Role of n-3 PUFAs in mood and cognitive disorders

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Mood and cognitive disorders and PUFA metabolism

Polyunsaturated fatty acids metabolism

Diet

Mood and cognitive disorders

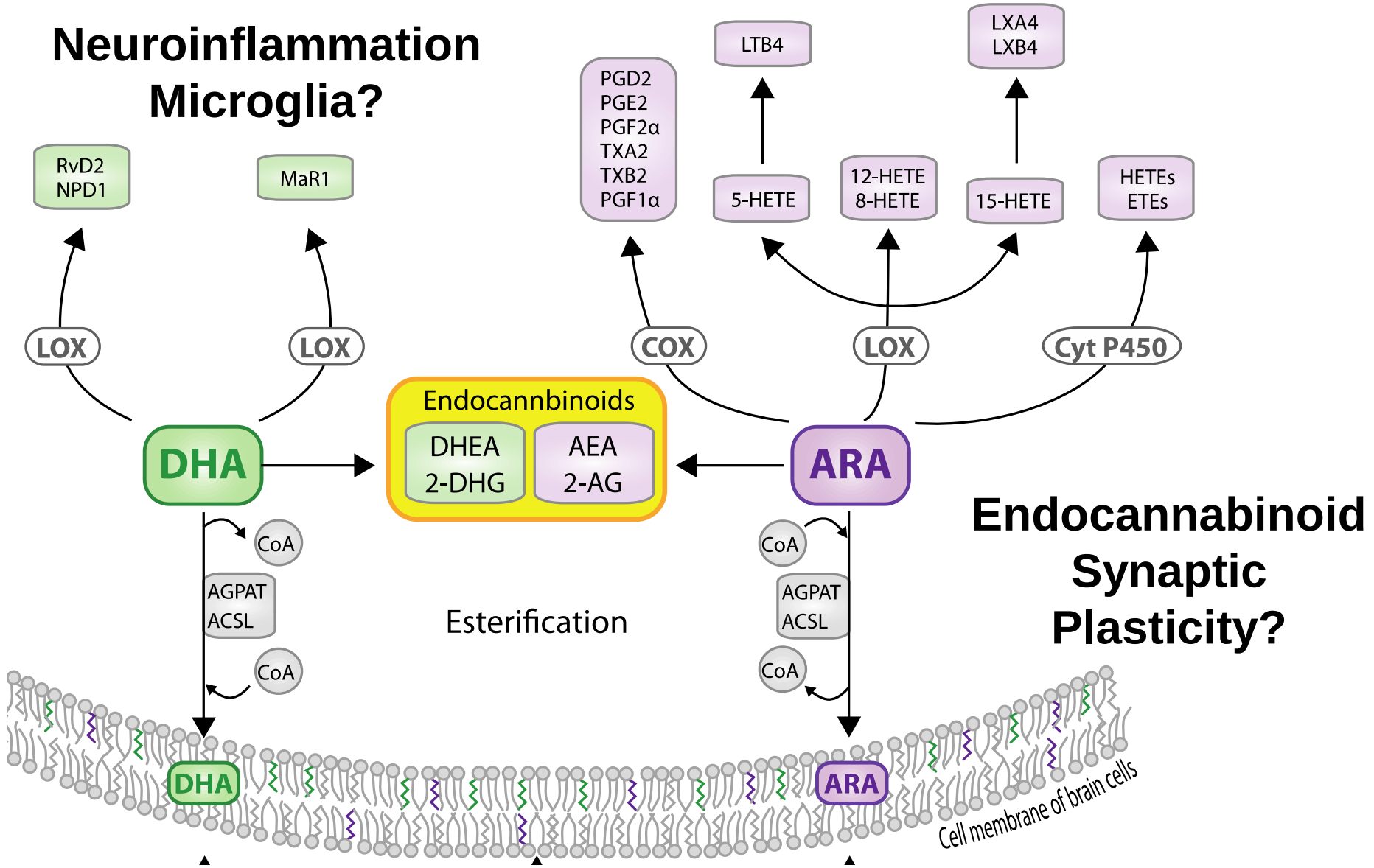
- Inverse relation between fish consumption and prevalence of depression and cognitive decline
- Decreased levels of n-3 PUFA in the blood and the brain of depressed subjects, of aged patients with cognitive impairment, patients diagnosed with PTSD
- In animal models, decreased dietary n-3 PUFA alters emotional behavior and memory
- Some positive effects of dietary intervention on depression, especially in combination with AD or in patients exhibiting inflammation

Polymorphism of PUFA metabolism genes

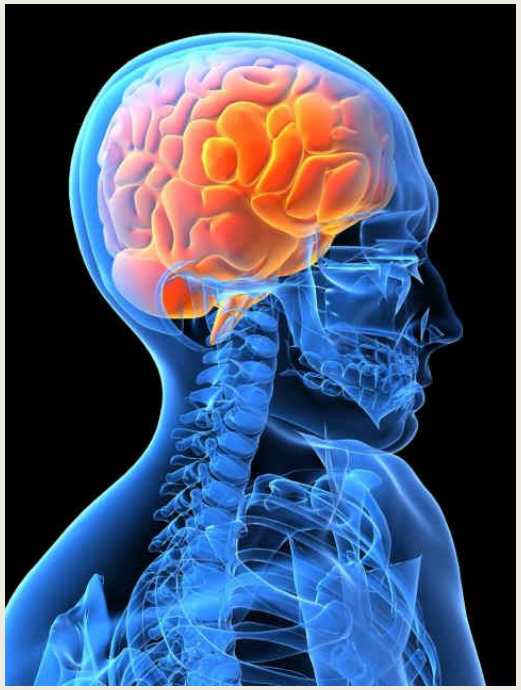
Brain PUFA content DHA/ARA

Bazinet and Layé, Nature Reviews Neuroscience, 2014, Joffre et al., PLEFA, 2014, McNamara et al., 2015, Su, 2015; Song et al., 2016; Layé et al., 2018; Layé, PLEFA, 2010; Layé et al., 2018; Larrieu and Layé, 2018, Sublette et al., 2011; Su et al., 2018

PUFA metabolism, neuroinflammatory pathways and synaptic activity

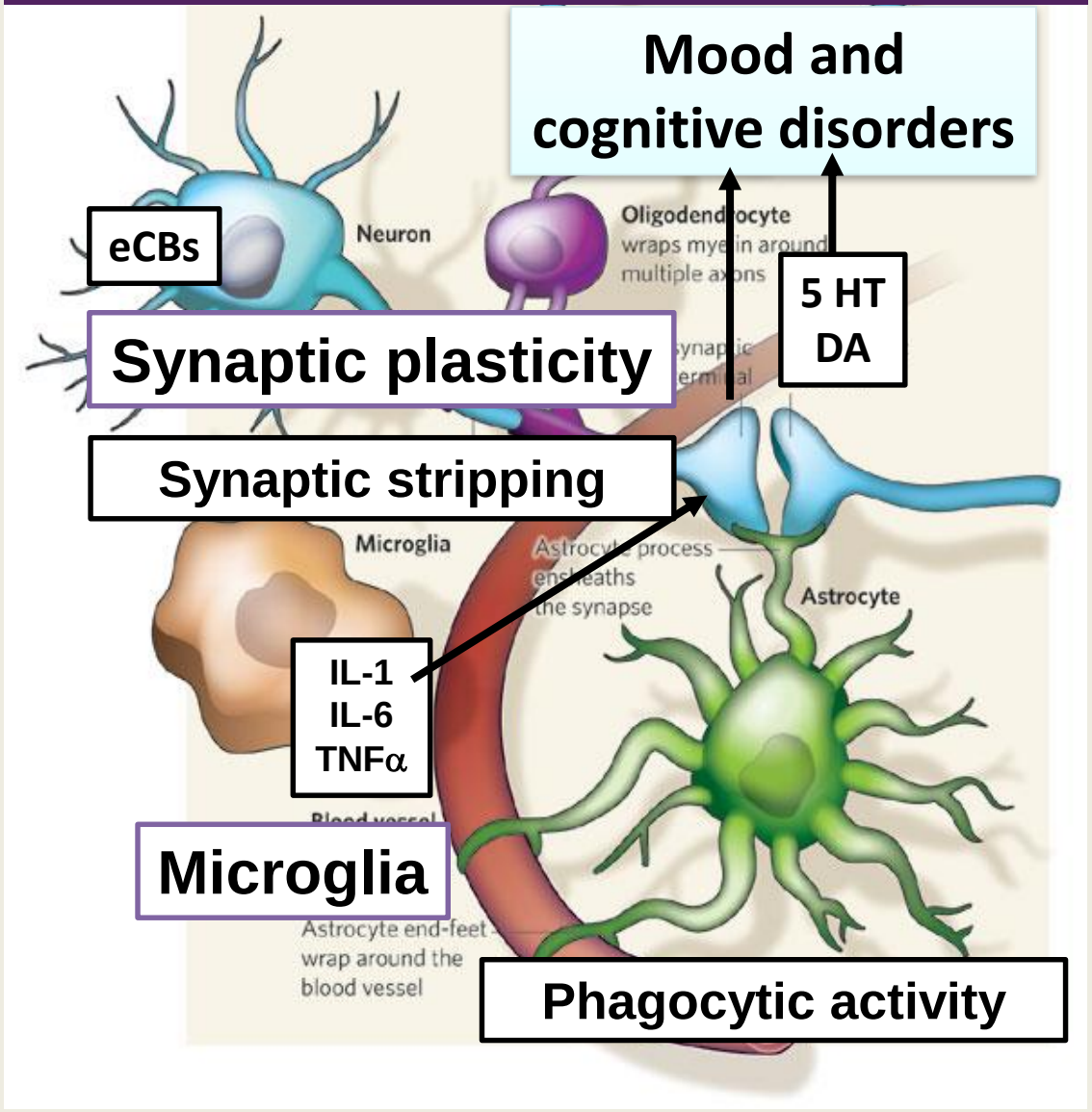


Bazinet and Layé, Nature Reviews Neuroscience, 2014; Bosch-Bouju and Layé, 2016



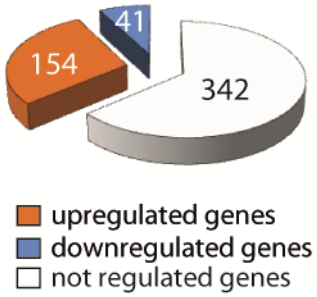
Polyunsaturated fatty acids?

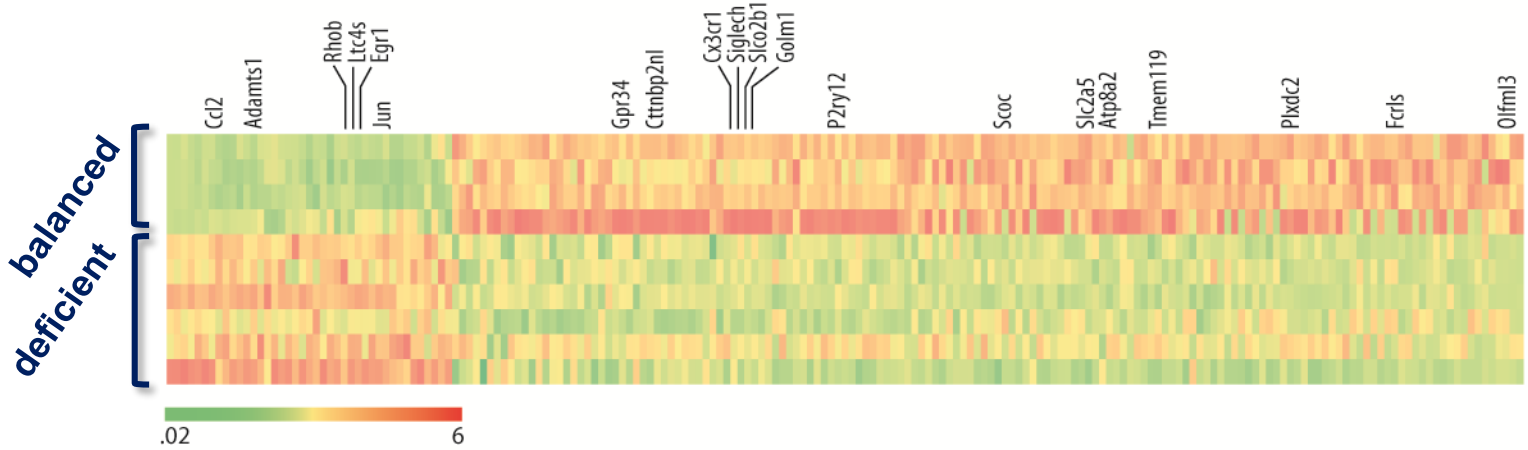
Neuron/glia interactions



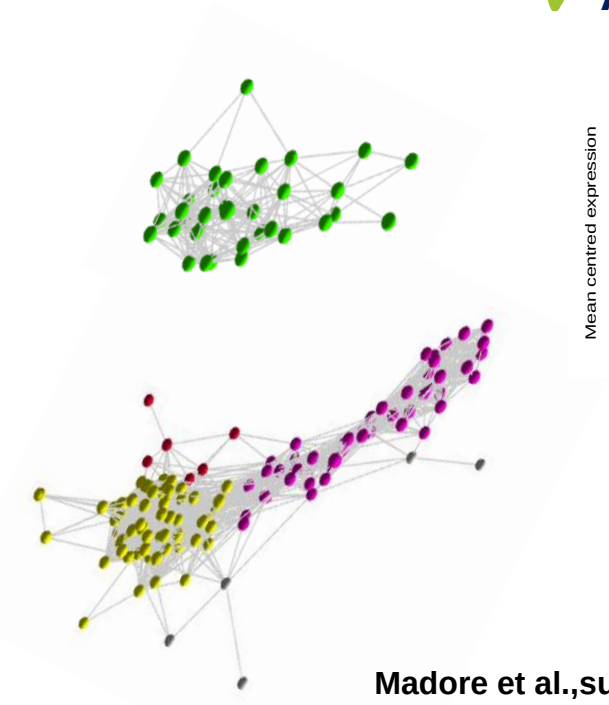
(Layé, 2010, Dantzer et al., 2008, Dantzer et al., 2014, Castanon et al., 2015)

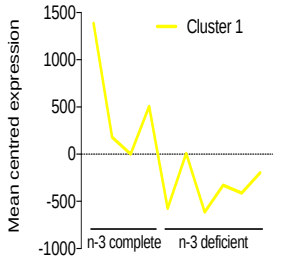
Microglia homeostatic signature is altered in the brain of n-3 deficient mice



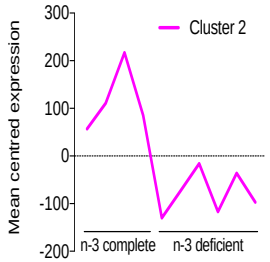


✓ **Alteration of microglial homeostatic signature**

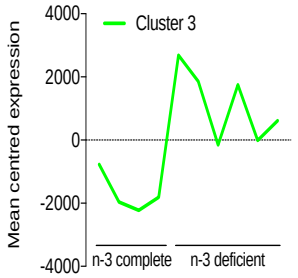




Homeostatic markers



Lipid markers

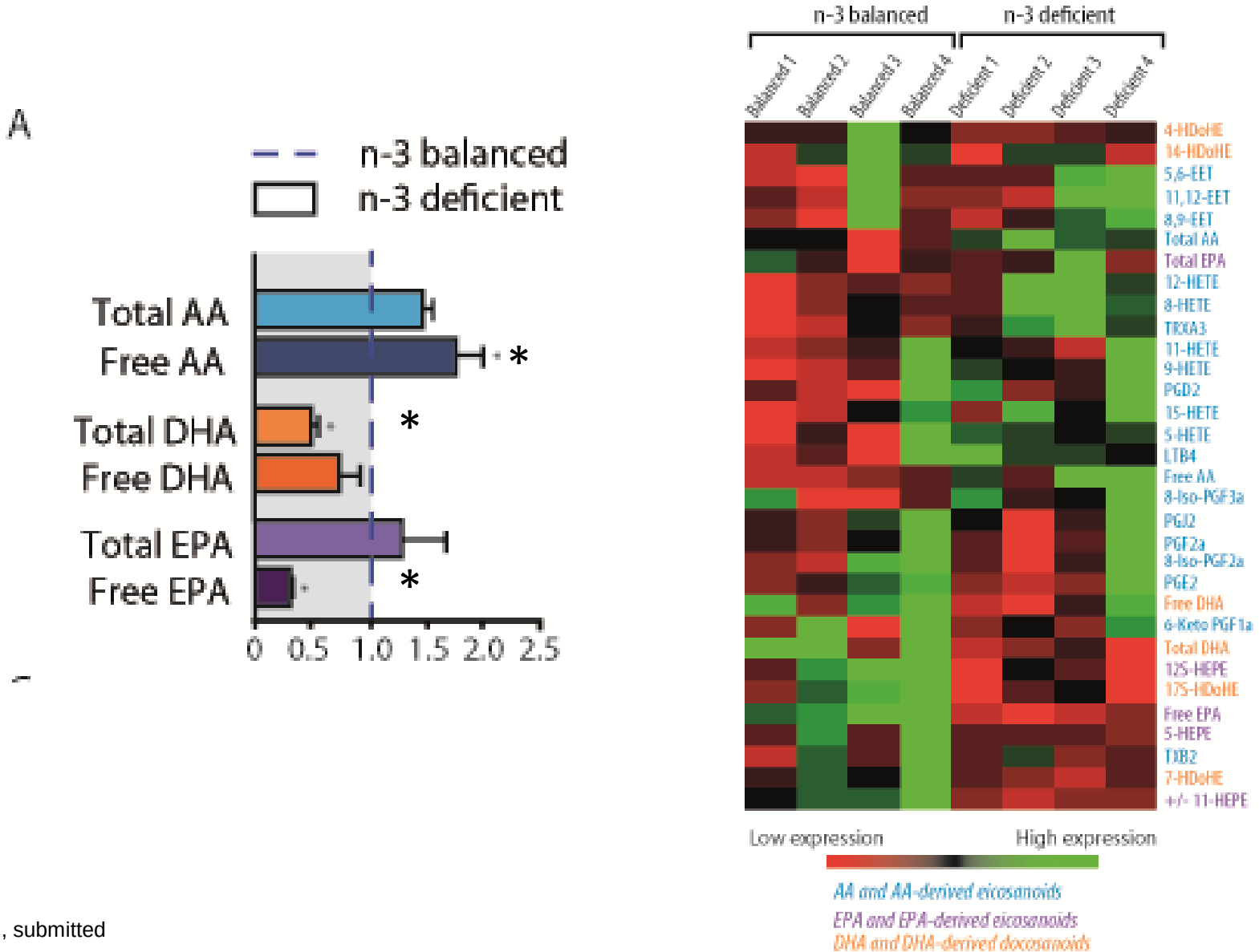


Immune markers

Madore et al.,submitted

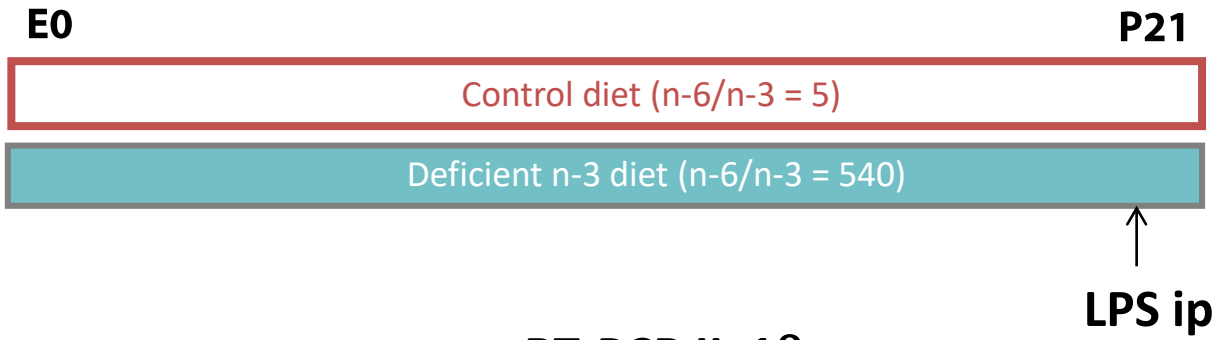
(Coll. O. Butovsky, Harvard Medical School, Boston USA)

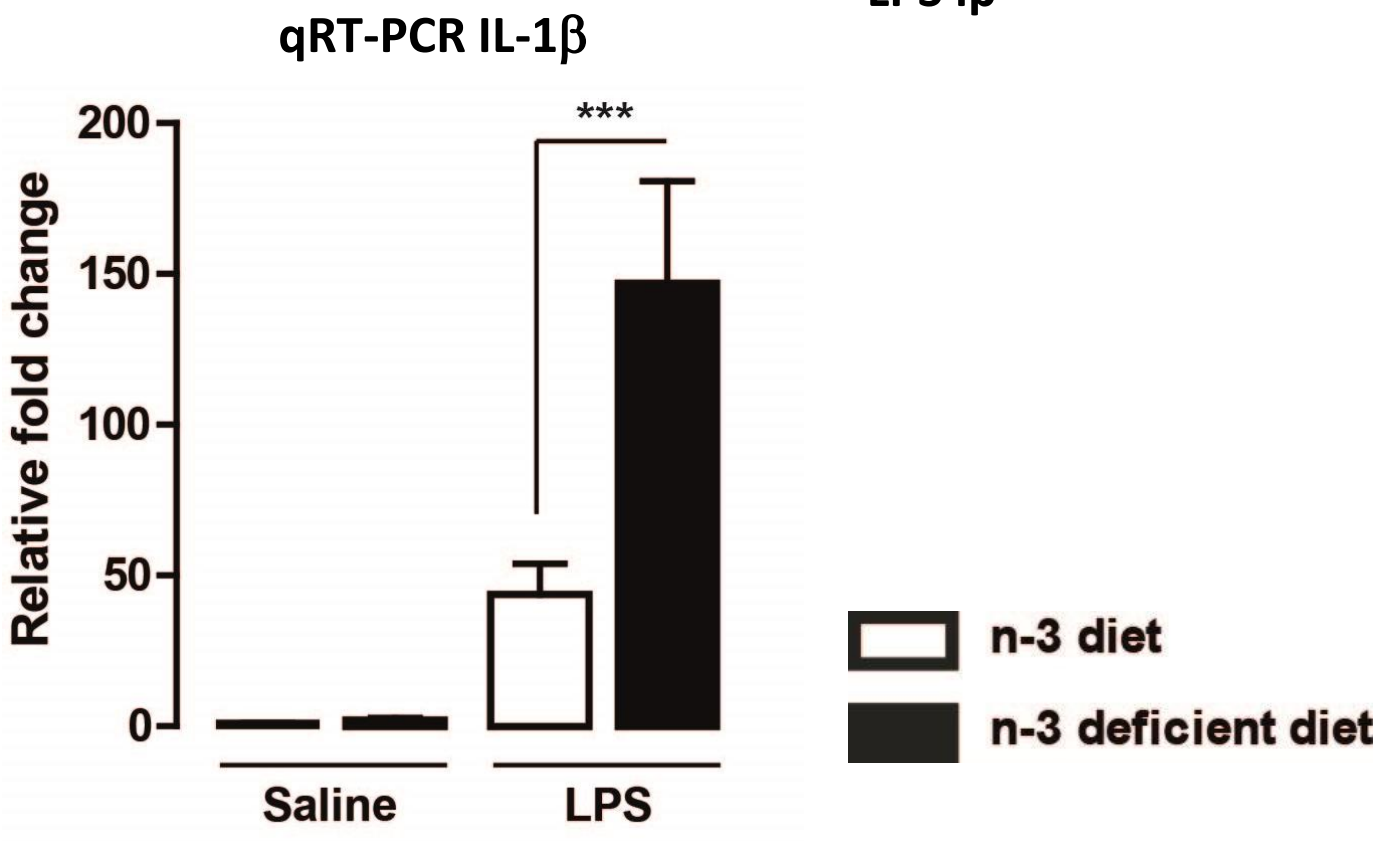
DHA levels and its derivate are decreased in the microglia of n-3 PUFA deficient mice



Madore et al., submitted

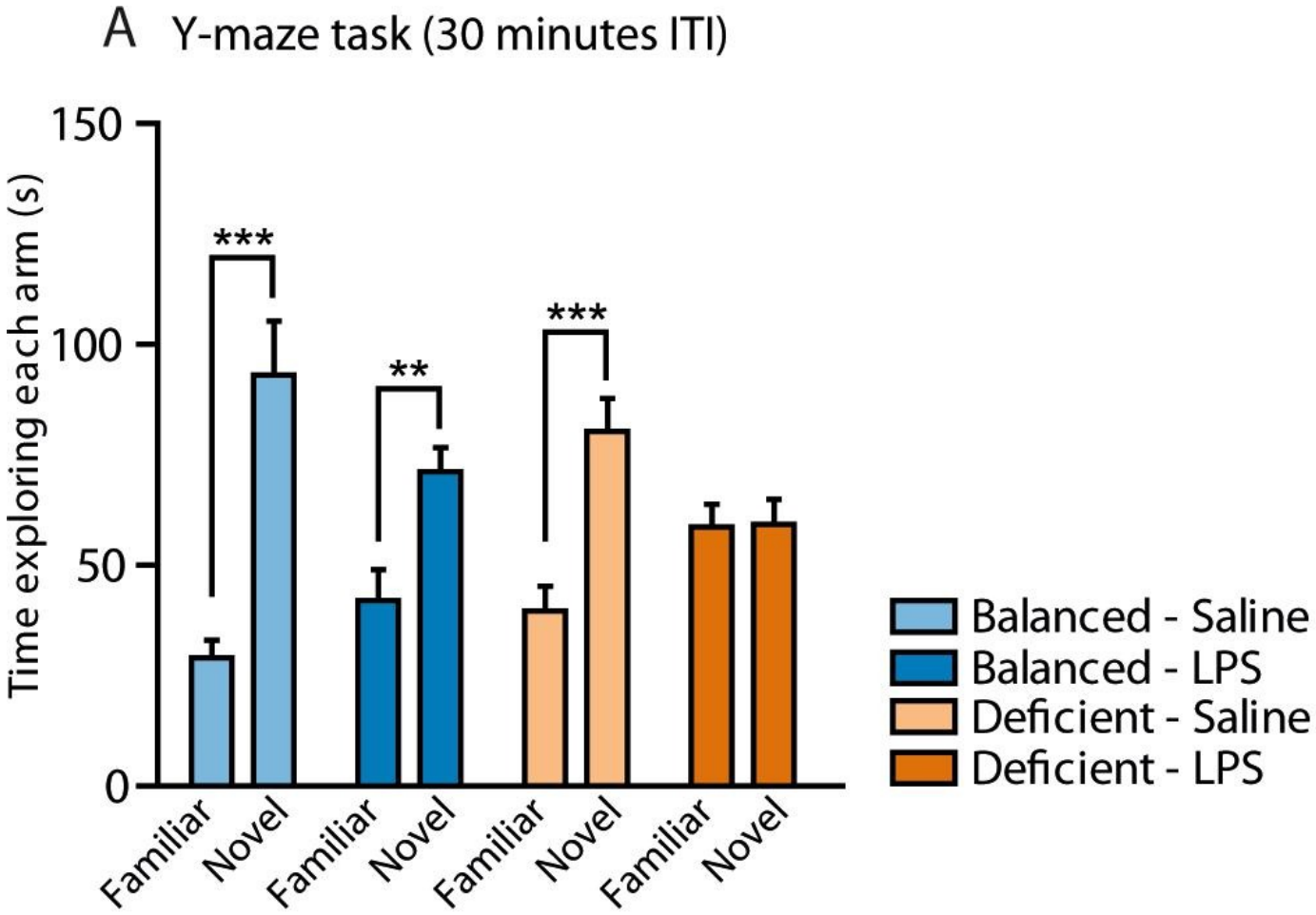
LPS administration activates proinflammatory cytokine expression in the hippocampus of n-3 deficient mice





(Madore et al., in preparation, Mingam et al., 2008)

n-3 PUFA dietary deficiency exacerbates inflammatory stimulus effect on neuroinflammation



Labrousse et al., 2018

Dietary PUFAs influence microglia activity, synaptic plasticity and memory

n-6 PUFAs/n-3 PUFAs

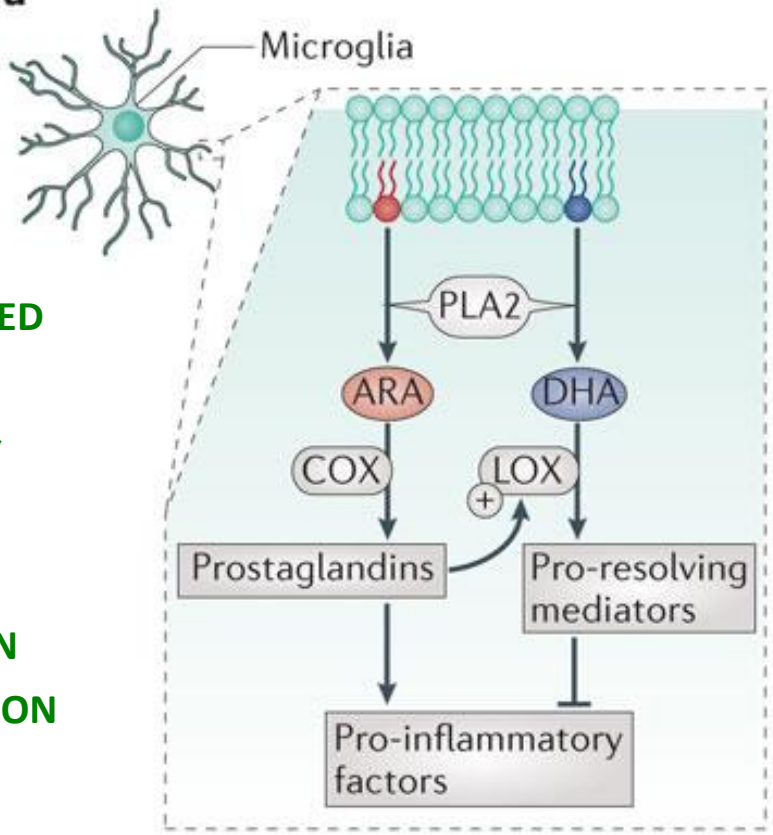
Sensitise to inflammation-induced memory deficit

Pro-inflammatory cytokines

Sustained neuroinflammation

Receptor dysregulation

Impaired synaptic plasticity



n-6 PUFAs/n-3 PUFAs

Protect from inflammation-associated memory deficit (LPS, aging)

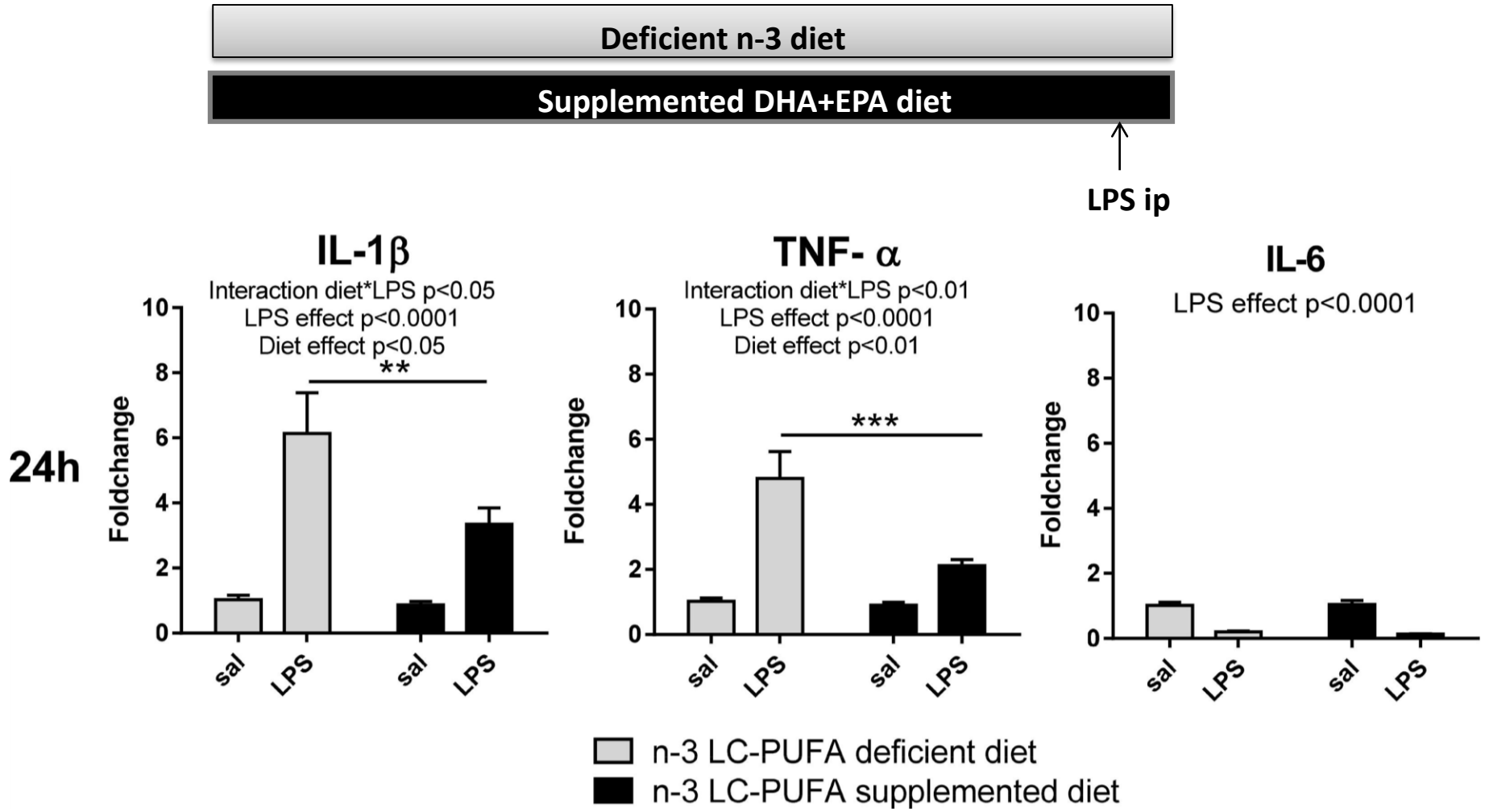
Anti-inflammatory cytokines

Faster resolution of neuroinflammation

DHA and its derivates act on microglia

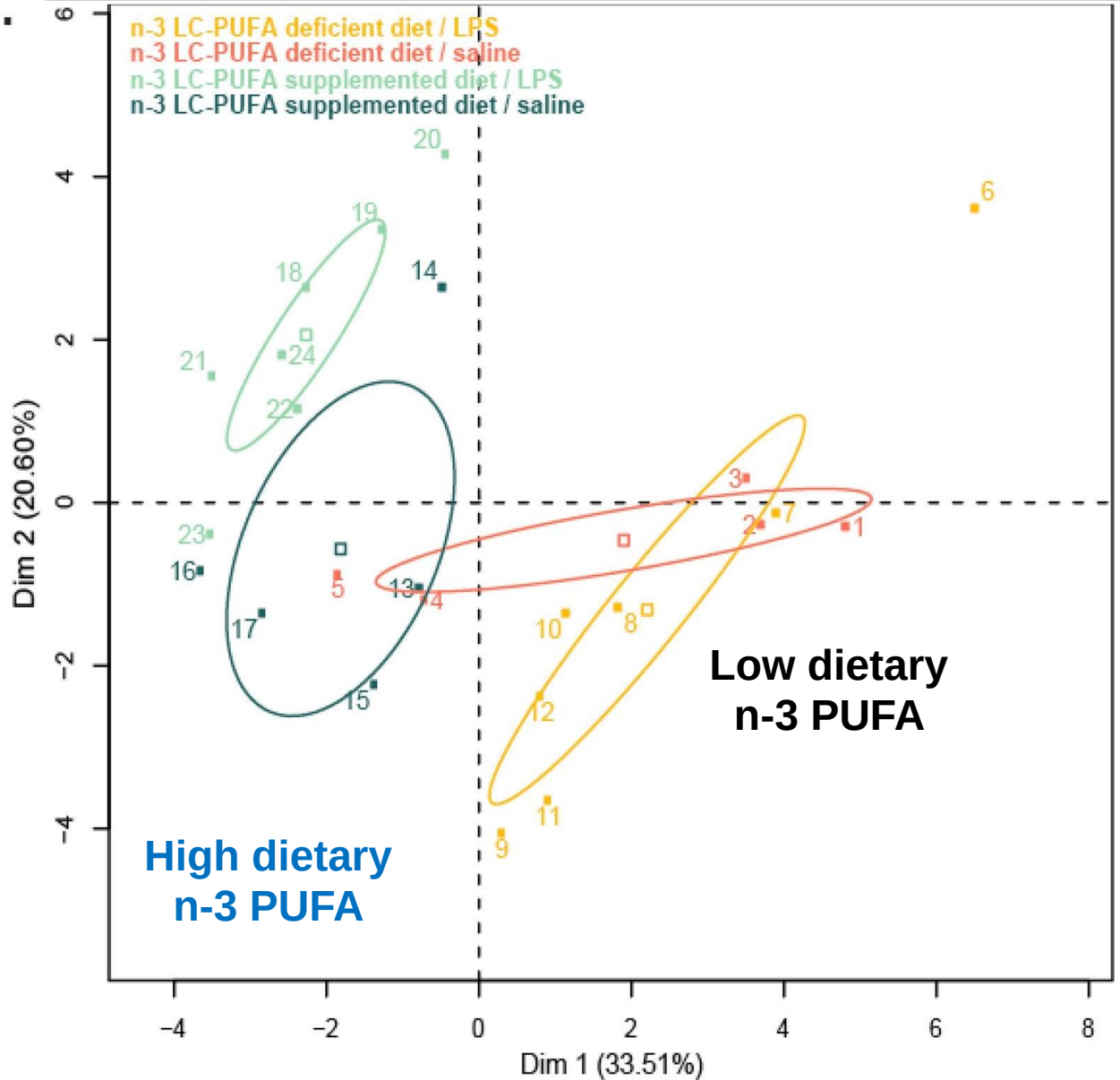
Delpech et al.,Neuropsychopharmacology, 2015a,b, DeSmedt et al., 2008, Joffre et al., 2014, Labrousse et al., 2012, Rey et al., BBI 2006, Mingam et al., 2008, Madore et al., 2014, Dinel et al.,2016; Letondor et al., 2016, Vauzour et al., 2015; Lepinay et al., 2015,Letondor et al., 2014, Dinel et al., 2016, Joffre et al., 2016

Dietary DHA potently reduces LPS-induced pro-inflammatory cytokine expression in the hippocampus



Rey et al., BBI 2018

Dietary DHA promotes a unique oxylipin pattern in the hippocampus



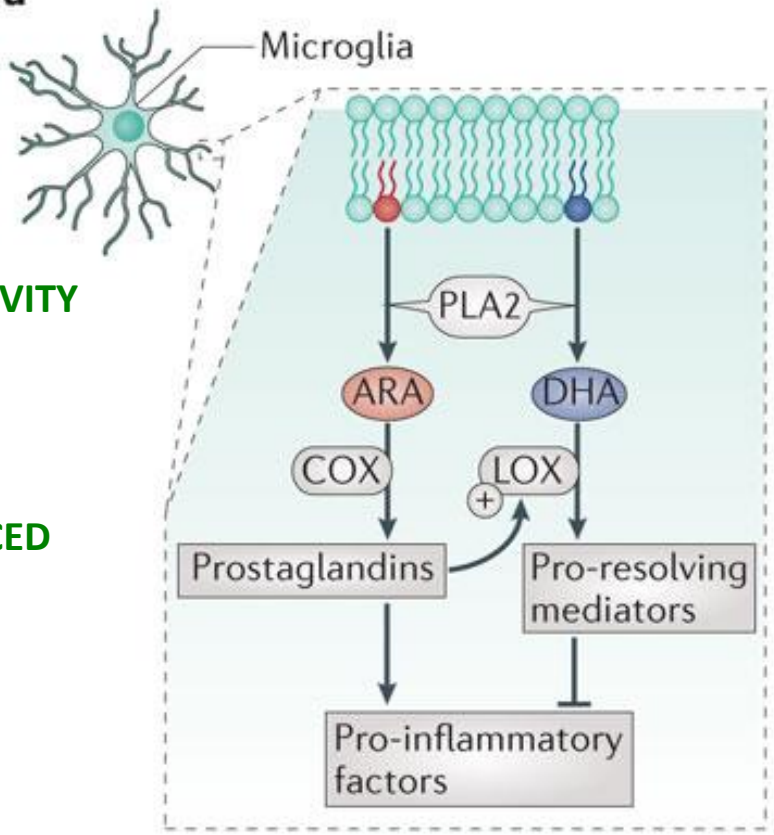
	Loadings [a]	
	Pattern 1	Pattern 2
6kPGF1a	0.100	-0.077
TxB2	0.308[b]	0.061
PGF2a	0.251[b]	0.219[b]
PGE2	0.257[b]	0.182
PGD2	0.137	0.240[b]
LxA4	0.278[b]	0.149
8isoPGA2	0.255[b]	0.083
5,6-DiHETE	0.311[b]	0.099
15dPGJ2	0.312[b]	0.015
13-HODE	0.250[b]	-0.047
9-HODE	0.144	-0.146
15-HETE	0.306[b]	0.000
8-HETE	0.276[b]	-0.006
12-HETE	-0.105	0.258[b]
5-HETE	-0.078	0.339[b]
5oxoETE	-0.146	0.385[b]
14,15-EET	0.041	0.300[b]
11,12-EET	-0.168	0.253[b]
8,9-EET	-0.001	0.297[b]
5,6-EET	-0.127	0.391[b]
18-HEPE	-0.229[b]	-0.015
17-HDoHE	0.020	0.177
14-HDoHE	-0.143	0.182

Increase of pro-resolving mediators
17-HDoHE from DHA
18-HEPE from EPA
11,12-EET, 8,9-EET and 5-oxoETE from AA

Dietary PUFAs influence microglia activity, synaptic plasticity and memory

Low dietary n-3 PUFA

High dietary n-3 PUFA



ALTERS MICROGLIA ACTIVITY

SENSITISE TO INFLAMMATION-INDUCED MEMORY DEFICIT

PROMOTES THE SYNTHESIS OF PRO-RESOLUTIVE OXYLIPINS

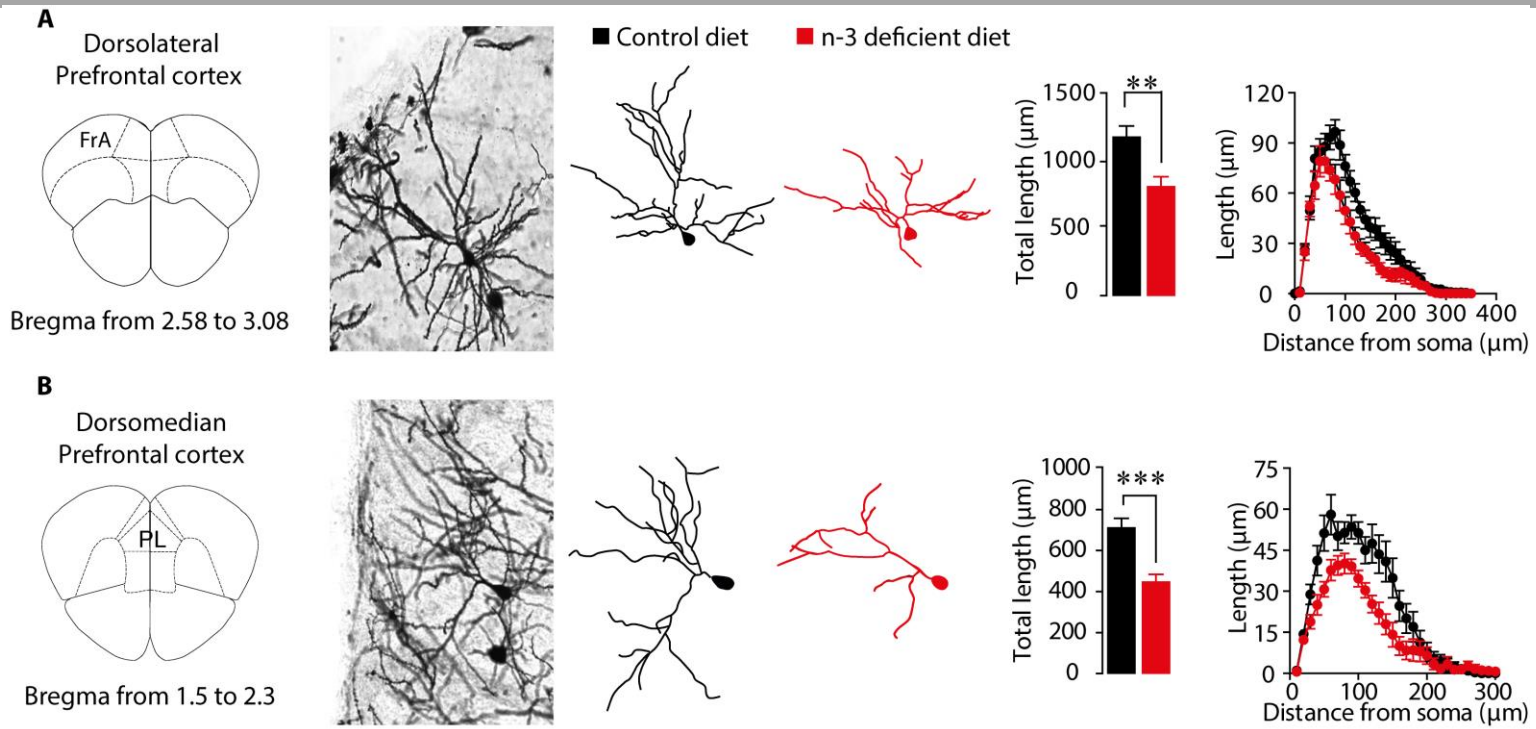
FASTER RESOLUTION OF NEUROINFLAMMATION

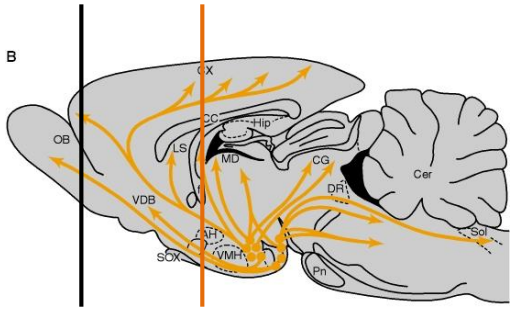
TARGETS MICROGLIA

PROTECTS FROM INFLAMMATION-INDUCED MEMORY DEFICIT (LPS, AGING)

Delpech et al.,Neuropsychopharmacology, 2015a,b, DeSmedt et al., 2008, Joffre et al., 2014, Labrousse et al., 2012, Rey et al., BBI 2006, Mingam et al., 2008, Madore et al., 2014, Dinel et al.,2016; Letondor et al., 2016, Vauzour et al., 2015; Lepinay et al., 2015,Letondor et al., 2014, Dinel et al., 2016, Joffre et al., 2016; Rey et al., 2018; Labrousse et al., 2018

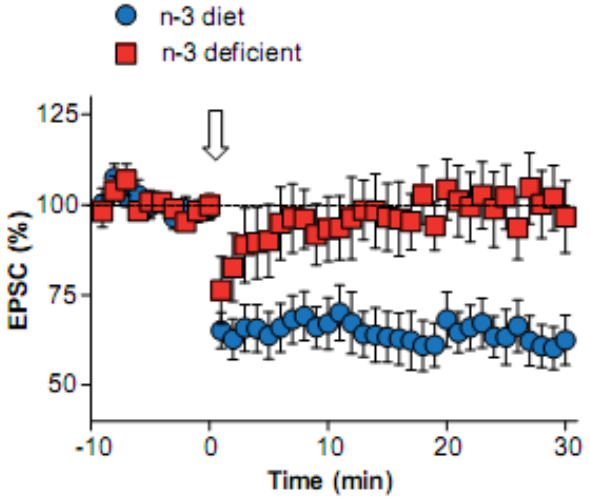
Synaptic plasticity is impaired in the hippocampus, the prefrontal cortex and the nucleus accumbens of n-3 deficient mice





Prefrontal cortex

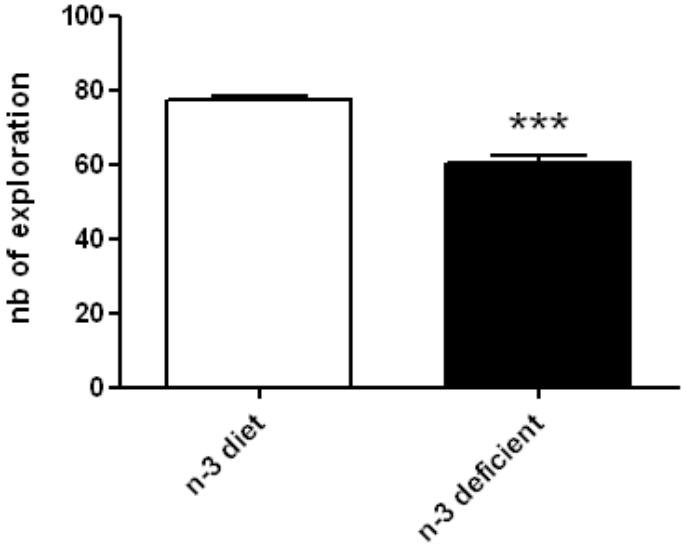
Nucleus Acc



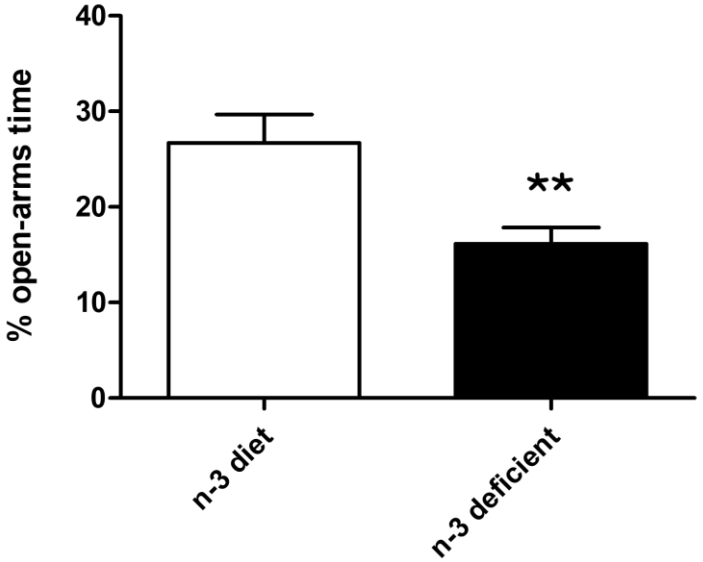
Lafourcade et al. Nature Neuroscience, 2011; Larrieu et al., 2014, 2015

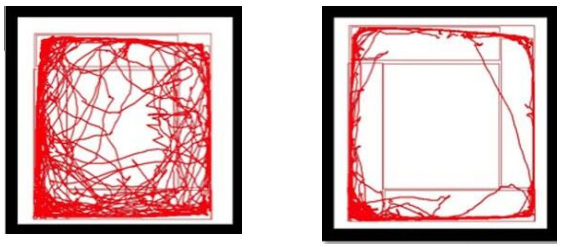
Dietary n-3 PUFA deficiency impairs emotional behavior in mice

Social behavior



Anxiety-like behavior (Open-Field test)



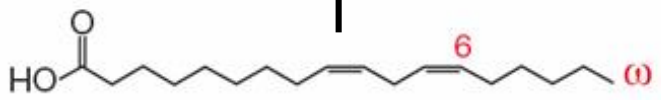


(Lafourcade et al. Nature Neuroscience, 2011, Larrieu et al., 2012, larrieu et al., 2014, Thomazeau et al., 2016)

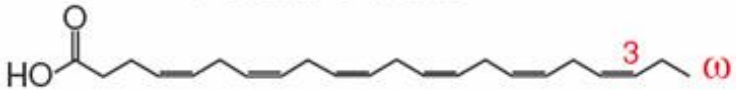
Conclusion

Corticosterone increase

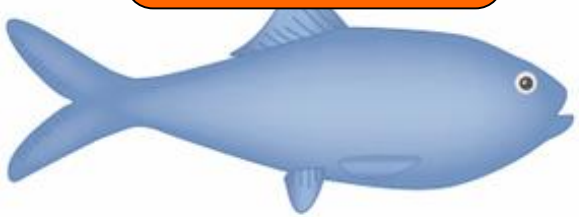
Social defeat



↑ n-6:n-3 ratio

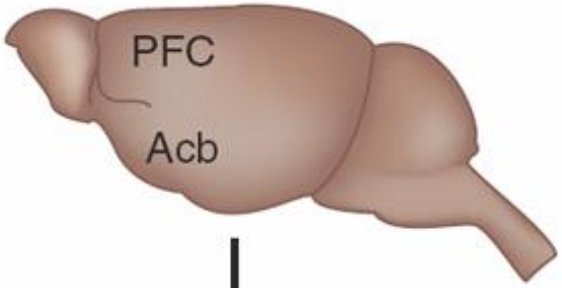


N-3 PUFA decrease



↓ Dendritic arborization

↓ CB_1R signaling and LTD



Changes in behavior and mood

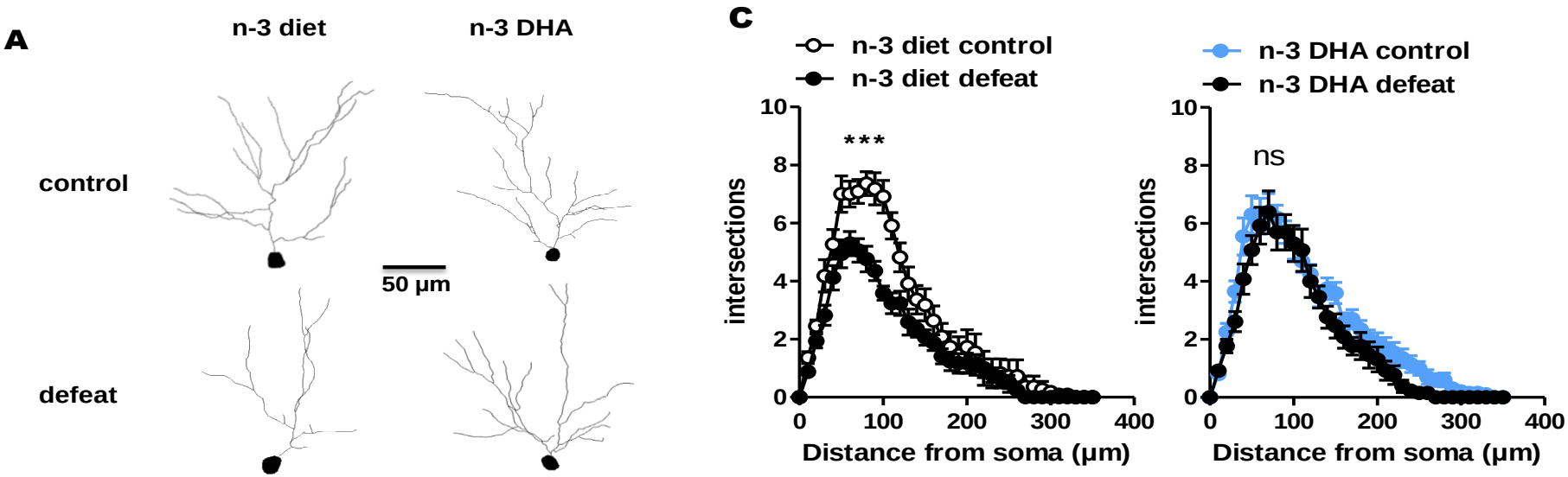
Marina Corral

A 2 months supplementation with LC n-3 PUFA improves Social defeat-induced dendritic arborization decrease

Control diet (n-6/n-3 = 5)

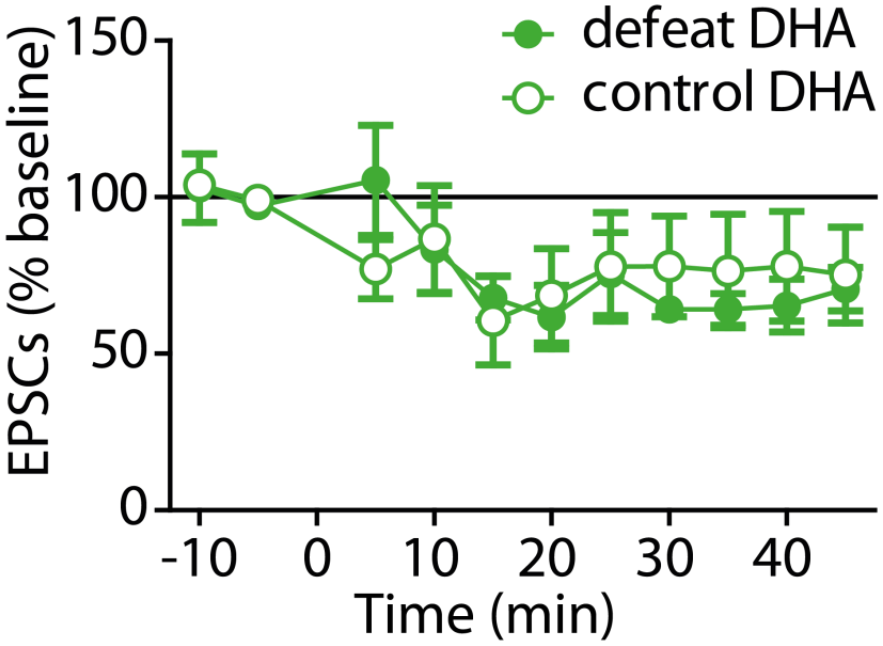
Supplemented DHA+EPA diet

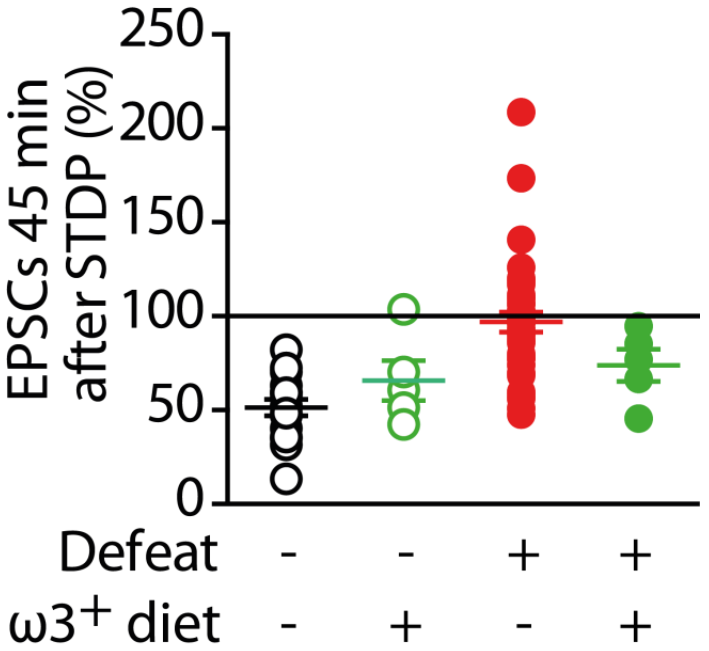
Chronic stress



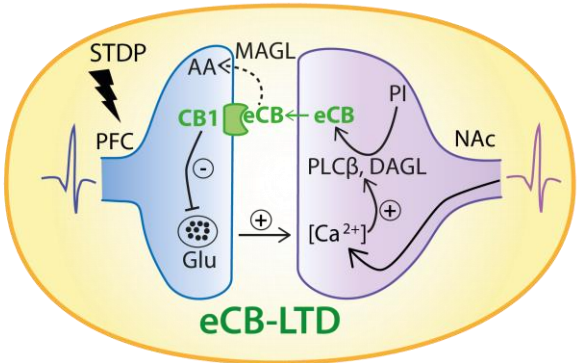
(Larrieu, et al., 2014)

A 2 months supplementation with LC n-3 PUFA improves Social defeat-induced eCB dependent plasticity





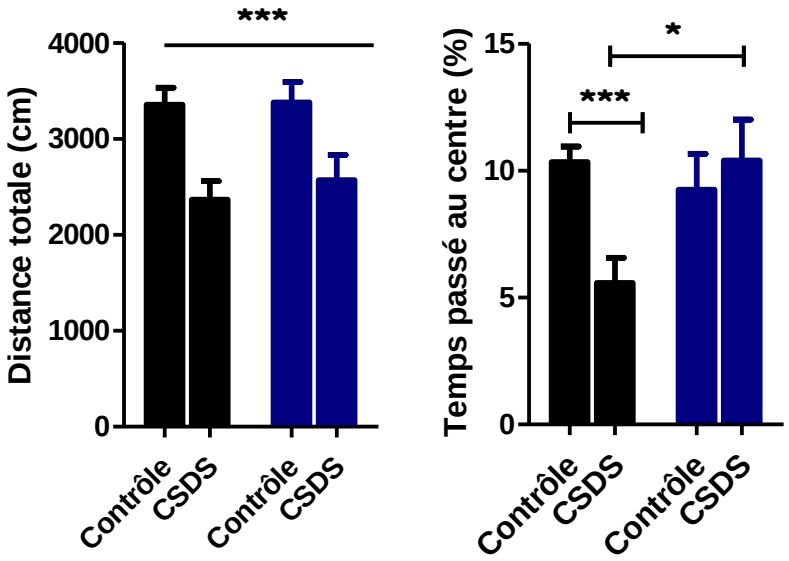
Nucleus Acc



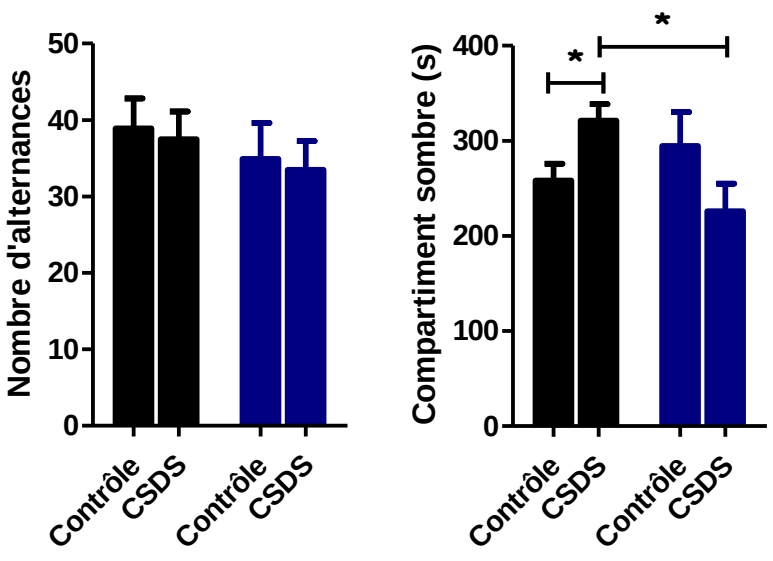
(Bosch-Bouju, DiMicelli et al., in preparation)

A 2 months supplementation with LC n-3 PUFA improves Social defeat-induced anxiety-like behavior

Open field



Dark-light box

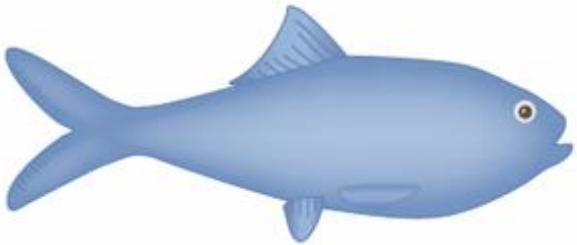


(Larrieu, et al., 2014)

Protective effect of DHA

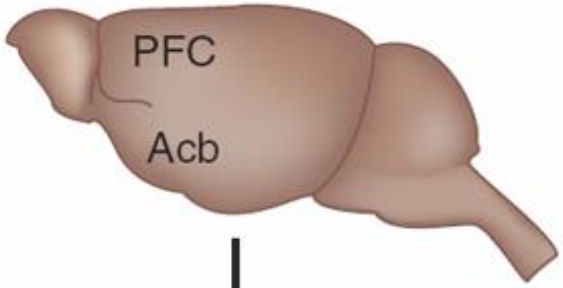
Social defeat

N-3 PUFA increase



↓ Dendritic arborization

↓ CB_1R signaling and LTD



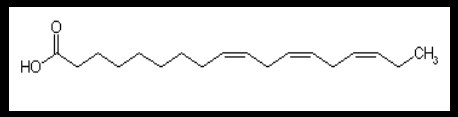
Changes in behavior and mood

(Larrieu, et al., 2014, Bosch-Bouju et al., in peparation, Bosch-Bouju et al., 2016)

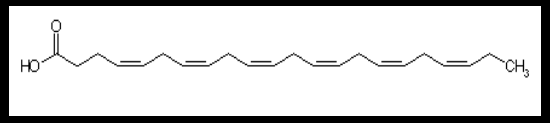
Marina Corral

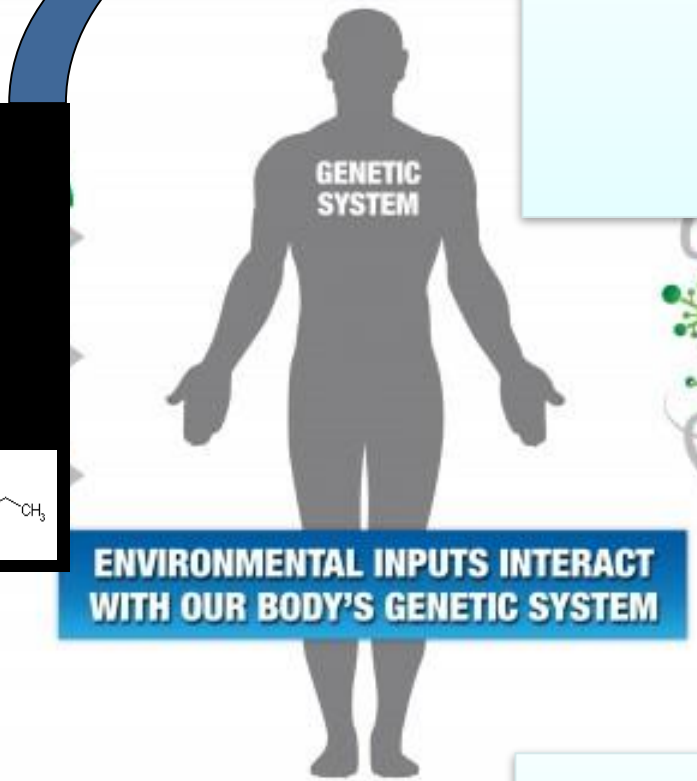
Dietary n-3 PUFAs modulate neuroinflammation, neuronal plasticity Memory, stress and anxiety

Alpha Linolenic Acid (18:3)



Docosahexaenoic Acid (DHA)





Synaptic plasticity
Neuronal integrity

Microglia activity
Neuroinflammation

Memory
Anxiety, stress, emotional behavior

Agnès Nadjar
Corinne Joffre
Anne-Laure Dinel
Xavier Fioramonti
Agnès Aubert
Alex Séré
Lydie Morel
Andy Greenhalgh
Mathieu DiMicelli
Zoé Husson
Fanny Decoeur
Hugo Martin
Chloé Lacabanne
Maud Martinat
Mathilde Chataigner

Past PhD/Post-docs
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Charlotte Rey
Virginie Labrousse
Thomas Larrieu
Charlotte Madore
Jean-Christophe Delpech
Aurore Thomazeau

Collaborations

R Bazinet, Toronto
ME Tremblay, Québec
O Butovsky, Boston
P Gressens, Paris
O Manzoni, Marseille
L Bretillon, Dijon
E Coutureau, Bordeaux
F Calon, Québec
C Bouju-Bosch, Bordeaux
V Pallet, Bordeaux
I Arnaudin, La Rochelle
G Luheshi, Montreal

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