SIMPOSIO DI BIOGERONTOLOGIA
L'invecchiamento del sistema adrenergico

Disfunzione adrenergica e demenza

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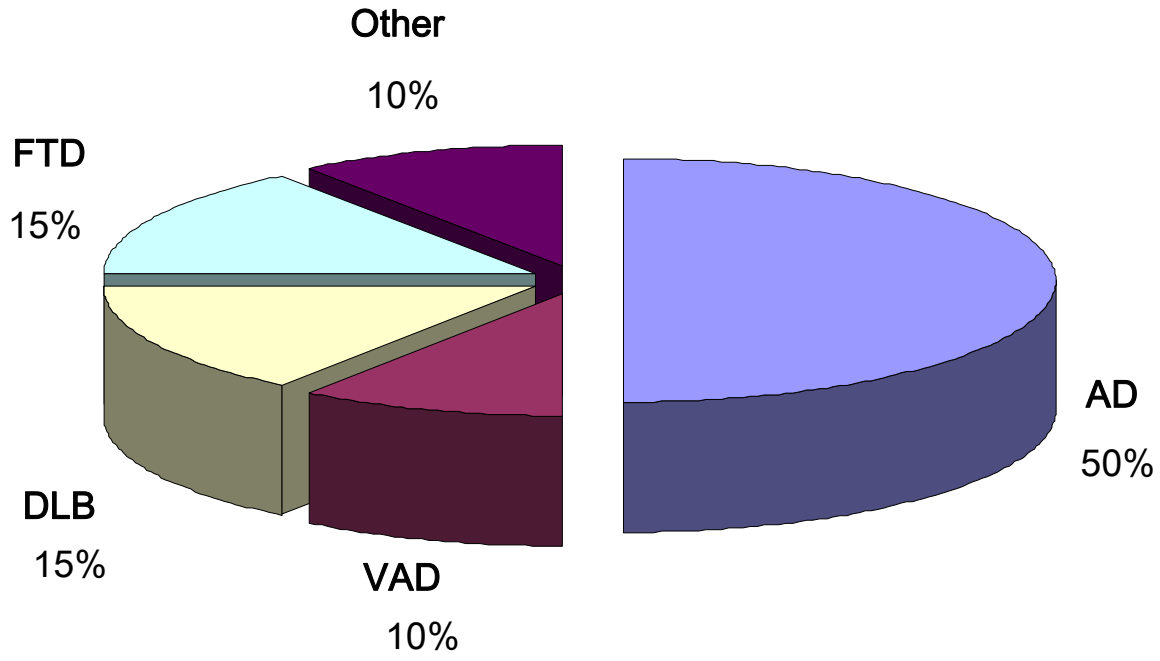
Imperial College London, UK

Prevalence of four major types of dementia



AD - Alzheimer's disease

VAD - vascular dementia

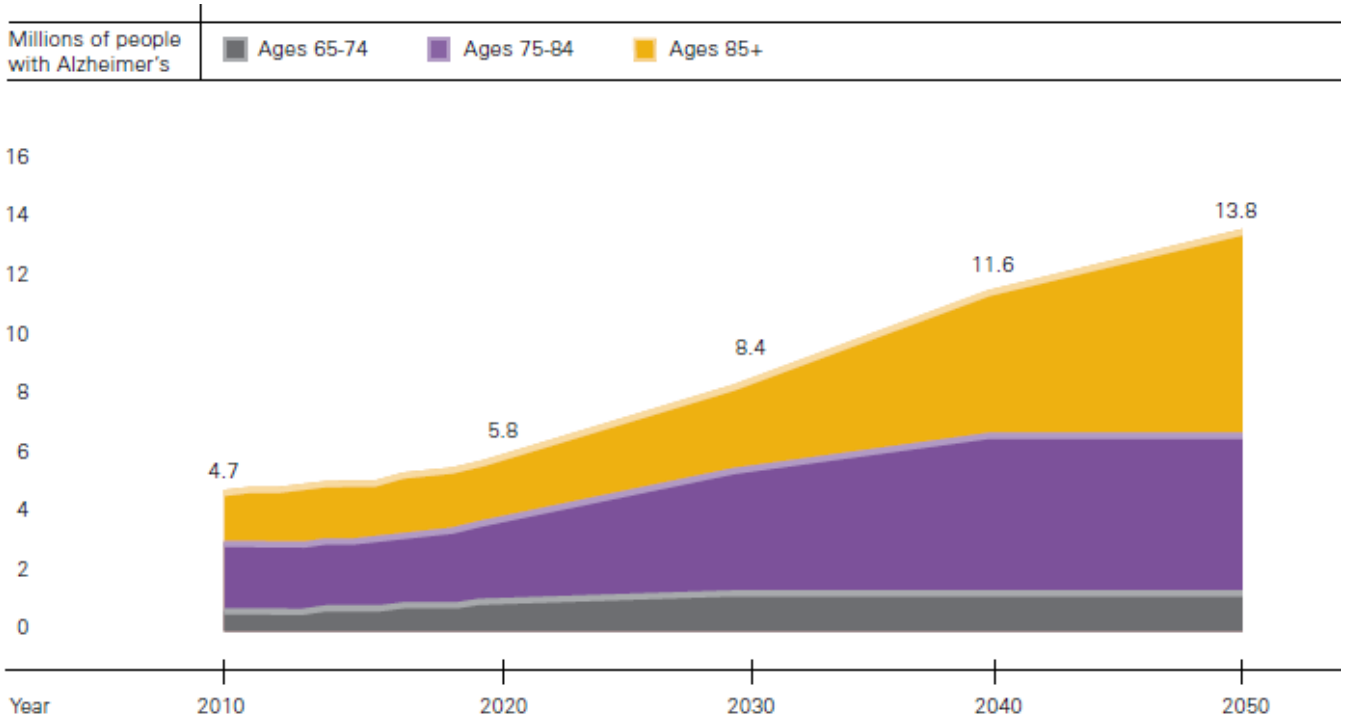
FTD - frontotemporal dementia

DLB- dementia with Lewy bodies

2015 Alzheimer's disease facts and figures, Alzheimer's Association US

Alzheimer's disease: figures

- 5.3 million Americans of all age have AD in 2015
- One in nine people age 65 and older (11%) has AD
- About one-third of people age 85 and older (32%) have AD
- Almost two-thirds of Americans with AD are women

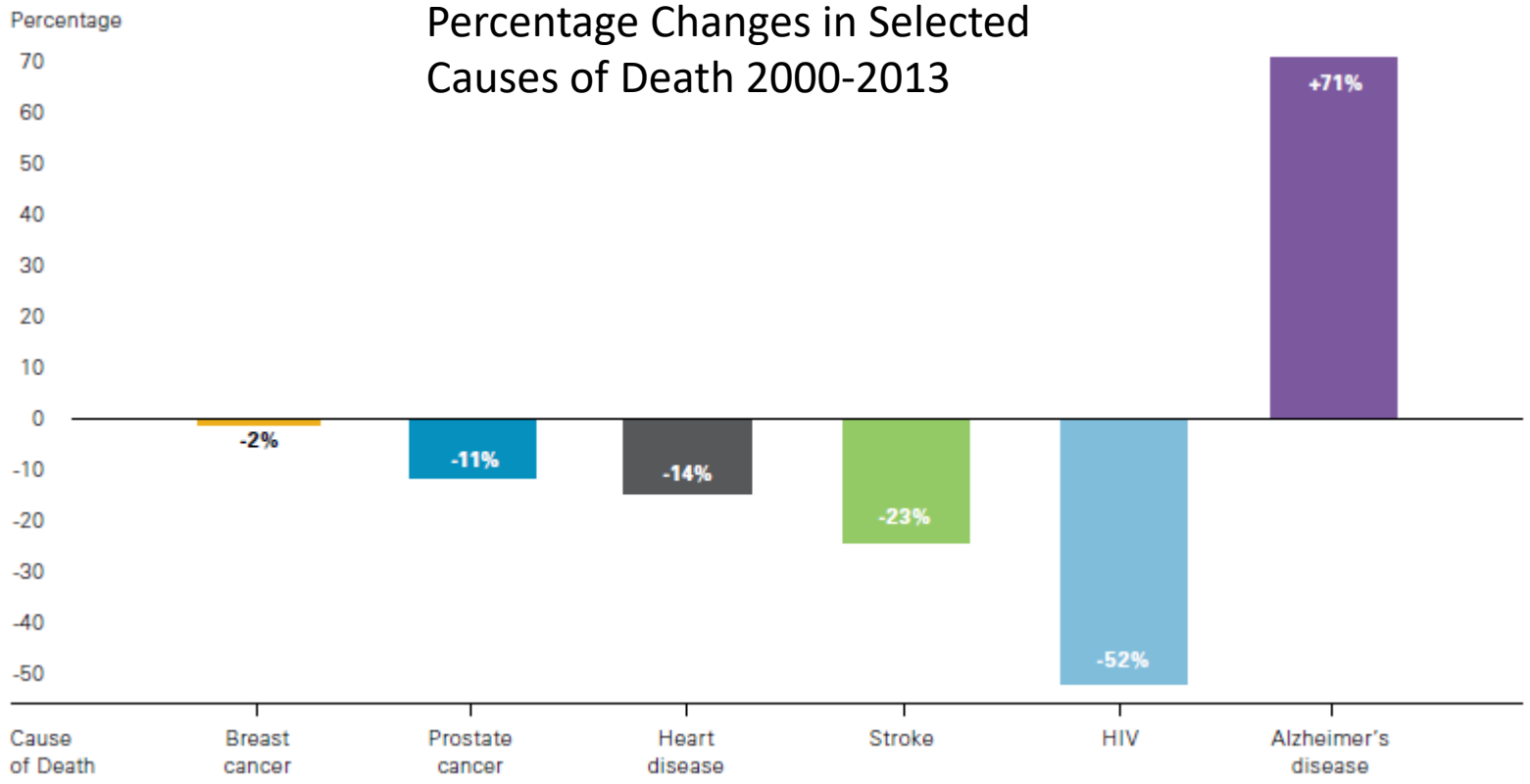


Projected Number of People over 65 in the US with AD

2015 Alzheimer's disease facts and figures, Alzheimer's Association US

Alzheimer's disease: mortality

- AD is the sixth-leading cause of death across all ages in the US and the fifth-leading cause of death for those aged 65 and older
- AD-related mortality significantly increased between 2000 and 2013



2015 Alzheimer's disease facts and figures, Alzheimer's Association US

Illness duration and health care costs

- Average survival for an AD patient aged over 65: 4-8 years after diagnosis
- 40 percent of the total number of years with AD is spent in the most severe stage of the disease
- Much of this time will be spent in a nursing home → nursing home admission by age 80 is 75% of people with AD, compared with 4% of the general population
- The long duration of illness contributes significantly to the public health impact of AD

	Beneficiaries with Alzheimer's Disease and Other Dementias	Beneficiaries without Alzheimer's Disease and Other Dementias
Inpatient hospital	$10,293	$4,138
Medical provider*	6,095	4,041
Skilled nursing facility	3,955	460
Nursing home	18,353	816
Hospice	1,821	178
Home health	1,460	471
Prescription medications**	2,787	2,840

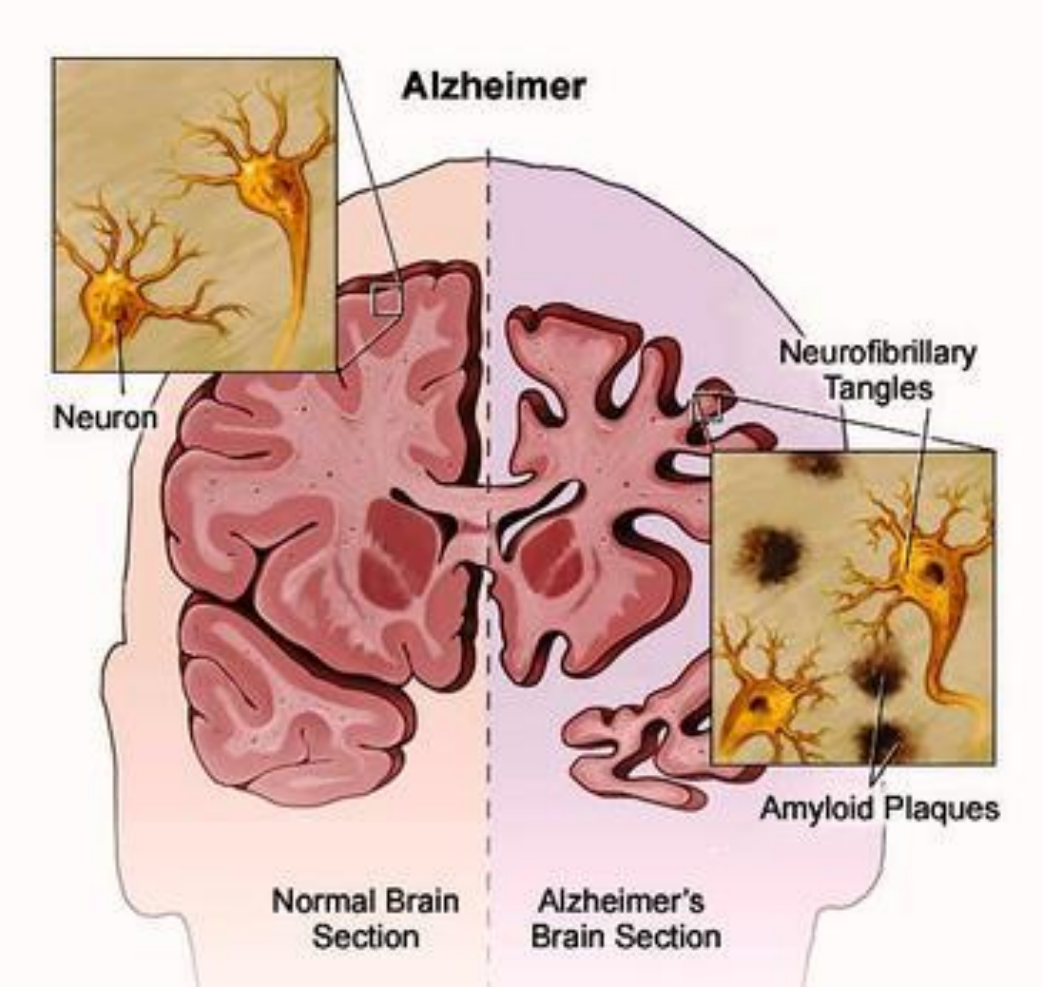
2015 Alzheimer's disease facts and figures, Alzheimer's Association US

Challenges in AD treatment

1. Early diagnosis → Development of new biomarkers

2. New therapeutic options → Interventional trials

AD pathogenesis

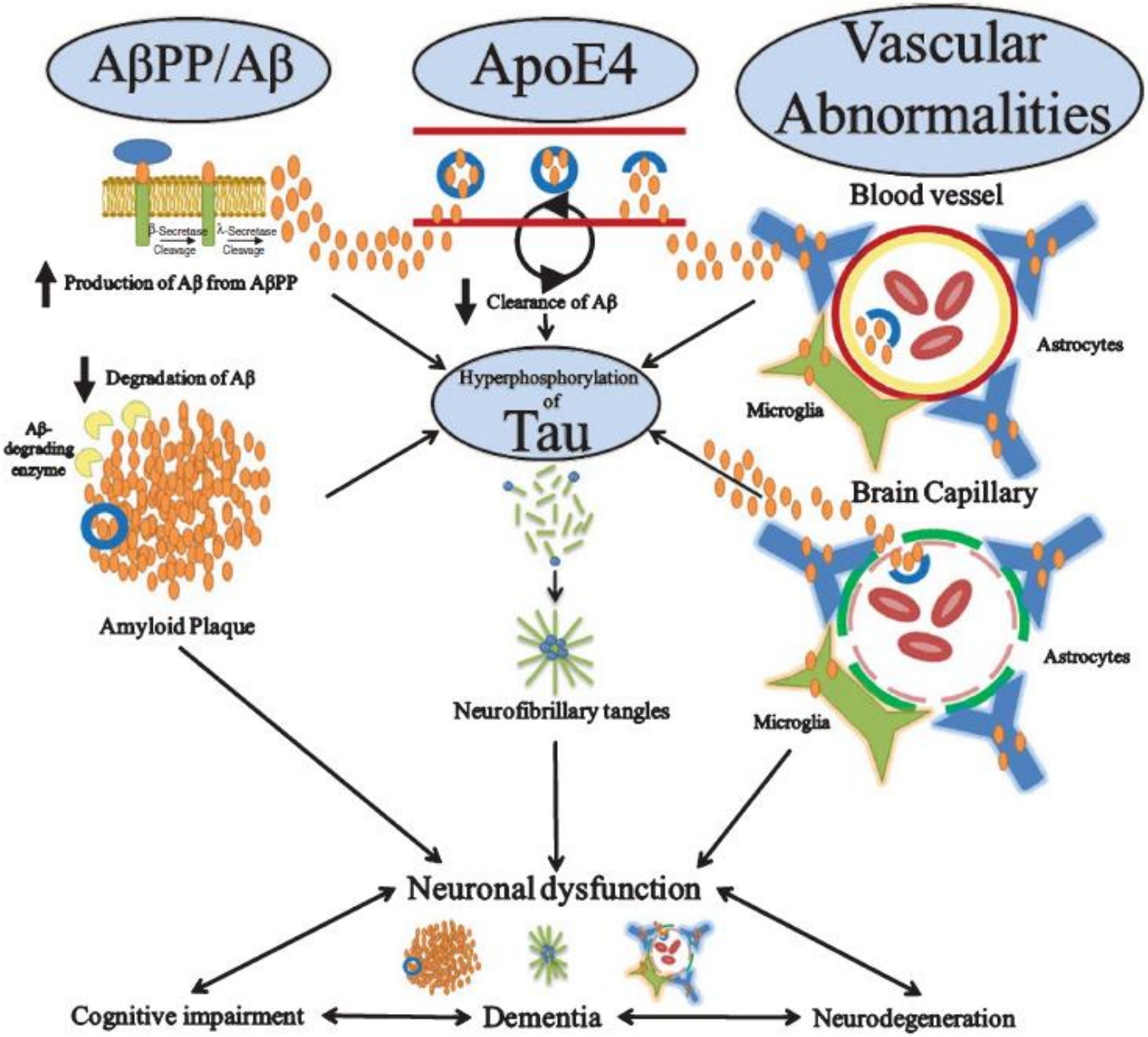


Two neuropathological hallmarks:
- Amyloid plaques
- Neurofibrillary tangles

Diffuse **brain atrophy** affecting:
• entorhinal cortex, hippocampus, amygdala and parahippocampus;
• cholinergic neurons in basal nucleus of Meynert;
• temporal, parietal and frontal cortex;

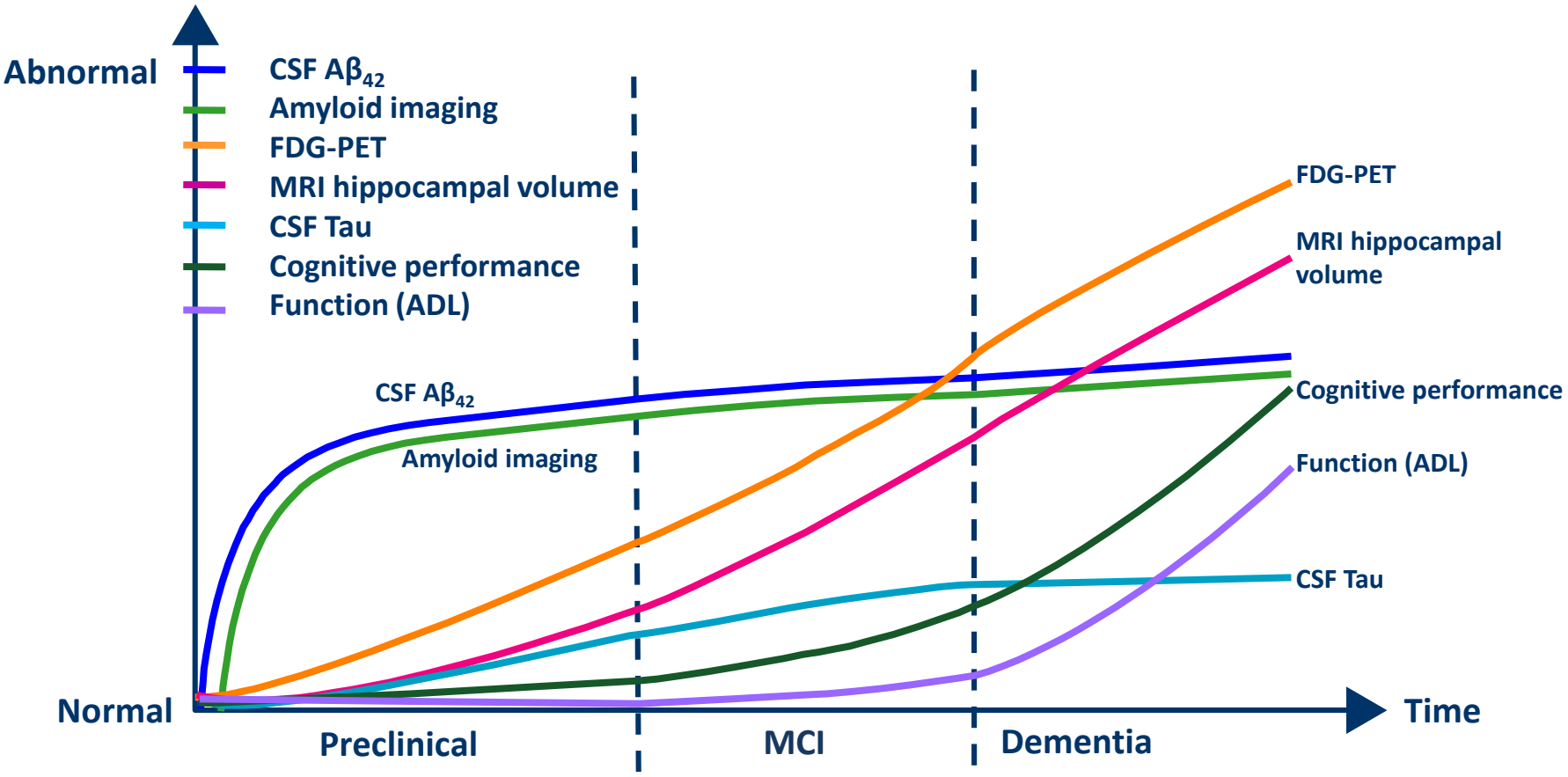
Risacher SL, Annu Rev Clin Psich 2013

Multifactorial AD pathogenesis



Femminella GD, JAD 2014

Biomarkers changes during AD progression

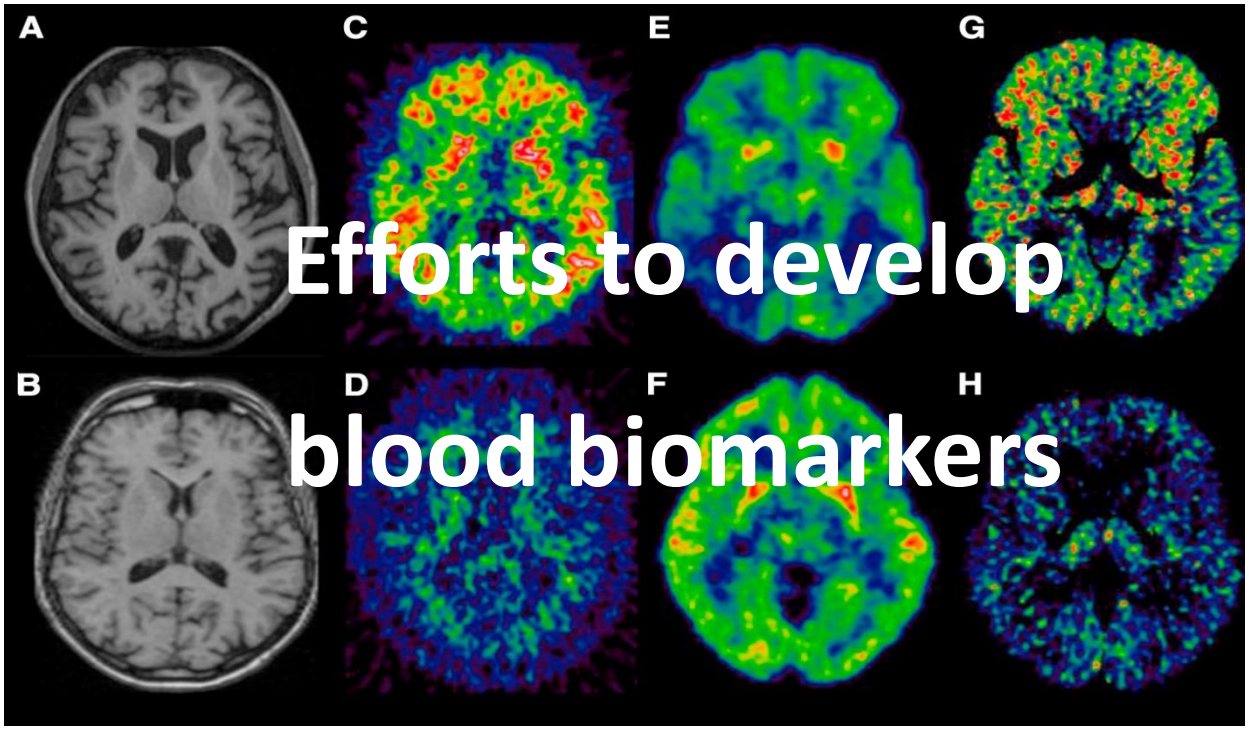


Aisen P, Alzheimer Dement 2010

Neuroimaging: strenghts and limitations

- In vivo evaluation of pathological processes
- Early detection of changes
- Quantification of AD pathology other than amyloid

- Availability & costs of PET/MRI scans
- Standardization of neuroimaging techniques
- Radioactivity (PET)



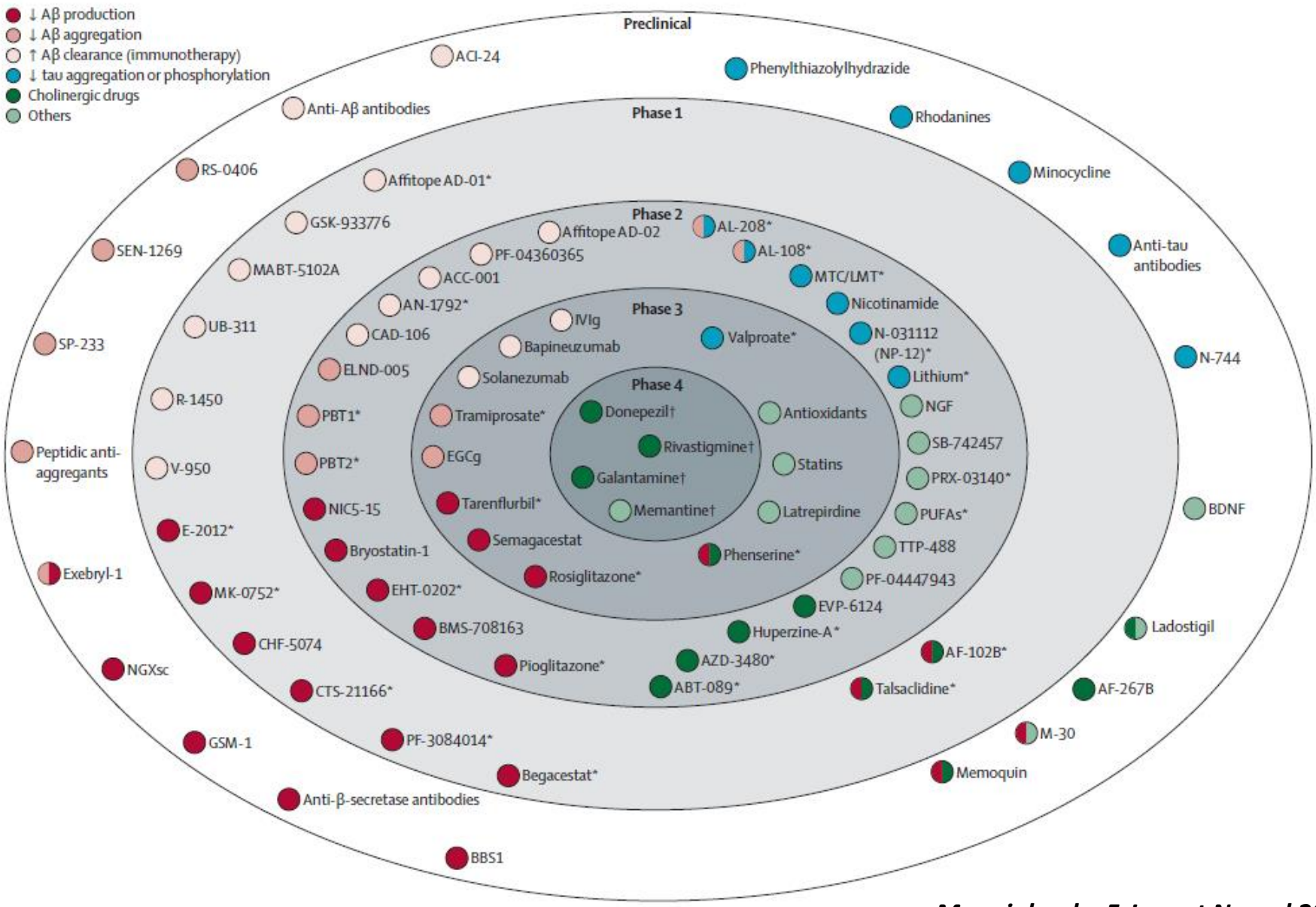
Femminella GD, Alzh & Dem. 2014

Challenges in AD treatment

1. Early diagnosis → Development of new biomarkers

2. New therapeutic options → Interventional trials

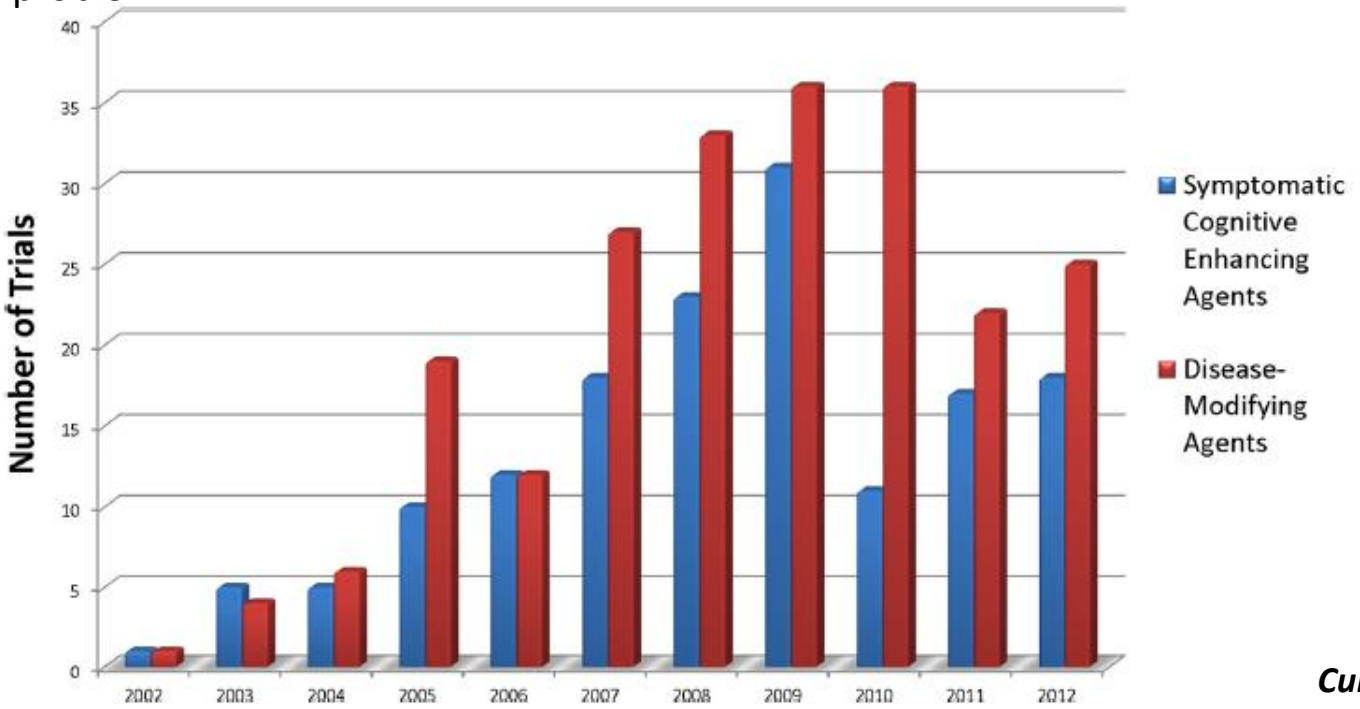
Drug development in Alzheimer's disease



Mangialasche F, Lancet Neurol 2010

Drug development in Alzheimer's disease

- In the decade 2002-2012, 413 AD trials were performed
- 78% were sponsored by pharmaceutical companies
- 36.6% of registered trials addressed symptomatic agents aimed at improving cognition, followed by trials of disease-modifying small molecules (35.1%) and trials of disease-modifying immunotherapies (18%)
- The overall success rate during the 2002 to 2012 period was 0.4% (99.6% failure)
- Relatively few clinical trials are undertaken for AD therapeutics, considering the magnitude of the problem

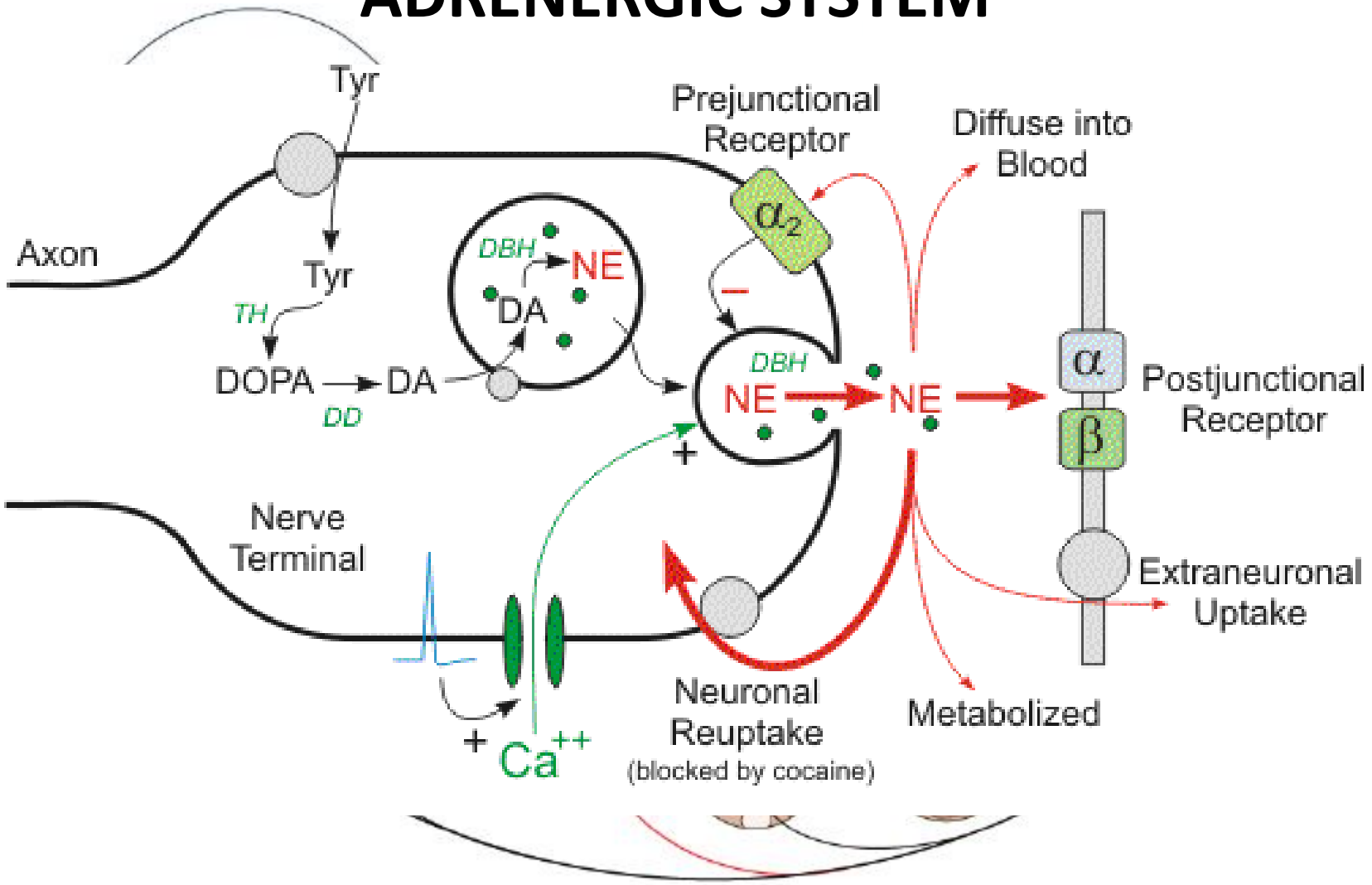


Cummings JL, Alz Res & Ther 2014

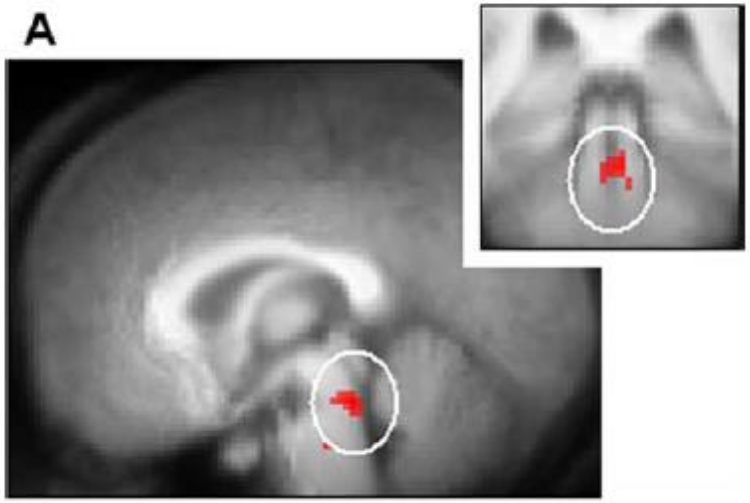
Search for biomarkers

New therapeutic targets

ADRENERGIC SYSTEM

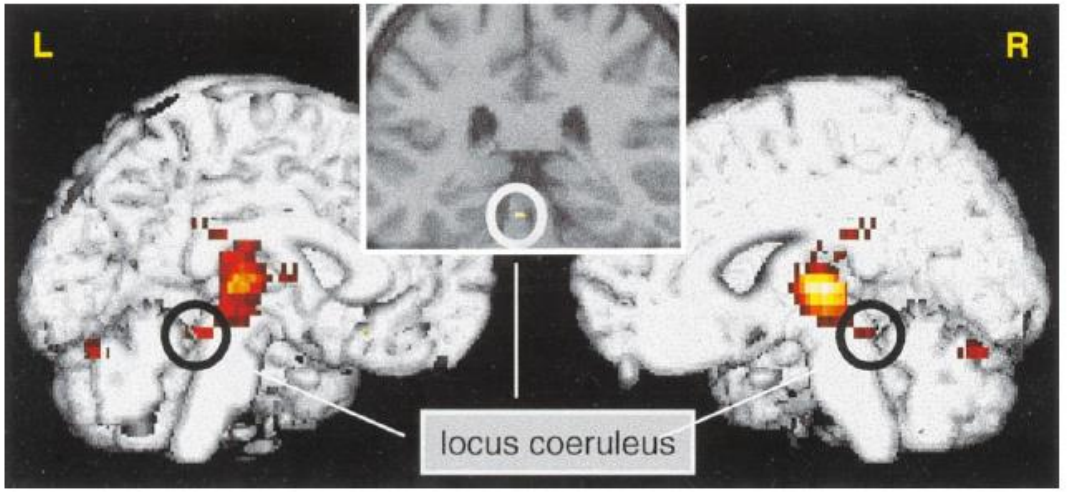


The Locus Ceruleus is involved in the retrieval of memories in humans



fMRI study: LC responds significantly during the recognition of events encoded in an emotional context.
Retrieval of emotional memories not only involve the interaction between the amygdala and the hippocampal formation but also the interplay between the amygdala and the LC.

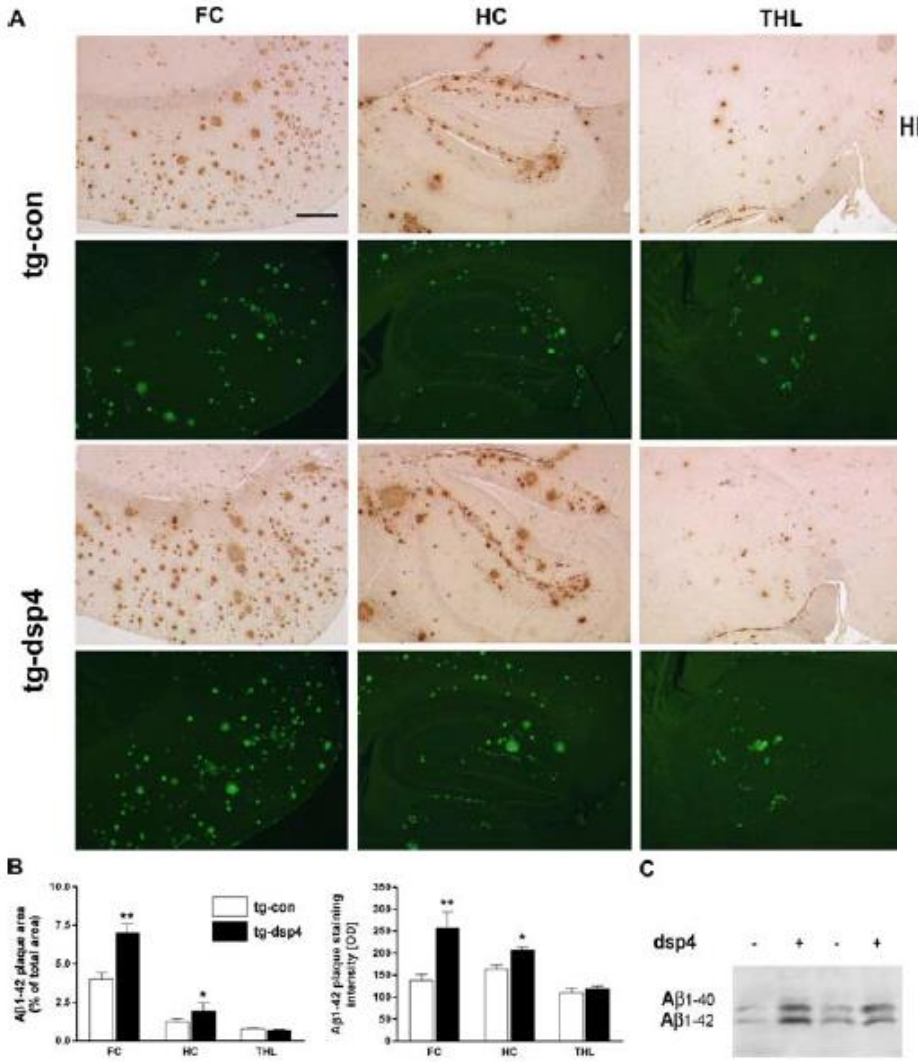
Sterpenich V, J Neurosci 2006



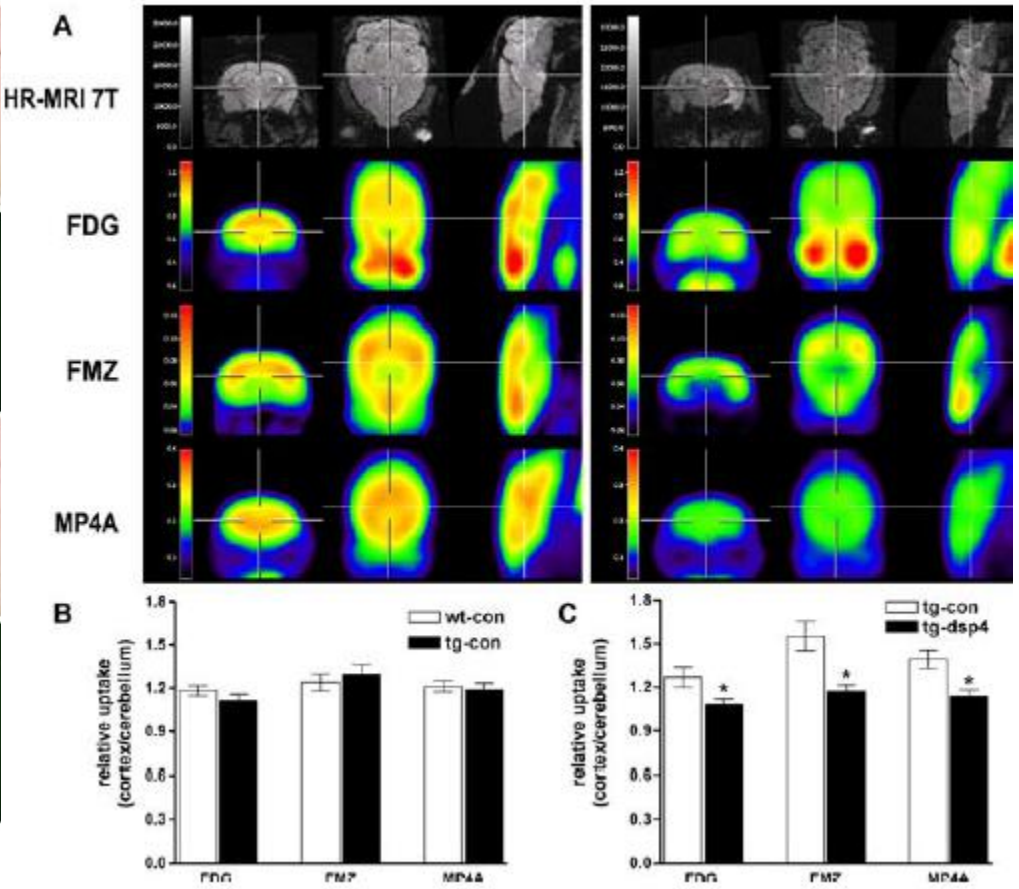
PET study: noradrenergic system mediates the functional integration of attentional brain systems.

Coull JT Neuroimage 1999

LC degeneration promotes AD pathogenesis in APP23 transgenic mice



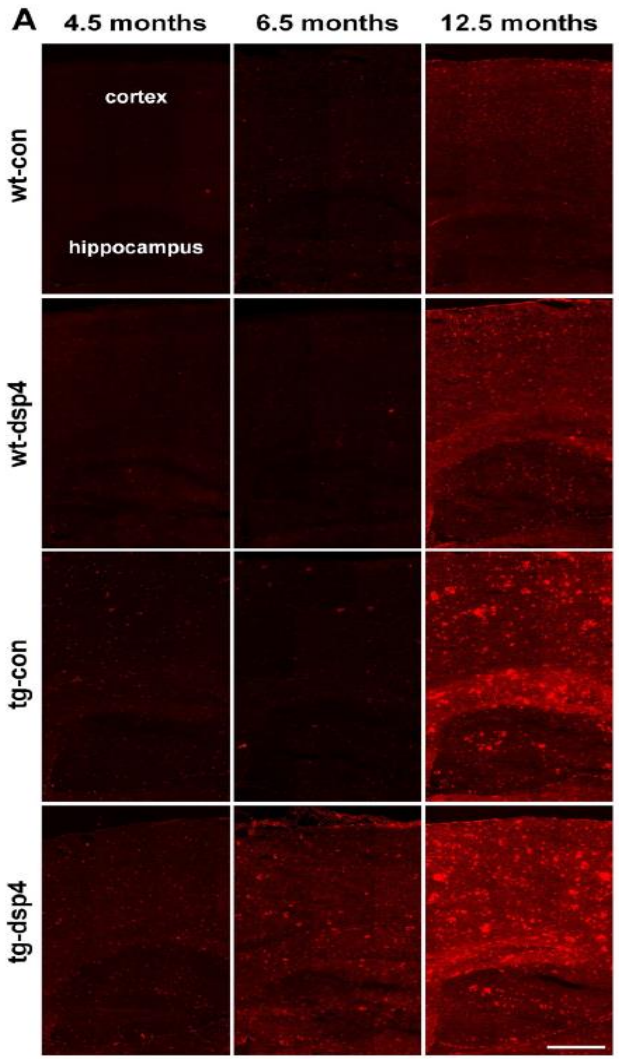
Increased deposition of amyloid peptides in NA-depleted APP23 mice



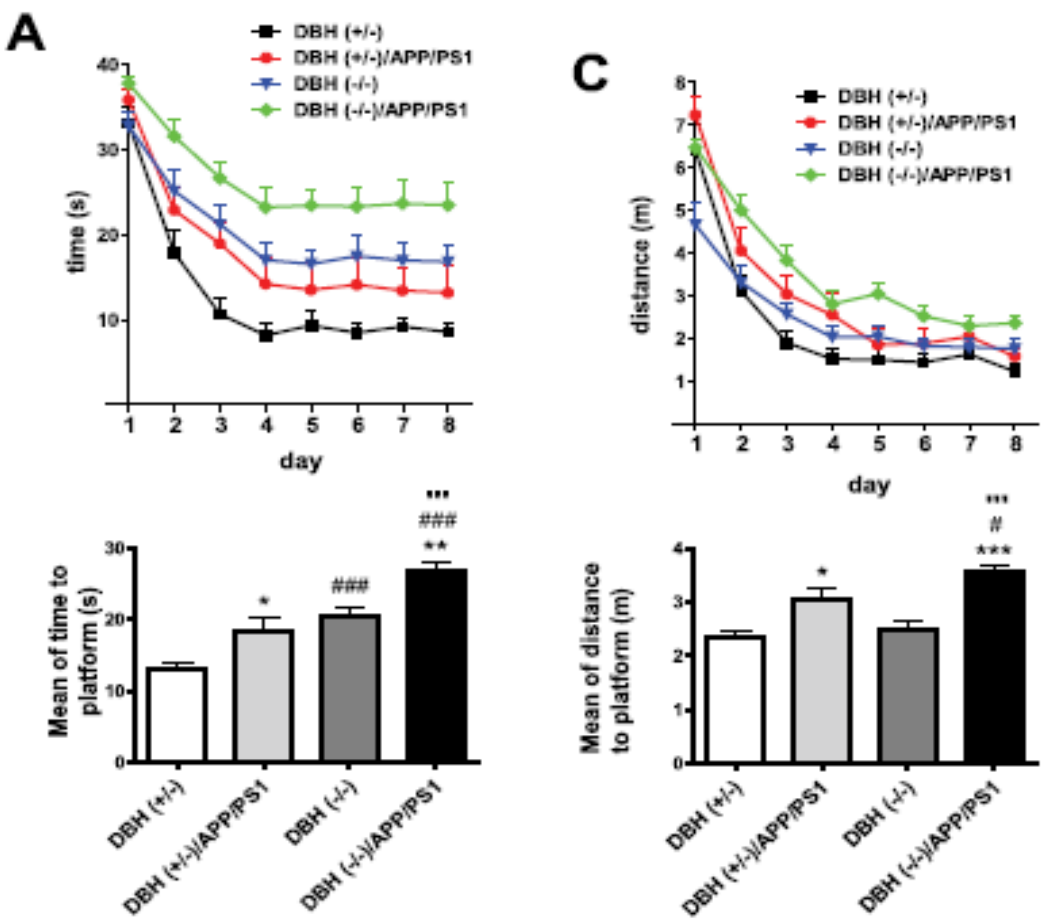
Altered cerebral glucose metabolism, neuronal integrity, and cholinergic function detected *in vivo* after noradrenergic depletion of APP23 mice

Heneka M, J Neurosci 2006

LC degeneration induces increased neuroinflammation and cognitive impairment in AD



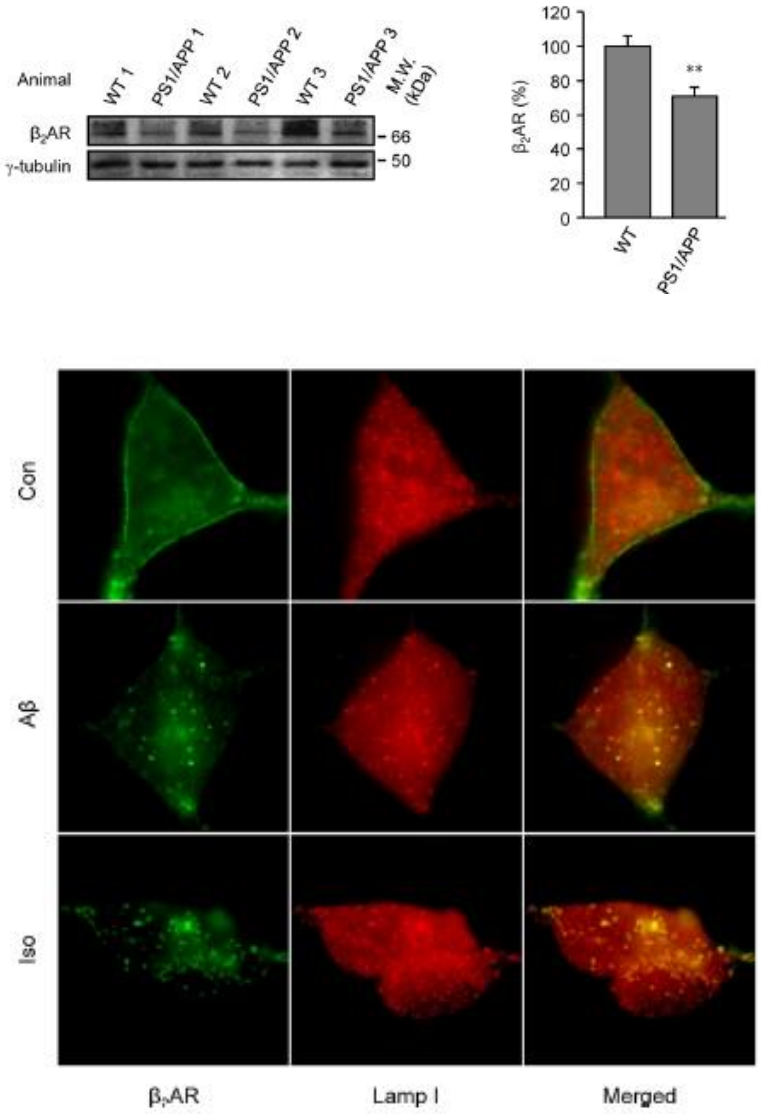
NE depletion influences microglial activation in APP/PS1 mice

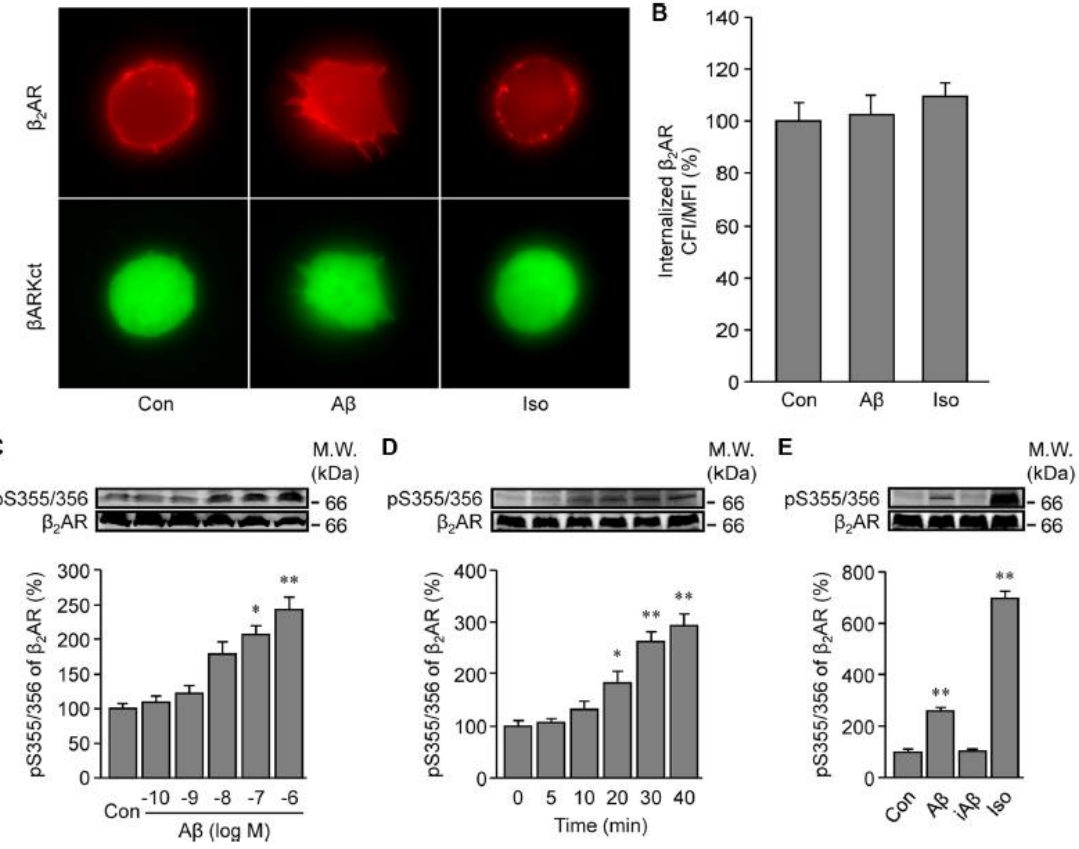


Morris water maze test: the combination of NA deficiency and the APP/PS transgene causes the most profound cognitive impairment.

Jardanhazi-Kurutz D 2011 & Hammerschmidt T 2013

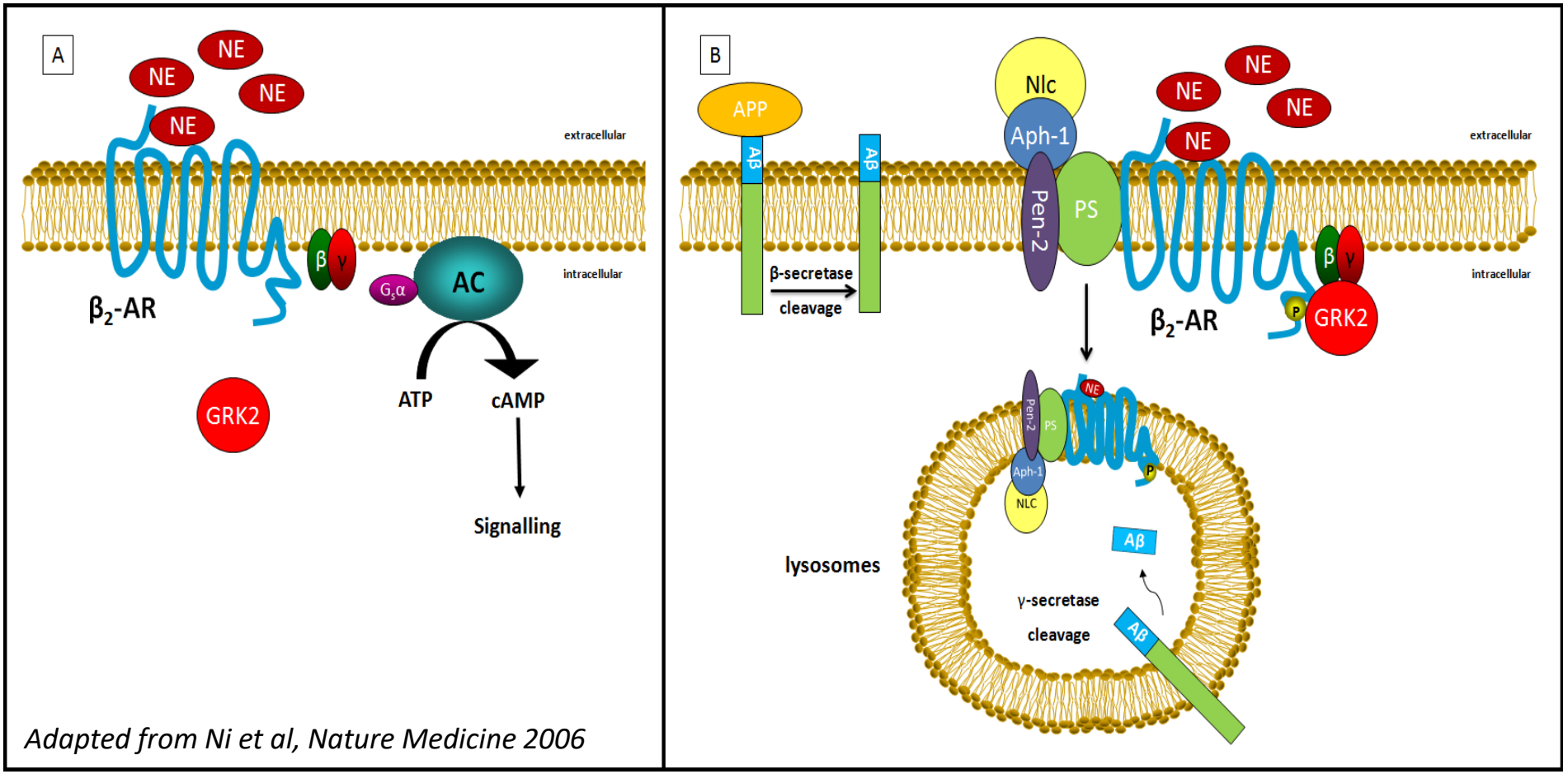
Amyloid β induces internalization and degradation of β2- AR in prefrontal cortical neurons





Wang D, JBC 2011

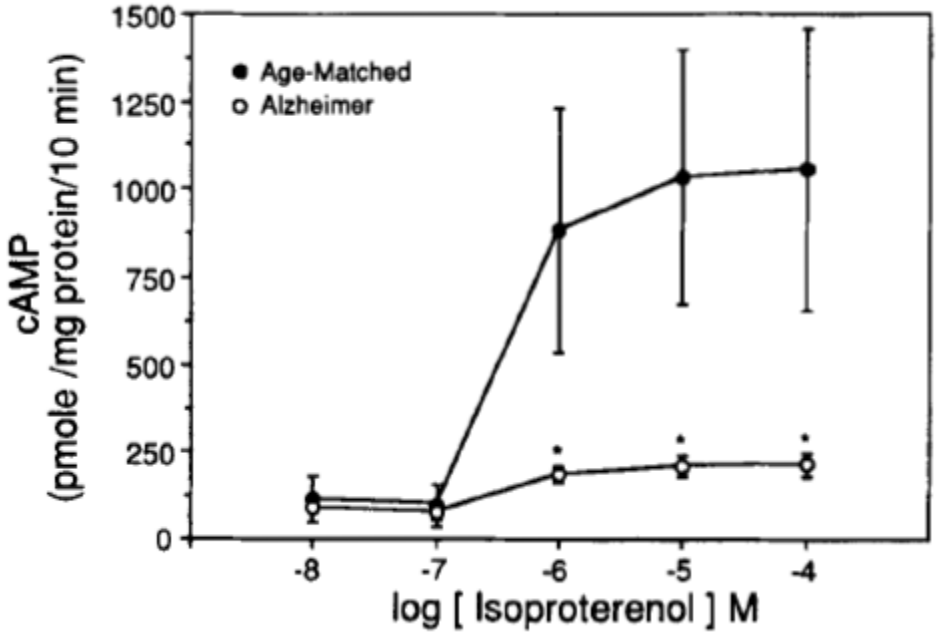
β_2-adrenergic receptors and G protein-coupled receptor kinase 2 (GRK2) in amyloid production

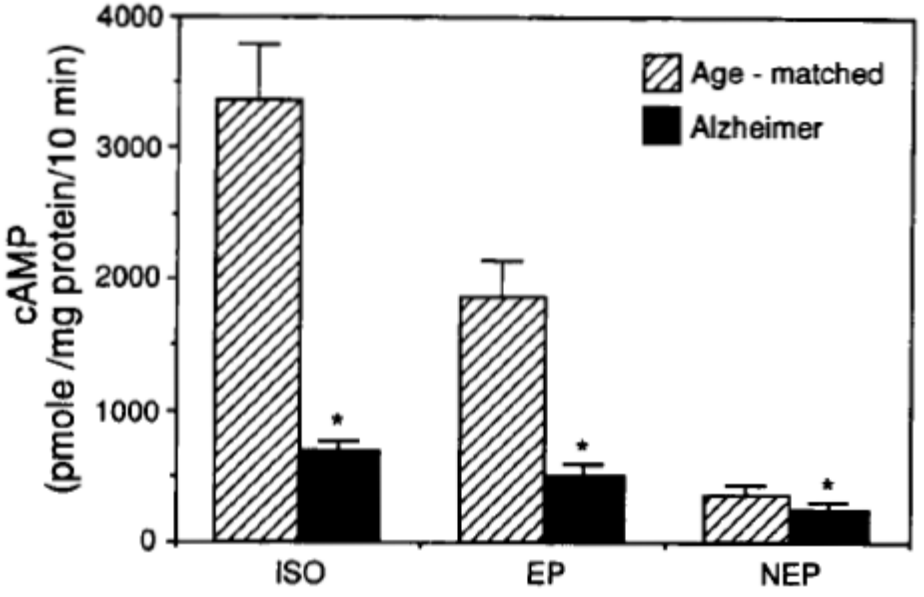


Adapted from Ni et al, Nature Medicine 2006

Femminella GD, JAD 2013

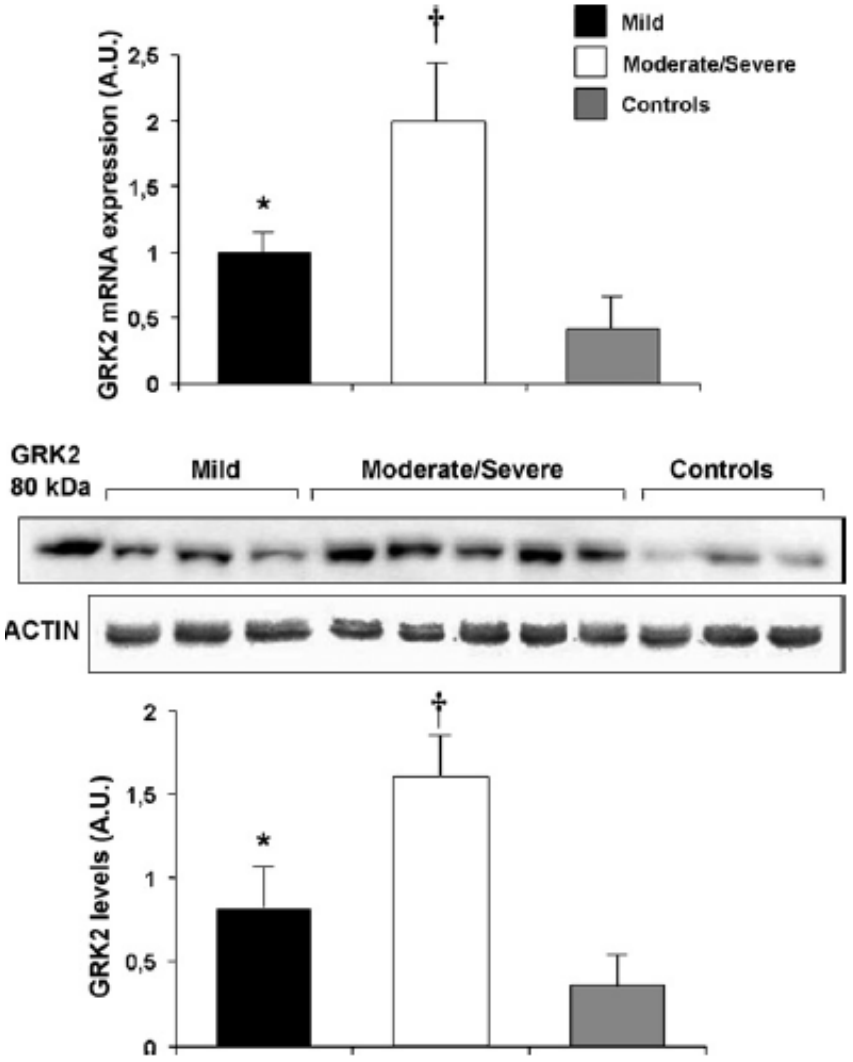
β-Adrenergic Receptor-stimulated cAMP formation is altered in cultured skin fibroblasts from AD subjects

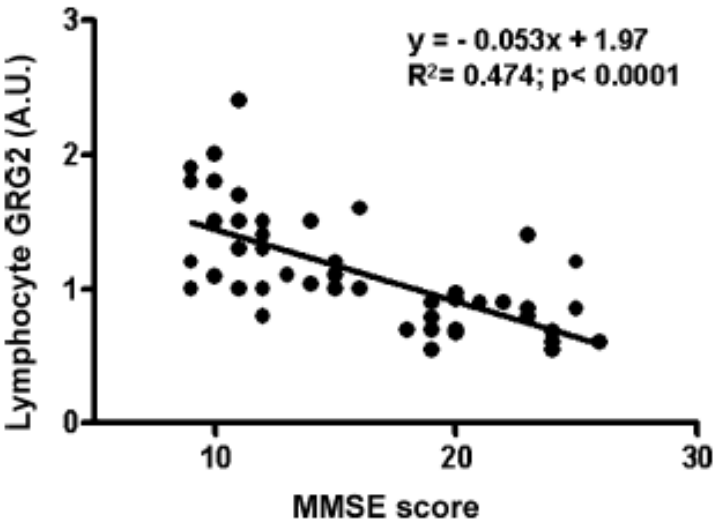




Huang HM, JBC 1993

Lymphocyte G-protein-coupled receptor kinase-2 is upregulated in patients with AD



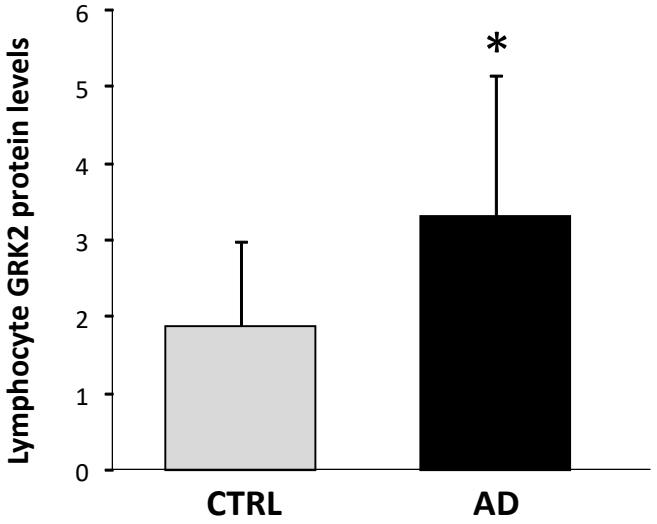


Leosco D, Neurosci Lett 2007

Our ongoing research

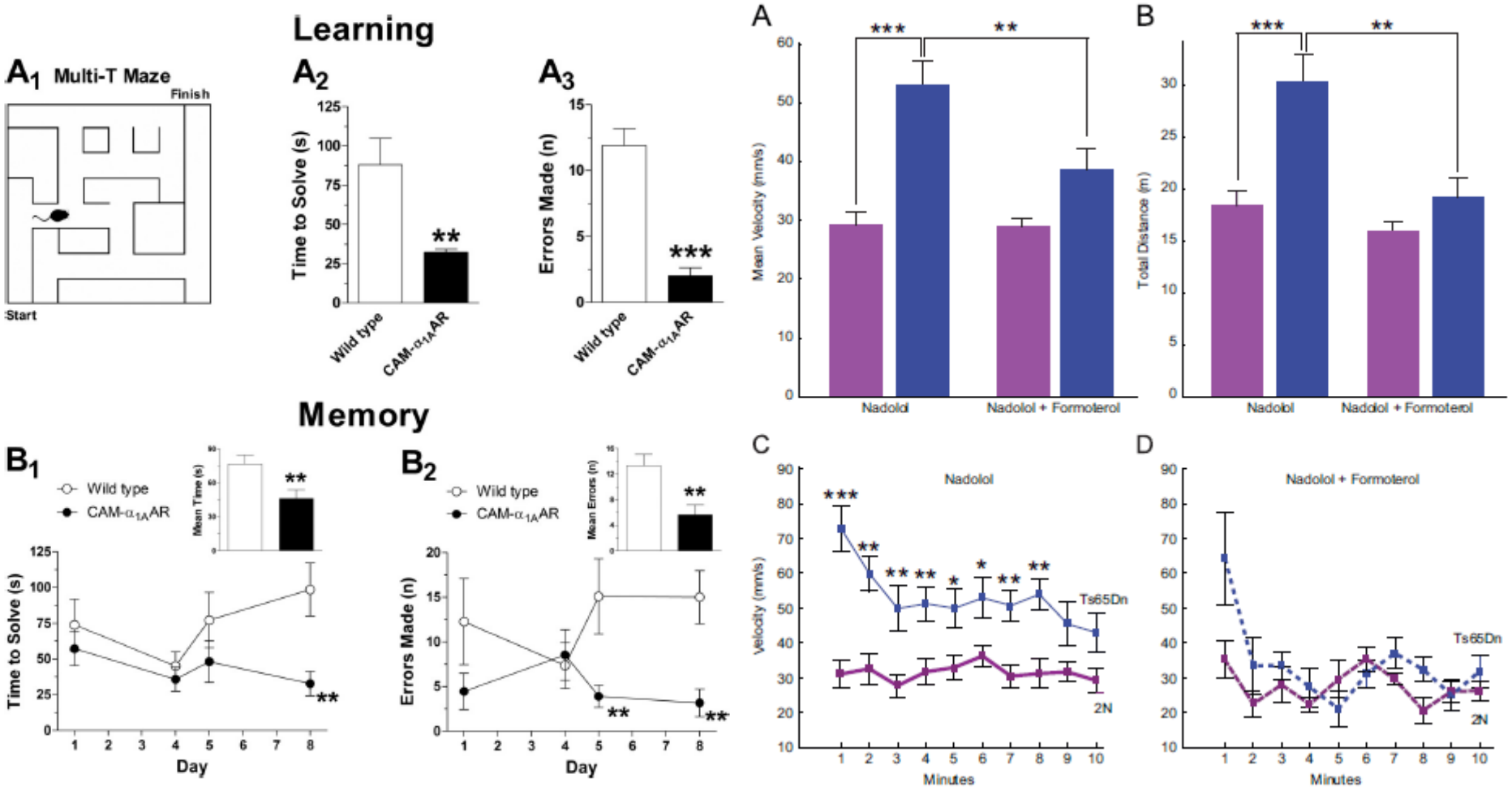
-74 subjects enrolled (healthy controls, MCI and AD subjects)

- At diagnosis → naive from AD medications
- Clinical and neuropsychological assessment
- Evaluation of lymphocyte GRK2 protein and mRNA levels
- Evaluation of membrane β-AR levels in lymphocytes
- Evaluation of autonomic dysfunction (heart rate variability)
- 1 year follow up



N=32
MMSE CTRL= 29.2 ± 0.97
MMSE AD= 20.4 ± 7.29

Therapeutic potential of AR modulation: agonists



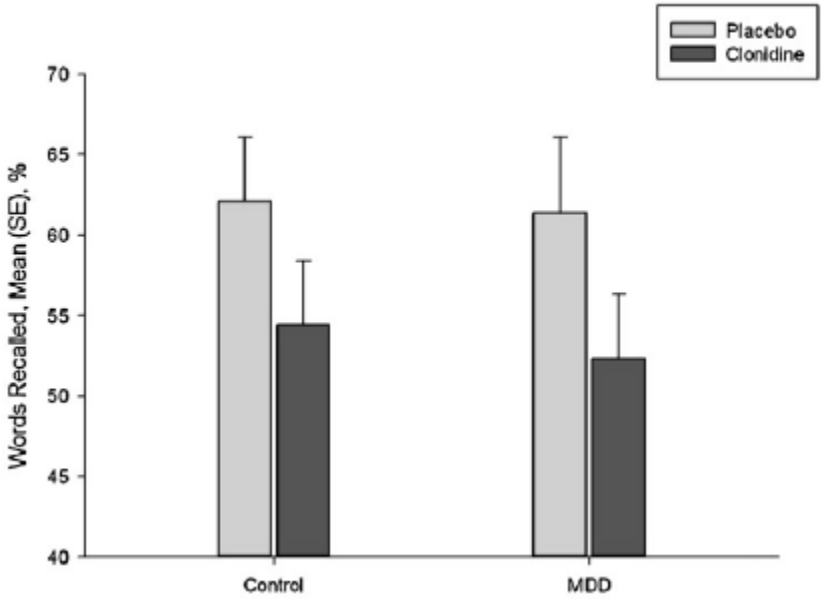
α1-agonism

β2-agonism

Doze VA, Mol Pharmacol 2011

Dang V, Biol Psych 2014

Therapeutic potential of AR modulation: agonists to the inhibitory α2-AR and NE transporter inhibitors



clonidine

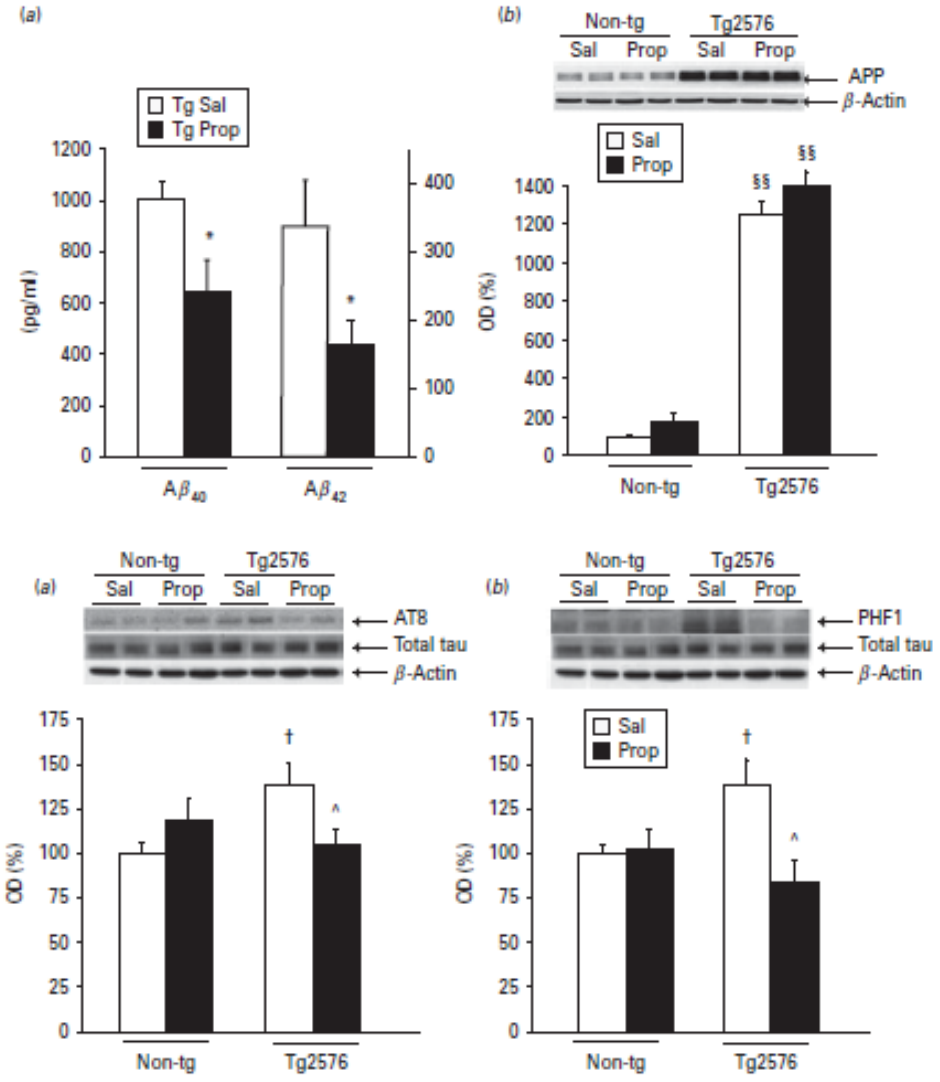
Measure	n	Baseline: Mean (SD)	Change: LS Mean (SE)	Between-Group p
ADAS-Cog total				0.300
ATX + CI	46	21.7 (10.7)	+0.6 (0.9)	—
PLA + CI	44	21.3 (10.4)	−0.8 (0.9)	—
MMSE total				0.475
ATX + CI	46	20.3 (4.5)	+1.2 (0.5)	—
PLA + CI	45	20.3 (4.2)	+0.7 (0.5)	—
CGI-S				0.335
ATX + CI	46	3.5 (0.7)	−0.0 (0.1)	—
PLA + CI	44	3.7 (0.6)	−0.1 (0.1)	—
NPI total				0.619
ATX + CI	46	6.8 (14.1)	+4.6 (1.7)	—
PLA + CI	45	8.4 (8.7)	+3.4 (1.8)	—
ADCS-ADL				0.212
ATX + CI	43	65.1 (6.8)	−0.6 (1.3)	—
PLA + CI	44	58.1 (14.2)	−3.0 (1.4)	—

atomoxetine

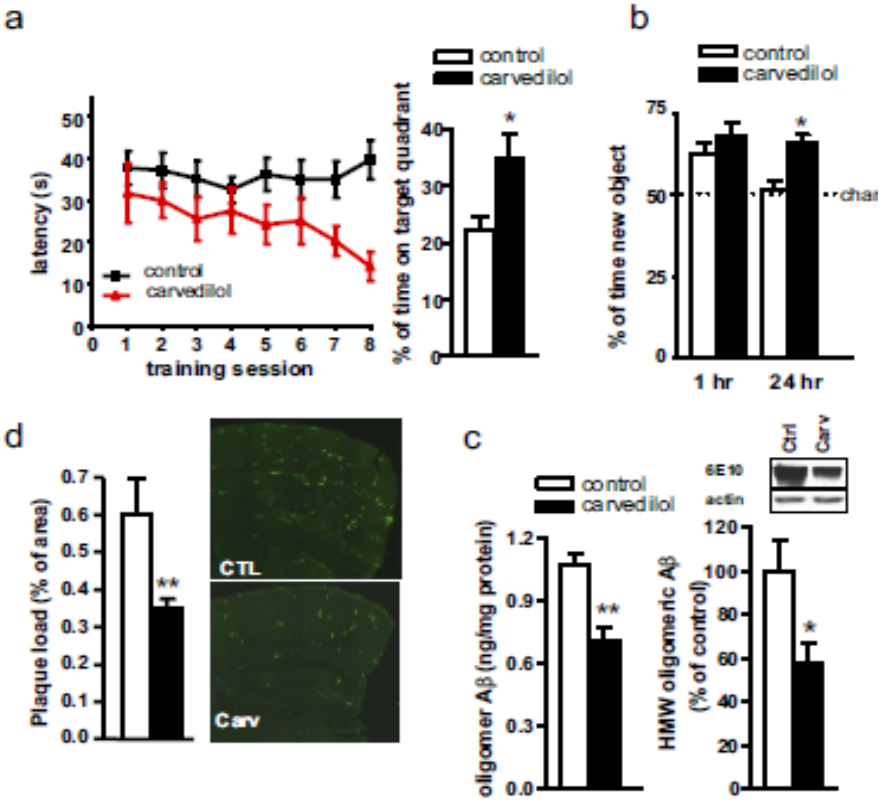
Kuffel A, Psychoneuroendrocr 2014

Mohs RC, Am J Ger Psych 2009

Therapeutic potential of AR modulation: β-AR antagonists



propranolol



carvedilol

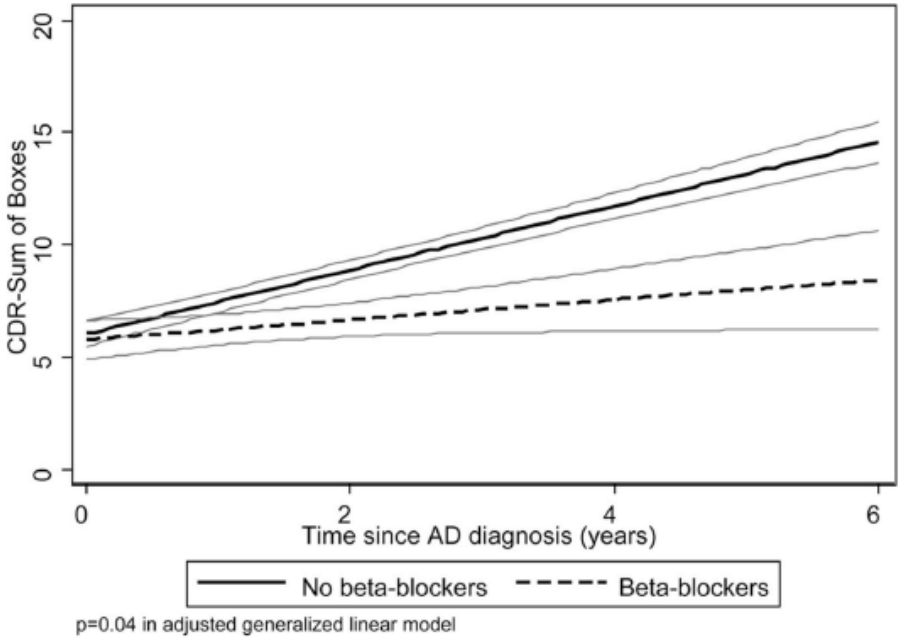
Dobarro M, Int J Neuropsy 2013

Wang J, Neurobiol Aging 2011

Therapeutic potential of AR modulation: evidence from anti-hypertensive use of β-AR antagonists

CDR Sum of Boxes vs. Medication Use

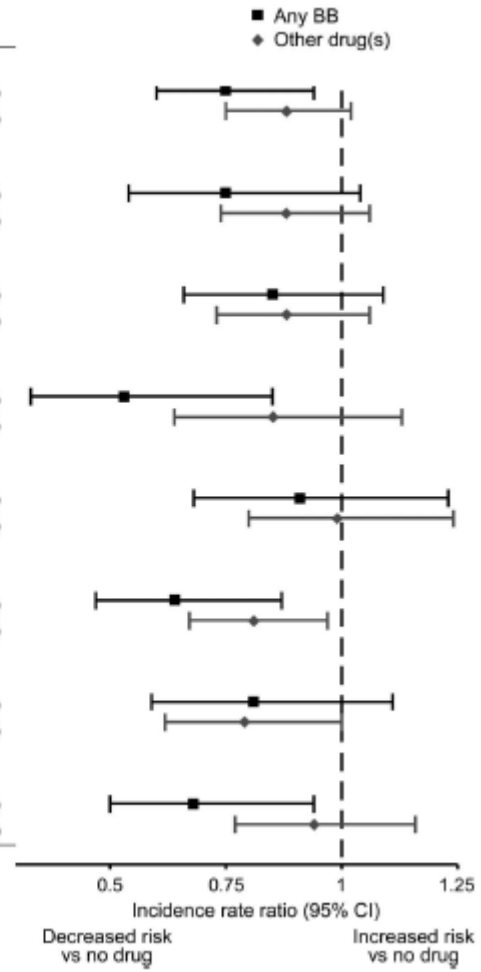
Variable	Univariate Models	
	Coeff (95% CI)	Coeff * Time (95% CI)
Statins	−.72 (−2.3, .85)	**−1.10 (−1.78, −.42)**
Beta-blockers	−.22 (−1.75, 1.32)	**−.92 (−1.57, −.25)**
Diuretics	.14 (−1.30, 1.58)	.53 (−.28, 1.34)
Time	**1.49 (1.31, 1.66)**	N/A



p=0.04 in adjusted generalized linear model

Rosenberg PB Am J Ger Psych 2008

	No. cases/ men	IRR (95% CI)
Use at baseline		
Any BB	108/335	0.75 (0.60-0.94)
Other drug(s)	363/956	0.88 (0.75-1.02)
Use at exams 4 and 6		
Any BB	45/112	0.75 (0.54-1.04)
Other drug(s)	220/464	0.88 (0.74-1.06)
No diabetes		
Any BB	82/228	0.85 (0.66-1.09)
Other drug(s)	226/602	0.88 (0.73-1.06)
With diabetes		
Any BB	24/100	0.53 (0.33-0.85)
Other drug(s)	122/323	0.85 (0.64-1.13)
Age ≤75 years		
Any BB	56/166	0.91 (0.68-1.23)
Other drug(s)	143/415	0.99 (0.80-1.24)
Age >75 years		
Any BB	52/169	0.64 (0.47-0.87)
Other drug(s)	220/541	0.81 (0.67-0.97)
PP <70 mmHg		
Any BB	56/168	0.81 (0.59-1.11)
Other drug(s)	168/462	0.79 (0.62-1.00)
PP ≥70 mmHg		
Any BB	52/167	0.68 (0.50-0.94)
Other drug(s)	195/494	0.94 (0.77-1.16)



Gelber RP Neurology 2013

Currently ongoing trials of AR modulators in AD

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Example: "Heart attack" AND "Los Angeles"
Search for studies: Search
Advanced Search | Help | Studies by Topic | Glossary

Find Studies | About Clinical Studies | Submit Studies | Resources | About This Site

Home > Find Studies > Search Results Text Size

17 studies found for: alzheimer | Interventional Studies | adrenergic
Modify this search | How to Use Search Results

Status	Study
Recruiting	Improving Beta-2 Adrenergic Signaling in Alzheimer's Disease **Conditions:** Alzheimer's Disease; Cognitive Dysfunction **Interventions:** Drug: Formoterol A; Drug: Formoterol B
Recruiting	Trial of Carvedilol in Alzheimer's Disease **Condition:** Alzheimer's Disease **Interventions:** Drug: Carvedilol; Drug: Placebo
Recruiting	Effects of Atomoxetine in Mild Cognitive Impairment **Condition:** Mild Cognitive Impairment **Interventions:** Drug: Atomoxetine; Drug: Placebo

Conclusions

✓**The LC is the unique source of NE in brain and it plays an important role in the regulation of vigilance and sleep-wake cycles. LC is also involved in attention, synaptic plasticity, memory formation and retrieval, decision making and performance facilitation**

✓**In AD, LC degeneration is observed early in the course of the disease**

✓**LC degeneration contributes to AD development and leads to dysregulation of adrenergic receptors and exacerbation of Aβ-induced neuroinflammation**

✓**The addition of LC lesion on top of mutant APP expression in mice seems to recapitulate more closely the neuropathological and cognitive features of clinical AD**

✓**Whether AR stimulation or inhibition might be beneficial in AD therapeutics is still unclear. Evidence support both hypothesis, making the picture not easy to delineate**

✓**Whatever is the prevalent role of AR system in AD, it is certain that further studies are needed, aiming at investigating both hypotheses comprehensively**

Thank you!