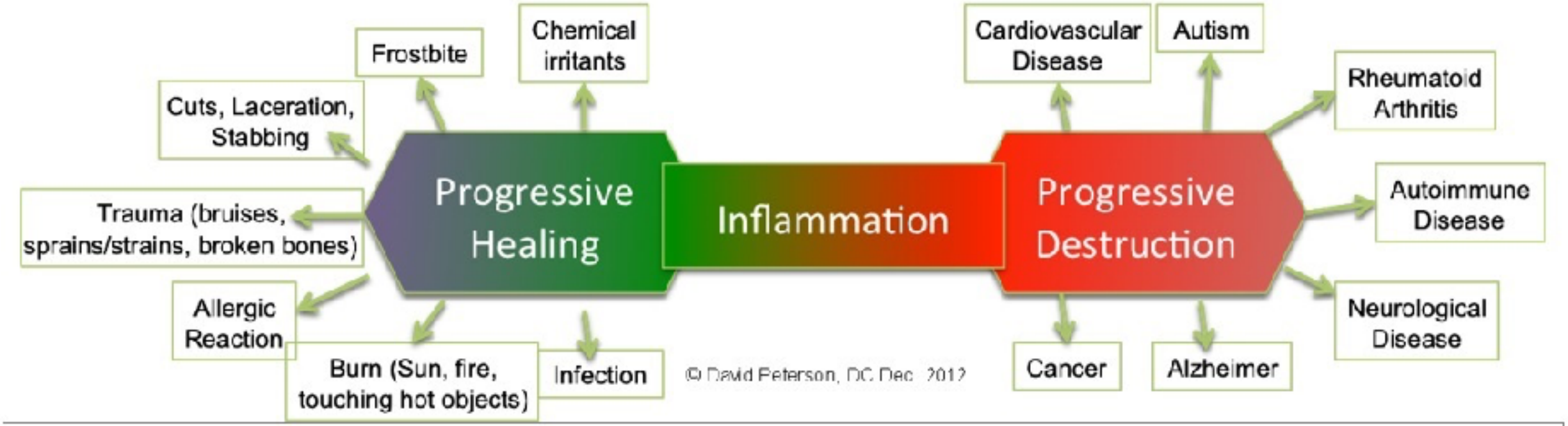


Figure 1: A brilliant example of how inflammation can lead to both health and disease

Sequelae of chronic inflammatory diseases in the light of altered energy regulation

Disease Sequelae	Pathophysiological elements in chronic inflammation leading to energy allocation to an activated immune system
• ***Depressive symptoms/fatigue***	Cytokine (e.g. IL-1β) driven sickness behavior and fatigue which increase time at rest (muscles and brain in an inactive state)
• ***Anorexia***	Consequences of sickness-behavior and fatigue
• **Malnutrition**	Consequences of anorexia and sickness behavior
• **Muscle wasting-cachexia**	Protein breakdown in muscles as a consequence of anorexia, sickness behavior and androgen deficit
• ***Cachectic obesity***	Protein breakdown in muscles as a consequence of anorexia and sickness behavior (protein breakdown>fat breakdown)
• ***Insulin(IGF-1) resistance (with hyperinsulinemia)***	Cytokine (e.g. TNF)-induced insulin signaling defects in the liver, muscle, and fat tissue but not in immune cells. Immune cells need insulin so that high insulin levels support the activity of the immune system (similar for IGF-1)
• **Dyslipidemia**	Cytokine-driven acute phase reaction of lipid metabolism leading to higher delivery of cholesterol and lipids to macrophages
• ***Increase of adipose tissue in the proximity of inflammatory lesions***	Present of adipose tissue surrounding lymph nodes and in the proximity of inflammatory lesions reflects a local store of energy-rich fuels (increased local estrogens might be important to drive local accumulation of adipose tissue.) Adipokines play a proinflammatory role.

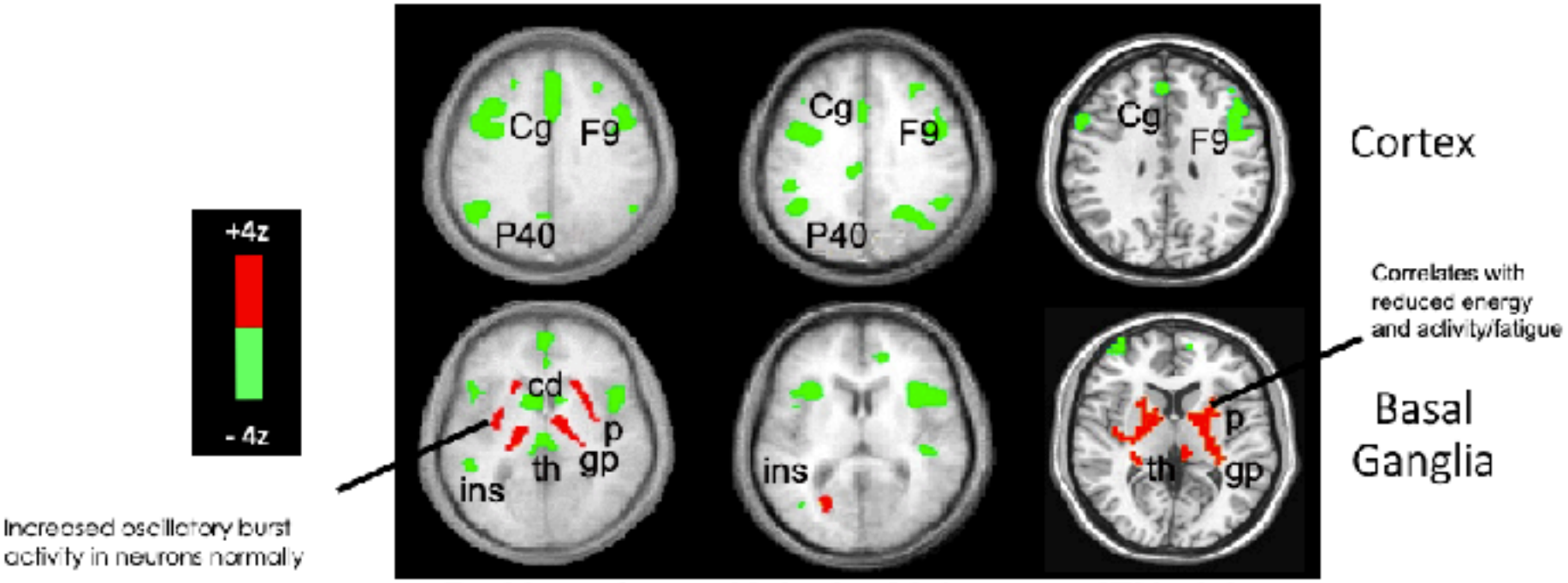
Sequelae of chronic inflammatory diseases in the light of altered energy regulation

Disease Sequelae	*Pathophysiological elements in chronic inflammation leading to energy allocation to an activated immune system*
Alterations of steroid hormone axes	*Cytokine/leptin-driven hypoandrogenemia supports muscle breakdown and protein delivery for gluconeogenesis and support of an activated immune system (alanine, glutamine). Cortisol-to-androgen preponderance in chronic inflammation is catabolic.*
Elevated sympathetic tone and local sympathetic nerve fiber loss	*Cytokine-driven increase of SNS activity increases gluconeogenesis and lipolysis. The parallel loss of sympathetic nerve fibers in inflamed tissue supports local inflammation [64]. It also stimulates lipolysis in the surrounding adipose tissue because sympathetic nerve fibers are increased there [65].*
Hypertension	Cytokine-driven activation of the water retention system due to systemic water loss during inflammation.
Decreased parasympathetic tone	*Cytokine-driven decrease in PSNS activity supports allocation of energy-rich fuels to an activated immune system*
Inflammation-related anemia	Cytokine-driven anemia is linked to reduced energy expenditure for erythropoiesis, increased time at rest, and insulin resistance (see above), all of which support energy allocation to the immune system
Osteopenia	High calcium and phosphorus are mandatory for energy-consuming reactions. Driven by cytokines and PTH-related peptide during inflammation. In addition, an activated SNS and HPA axis stimulate bone resorption

J Mol Med (2012) 90:523-534

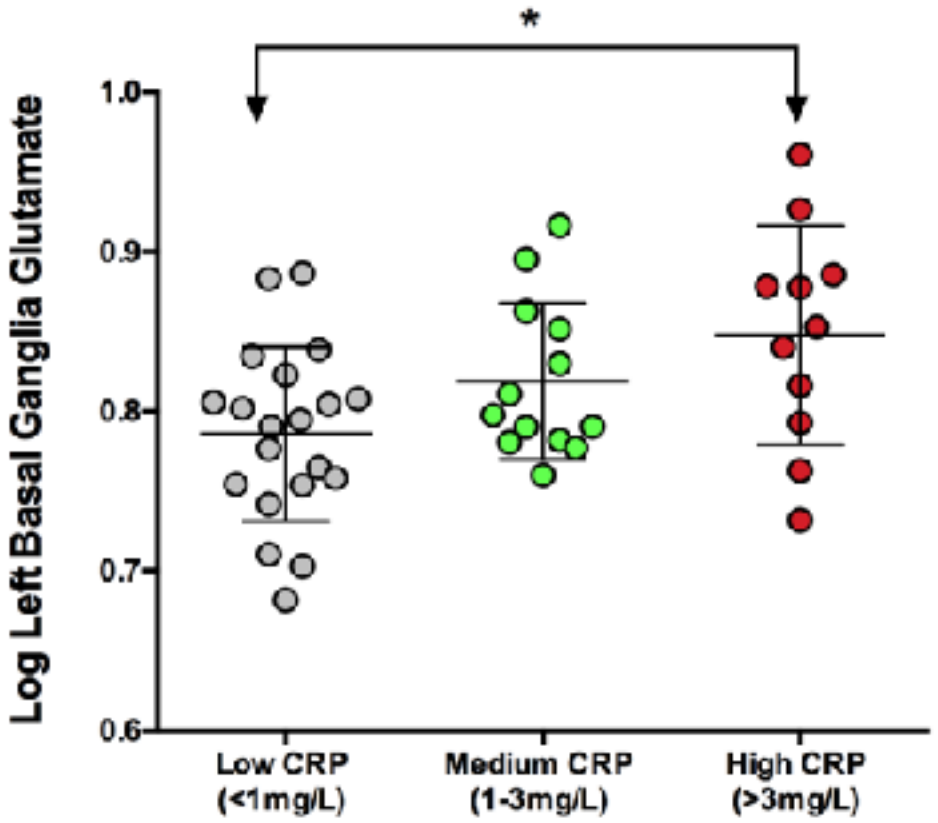
IFN-alpha Alters Basal Ganglia Resting State Glucose Metabolism

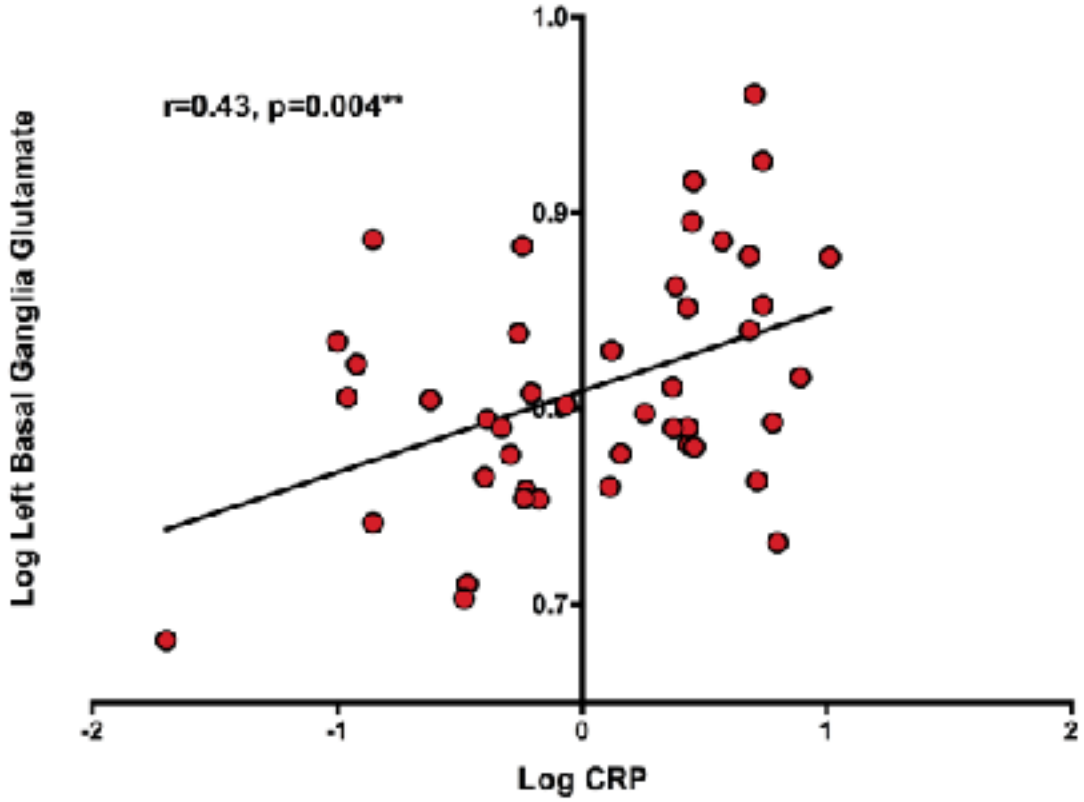
^{18}FDG PET Scans



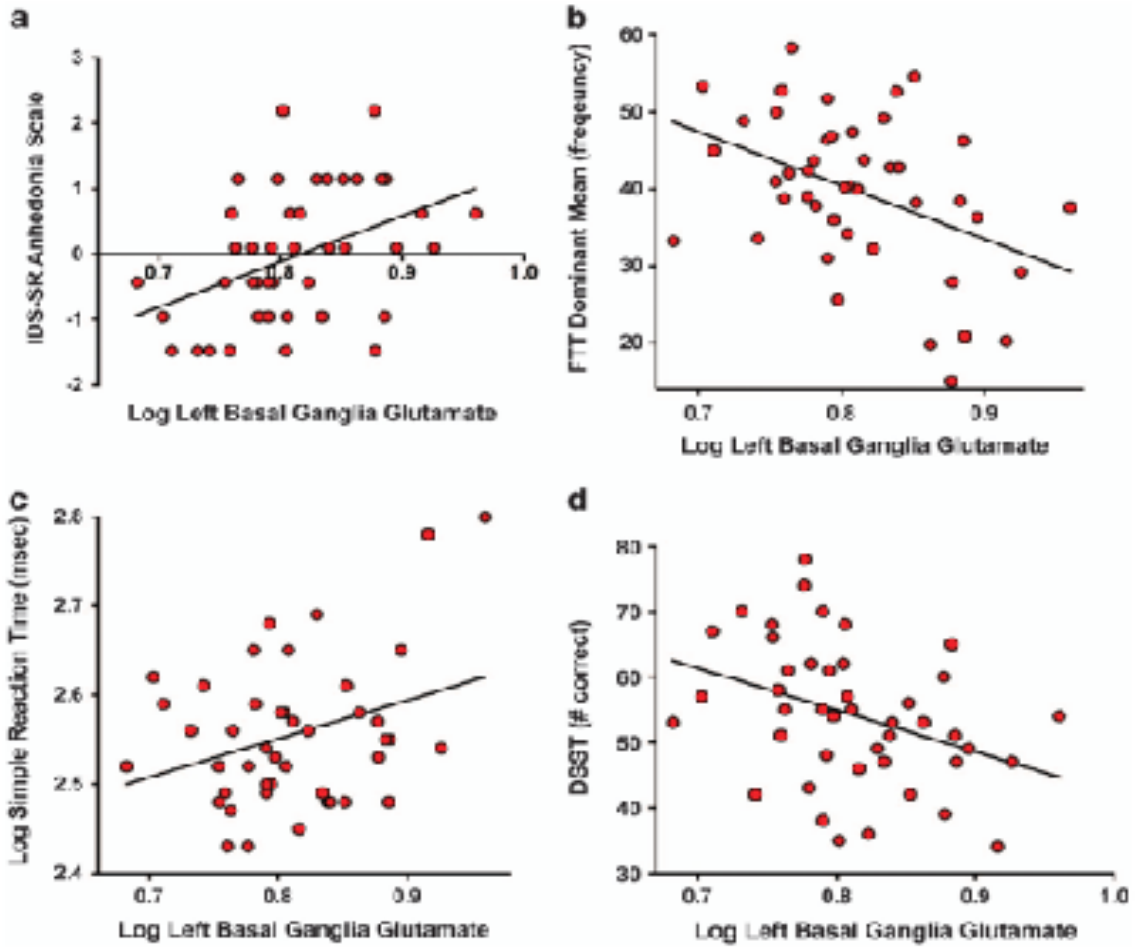
Parkinson's and Unipolar PET Scans courtesy of HS Mayberg 2002

Increased CRP is Associated with Increased Basal Ganglia Glutamate in Patients with Major Depression



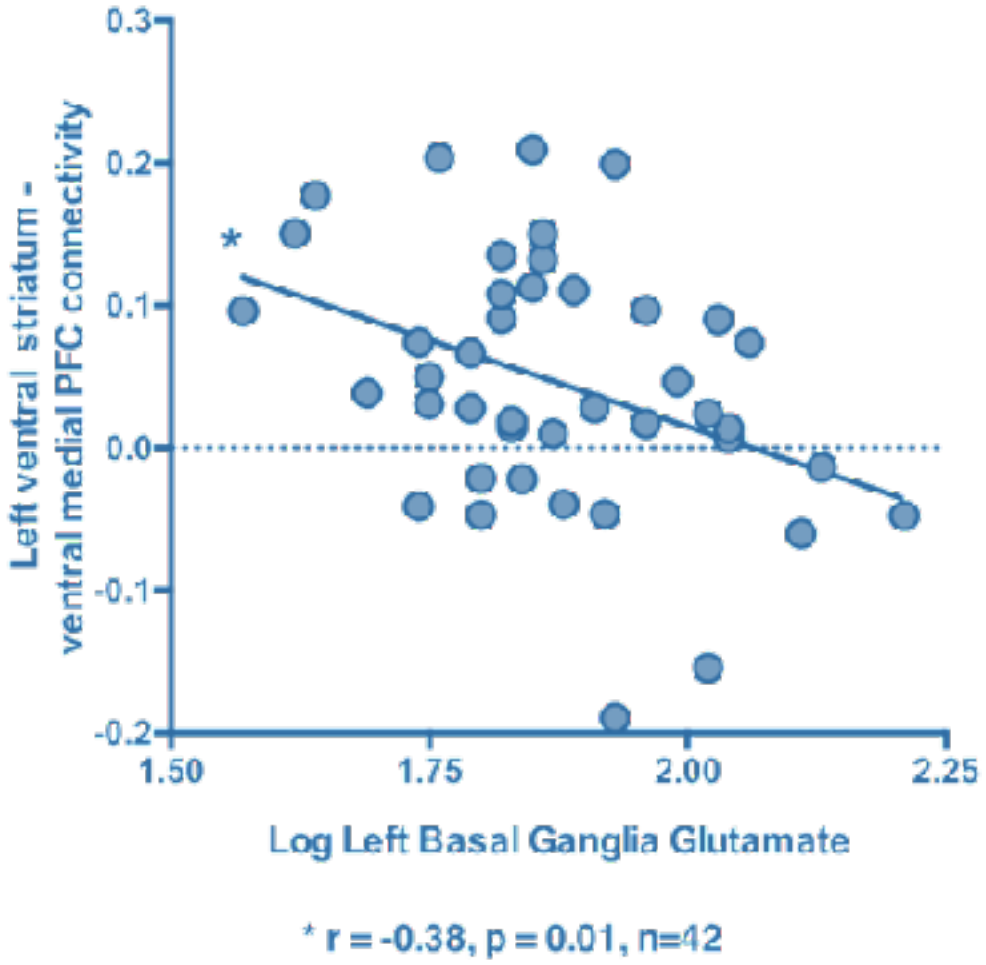


Basal Ganglia Glutamate Increases Are Associated with Decreased Motivation and Motor Speed in Depression



Source: Haroon et al: Molecular Psychiatry In Press

Basal Ganglia Glutamate Increase are associated with Decreased Ventral Striatum to PFC Connectivity in Patients with Major Depression



Overall MDD Summary

- Some individuals with MDD have elevated peripheral markers of inflammation
- Peripheral markers of inflammation are associated with decreases in dopamine and increased glutamate in some subjects
- These changes are associated with increased basal ganglia activity, decreased functional conductivity, decreased motivation and motor speed
- Preliminary data suggests that anti-inflammatory therapies and more dopaminergic antidepressants may be effective

Omega-3 Fatty Acids - DHA and EPA

Long-chain polyunsaturated omega-3 fatty acids

- Primarily in fish oil and other marine sources
- Mechanism may involve neuronal membrane stabilization, anti-inflammatory effects

Docosahexaenoic acid (DHA) (22:6, omega-3)

Eicosapentaenoic acid (EPA) (20:5, omega-3)

EPA vs. DHA vs. Placebo

- 177 subjects with MDD: Mean Ham-D= 19
- Randomized 1 gm/day EPA-enriched, 1gm/day DHA-enriched or placebo for 8 weeks
- Overall MMRM analysis of change in HAM-D-17 scores over 8 weeks of treatment, we found no significant difference among EPA-enriched treatment (mean change = -10.34), DHA-enriched treatment (mean change = -9.26), and placebo (mean change = -9.49).
- Standardized treatment effect sizes indicated very modest superiority of EPA-enriched treatment over placebo or the DHA-enriched formulation (effect sizes of -0.179 and -0.228, respectively)
- A negligible treatment difference between DHA-enriched treatment and placebo (effect size of +0.049).

Source: Mischoulon et al submitted

Hypotheses

- Some subjects with MDD have a subtype characterized by chronic inflammation

- Subjects with MDD and chronic inflammation will be more likely to respond to monotherapy with EPA than either DHA or placebo

Spearman Correlations among Baseline Values of Body Mass Index (BMI) and 5 Inflammatory Markers – 155 Subjects in Analysis Sample.

MH Rapaport et al Mol Psych 2015

Spearman Correlation
Prob>|r| under H0: Rho=0
Number of Observations

	BMI	hs-CRP	IL-6	IL-1ra	Leptin	Adiponectin
BMI	1.00000 144	0.53975 <.0001 144	0.53498 <.0001 144	0.28638 0.0005 144	0.59369 <.0001 144	-0.40527 <.0001 144
hs-CRP	0.53975 <.0001 144	1.00000 155	0.55478 <.0001 155	0.35191 <.0001 155	0.49741 <.0001 155	-0.19647 0.0143 155
IL-6	0.53498 <.0001 144	0.55478 <.0001 155	1.00000 155	0.42240 <.0001 155	0.47583 <.0001 155	-0.24568 0.0021 155
IL-1ra	0.28638 0.0005 144	0.35191 <.0001 155	0.42240 <.0001 155	1.00000 155	0.24844 0.0018 155	-0.18271 0.0229 155
Leptin	0.59369 <.0001 144			0.24844 0.0018 155	1.00000 155	0.02612 0.7470 155
Adiponectin	-0.40527 <.0001 144	-0.19647 0.0143 155	-0.24568 0.0021 155	-0.18271 0.0229 155	0.02612 0.7470 155	1.00000 155

The Number of high markers of inflammation by BMI Category within Gender

MH Rapaport et al Mol Psych 2015

	Females (N = 86)			Males (N = 58)		
	Underweight or Normal Weight	Overweight	Obese	Underweight or Normal Weight	Overweight	Obese
N	39	18	29	12	27	19
%	45.3	20.9	33.7	20.7	46.6	32.8
Number of High Inflammatory Biomarkers						
4 or 5	0 (0.0)	0 (0.0)	14 (48.3)	0 (0.0)	2 (7.4)	4 (21.0)
2 or 3	3 (7.7)	5 (27.8)	11 (37.9)	3 (25.0)	4 (14.8)	10 (52.6)
1	12 (30.8)	8 (44.4)	2 (6.9)	6 (50.0)	14 (51.8)	3 (15.8)
None	24 (61.5)	5 (27.8)	2 (6.9)	3 (25.0)	7 (25.9)	2 (10.5)
Any High Inflammatory Biomarker	15 (38.5)	13 (72.2)	27 (93.1)	9 (75.0)	20 (74.1)	17 (89.5)

Summary

- 25/29 (86%) of obese women with MDD have 2 or more high markers of inflammation.
- 14/19 (74%) of obese men with MDD have 2 or more high markers of inflammation.

Change in HAMD-17 Total Score from Baseline to Treatment Week 8 by Number of High Inflammatory Markers a.

Inflammatory Group Based on Number of High Inflammatory Markers	Least-Square Means (se) of Change at Treatment Week 8			Significance of Treatment-by-Time Interaction	Standardized Treatment Effect Size at Treatment Week 8 [b]		
	EPA LS-Mean (se) [N]	DHA LS-Mean (se) [N]	Placebo LS-Mean (se) [N]	Fdf (P-Value)	EPA vs. PLA	DHA vs. PLA	EPA vs. DHA
4 or 5 High (N=21)	-11.14 (1.79) [10]	-4.90 (2.17) [7]	-5.02 (2.52) [4]	0.94 2, 79.8 (P=0.396)	- 1.11	+ 0.02	- 1.10
2 or 3 High (N=38)	-12.38 (1.47) [13]	-11.52 (1.35) [13]	-9.43 (1.35) [12]	0.70 2, 135 (P=0.498)	- 0.59	- 0.44	- 0.17
1 High (N=50)	-11.76 (1.28) [13]	-7.31 (1.11) [17]	-10.80 (1.10) [20]	1.20 2, 177 (P=0.303)	- 0.20	+ 0.73	- 0.97
0 High (N=46)	-7.78 (0.85) [16]	-11.65 (0.96) [14]	-10.85 (0.83) [16]	4.09 2, 215 (P=0.018)	+ 0.91	- 0.23	+ 1.11

a. MMRM analysis of N=155 evaluable subjects with all five biomarkers at baseline.
b. By Cohen's d effect size = (difference between LS-Mean change) / pooled sd for each pair of treatments (sd per group computed from se of LS-Mean from MMRM). A negative effect size indicates that the 1st group improves more than the 2nd (has a larger negative LS-mean change).

Study Summary

- Subjects with 4-5 high inflammatory markers treated with EPA demonstrated large effect size improvements on HAMD-17 when compared to DHA or placebo.

- Among subjects treated with placebo, those with 4-5 high inflammatory markers had the *least* HAMD-17 improvement, while those with 0 high inflammatory markers had the *most* improvement..

- Obese subjects with MDD were much more likely to manifest a high inflammatory state and have multiple high markers of inflammation. This was particularly true for ***women.***

OMEGA-3 FATTY ACIDS FOR MDD WITH HIGH INFLAMMATION: A PERSONALIZED APPROACH: AN UG3

Mark H. Rapaport, MD, Maurizio Fava, MD, David Mischoulon, MD, PhD, Boadie Dunlop, MD, Jennifer Felger, PhD, Becky Kinkead, PhD, Andrew Miller, MD, Jeffrey Rakofsky, MD, Pamela Schettler, PhD, Thomas Ziegler, MD, Andrew Nierenberg, MD, Jonathan Alpert, PhD, Christina Dording, MD, Stephania Fava, PhD

Funding: NCCIH UG3AT008857

Flow of Randomized Subjects by Treatment Group

Subject Status	1g/day	2g/day	4g/day	Placebo	Total
Randomized (n)	15	15	16	15	61
Evaluable (n)	15	14	16	12	57
% of Those Randomized	100.0%	93.3%	100.0%	80.0%	93.4%
Analyzable Data to Visit 9 (Treatment Week 12) (n)	14	11	13	10	48
% of Those Randomized	93.3%	73.3%	81.2%	66.7%	78.7%

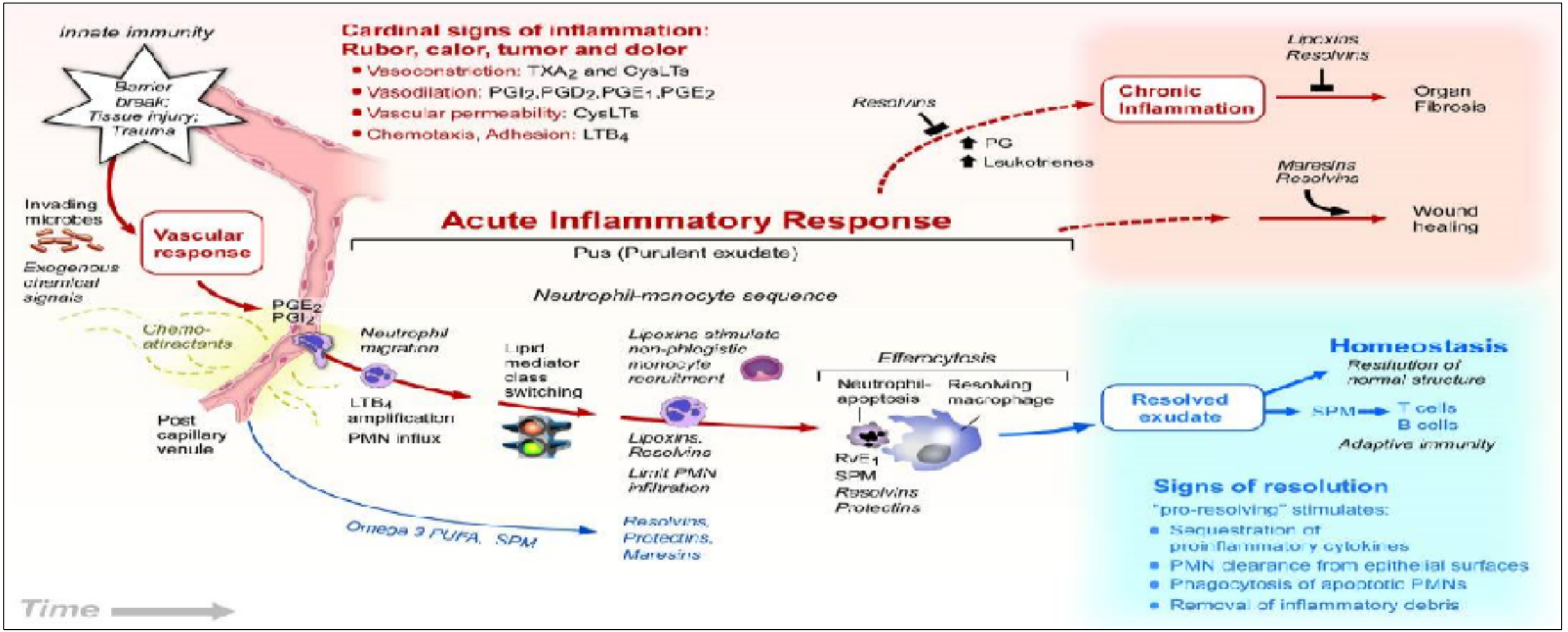
IDS-C30 Response (≥50% Reduction in Total Score)
(n=48 Completers)

Tx Week	1g/day n/n (%)	2g/day n/n (%)	4g/day n/n (%)	Placebo n/n (%)	EPA Dose vs. Placebo	Risk Ratio: EPA Dose vs. Placebo	Odds Ratio: EPA Dose vs. Placebo
Week 8	3/13 (23.1)	4/11 (36.4)	8/13 (61.5)	5/10 (50.0)	1g vs. Pla 2g vs. Pla 4g vs. Pla	0.461 0.727 1.231	0.300 0.571 1.600
Week 12	5/14 (35.7)	4/11 (36.4)	9/13 (69.2)	4/10 (40.0)	1g vs. Pla 2g vs. Pla 4g vs. Pla	0.893 0.909 1.731	0.833 0.857 3.375
Both Tx Week 8 and 12	3/13 (23.1) Includes all 3 responders at Wk 8	4/11 (36.4) Includes all 4 responders at Wk 8	6/13 (46.2) Includes 6 of 8 responders at Wk 8	2/10 (20.0) Includes 2 of 5 responders at Wk 8	1g vs. Pla 2g vs. Pla 4g vs. Pla	1.154 1.818 2.308	1.200 2.286 3.429

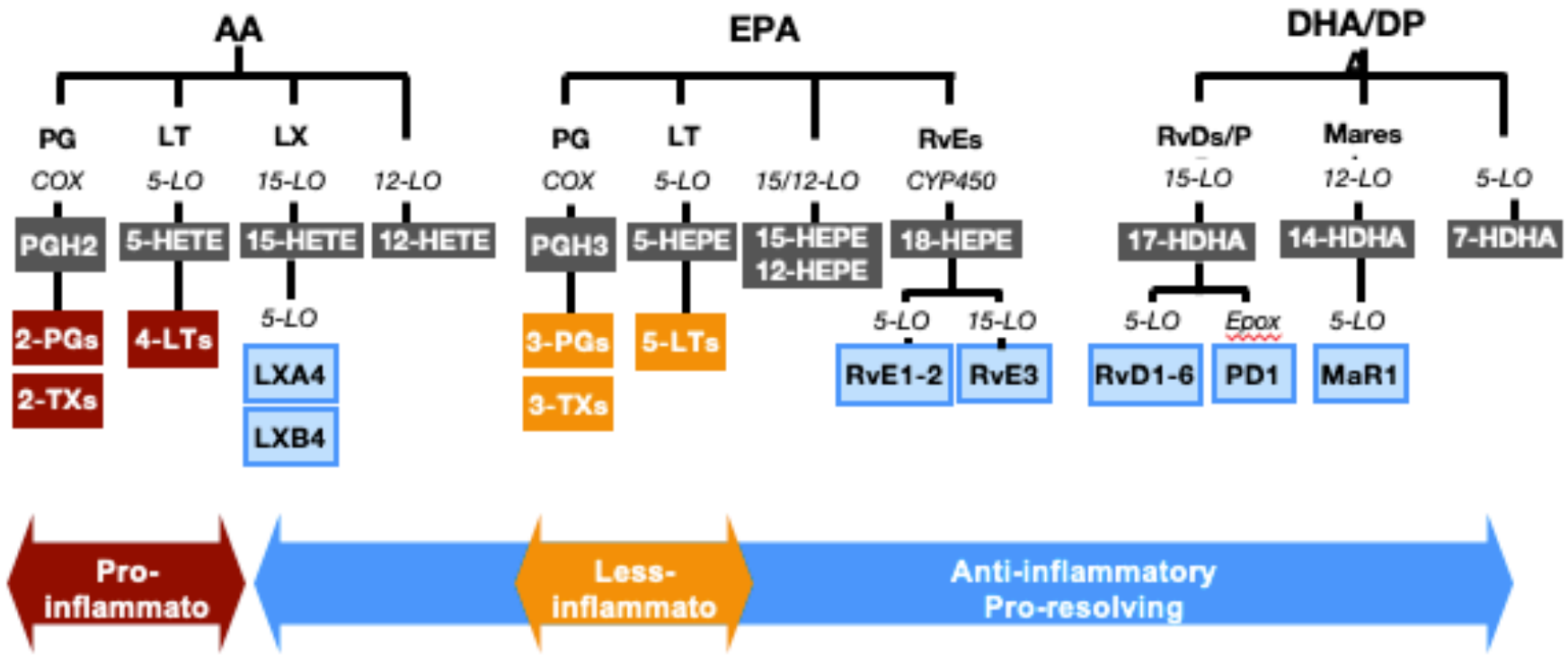
Correlation of % Change in IDS-C30 with % Change Plasma hs-CRP
(n=48 Completers)

Percent Change from Baseline	Spearman Rank-Order Correlation with Percent Change in IDS-C30 at Treatment Week 12 (Correlation, p=value, and n)			
	1g/day	2g/day	4g/day	Placebo
Plasma hs-CRP	-0.129 p=0.694 13	-0.091 p=0.790 n=11	0.753 p=0.003 13	0.164 p=0.652 10

Lipid mediators in the acute inflammatory response, resolution and other outcomes



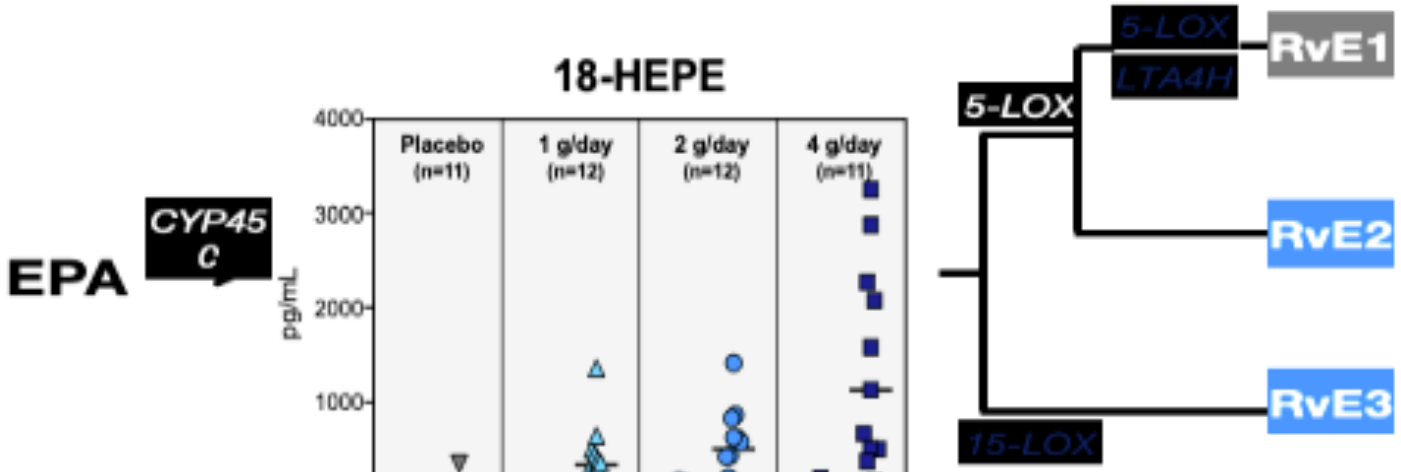
SPM biosynthetic pathways

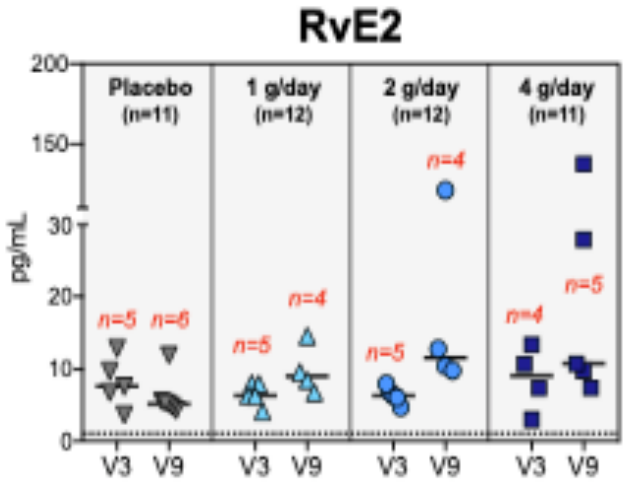


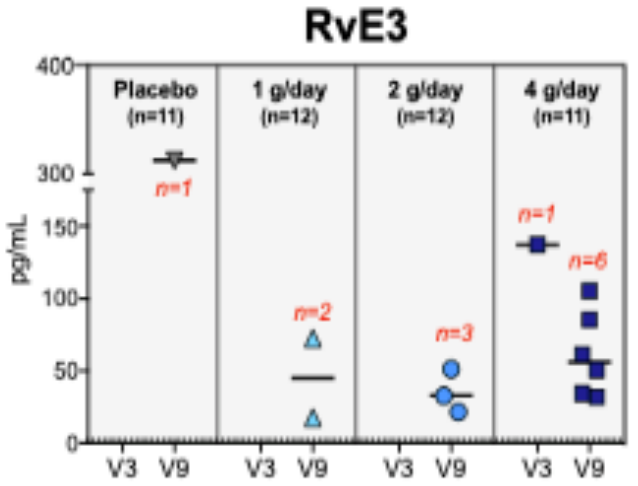
IVC Resolvin E1, E2, and E3 all have antidepressant activity in the LPS-induced mouse model of depression

Deyama et al Int J Neuropscyhophamacol. 2017:20; 571-584;
Deyama et al j.jphs.2018.09.006

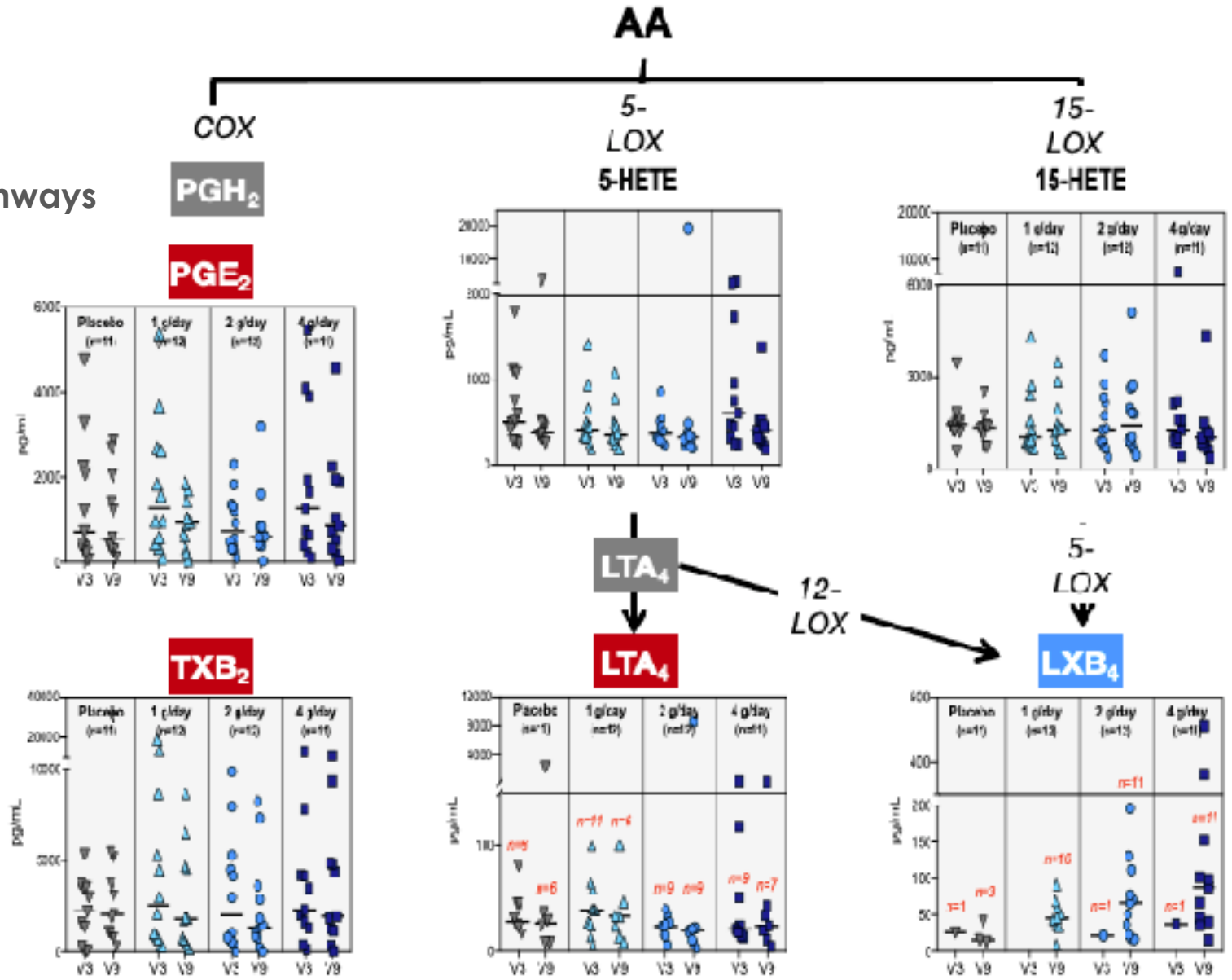
EPA-derived RvEs







AA-derived SPM biosynthetic pathways



4 GM EPA GROUP

Responders (means)

- 33% hs-CRP decrease
- 18-HEPE: 2196.96
- RvE2: 30.94
- RvE3: 53.11

Non-responders (means)

- 14% hs-CRP increase
- 18-HEPE: 399.82
- RvE2: 0
- RvE3: 12.65

Where are we going?

- A four site RO1 application to NIA investigating the year long effects of 4 g EPA/1 gDHA in subjects with cognitive impairment, depressive symptoms, and hs-CRP>3

- EPA augmentation in TRD R33