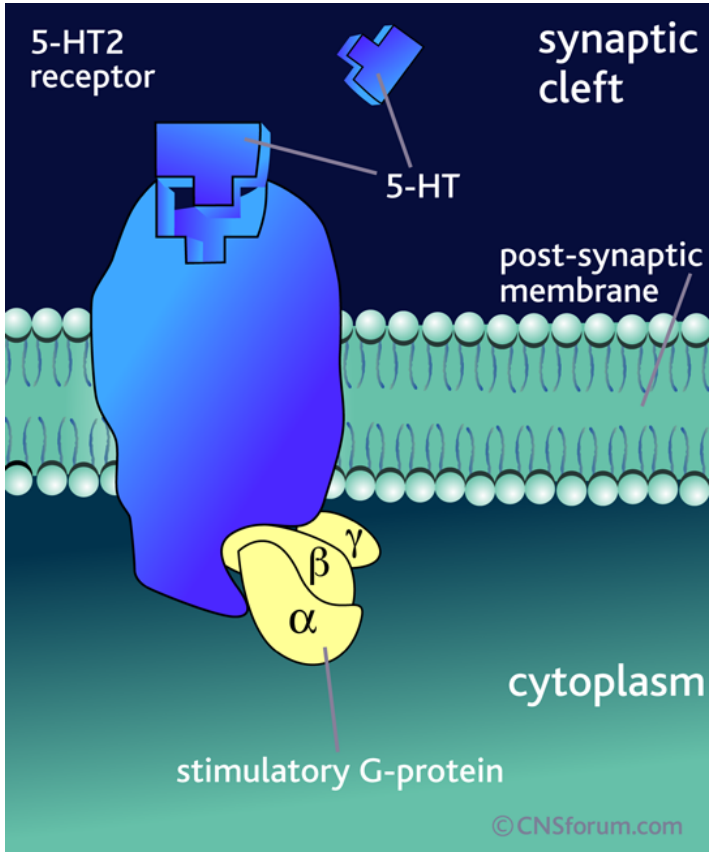
Serotonergic receptors: the new targets in the treatment of Alzheimer's disease



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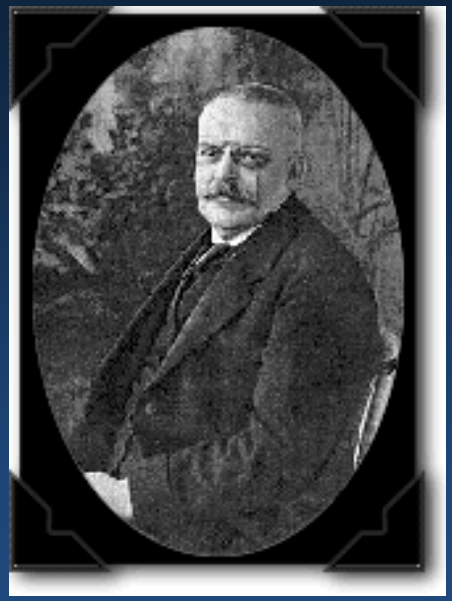
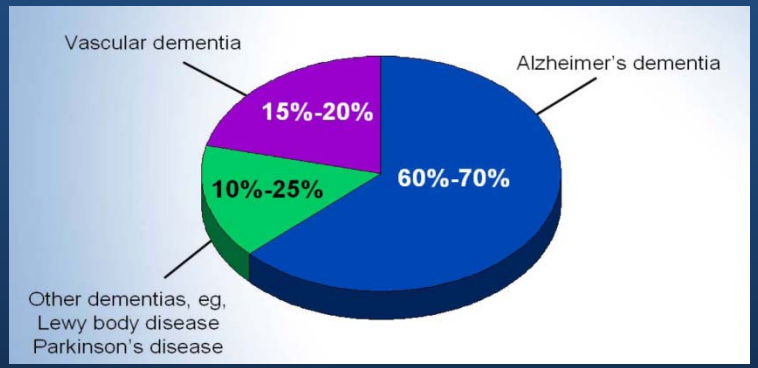
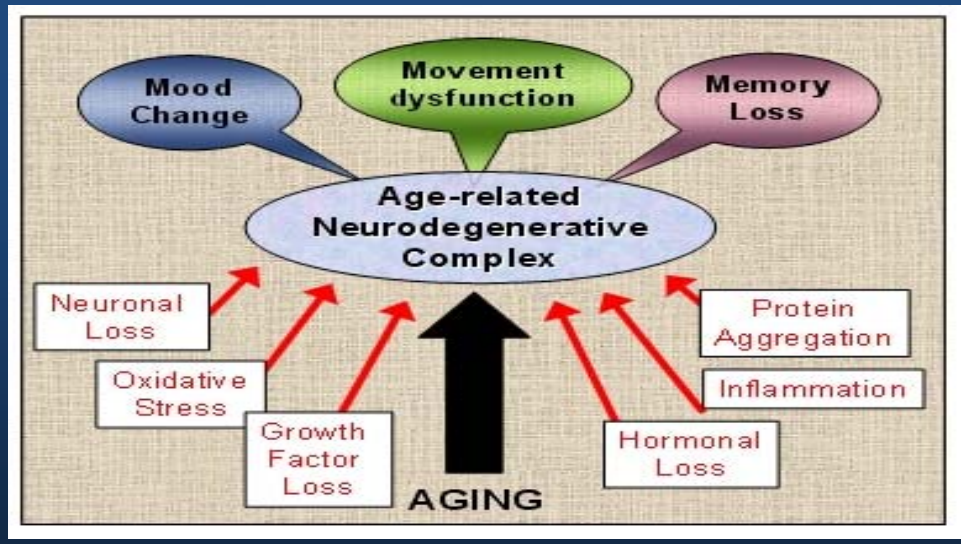
Malta 24.10.2013.



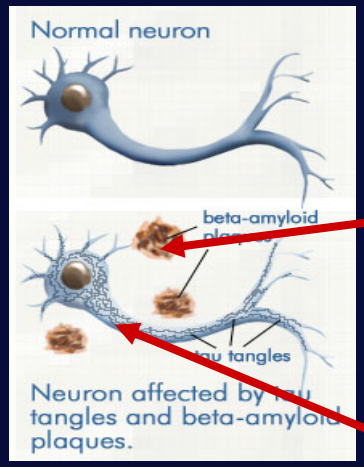
Alzheimer's disease

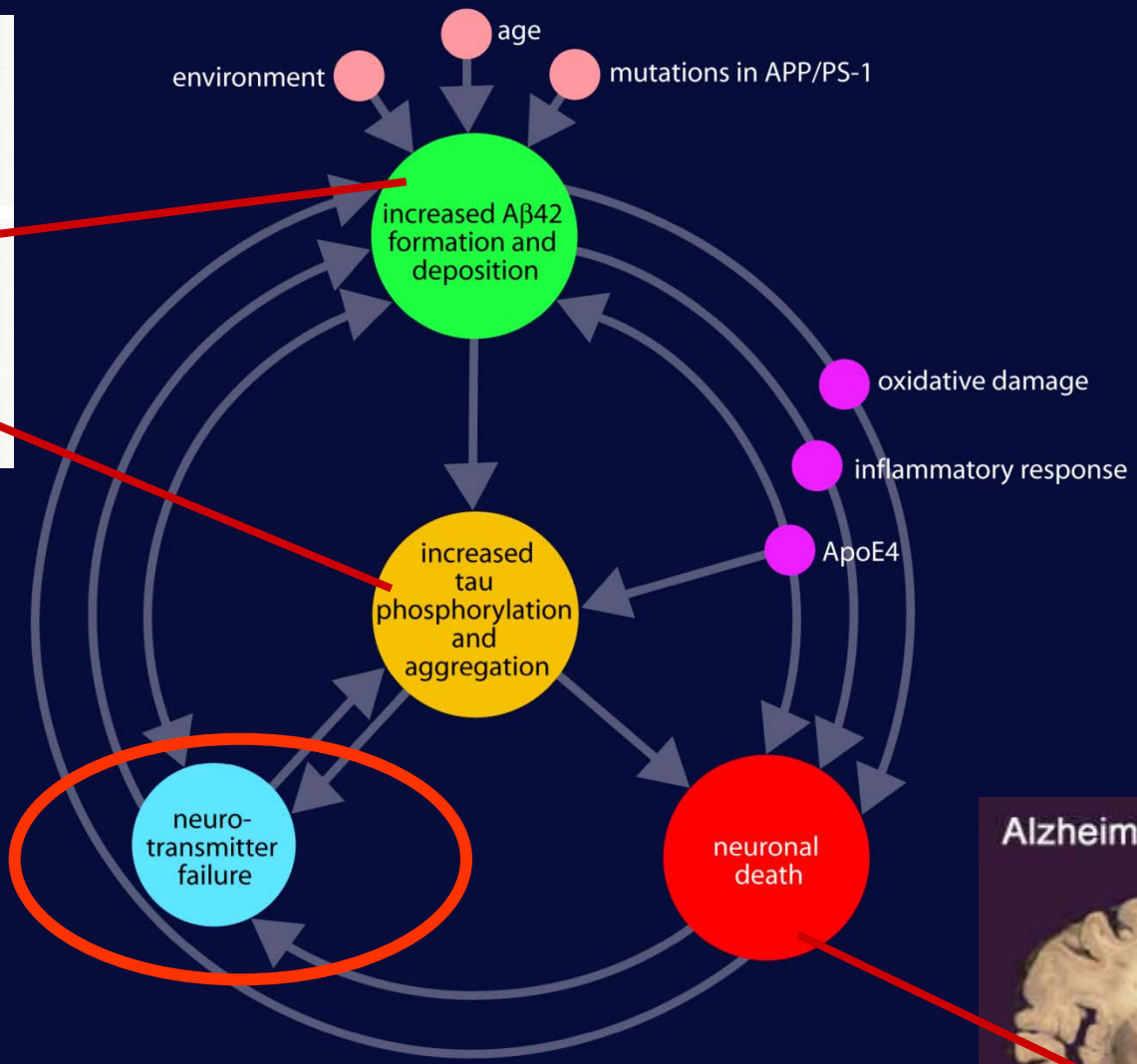
Symptoms and risk factors

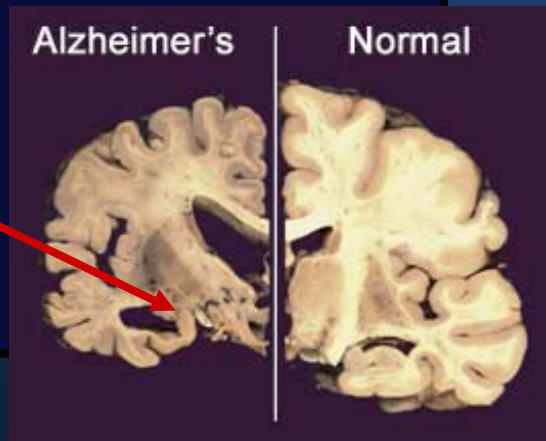




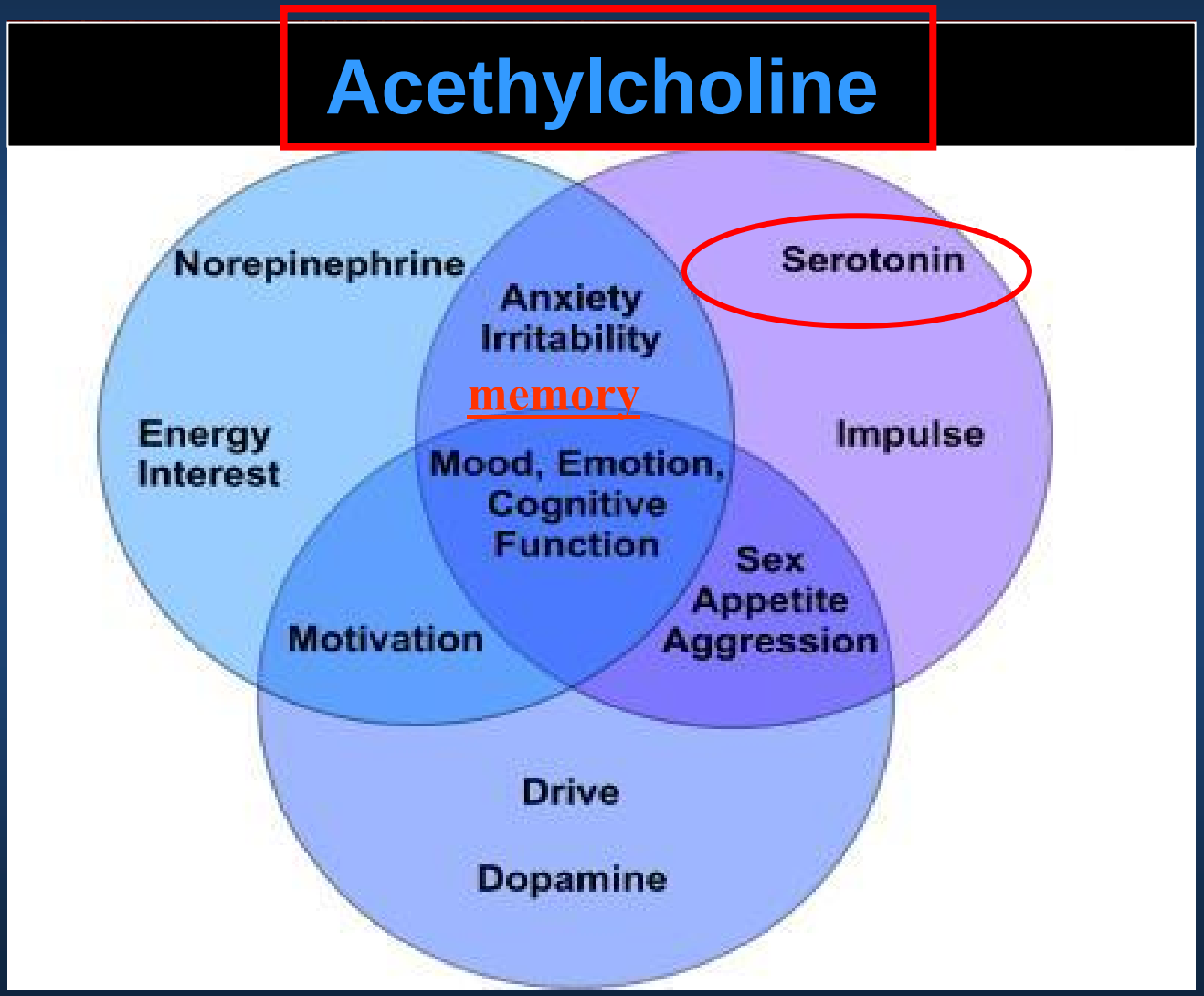
Pathological mechanisms in Alzheimer's disease



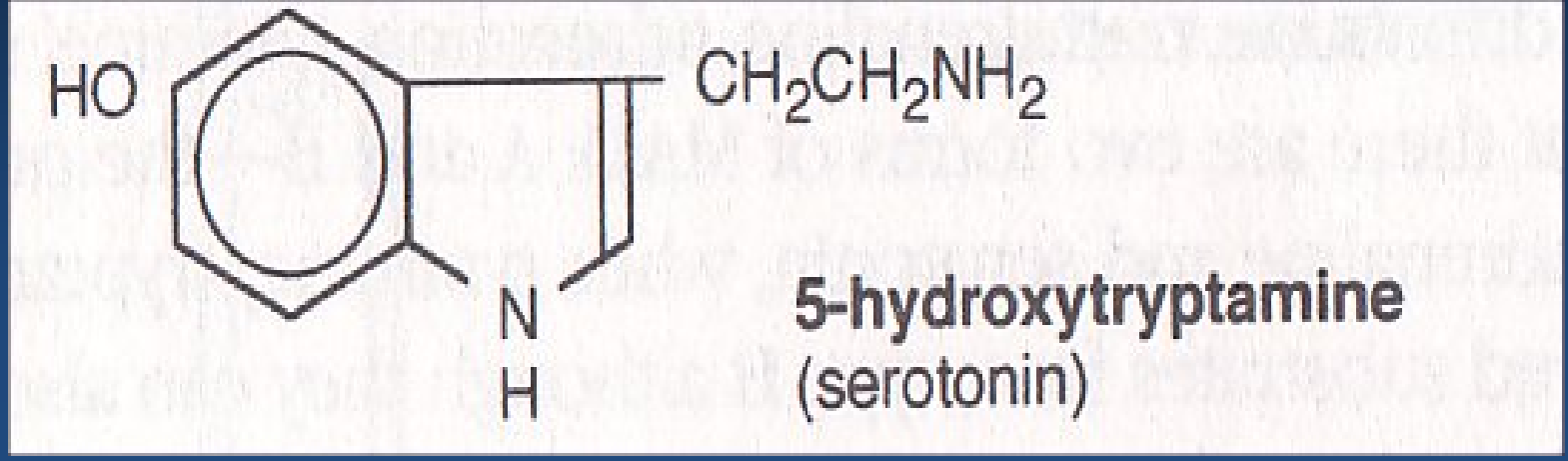




Neurotransmitters in AD

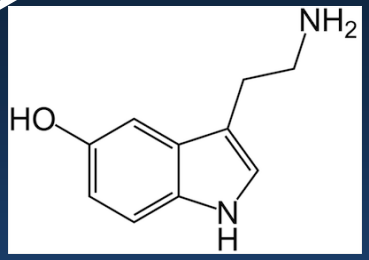


Serotonin

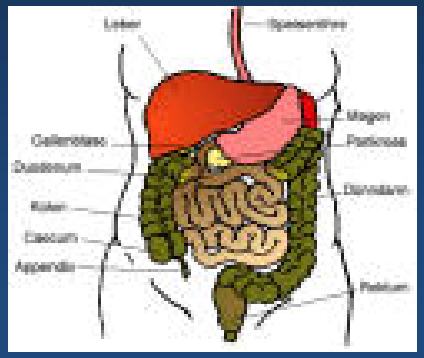


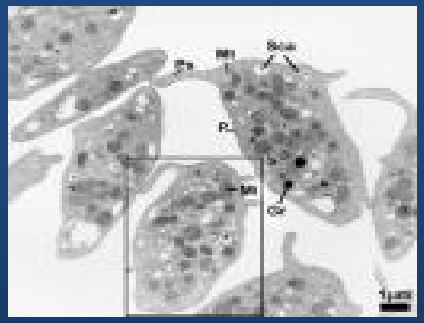
Serotonin

95%
hormone

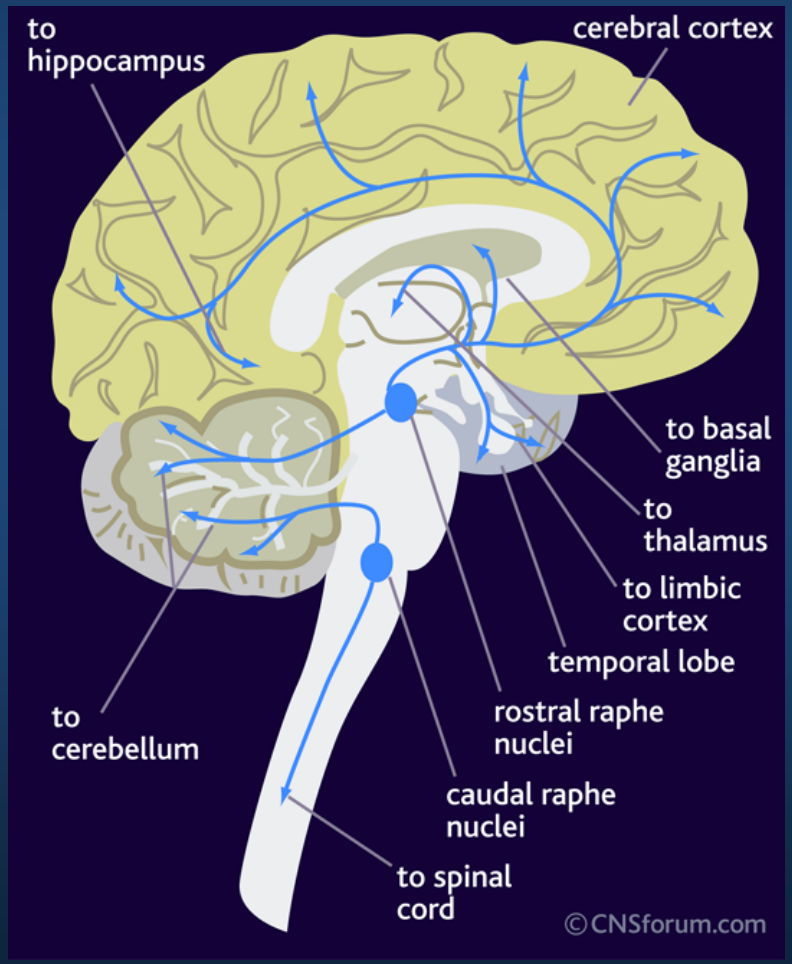


5%
neurotransmitter





BBB

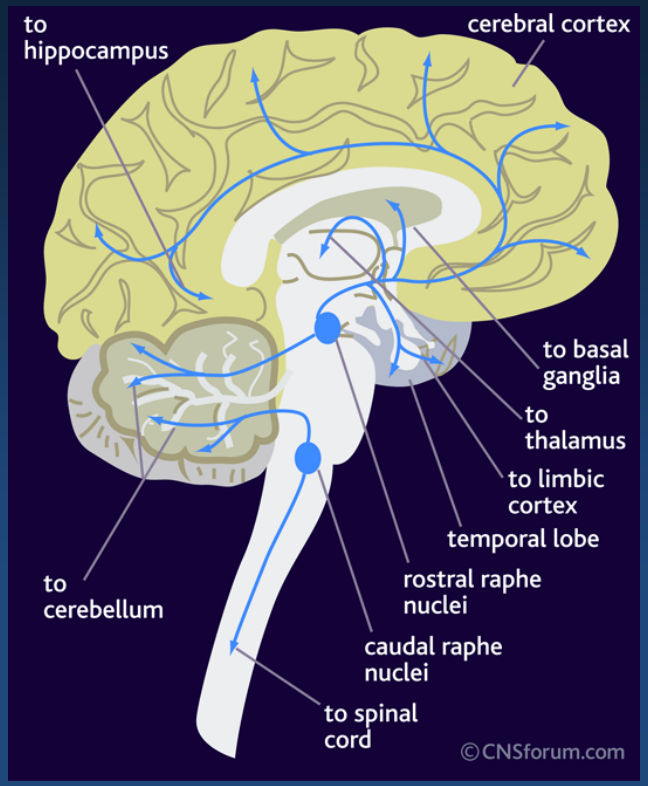


peristaltic
vomiting
platelet aggregation and homeostasis
mediator of inflammation
tonus of blood vessels

SEROTONIN
neurotransmitter in CNS
regulates:

mood
appetite (feeding)
body weight
pain
sleep
circadian rhythm
termoregulation

Altered function in neuropsychiatric disorders



"It is possible that the serotonin in our brain plays an essential part in keeping us sane....."

Sir John Gaddum, 1954

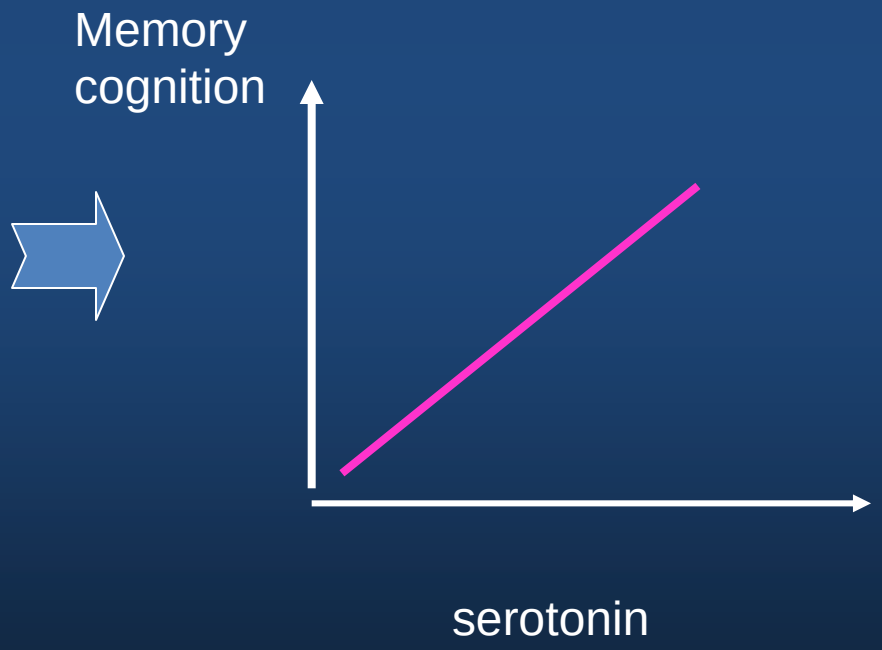
The serotonergic system in ageing and Alzheimer's disease

José Julio Rodríguez [a,b,c,d,*], Harun N. Noristani [e], Alexei Verkhratsky [a,b,c,e,**]

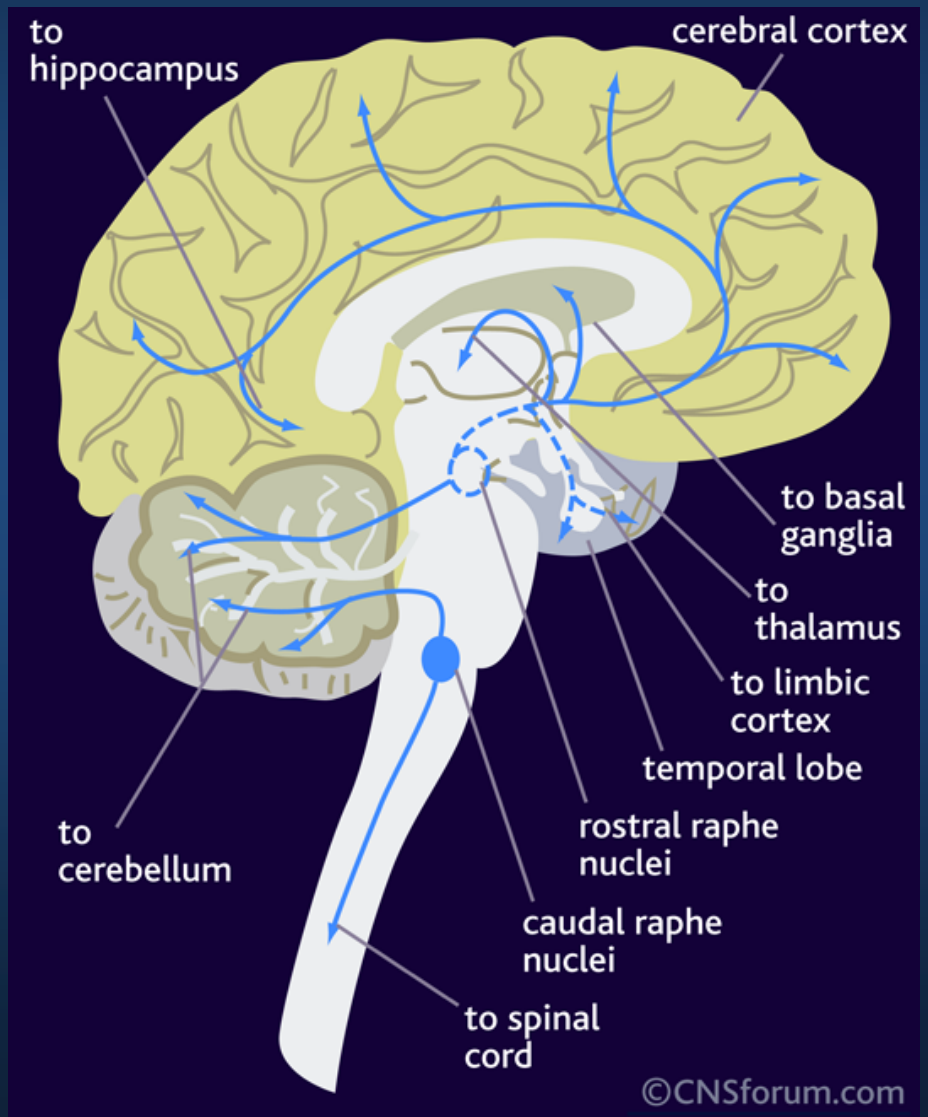
Progress in Neurobiology 99 (2012) 15–41

Reduced 5-HT neurotransmission impairs learning and memory functions

Increased 5-HT neurotransmission is associated with improved memory and cognitive performance

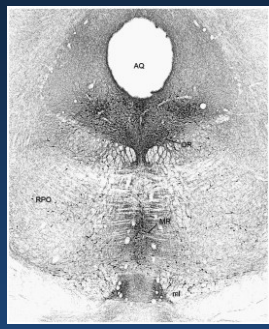


The serotonin pathways in Alzheimer's disease

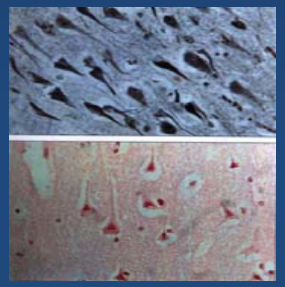


Transmission of serotonin descending from the rostral raphe nuclei to the limbic cortex and temporal lobe is decreased in Alzheimer's disease compared with normal. The other major pathways for serotonin transmission, which project to the cerebellum and frontal lobe and descend the spinal cord, remain unchanged.

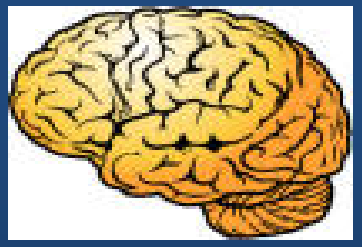
Serotonergic system in Alzheimer's disease



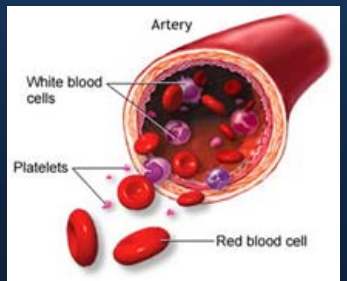
- Progressive accumulation of neurofibrilar tangles in neurons and senile plaques in the region of serotonergic cell bodies



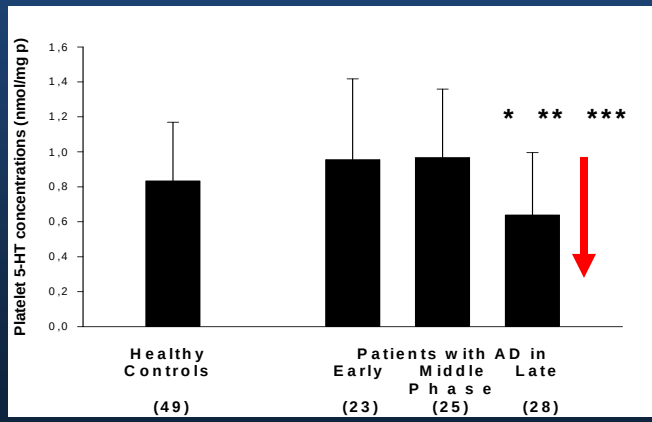
- Reduced number of neurons



- Decreased serotonin levels in cortex, hippocampus, striatum (30%)



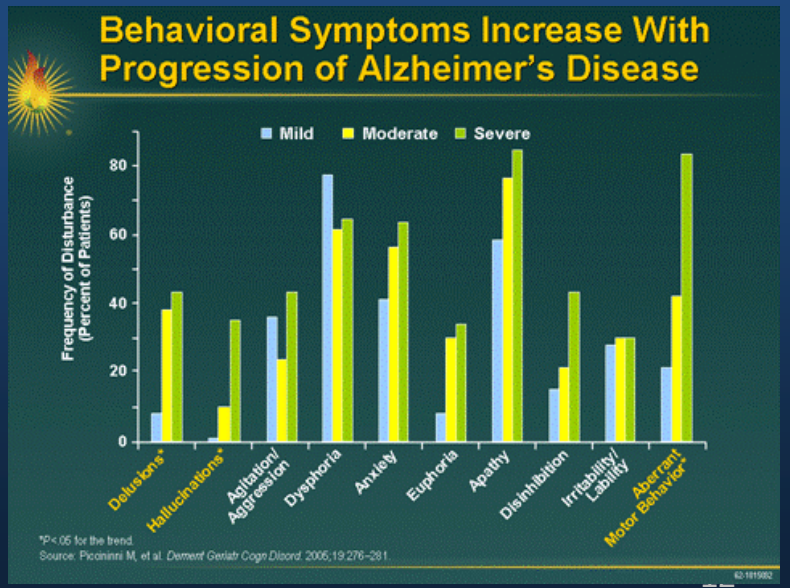
- Decreased platelet 5-HT levels



Mück Šeler et al., 2009.

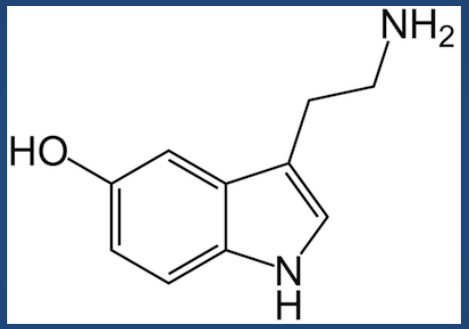
Serotonin in AD
Behavioral and Psychological Symptoms of Dementia
BPSD

- **Appears in 70-90% of patients**
- **Influence the progress of AD**
- **Stress for patients and caregivers**
- **Interaction of several factors (psychological, biological, genetical...)**



Symptoms of BPSD

- Agitation: repeat movement, aimless wandering
- Agression: verbal, physical
- Depression: tearfulness, anxiety, guilt
- Apathy: loss of interest
- Psychosis: delusion, halucination
- Changes in appetite and sleep

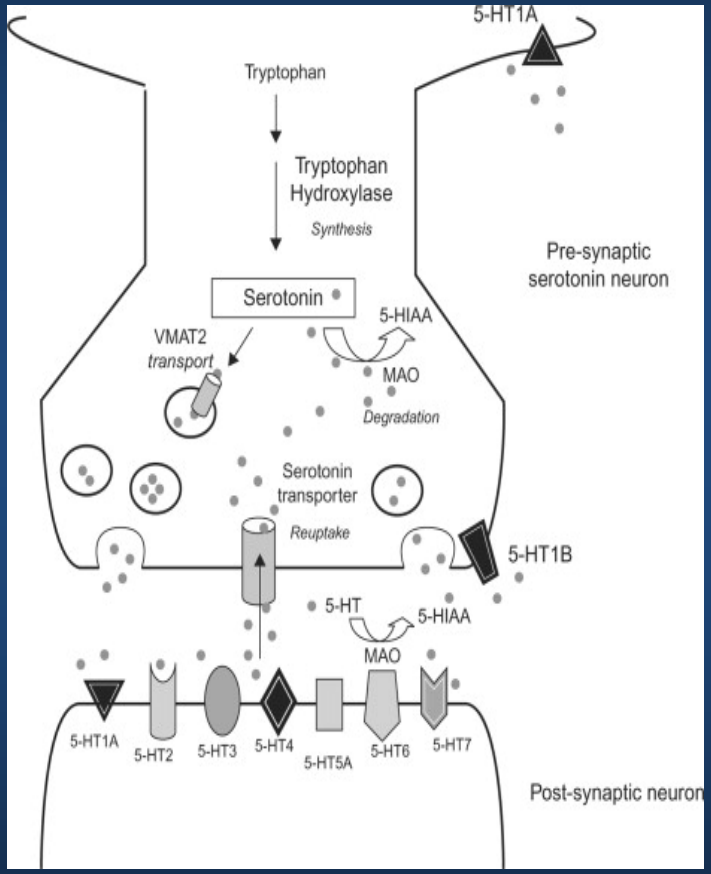


serotonin

- Treatment with antidepressants and antipsychotics

Serotonergic sistem is highly complex:

- **Multiple receptor subtypes**
- **Receptor regulate complex signal transduction pathways**
- **Serotonergic receptors as targets**



Serotonergic receptors

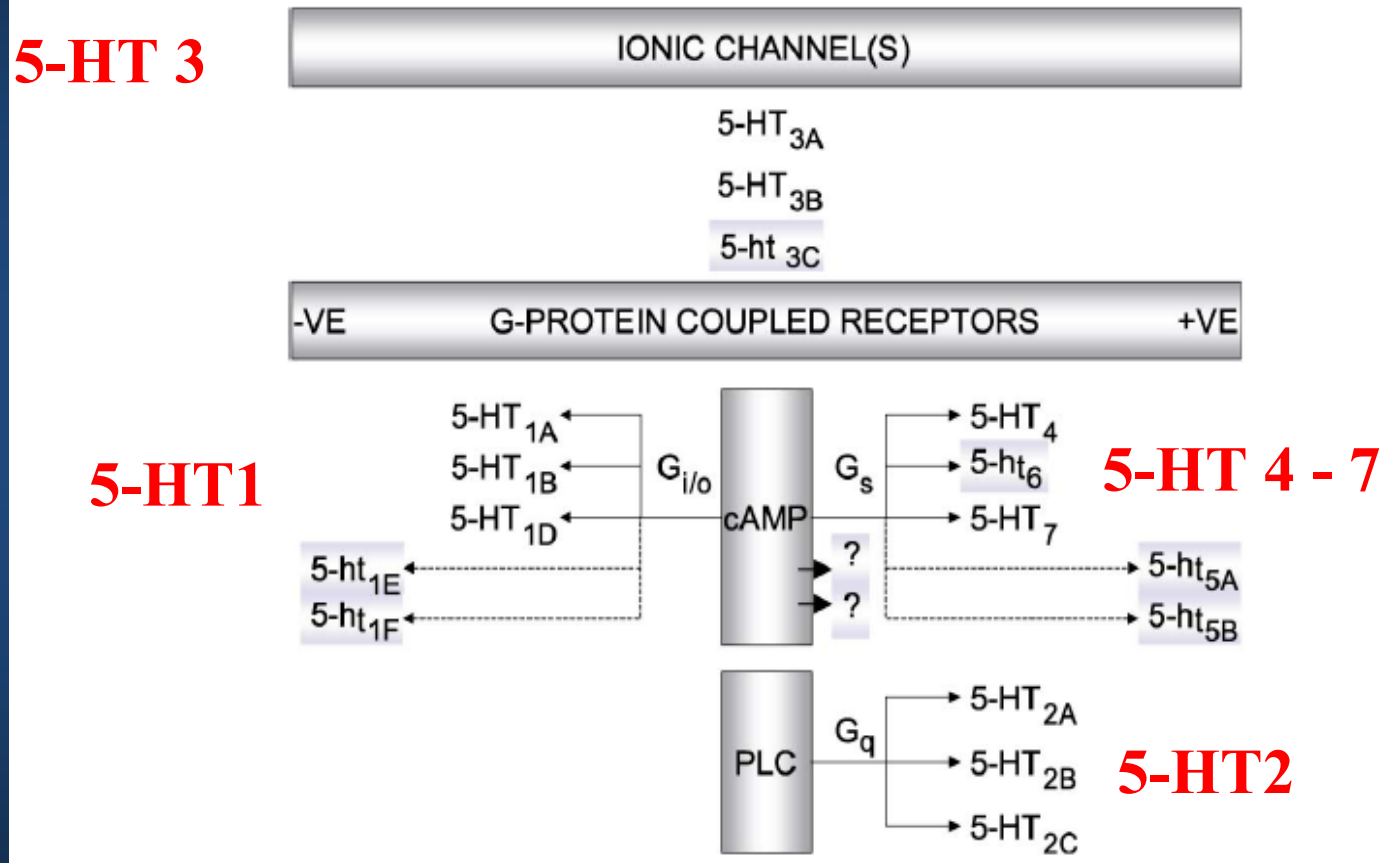
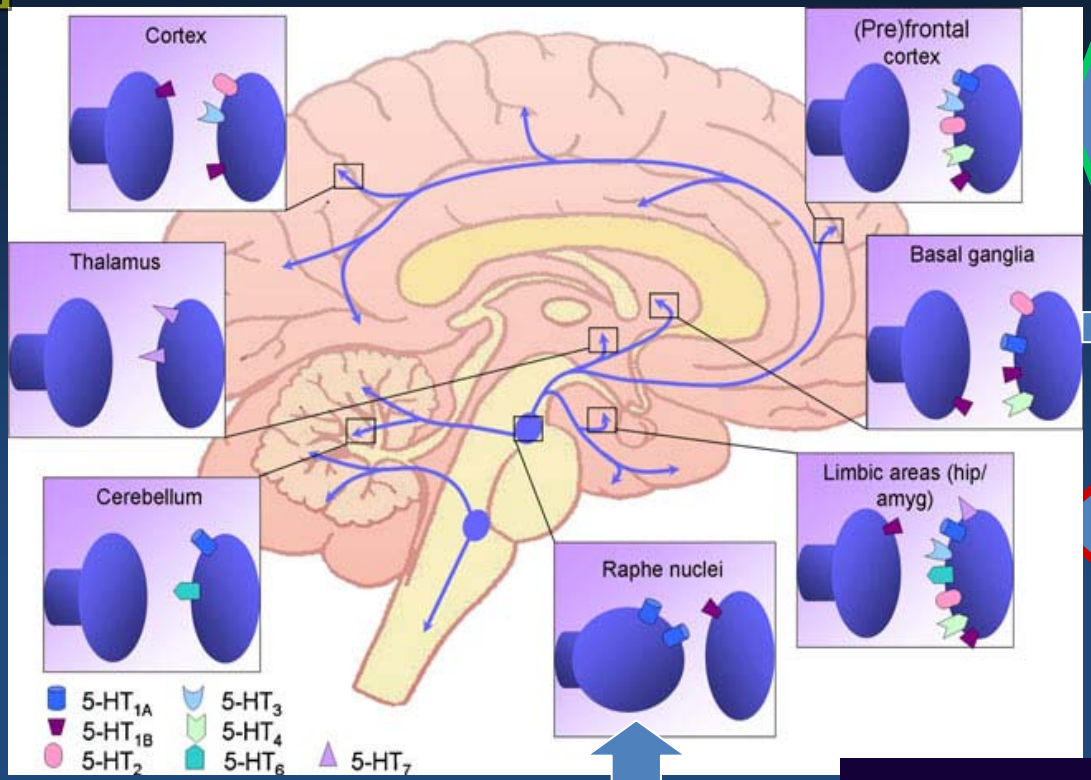


Fig. 1. Graphical representation of the current classification of 5-HT receptors. Receptor subtypes represented by coloured boxes and lower case designate receptors that have not been demonstrated to definitively function in native systems. Abbreviations: 3′-5′ cyclic adenosine monophosphate (cAMP); phospholipase C (PLC); negative (−ve); positive (+ve).



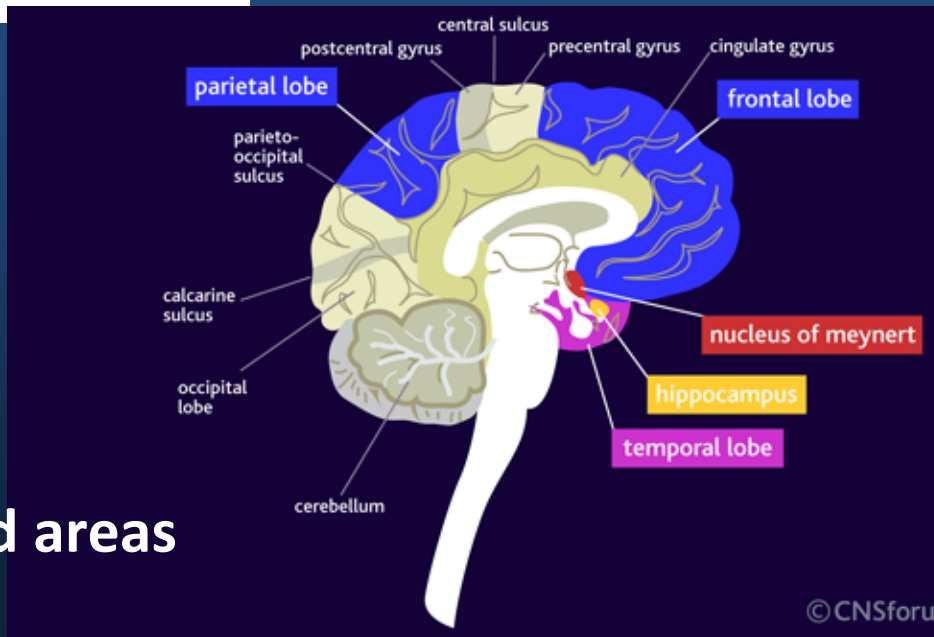
5-HT1A
5-HT1B
5-HT2
5-HT3
5-HT4

5-HT1A
5-HT1B
5-HT2
5-HT4

5-HT1A
5-HT1B
5-HT2
5-HT3
5-HT4
5-HT6
5-HT7

5-HT1A
5-HT1B

Distribution of serotonergic receptors

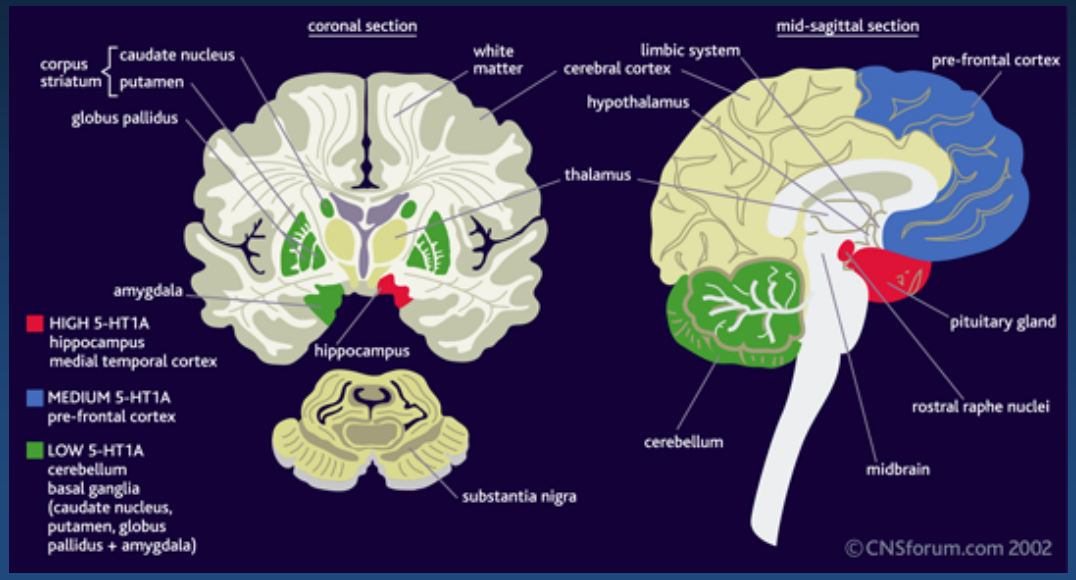


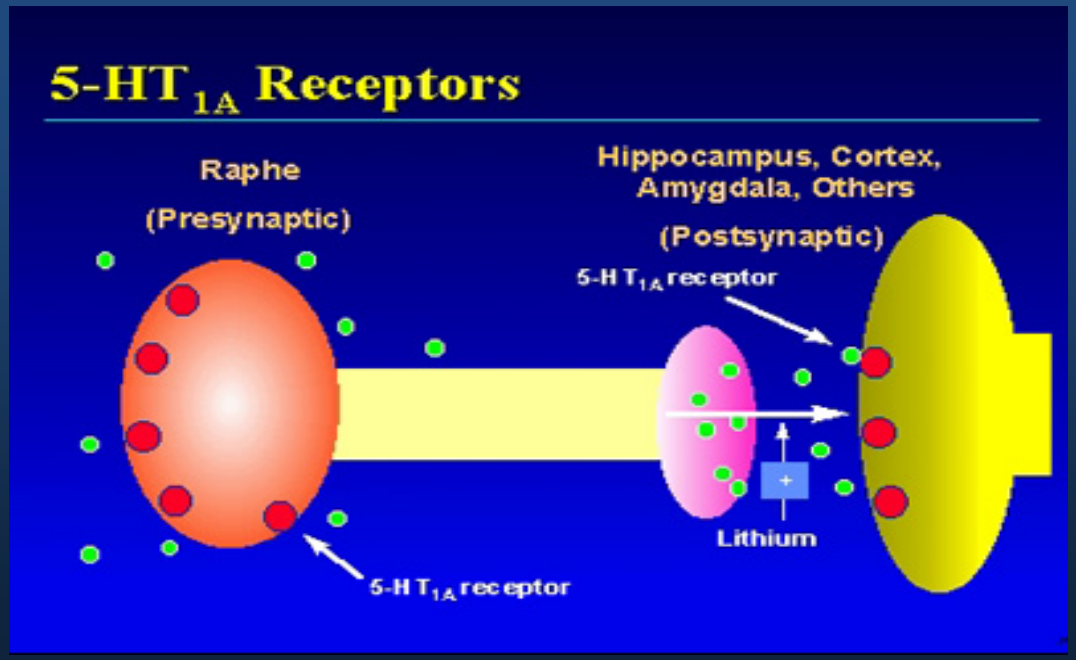
Dementia - Affected areas

5-HT1A receptors

Among the most abundant and widely distributed 5-HT receptors

Distribution of 5-HT1A receptors





In the brain regions:

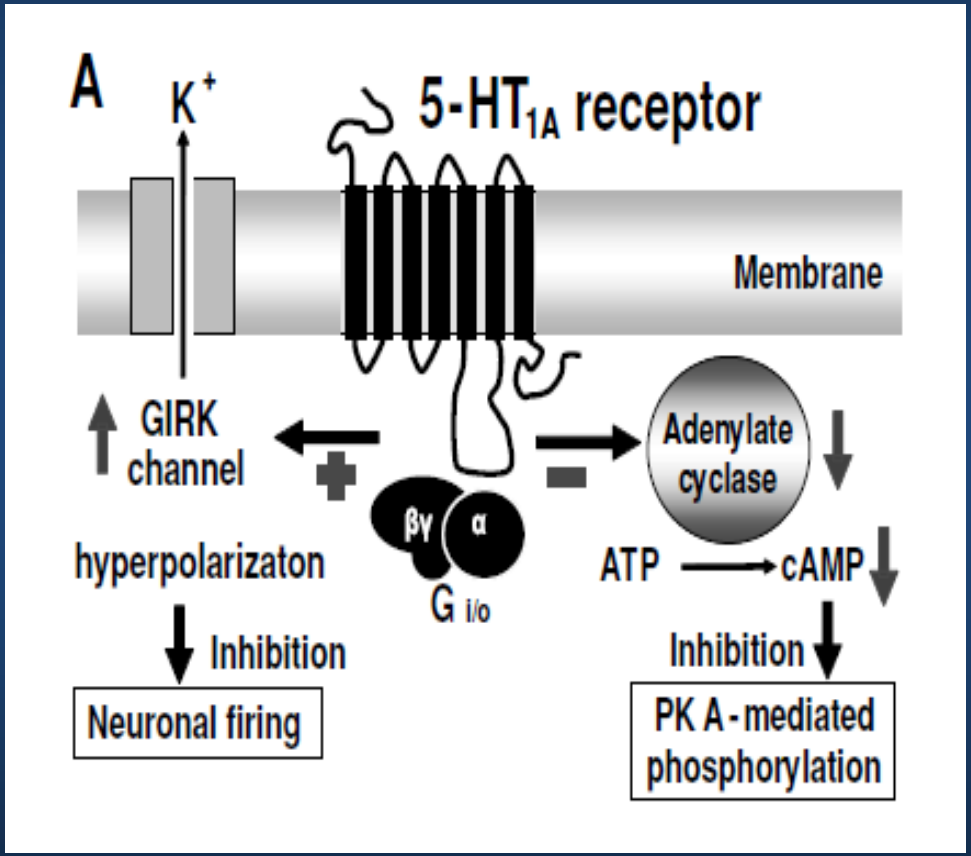
Hippocampus
Prefrontal cortex

On the neuron:

Presynaptic (autoreceptors)

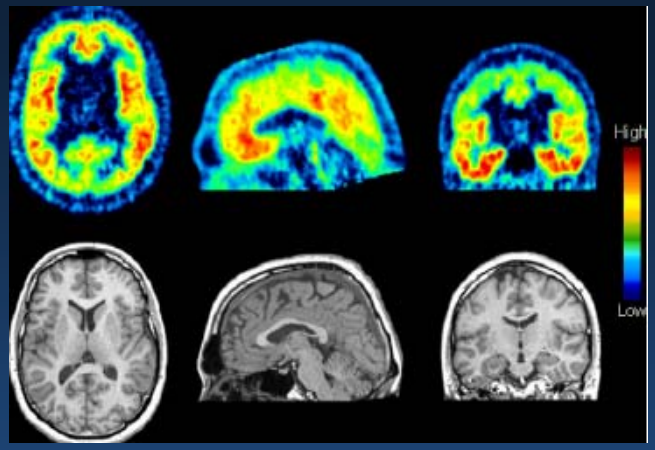
Postsynaptic (heteroreceptors)

Critical role in the regulating the activity of the entire serotonin system
Over-expression implicated in reducing 5-HT neurotransmission



Inhibition of the neuronal signaling:

- **Associated with inhibitory G-protein (Gi)**
- **Inhibits adenylate cyclase**
- **Decrease production of cyclic AMP (cAMP)**
- **Inactivates protein kinase A (PKA)**



5-HT1A and cognition in healthy persons

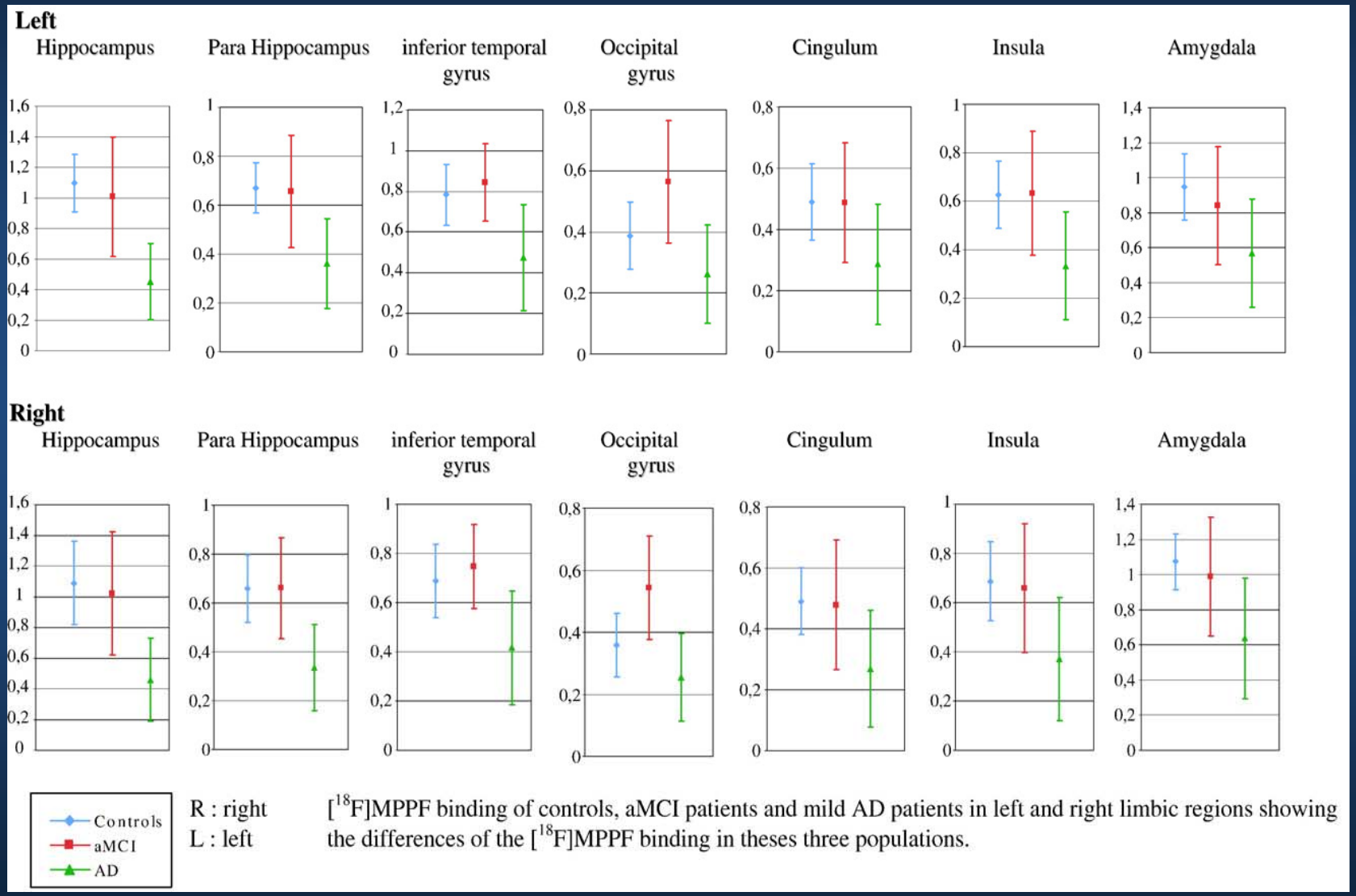
Table 1
Summary of findings in PET studies investigating the relationship between 5-HT HT_{1A} receptor BP and cognitive functions

Study	Sample		Radioligand	MMS	Correlation between 5-HT1A BP and main cognitive functions		
	Subjects	*n*			Verbal memory	Non-verbal memory	Executive functions
Yasuno et al. [117]	Controls	16	[11C]WAY100635		Negative correlation in HC	Negative correlation in HC	
Borg et al. [13]	Controls	24	[11C]WAY100635		No correlations	No correlations	No correlations
Borg et al. (unpublished data)	Controls	54	[11C]WAY100635		No correlations	No correlations	No correlations
Kepe et al. [49]	AD	8	[18F]MPPF	Positive correlation in HC and raphe	Positive correlation in HC and raphe post hoc		
	MCI	6					
Truchot et al. [110]	AD	10	[18F]MPPF	No correlations	No correlations	No correlations	No correlations
	MCI	11					

Possible explanations for the discrepant findings include differences in specificity and sensitivity of the neurocognitive test procedures used, methodological differences and potential variation in the samples due to ethnic background.

Borg (2008)

A decrease of MPPF binding to 5-HT1A receptors in the hippocampus and in the parahippocampus in mild AD (PET study)



[^{18}F]MPPF binding of controls, aMCI patients and mild AD patients in left and right limbic regions showing the differences of the [^{18}F]MPPF binding in theses three populations.

Truchot et al., 2008

Serotonin 1A receptors in the living brain of Alzheimer's disease patients

Vladimir Kepe*, Jorge R. Barrio*†, Sung-Cheng Huang*, Linda Ercoli‡, Prabha Siddarth‡, Kooresh Shoghi-Jadid*, Gregory M. Cole§, Nagichettiar Satyamurthy*, Jeffrey L. Cummings¶, Gary W. Small‡, and Michael E. Phelps*†

702–707 | PNAS | January 17, 2006 | vol. 103 | no. 3

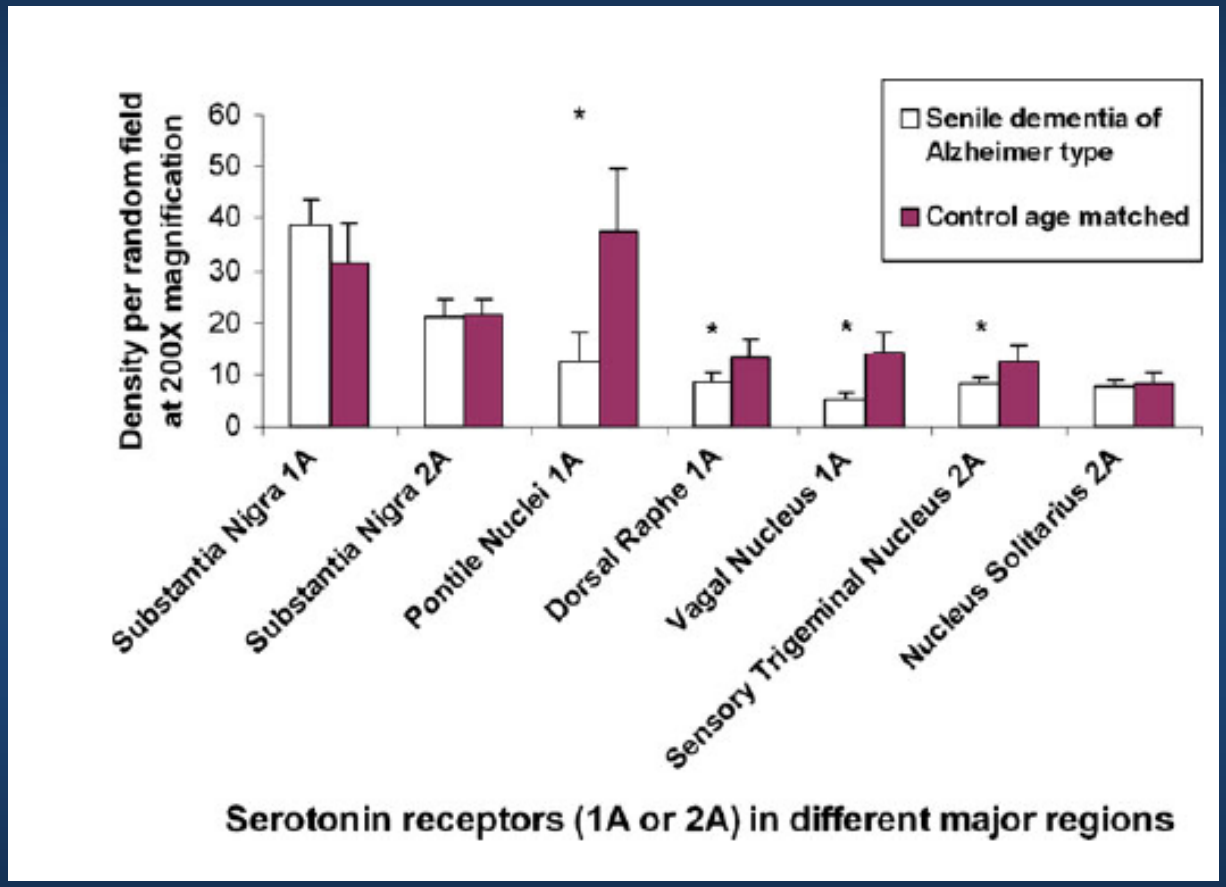
Table 1. Results of [F-18]MPPF PET quantitative data analysis

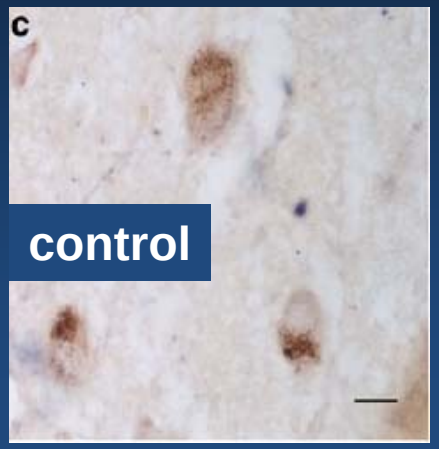
	Hippocampus	Raphe nuclei	Frontal lobe	Parietal lobe	LTL	PCG
Control	1.62 ± 0.07	0.63 ± 0.09	0.49 ± 0.15	0.63 ± 0.15	0.82 ± 0.17	0.68 ± 0.06
MCI	1.41 ± 0.14*	0.52 ± 0.11	0.44 ± 0.12	0.43 ± 0.11	0.80 ± 0.11	0.56 ± 0.12
AD	1.18 ± 0.27‡	0.37 ± 0.20†	0.41 ± 0.13	0.48 ± 0.13	0.73 ± 0.16	0.56 ± 0.20

MPPF results are given as mean BP ± 1 SD. Statistical significance of separation from the control group (ANCOVA): *, $P < 0.05$; †, $P < 0.01$; ‡, $P < 0.001$.

mild to moderate AD

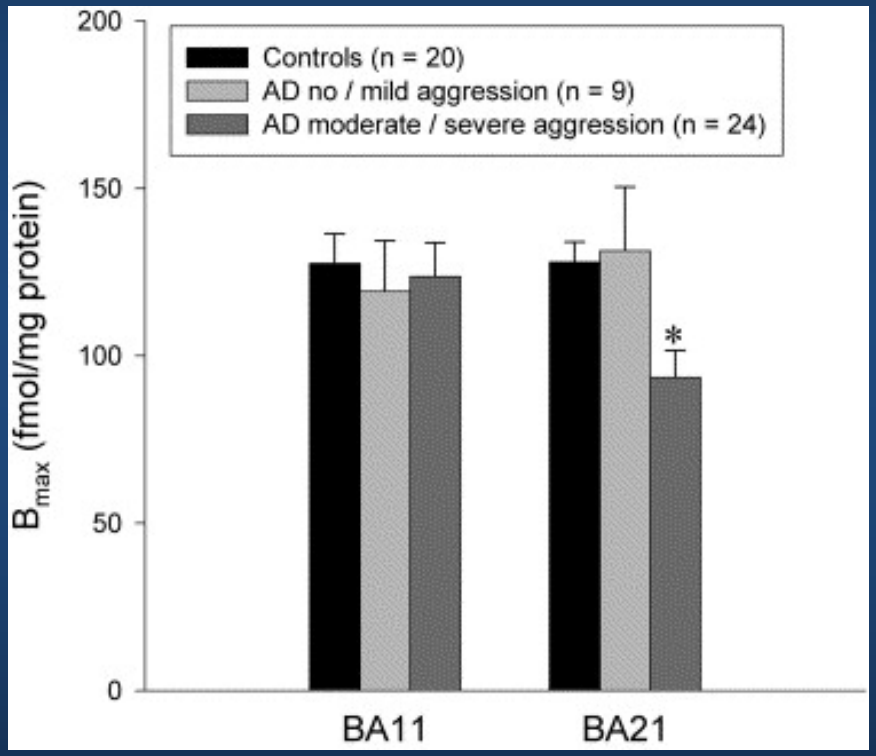
The density of 5-HT1A receptors (post mortem)





L. Y. Yeung · H. F. Kung · David T. Yew AGE (2010) 32:483–495

The number of 5-HT1A receptors is decreased in temporal cortex (BA21) of AD patients with aggressive behaviour



Lai et al 2003

Synthesis, Docking Studies and Biological Evaluation of Benzo[*b*]thiophen-2-yl-3-(4-arylpiperazin-1-yl)-propan-1-one Derivatives on 5-HT_{1A} Serotonin Receptors

Hernán Pessoa-Mahana

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2012, *17*, 1388-1407

benzo[*b*]thiophene compounds synthesized in this study.

In vitro

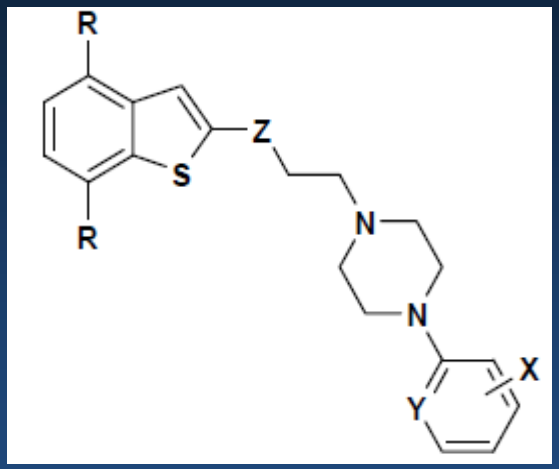
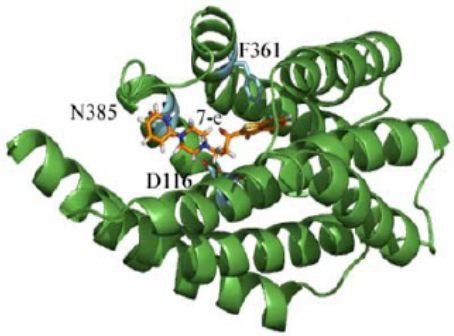


Figure 3. Compound **7e** docked to 5-HT_{1A} molecular model receptor. Interacting residues with compound **7e** are shown in bold.

Ki= 2.3 µM



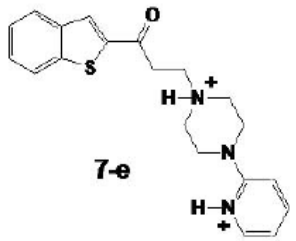
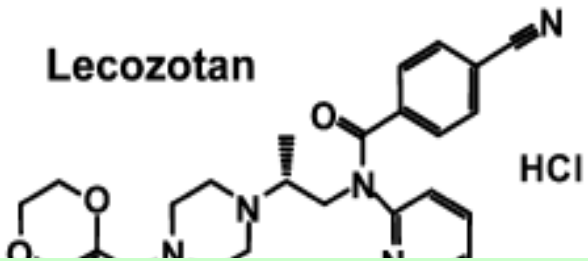


Table 3. Inhibition % for benzo[*b*]thiophene arylpiperazine derivatives.

Entry	Y	X	R	Inhibition (%)	Entry	Y	X	R	Inhibition (%)
6a	CH	H	OMe	2 ± 2	**7-d**	CH	2-OMe	H	52 ± 7
6b	CH	2-F	OMe	14 ± 2	**7-e**	N	H	H	60 ± 4
6c	CH	4-F	OMe	0 ± 3	**7-f**	CH	4-NO_2	H	0 ± 4
6d	CH	2-OMe	OMe	44 ± 2	**8-a**	CH	H	OMe	24 ± 4
6e	N	H	OMe	17 ± 5	**8-b**	CH	2-F	OMe	21 ± 1
6f	CH	4-NO_2	OMe	0 ± 3	**8-c**	CH	4-F	OMe	23 ± 3
7a	CH	H	H	..... [a]	**8-d**	CH	2-OMe	OMe	38 ± 0
7b	CH	2-F	H	33 ± 3	**8-e**	N	H	OMe	27 ± 3
7c	CH	4-F	H	31 ± 7	**8-f**	CH	4-NO_2	OMe	14 ± 2

[a] not measured.

5-HT_{1A}R by radioligand binding assays, using [^{3}H]-8-OH-DPAT in rat cerebral cortex membranes.



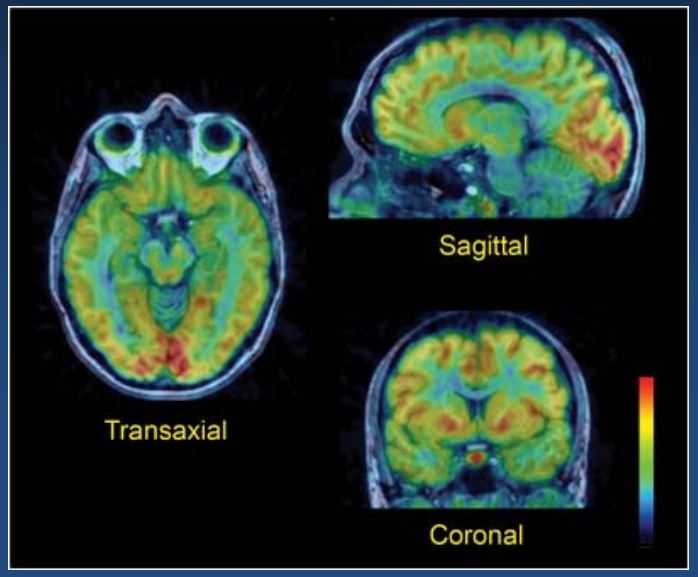
Lecozotan IR was safe and well tolerated after administration of multiple oral doses up to 5mg q12h in young and elderly subjects. These results support the development of lecozotan in patients with Alzheimer's disease.
(Parks et al., 2008)

Delays

Lecozotan (SRA-333)
5-HT1A receptor antagonist (Ki = 1.6 nM)
enhances the potassium-stimulated release of acethylcoline and glutamate
4-Cyano-*N*-[(2*R*)-2-[4-(2,3-dihydro-1,4-benzodioxin-5-yl)-1-piperazinyl]propyl]
-*N*-2-pyridinylbenzamide hydrochloride

5-HT1B receptors

Distribution of 5-HT1B/1D receptors



Putamen
Ventral striatum
Occipital cortex

Varnas et al ., 2011

Autoreceptors: nerve terminals
Heteroreceptors: postsynaptic neuron)

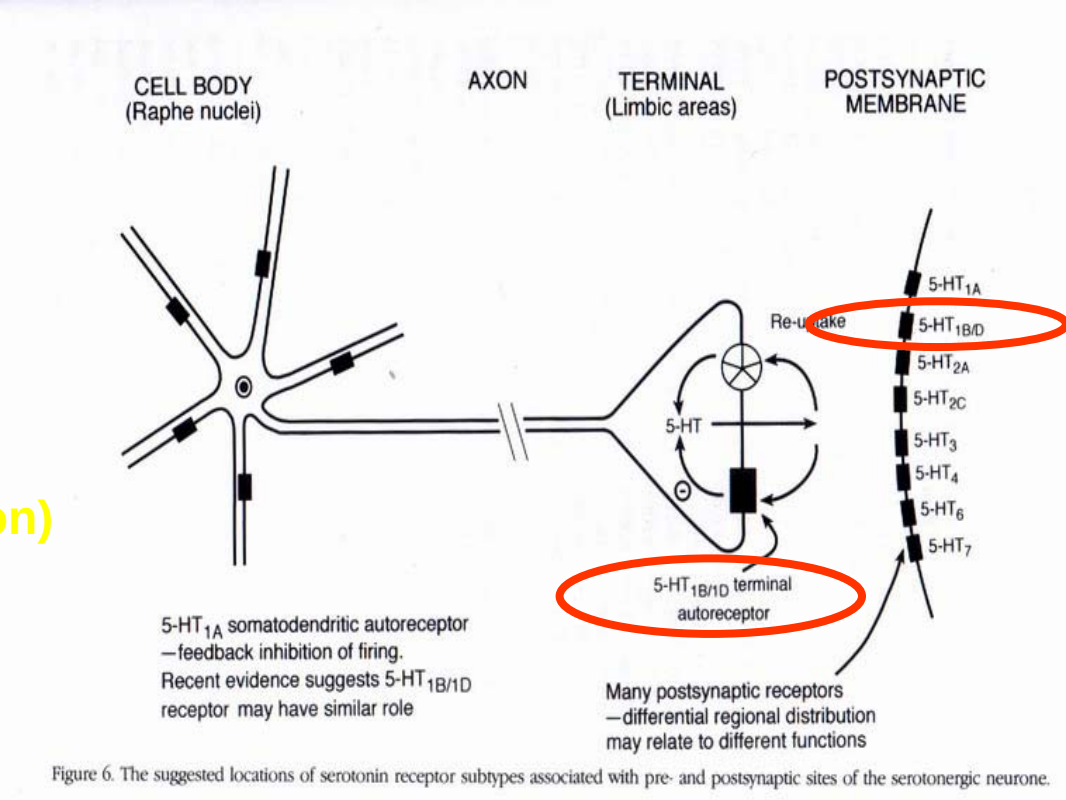


Figure 6. The suggested locations of serotonin receptor subtypes associated with pre- and postsynaptic sites of the serotonergic neurone.

The number of 5-HT1B receptors in the brain of patients with AD

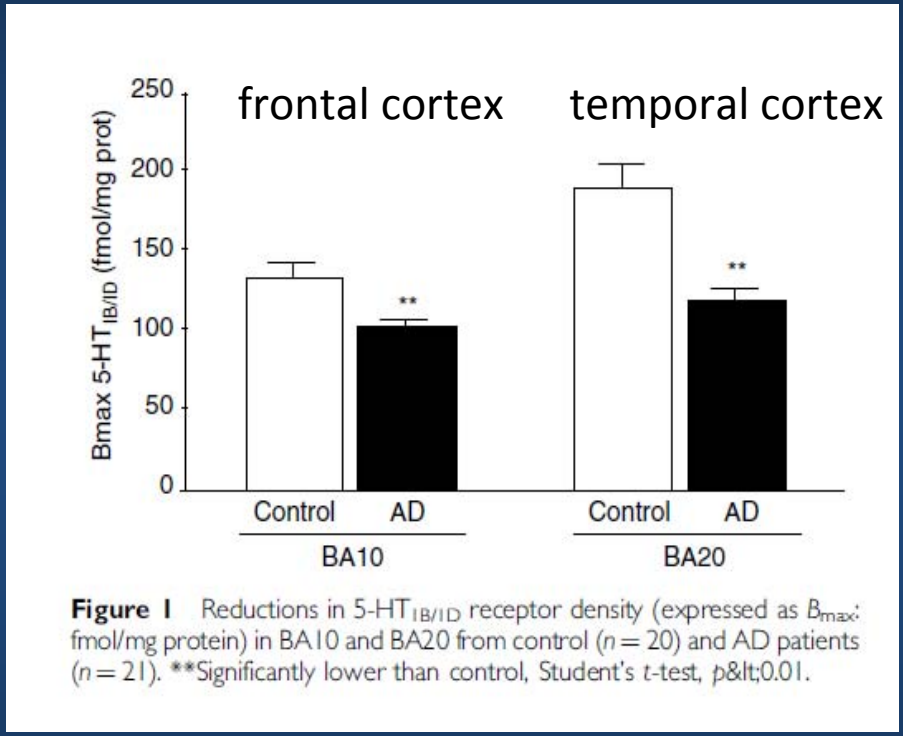


Figure 1 Reductions in 5-$HT_{1B/1D}$ receptor density (expressed as B_{max}: fmol/mg protein) in BA10 and BA20 from control ($n = 20$) and AD patients ($n = 21$). **Significantly lower than control, Student's t-test, p<0.01.

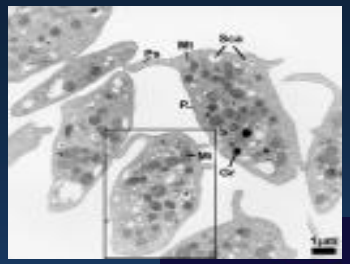
Activation of 5-HT1B receptors in AD associated with poorer memory

5-HT1B decrease acethylcholine releases

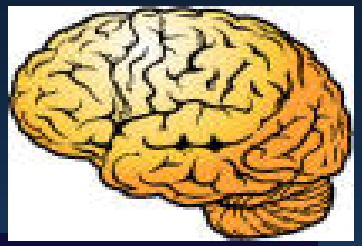
Anti-dementia compunds unknown

Garcia Alloza et al., 2004

5-HT2 receptors



5–HT 2 receptors



platelets
smooth muscle
PNS
CNS
gastric fundus
choroid plexs

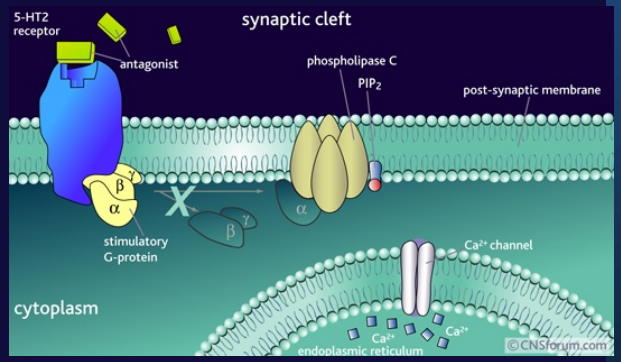
2A
2B
2C

α-methyl 5-HT
LSD (CNS)

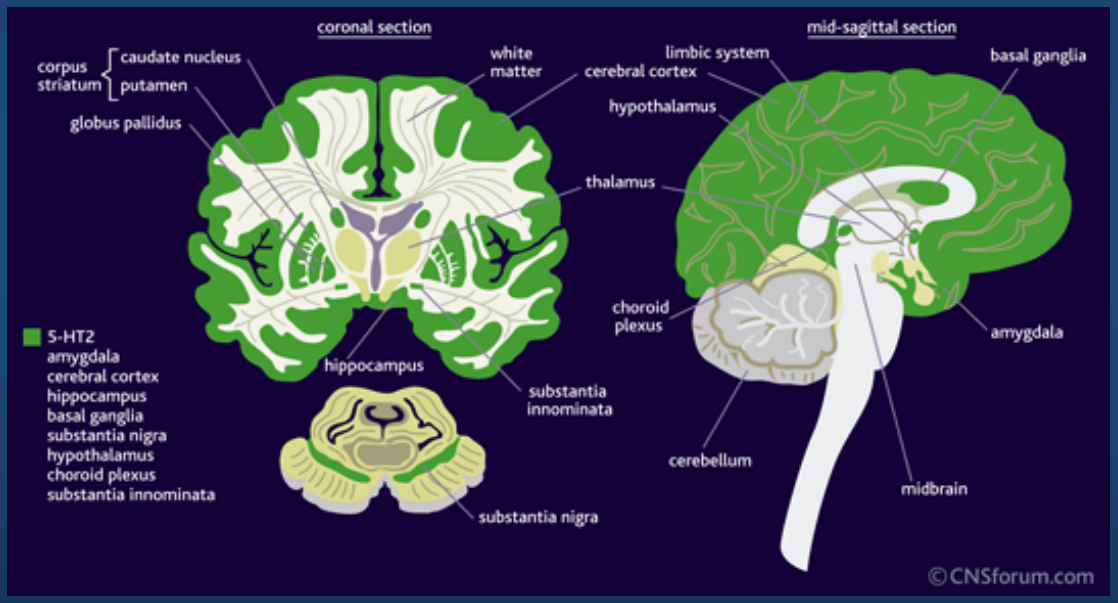
cyproheptadine
ketanserin
LSD (PNS)
methysergide

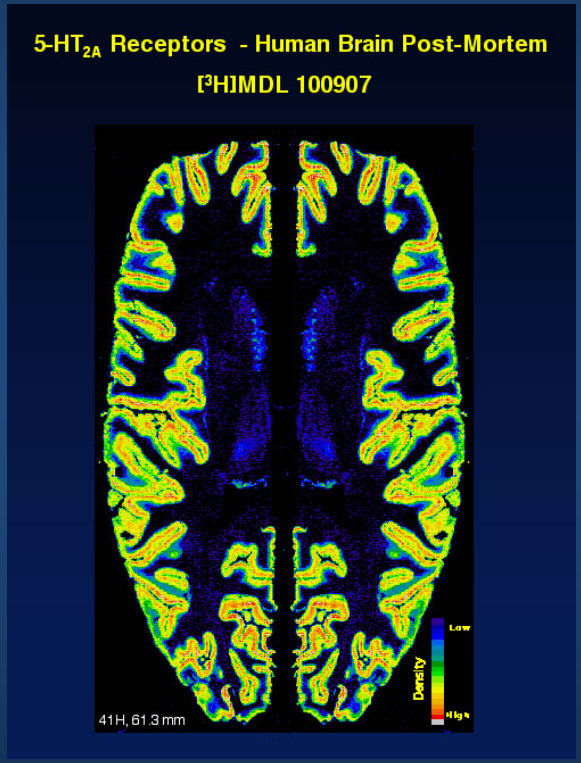
activation of phospholipase C, IP3 formation, DAG casade, uncrease in Ca^{2+}

5-HT receptor subtype
location
2nd messenger effect
agonists
antagonists



5-HT2 receptors in CNS

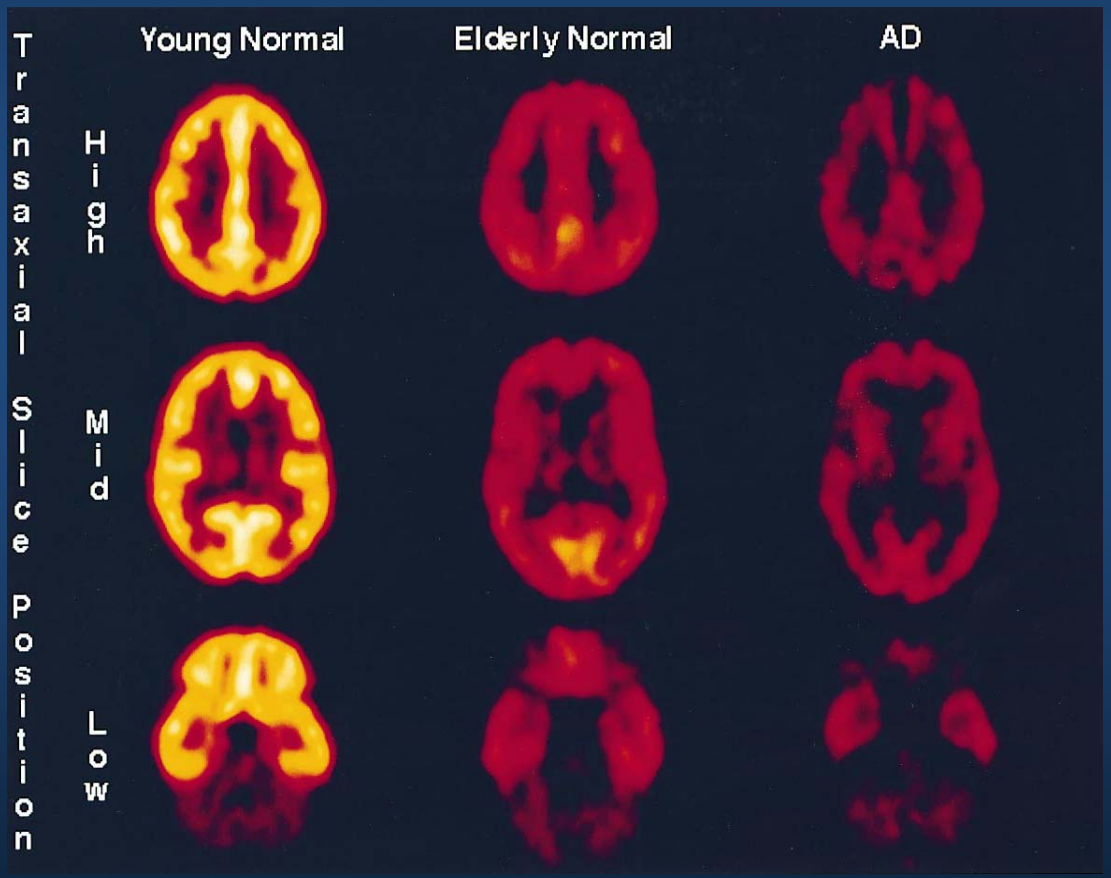




The number of 5-HT2A receptors during aging in prefrontal cortex

(PET study with [18F]altanserin)

20 years **66 years** **67 years**



Meltzer et al., 1999

Table 1. *Regional decrease in 5HT2 receptors in Alzheimer's disease*

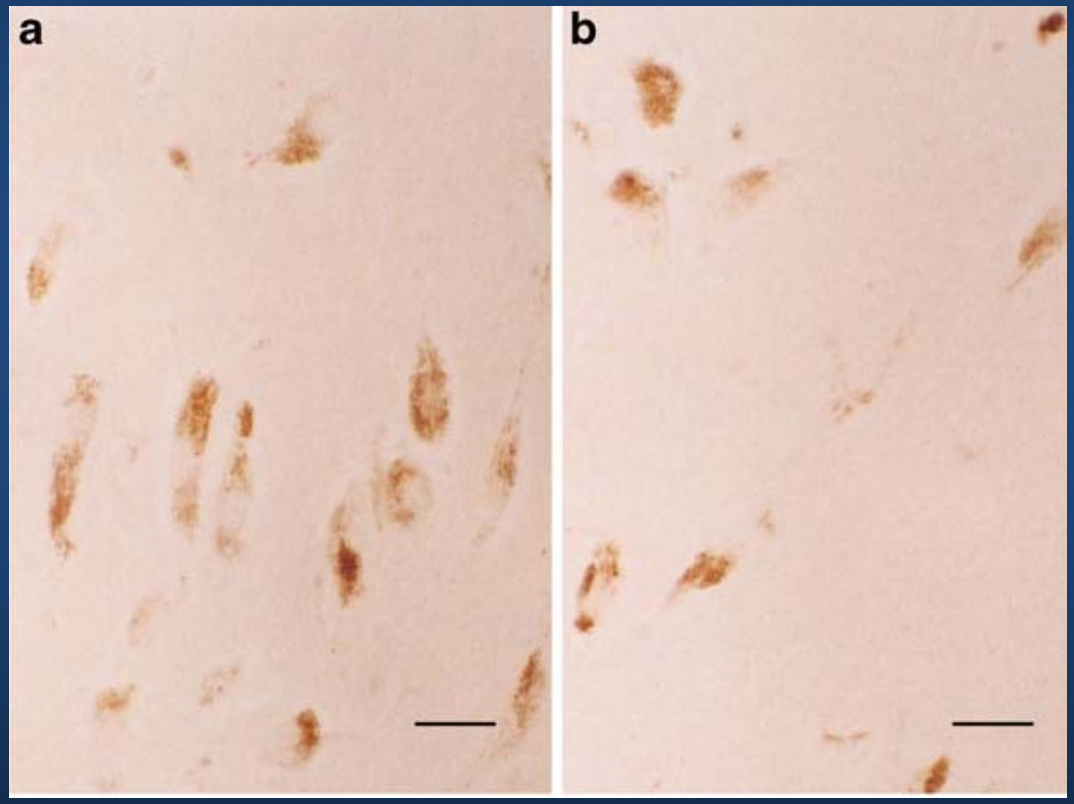
	Frontal	Temporal	MTL	Parietal	SM	Occipital
Blin et al. (1993)	+++	+++		++		+
Meltzer et al. (1999)	+++	+++	+++		+++	
Versijpt et al. (2003)	++			++	+++	++

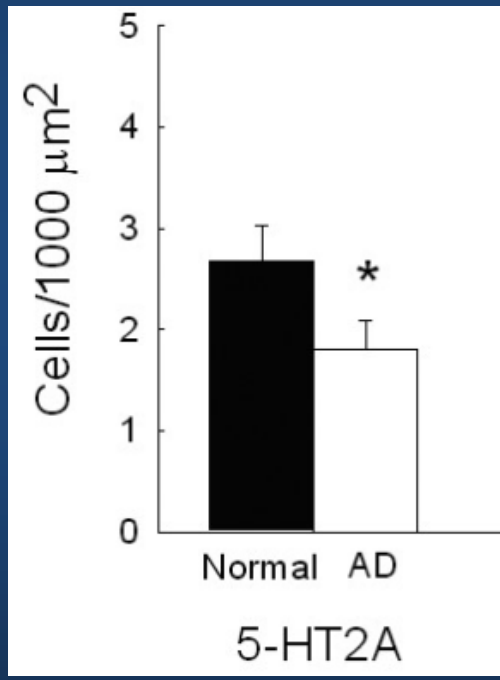
MTL Medial temporal lobe; *SM* sensorimotor cortex.

(Salmon , J Neural Transm 114:1179, 2007)

Decreased number of 5-HT2A positive cells in AD

Healthy control **AD**





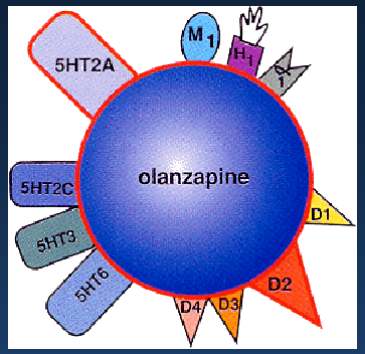
Lorke et al., 2006

Decreased binding to 5-HT2A in MCI

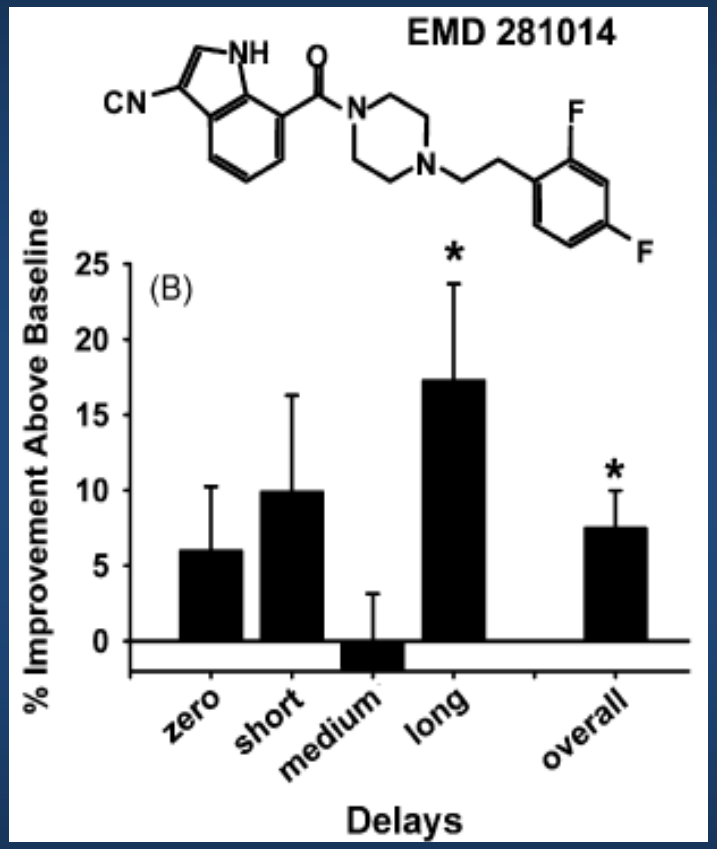
Table 2
5-HT_{2A} receptor binding in grey matter in patients with MCI compared to controls

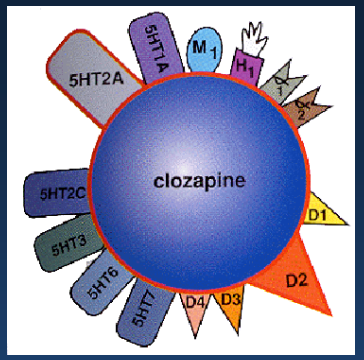
	Not corrected for atrophy		
	Control subjects ($n = 17$) (ml/ml)	MCI subjects ($n = 16$) (ml/ml)	Difference (%)
Posterior cingulate gyrus	1.08 ± 0.31	0.84 ± 0.39	ns
Primary sensorimotor cortex	0.55 ± 0.24	0.35 ± 0.20	−37*
Anterior cingulate gyrus	0.97 ± 0.32	0.58 ± 0.32	−39**
Parietal cortex	0.89 ± 0.28	0.63 ± 0.29	−29*
Superior frontal gyrus	0.77 ± 0.27	0.53 ± 0.27	−31*
Insula	0.96 ± 0.35	0.60 ± 0.29	−38**
Orbitofrontal cortex	0.88 ± 0.32	0.59 ± 0.36	−33*
Medial/inferior temporal gyri	1.05 ± 0.30	0.78 ± 0.31	−26*
Occipital cortex	1.00 ± 0.33	0.80 ± 0.32	ns
Medial/inferior frontal gyri	0.88 ± 0.29	0.60 ± 0.27	−33**
Superior temporal gyrus	0.99 ± 0.32	0.65 ± 0.31	−34**
Caudate nucleus	−0.04 ± 0.22	−0.03 ± 0.19	ns
Putamen	0.46 ± 0.23	0.46 ± 0.16	ns
Thalamus	0.05 ± 0.19	0.01 ± 0.17	ns
entorhinal cortex	−0.02 ± 0.23	−0.08 ± 0.22	ns
Hippocampus	0.10 ± 0.28	0.07 ± 0.21	ns

Hasselbach 2008



5-HT2A antagonist EMD 281014

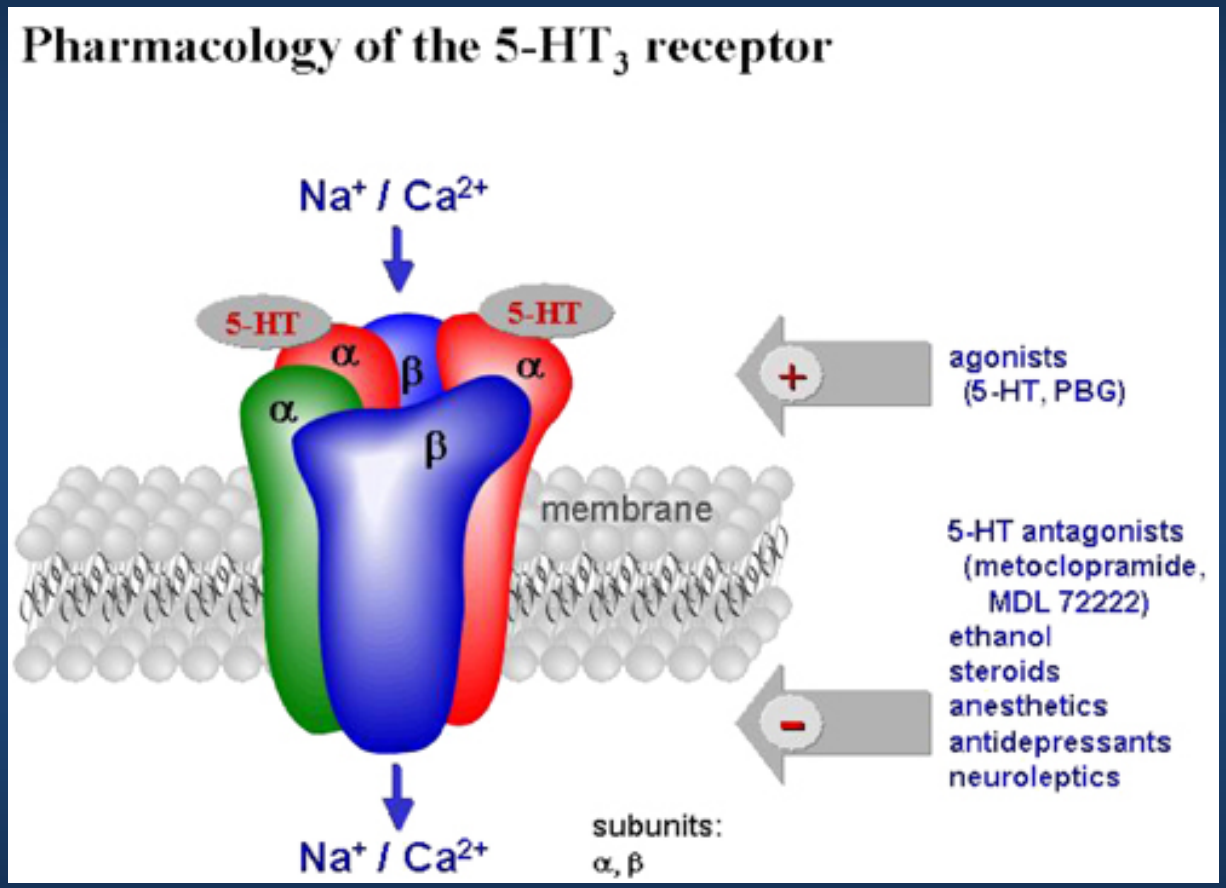




improves working memory function in young and aged monkeys, (Terry et al., 2005)

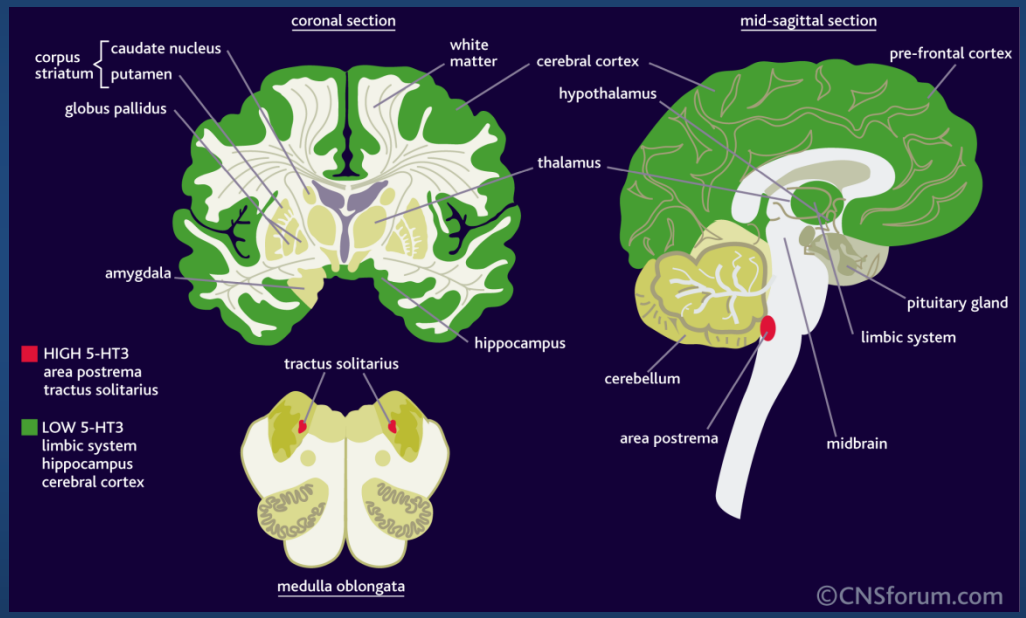
5-HT3 receptors

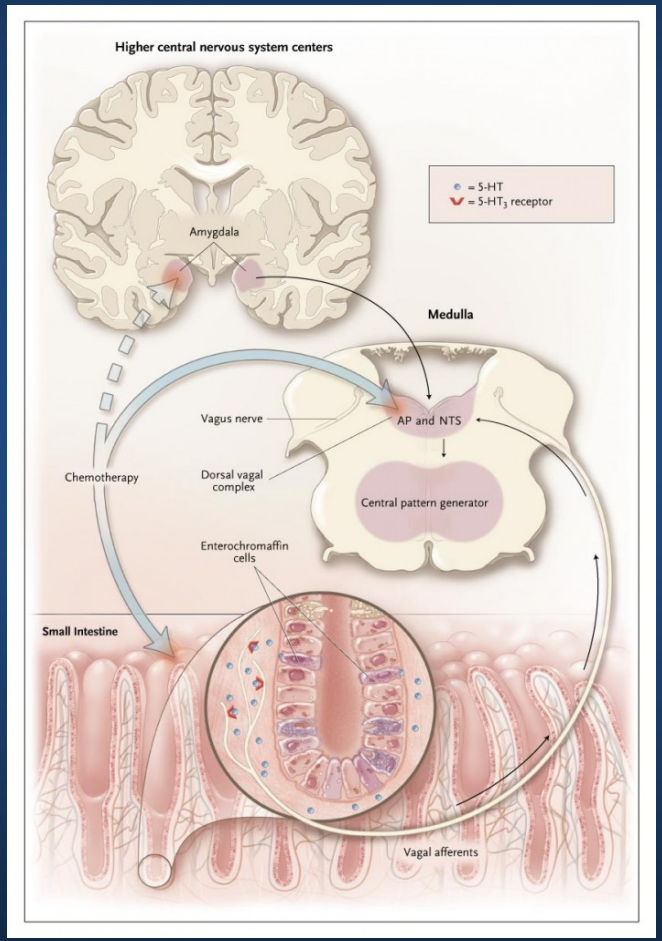
5-HT3 receptors



A cation-selective ligand-gated ion channel
Increases intracellular cations such as Ca^{2+}, Na^{+} and K^{+}

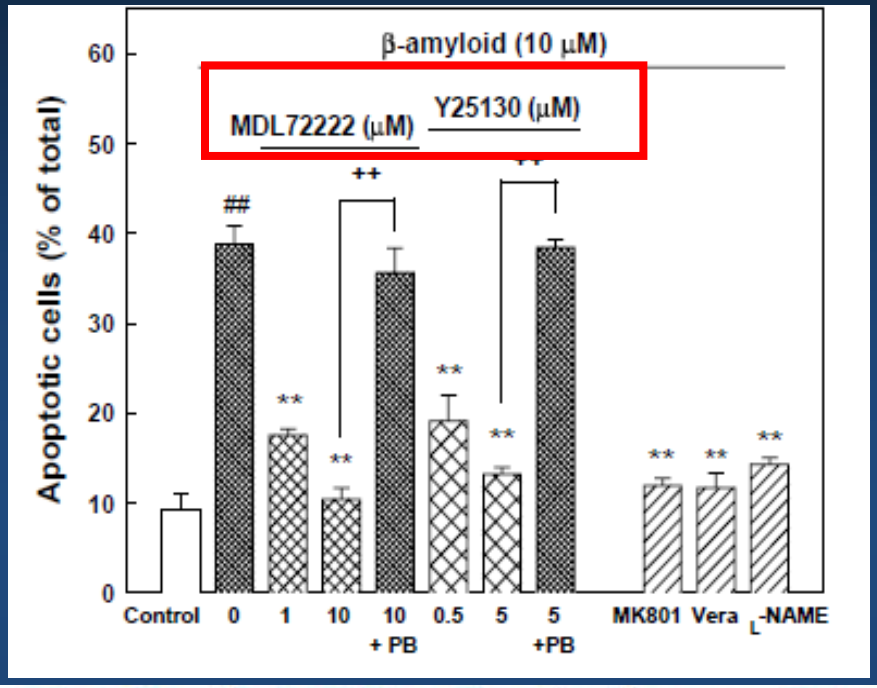
Peripheral and central 5-HT3 receptors





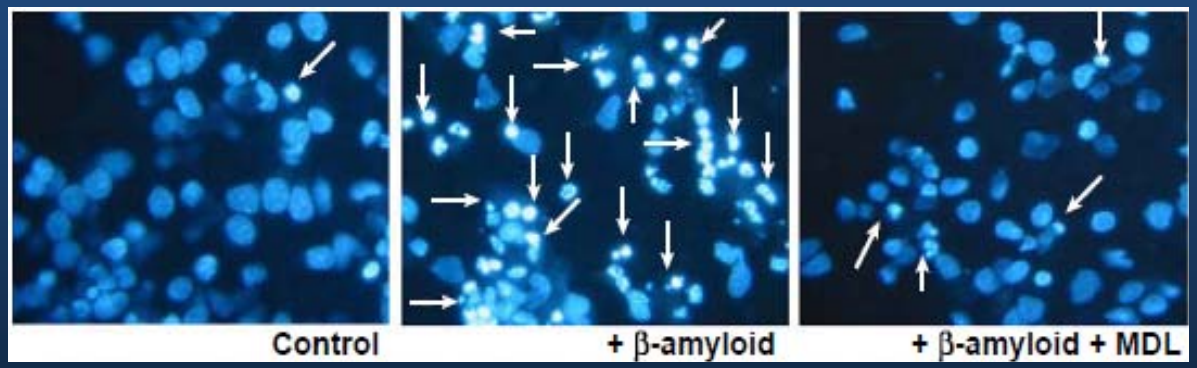
Antagonists of 5-HT3 have antiemetic properties

5-HT3 receptor antagonists induce cognitive enhancing effects



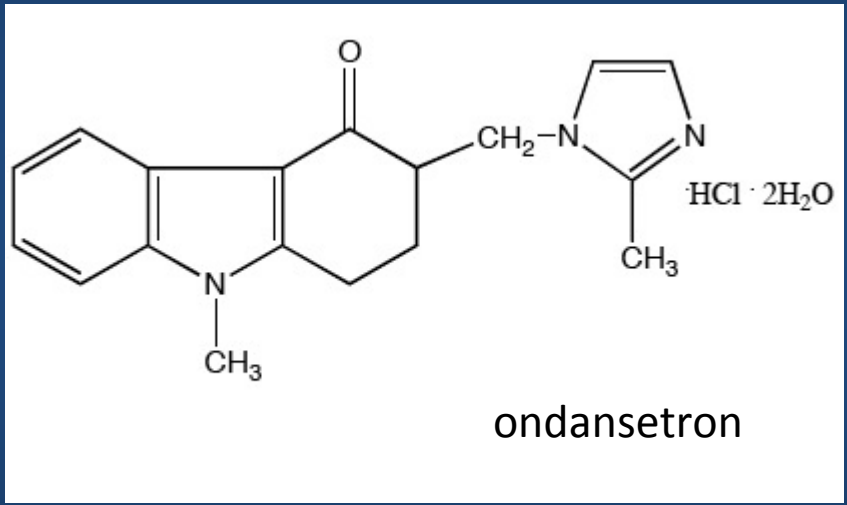
Ban i Seong 2005

PB = 1-phenylbiguanide

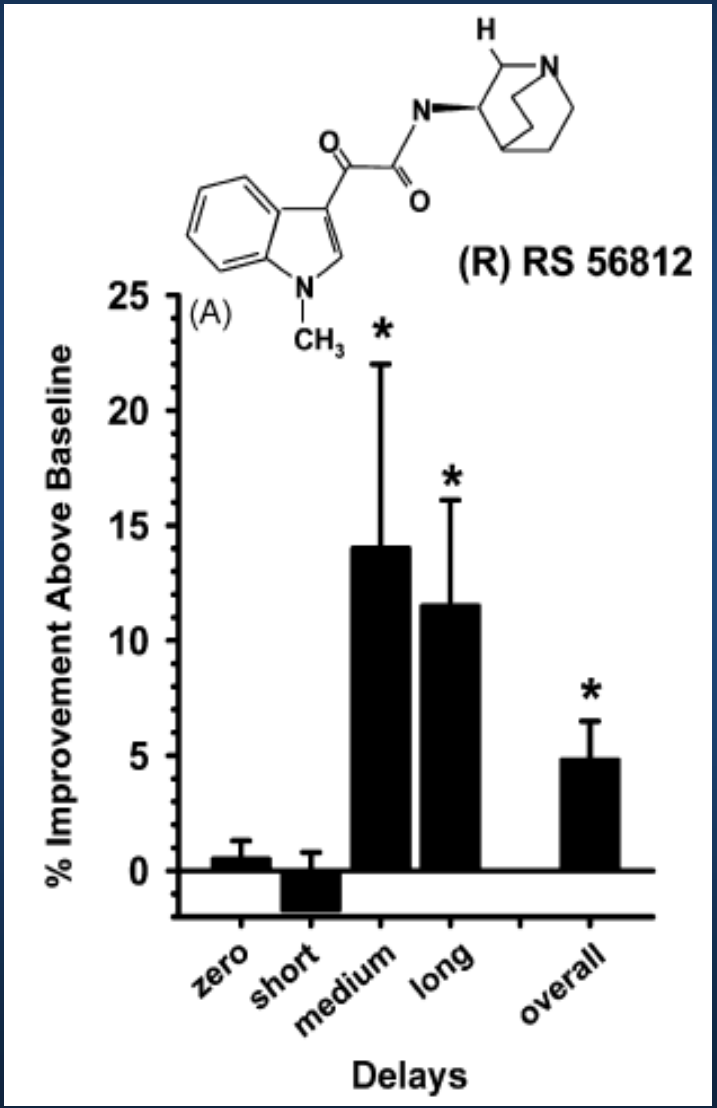


In vitro antagonists of 5-HT3 receptors reduced ß-amyloid-induced apoptosis of cortical neurons

5-HT 3 antagonists

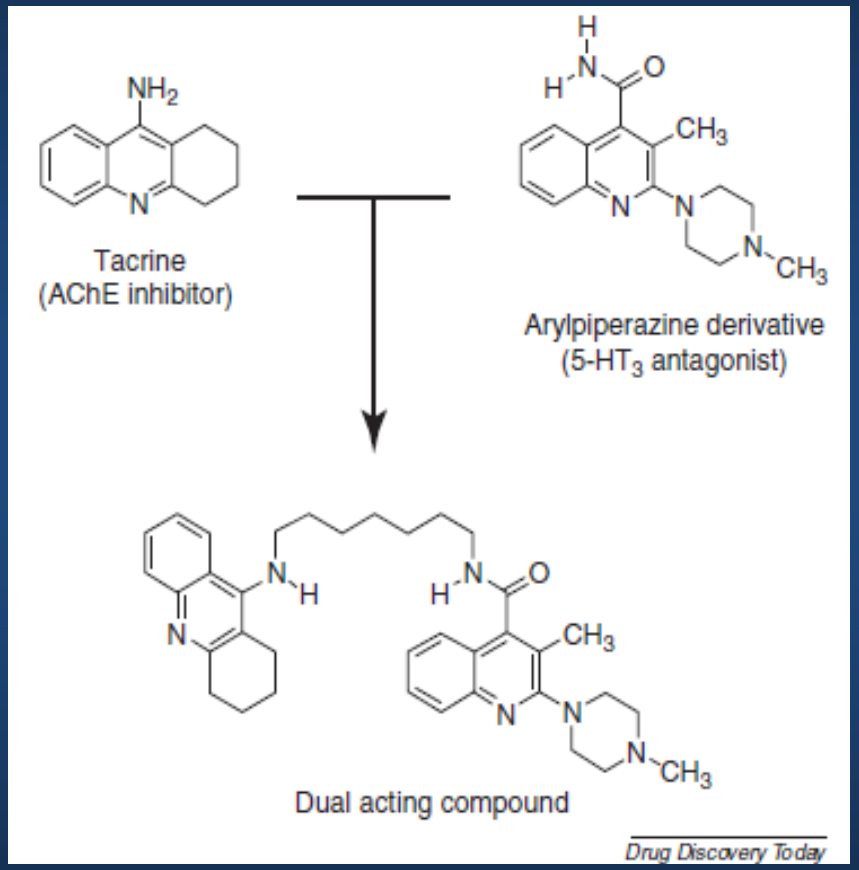


ondansetron



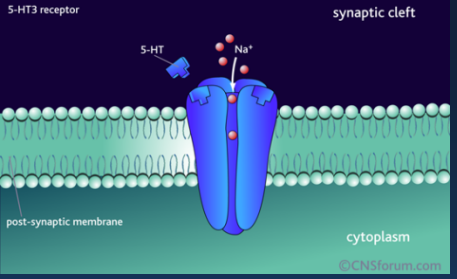
Pro-cognitive effects

The high-affinity 5-HT3 receptor antagonist with potent acetylcholinesterase (AChE) inhibitory activity

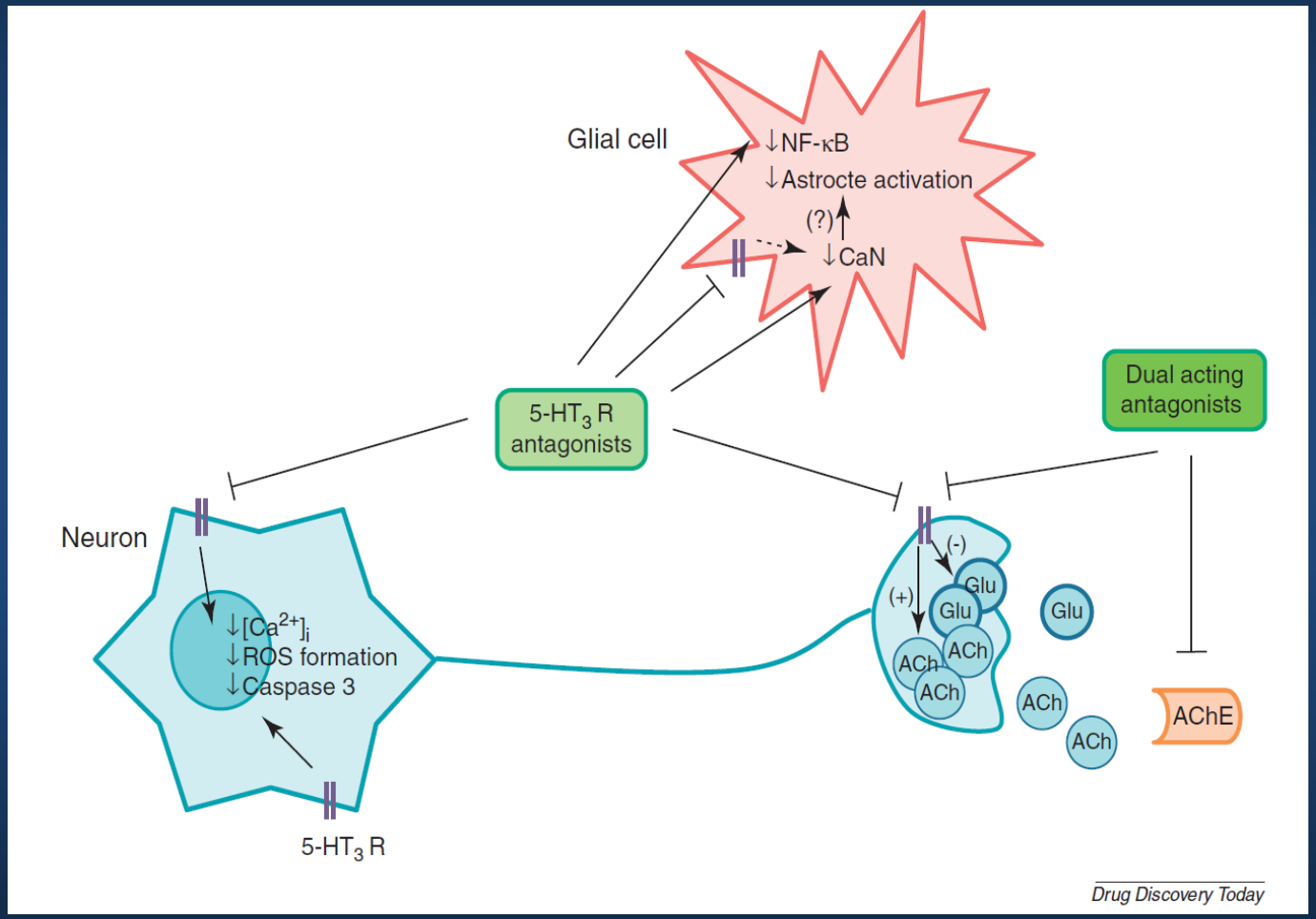


for 5-HT3 receptors Ki = 5.6 ± 0.02 nM
for human AChE = IC_{50} = 4.1 ± 0.60 nM

Fakhfouri et al., Drug Discovery Today, 17:741, 2012



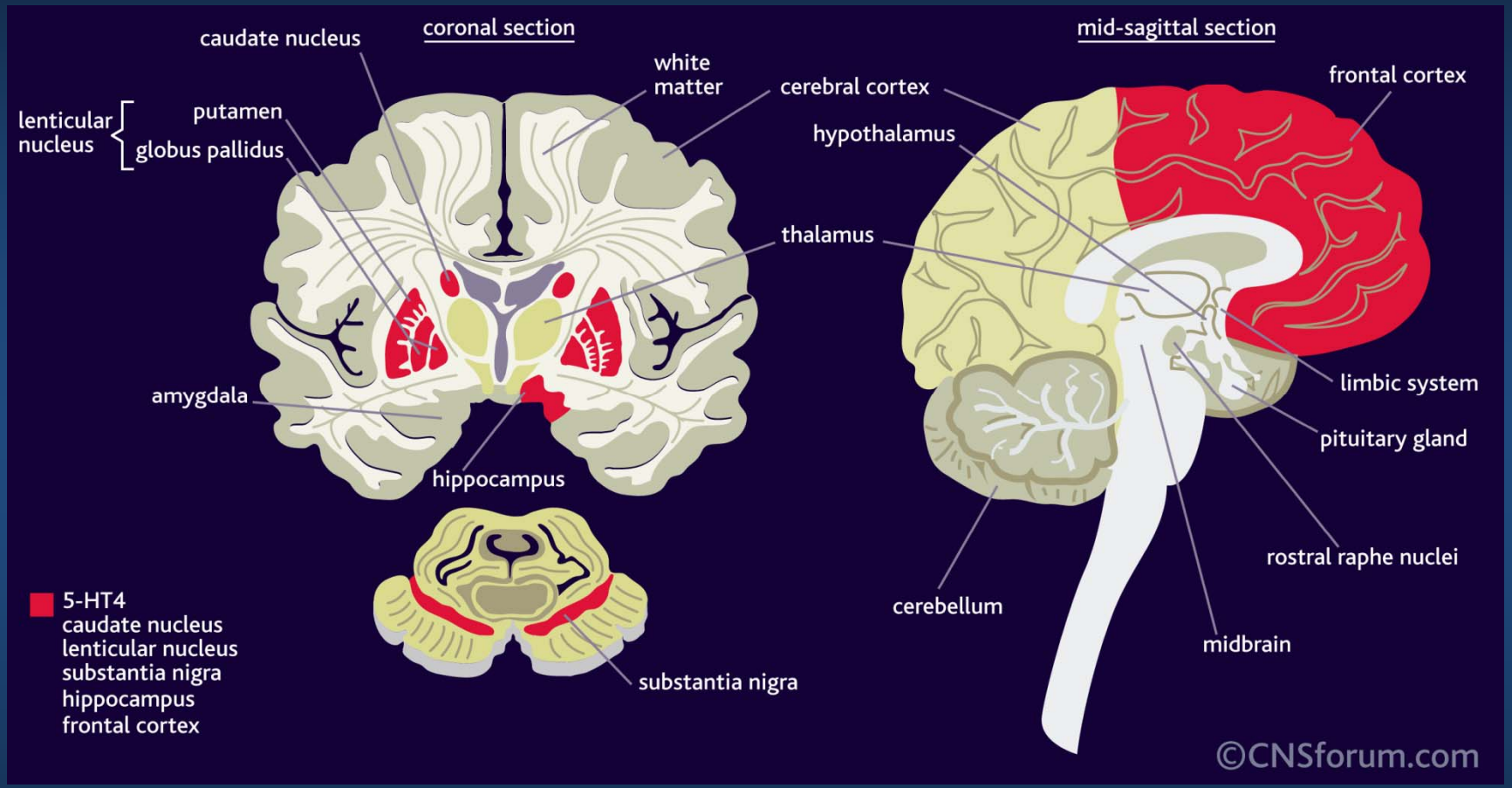
5-HT3 receptors antagonist



Inhibit glutamate release
Increase acethylcholine release

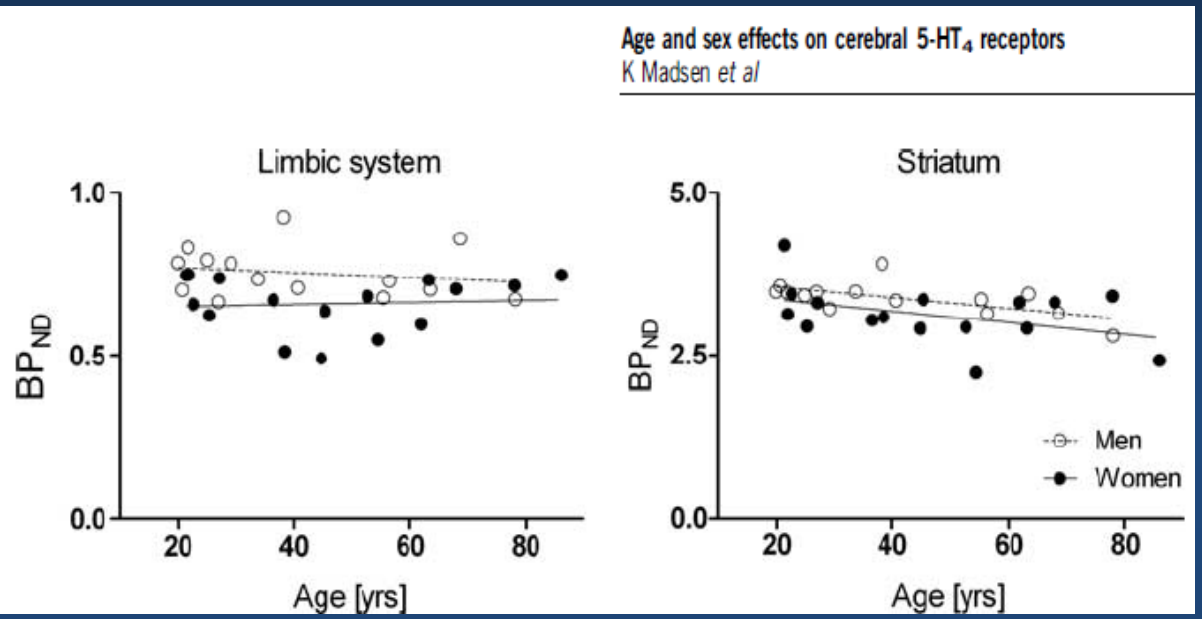
5-HT4 receptors

5-HT4 receptors

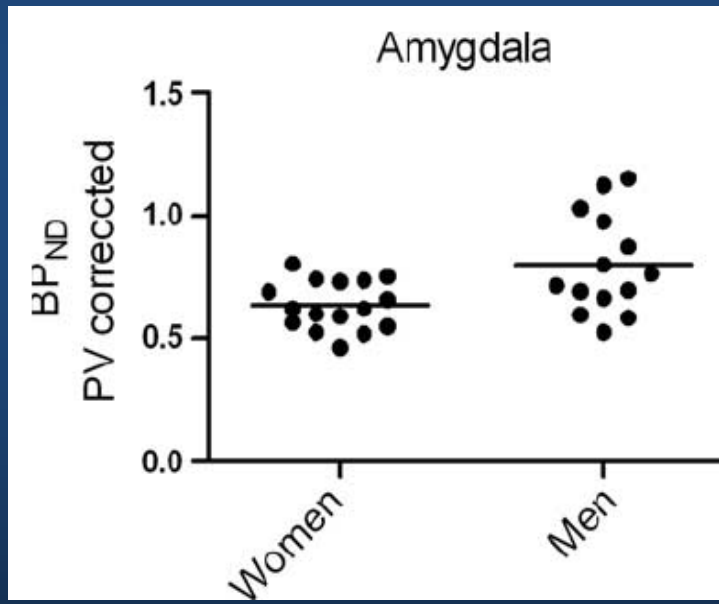


Frontal cortex
Hippocampus
Substania nigra

5-HT4, aging; PET study (Madsen et al., 2011)

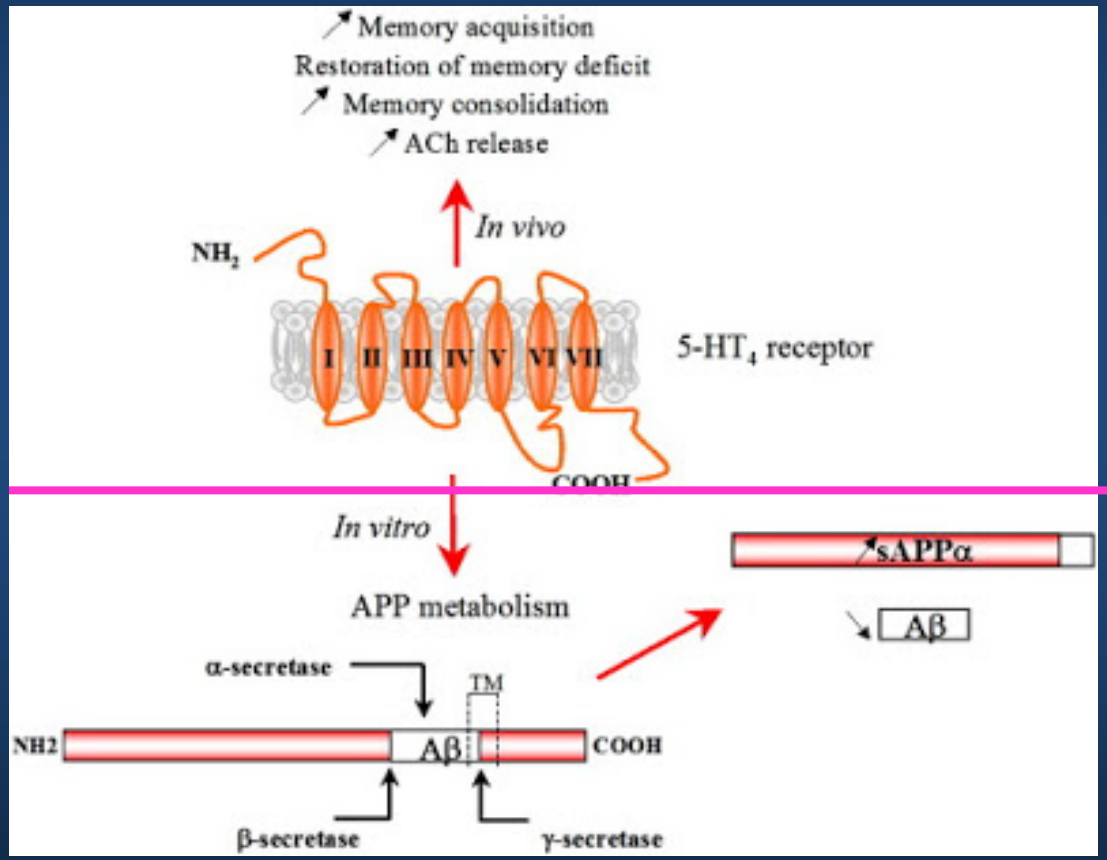


A decline with age of 1% per decade only in striatum



Women have lower 5-HT4 receptor binding
13% in limbic system
19% in amygdala

5-HT4-receptor agonists have the potential to modify the pathogenesis of Alzheimer's disease. **(Lezoualc'h, 2007)**



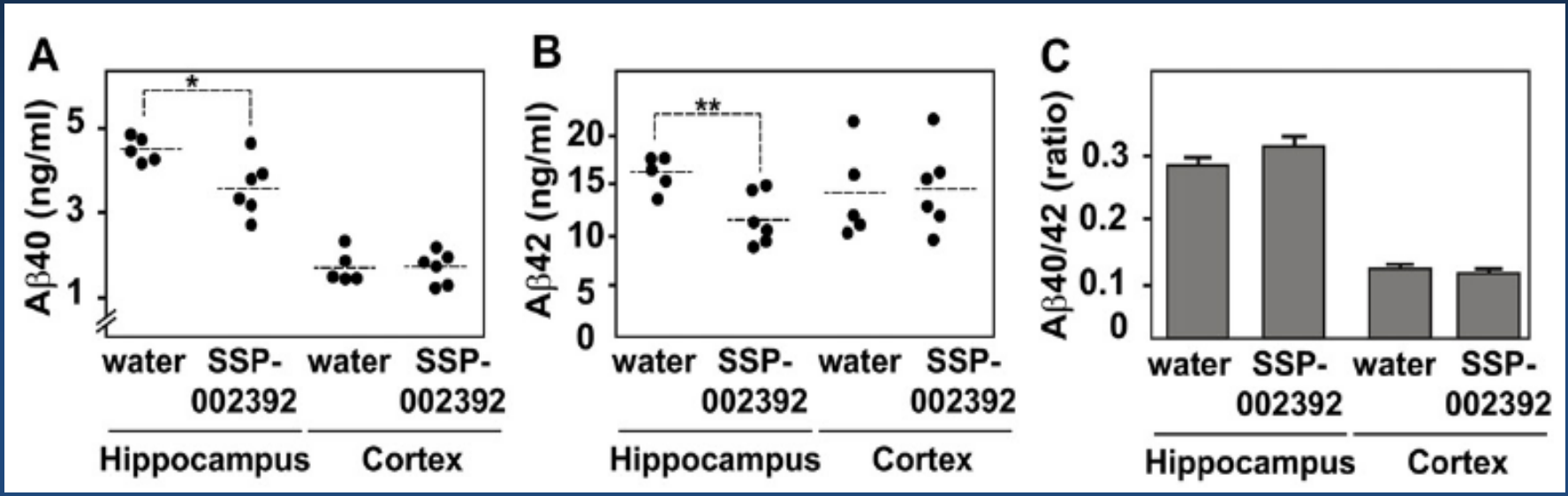
•In vivo:
•facilitate ACh release in rat frontal cortex and hippocampus

•modulate memory performance in behavioural experiments

In vitro:
•increase the extracellular release of sAPPα
•decrease amyloid β-peptide secretion in primary neurons.

•memory-enhancing effects neuroprotective and neurotrophic properties

5-HT4 receptor agonist SSP-002392 (Ki 0.5 nmol/L)

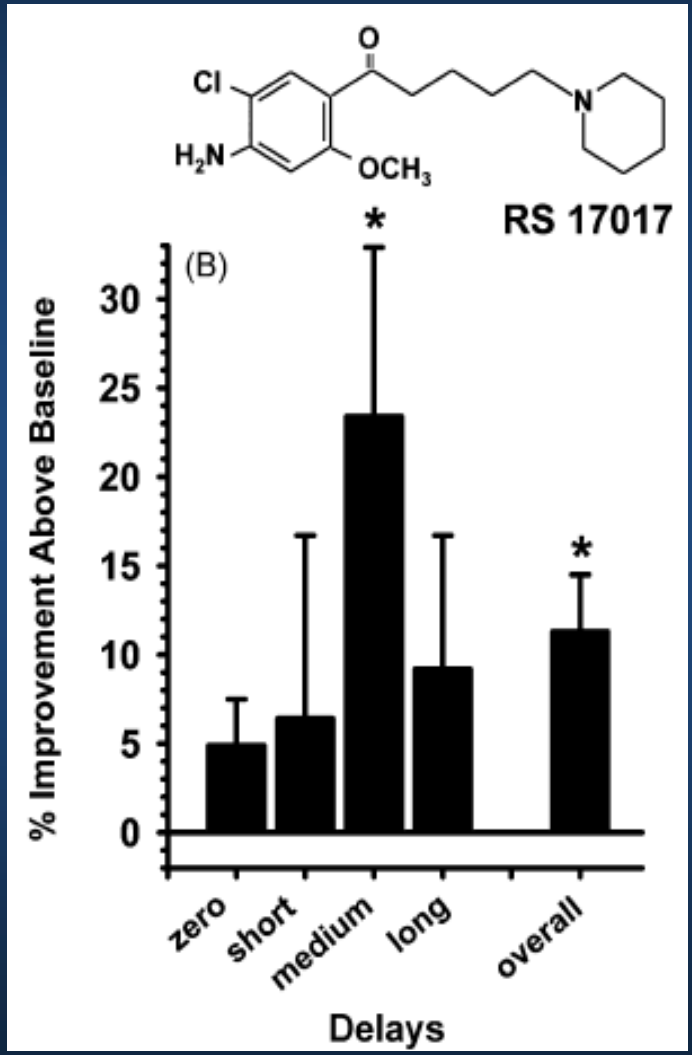


some evidence that 5-HT4 receptor agonist treatment can decrease Aß pathology in a murine model of Alzheimer's disease.

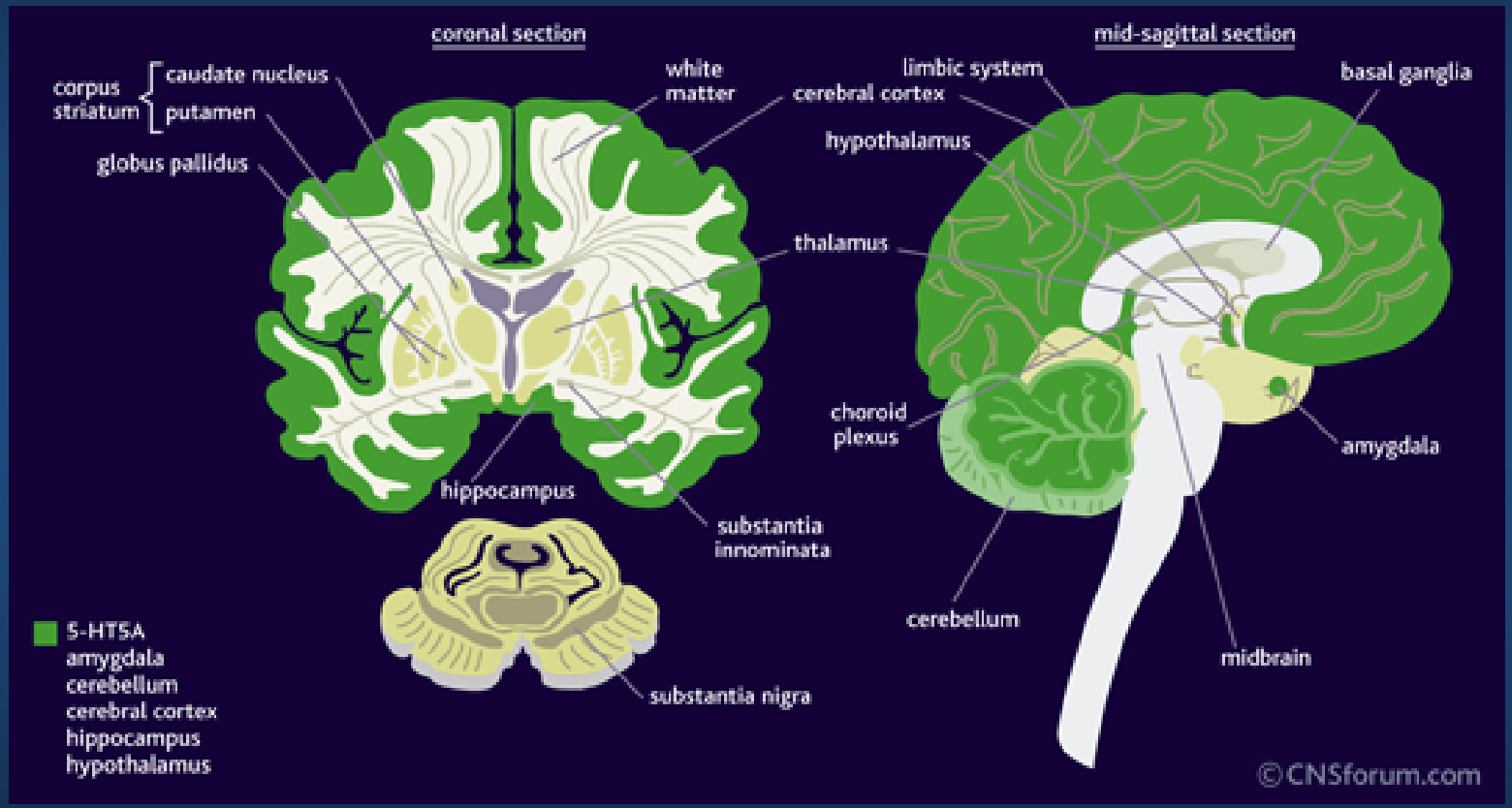
The results suggest that the 5-HT4 receptor agonist SSP-002392 might modify Aß levels in the brain during the early stages of disease.

Tesseur et al.,: Chronic 5-HT4 receptor activation decreases Aß production and deposition in hAPP/PS1 mice. Neurobiology of Aging 2013; 34: 1779

5-HT4 agonist in aged macaques



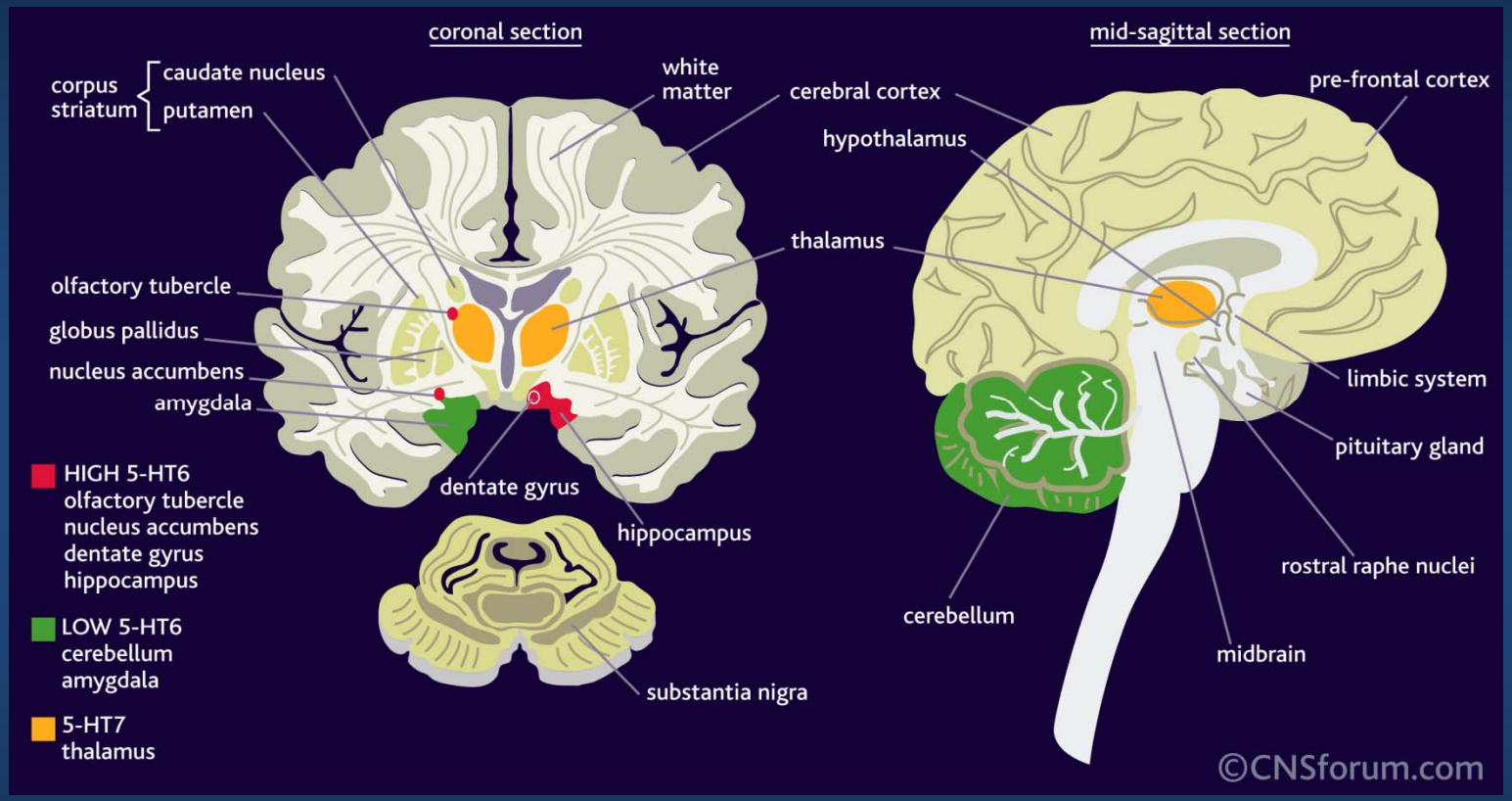
5-HT5 receptors



No specific and selective comounds

5-HT6 receptors

5-HT6 receptors



learning
memory
feeding

The number of 5-HT6 receptors is decreased in AD

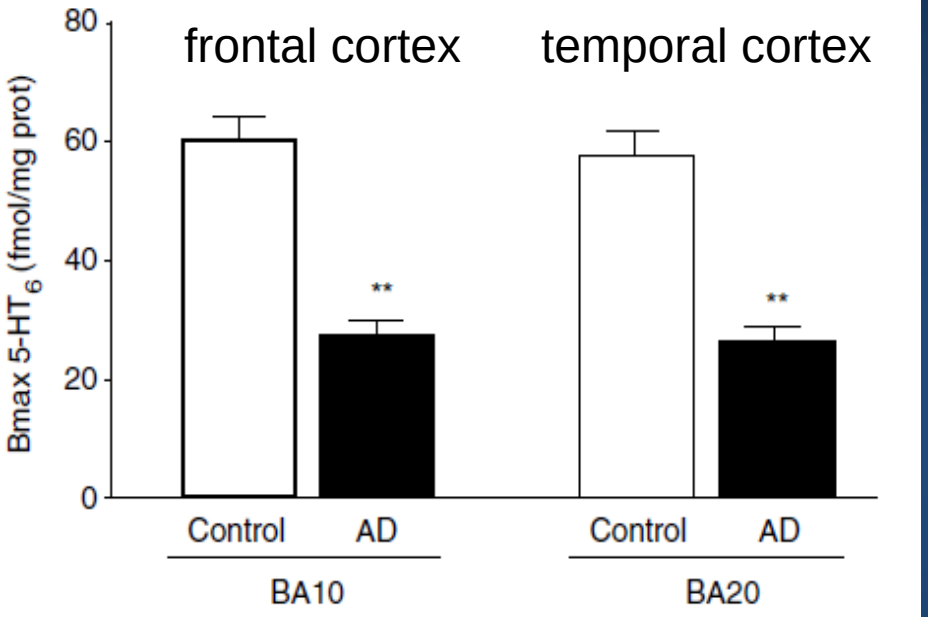
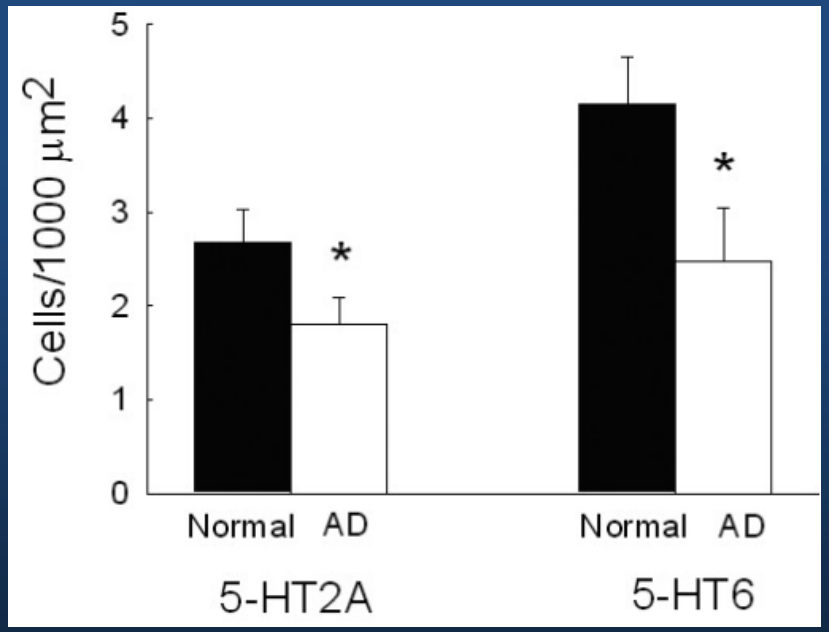


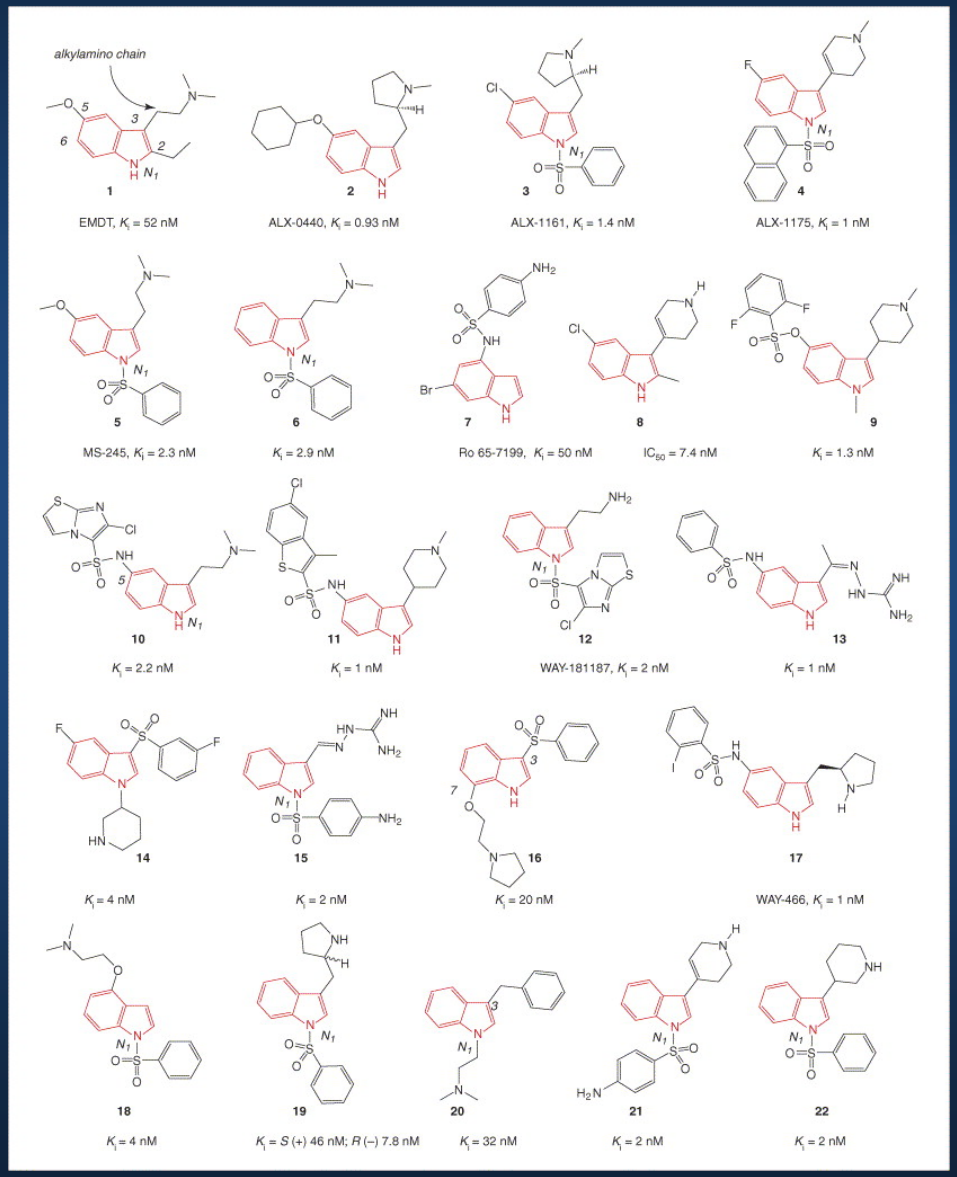
Figure 2 Reductions in 5-HT_6 receptor density (expressed as B_{max}: fmol/mg protein) in BA10 and BA20 from control ($n = 20$) and AD patients ($n = 21$). **Significantly lower than control, Student's t-test, p<0.01.

Garcia Alloza et al., 2004



Lorke et al., 2006

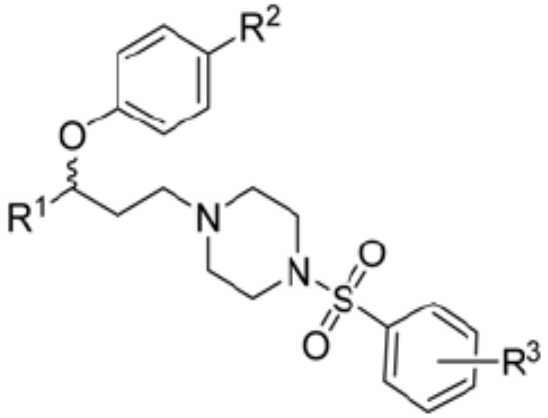
5-HT 6 receptors the new target fot the treatment of AD



- Antagonism of 5-HT6 receptors leads to an increase in the release of Ach
- Stimulate glutamatergic cholinergic transmission

Synthesis and Biological Evaluation of Arylsulfonylpiperazine Derivatives as 5-HT_6 Receptor Ligands

Sun Ah Jeon, Hyunah Choo, Woo-Kyu Park,[†] Hyewhon Rhim, Soo Y. Ko,[‡] Yong Seo Cho, Hun Yeong Koh,[§] and Ae Nim Pae[*]



1 R^1 = phenyl, R^2 = CF_3

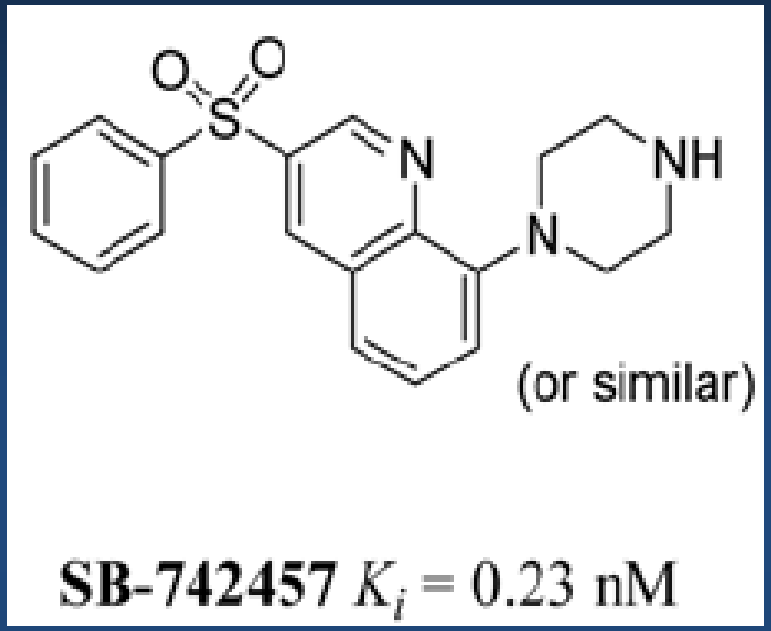
2 R^1 = ethyl, R^2 = CF_3

3 R^1 = ethyl, R^2 = CN

R^3 = H, F, Cl, CH_3, OMe or dimethyl

. Structures of arylsulfonylpiperazine derivatives.

5-HT6 antagonist in clinical trials

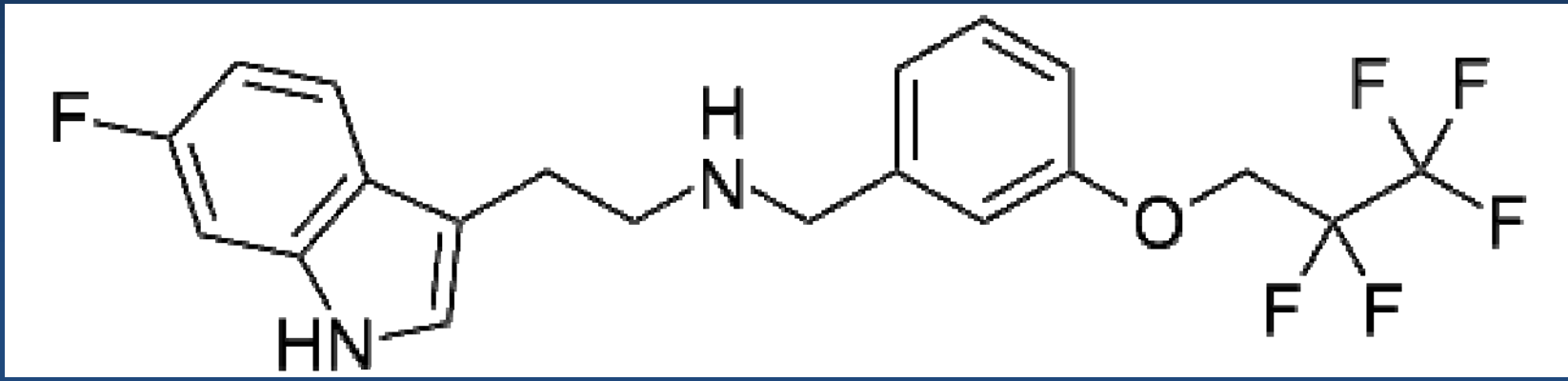


Double-blind, controlled phase II study of a 5-HT6 receptor antagonist, SB-742457, in Alzheimer's disease . (Maher-Edwards et al., 2010)

Conclusion: SB-742457 was generally safe and well tolerated and may be efficacious in AD

Lu AE58054

a selective 5-HT6 antagonist



2-(6-fluoro-1H-indol-3-yl)-N-(3-(2,2,3,3,3-pentafluoropropoxy)benzyl)ethanamine

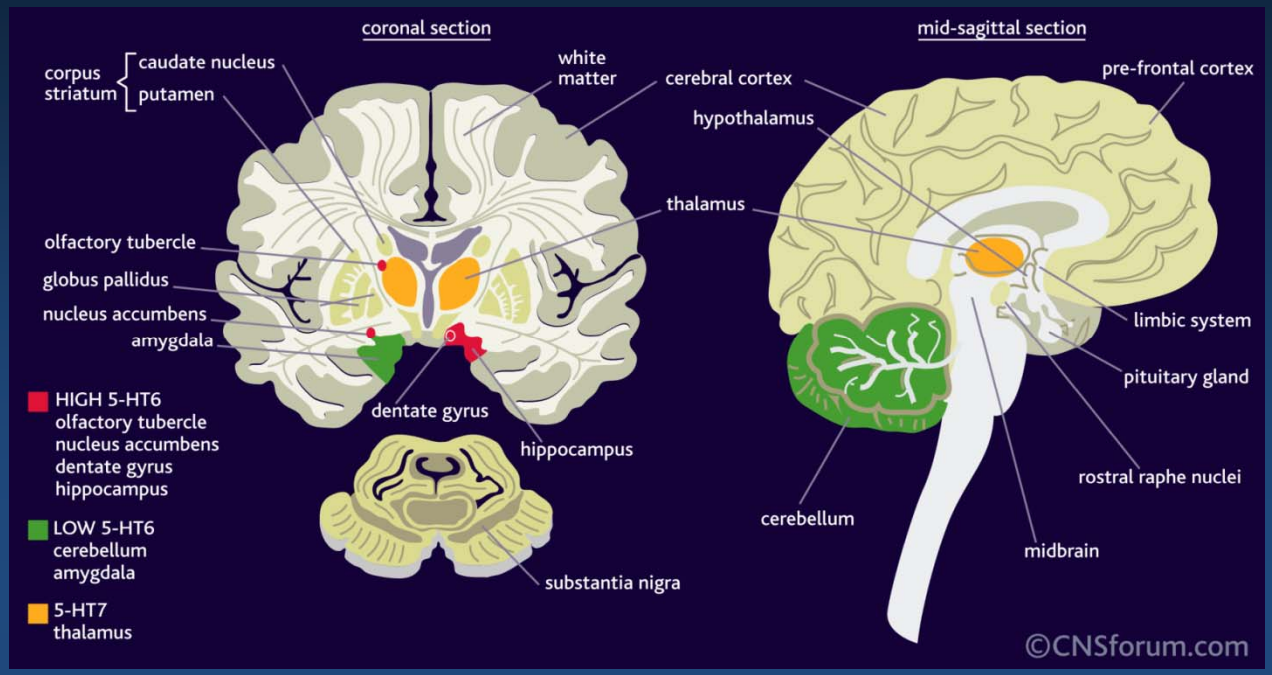
Phase III clinical trials

3 000 patients with mild-to moderate AD

In a dose of 10-60 mg in combination with donepezil 10 mg/day

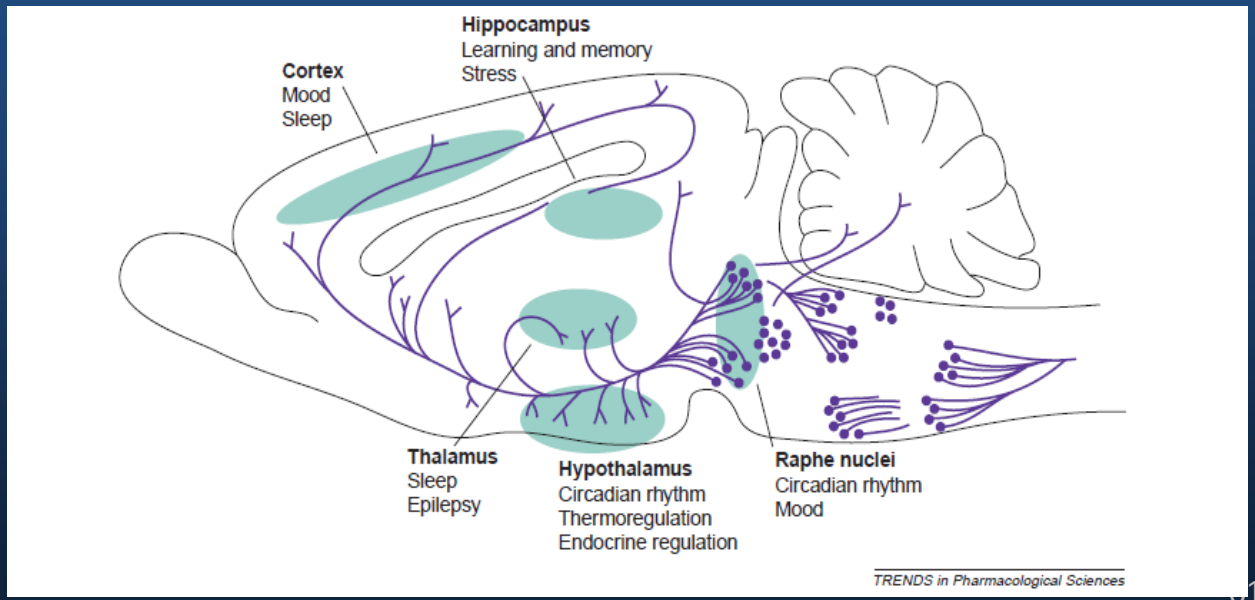
5-HT7 receptors

5-HT7 receptors



Thalamus
Hippocampus
Hypothalamus

cognitive function
sleep
diurnal rhythm
pain
mood



Effects of 5-HT_7 receptor inactivation or blockade in animal behavioral models of learning and memory.

Model	Method	Effect	Reference
Novel location recognition	Knockout mice	Reduced exploration	Sarkisyan and Hedlund, 2009
	SB-269970	Reduced exploration	Sarkisyan and Hedlund, 2009
Novel object recognition	Knockout mice	No change	Sarkisyan and Hedlund, 2009
	SB-269970	No change	Sarkisyan and Hedlund, 2009
	Sprague-Dawley rats with reduced spontaneous locomotor activity[1]	Increased exploration	Ballaz et al., 2007b
	Same rats + SB-269970	Reduction of exploration change	Ballaz et al., 2007b
Barnes maze	Knockout mice, 12-session habituation	No change	Roberts et al., 2004
	Knockout mice, 1 month	No change	Roberts et al., 2004
	retention		Sarkisyan and Hedlund, 2009
	Knockout mice, escape box moved or removed	Increased time spent at original location of escape box	Sarkisyan and Hedlund, 2009
Cued fear conditioning	Knockout mice	No change	Roberts et al., 2004
Contextual fear conditioning	Knockout mice	Impaired conditioning	Roberts et al., 2004
Radial arm maze	SB-269970	No change in working memory	Gasbarri et al., 2008
	SB-269970	Improved reference memory	Gasbarri et al., 2008
Operant food conditioning	Knockout mice	No change	Roberts et al., 2004
Pavlovian/instrumental	SB-269970, DR4004	Reversal of 8-OH-DPAT-induced increase in conditioning	Meneses, 2004
	SB-269970	Reversal of AS19-induced increase in conditioning	Perez-Garcia and Meneses, 2005
	SB-269970, DR4004	Reversal of scopolamine or dizoclipine-induced amnesia	Meneses, 2004
Passive avoidance	SB-269970	No change (standard protocol)	Eriksson et al., 2008
	SB-269970	Impaired memory (modified protocol)	Eriksson et al., 2008
	SB-269970	Enhanced 8-OH-DPAT-induced amnesia	Eriksson et al., 2008

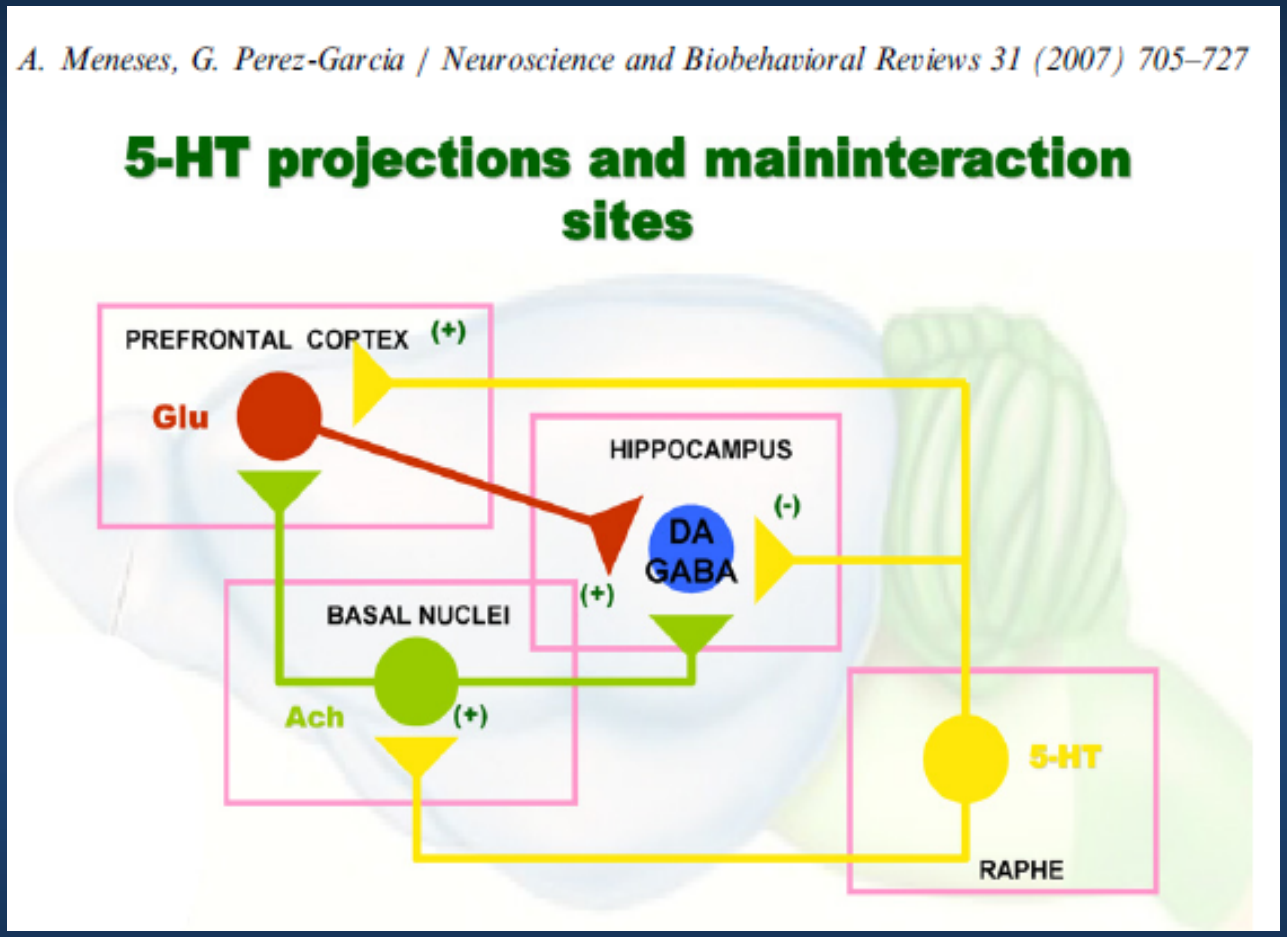
?

Are the changes in the 5-HT markers (receptors) in the AD primary
or
secondary (retrograde) due to the loss of target (postsynaptic) neurons in regions of the nerve endings

?

Do they directly or indirectly contributing to the physiological and pharmacological basis of memory and its pathogenesis
or
they represent protective or adaptable mechanisms
(at least in initial stages)

Serotonin and other neurotrasmitters



Mainly 5-HT projections are showed in brain areas important for memory. 5-HT receptors acting as heteroreceptors modulate release of other neurotransmitters.

Take home points

- Serotonergic system could be involved in the etiology and treatment of AD; neuroprotective effects of serotonin?

- 5-HT1A, 5-HT4 and 5-HT6 receptors are densely expressed in brain regions innervated by serotonergic projections from the raphe nuclei and are associated with learning and memory.

- It has been hypothesized that 5-HT1A (lecozotan), 5-HT3 and 5-HT6 antagonists and 5-HT4 agonists might function as the effective treatment of the cognitive deficits associated with AD, as they have been shown to improve cognitive performance in multiple animal models of learning and memory.

Thank you for your attention....

Malta 24. 10. 2013.