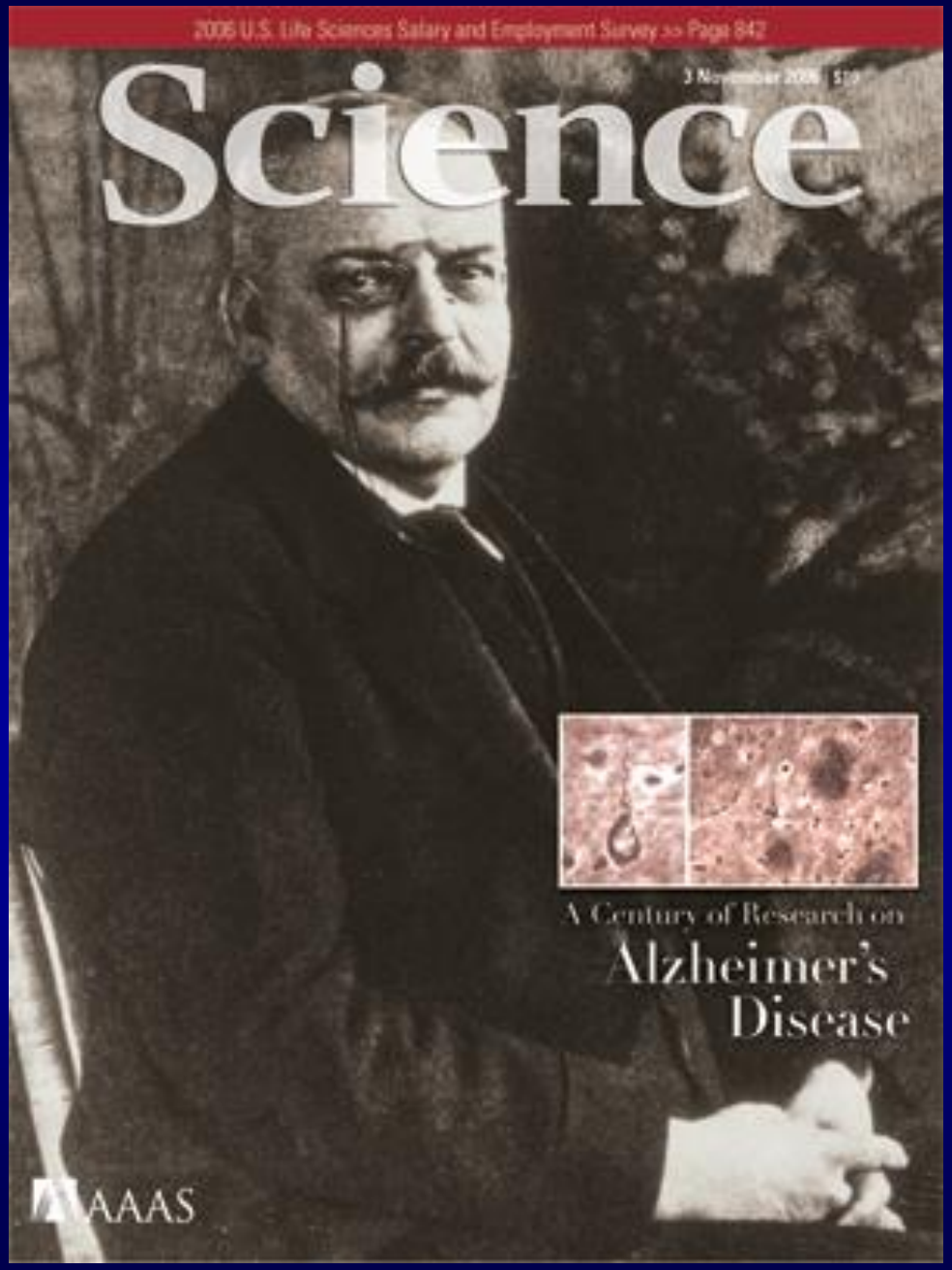


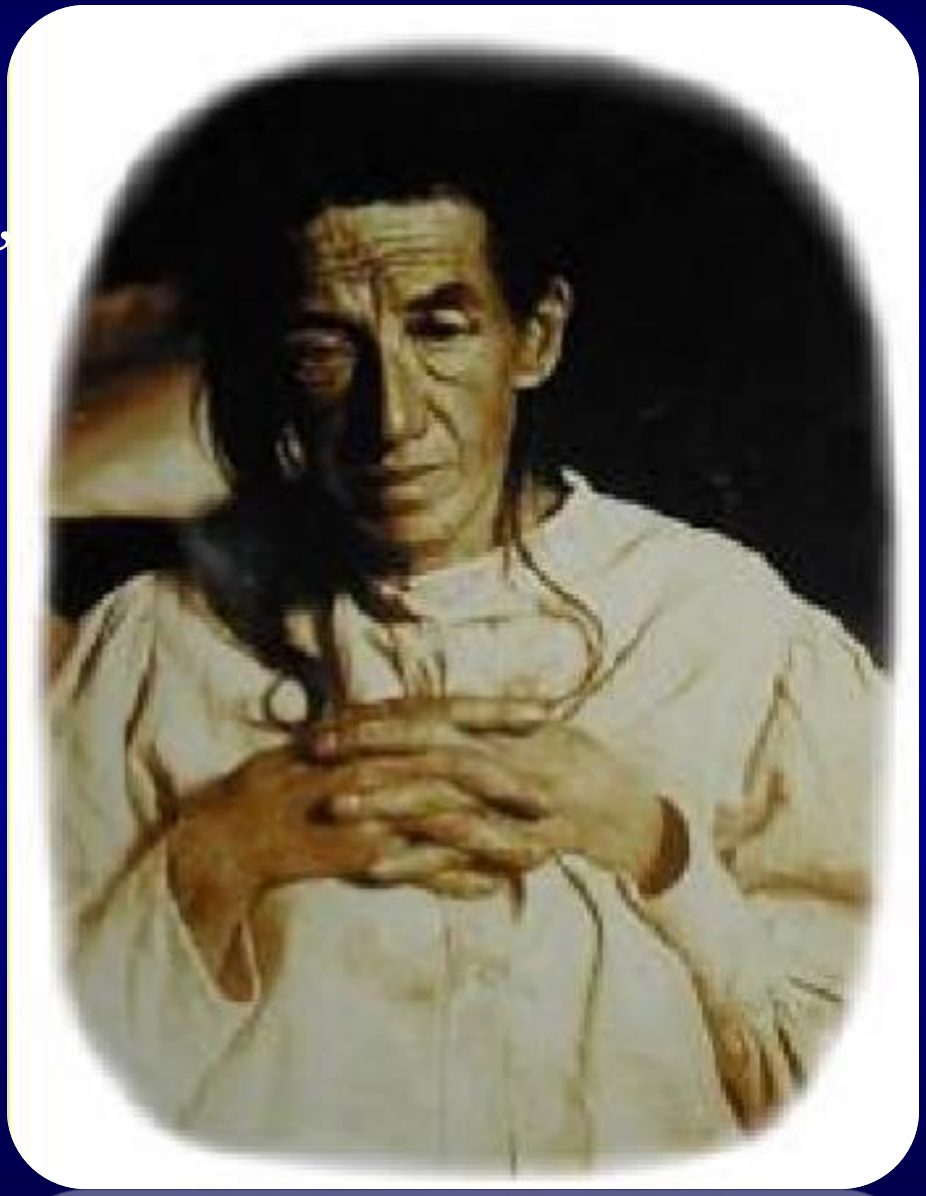
Auguste D: Alzheimer's 1st patient

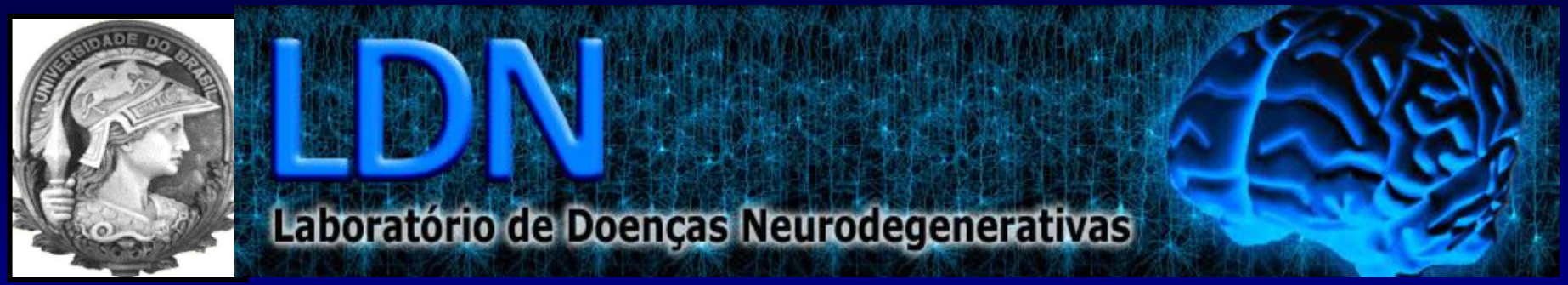
Figure: Auguste D
June 18, 1902 at asylum for the insane and epileptics in Frankfurt on Main.

- Memory loss
- Difficulties in communication, learning, thinking and reasoning

- Mood alterations
(depression, apathy, etc)

- Behavioral symptoms: delusions, hallucinations





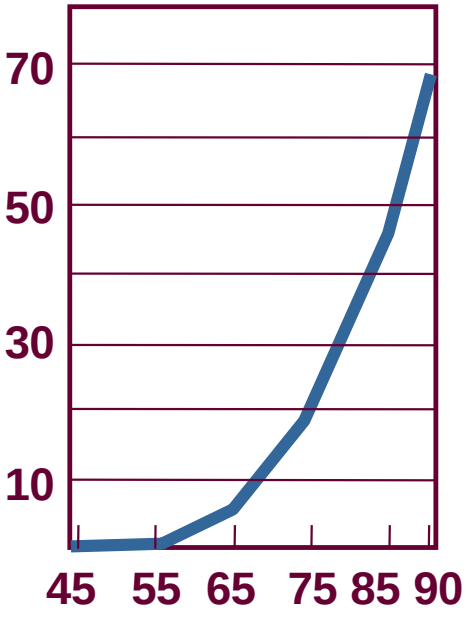
Instituto de Biofísica Carlos Chagas Filho &
Instituto de Bioquímica Médica Leopoldo de Meis
Universidade Federal do Rio de Janeiro

Connecting memory loss and non-cognitive symptoms in Alzheimer's disease

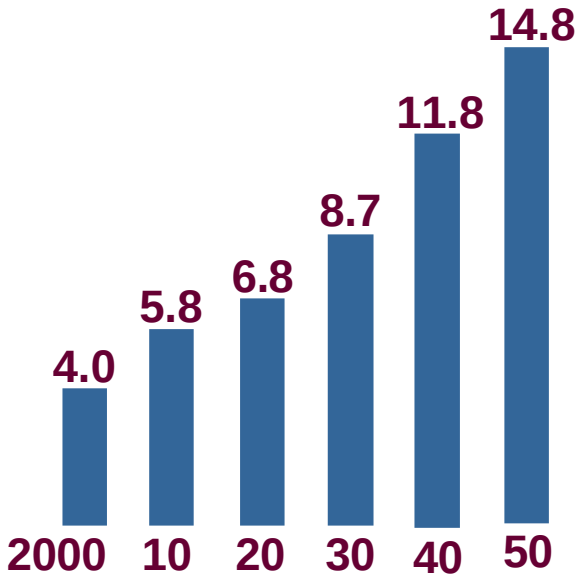
Sérgio T. Ferreira

Reunião Magna
Academia Brasileira de Ciências
May 2017

AD: Incidence and prevalence



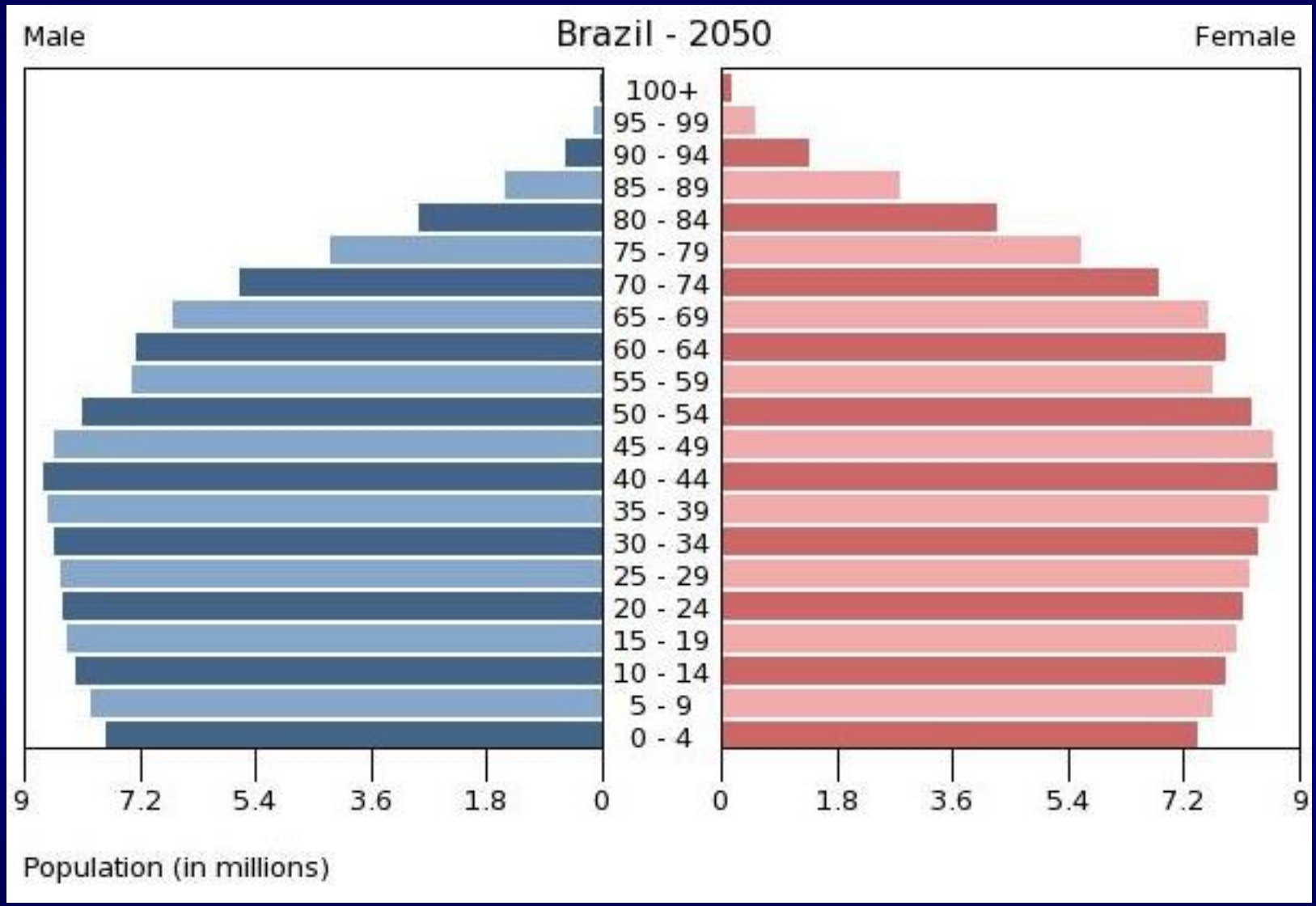
USA, 1997



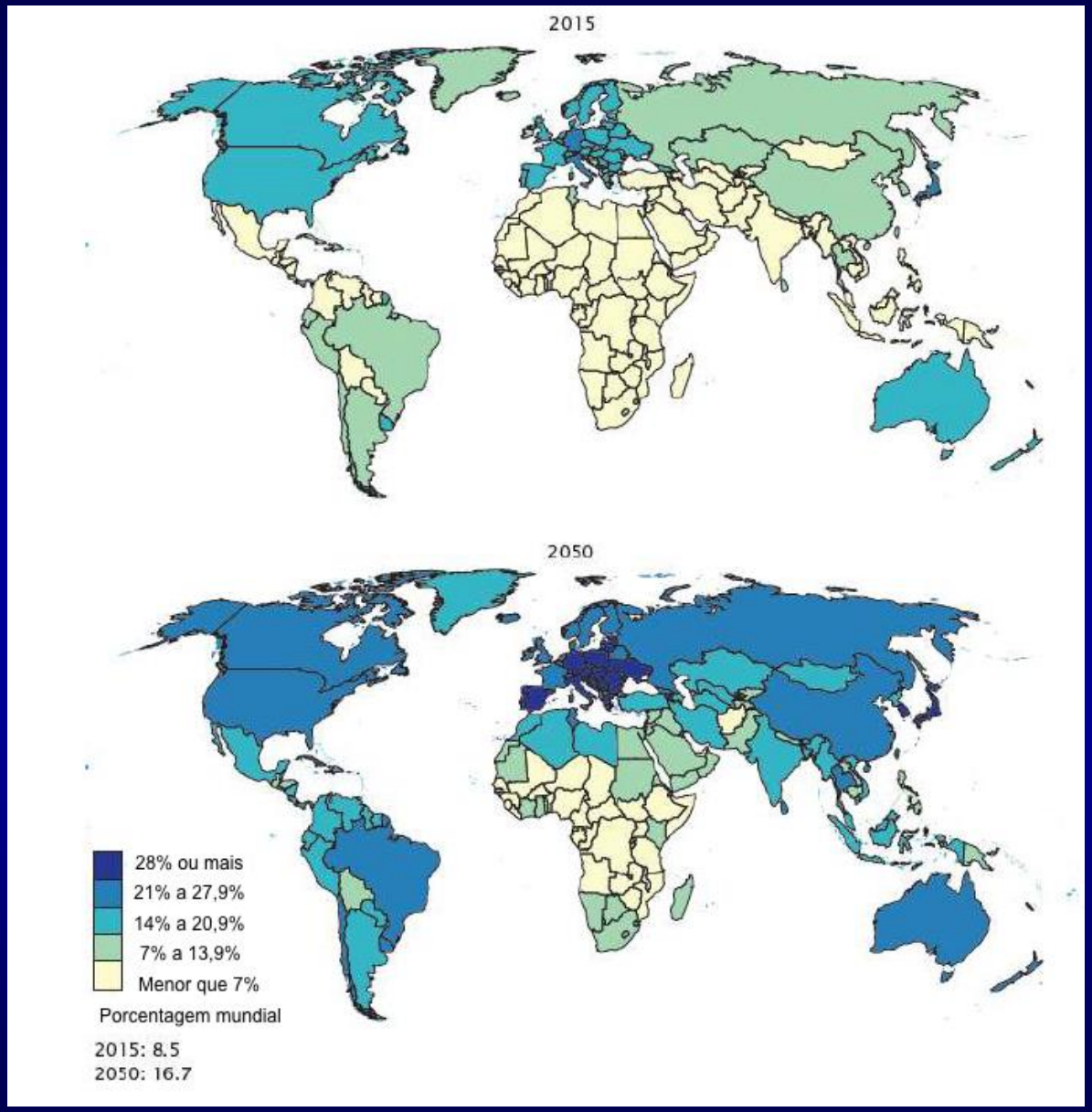
USA, 1997

Age is the main risk factor

Projected demographic distribution, Brazil/2050



Worldwide burden of Alzheimer's disease



US$ 600 Billion

US$ 2.1 Trillion

US Census Bureau, 2013/2014

Older Adults and Depression

Learn the signs and find treatment.

Do you feel very tired, helpless, and hopeless?
Have you lost interest in many of the activities and interests you previously enjoyed?
Are you having trouble working, sleeping, eating, and functioning?
Have you felt this way day after day?

If you answered yes, you may be experiencing depression.

As you get older, you may go through a lot of changes—death of loved ones, retirement, stressful life events, or medical problems. It's normal to feel uneasy, stressed, or sad about these changes. But after adjusting, many older adults feel well again.

Depression is different. It is a medical condition that interferes with daily life and normal functioning. It is not a normal part of aging, a sign of weakness, or a character flaw. Many older adults with depression need treatment to feel better.

Types of Depression

There are several types of depression. The most common include:

- **Major Depression**—severe symptoms that interfere with your ability to work, sleep, concentrate, eat, and enjoy life. Some people may experience only a single episode within their lifetime, but more often, a person may experience multiple episodes.
- **Persistent Depressive Disorder (Dysthymia)**—depression symptoms that are less severe than those of major depression, but last a long time (at least two years).
- **Minor Depression**—depression symptoms that are less severe than those of major depression and dysthymia, and symptoms do not last long.

Do you know the signs?

Depression may sometimes be undiagnosed or misdiagnosed in some older adults because sadness is not their main symptom. They may have other, less obvious symptoms of depression or they may not be willing to talk about their feelings. It is important to know the signs and seek help if you are concerned.

NIH National Institute of Mental Health

Connecting Alzheimer's to depression

ORIGINAL CONTRIBUTION

Depression as a Risk Factor for Alzheimer Disease

The MIRAGE Study

Robert C. Green, MD, MPH; L. Adrienne Cupples, PhD; Alex Kurz, MD; Sanford Auerbach, MD; Rodney Go, PhD; Dessa Sadovnick, PhD; Ranjan Duara, MD; Walter A. Kukull, PhD; Helena Chui, MD; Timi Edeki, MD, PhD; Patrick A. Griffith, MD; Robert P. Friedland, MD; David Bachman, MD; Lindsay Farrer, PhD

Arch Neurol 2003

ORIGINAL ARTICLE

Depression and Risk for Alzheimer Disease

Systematic Review, Meta-analysis, and Metaregression Analysis

Raymond L. Ownby, MD, PhD, MBA; Elizabeth Crocco, MD; Amarilis Acevedo, PhD; Vineeth John, MD; David Loewenstein, PhD

Arch Gen Psychiatry 2006

Connecting Alzheimer's to depression

History of depression, depressive symptoms, and medial temporal lobe atrophy and the risk of Alzheimer disease

Neurology 2008

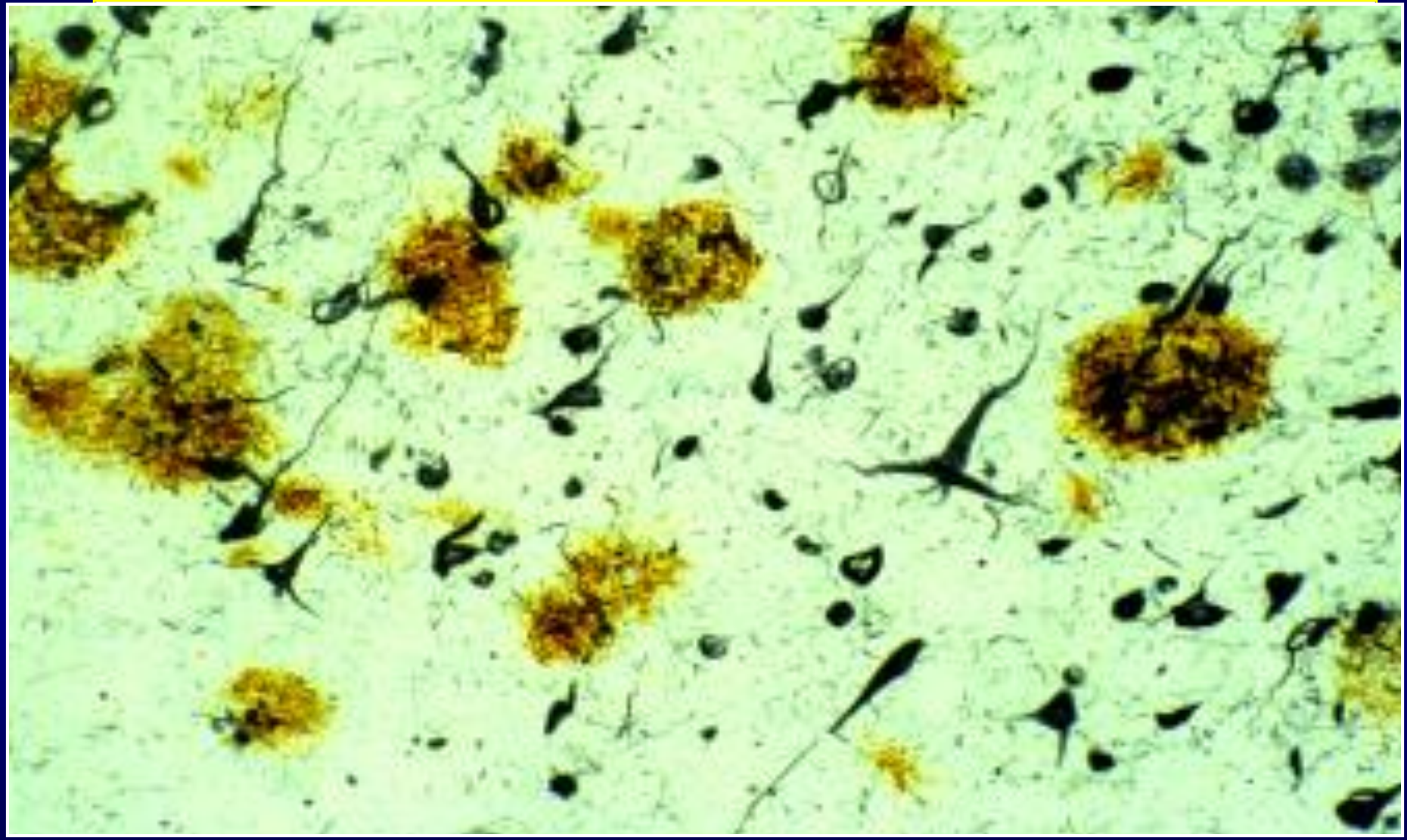
Molecular/cellular mechanisms underlying the association between depression and Alzheimer's disease remain to be elucidated

Outline

- Introduction: AD and Aβ oligomers (AβOs)
- Impact of AβOs on synapses and memory in rodents
- AβOs, brain inflammation and memory deficits in rodents
- AβO-induced brain inflammation and depressive-like behavior in rodents

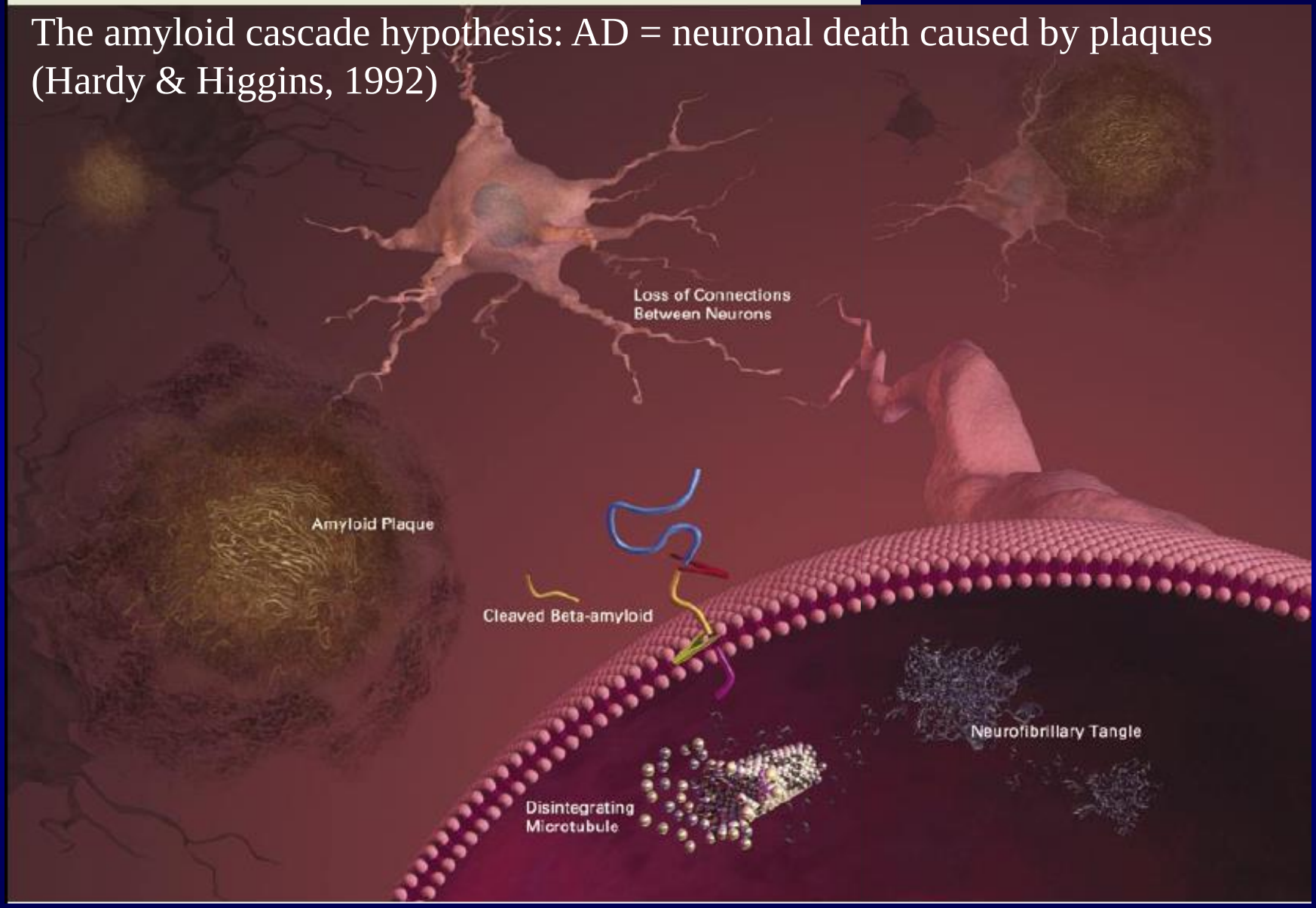
AD and Aβ oligomers

AD: dementia with plaques and tangles



The Main Characteristics of AD

The amyloid cascade hypothesis: AD = neuronal death caused by plaques (Hardy & Higgins, 1992)



Health & Human Services Progress Report on AD 2004-2005

Physical Basis of Cognitive Alterations in Alzheimer's Disease: Synapse Loss Is the Major Correlate of Cognitive Impairment

Robert D. Terry, MD,* Eliezer Masliah, MD,* David P. Salmon, PhD,* Nelson Butters, PhD,†
Richard DeTeresa, BS,* Robert Hill, PhD,* Lawrence A. Hansen, MD,* and Robert Katzman, MD*

We present here both linear regressions and multivariate analyses correlating three global neuropsychological tests with a number of structural and neurochemical measurements performed on a prospective series of 15 patients with Alzheimer's disease and 9 neuropathologically normal subjects. The statistical data show only weak correlations between psychometric indices and plaques and tangles, but the density of neocortical synapses measured by a new immunocytochemical/densitometric technique reveals very powerful correlations with all three psychological assays. Multivariate analysis by stepwise regression produced a model including midfrontal and inferior parietal synapse density, plus inferior parietal plaque counts with a correlation coefficient of 0.96 for Mattis's Dementia Rating Scale. Plaque density contributed only 26% of that strength.

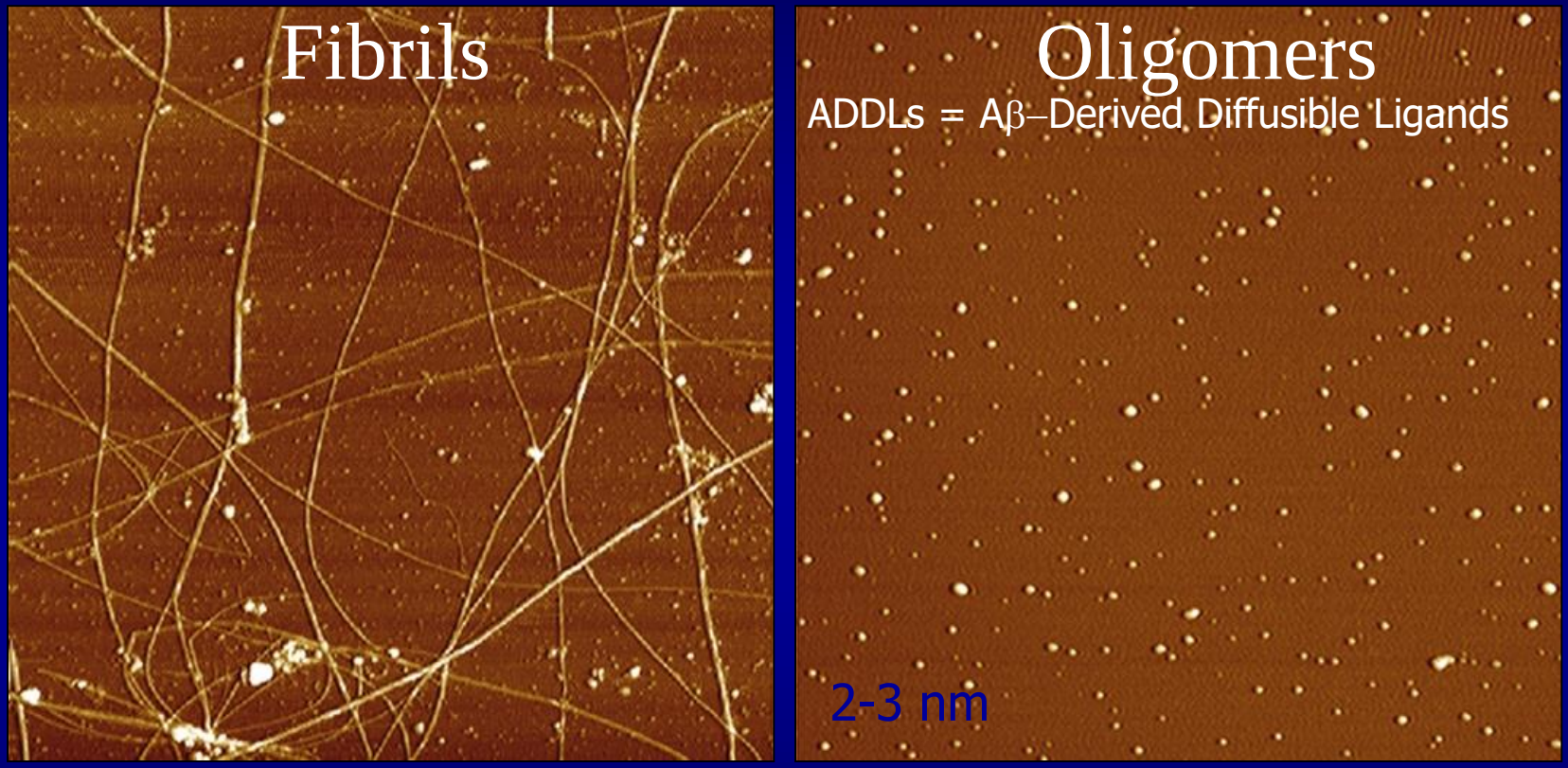
Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, Hansen LA, Katzman R. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann Neurol 1991;30:572–580

Is AD really caused by plaques??

A missing link?

Aβ oligomers: The hidden toxins

William L. Klein, Northwestern University

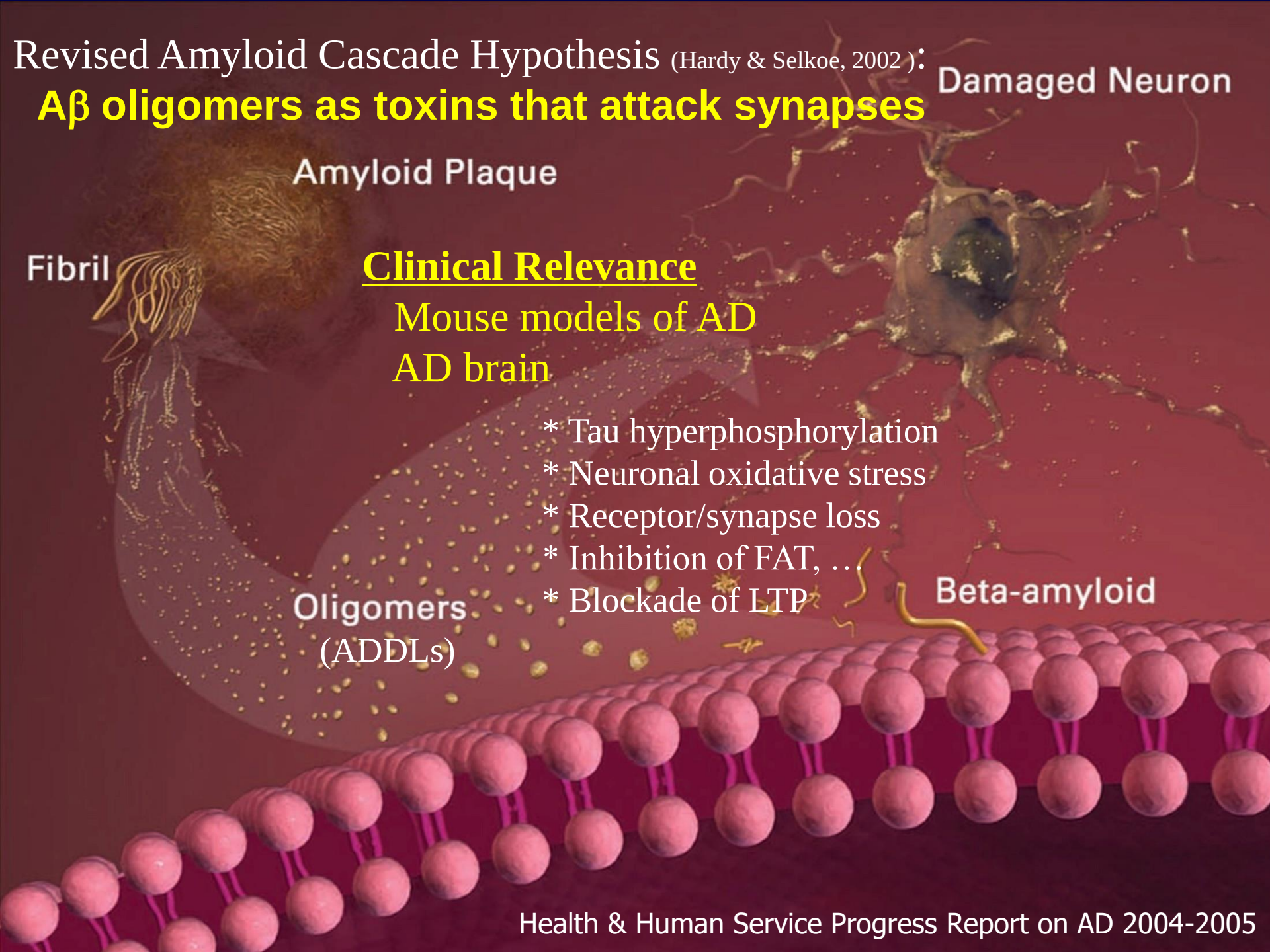


- Aβ oligomers: neurotoxins that inhibit long term potentiation (LTP) - Disrupt functional plasticity

Lambert et al., 1998 PNAS

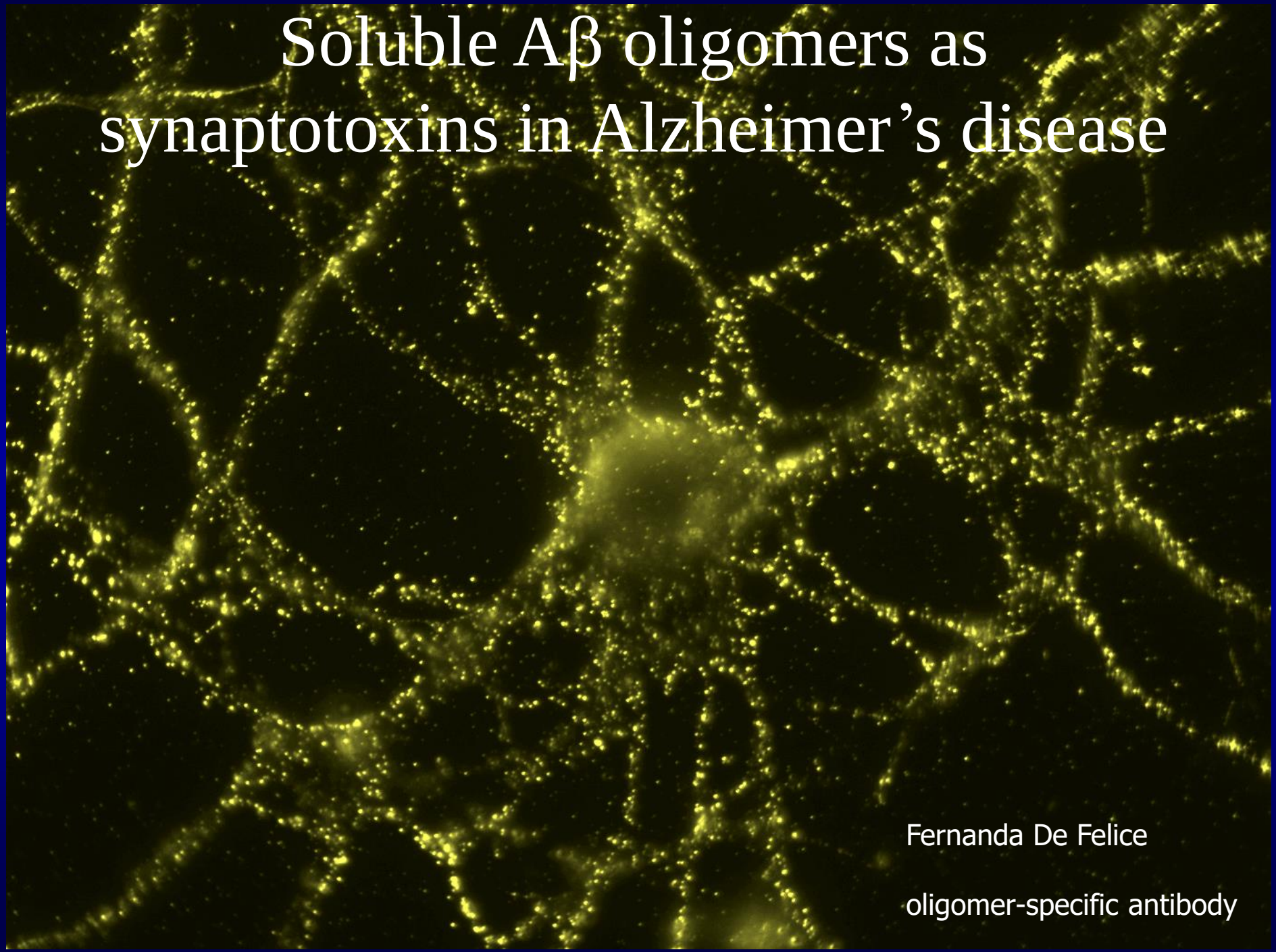
Revised Amyloid Cascade Hypothesis (Hardy & Selkoe, 2002):

Aβ oligomers as toxins that attack synapses



Health & Human Service Progress Report on AD 2004-2005

Soluble Aβ oligomers as synaptotoxins in Alzheimer's disease

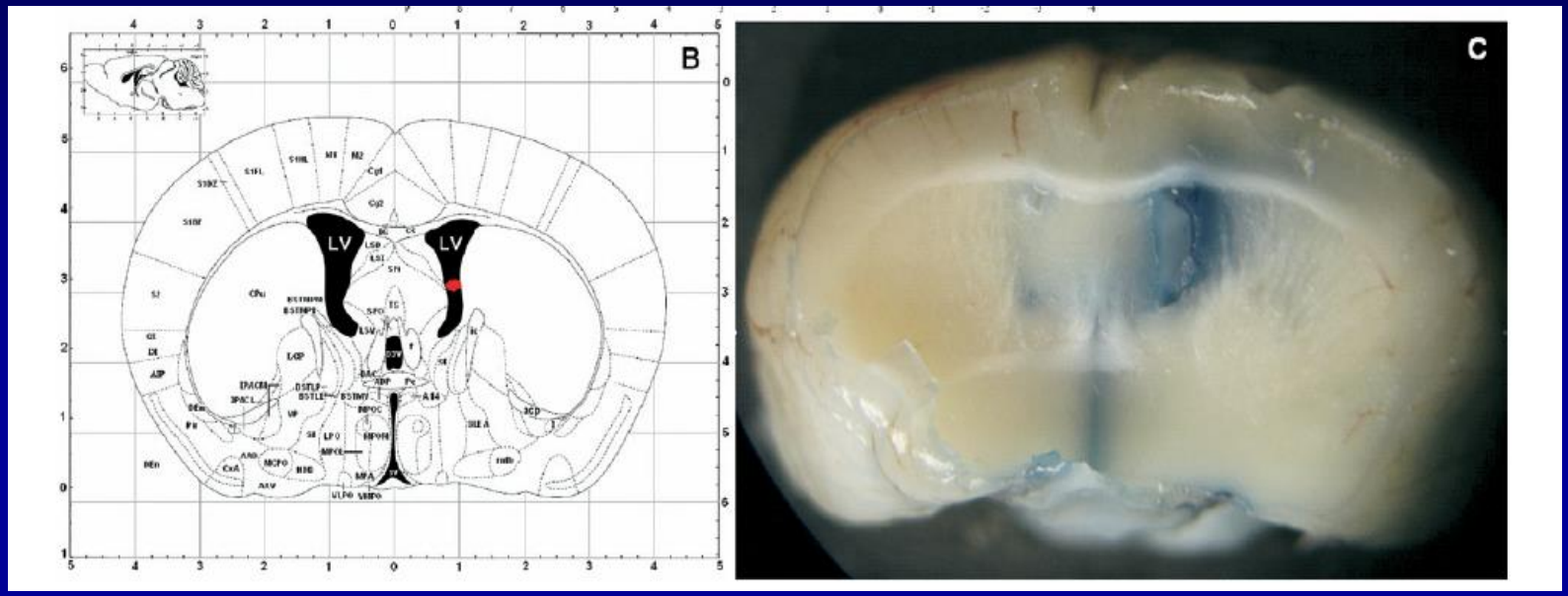


Fernanda De Felice

oligomer-specific antibody

Impact of AβOs on synapses and memory in rodents

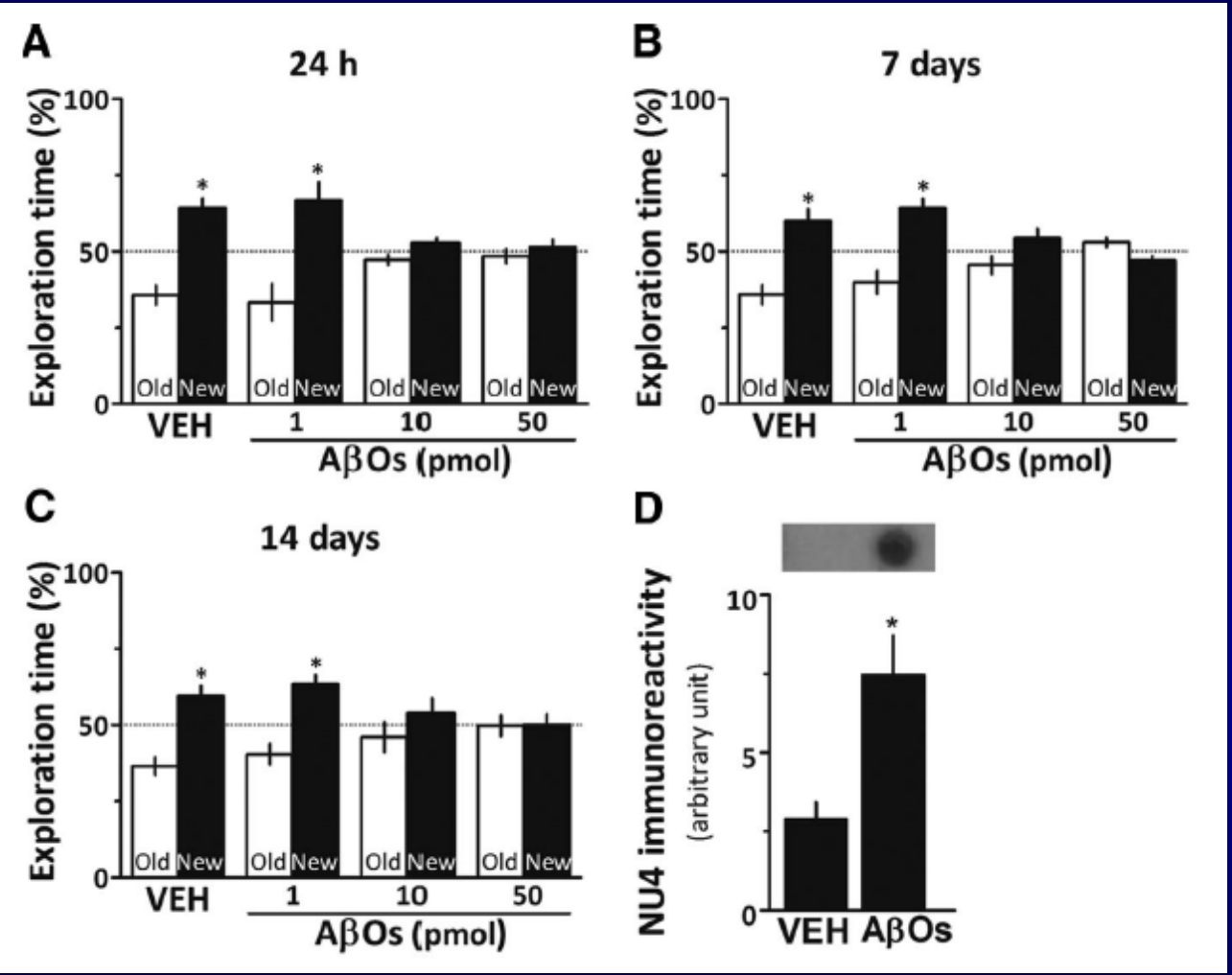
i.c.v. injection of AβOs in mice



Claudia P. Figueiredo

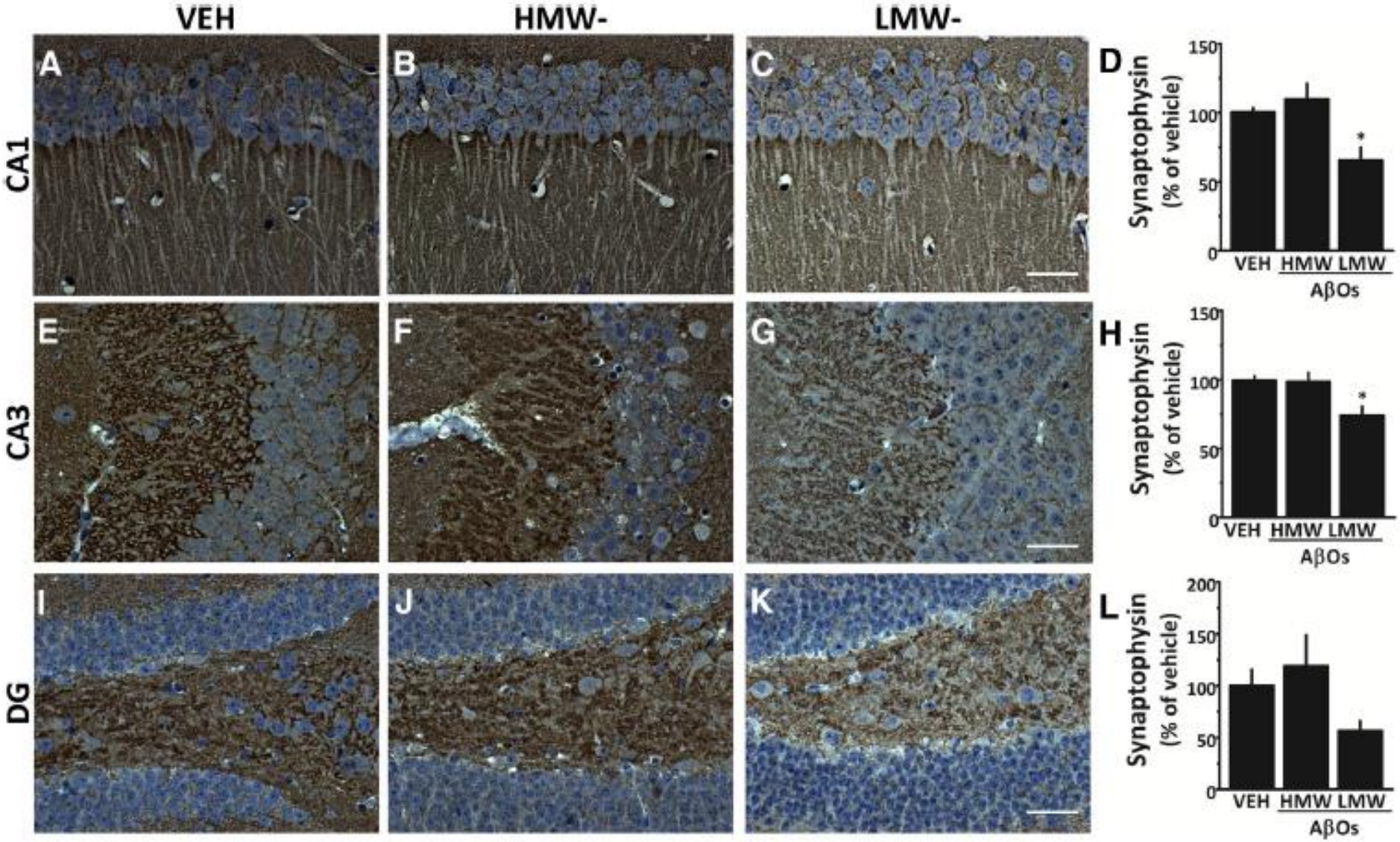
Julia R. Clarke

AβOs (i.c.v.) cause rapid, persistent memory deficit in mice



Figueiredo, Clarke et al., 2013
J. Neurosci.

AβOs instigate SYP loss in the hippocampus



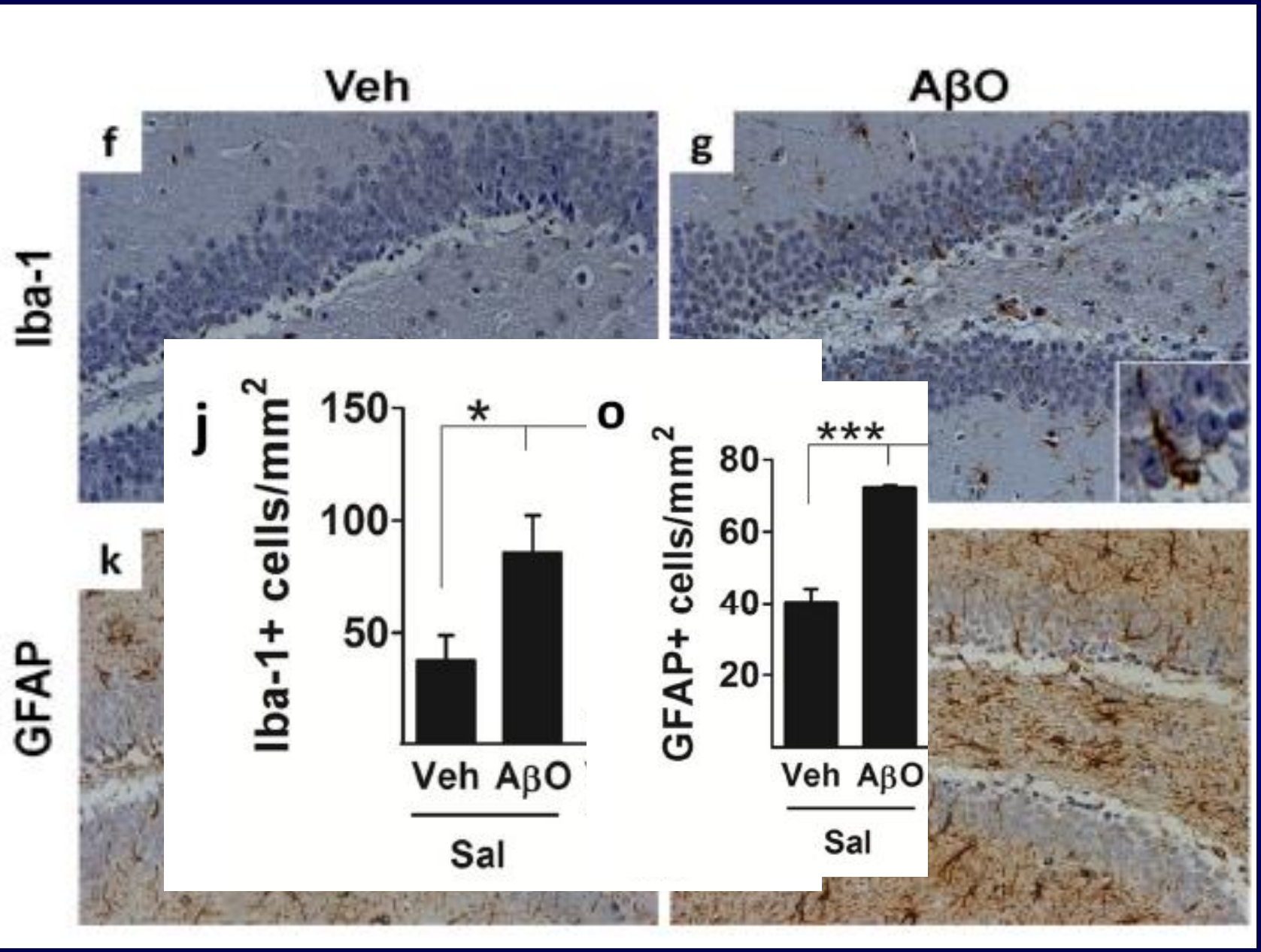
Figueiredo et al. (2013) J. Neurosci.

Neuroinflammation in Alzheimer's disease

Michael T Heneka, Monica J Carson, Joseph El Khoury, Gary E Landreth, Frederic Brosseron, Douglas L Feinstein, Andreas H Jacobs, Tony Wyss-Coray, Javier Vitorica, Richard M Ransohoff, Karl Herrup, Sally A Frautschy, Bente Finsen, Guy C Brown, Alexei Verkhratsky, Koji Yamanaka, Jari Koistinaho, Eicke Latz, Annett Halle, Gabor C Petzold, Terrence Town, Dave Morgan, Mari L Shinohara, V Hugh Perry, Clive Holmes, Nicolas G Bazan, David J Brooks, Stéphane Hunot, Bertrand Joseph, Nikolaus Deigendesch, Olga Garaschuk, Erik Boddeke, Charles A Dinarello, John C Breitner, Greg M Cole, Douglas T Golenbock, Markus P Kummer

www.thelancet.com/neurology **Vol 14 April 2015**

Microgliosis and astrocytosis induced by AβOs



Ledo et al., Mol. Psychiatry 2013

A monkey model of AD

The Journal of Neuroscience, October 8, 2014 • 34(41):13629–13643 • 13629

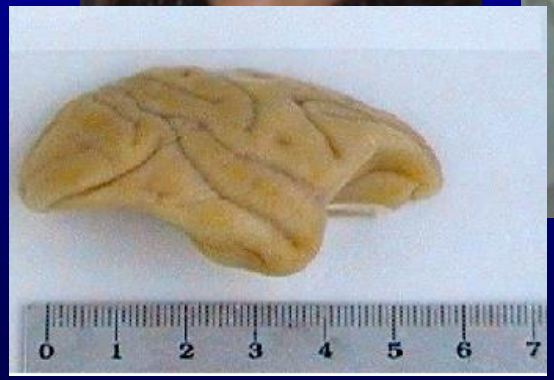
Neurobiology of Disease

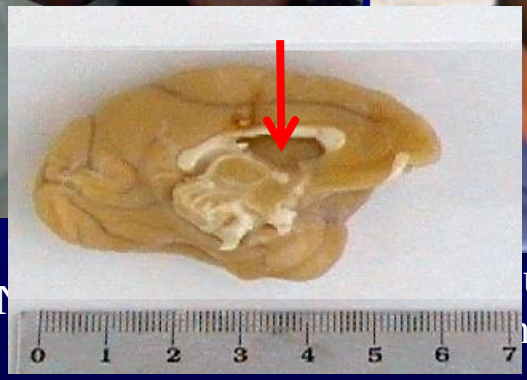
Alzheimer's Disease-Like Pathology Induced by Amyloid-β Oligomers in Nonhuman Primates

Leticia Forny-Germano,[1,2] Natalia M. Lyra e Silva,[1*] André F. Batista,[1*] Jordano Brito-Moreira,[1] Matthias Gralle,[1] Susan E. Boehnke,[3] Brian C. Coe,[3] Ann Lablans,[3] Suelen A. Marques,[4] Ana Maria B. Martinez,[2] William L. Klein,[5] Jean-Christophe Houzel,[2] Sergio T. Ferreira,[1] Douglas P. Munoz,[3†] and Fernanda G. De Felice[1†]

Fernanda De Felice

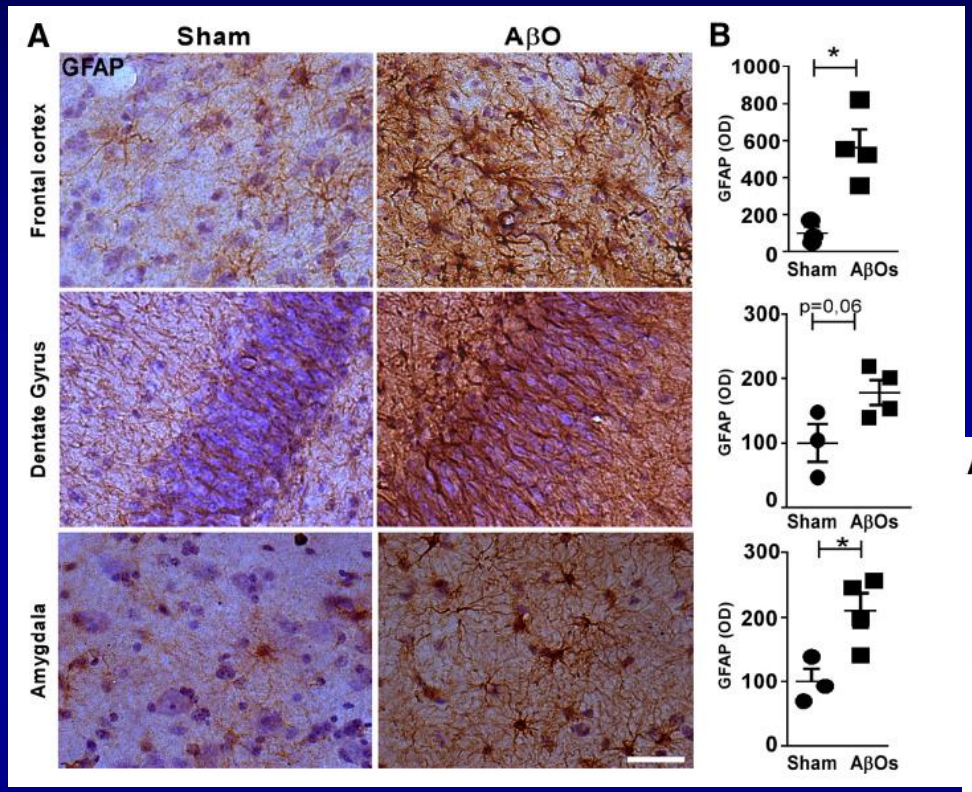
Cynomolgus monkey
Macaca fascicularis



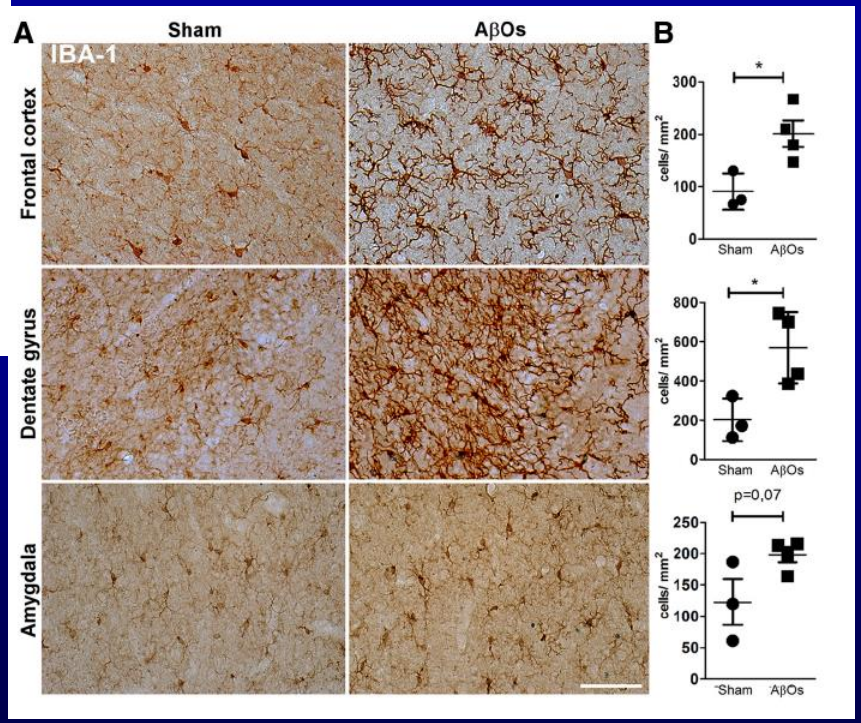


ug Munoz
's University

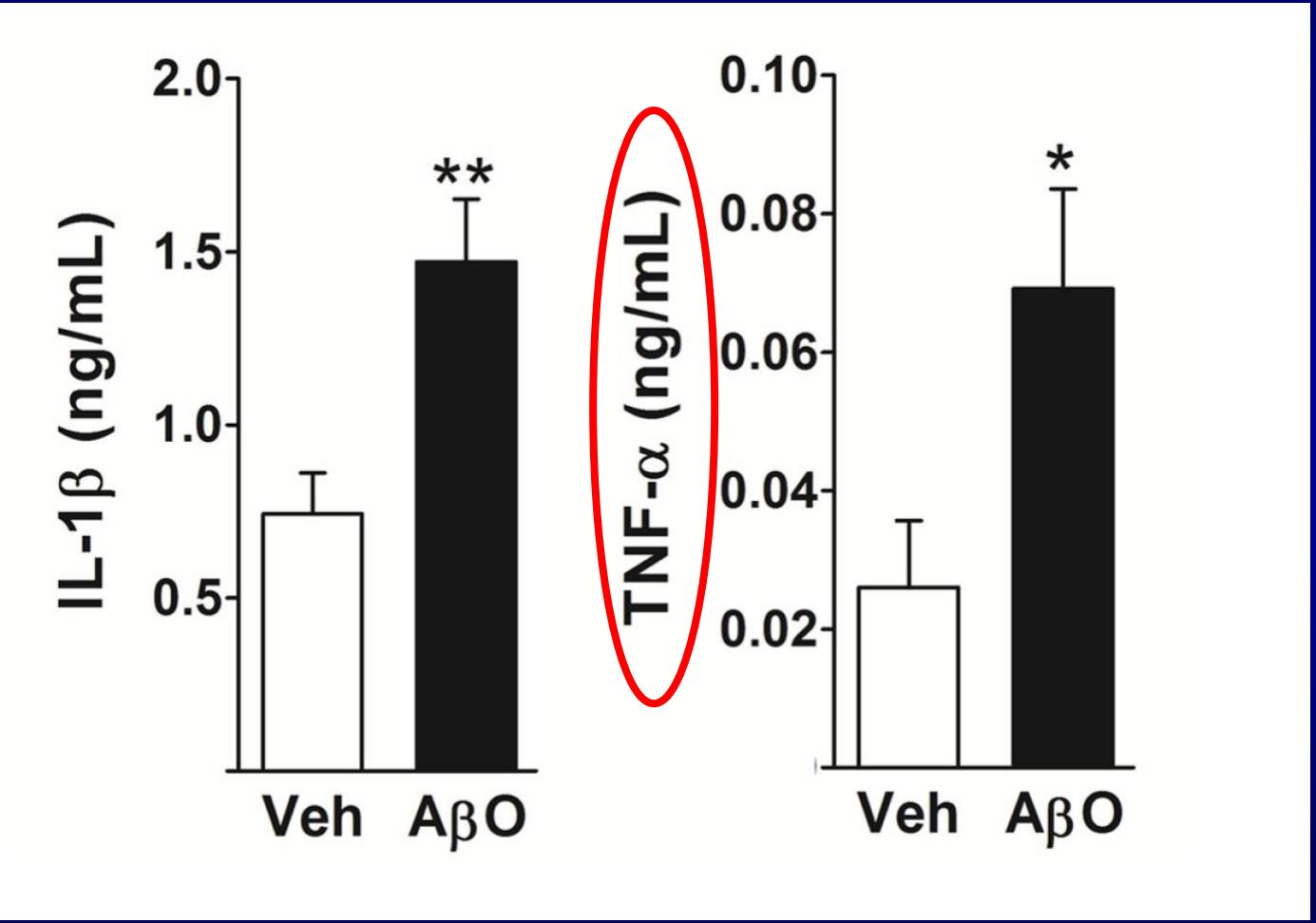
Astrogliosis and microgliosis in AβO-injected monkey brains



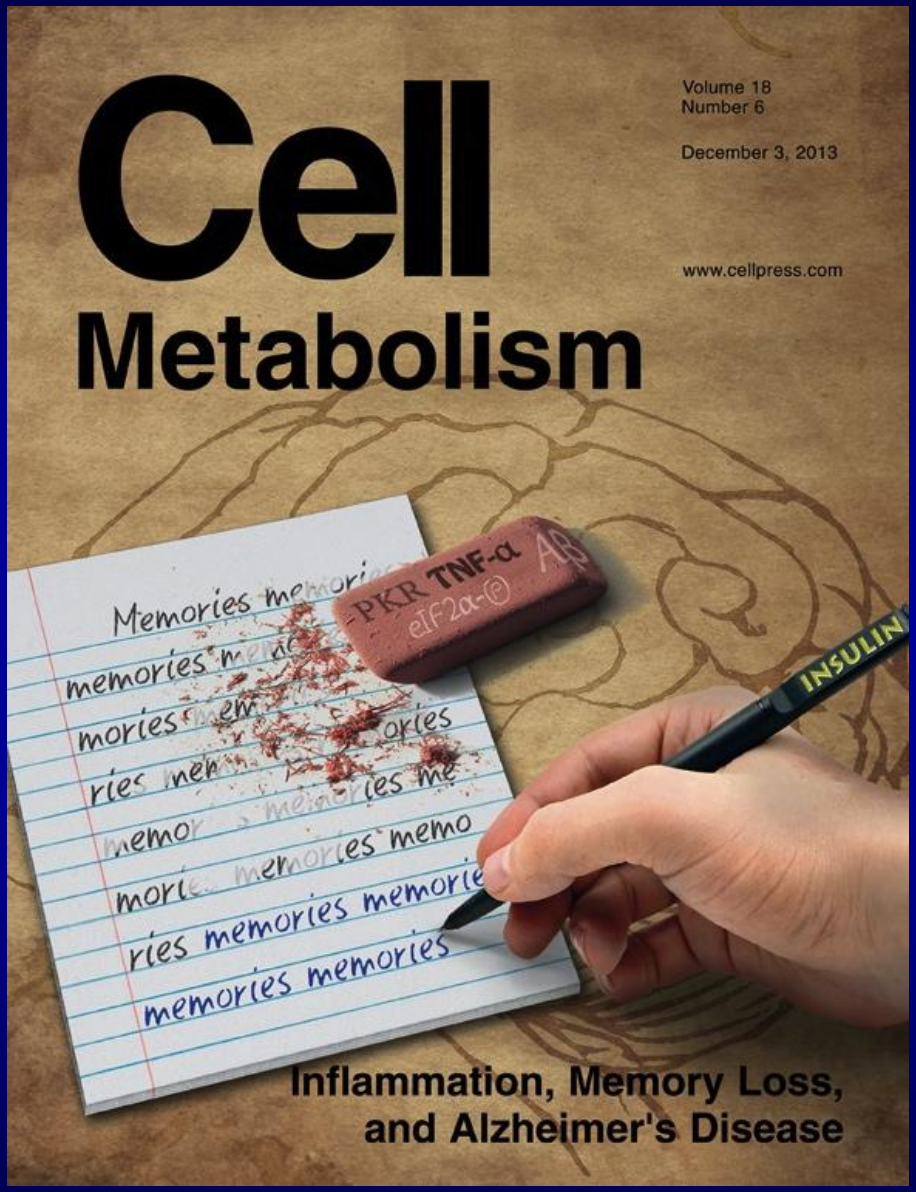
Forny-Germano et al., 2014
J. Neurosci.



AβOs increase levels of proinflammatory cytokines in the mouse brain



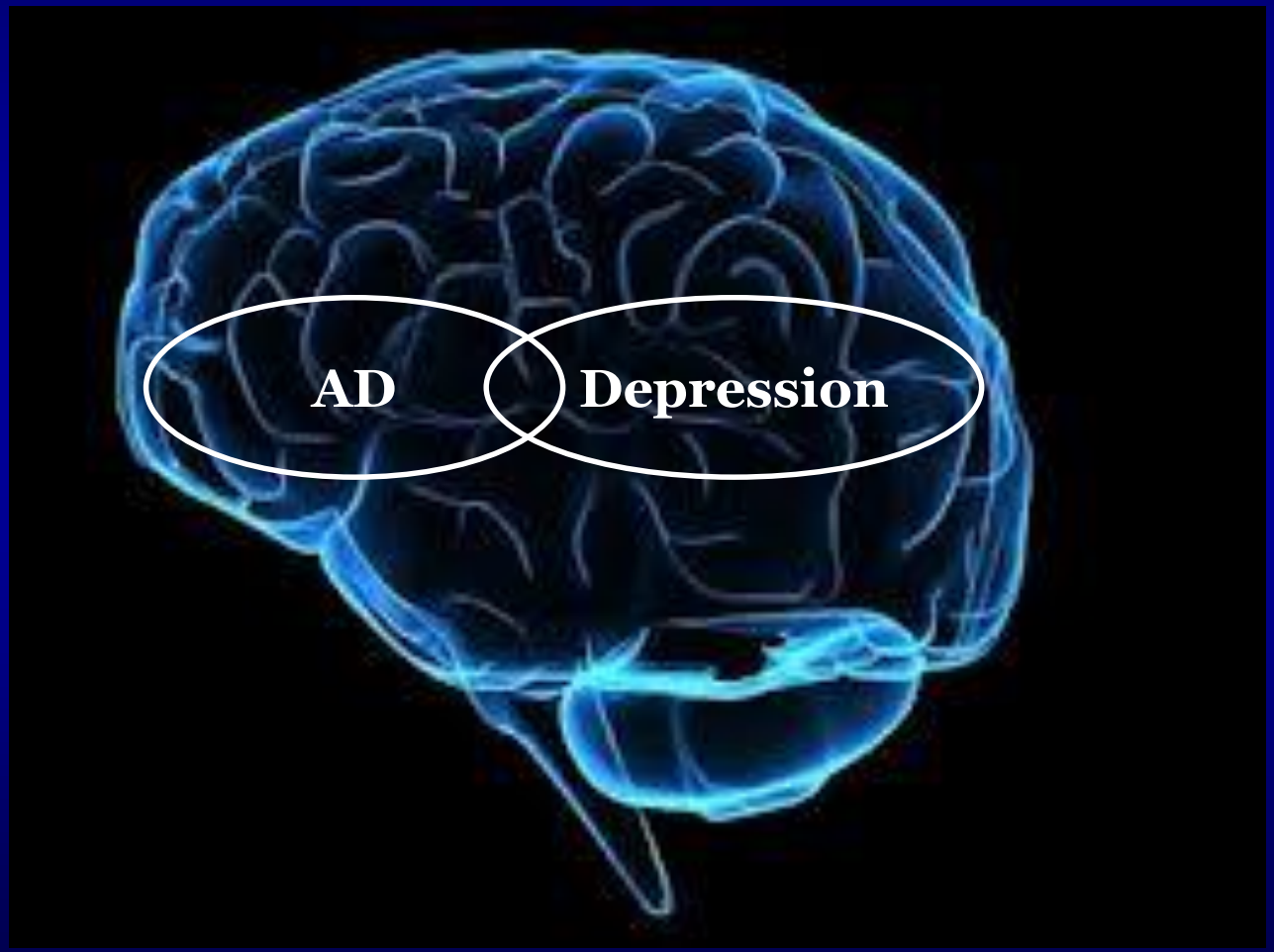
Ledo et al., Mol. Psychiatry 2013



Art by Marcelo Vieira

AD, brain inflammation and depression

A molecular link between AD and depression ?



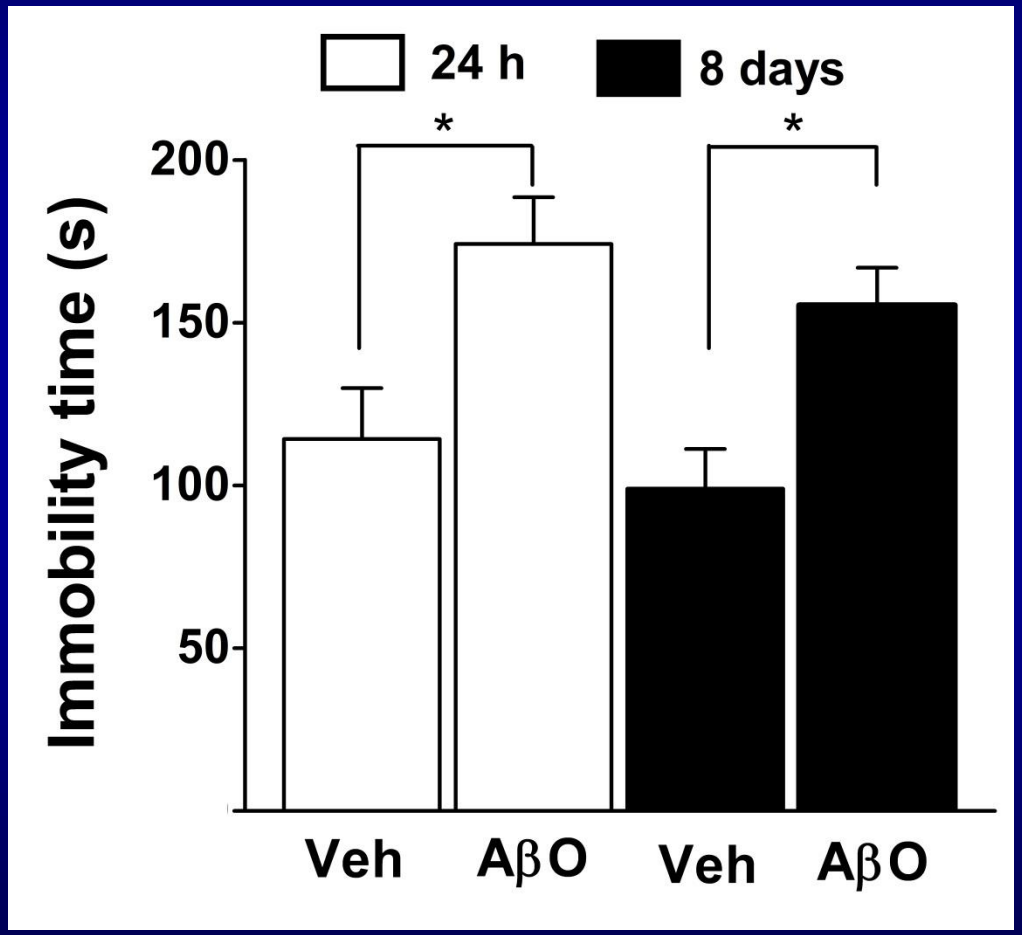
Evaluating depressive-like behavior in rodents

TABLE 27.1 *Experimental Access to Key Symptoms of Depression*

Symptoms	*Experimental Measures in Animal Models*
Despair *	Increased immobility in forced swim and tail suspension tests
Anhedonia *	Decrese in intracranial self-stimulation Decreased sucrose preference Reduce sexual interest
Increased Anxiety	Unconditioned and conditioned avoidance Supression of punished responding Conditioned freezing Ultrasonic vocalization
Impaired Cognition *	Impairment in hippocampus-dependent learning Tasks
Activity changes	Decreased home cage activity Decreased locomotion in novel environments
Sleep changes	Flattening of circadian rhythm (sleep/wakefulness) Increased rapid-eye-movement density
Changes in appetite	Hyperfagia/Hypophagia-anorexia Carbohydrate preference
Metabolic syndrome	Increased ratio of visceral and subcutaneous fat Altered glucose metabolism

Adapted from Eric Nestler, 2011; In: Neurobiology of Mental Illness

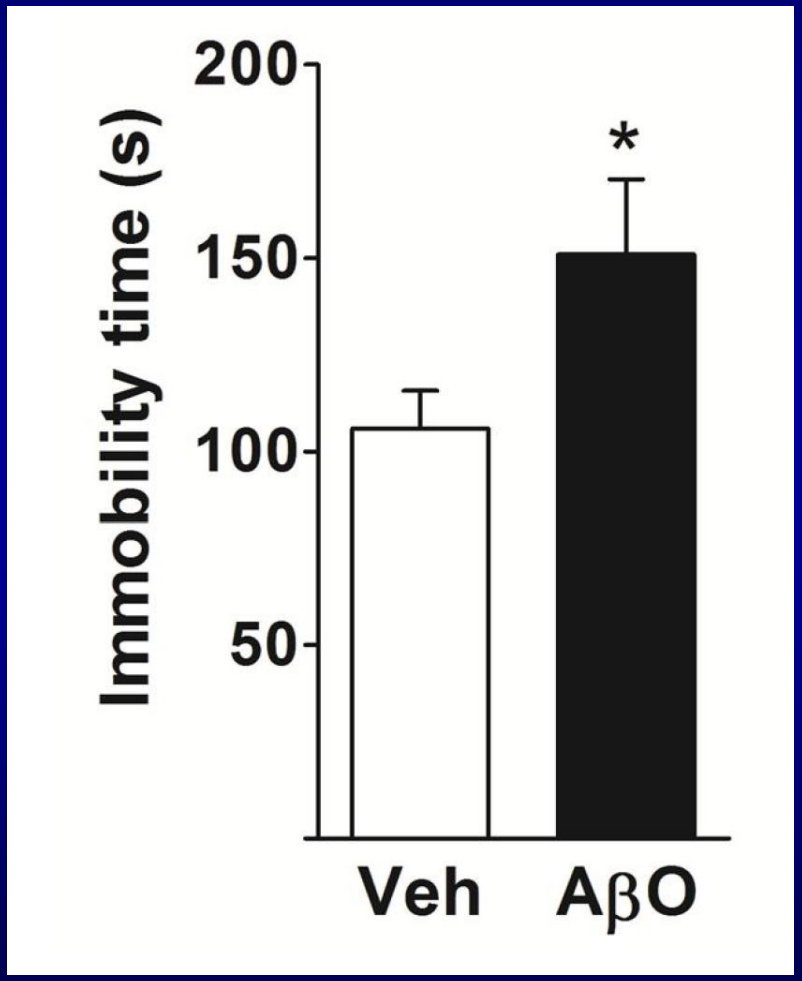
AβOs increase immobility time in the forced swim test

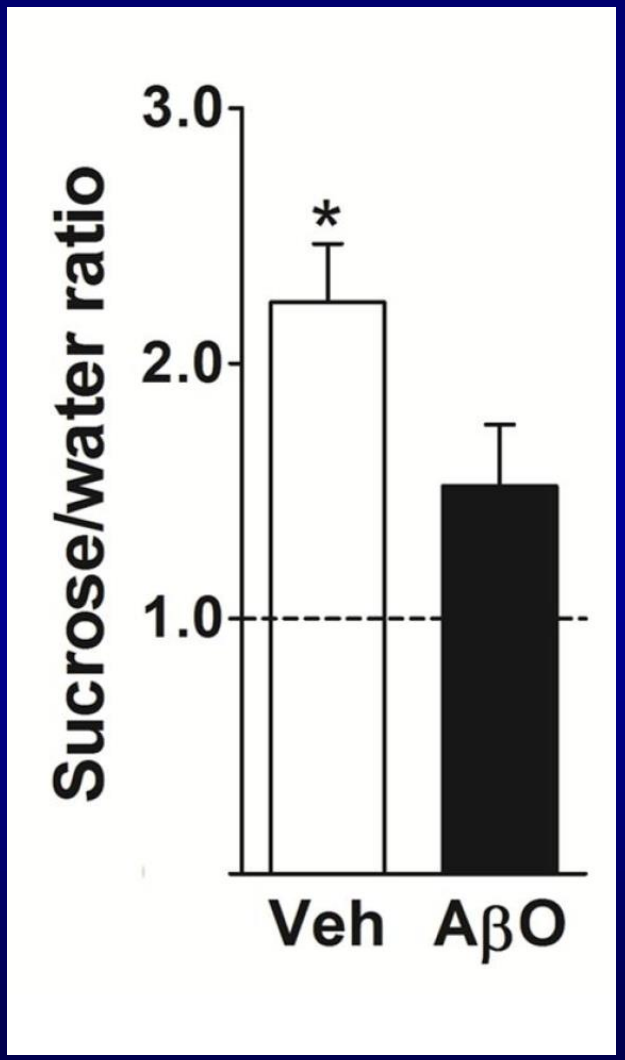


Ledo et al., 2013
Mol. Psychiatry

Jose Henrique Ledo

AβOs increase immobility time in tail suspension and reduce sucrose preference





Ledo et al., 2013
Mol. Psychiatry

Could inflammation mediate the impact of AβOs on mood ?

From inflammation to sickness and depression: when the immune system subjugates the brain

Robert Dantzer‡, Jason C. O'Connor*, Gregory G. Freund*‡, Rodney W. Johnson* and Keith W. Kelley*‡*

NATURE REVIEWS | NEUROSCIENCE

12106 • The Journal of Neuroscience, November 30, 2016 • 36(48):12106 –12116

Neurobiology of Disease

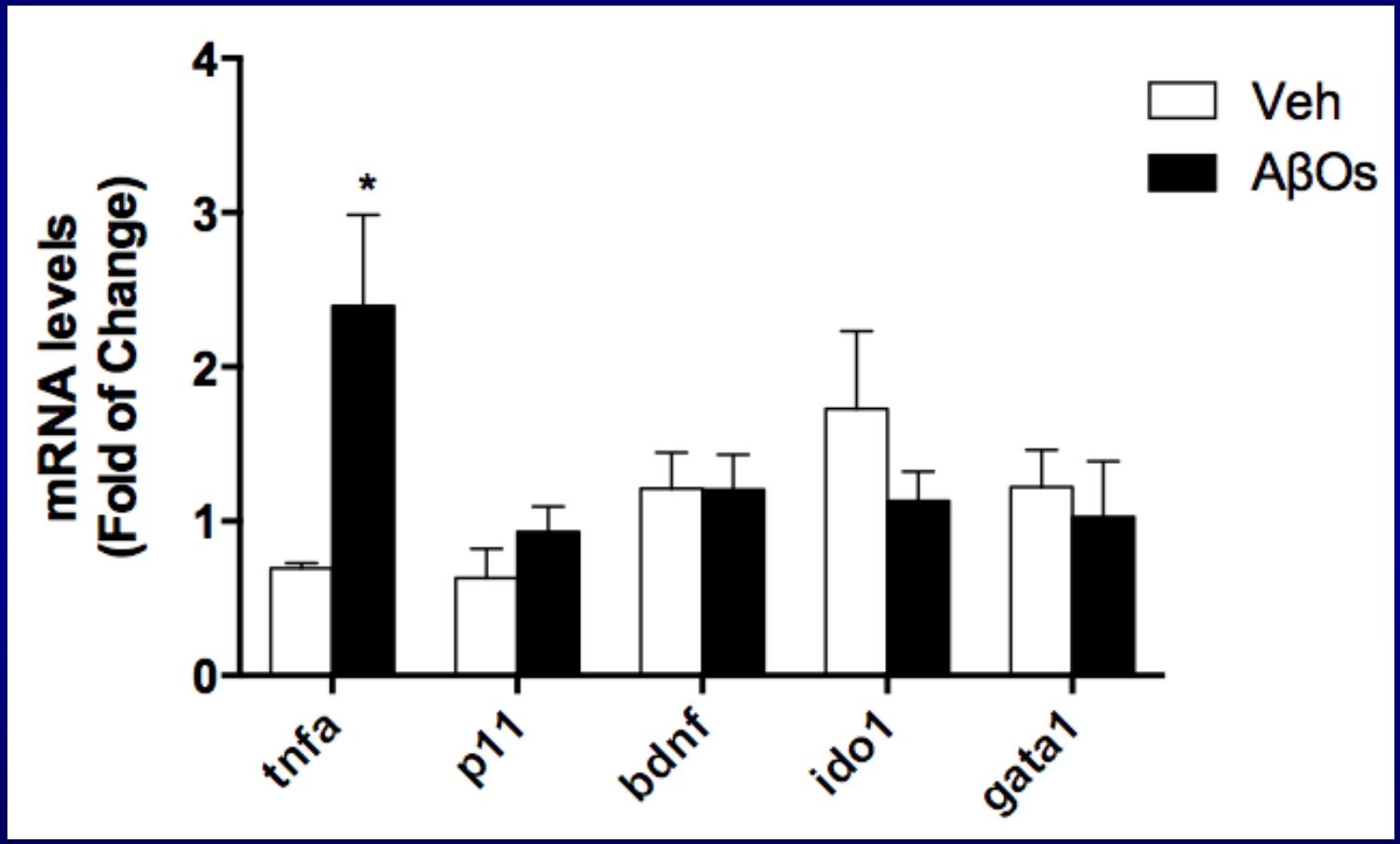
Cross Talk Between Brain Innate Immunity and Serotonin Signaling Underlies Depressive-Like Behavior Induced by Alzheimer's Amyloid-β Oligomers in Mice

Jose Henrique Ledo,[1] Estefania P. Azevedo,[1] Danielle Beckman,[1] Felipe C. Ribeiro,[1] Luis E. Santos,[2] Daniela S. Razolli,[4] Grasielle C. Kincheski,[1] Helen M. Melo,[1] Maria Bellio,[3] Antonio L. Teixeira,[5] Licio A. Velloso,[4] Debora Foguel,[1] Fernanda G. De Felice,[1,6] and Sergio T. Ferreira[1,2]

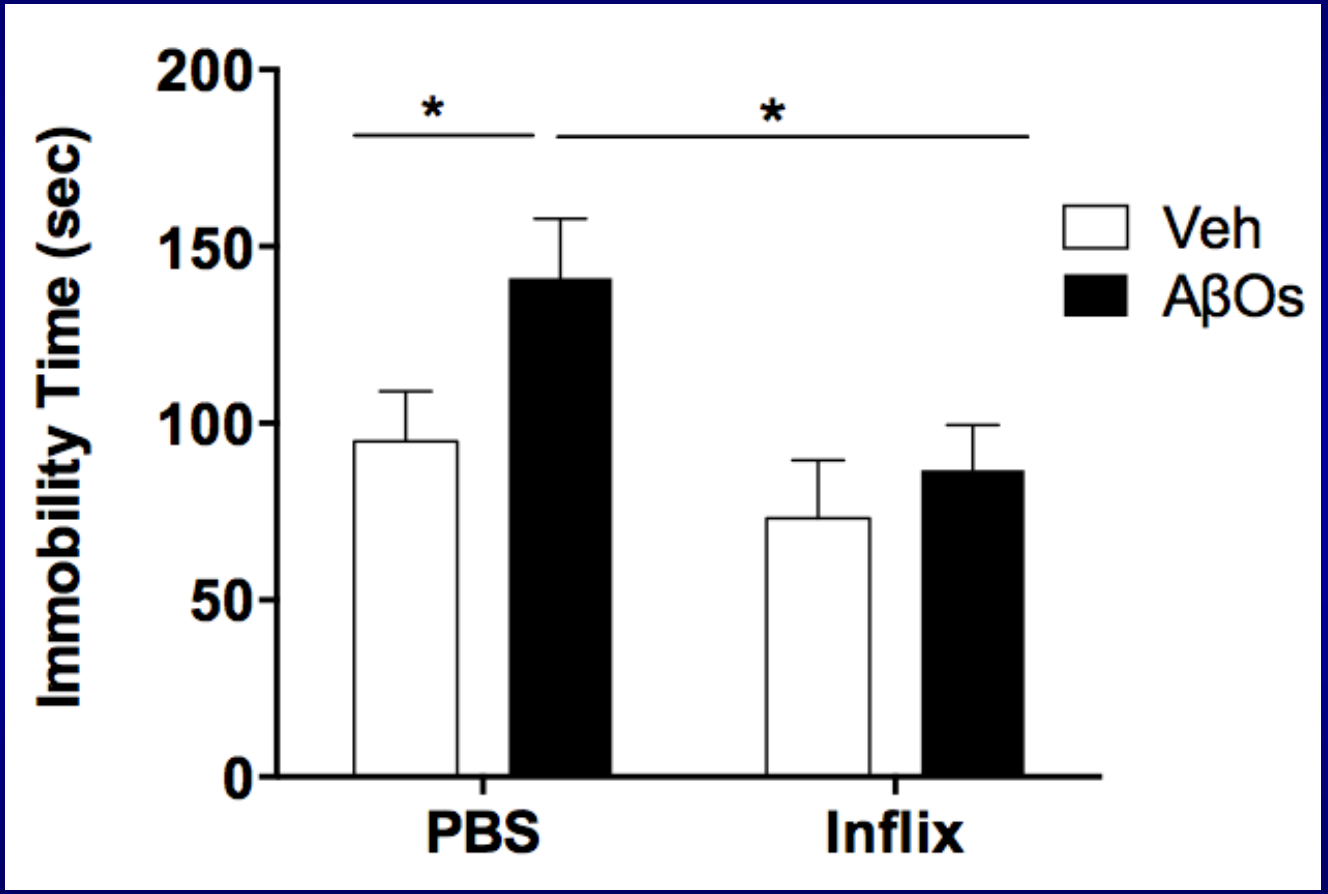
Jose Henrique Ledo

Danielle Beckman

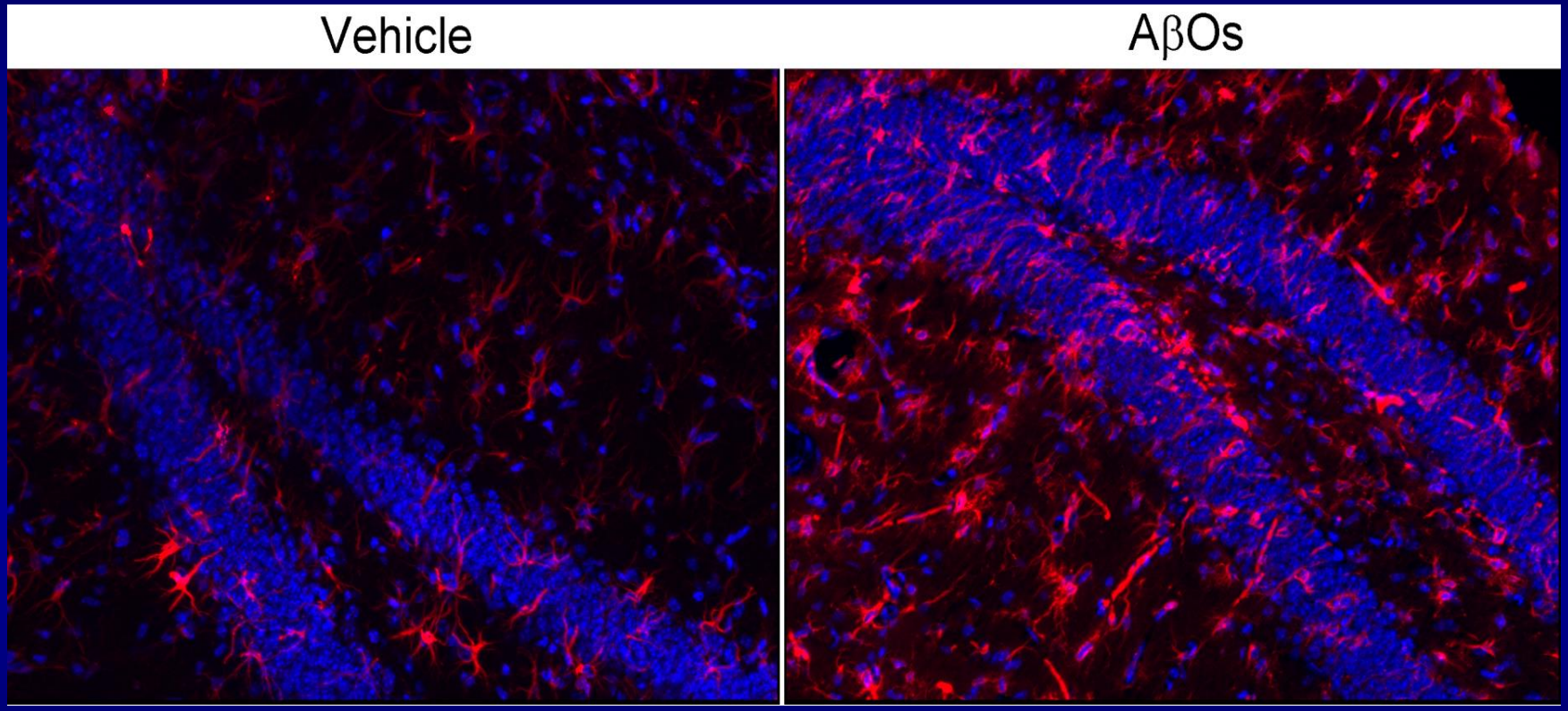
AβOs increase expression of TNF-α, but not of other genes related to depressive behavior



TNF-α drives depressive-like behavior induced by AβOs

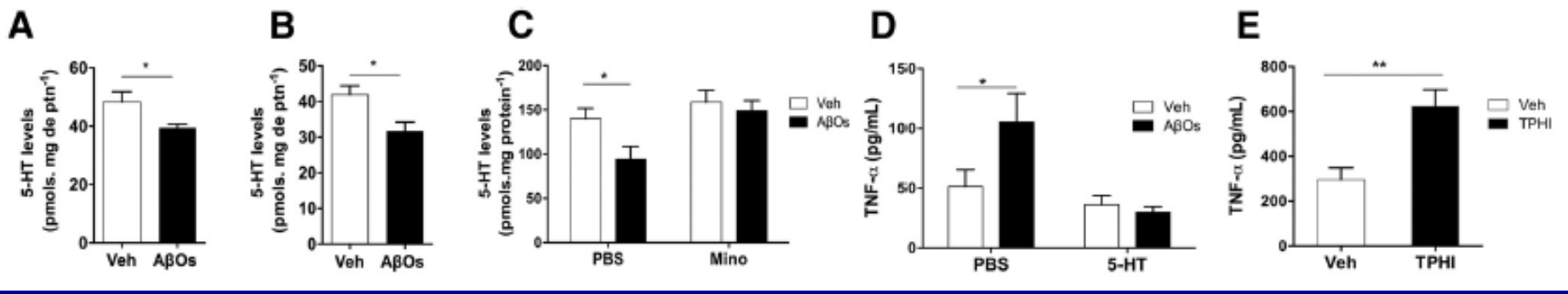


Increased Iba-1 immunoreactivity in AβO-injected mice



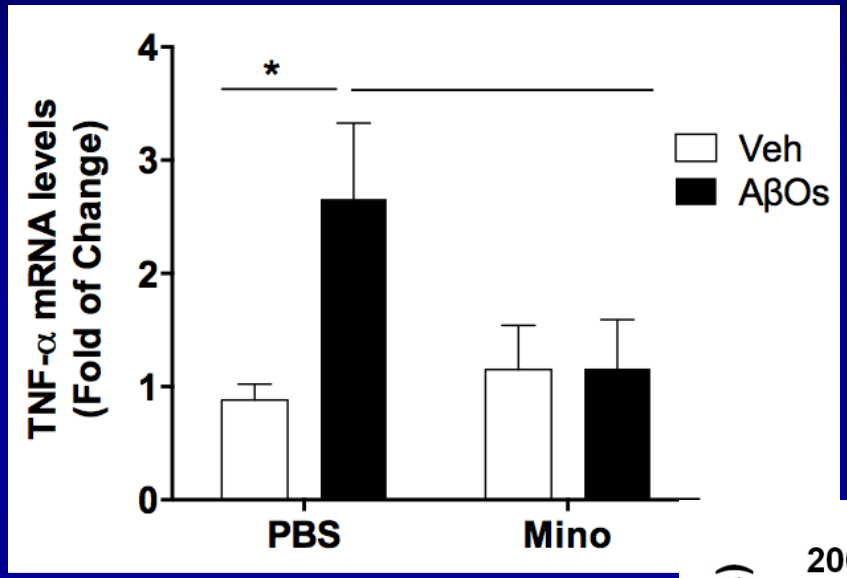
Ledo et al., 2016
J. Neurosci.

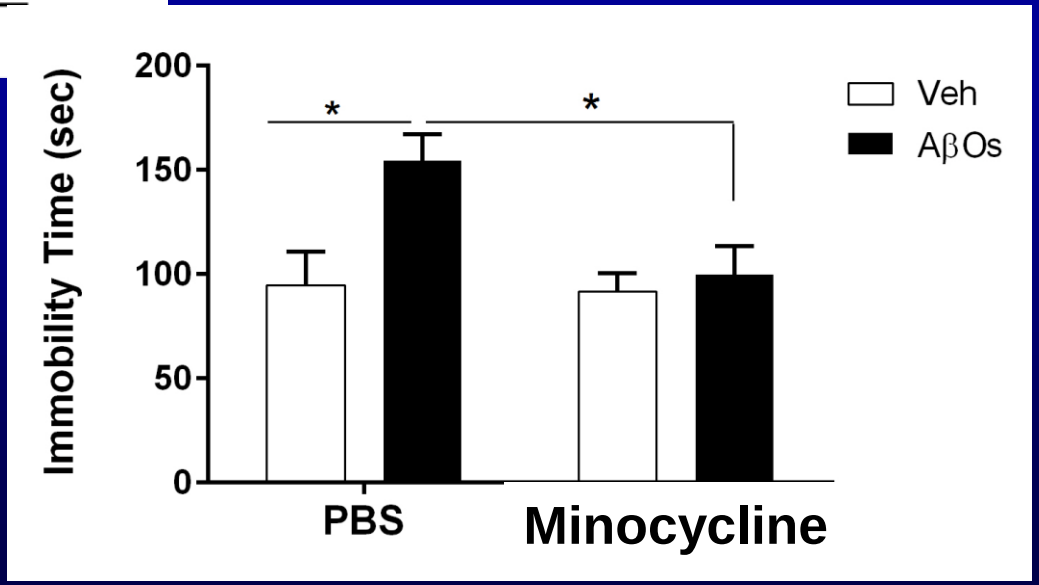
Cross talk between microglial activation and 5-HT

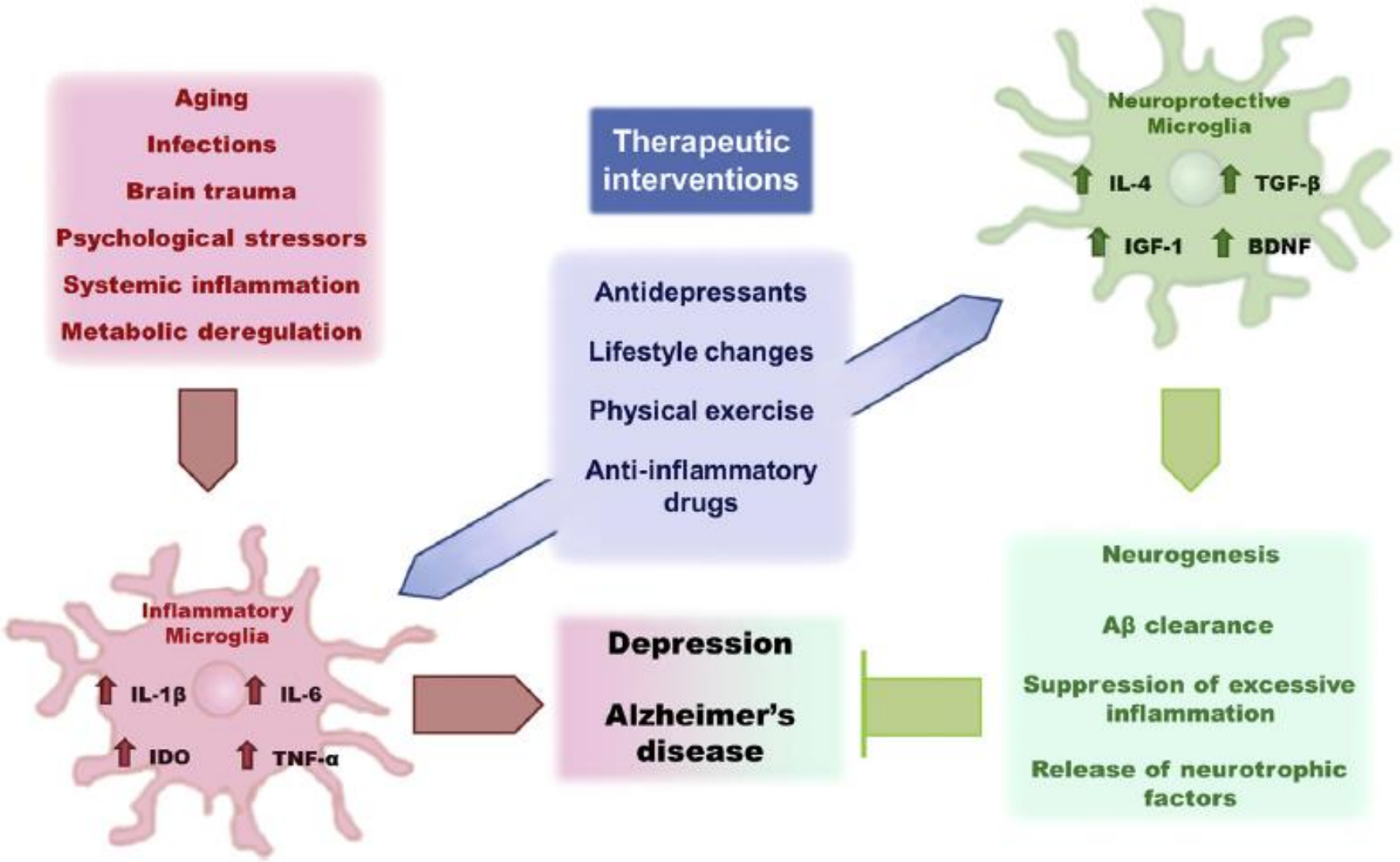


hippocampus PFC

Microglia-derived TNF-α drives depressive-like behavior induced by AβOs






Aging
Infections
Brain trauma
Psychological stressors
Systemic inflammation
Metabolic deregulation
Therapeutic interventions
Antidepressants
Lifestyle changes
Physical exercise
Anti-inflammatory drugs
Neuroprotective Microglia
IL-4
TGF-β
IGF-1
BDNF
Inflammatory Microglia
IL-1β
IL-6
IDO
TNF-α
Depression
Alzheimer's disease
Neurogenesis
Aβ clearance
Suppression of excessive inflammation
Release of neurotrophic factors

Collaborators

Federal University of Rio de Jameiro

Fernanda G. De Felice

Claudia P. Figueiredo
Julia R. Clarke
Debora Foguel
Maria Bellio

Northwestern University

William L. Klein

Queen's University, Kingston

Douglas P. Munoz

University of Campinas

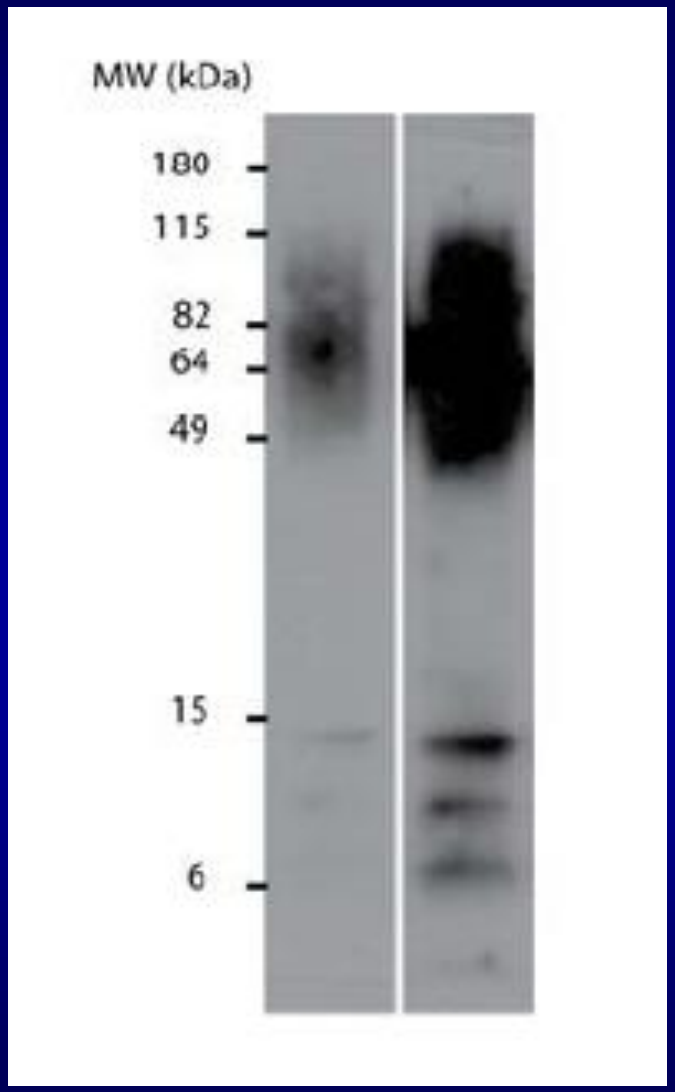
Licio A. Velloso

A typical day at the lab…


INNT
National Institute
of Translational
Neuroscience
CNPq
Conselho Nacional de Desenvolvimento
Científico e Tecnológico
FAPERJ
Fundação Carlos Chagas Filho de Amparo
à Pesquisa do Estado do Rio de Janeiro

Western blot of synthetic AβO preparation

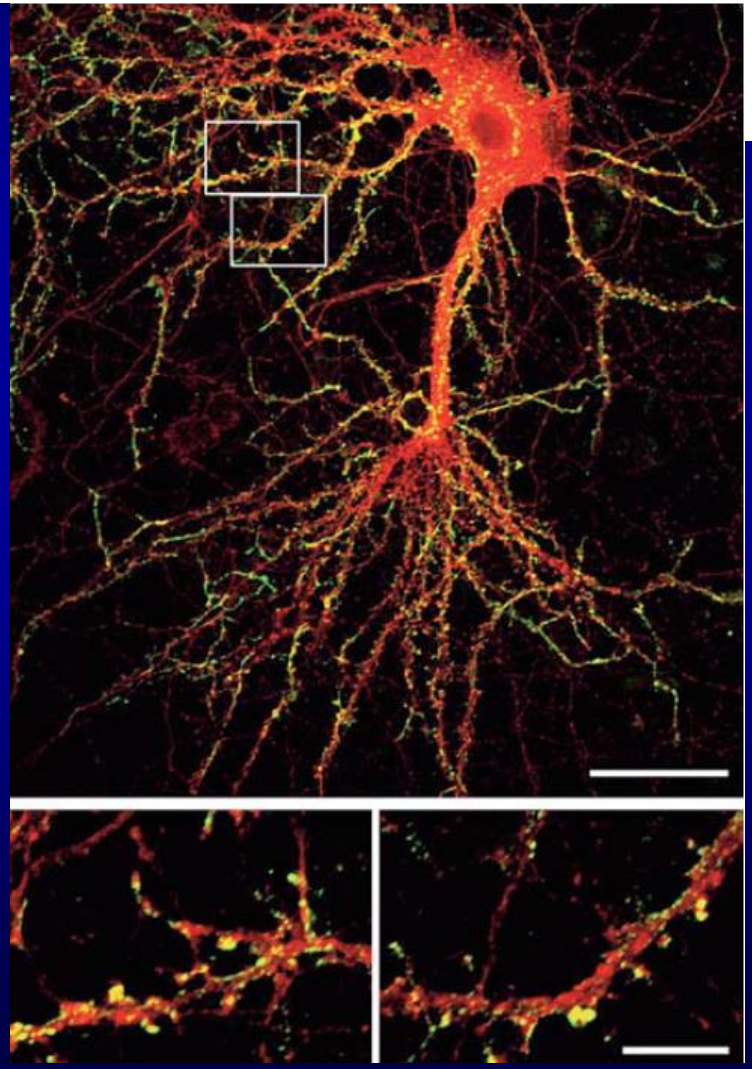
Sofia Jürgensen



Jürgensen et al. (2011) J. Biol. Chem.

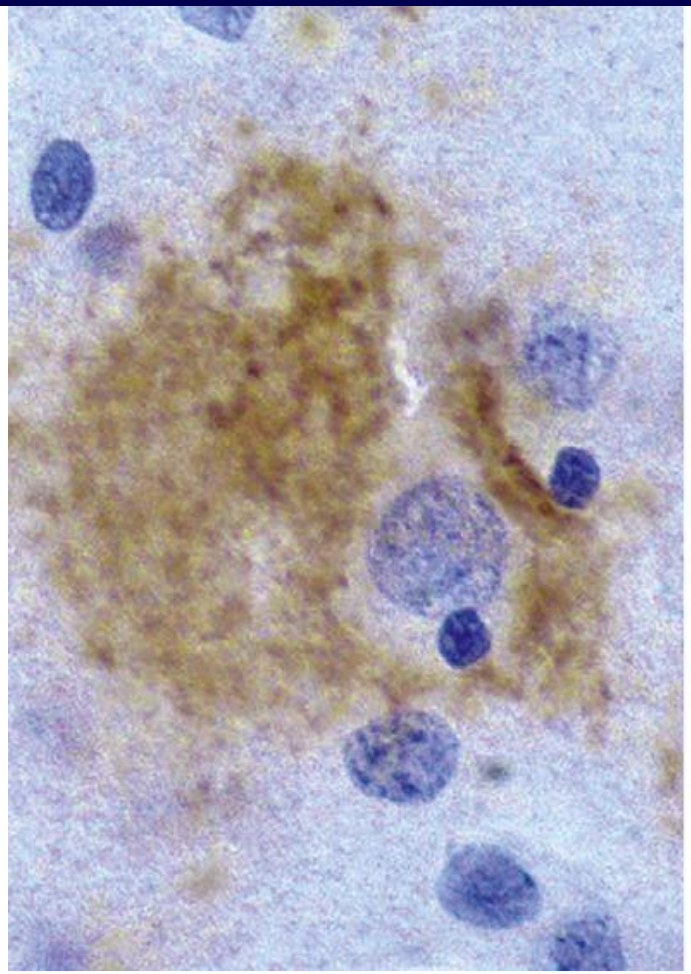
Molecules that Disrupt Memory Circuits in Alzheimer's Disease: The Attack on Synapses by Aβ Oligomers (ADDLs)

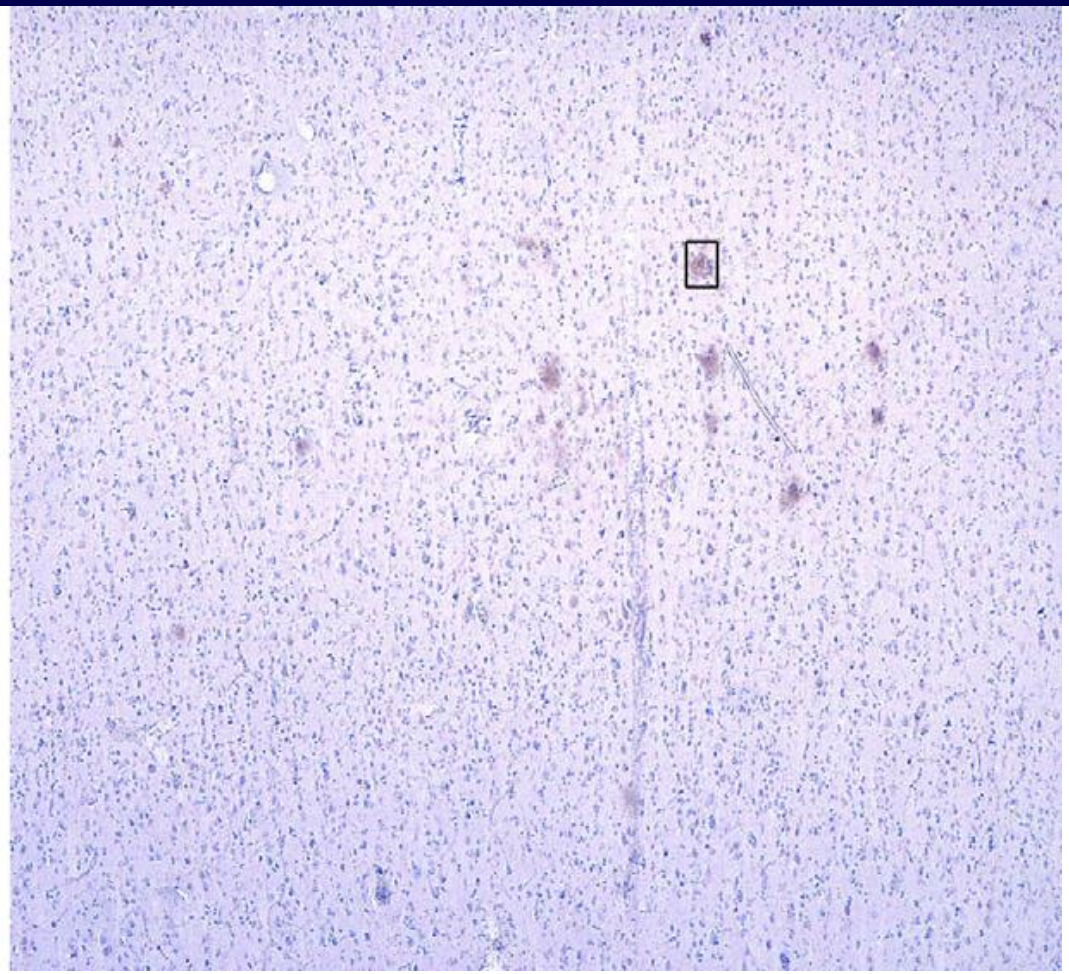
William L. Klein[1], *Pascale N. Lacor*[1], *Fernanda G. De Felice*[1], and *Sergio T. Ferreira*[1]



Bontempi et al.
Memories: Molecules and Circuits

Perineuronal staining in AD brain…

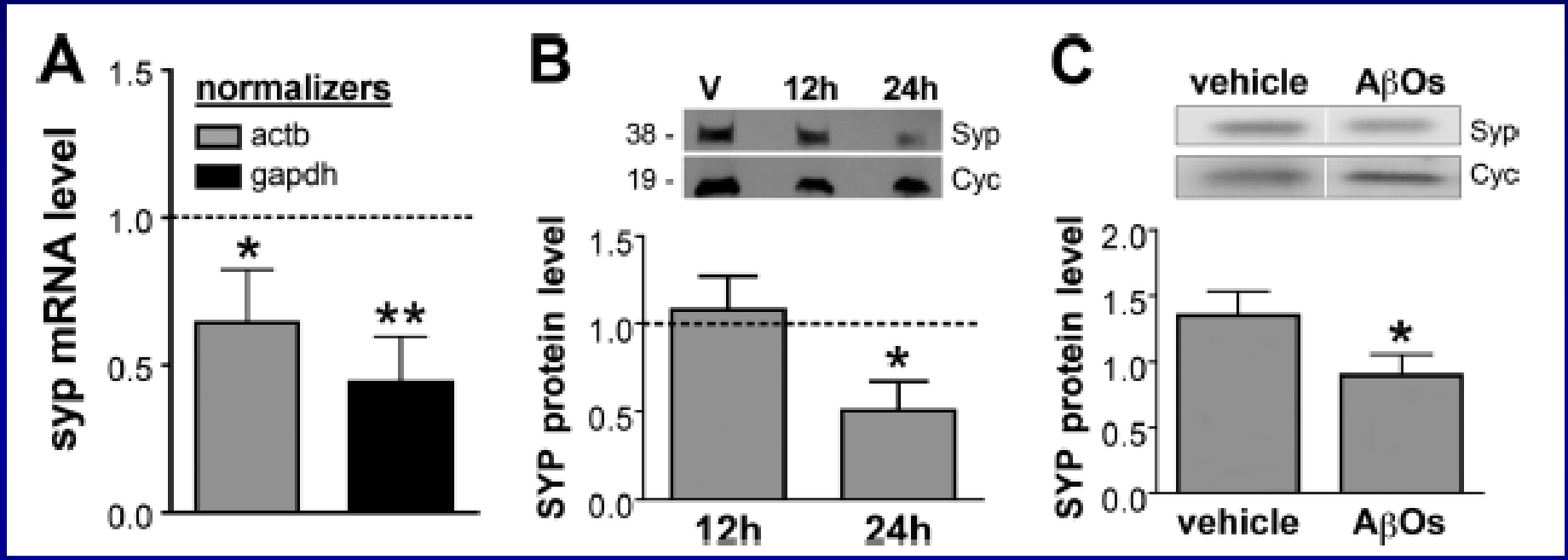




The Aβ oligomer hypothesis for synapse failure and memory loss in Alzheimer's disease

Ferreira & Klein, NLM 2011

AβOs downregulate synaptophysin expression in rodent and human neurons

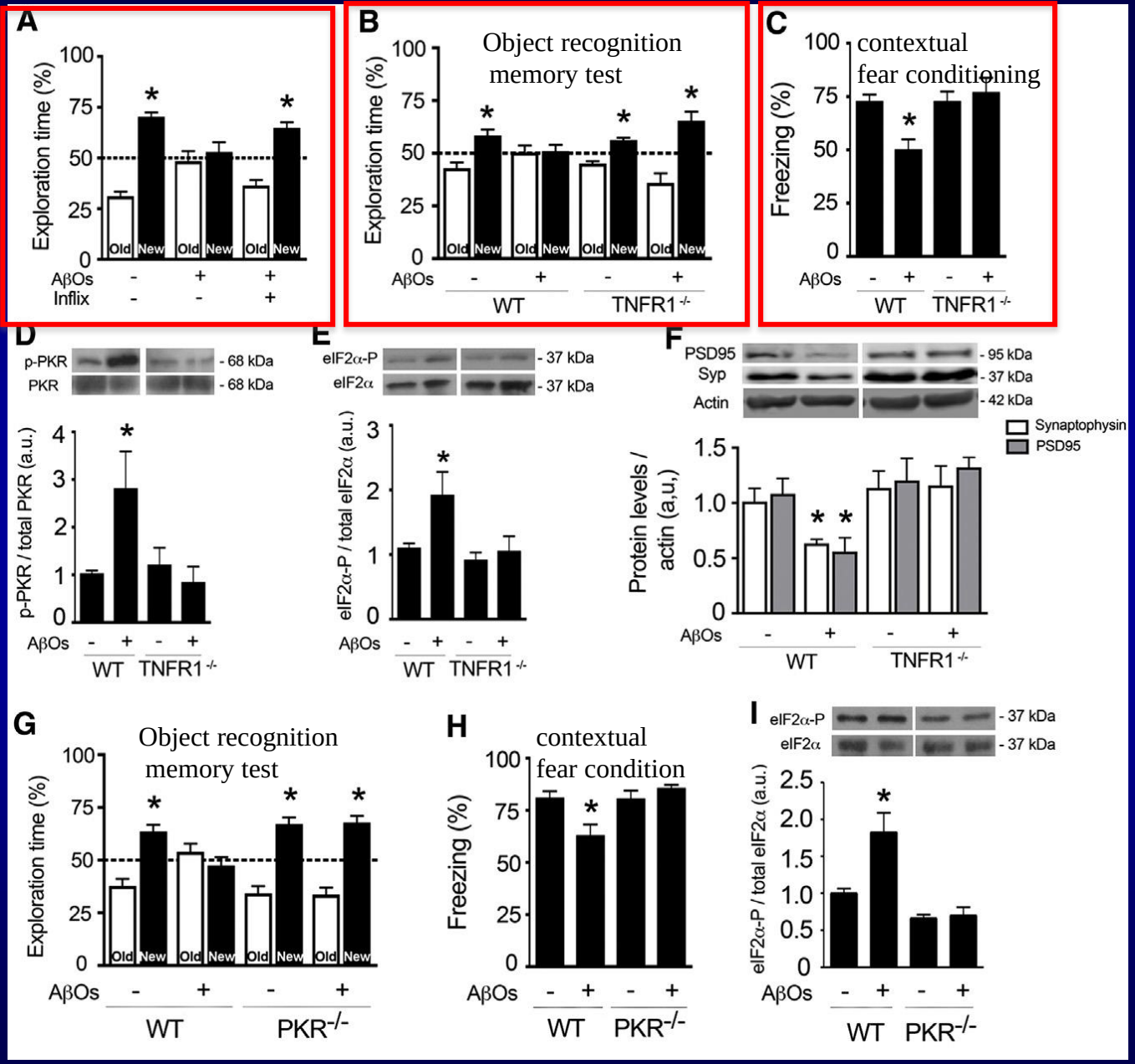


Sebollela et al., 2012
J. Biol. Chem.

Adriano Sebollela

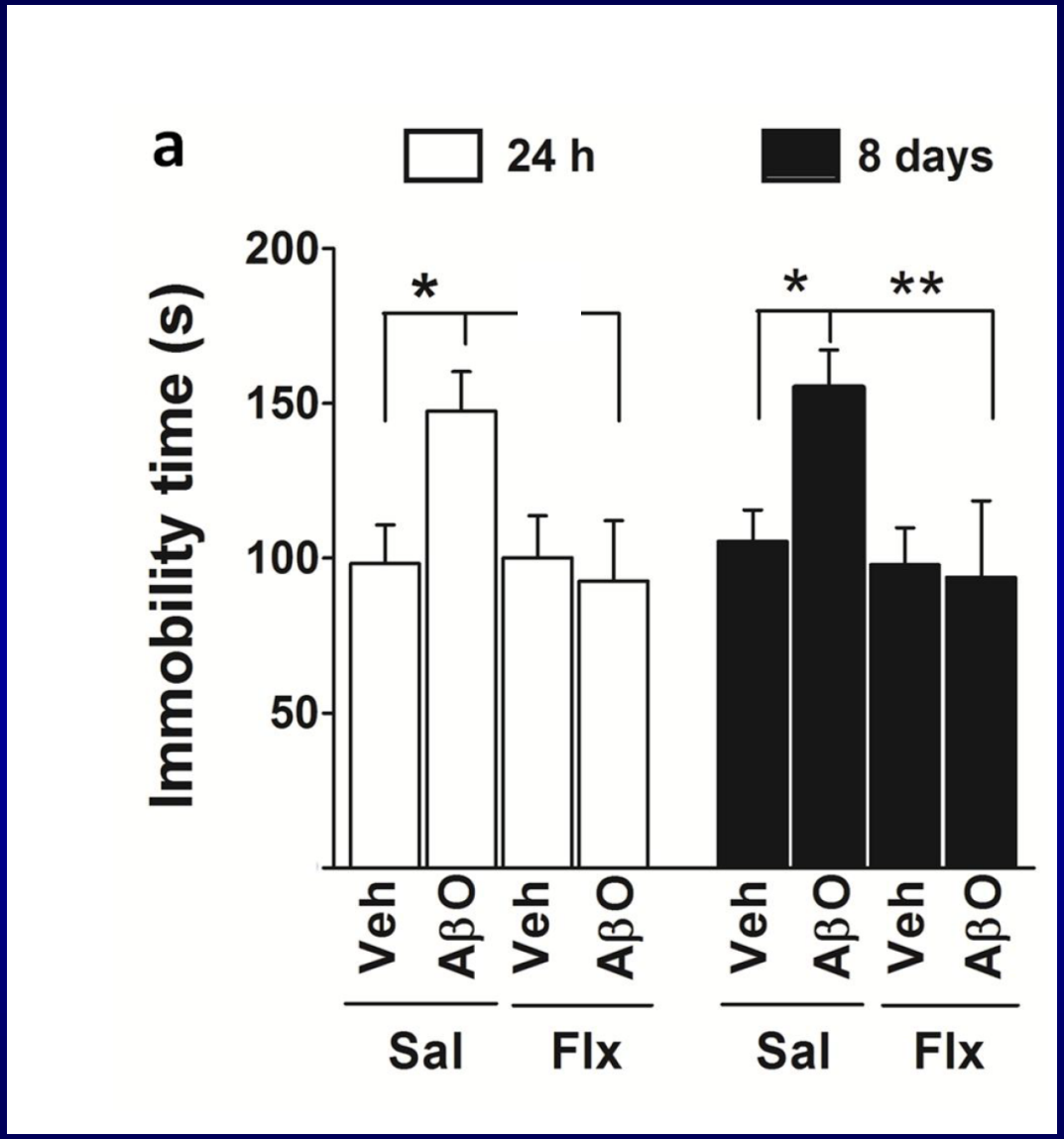
TNF-α mediates AβO-induced cognitive impairment in mice

Mychael Lourenco



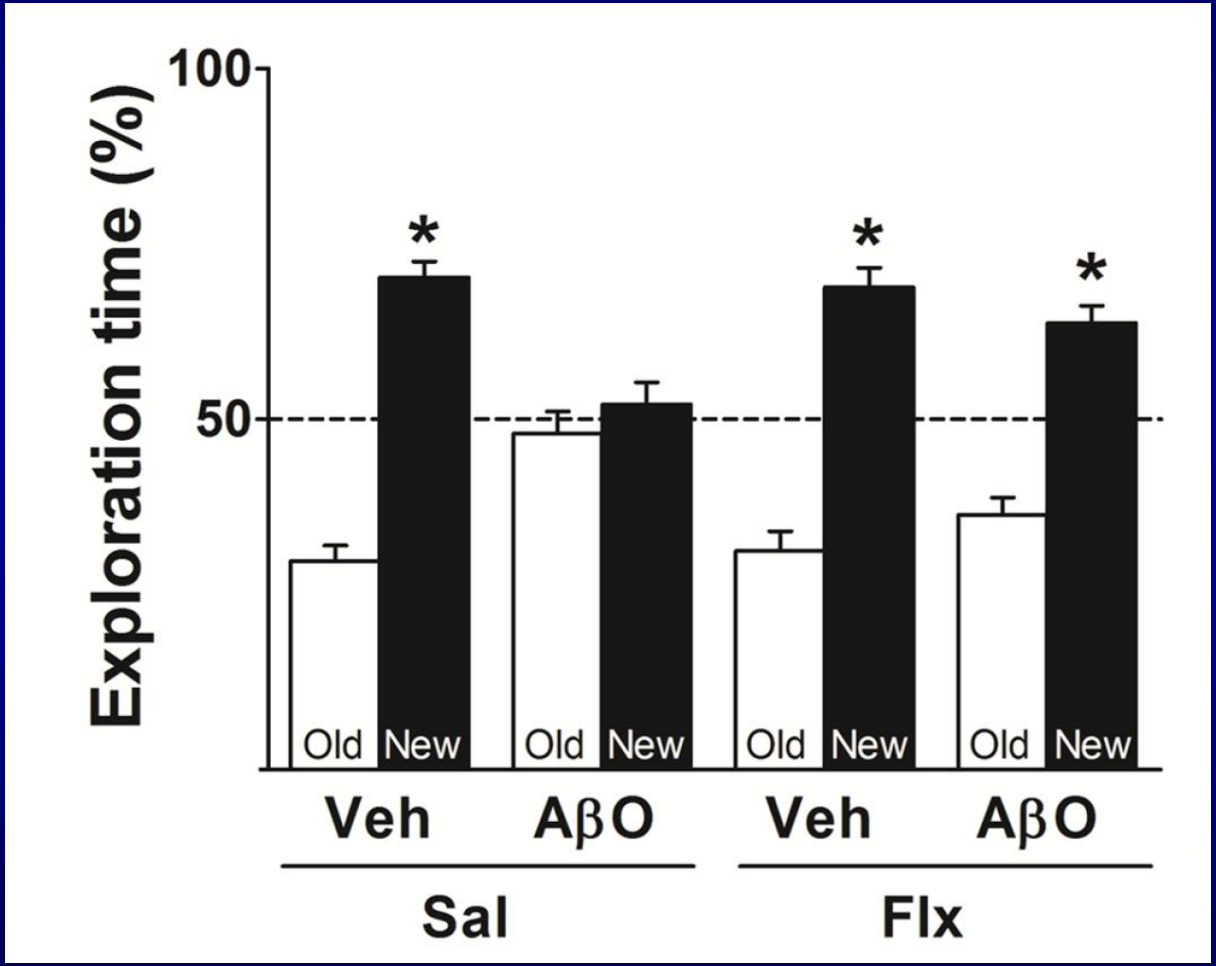
Lourenco et al., Cell Metab. 2013

Forced swim test



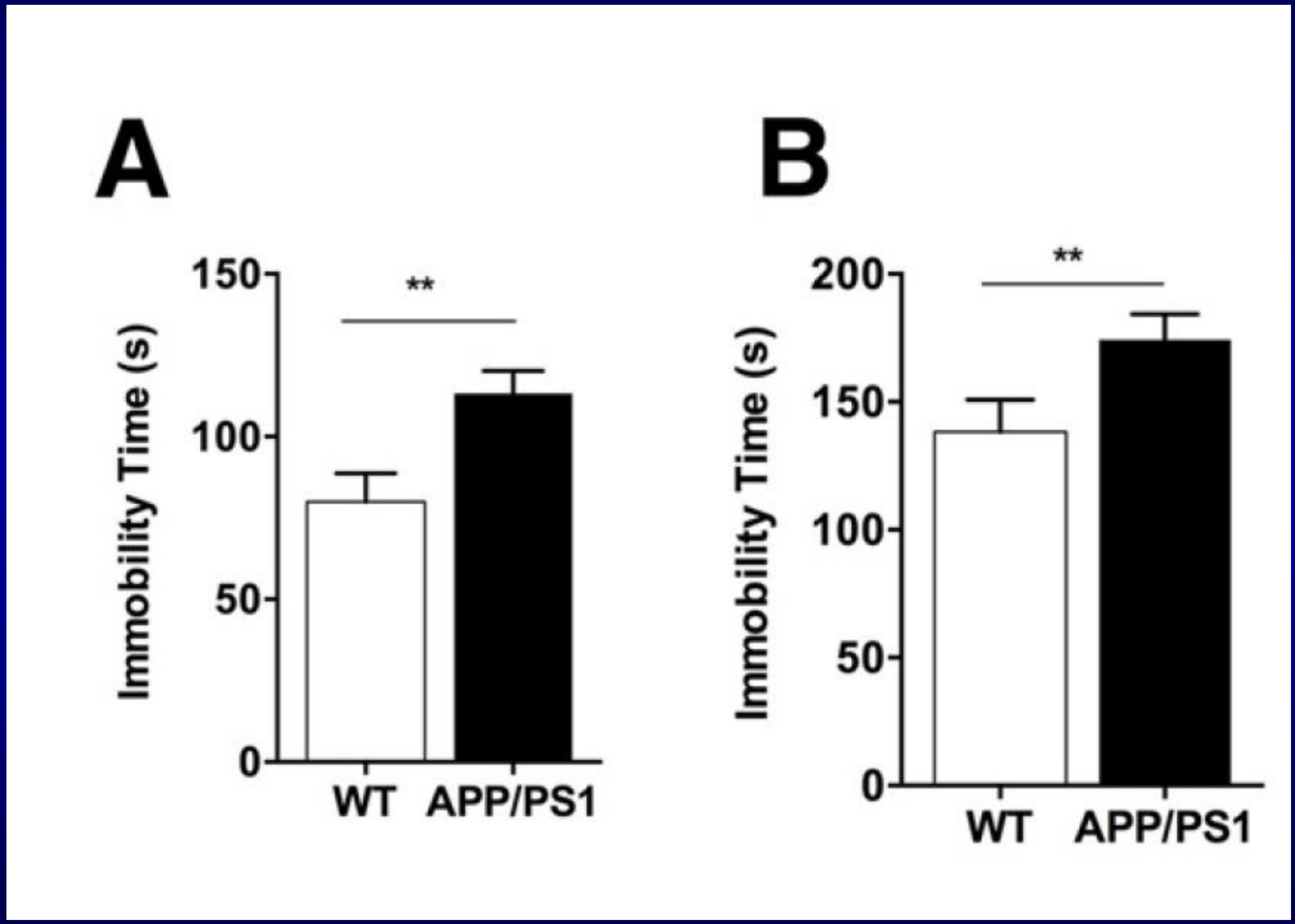
Ledo et al., 2013
Mol. Psychiatry

Fluoxetine prevents memory deficit induced by AβOs

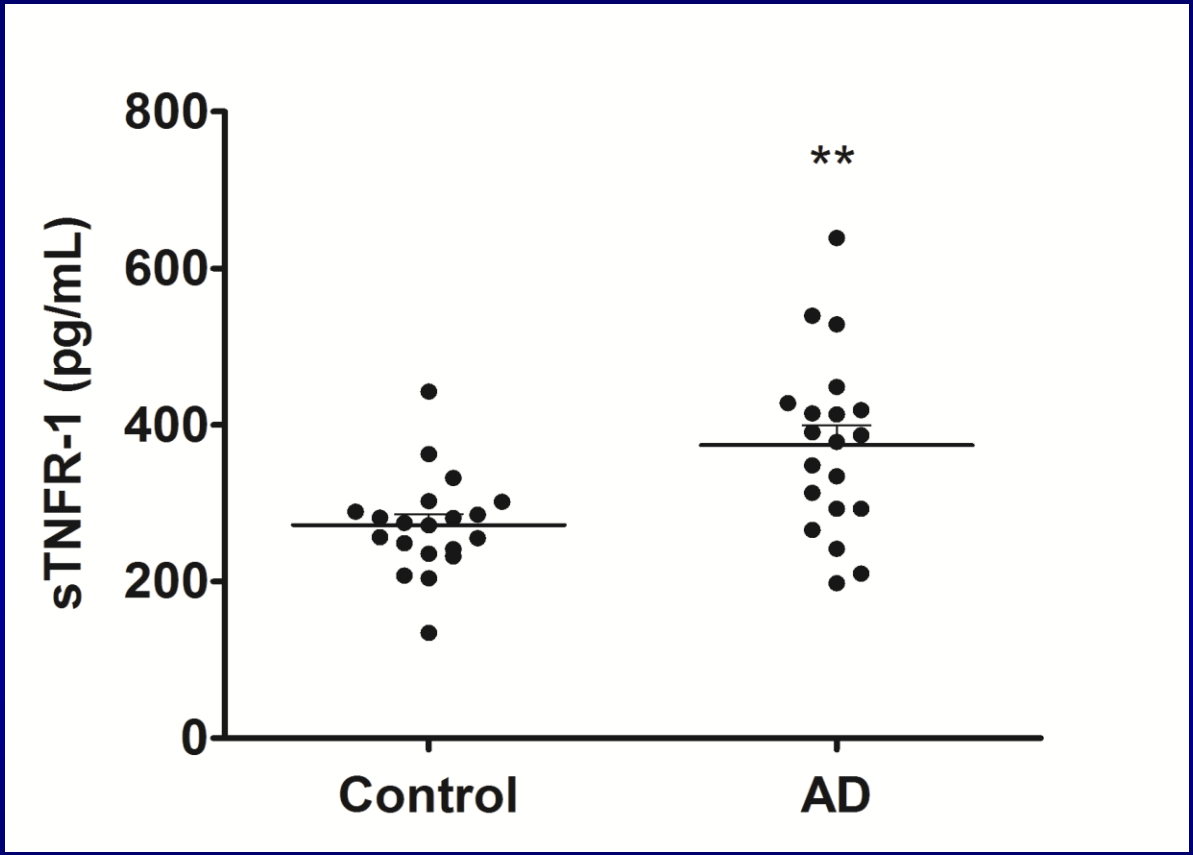


Ledo et al., Mol. Psychiatry 2013

Depressive-like behavior in a transgenic mouse model of AD

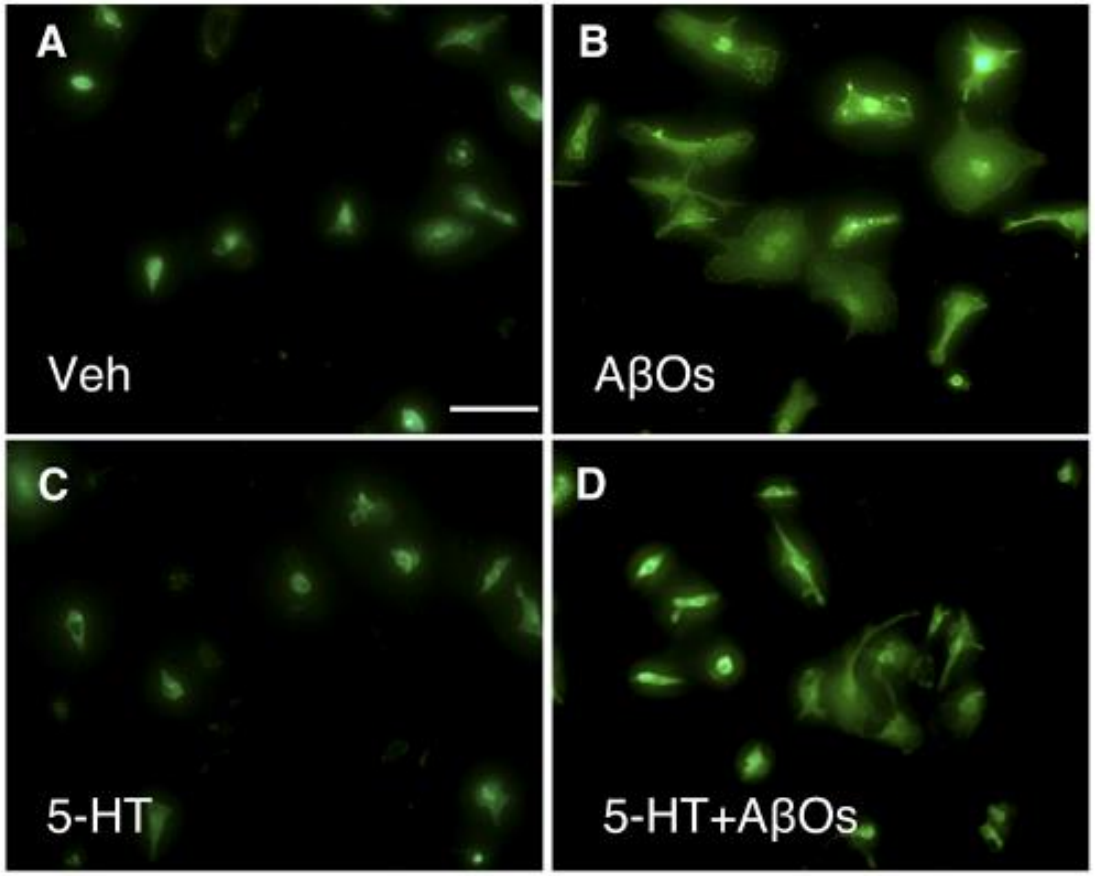


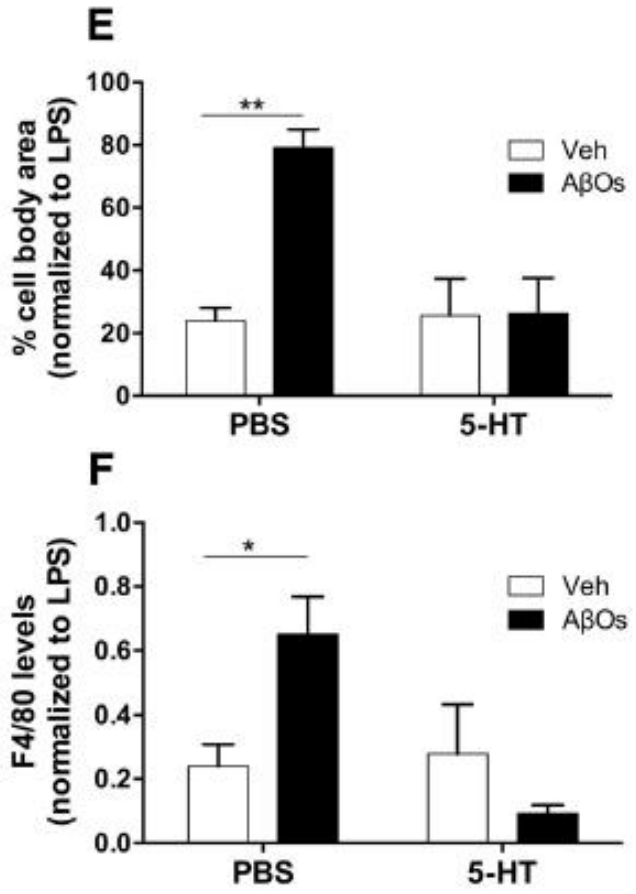
Increased levels of sTNFR1 in the plasma of AD patients



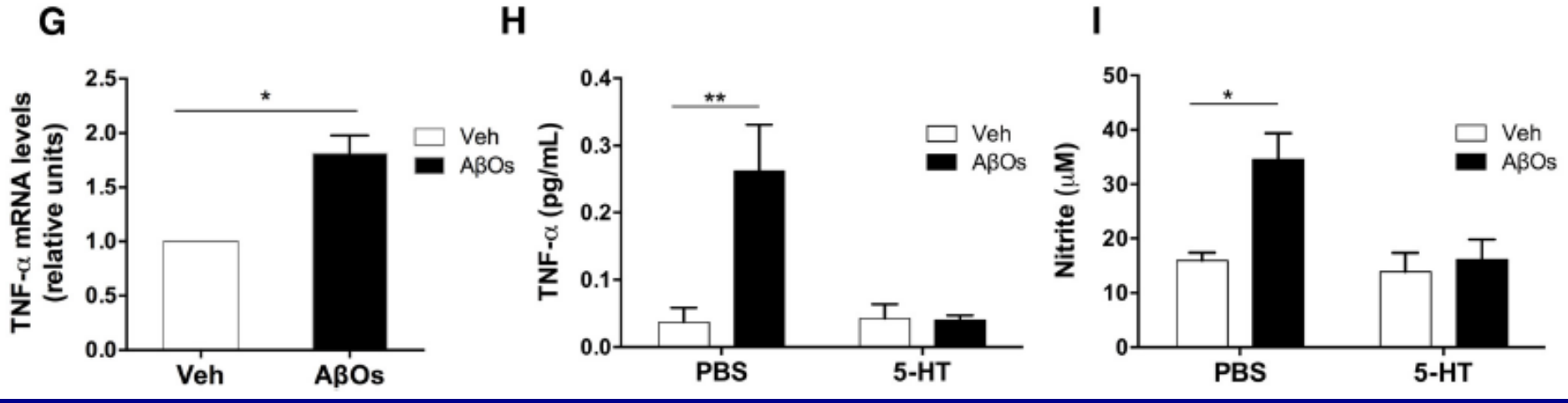
Ledo et al., submitted

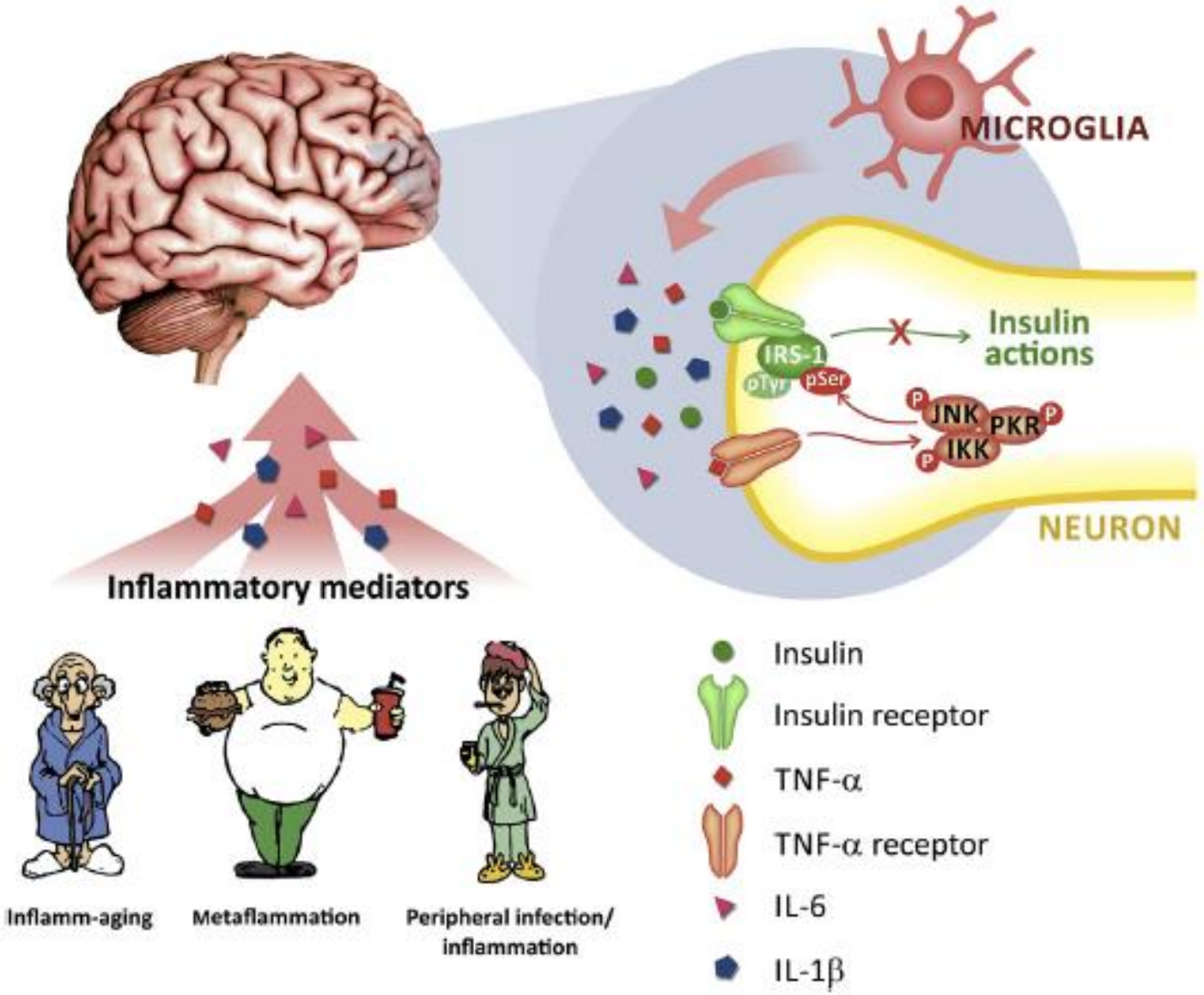
AβOs directly activate microglia in vitro





AβOs activate microglia in vitro




MICROGLIA
Insulin actions
IRS-1
pTyr
pSer
JNK
PKR
IKK
NEURON
Inflammatory mediators
Inflamm-aging
Metaflammation
Peripheral infection/ inflammation
Insulin
Insulin receptor
TNF-α
TNF-α receptor
IL-6
IL-1β