

Contributions of translational behavioral neuroscience to the advanced diagnostic and therapeutic approaches towards dementia

Lydia Giménez Llort, Ph.D.

Dept. de Psiquiatria i Medicina Legal

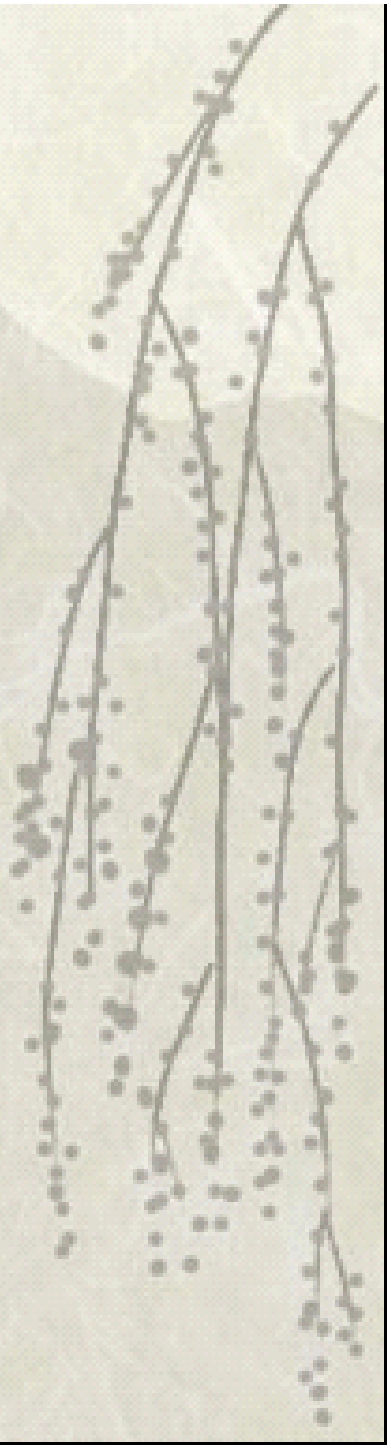
Institut de Neurociències

Universitat Autònoma de Barcelona

UAB Institut de Neurociències UAB

Old age is the zenith of life,
a time for rest, reflection ,
wisdom and truth

Goethe



But...

Goethe and Bergman

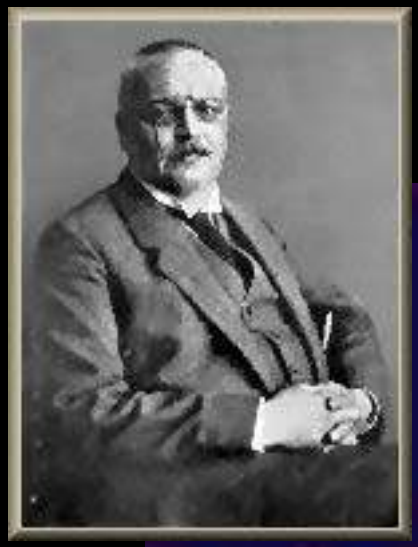
are not always right



A complex pattern

Germany, 1907

- female, 51 years old
- cognitive impairment
- amnesia
- aphasia
- apraxia
- dementia
- paranoid illusions
- violent behavior
- postmortem brain pathology
  - neuritic deposits
  - neurofibrillar tangles







The Umbrella effect

Lydia Giménez-Llort, 2014





The Umbrella effect

Lydia Giménez-Llort, 2014





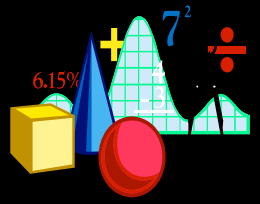
The Umbrella effect

Lydia Giménez-Llort, 2014











The other patient

A complex clinical history

Dementia

1. STM & LTM
2. Abstract thinking
3. Judgement
4. High cognitive functions

BPSD Behavioral and Psychological sympthoms of dementia

Agitation, aggressive, psychosis, anxiety

5-15% AD + major depression

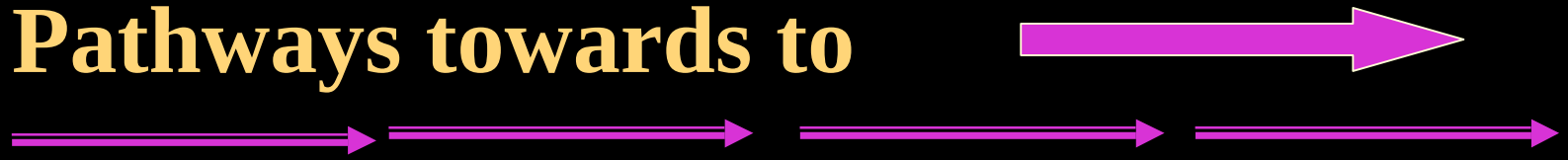
20-40% AD + illusions and hallucinasions

Sundawning behavior





Pathways towards to



Genetic
Environmental

Production BA

Synaptic disfunction

Oxidative Stress
disregulation Ca^{++}

Impaired
Plasticity and
Neurogenesis

Formation NFT
and apoptosis

Pathways away from



REDUCTION of RISK

Cognitive Stimulation
Exercise
Caloric restriction
Immunization BA
BACE i g-secretases Inhibitors
Fatty acids modulators (cholesterol)

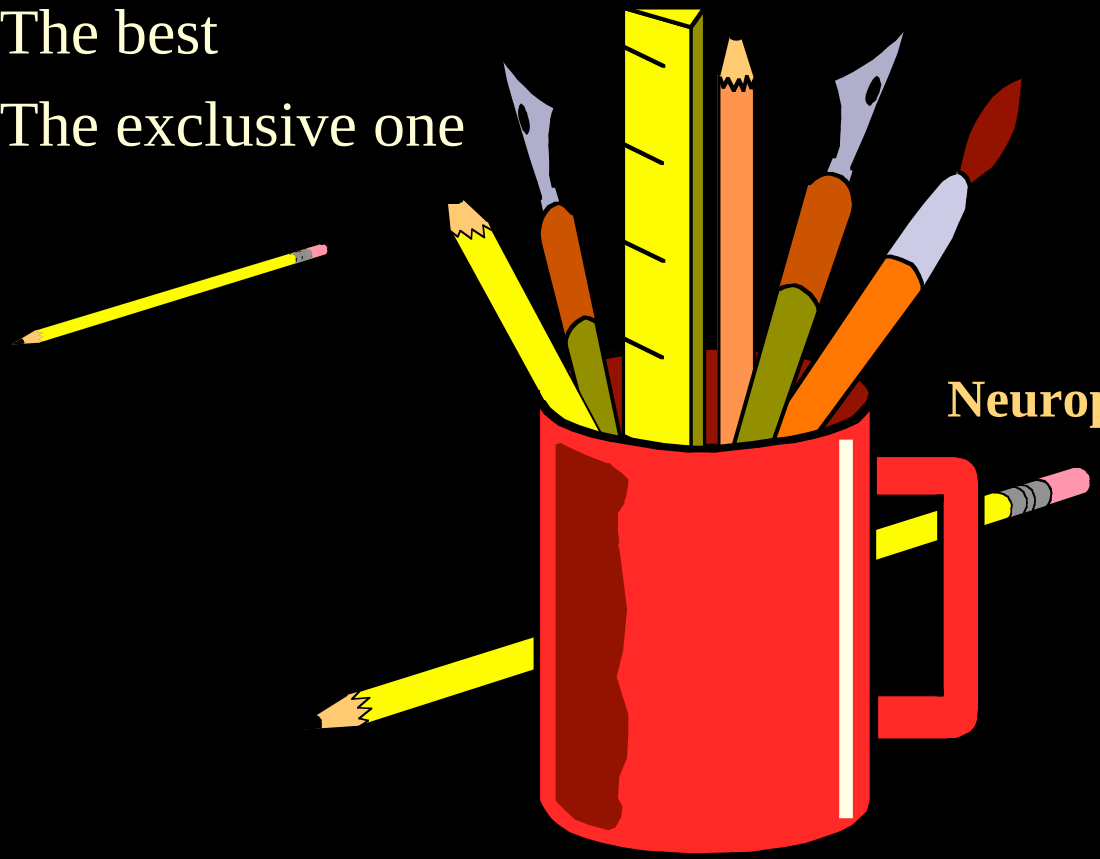
TREATMENT

Immunization BA
Quelants Cu^{+} i Fe^{++}
BACE i g-secretases inhibitors
Antioxidants and B vit
Antiinflammatory agents
Neurotrophic factors
Fatty acids modulators (cholesterol)
Cholinergic enhancers
Antidepressants

Mattson, Nature 2004

The complexity of the therapeutical strategies

The unique
The best
The exclusive one



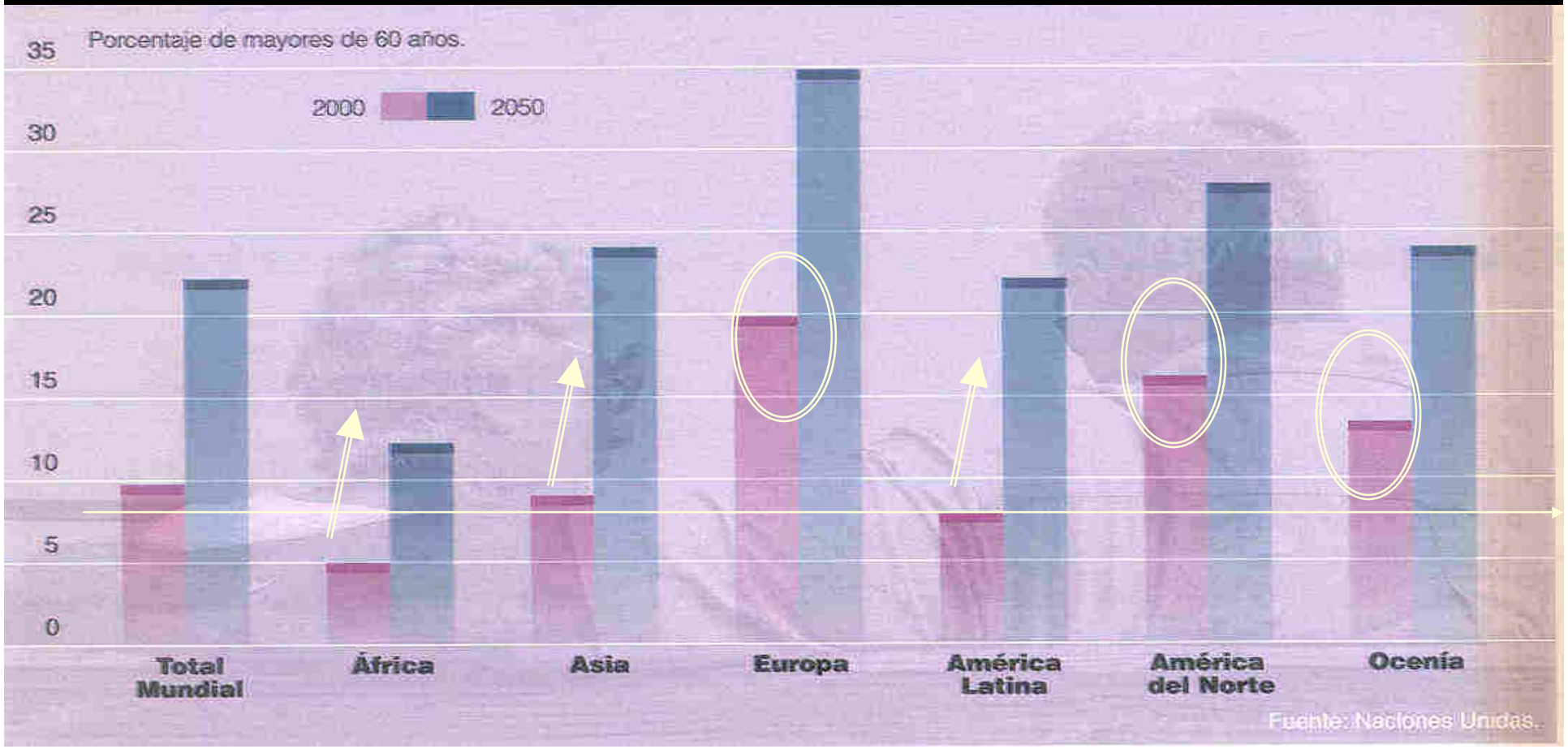
Cognition & Memory
Cholinergic deficits

Behavioral Alterations
Neurotransmitters

Neuroprotection & Regeneration
Glutamate antagonists
Genetic Strategies
Growth Factors

Behavioral Neuroscience

- ✓ Validation (Guideliness)
- ✓ Screening and validation of the model



Behavioral Neuroscience

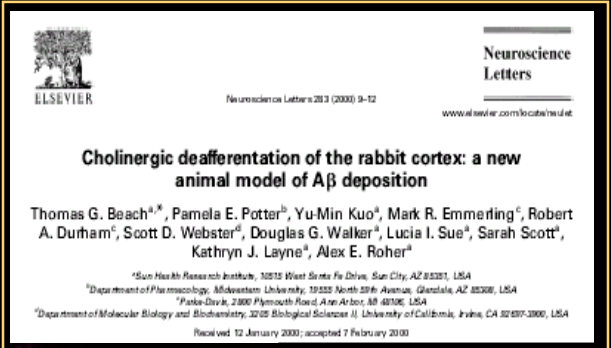
- ✓ Validation (Guideliness)
- ✓ Screening and validation of the model
- ✓ Multidimensional: focus BPSD and DLA
- ✓ Translational, Longitudinal
- ✓ Gender dependent



Ademuz, 1968

- ✓ Life events + Life style (Non-Pharmacological)
- ✓ External intervention (Pharmacol, Molecular, other)
- ✓ Prevention + Therapeutics





Neuroscience Letters

Neuroscience Letters 283 (2000) 9–12

www.elsevier.com/locate/neulet

Cholinergic deafferentation of the rabbit cortex: a new animal model of Aβ deposition

Thomas G. Beach[a,*], Pamela E. Potter[b], Yu-Min Kuo[a], Mark R. Emmerling[c], Robert A. Durham[c], Scott D. Webster[d], Douglas G. Walker[a], Lucia I. Sue[a], Sarah Scott[a], Kathryn J. Layne[a], Alex E. Roher[a]

[a]Sun Health Research Institute, 10515 West Santa Fe Drive, Sun City, AZ 85351, USA
[b]Department of Pharmacology, Midwestern University, 19555 North 59th Avenue, Glendale, AZ 85308, USA
[c]Parke-Davis, 2800 Plymouth Road, Ann Arbor, MI 48105, USA
[d]Department of Molecular Biology and Biochemistry, 3205 Biological Sciences II, University of California, Irvine, CA 92697-3900, USA

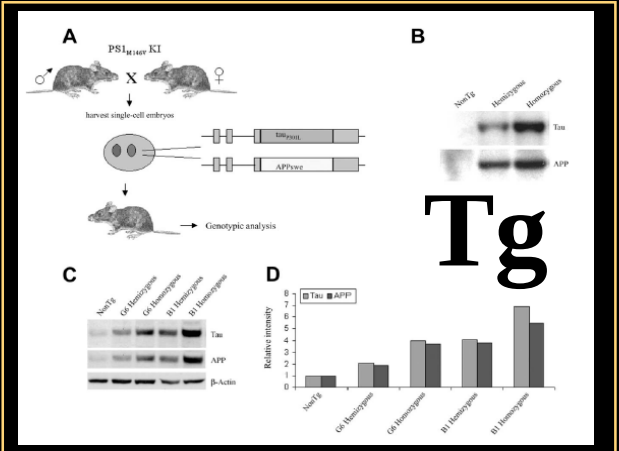
Received 12 January 2000; accepted 7 February 2000





Senescence Accelerated Mice
Premature Aging Mice

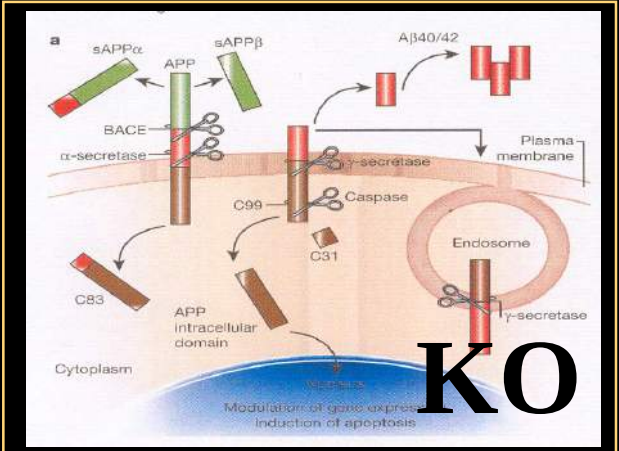
Administration of Beta-amyloid



Games *et al.*, 1995

Alzheimer-like neuropathology in transgenic mice overexpressing V171F B-amyloid precursor protein

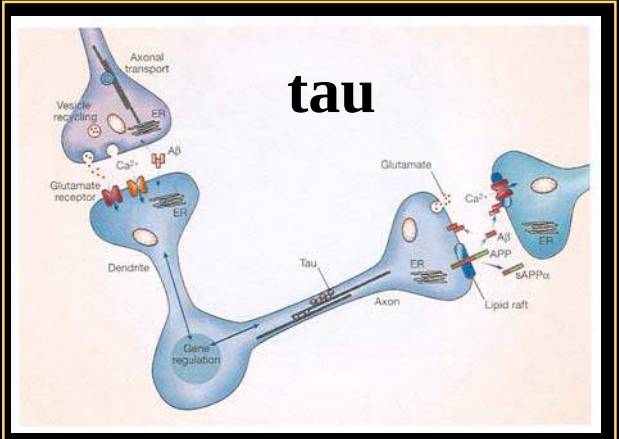
Nature, 373:523-527.



Luo et al. 2001.

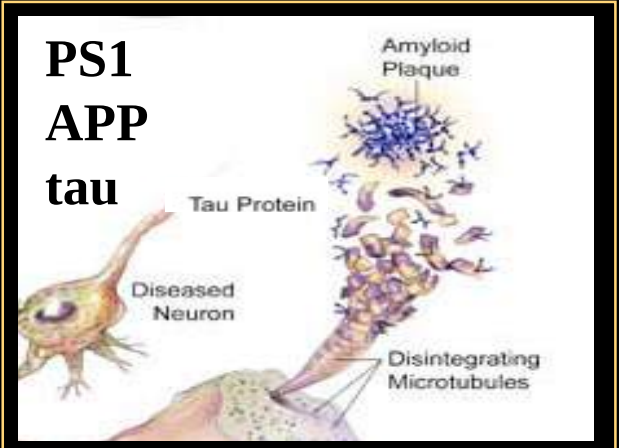
Mice deficient in BACE1, the Alzheimer's B-secretase, have normal phenotype and abolished B-amyloid generation.

Nat Neurosci. 4: 231-232.



Lucas *et al.*
Embo J 2001; 20 (1-2): 27-39

Engel *et al.*
Neurobiol Aging 2005



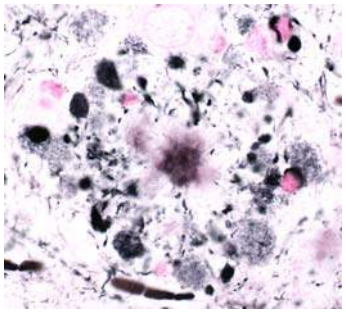
Oddo *et al.*

Triple-transgenic of Alzheimer's disease with plaques and tangles: Intracellular AB and synaptic dysfunction.

Neuron 2003; 39: 409-421



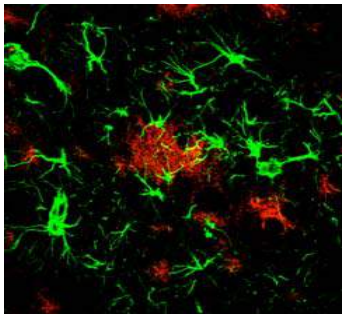
3xTgAD



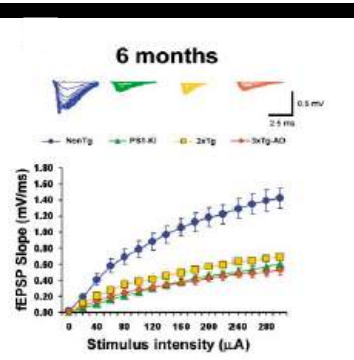
BA



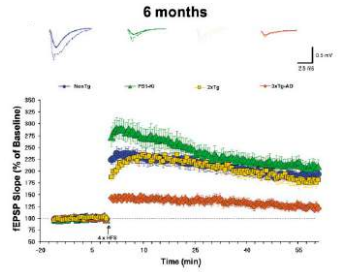
PHF



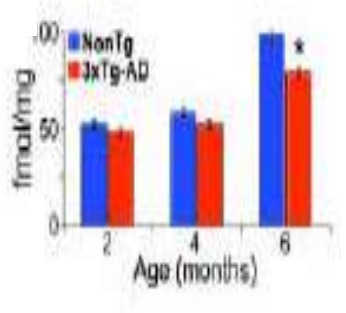
Gliosi



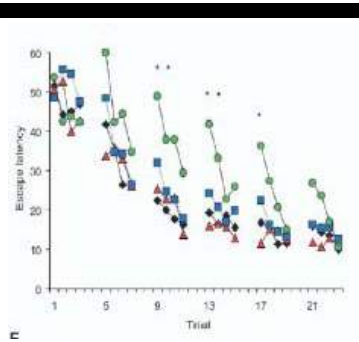
Def.fEPSP



Def.LTP



Def.α7nAChR



Def.L&M

Oddo *et al.*

Triple-transgenic of Alzheimer's disease with plaques and tangles: Intracellular AB and synaptic dysfunction.

Neuron 2003; 39: 409-421

3xTgAD

PSD $_{M164V}$

APP $_{Swe}$

tau $_{P301L}$

Available online at www.sciencedirect.com
ScienceDirect
Neuroscience and Biobehavioral Reviews 31 (2007) 125–147
NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS
www.elsevier.com/locate/neubiorev

Review

Modeling behavioral and neuronal symptoms of Alzheimer's disease in mice: A role for intraneuronal amyloid

L. Giménez-Llort[a,*], G. Blázquez[a], T. Cañete[a], B. Johansson[b,c], S. Oddo[d], A. Tobeña[a], F.M. LaFerla[d], A. Fernández-Teruel[a]

[a]Medical Psychology Unit, Department of Psychiatry and Forensic Medicine, School of Medicine, Institute of Neuroscience, Autonomous University of Barcelona, 08193 Bellaterra, Barcelona, Spain
[b]Department of Neuroscience, Karolinska Institutet, KS CMM L8:01, SE-171 76 Stockholm, USA
[c]Department of Clinical Neuroscience, Karolinska Institutet, KS CMM L8:01, SE-171 76 Stockholm, Sweden
[d]Department of Neurobiology and Behavior, University of California, Irvine, CA 92697-4545, USA

Abstract

The amyloid Aβ-peptide (Aβ) is suspected to play a critical role in the cascade leading to AD as the pathogen that causes neuronal and synaptic dysfunction and, eventually, cell death. Therefore, it has been the subject of a huge number of clinical and basic research studies on this disease. Aβ is typically found aggregated in extracellular amyloid plaques that occur in specific brain regions enriched in nAChRs in Alzheimer's disease (AD) and Down syndrome (DS) brains. Advances in the genetics of its familiar and sporadic forms, together with those in gene transfer technology, have provided valuable animal models that complement the traditional cholinergic approaches, although modeling the neuronal and behavioral deficits of AD in these models has been challenging. More recently, emerging evidence indicates that intraneuronal accumulation of Aβ may also contribute to the cascade of neurodegenerative events and strongly suggest that it is an early, pathological biomarker for the onset of AD and associated cognitive and other behavioral deficits. The present review covers these studies in humans, in in vitro and in transgenic models, also providing more evidence that adult 3 × Tg-AD mice harboring $PS1_{M146V}$, APP_{Swe}, tau_{P301L} transgenes, and mimicking many critical hallmarks of AD, show cognitive deficits and other behavioral alterations at ages when overt neuropathology is not yet observed, but when intraneuronal Aβ, synaptic and cholinergic deficits can already be described.
© 2006 Elsevier Ltd. All rights reserved.

Keywords: Intraneuronal amyloid; Animal models; 3xTgAD mice; Learning and memory; Neuropsychiatric-like symptoms; Activity; Circadian rhythms; Emotion; Psychosis

Contents

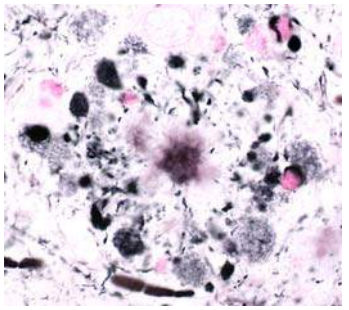
1. Introduction . . . 126
2. Molecular aspects of intraneuronal amyloid accumulation. . . . 126
3. Modeling the cognitive symptoms of AD in rodents . . . 127
   3.1. Earlier, cholinergic studies . . . 128
   3.2. Animal models for AD using gene transfer strategies . . . 128
   3.3. Searching for neuronal correlates of early cognitive deficits of AD . . . 129
   3.4. Studying the consequences of Aβ and nAChRs interactions . . . 130
   3.5. The relevance of longitudinal studies . . . 130
4. Modeling the neuropsychiatric symptoms of dementia . . . 131

*Corresponding author. Tel.: +34 93 581 2378; fax: +34 93 581 1435.
E-mail address: lidia.gimenez@uab.cat (L. Giménez-Llort).

0149-7634/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neubiorev.2006.07.007



3xTgAD

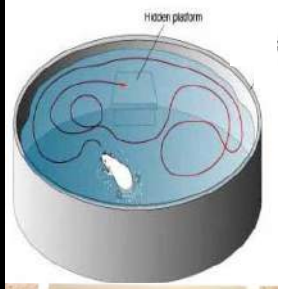


BA



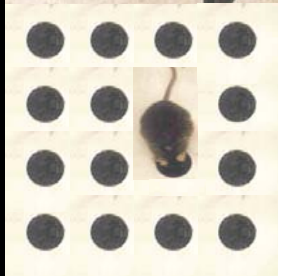
PHF

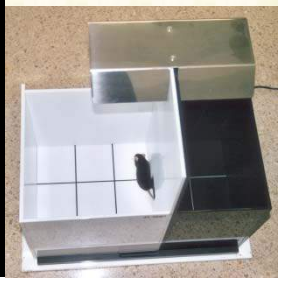
*PS1*M146V, *APP*Swe and *tau*P301L transgenes







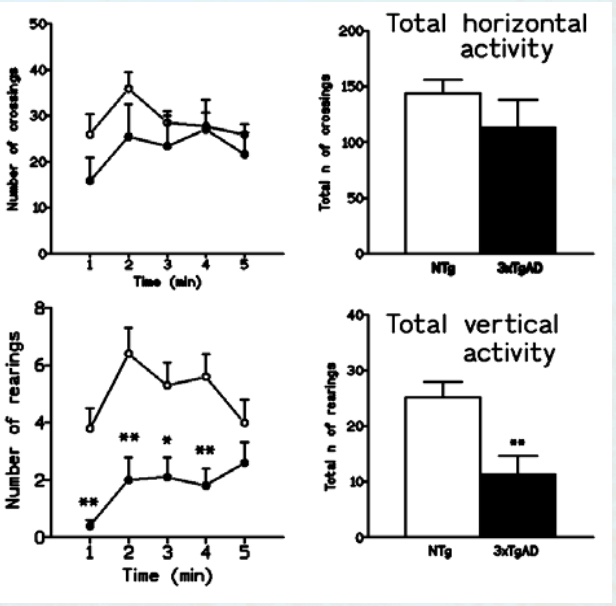




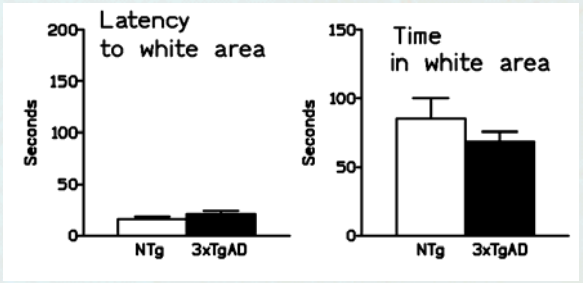
BPSD-like changes
2.5 month old 3xTgAD mice

Open-field





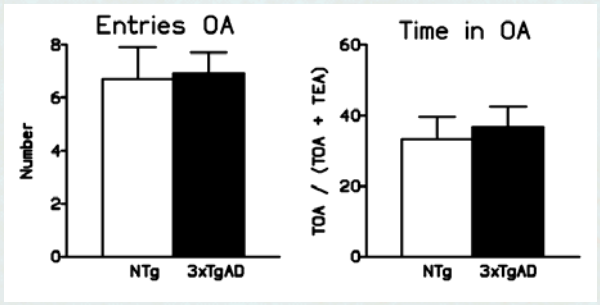
Black-white box

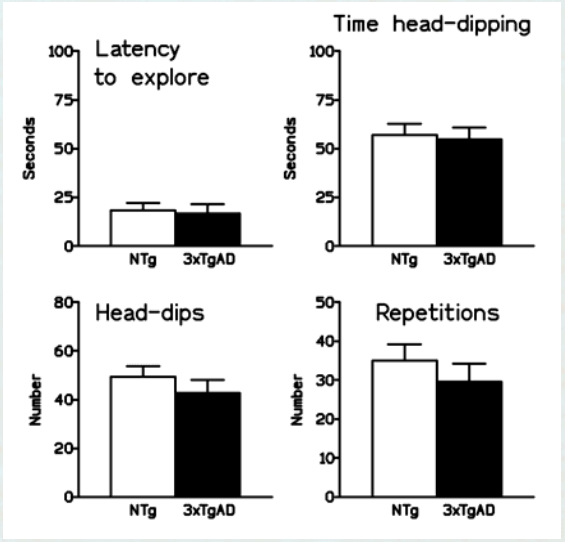




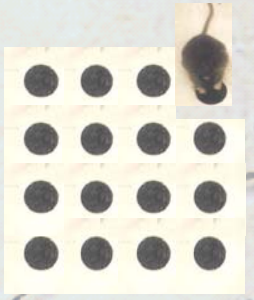
Plus-maze







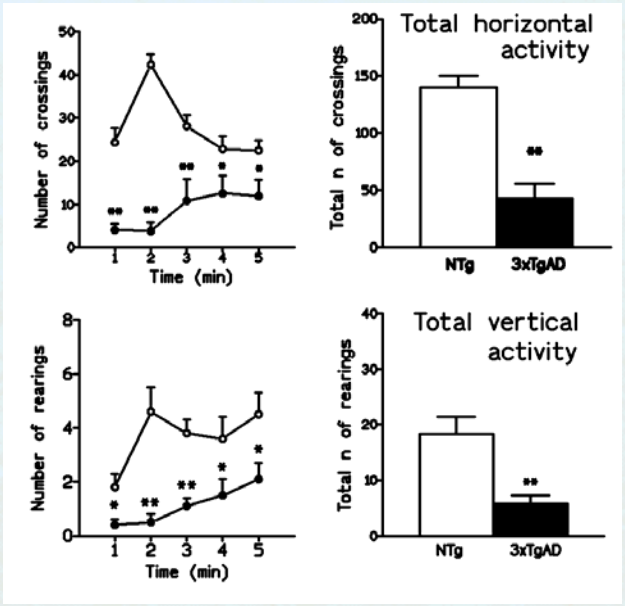
Boissier's hole-board



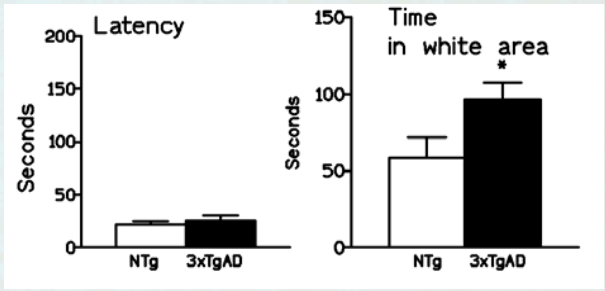
Changes BPSD-like in 6 month old 3xTgAD mice

Open-field



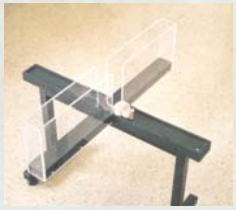


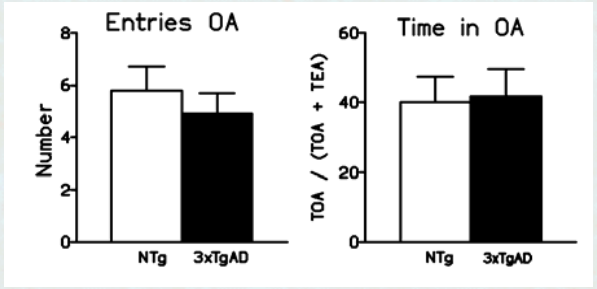
Black-white box

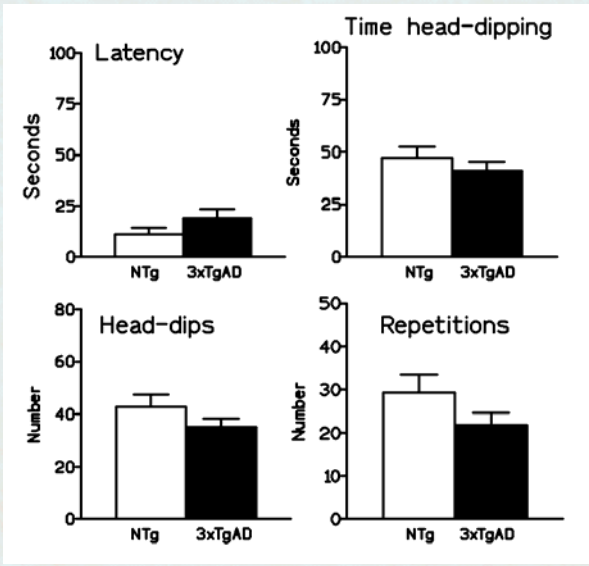




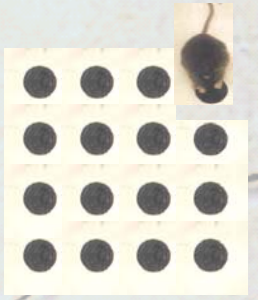
Plus-maze







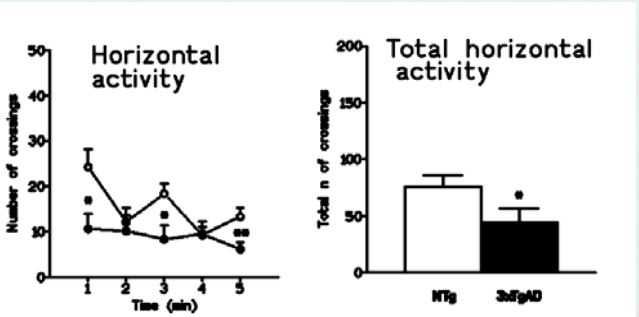
Boissier's hole-board



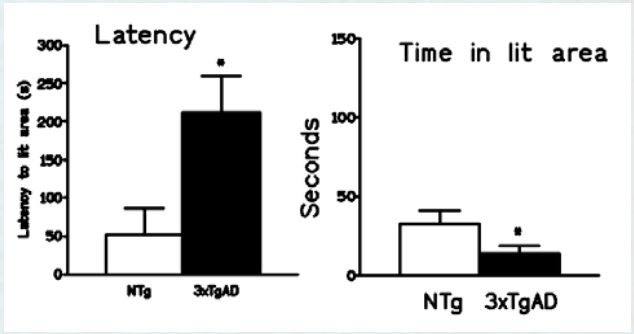
Alterations BPSD-like
12 month old 3xTgAD mice

Open-field





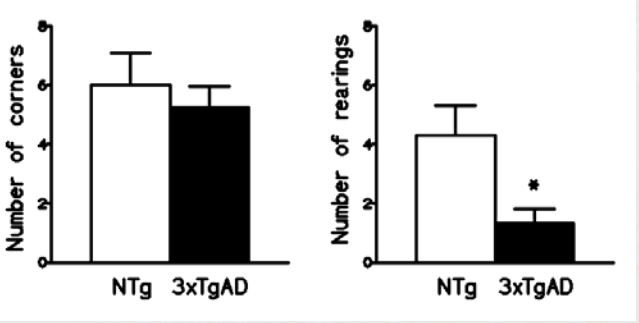
Dark-light box

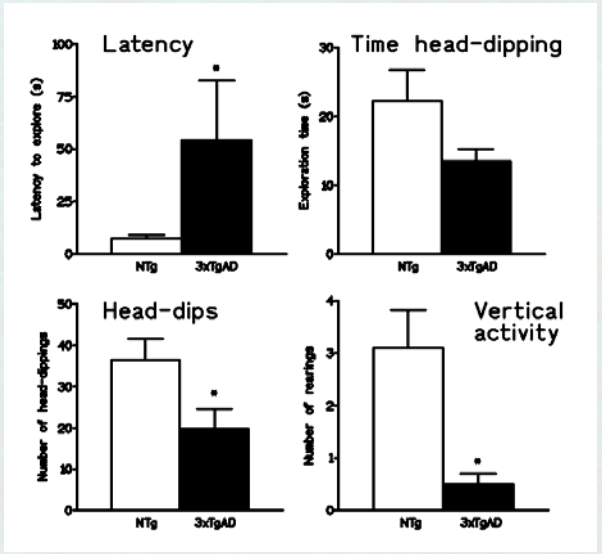




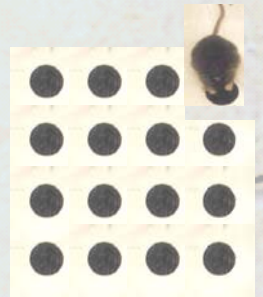
Corner test



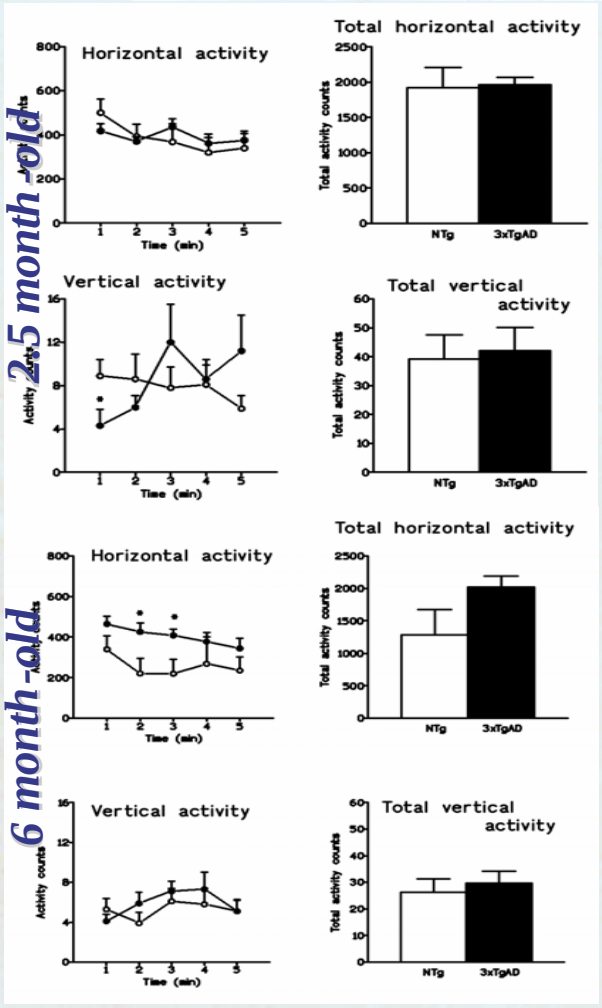


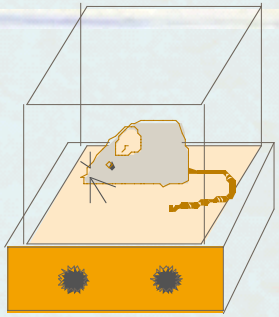


Boissier 's hole-board



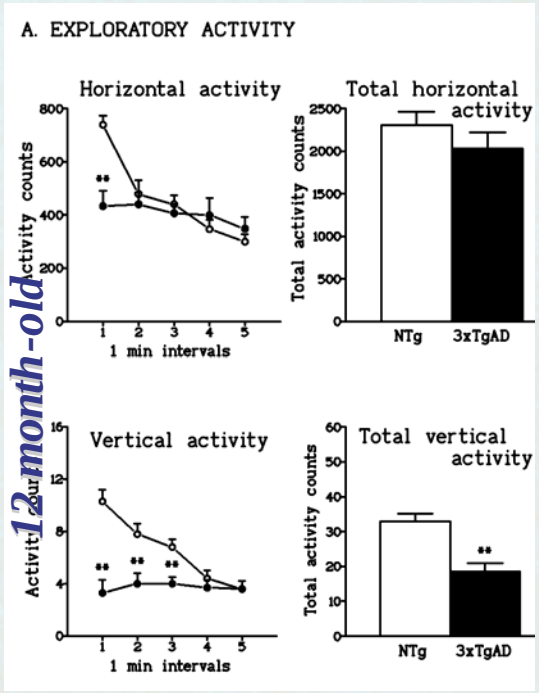
Changes and deficits
Exploration and Spontaneous Activity

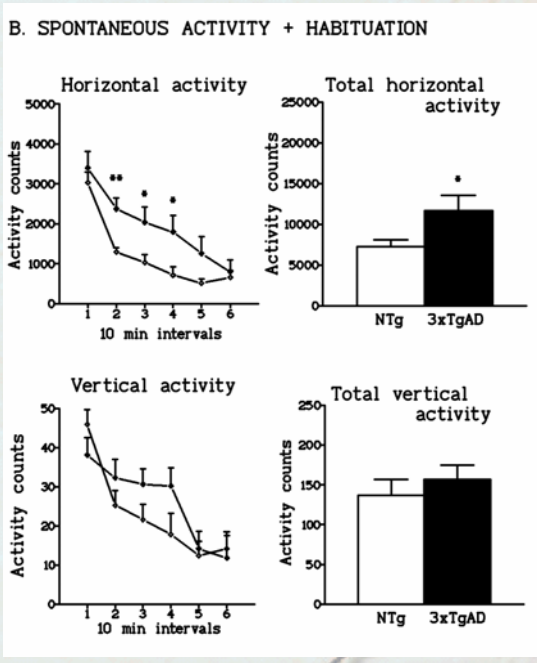




Actimeter cages

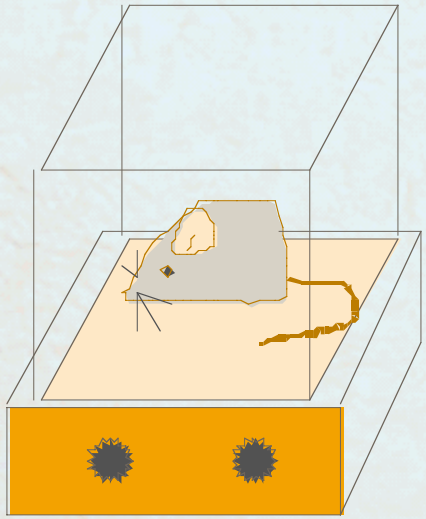
(5 min)

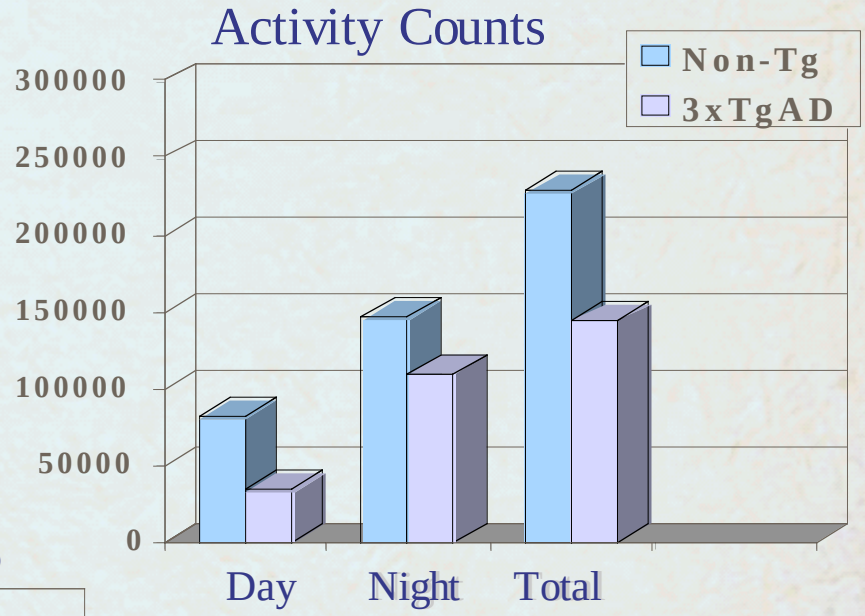


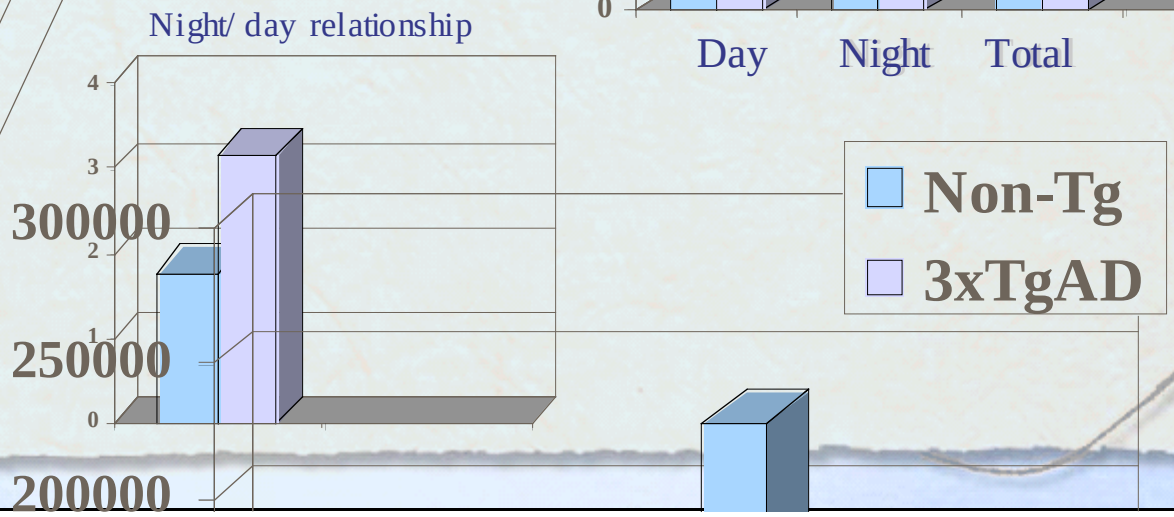


Sundawning-like behavior

***Actimeter* (24h)**



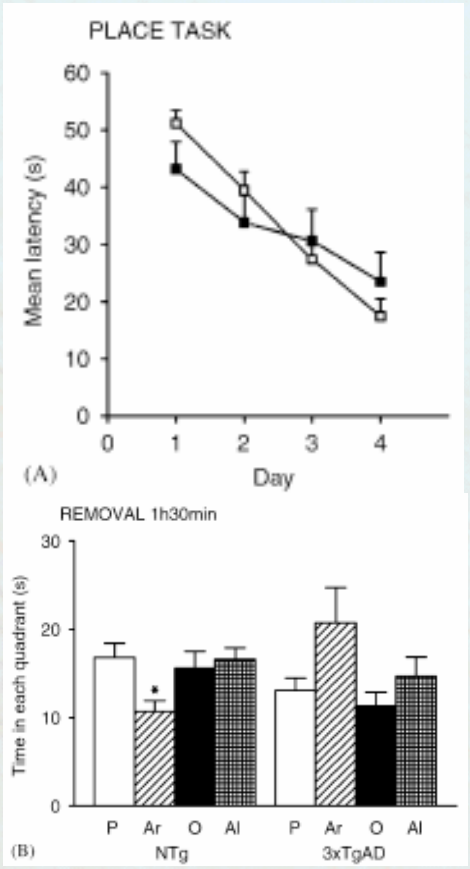




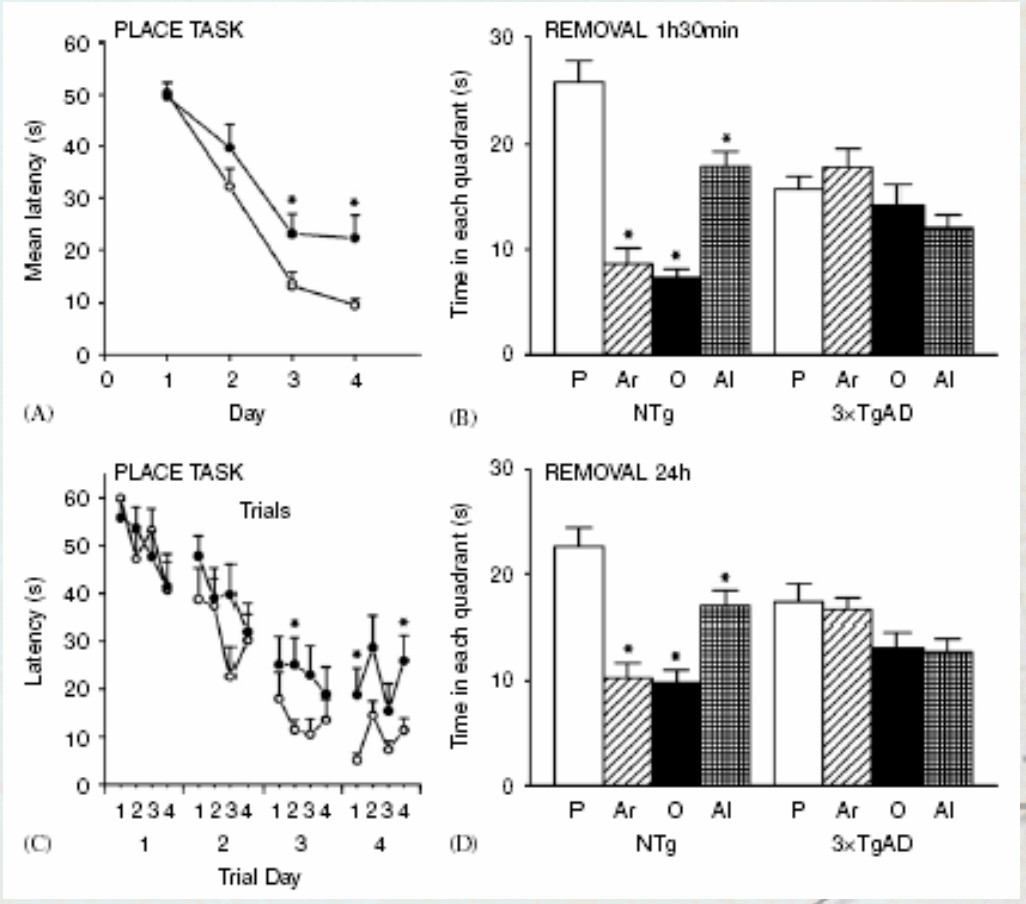
Learning and Memory Deficits

Morris Water Maze

2.5 month old



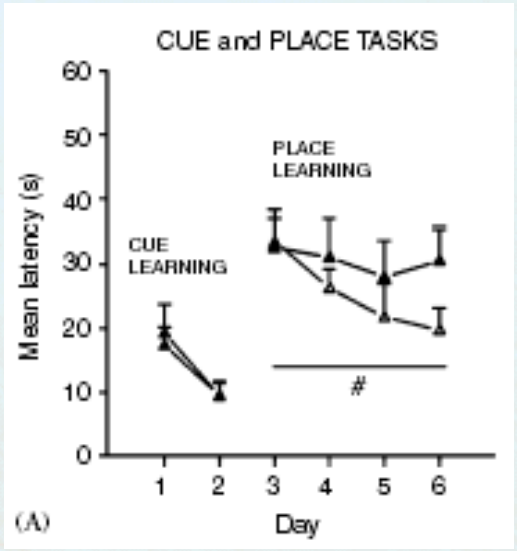
6 month old

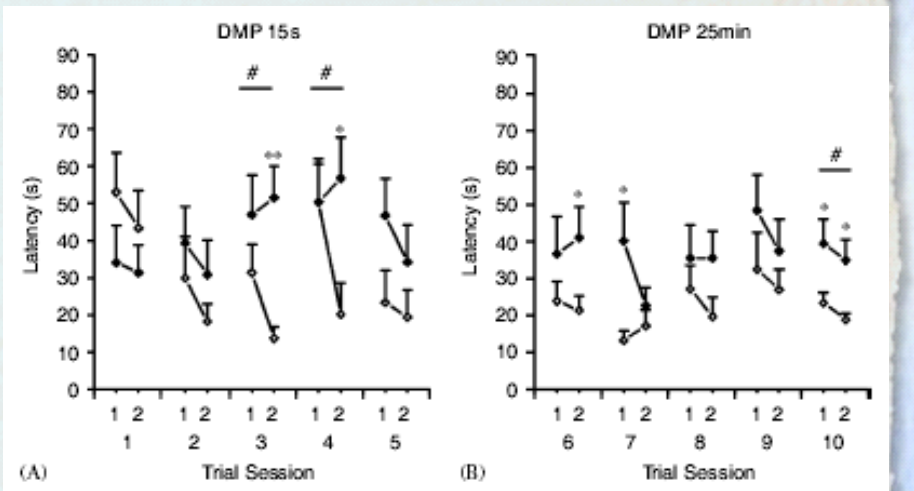


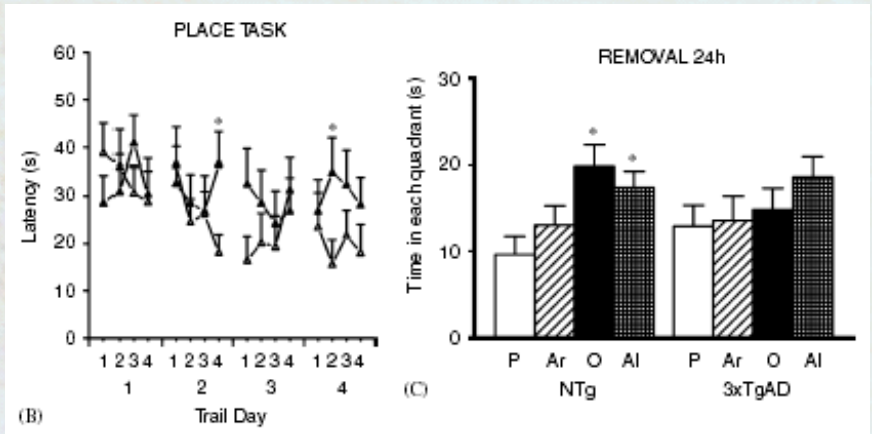
Learning and Memory deficits

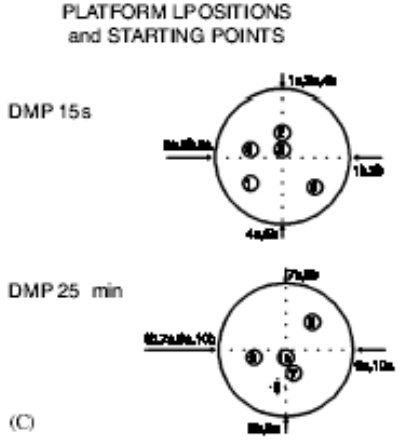
Morris Water Maze

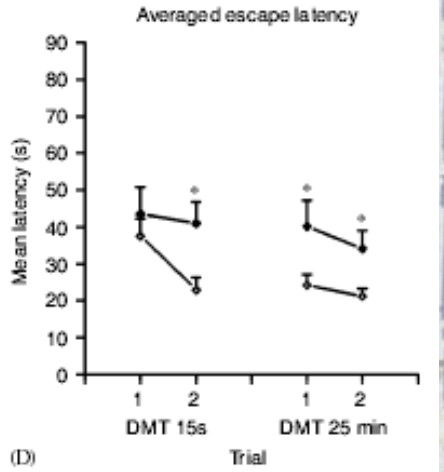
12 month old











Behavioral screening of 3xTgAD mice

	Activity cages	Open-field	Plus-Maze or Corner test	Hole-board	Dark/light box
2.5 month-old	Total horizontal activity Total vertical activity	Total horizontal activity Total vertical activity	PM Entries OA Time in OA	Latency to explore Head-dips	Latency to white area Time in white area
6 month-old	Total horizontal activity Total vertical activity	Total horizontal activity Total vertical activity	PM Entries OA Time in OA	Latency Head-dips	Latency Time in white area
12 month-old	Total horizontal activity Total vertical activity	Total horizontal activity Total vertical activity	CT Number of corners Number of rearings	Latency Head-dips	Latency Time in lit area

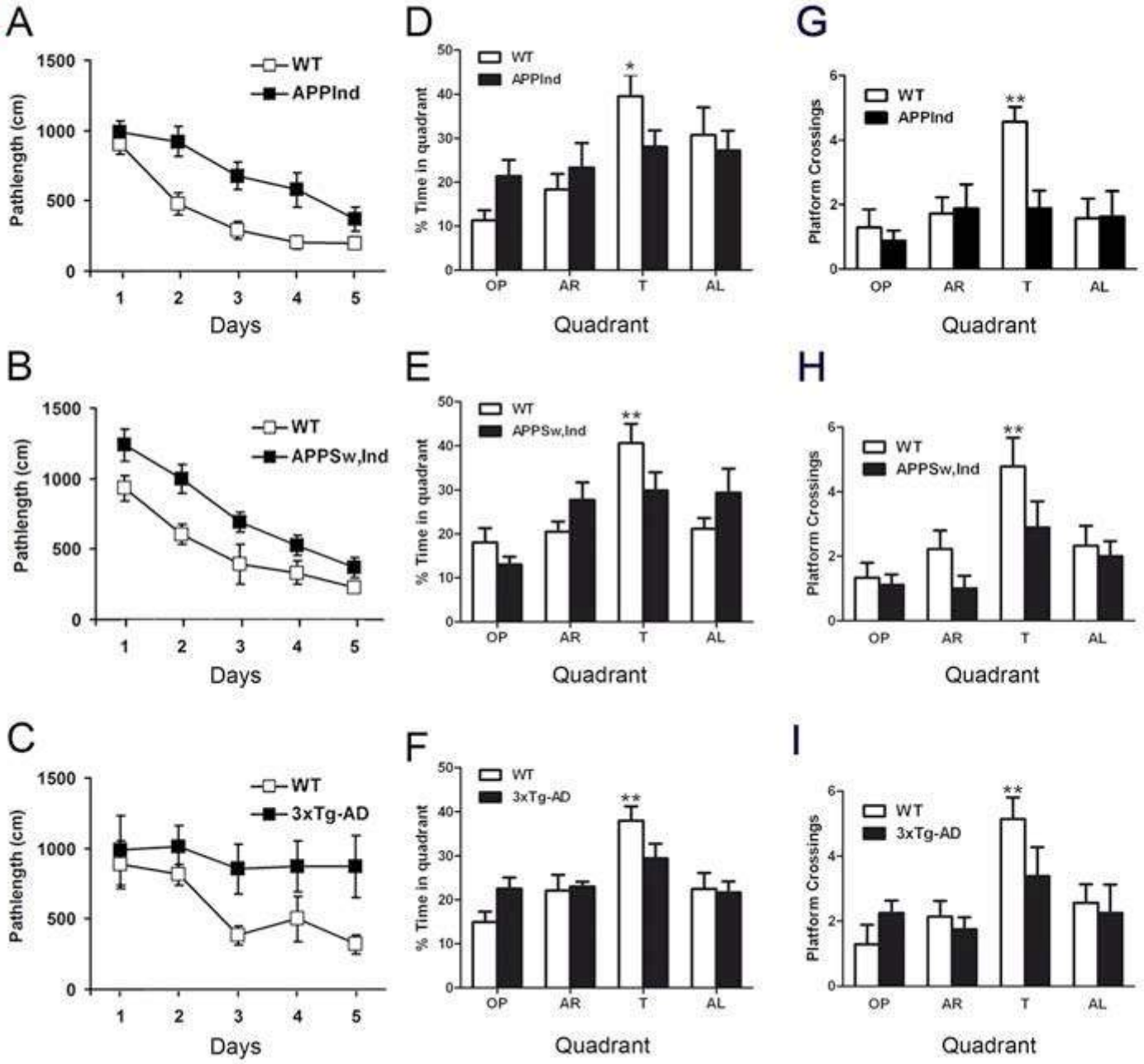
Table 1. Temporal course of behavioral changes observed in males and females of a Spanish colony of 3×Tg-AD versus NTg mice

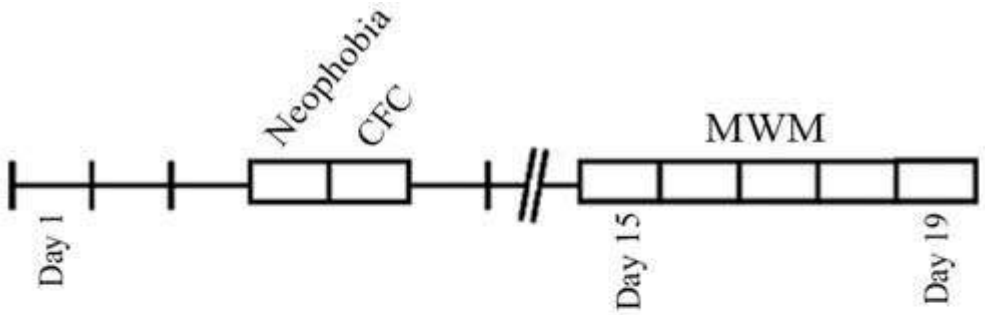
Behavior parameters	Stages of neurodegeneration			
	Onset (2.5 m)	Early stages (4 m)	Moderate stages (6 m)	Advanced stages (12 m or more)
Increased sensorimotor function	n.s.	n.s.	+	++
BPSD-like symptoms				
Emotionality	+	+	++	+++
Neofobia	n.s.	+.	n.s.	+++
Reduced exploration in ansiogenic places	+	++	++	+++
Anxiety-like behaviors	+	++	++	+++
Hyperactivity	n.s.	+	+	++
Desinhibition	n.s.	n.a.	++	n.s.
Impulsivity	n.s.	n.a.	+	+++
Reduced novelty seeking	n.s.	n.a	n.s.	n.a.
Dysfunction of startle response	n.a.	n.a.	+	n.a.
Dysfunction of prepulse inhibition	n.a.	n.a.	+	n.a.
Cognition				
Spatial Working memory deficits	n.s.	n.a.	+	+++
Spatial Short-term memory deficits	n.s.	n.a.	n.s.	+++
Spatial Long-term memory deficits	n.s.	+	++	+++
Instrumental conditioning deficits	n.a.	n.a.	++	n.a.
Alteration Circadian rhythms	n.a.	n.a.	+	+++

Notes: Genotype effects: n.s. non-significant differences. n.a. not assessed in our colony of mice. +, ++, +++ : higher levels in 3×Tg-AD than NTg mice ($P < 0.05$, $P < 0.01$, and $P < 0.001$, respectively). The appearance of AD pathology at different ages: 2.5 months (onset of AD; no neuropathological manifestation); four months (early stages; intracellular Aβ immunoreactivity); six months (moderate stages; extracellular Aβ deposits but still no tau alterations); 15 months (advanced stages; Aβ deposits in many cortical regions and tau hyperphosphorilation). Refs. [30, 60, 63–65].

CORRECTED PROOF

Spatial memory deficits in APP and 3xTg-AD mice





Transgenic mice:

$APP_{Sw,Ind}$

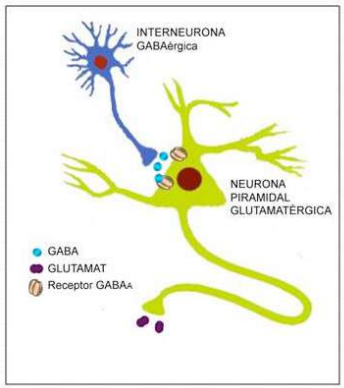
APP_{Ind}

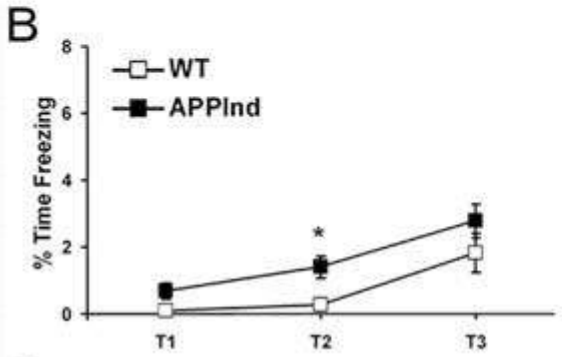
3xTg-AD

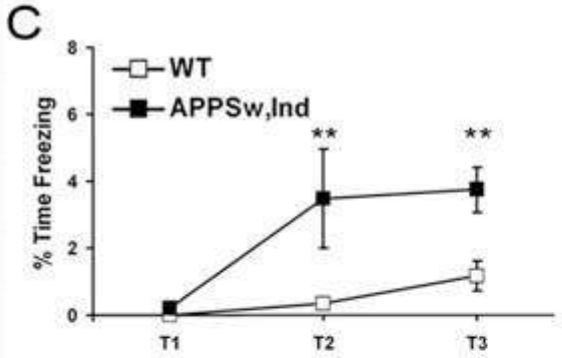
Fear conditioning: context and cued

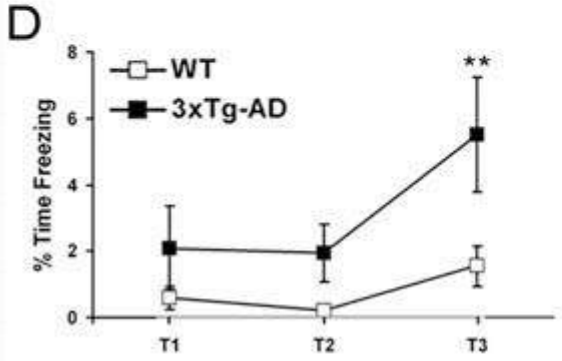


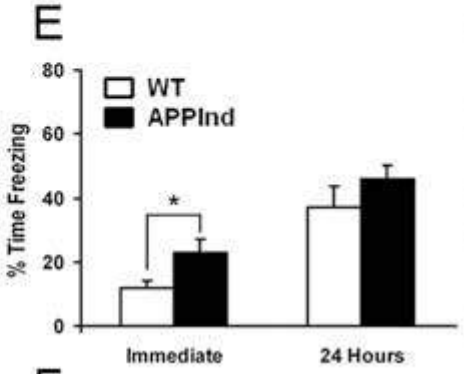
BLA: Basolateral amygdala

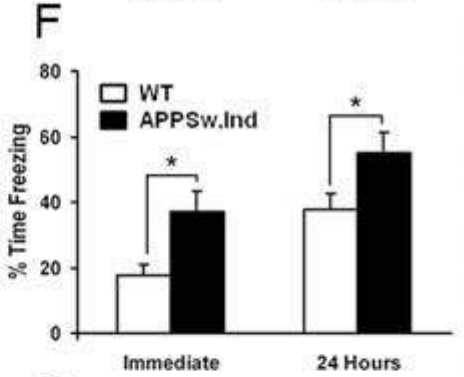


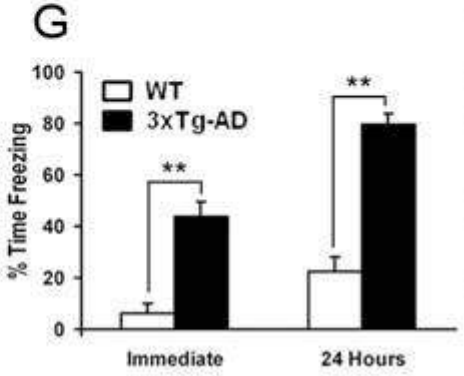




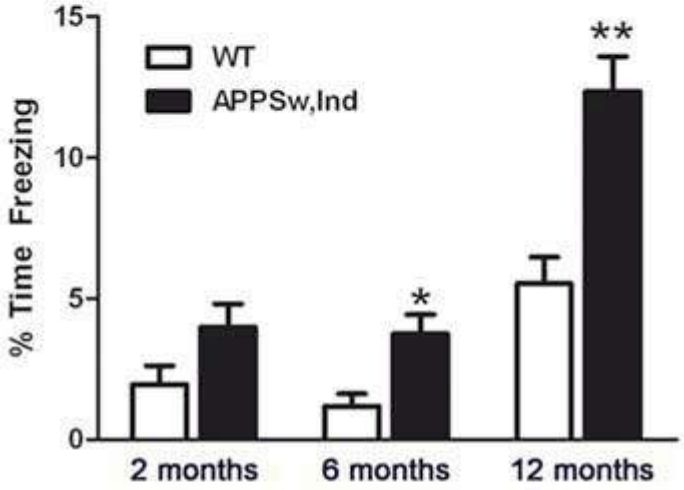


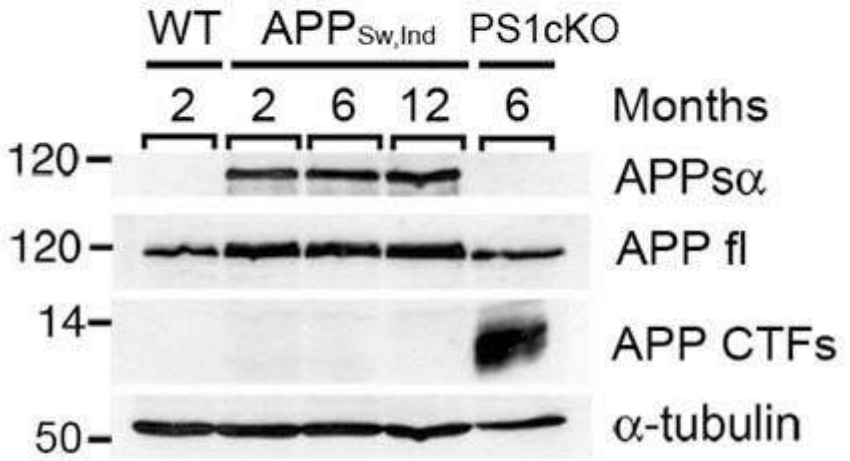


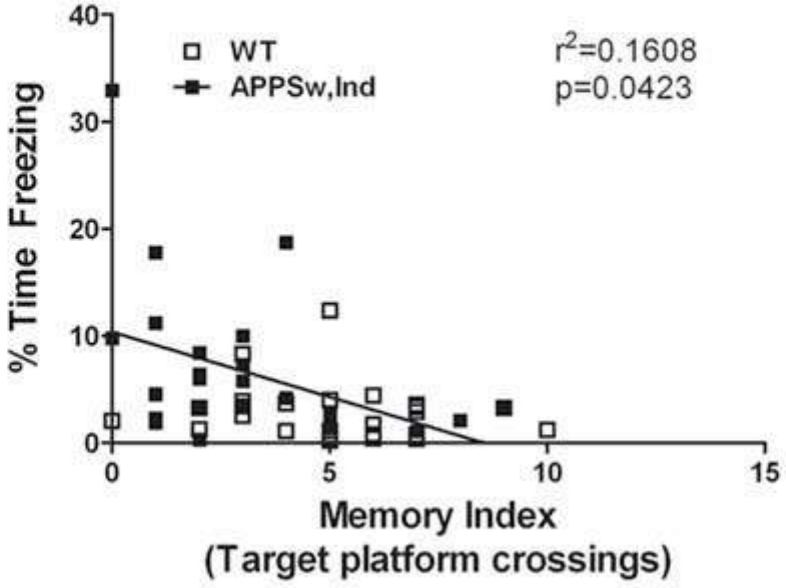




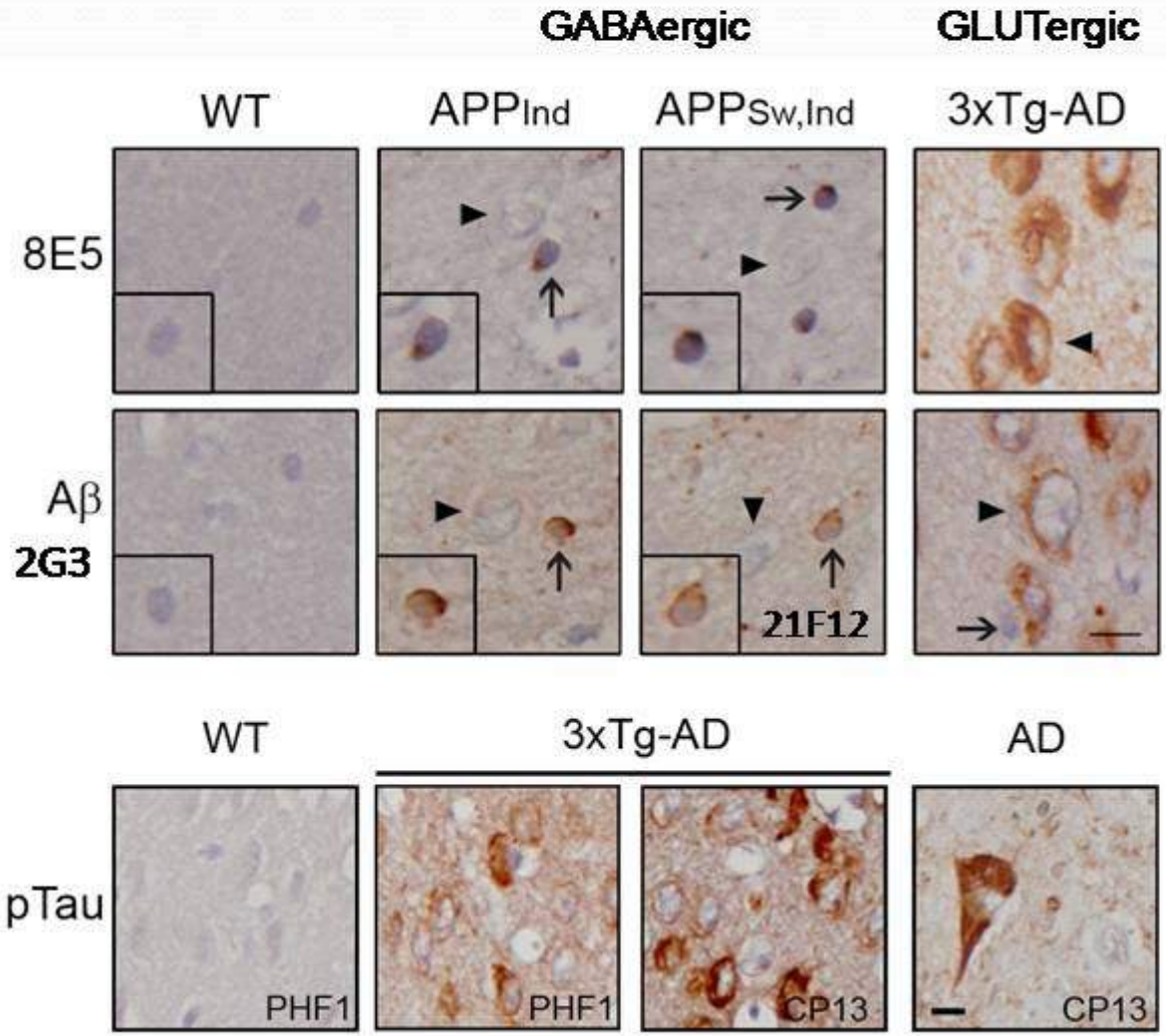
Age-dependent fear symptoms in $APP_{Sw,Ind}$ transgenic mice

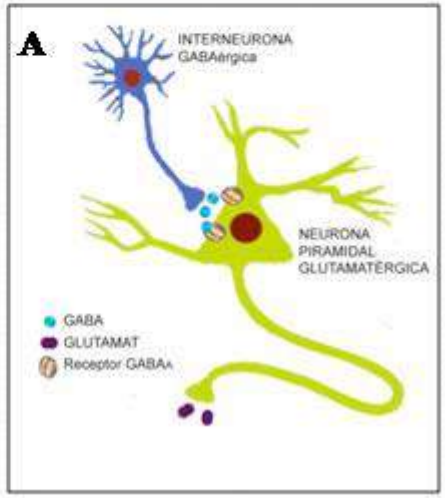


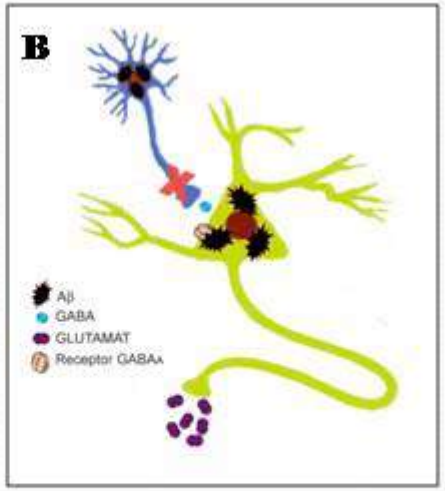




Intraneuronal Aβ accumulation in the basolateral amygdala of AD mice







ARCHIVAL REPORT

Intraneuronal β-Amyloid Accumulation in the Amygdala Enhances Fear and Anxiety in Alzheimer's Disease Transgenic Mice

Judit España, Lydia Giménez-Llort, Jorge Valero, Alfredo Miñano, Alberto Rábano, José Rodriguez-Alvarez, Frank M. LaFerla, and Carlos A. Saura

Background: Alzheimer's disease (AD) is characterized by progressive memory decline and neuropsychiatric symptoms. Despite common emotional symptoms in AD such as anxiety and fear are associated with a more rapid cognitive decline, the pathological mechanisms involved in these behavioral changes remain largely elusive. In this study, we examined the pathological mechanisms of emotional behavior in well-established AD transgenic mice expressing human mutant β-amyloid (Aβ) precursor protein (APP_{Ind} and $APP_{Sw,Ind}$) and tau (3xTg-AD).

Methods: We evaluated unconditioned and conditioned fear-induced freezing behavior and spatial memory in APP_{Ind}, $APP_{Sw,Ind}$, and 3xTg-AD transgenic mice. The Aβ and tau pathologies and signaling pathways involved in emotional processing were studied by immunohistochemistry and immunoblotting analyses.

Results: The APP_{Ind}/$APP_{Sw,Ind}$ and 3xTg-AD transgenic mice displayed at early ages enhanced innate and conditioned fear symptoms and spatial memory deficits coinciding with enhanced accumulation of Aβ in γ-aminobutyric acid (GABA)ergic and glutamatergic neurons, respectively, of the basolateral amygdala (BLA). Similarly, the number of neurons with intraneuronal Aβ40 and Aβ42 was significantly increased in the BLA of human AD brains. Fear responses might reflect an influence of anxiety, because the anxiolytic compounds valproate, diazepam, and buspirone reduced efficiently unconditioned and conditioned fear responses in APP transgenic mice. In addition, phosphorylation of extracellular signal-regulated kinase (ERK)1/2, which is critical for acquisition and consolidation of fear conditioning, was increased in the amygdala of APP transgenic mice after cued conditioning.

Conclusions: We propose a deleterious role of intraneuronal Aβ on amygdala-dependent emotional responses by affecting the extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK) signaling pathway.

0006-3223/09/$36.00
doi:10.1016/j.biopsych.2009.06.015

BIOL PSYCHIATRY 2009;xx:xxx
© 2009 Society of Biological Psychiatry

Behavioral Neuroscience

- ✓ Validation (Guideliness)
- ✓ Screening and validation of the model

  - ❑ Neuroimmunosenescence
  - ❑ White Paper for the Use of Atypical Antypsichotics in AD patients
  - ❑ Metabolic syndrom

Behavioral Neuroscience

- ✓ Validation (Guideliness)
- ✓ Screening and validation of the model

- ✓ Life events + Life style (Non-Pharm)
- ✓ Ethogram + Social behavior
  - ❑ Soledad
  - ❑ Permanent Family Structure
  - ❑ Carmen

Behavioral Neuroscience

- ✓ Validation (Guideliness)
- ✓ Screening and validation of the model

- ✓ Life events + Life style (Non-Pharm)
  - ❑ Early postnatal and Late Handling
  - ❑ Environmental Enrichment
  - ❑ Exercice_ Forced (Treadmill)
  - ❑ Exercice_Voluntary (Wheel)

Behavioral Neuroscience

- ✓ Validation (Guideliness)
- ✓ Screening and validation of the model
- ✓ Life events + Life style (Non-Pharm)
- ✓ External actions (Pharmacol, Molecular)
  - ❑ Huprine X, Huperzina A, Dine 3
  - ❑ Memantine ± Mynocycline
  - ❑ New Marine drugs
  - ❑ 5HT4
  - ❑ sc-Fv-h3D6

Neuroimmunomodulation

Models of Aging of NeuroImmunomodulation: Strategies for Its Improvement

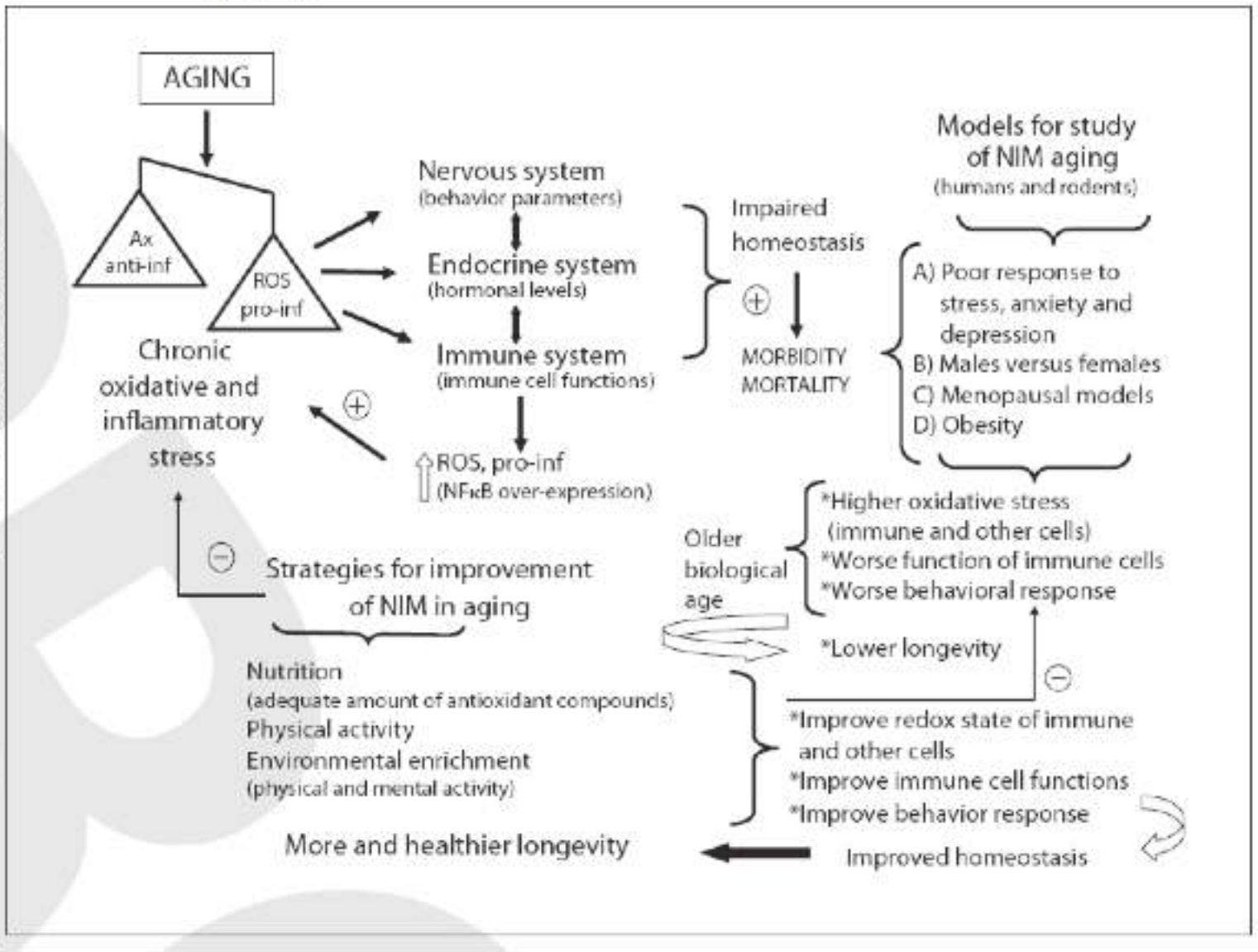
PROOF Copy for personal use only

Monica Del Fierro[a] · Lydia Giménez-Llort[b]

Key Words

Abstract

KARGER



NeuroImmunoModulation

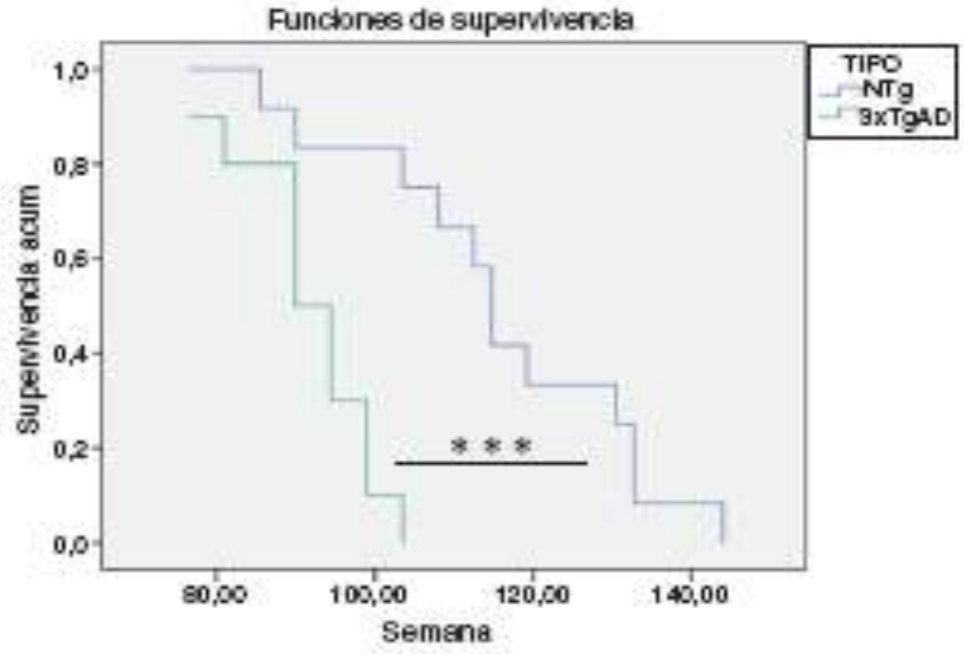
Neuroimmunomodulation 2008;15:331–343
DOI: 10.1159/000156475

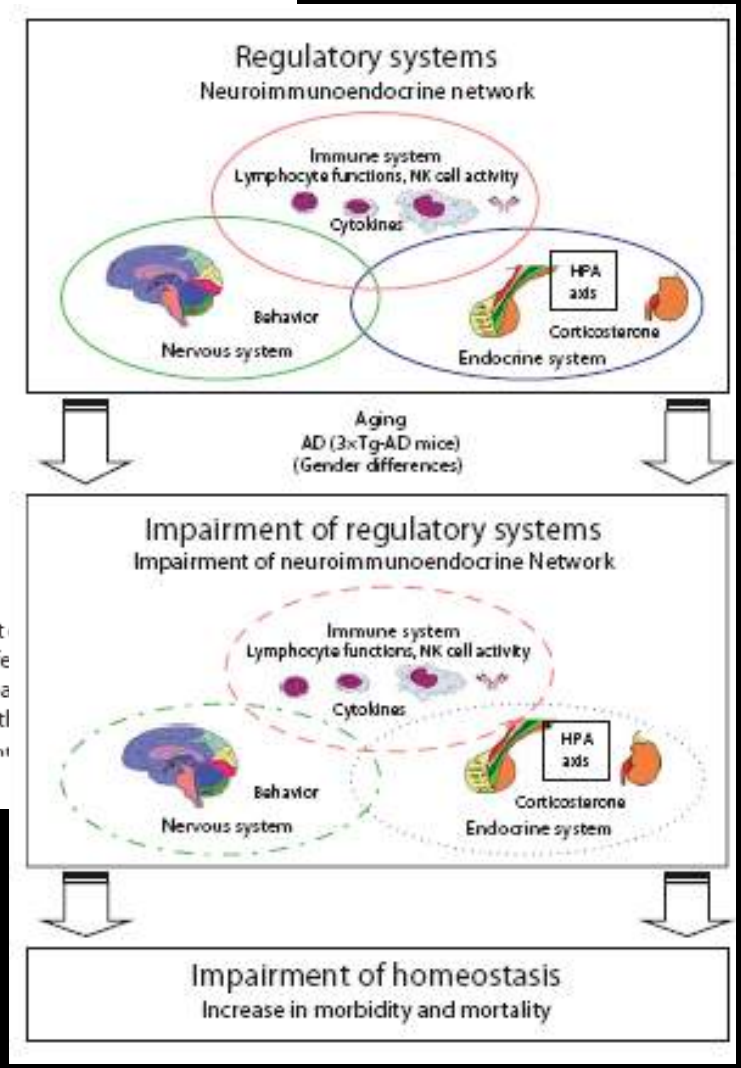
Published online: November 26, 2008

Gender-Specific Neuroimmunoendocrine Aging in a Triple-Transgenic 3×Tg-AD Mouse Model for Alzheimer's Disease and Its Relation with Longevity

Lydia Giménez-Llort[a] Lorena Arranz[b] Ianire Maté[b] Mónica De la Fuente[b]

[a]Department of Psychiatry and Forensic Medicine, Institute of Neuroscience, Autonomous University of Barcelona, Bellaterra, and [b]Department of Physiology (Animal Physiology II), Faculty of Biology, Complutense University of Madrid, Madrid, Spain





Neuroimmunomodulation

DOI: 10.1159/000158475

Gender-Specific Neuroimmunoendocrine Aging in a Triple-Transgenic 3×Tg-AD Mouse Model for Alzheimer's Disease and Its Relation with Longevity

Lydia Giménez-Llort[a] Lorena Arranz[b] Ianire Maté[b] Mónica De la Fuente[b]

[a]Department of Psychiatry and Forensic Medicine, Institute of Neuroscience, Autonomous University of Barcelona, Bellaterra, and [b]Department of Physiology (Animal Physiology II), Faculty of Biology, Complutense University of Madrid, Madrid, Spain

© Free Author Copy – for personal use only

ANY DISTRIBUTION OF THIS ARTICLE WITHOUT WRITTEN CONSENT FROM S. KARGER AG, BASEL IS A VIOLATION OF THE COPYRIGHT

Written permission to distribute the PDF will be granted against payment of a permission fee, which is based on the number of accesses required. Please contact permission@karger.ch

Key Words
Immunosenescence · Triple-transgenic · 3×Tg-AD mice · Leucocytes · Chemotaxis · Lymphoproliferation · Stress · Anxiety · Behavioral and psychological symptoms of dementia

Abstract
In the present work, we briefly review the evidence on the key role played by the neuroimmunoendocrine network in the etiopathogenesis of Alzheimer's disease (AD) and provide new behavioral, immune and endocrinological data obtained on old male and female triple-transgenic 3×Tg-AD mice harboring $PS1_{M146V}$, APP_{SWE} and tau_{P301L} transgenes in contrast to wild type animals. The results indicate that several aspects of the impairment of the neuroimmunoendocrine network that occurs with aging are more evident in the 3×Tg-AD mice, especially in males. This supports the hypothesis of a premature immunosenescence as a pathogenetically relevant factor in AD which was found to be enhanced in the 3×Tg-AD males, suggesting that this could also be responsible for the increased morbidity and mortality of these subjects. Therefore, future research on strategies that could improve the immune system and the other regulatory systems, such as the nervous and the endocrine system, as well as their communication, could have preventive and/or therapeutical effects on that disease. The results also show the relevance of gender differences that should be taken into consideration in both basic and clinical research for assessing new strategies for the control of AD.

Copyright © 2006 S. Karger AG, Basel

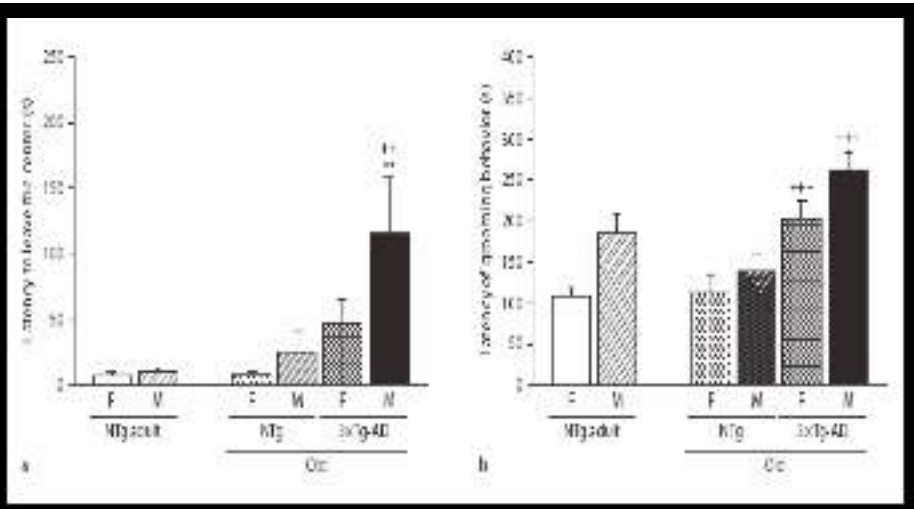
Introduction

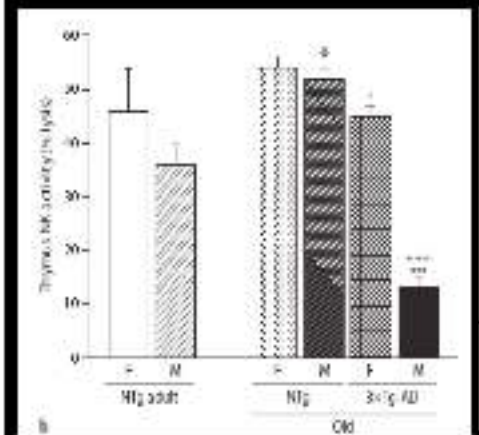
The neurobiology of aging has been one of the most rapidly expanding areas of scientific endeavor over the past 2 decades. Most efforts have been focused on understanding the neuronal mechanisms underlying age-related neurodegenerative disorders, whose prevalence in the elderly is dramatically increasing in parallel to that of life expectancy and social aging. This is the case for Alzheimer's disease (AD), the most common neurodegenerative disorder and cause of senile dementia with complex neuropsychiatric symptoms, and the target of a large and important body of clinical and basic research. The main pathological hallmarks of AD are the aberrant protein aggregates, amyloid plaques, comprising the amyloid β (Aβ) peptide, and neurofibrillary tangles that consist of hyperphosphorylated tau protein. Other neurodegenerative changes include progressive neuronal and synaptic dysfunction and, eventually, cell death [1–3]. Upregula-

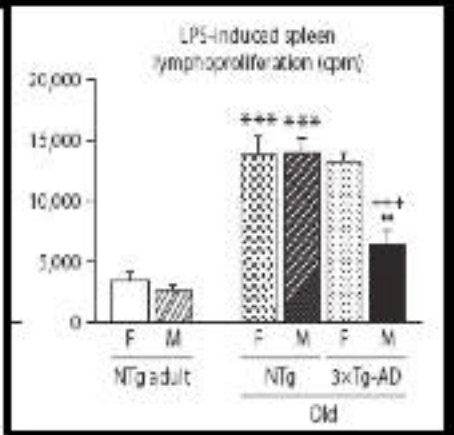
KARGER

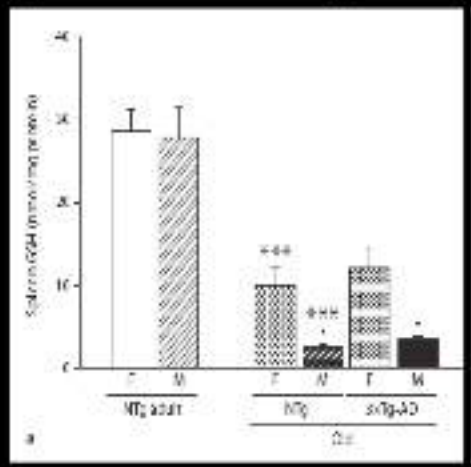
© 2006 S. Karger AG, Basel
0251–7906/06/0–0000$21.50/0

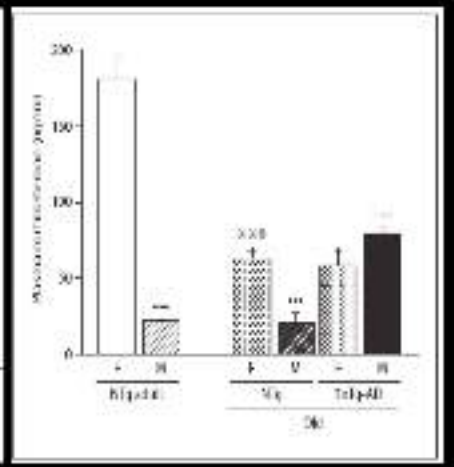
Lydia Giménez-Llort
Department of Psychiatry and Forensic Medicine
Institute of Neuroscience, Autonomous University of Barcelona
E-08193 Bellaterra (Barcelona), Spain
Tel. +34 93 581 2214, Fax +34 93 581 1484, E-Mail lidia.gimenez@uab.cat











Crosstalk between Behavior and Immune System in AD

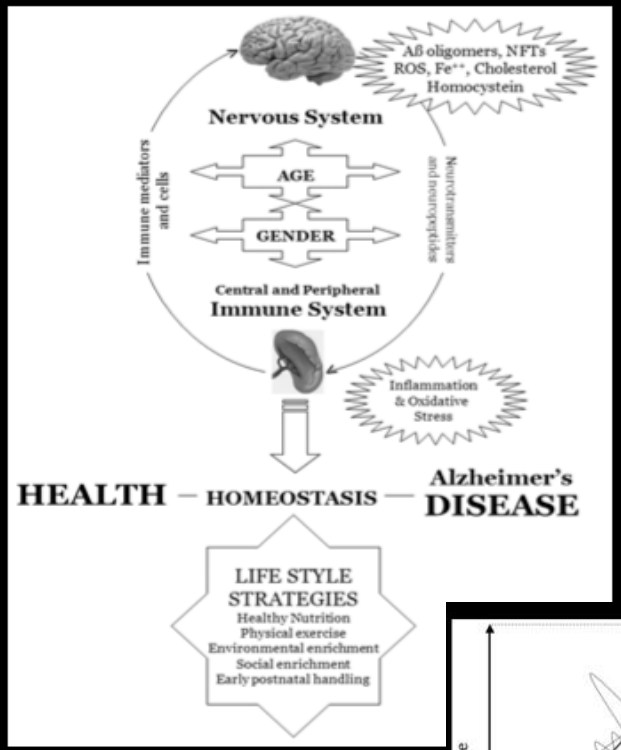
Giménez-Llort et al., Current Pharmaceutical Design, 2014

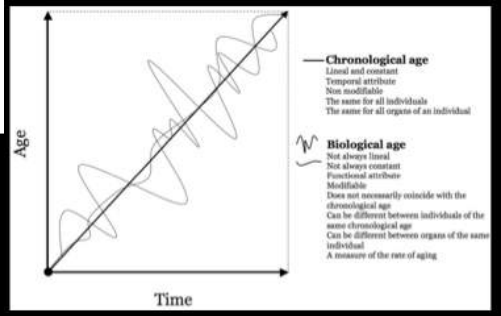

aptara

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

Peripheral immune system and neuroimmune communication impairment in a mouse model of Alzheimer's disease

Lycia Giménez-Llort,[1] Isaure Maté,[2] Rashed Manassra,[2] Carmen Vida,[2] and Mónica De la Fuente[2]





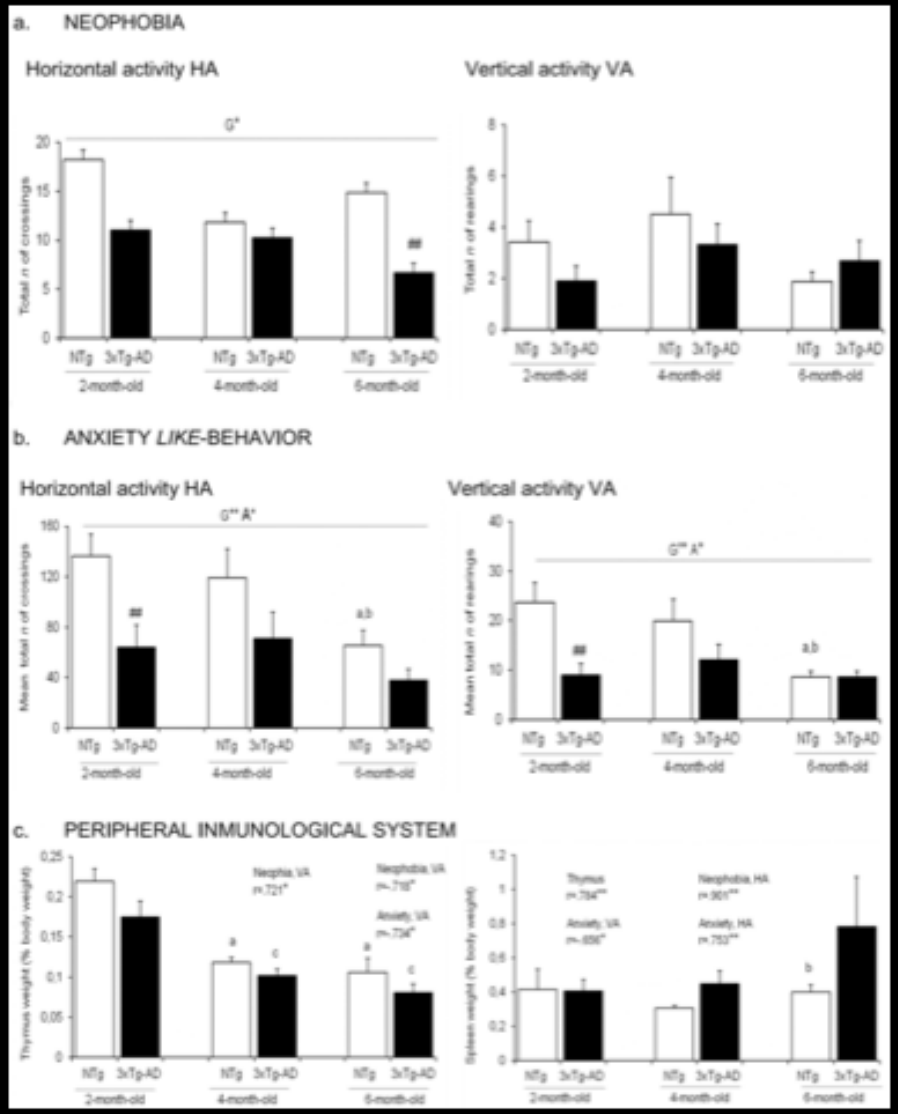
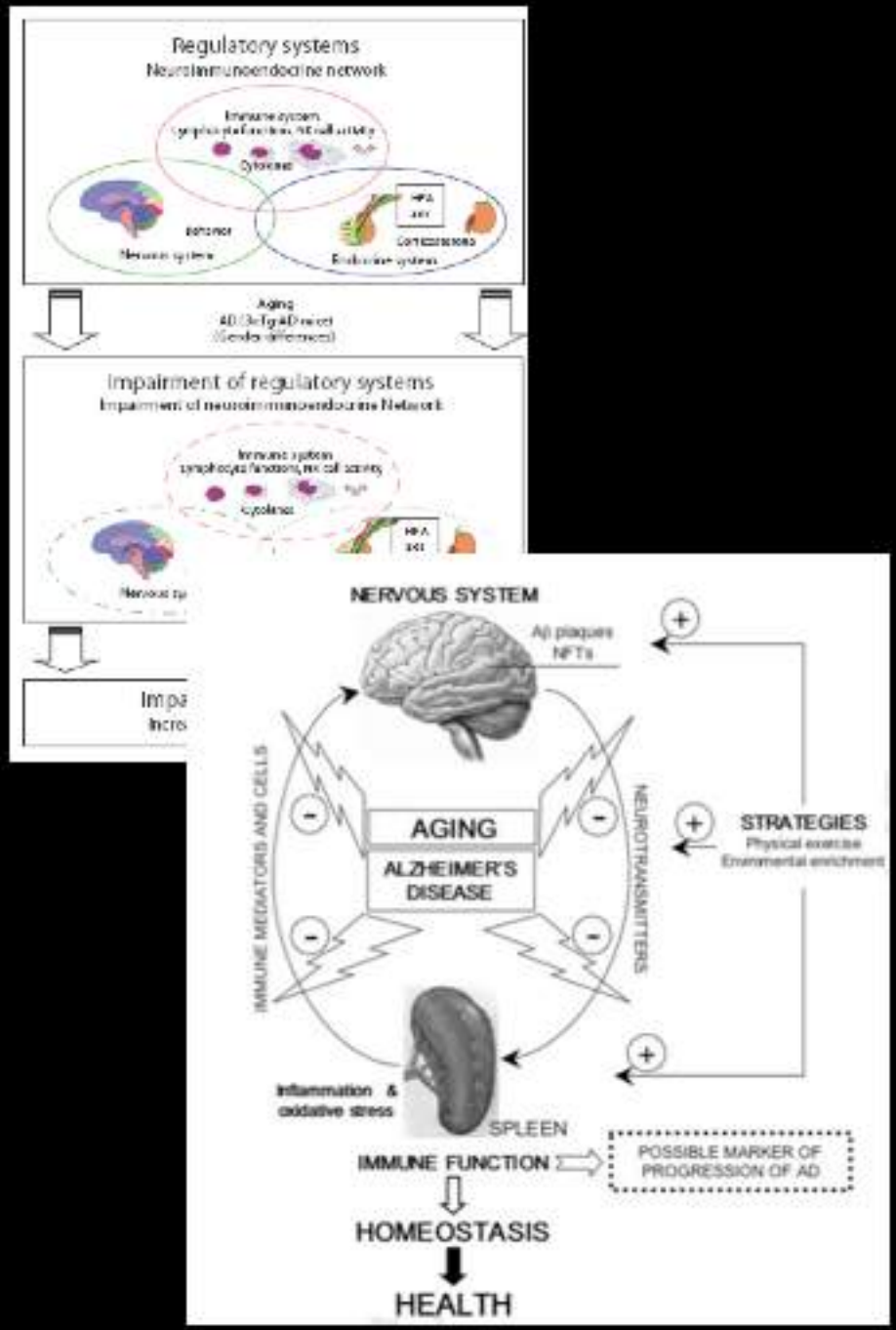


Table 2. Several functional parameters in immune cells from young to old 3×Tg-AD versus NTg female mice

	3×Tg-AD vs. NTg			
Parameters (function)	2.5 months	4 months	9 months	15 months
Chemotaxis	=	↓↓↓	↓↓↓	↑↑↑
Proliferation	=	↓↓	↓↓	=
NK	=	↓	=(↓)	=
IL-2 secretion	n.a.	↓	=(↓)	↑

Table 3. Oxidative stress parameters (antioxidants and oxidants) in the spleen of young and adult 3×Tg-AD versus NTg mice

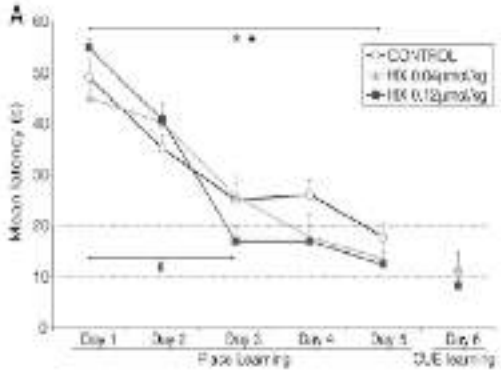
Parameters	3×Tg-AD vs. NTg
Antioxidant	
TG	↓↓↓
GPx	↓↓
GR	↓
Oxidant	
XO	↑↑

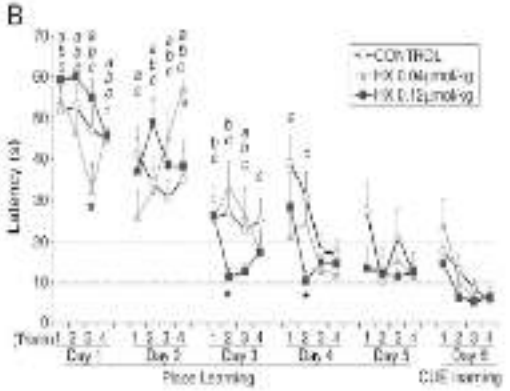


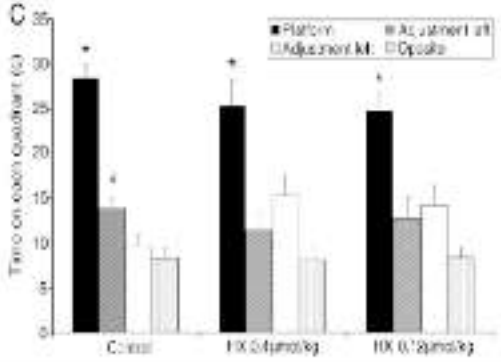


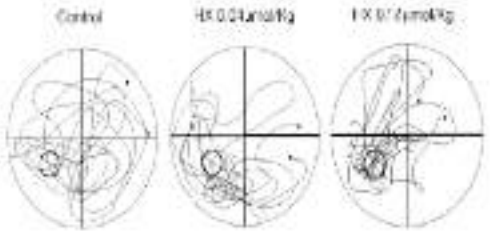
Pharmacology, Biochemistry and Behavior

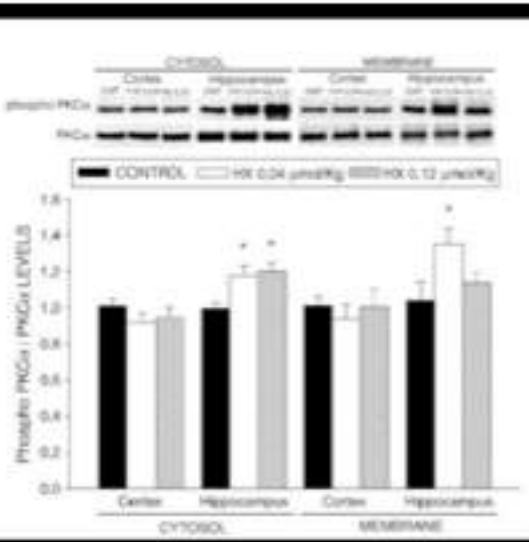
Behavioural effects and regulation of PKCα and MAPK by hyperforin in rodents and mice

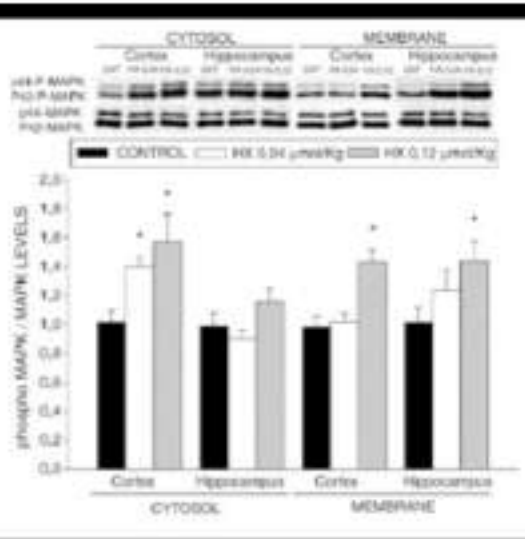












Original Paper

Neuro-degenerative Diseases

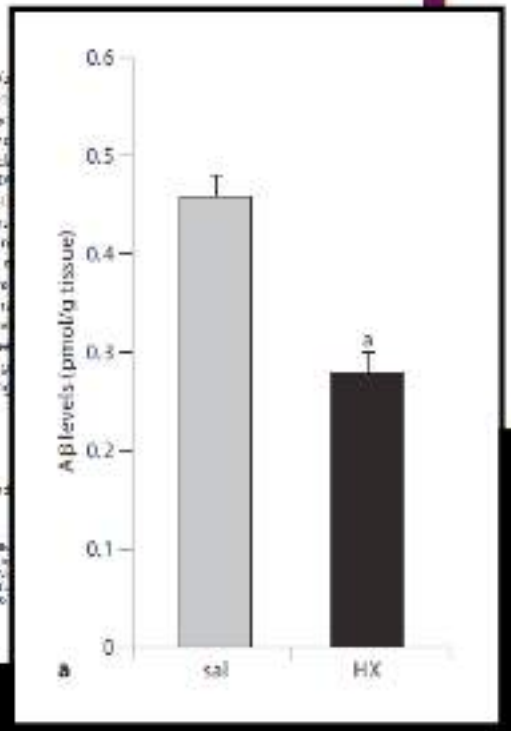
Effect of Huprine X on β-Amyloid, Synaptophysin and α7 Neuronal Nicotinic Acetylcholine Receptors in the Brain of 3xTg-AD and APPswe Transgenic Mice

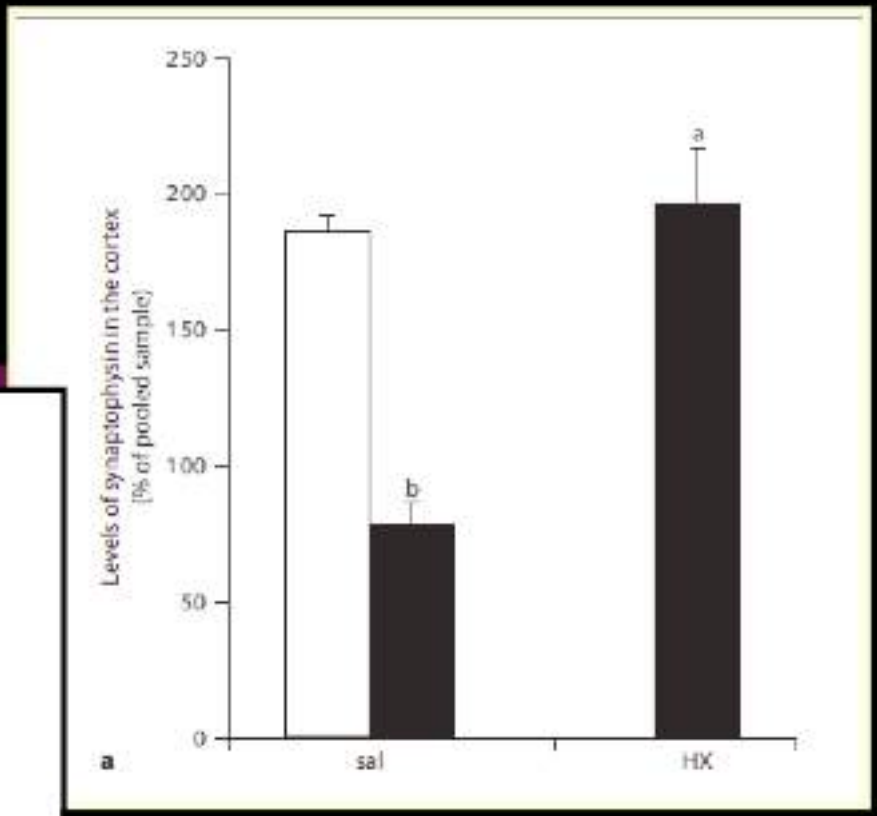
Monika M. Haedberg[a] M. Victoria Cos[b] Miriam Ratia[b] Daniel Gonzalez[a]
Christina Unger Lithner[a] Pelayo Camps[b] Diego Muñoz-Torrero[b] Albert Badia[b]
Lydie Giménez-Llort[c] Agneta Nordberg[a]

Key Words
Acetylcholinesterase inhibitor · β-Amyloid · Alzheimer's disease · Nicotinic acetylcholine receptors · Transgenic mice

Abstract
Background: Several studies implicate acetylcholinesterase (AChE) in the pathogenesis of Alzheimer's disease (AD), raising the question of whether inhibition of AChE also might have a disease-modifying action. Huprine X (HX), a reversible AChE inhibitor hybrid of tacrine and huperzine A, was shown to affect the amyloidogenic processing in vitro. In this study the aim was to investigate whether HX could affect the AD-related neuropathology in vivo in two mouse models. **Methods:** Tg2576 (K670M/N671L) APPswe and 3xTg-AD (K670M/N671L, P301M/4R, M146V) PS1KI mice were treated with HX (0.12 μmol/kg, i.p., 21 days) at ages of 6–7 months. Human β-amyloid (Aβ) was measured by ELISA, synaptophysin by Western blot and α7 nicotinic acetylcholine receptors (nAChRs) were analyzed by [^{125}I]α-bungarotoxin autoradiography. **Results:** Treatment with HX reduced insoluble

KARGER



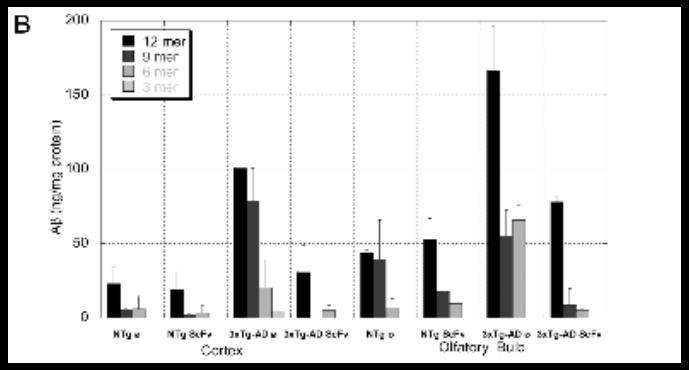


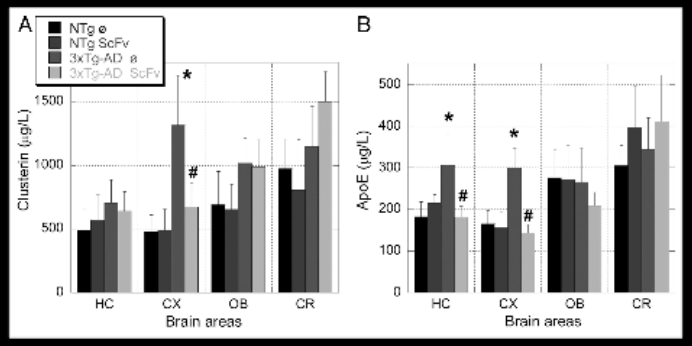
ScFv-h3D6 IMPROVES COGNITION AND MODIFIES THE Aβ-PEPTIDE AGGREGATION PATHWAY IN 3xTg-AD MOUSE MODEL OF ALZHEIMER'S DISEASE

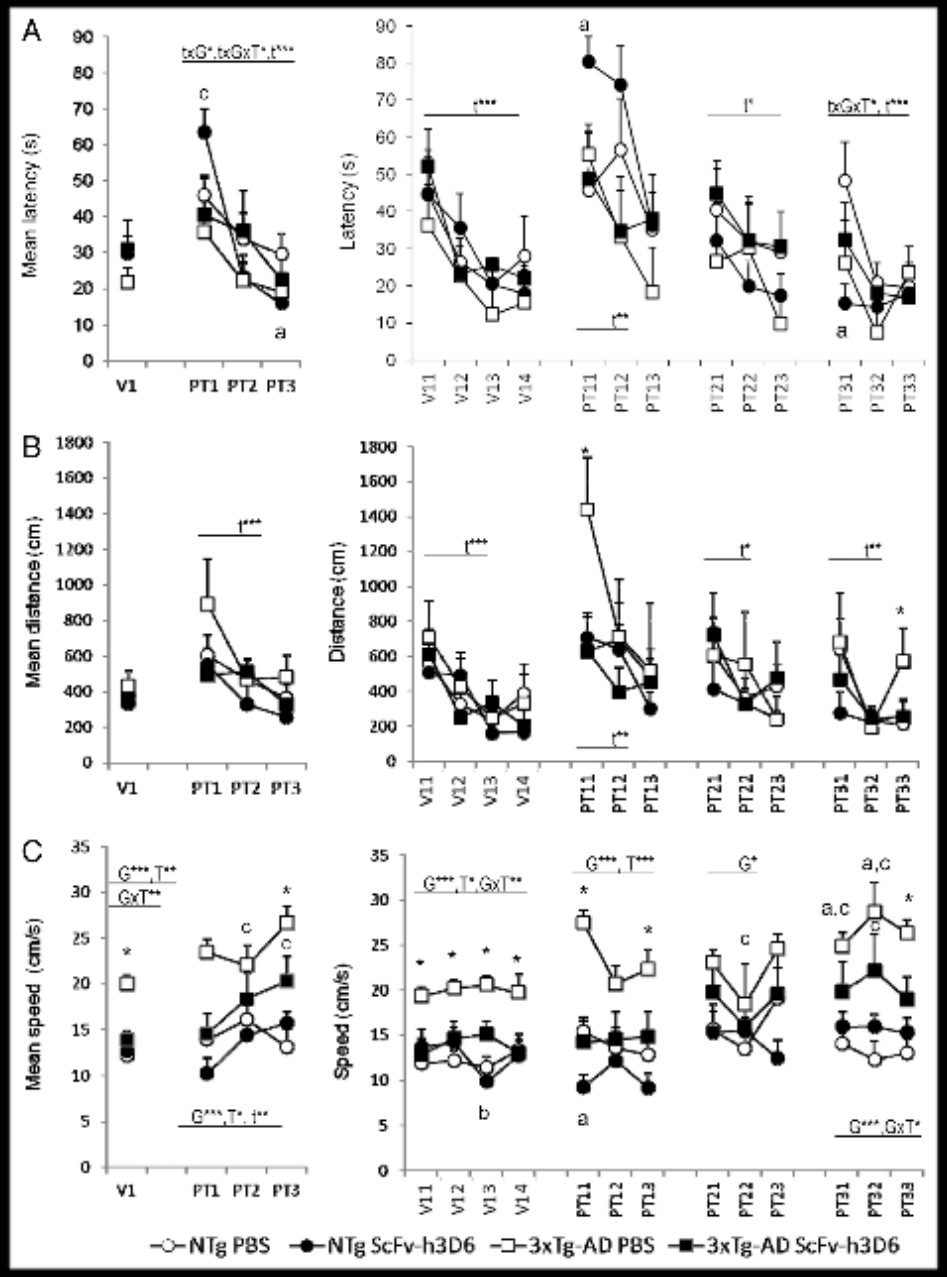
Giménez-Llort et al., mAbs 5:5, 1-13, 2013

single-chain variable fragment scFv-h3D6, which has been shown to be capable of avoiding the *in vitro* toxicity induced by the Aβ peptide in neuroblastoma cell-cultures by withdrawing Aβ oligomers from the amyloid pathway

Villegas, UAB







Biological bases of environmental stimulation in NDD

Handling (PND1 -PND21)



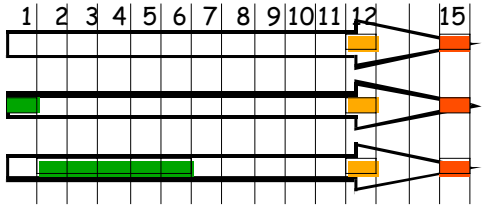
Enrichment (PND21 -6m)



Strategies

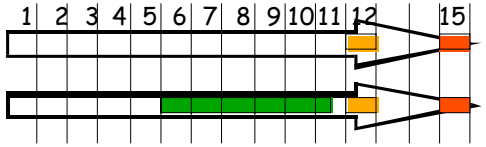
Preventive

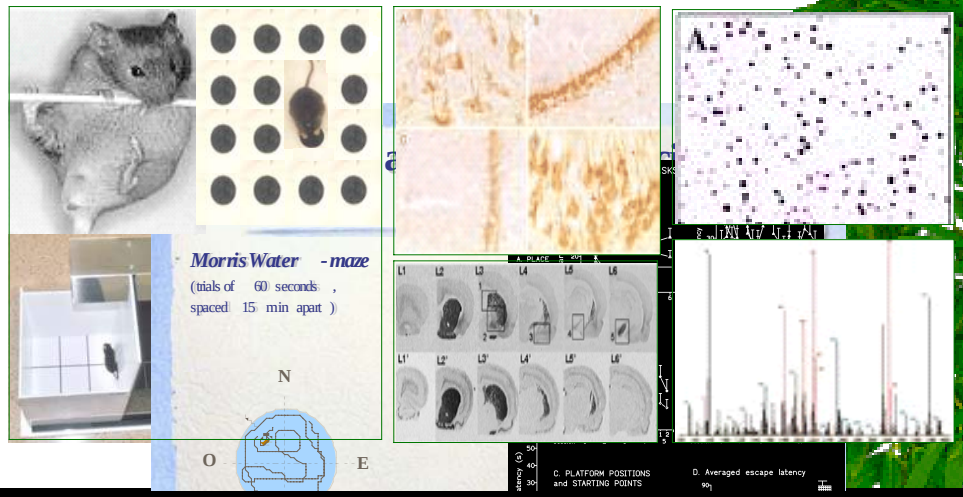
Control
Handling
EE



Therapeutical

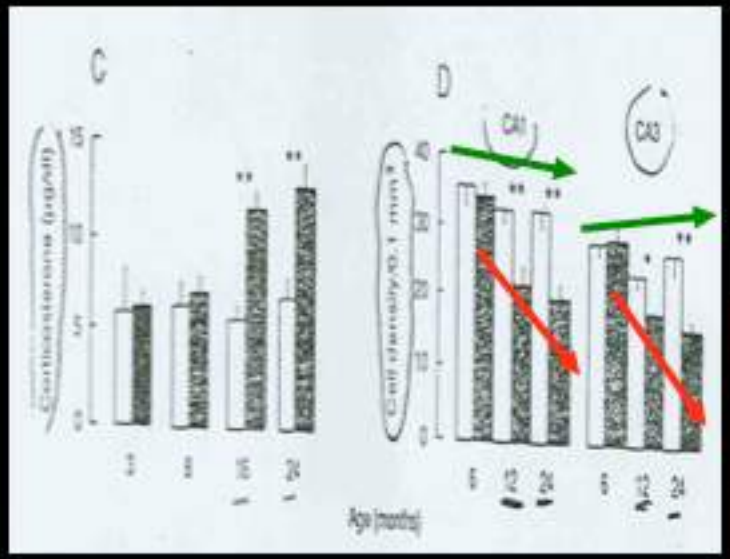
Control
EE





Handling (PND1-PND21)





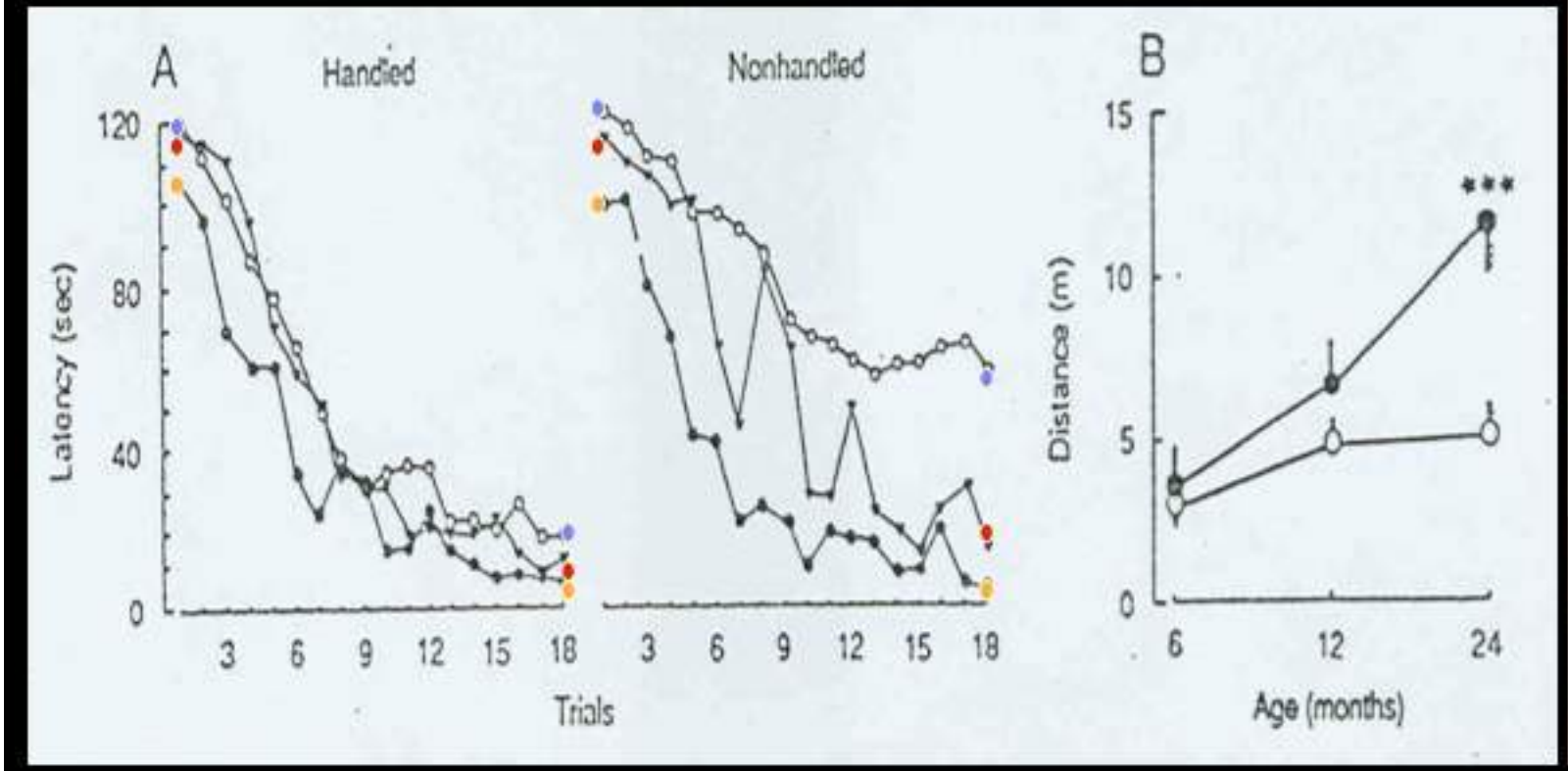










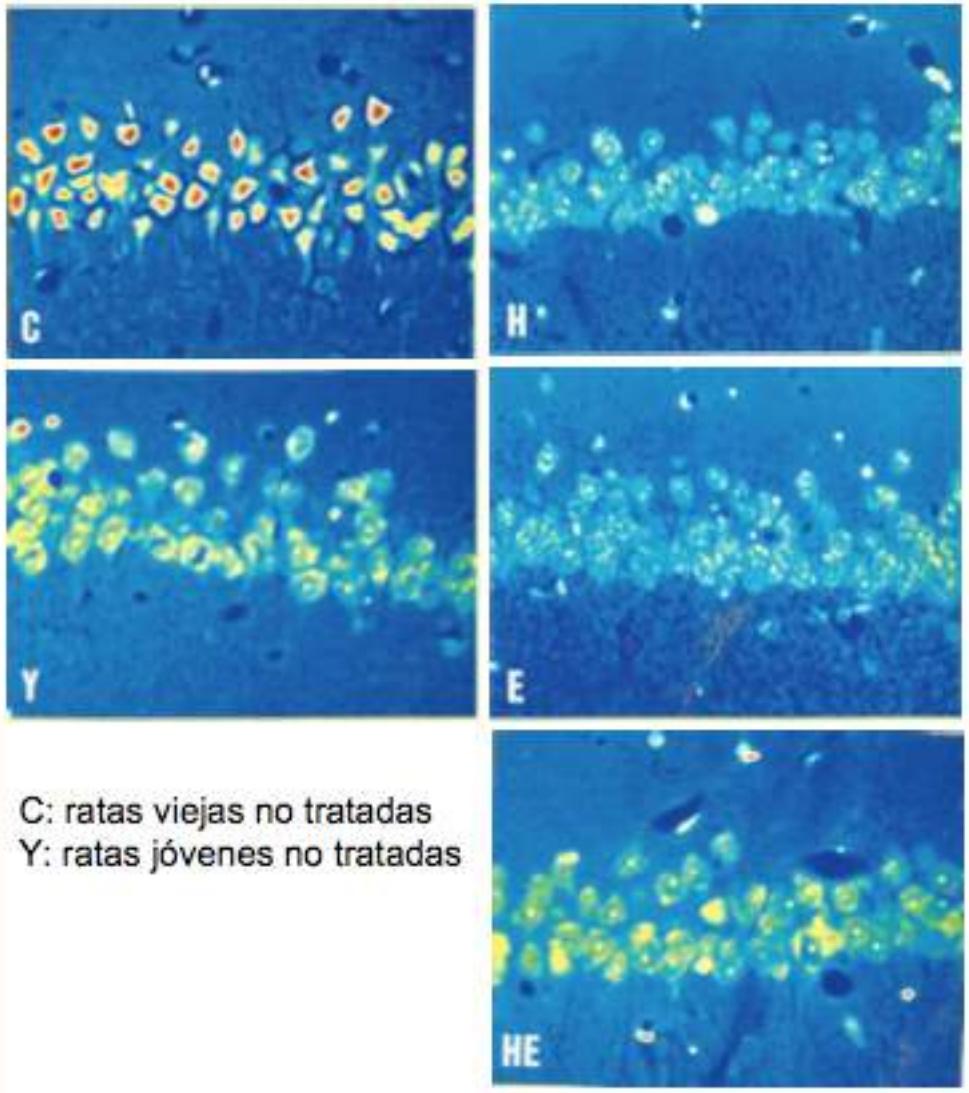




Enriquecimiento (PND21-6m)



Efectos de los tratamientos de handling (H), enriquecimiento ambiental (E) y su combinación (HE) en la morfología neuronal de la región CA1 en ratas RLA

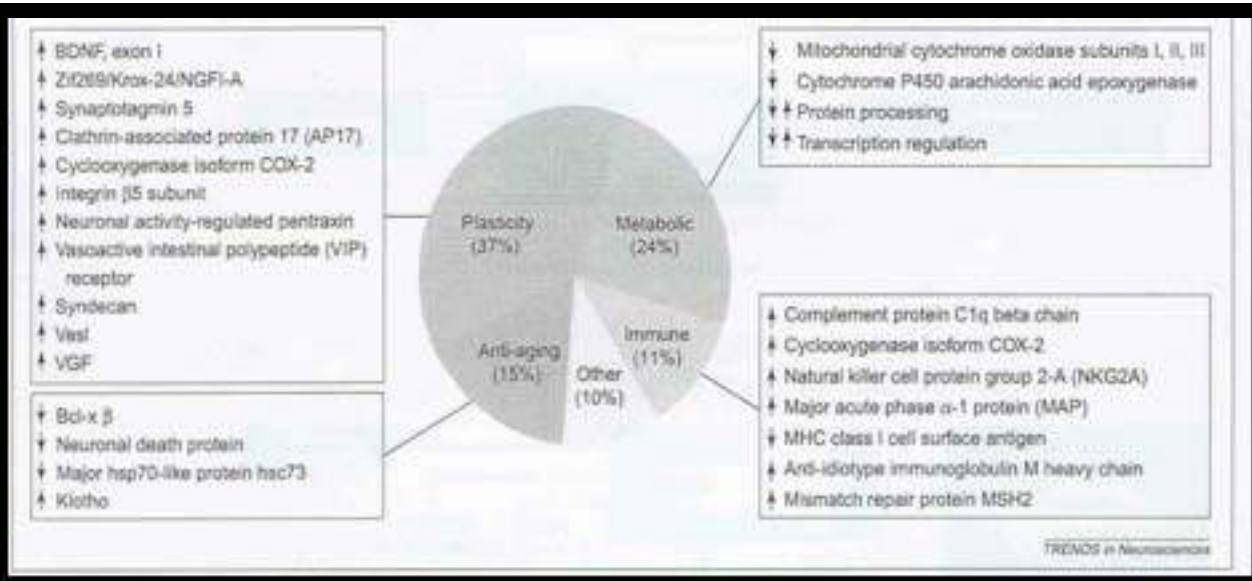


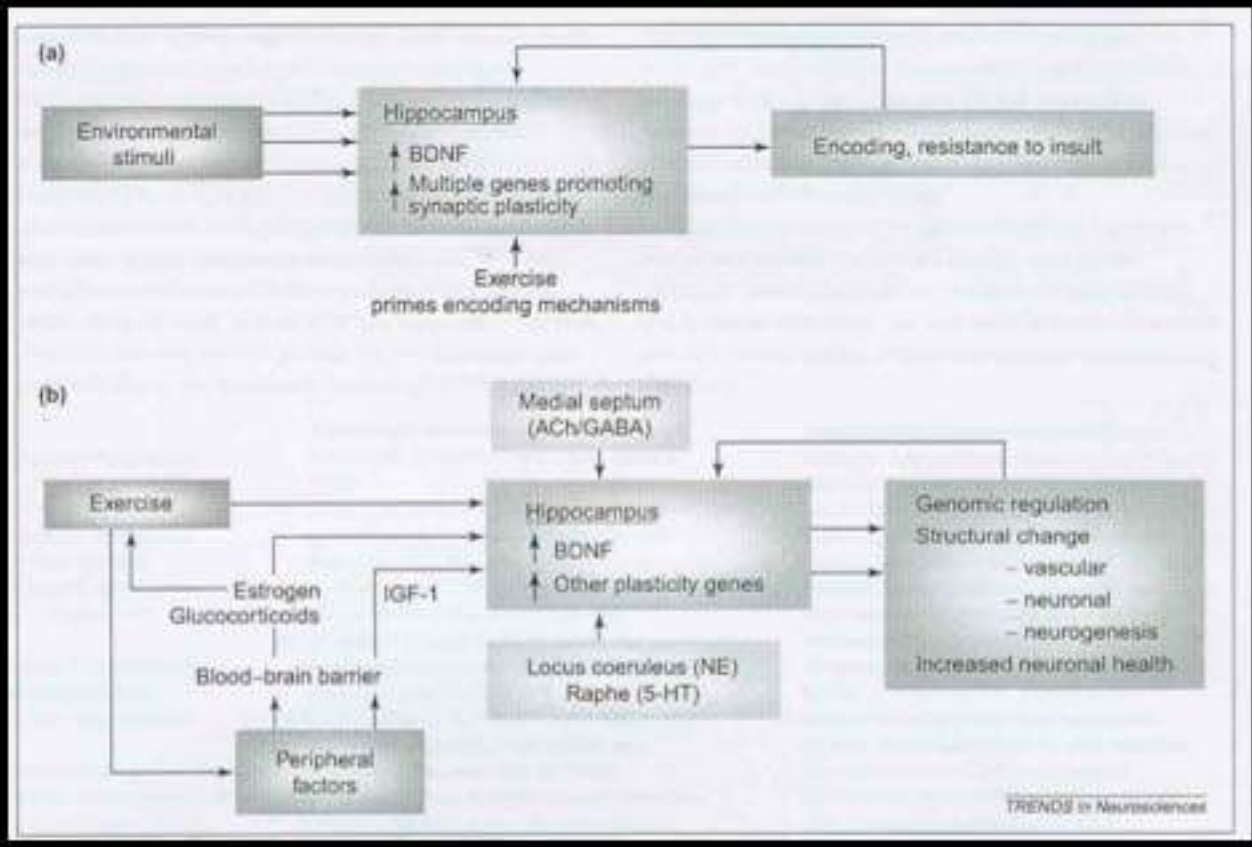
C: ratas viejas no tratadas
Y: ratas jóvenes no tratadas

Fernández-Teruel et al., Behav. Genetics, 1997

Enriquecimiento (PND21-6m)







Effect of Environmental Enrichment on the Immunoendocrine Aging of Male and Female Triple-Transgenic 3xTg-AD Mice for Alzheimer's Disease

Lorena Arranz*, Nuria M. De Castro*, Isabel Baeza*, Lydia Giménez-Llort* and Mónica De la Fuente*
*Department of Physiology (Animal Physiology II), Faculty of Biology, Complutense University of Madrid (UCM), Madrid, Spain

Table 1
Effect of environmental enrichment on the mortality ratio in 3xTgAD mice from early (6 month-old) to advanced (15 month-old) stages of the disease

	NTg		3xTgAD	
Control	Male ($n=9$)	0%	Male ($n=9$)	33%
	Female ($n=10$)	0%	Female ($n=10$)	10%
Environmental enrichment	Male ($n=8$)	0%	Male ($n=11$)	45%
	Female ($n=12$)	0%	Female ($n=9$)	11%

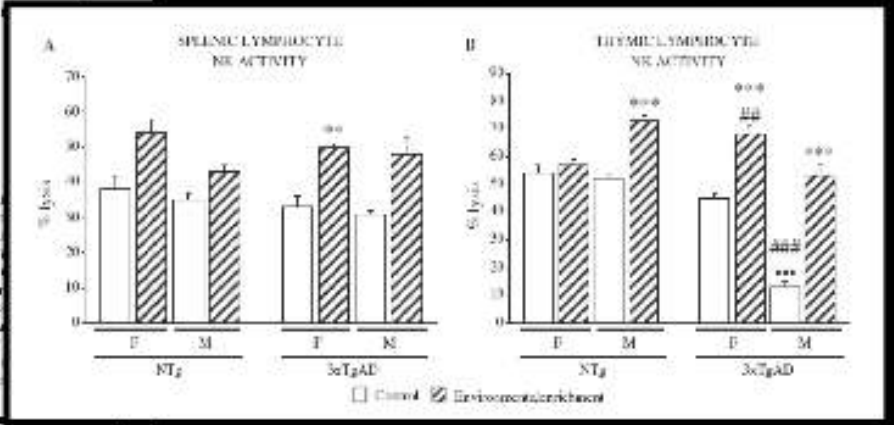
Cognitive and emotional profiles of aged Alzheimer's disease (3 × TgAD) mice: Effects of environmental enrichment and sexual dimorphism

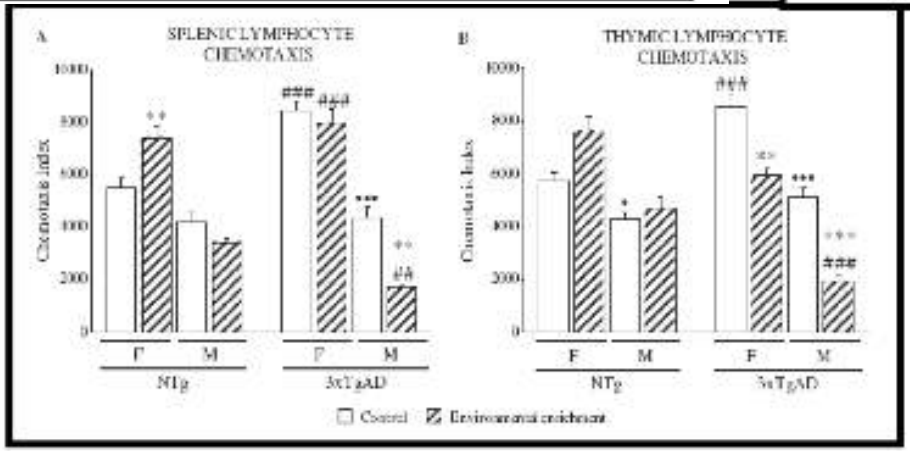
Gloria Blázquez*, Toni Cañete, Adolf Tobeña, Lydia Giménez-Llort, Alberto Fernández-Teruel

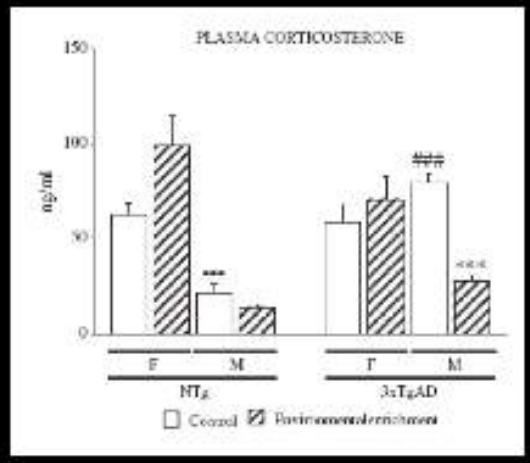
Medical Psychology Unit, Department of Psychiatry and Forensic Medicine, Institute of Neuroscience, Autonomous University of Barcelona, 08193 Bellaterra, Spain

HIGHLIGHTS

- Aged 3 × TgAD mice show deficits in spatial learning, short-term and working memory.
- 3 × TgAD mice show signs of increased anxiety and normal sensorimotor functions.
- Sexual dimorphism is reflected by increased behavioral inhibition in males.
- Sexual dimorphism is reflected by increased cognitive deficits in females.
- Environmental enrichment in adulthood induces beneficial effects on working memory.







SAGE-Hindawi Access to Research
International Journal of Alzheimer's Disease
Volume 2010, Article ID 120914, 17 pages
doi:10.4061/2010/120914

Research Article

Gender-Specific Neuroimmunoendocrine Response to Treadmill Exercise in 3xTg-AD Mice

Lydia Giménez-Llort,[1] Yoelvis Garcia,[2] Karla Buccieri,[1] Susana Revilla,[2] Cristina Suñol,[2] Rosa Cristòfol,[2] and Coral Sanfeliu[2]

[1] *Medical Psychology Unit, Department of Psychiatry and Forensic Medicine, Institute of Neuroscience, Autonomous University of Barcelona, Bellaterra, 08193 Barcelona, Spain*
[2] *Institute of Biomedical Research of Barcelona (IIBB), CSIC-IDIBAPS, 08036 Barcelona, Spain*

Correspondence should be addressed to Lydia Giménez-Llort, lidia.gimenez@uab.cat

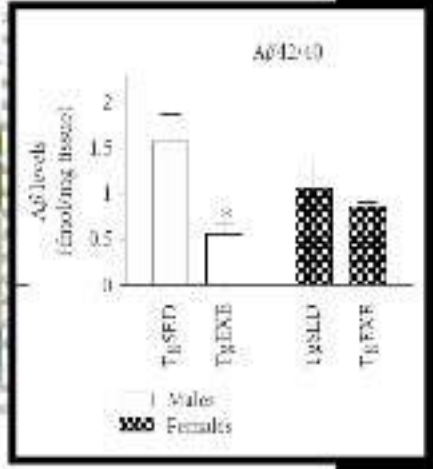
Received 16 May 2010; Accepted 9 August 2010

Academic Editor: Gemma Casadesus

Copyright © 2010 Lydia Giménez-Llort et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The 3xTg-AD mouse develops a progressive Alzheimer's disease (AD)-like brain pathology that causes cognitive- and neuropsychiatric-like symptoms of dementia. Since its neuroimmunoendocrine axis is likewise impaired, this mouse is also useful for modelling complex age-related neurodegeneration. This study analyzed behavioral, physiological, neurochemical, pathological and immunoendocrine alterations in male and female 3xTg-AD mice and assessed the effects of a short therapy of forced physical exercise at the moderate pathology stage of 4 months of age. Gender effects were observed in most AD-related pathology and dysfunctions. Five weeks of treadmill training produced beneficial effects, such as the reduction of brain oxidative stress and GABA-A receptor dysfunction in males and improvement of sensorimotor function in females. In both sexes, exercise decreased the brain amyloid β 42/40 ratio levels. The results highlight the importance of analysing experimental therapies in both mouse model genders in order to improve our understanding of the disease and develop more appropriate therapies.





Effects of exercise

Increases cerebral function
Protects from neurodegeneration
Improves cognition and emotiosn (Depr)

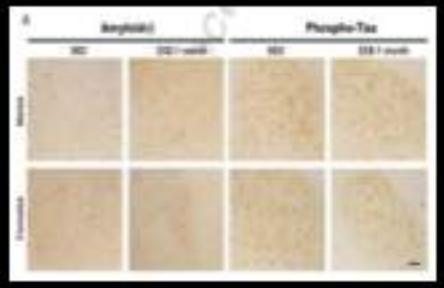
Oxidative stress
Atenuates ROS production
Increases antioxidant capacity

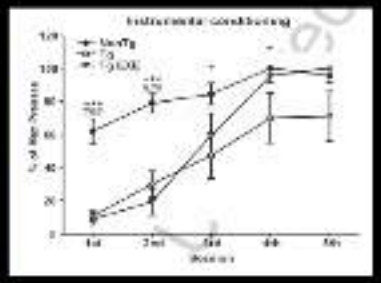
Growth factors
BDNF, VEGF, FGF-2, NGF, IGF-1
Gens for synaptic plasticity, L&M
Neurogenesis &Angiogenesis

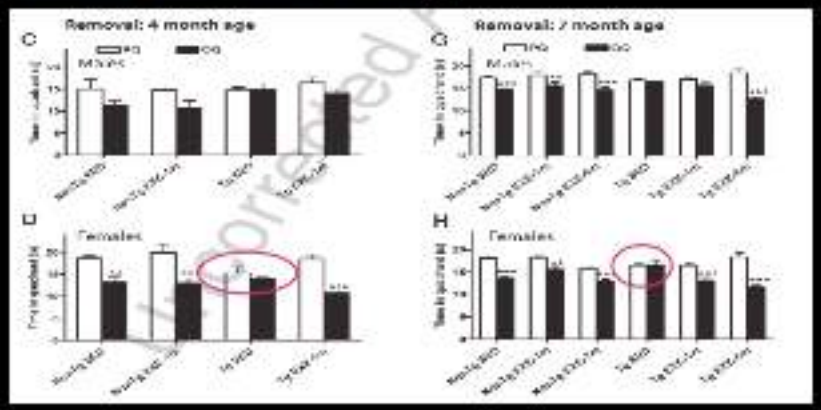
Beta-amiloid neuropathology
Increases proteasoma degradation

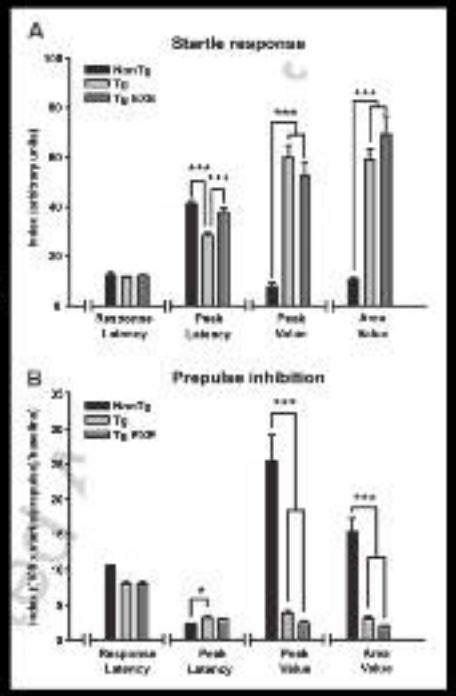
MAPK, PI3K, PI/Akt signalling
pCREB transcription factor
NMDA (NR2A NR2B)

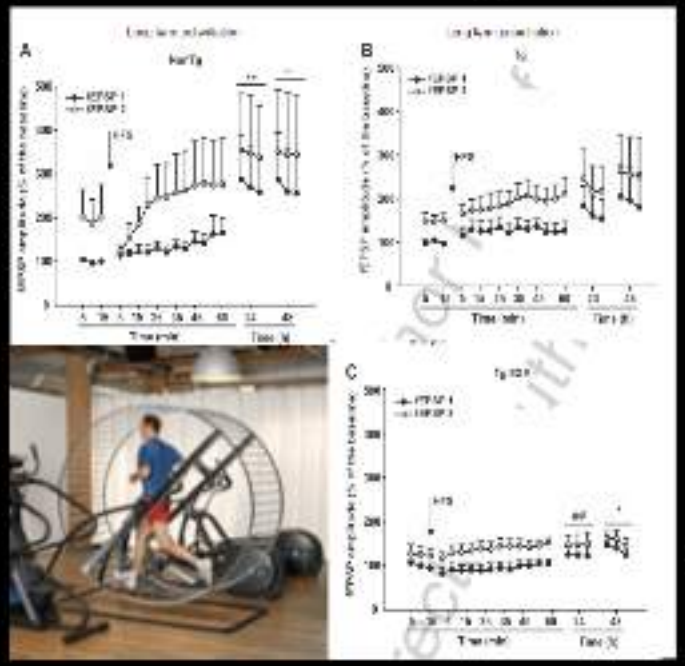

Physical Exercise Protects Against Alzheimer's Disease in 3xTg-AD Mice

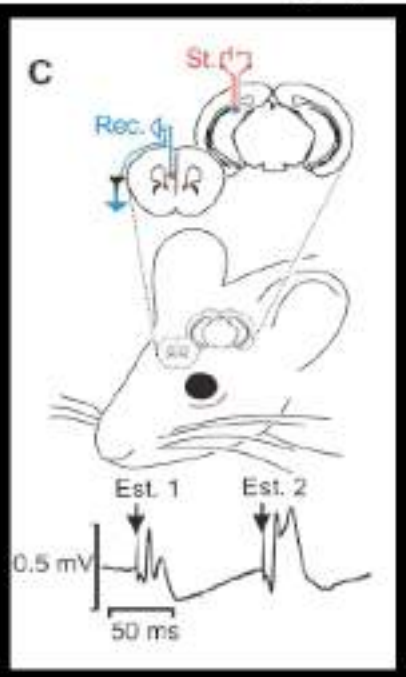


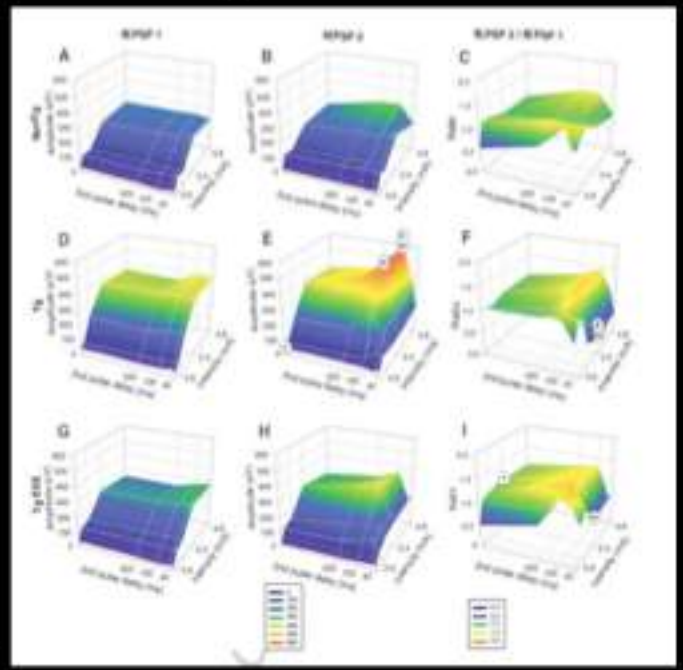












ELSEVIER

Neurobiology of Aging 31 (2010) 1124–1134

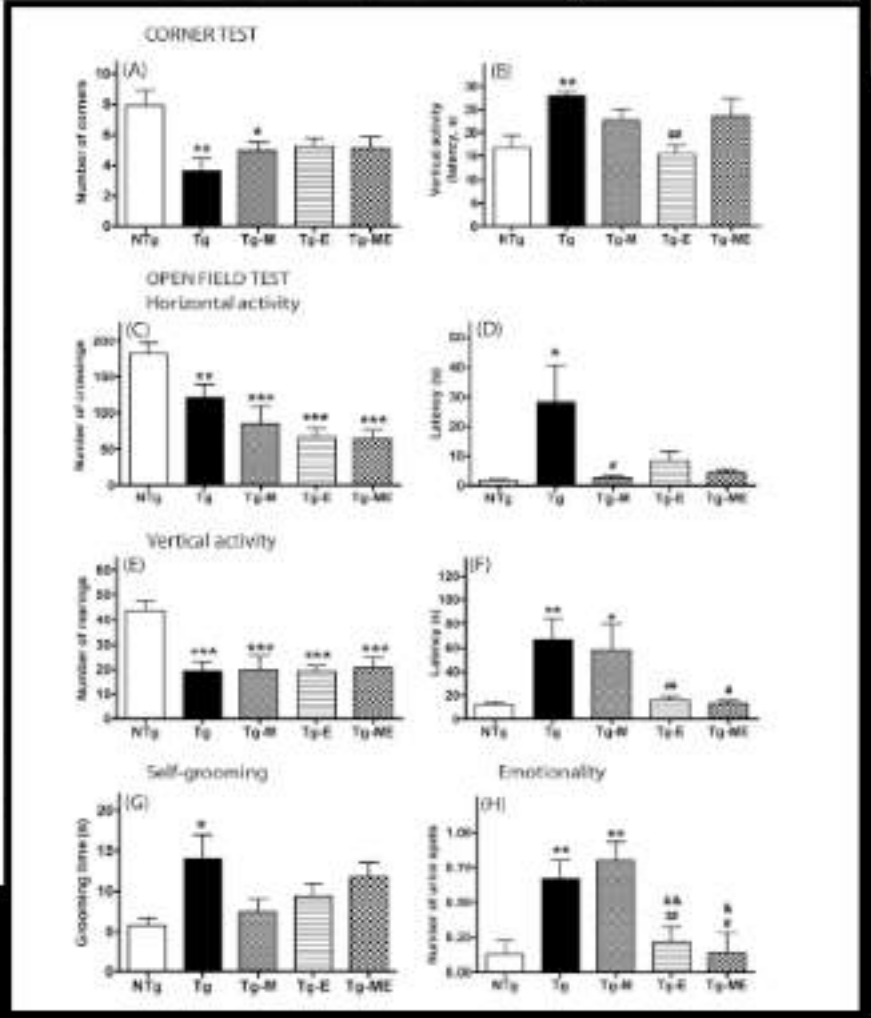
NEUROBIOLOGY OF AGING

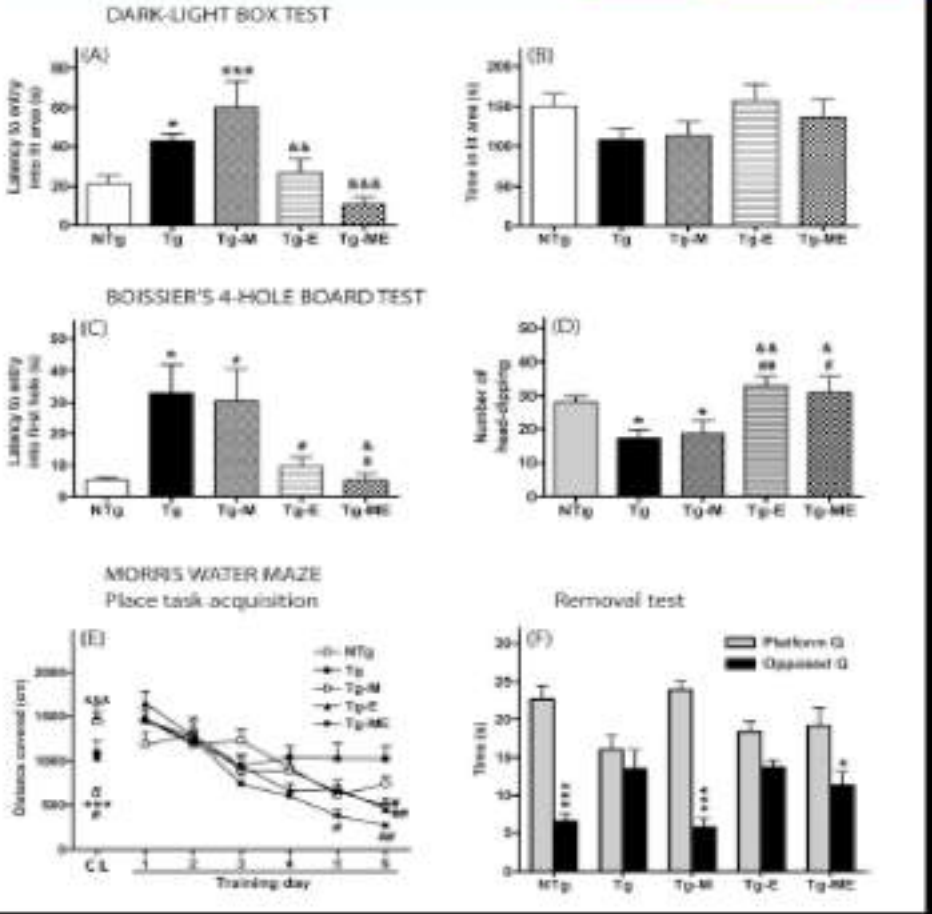
www.elsevier.com/locate/neuaging

Melatonin plus physical exercise are highly neuroprotective in the 3xTg-AD mouse

Yoelvis García-Mesa[a], Lydia Giménez-Llort[b], Luis C. López[c], Carmen Venegas[a], Rosa Cristófol[a], Germain Escames[c], Darío Acuña-Castroviejo[c], Coral Sanfeliu[a,*]

	M	Ex	ME
Immunosenescence (Thy)			
BAT involution			
Sensorimotor tasks (coordination)			
BPSD (CT, OF, HB)			
L&M (PT acquisition)			Sing
L&M (RM)			(*)





ELSEVIER

Neurobiology of Aging 31 (2010) 1124–1134

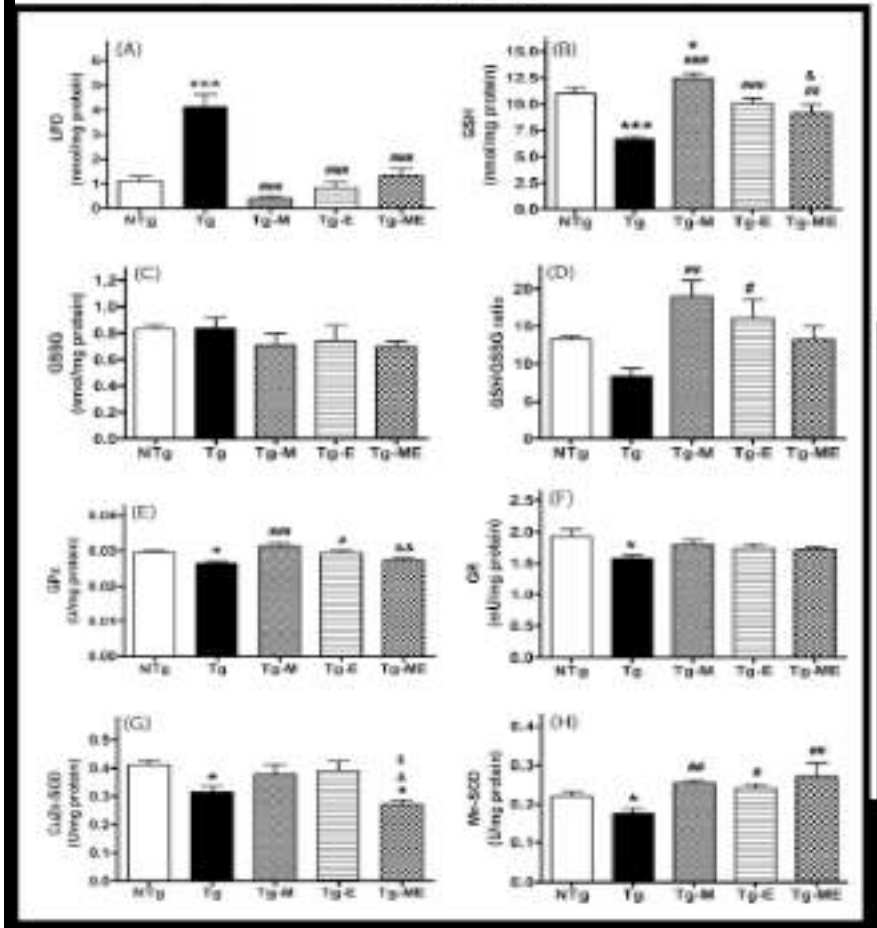
NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

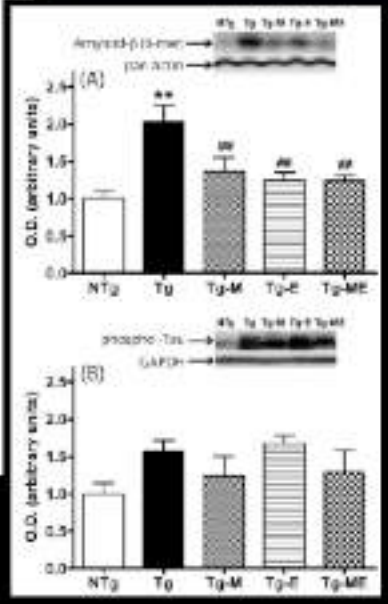
Melatonin plus physical exercise are highly neuroprotective in the 3xTg-AD mouse

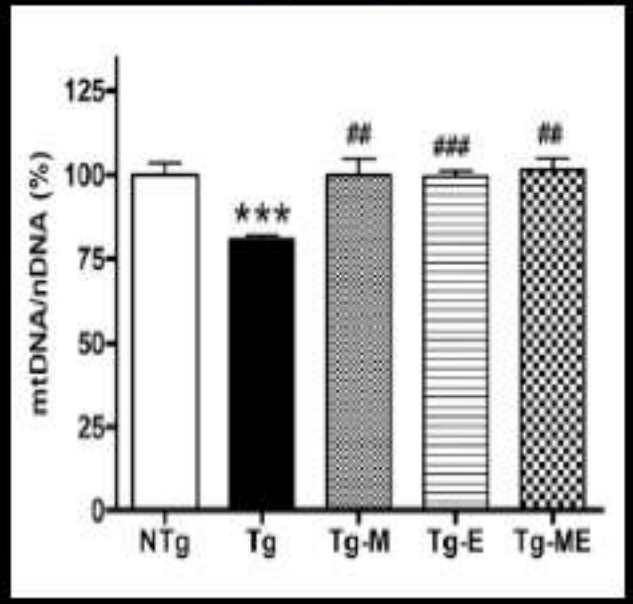
Yoelvis García-Mesa[a], Lydia Giménez-Llort[b], Luis C. López[c], Carmen Venegas[a], Rosa Cristófol[a], Germain Escames[c], Darío Acuña-Castroviejo[c], Coral Sanfeliu[a,*]

[a] Institute of Biomedical Research of Barcelona (IIBB), CSIC, IDIBAPS, Barcelona, Spain
[b] Institute of Neuroscience and Medical Psychology Unit, Department of Psychiatry and Forensic Medicine, Autonomous University of Barcelona, Barcelona, Spain
[c] Instituto de Biotecnología, Departamento de Fisiología, Centro de Investigación Biomédica, Parque Tecnológico de Ciencias de la Salud, Universidad de Granada, Granada, Spain



	M	Ex	ME
Immunosenescence (Thy)			
BAT involution			
Sensorimotor tasks (coordination)			
BPSD (CT, OF, HB)			
L&M (PT acquisition)			Sing
L&M (RM)			(*)
BA			
Tau (AT8)			
Redox status Cx			
CoQ9 and Respiratory chain complex			
mtDNA/nDNA			





ELSEVIER

Neurobiology of Aging 33 (2012) 1124.e11–1124.e20

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Melatonin plus physical exercise are highly neuroprotective in the 3xTg-AD mouse

Yoelvis García-Mesa[a], Lydia Giménez-Llort[b], Luis C. López[c], Carmen Venegas[a], Rosa Cristófol[a], Germain Escames[c], Darío Acuña-Castroviejo[c], Coral Sanfeliu[a,*]

[a] Institute of Biomedical Research of Barcelona (IIBB), CSIC, IDIBAPS, Barcelona, Spain

[b] Institute of Neuroscience and Medical Psychology Unit, Department of Psychiatry and Forensic Medicine, Autonomous University of Barcelona, Barcelona, Spain

[c] Instituto de Biotecnología, Departamento de Fisiología, Centro de Investigación Biomédica, Parque Tecnológico de Ciencias de la Salud, Universidad de Granada, Granada, Spain

Received 5 July 2011; received in revised form 7 November 2011; accepted 10 November 2011

ABSTRACT

Alzheimer's disease (AD) is a devastating age-related neurodegen
lifestyle options and over-the-counter drugs that it has been suggeste
unclear whether they will have any therapeutic value against AD. We
from 4 to 12 months, therefore from incidence to advanced phases o
showed differential patterns of neuroprotection for the 2 treatments. M
melatonin decreased hyperphosphorylated tau. Melatonin was effe
Voluntary physical exercise protected against behavioral and psycho
and sensorimotor. Both treatments protected against cognitive impai
(mRNA) immunology only the combined treatment of physical exer
completion. Therefore, melatonin plus physical exercise may exert co
disturbances present in AD.

© 2012 Elsevier Inc. All rights reserved.

Keywords: Alzheimer's disease; Mitochondrial aging; 3xTg AD mice; Melat

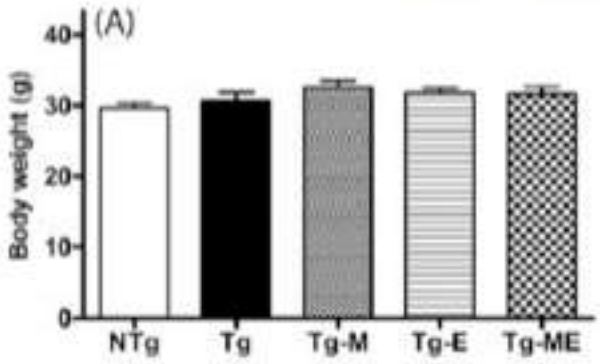
1. Introduction

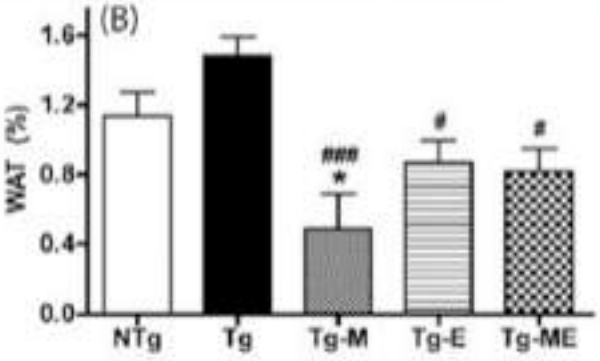
Healthy lifestyle options such as physical exercise, ca-
loric restriction, and a diet rich in antioxidant food increase
physical reserve and delay symptoms of aging and hence
they may protect against age-associated diseases (Dalffner,
2010; Joseph et al., 2009; Middleton and Yaffe, 2010;
Smith et al., 2010). The health-promoting lifestyle interven-
tion known as the most effective to date is aerobic exercise

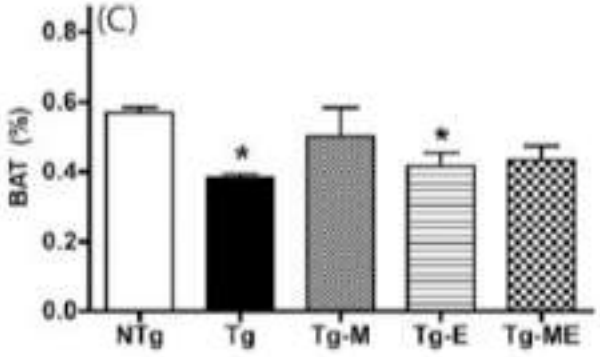
* Corresponding author at: IIBB-CSIC, IDIBAPS, Rosselló 161, 6th
Floor, 08036 Barcelona, Spain. Tel.: +34 93 3638308; fax: +34 93
3638301.
E-mail address: coral.sanfeliu@iibb.csic.es (C. Sanfeliu).

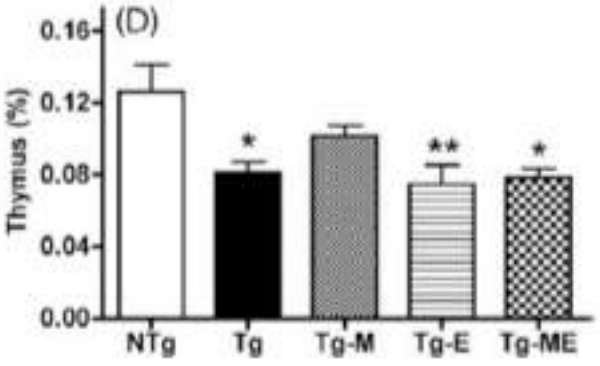
0197-4580/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.neurobiolaging.2011.11.031

	M	Ex	ME
Immunosenescence (Thy)			
BAT involution			
Sensorimotor tasks (coordination)			
BPSD (CT, OF, HB)			
L&M (PT acquisition)			Sing
L&M (RM)			(*)
BA			
Tau (AT8)			









Behavioural Brain Research 271 (2014) 140–146

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Short Communication

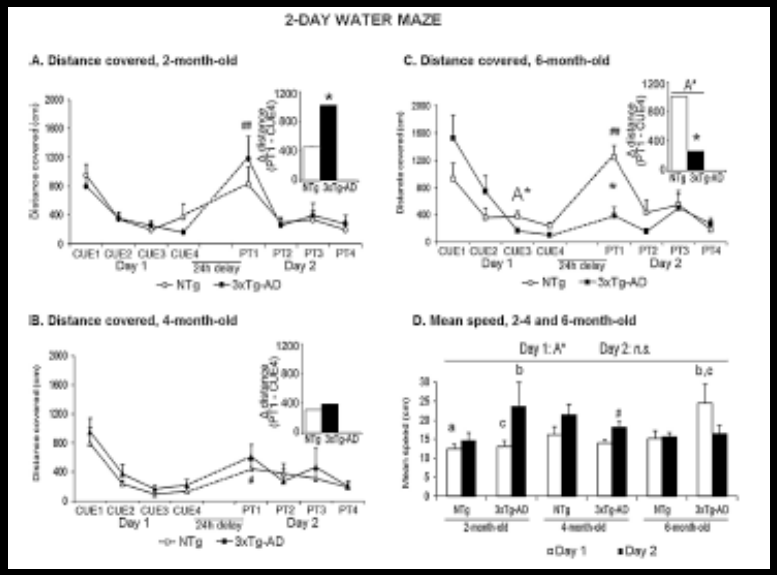
Neophobia, NQO1 and SIRT1 as premorbid and prodromal indicators of AD in 3xTg-AD mice

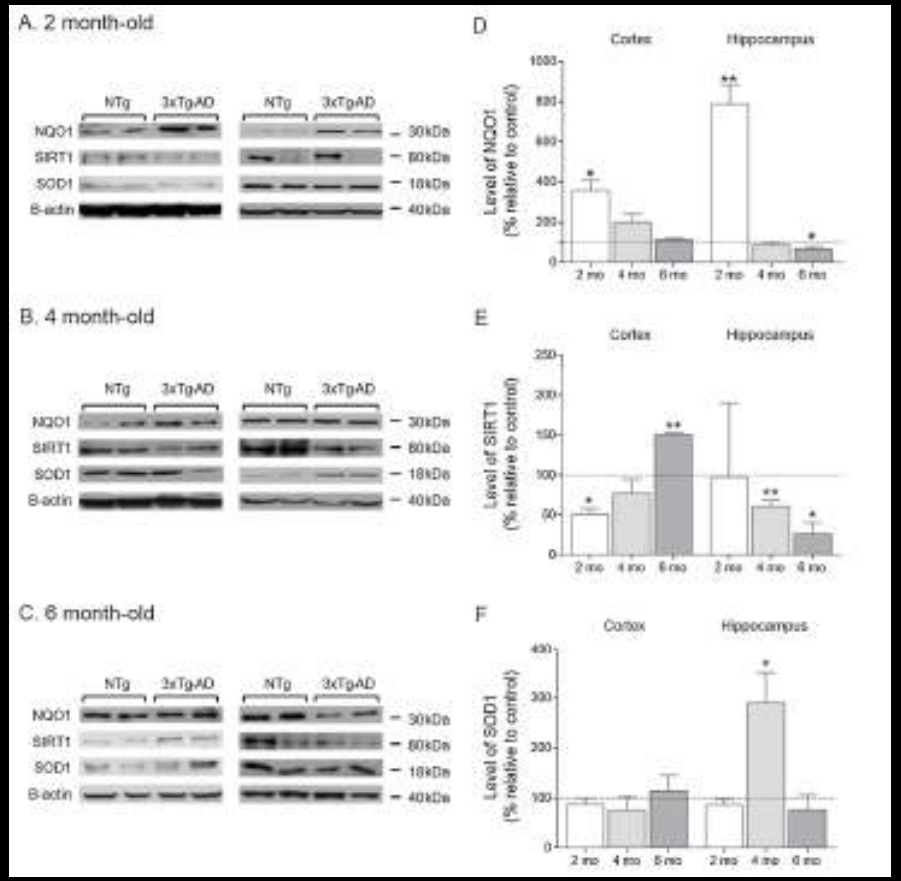
Virginia Torres-Lista [a,b,1], Cristina Parrado-Fernández [c,d,1], Ismael Alvarez-Montón [a,b], Javier Frontiñán-Rubio [c], Mario Durán-Prado [c,d], Juan Ramón Peinado [c,d], Björn Johansson [e], Francisco Javier Alcaín [c,d,e], Lydia Giménez-Llort [a,b,**]

[a] Department of Psychiatry and Forensic Medicine, Faculty of Medicine, Universitat Autònoma de Barcelona, Bellaterra, Spain
[b] Institut de Neurociències, Faculty of Medicine, Universitat Autònoma de Barcelona, Bellaterra, Spain
[c] Department of Medical Sciences, Faculty of Medicine of Ciudad Real, University of Castilla-La Mancha, Ciudad Real, Spain
[d] Centro Regional de Investigaciones Biomédicas, Universidad de Castilla-la Mancha, Spain
[e] Department of Neuroscience, Karolinska Institutet, KI-CMM L8:01, SE-171 76 Stockholm, Sweden

HIGHLIGHTS

- Latency of rearing was the first behavioral indicator of premorbid AD (Pre-AD).
- Prodromal AD was clearly defined by cognitive deficits at 6 months of age.
- High levels of cortical and hippocampal NQO1 were a redox indicator of Pre-AD.
- SOD1 was changed only in hippocampus at 4 months of age, before prodromal AD.
- SIRT1 levels had opposite regional and temporal premorbid/prodromal patterns.





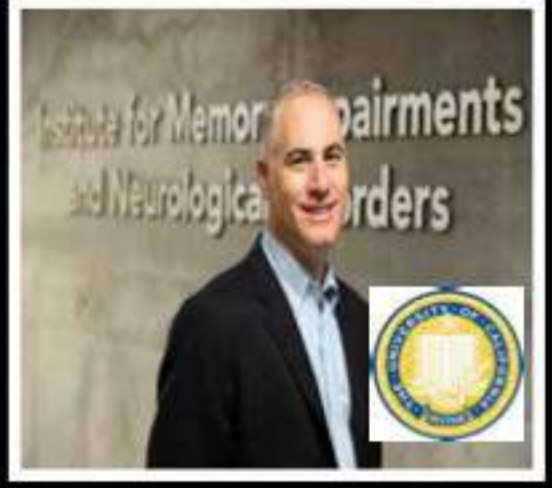


INc
Institut de Neurociències

UAB
Universitat Autònoma de Barcelona



3xTgAD



EME2006-140267
EME2006/13-140335
SAF2006-13642
Fundació La Marató 062930
MEMOSAD FP7
Instituto Salud Carlos III PI10/00283
Fundació La Marató 11531

COST-Action TD-1005
SGR 2006 & SGR 2010
RETICEF 06/0013/003
ENEROINN 910379
4the5.net
Neurodege.net
Envellir bé · Saber envejecer. org











INc Institut de Neurociències

UAB Universitat Autònoma de Barcelona



3xTgAD



EME2006-140267
EME2006/13-140335
SAF2006-13642
La Marató Tv3 162930
MEMOSAD EU
SGRAF042271
FIS ISC3 PI10/00561









Karolinska Institutet, Center Molecular Medicine Björn Johansson, SantiSole-Doménech

UCM, Dept Animal Fisiology Mónica de la Fuente

CSIC, IDIBAPS, Dept Pharmacol & Toxicol Coral Sanfeliu, Rosa Cristòfol, Yoelvis García

USC, University Santiago Compostela, Dept Pharmacology, Carmen Vale & Luis Botana

UAB, INc, Dept Biochemistry & Molecular Biology Carlos Saura, Jorge Valero & Judit España

UAB, INc, Dept Pharmacol & Toxicol Victoria Clos, Albert Badia, Miriam Ratia

UPV EHU, Universidad del Pais Vasco, Dept Pharmacology Rafael Rodríguez-Puertas

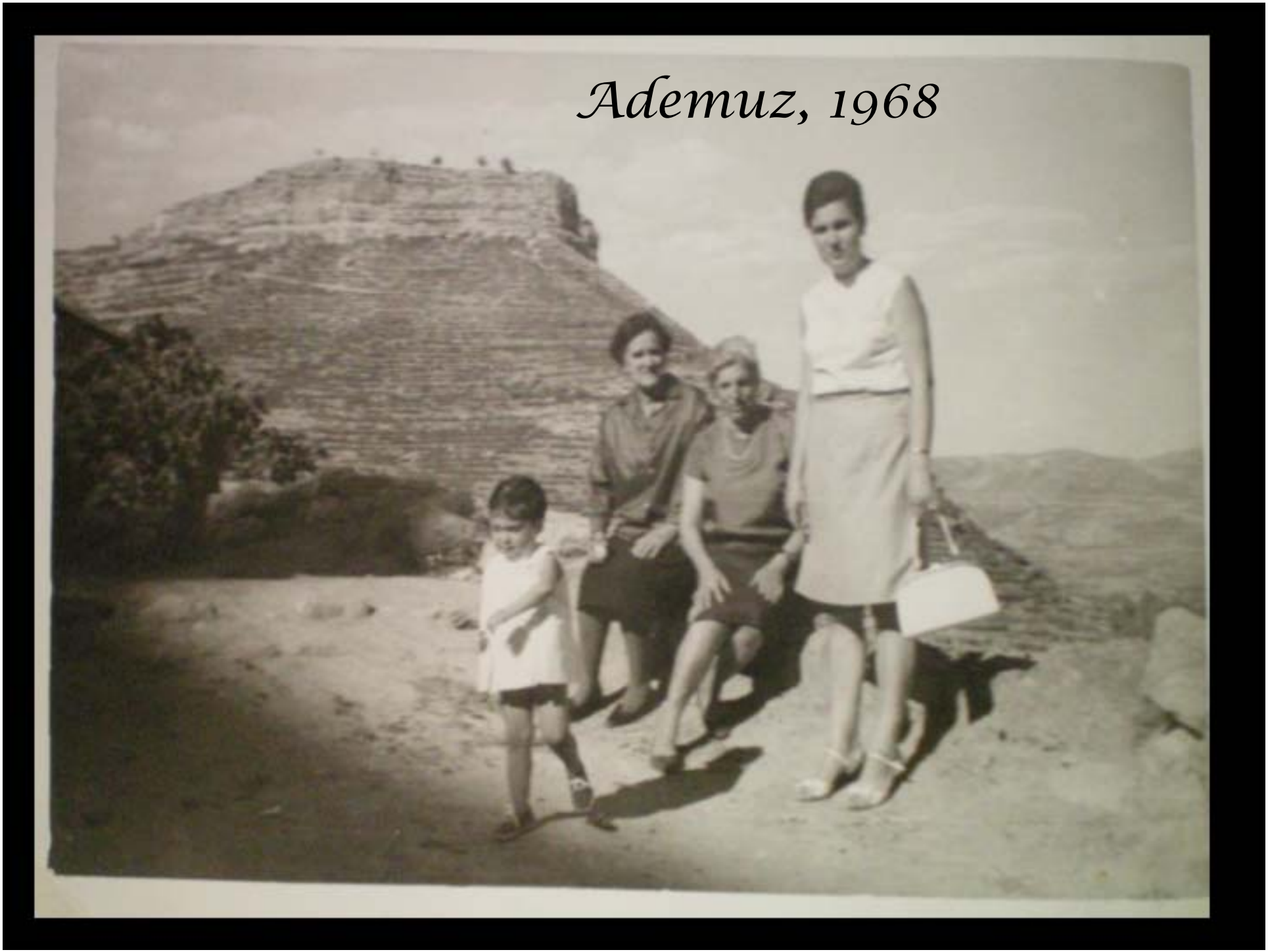
CSIC, IDIBAPS, Dept Neuroscience Teresa Vilaró, Ana Miralles

UAB, Science, Dept Biochemistry Sandra Villegas

UdG, Hospital, Sta Caterina Secundino López-Sousa

cost
EUROPEAN COOPERATION IN SCIENCE AND TECHNOLOGY




Ademuz, 1968