Instituto de Investigaciones Regionales Hideyo Noguchi

Universidad Autonoma de Yucatan, 15 de noviembre de 2019

El papel de la acetilcolina en la generación de los estados de conciencia

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Son siglos o millenios que el Humano ha tratado de explicar la conciencia

Problema filosófico, ético, legal:

¿Cual es la relación entre consciencia y pensamiento?
¿Todos los seres vivientes, incluso los animales, tienen consciencia?
¿Los criminales psicóticos antisociales, tienen una consciencia trastornada?

¿Que es la conciencia?

Perspectiva neurobiologica

Br Foreign Med Chir Rev. 1860 Oct; 26(52): 406–423.PMCID: PMC5178519
PMID: 30163413

Mind and Brain; or, the Correlations of Consciousness and Organization; with Their Applications to Philosophy, Zoology, Physiology, Mental Pathology, and the Practice of Medicine

Review IX.

1. *Mind and Brain: or, the Correlations of Consciousness and Organization; with their Applications to Philosophy, Zoology, Physiology, Mental Pathology, and the Practice of Medicine.* By Thomas Laycock, M.D., &c. &c., Professor of the Practice of Medicine, &c., in the University of Edinburgh. Two vols.—*Edinburgh.* 8vo, pp. 920.
2. *On Obscure Diseases of the Brain, and Disorders of the Mind: their Incipient Symptoms, Pathology, Diagnosis, Treatment, and Prophylaxis.* By Forbes Winslow, M.D., D.C.L., &c. &c.—*London.* 8vo, pp. 744.

The conflicting and unsatisfactory results of abstract speculations on the constitution and powers of the human mind, have long been a source of regret and discouragement; every attempt, therefore, which is in any degree judicious, to place mental philosophy on a surer basis than that on which it has hitherto rested, is to be entertained with candour, and, in so far as it may conduce to the desired end, to be accepted with thankfulness. Such an attempt has been made by Dr. Laycock, and not without success, in the work which stands first in the heading of the present article.

The failure which has hitherto attended such inquiries is attributed by Dr. Laycock to a variety of causes, among the chief of which may be mentioned the disjunction of mental philosophy from physiology, and the study of disease—the neglect of comparative psychology—the fact that the conclusions of metaphysicians have not been sufficiently tested by the general experience of mankind—and the influence of prejudices derived from speculative theology, and a supposed antagonism between revelation and science. His perception of these sources of error, and of the most likely means of obviating them, give a considerable value to his work, notwithstanding an essential faultiness in his method, and the introduction of a great many speculative views, which, we think, had far better have been omitted.

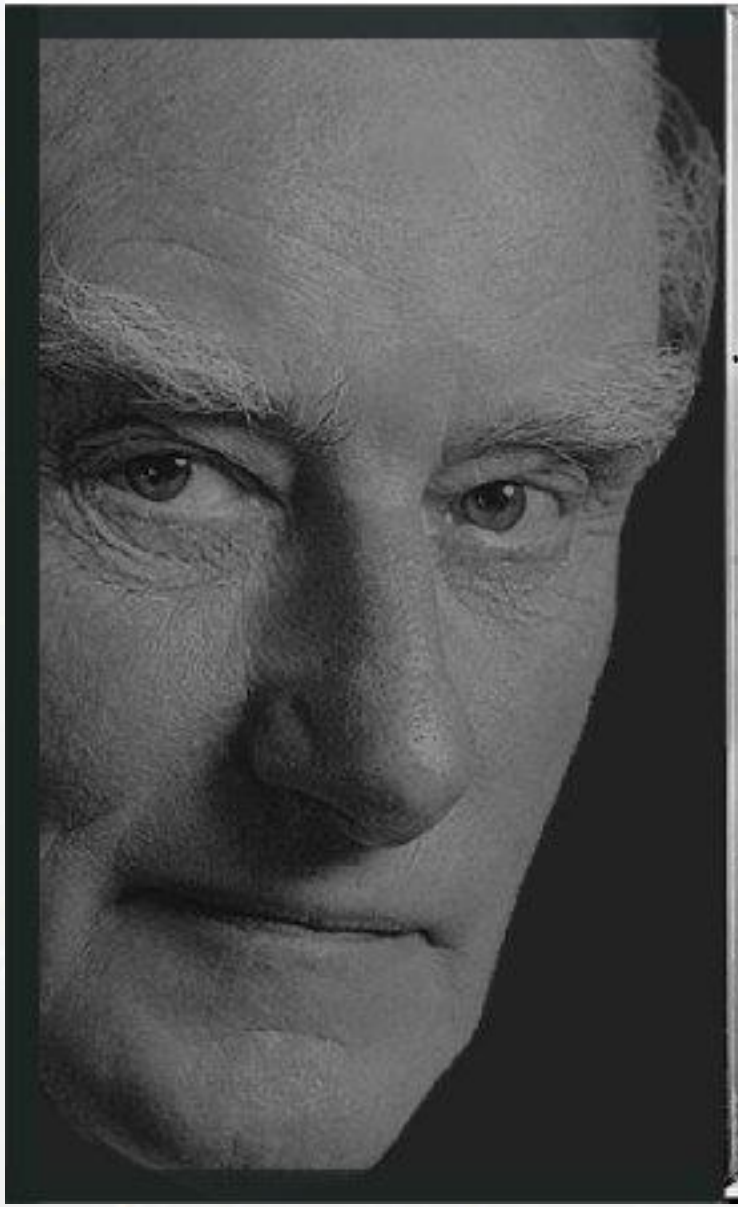
Anticipating, from the title, a work of a much more practical character, we were disappointed to find that a theory lay at the root of the whole matter. This theory is a sort of combination of the philosophy of Plato with the physiology of Stahl.* Dr. Laycock attributes not only the activities of mind, but those of life also, to "an immanent inherent energy, ever operative, which is not a mere physical or material agent, and which can only be conceived as an actually adapting force, manifested in the phenomena of life" (vol. i. p. 2). This "energy," "mind," or "soul,"† is not, however, in itself,

* Dr. Laycock regards Stahl's hypothesis of a common cause of mind and life, as a revival of that of Aristotle. But there was this great difference between them—that Aristotle, while he ascribed the nutritive, sensitive, appetitive, and motory functions to a kind of soul common to man, animals, and plants, regarded the thinking faculty as appertaining to another kind of soul, capable of separate and independent existence.

† Dr. Laycock, at different times, applies all these terms to what he regards as the common cause of life and mind. It seems to us that there can be no clear reasoning on the subject of mind, while the term "mind" is used, as it continually is, by writers, in two different acceptations. It is used sometimes to designate the aggregate phenomena of thought and feeling, and at others to designate a something different from the body—whether separable from it or not—which is the cause of those phenomena. In the latter sense it seems synonymous with *soul.* Now we think that the term "mind," and its corresponding adjective "mental," should be restricted to the phenomena, and the term "soul," to the supposed cause alluded to. Of course, the materialist will have nothing to do with *soul;* but with him the terms "mind" and "mental" will still apply to the phenomena of thought, though he regards these merely as functions of the *brain.* We are convinced that the limitation of terms here proposed would prevent a good many logomachies.

endowed with consciousness, which is developed only through the functions of the brain, but is, as it were, the unconscious vehicle of certain "archetypal" or "teleiotic" ideas, derived from the Divine mind, and carried into effect in the vital organs and functions.

Now, Dr. Laycock's theory may, perhaps, be as good as any other. But any theory accepted as a basis of scientific investigation, is decidedly objectionable on the ground that facts which will not conform to it are extremely apt to be overlooked, or unfairly dealt with, even where there is no intentional want of candour on the part of the theorist. It would not, we think, be difficult to point out several instances in which our author has been led, by his theory, to overlook or ignore subjects worthy of attention; but we will confine ourselves to one—namely, the possibility of a communication between departed spirits and men still living in the body. There is a great mass of alleged facts bearing on this point, which in times past were universally accepted by popular superstition, and pretty extensively even by learned credulity, but which were contemptuously dismissed by the philosophic scepticism of the last century. In the present day, there is a strong disposition in many quarters to subject them to a rigid and impartial scrutiny. This is the only fair and philosophical procedure with regard to them, and on the result of such scrutiny they must stand or fall. Dr. Laycock, however, comes to a summary decision, asserting, as to the possibility alluded to, that "as a speculative proposition it is useless even if true," while "it is practically pronounced by the enlightened experience of mankind to be false" (vol. i. p. 100). We differ from him both as to the value of the proposition if true, and as to the sufficiency of the ground on which he declares it false. If true, so far from being useless, it would at once solve, in the affirmative, the important problem of the immortality of the soul, and would, moreover, disprove the *necessary* dependence of consciousness and thought on cerebral action. Again, we cannot yield much deference to so vague an authority as that of "the enlightened experience of mankind." There is, doubtless, a common experience of mankind relating to ordinary matters, which must be held as authoritative, and from which no appeal can be allowed, because men of all ages and nations have been so unanimous therein, that if any individual oppose his own peculiar convictions to such experience we at once pronounce him perverse or insane; but this certainly entirely ceases when there are diversities in the experience, and we are called upon to decide



Francis Crick Memorial Conference

Cambridge, UK, July 7th 2012

Registration:
www.fcmconference.org

Consciousness in Human and Non-Human Animals

"How our brains work is of vital interest to us all, so why shilly-shally."
(F. Crick, 2000)

Speakers:
Christof Koch
Stephen Hawking
Philip Low
Irene Pepperberg
Bruno van Swinderen
David B. Edelman
Edward Boyden
Diana Reiss
Donald Pfaff
Ryan Remedios
Harvey Karten
Franz X. Vollenweider
Naotsugu Tsuchiya
Melanie Boly
Steven Laureys

Francis Crick (1916-2004), The Francis Crick Chalkboard, Philip Low Collection, La Jolla, CA, USA.

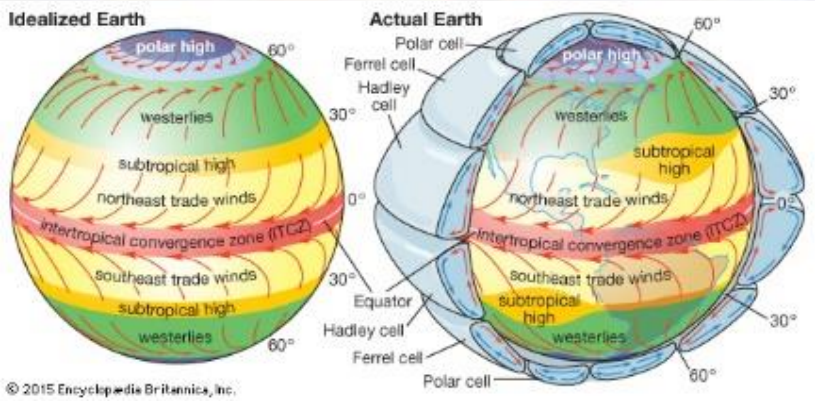
La consciencia existe también en los animales superiores

¿En que difiere la consciencia en los diferente animales?

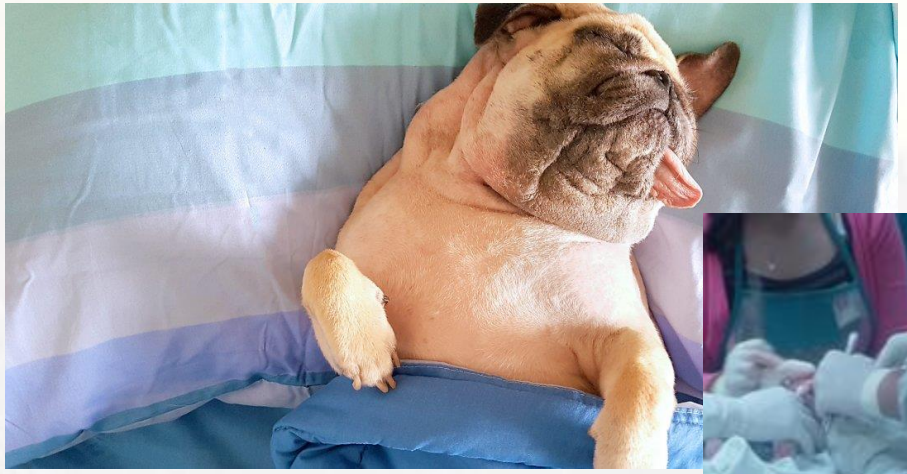
?Porque? y ?como? investigar la consciencia?

- Todos sabemos que el aire existe
- No se puede ver
- Es útil saber que existe

¿Como explicas que es el aire?



Nivel básico de ausencia (temporal) de consciencia: sueño y anestesia

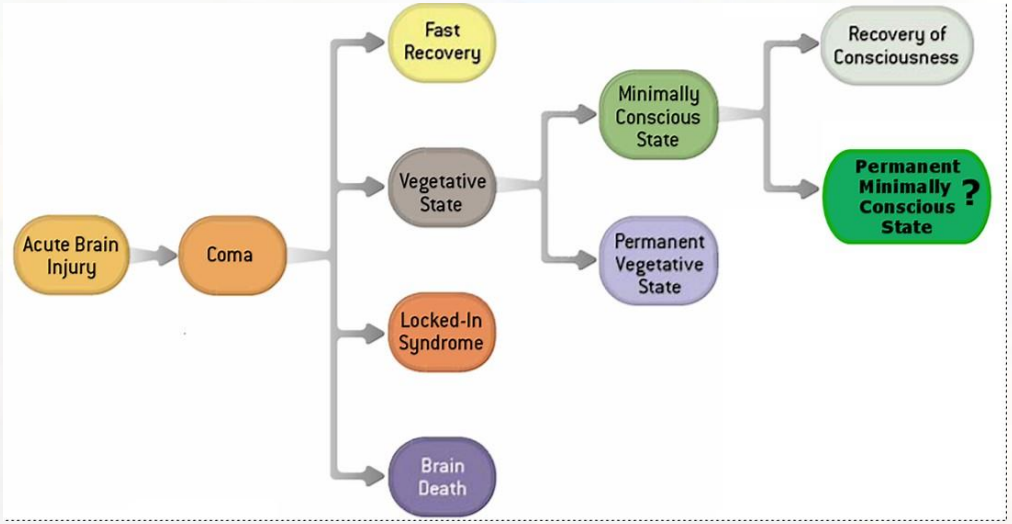


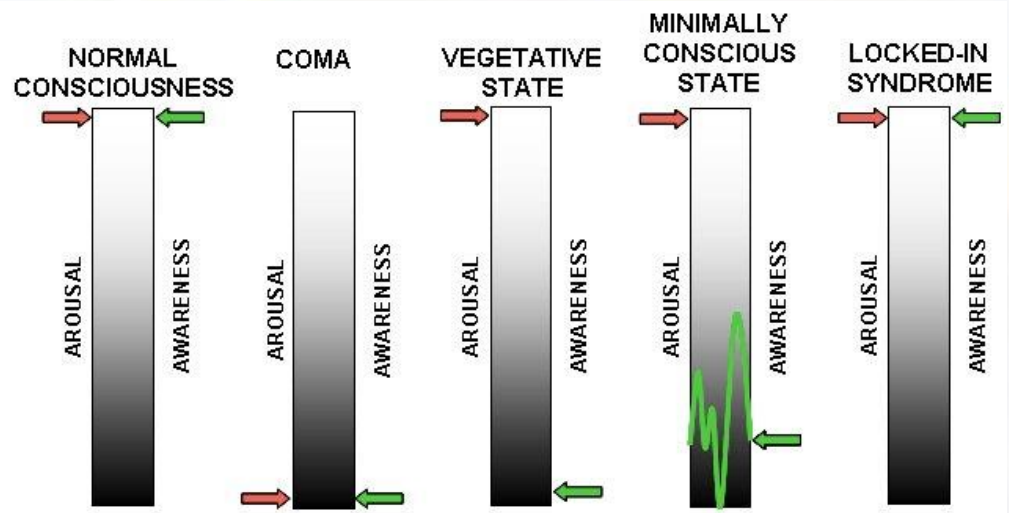
coma

sueño

anestesia

Lesiones o enfermedades pueden llevar a perdidas de consciencia mas duraderas

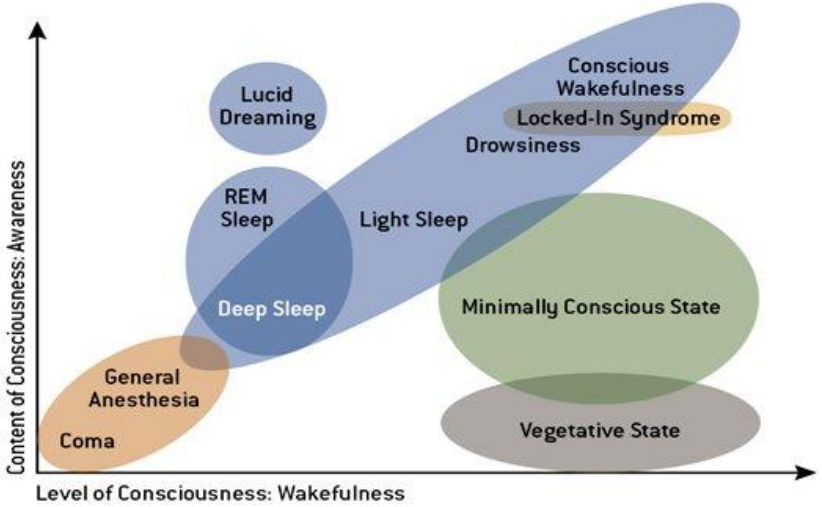




The Unconscious Brain

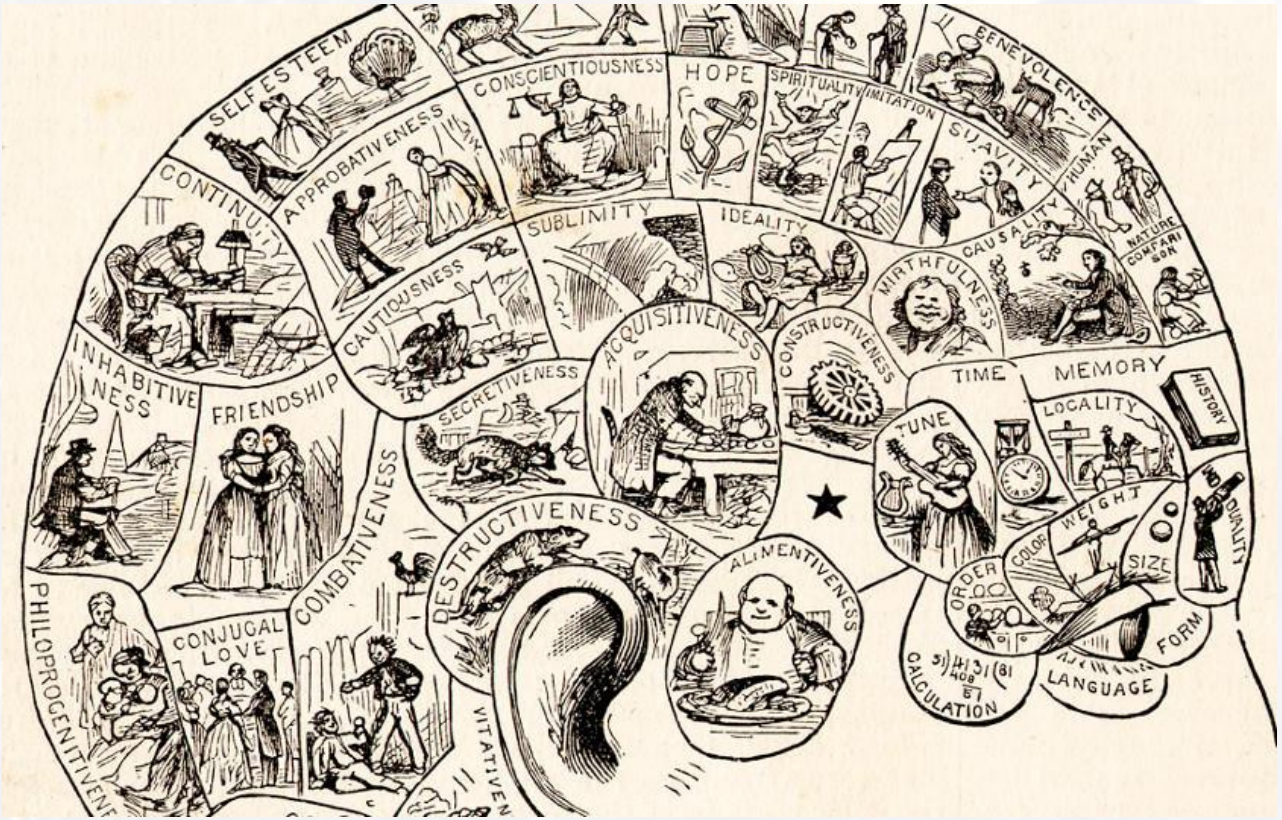
New research is allowing neuroscientists to make clear distinctions between characteristics of unconsciousness.

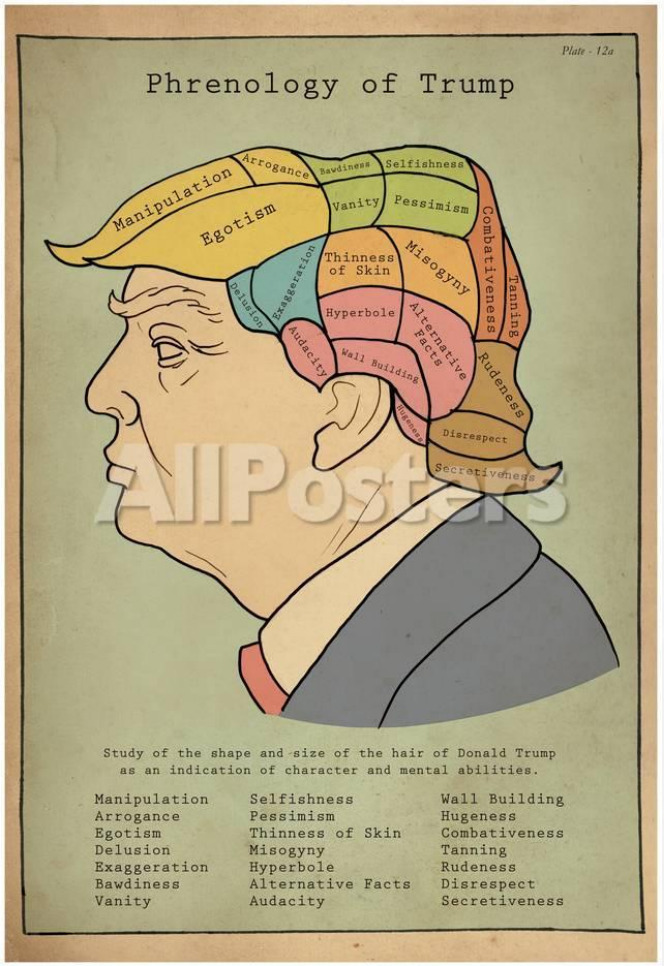
CONDITION	CONSCIOUS	MOTOR FUNCTION	HEARING	EYESIGHT	COMMUNICATION	EMOTION
Coma	No	Some reflexes intact	None	None	None	None
Vegetative state	No	Occasional random movements; withdraws from a pinch	Startles at loud noises	Eyes wince at bright light or when startled	None	Reflexive/ random crying or smiling
Minimally conscious state	Partially	Reaches for objects; may grab and hold them	Sometimes responds to commands with blinking or body movement	Tracks moving objects with eyes	Occasionally forms intelligible sounds or gestures	At times smiles at jokes or cries when sad



Que clase de respuesta buscamos?

La respuesta no está en la frenología, la pseudociencia que trataba de localizar las funciones humanas en ubicaciones precisas del cerebro.



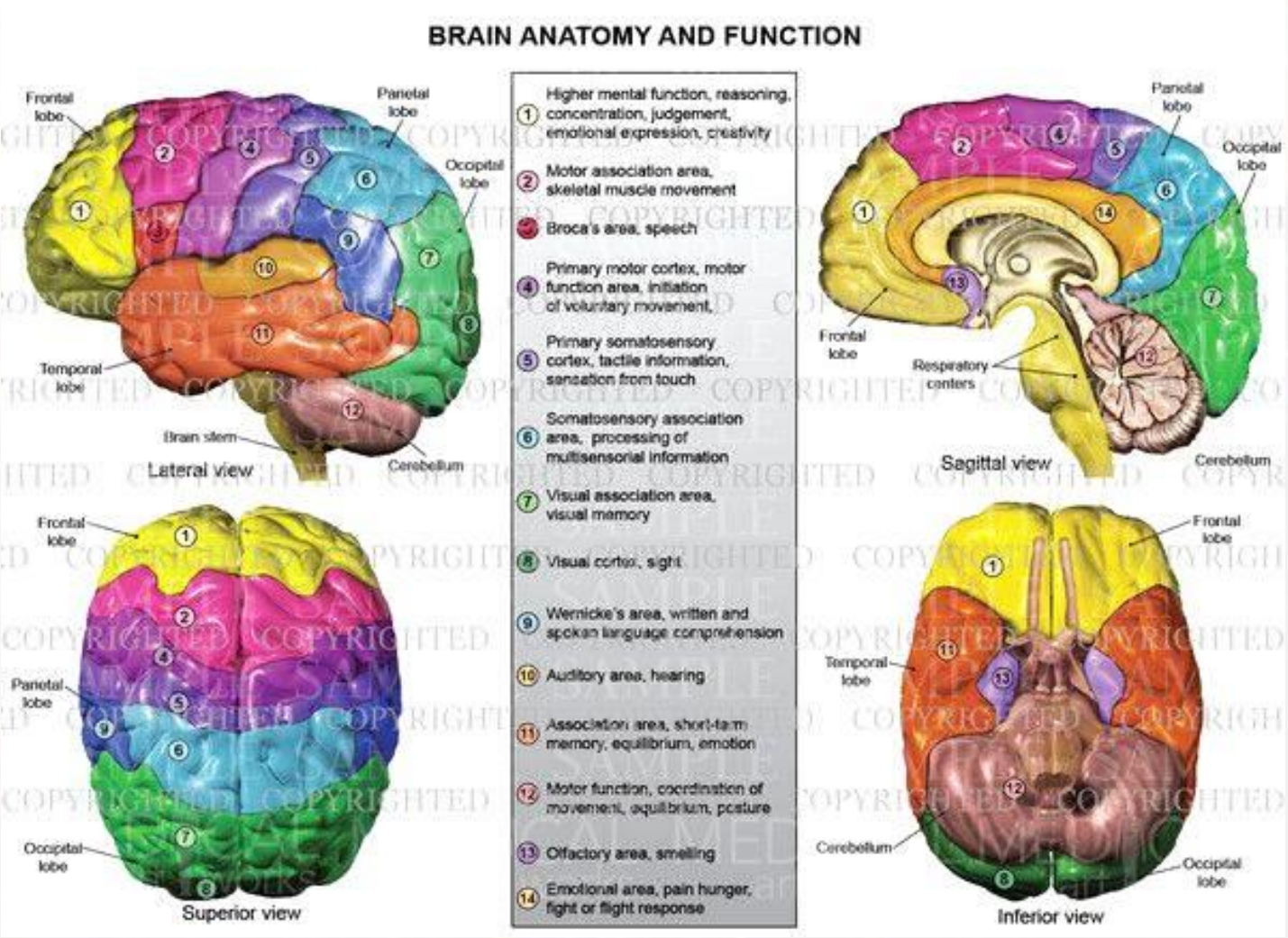


Sustratos organicos de la consciencia

Como la mayoría de las funciones cerebrales, la consciencia utiliza varios circuitos neuronales, y está parcialmente delocalizada:

Diferentes partes del cerebro son responsables de varios aspectos de la consciencia.

Necesidad de referirnos a la anatomía funcional del cerebro



Consciencia (Merriam Webster dictionary)

the state of being characterized by sensation, emotion, volition, and thought

Presencia de las siguientes facultades mentales:

- **Sensacion (vista, oído, tacto, etc.)**
- **Emocion (capacidad de sentir placer, dolor, rabia, alegría, etc.)**
- **Voluntad (capacidad de tomar decisiones o elecciones)**
- **Pensamiento (tenerlo y poderlo reportar)**

Cada una de estas categorias implica la capacidad mental de

1) **representar un fenómeno (interno o externo), y, finalmente**

2) **Representar su representación y manipular la misma representación *separadamente***

sensación

mundo externo

representación directa (cerebro)

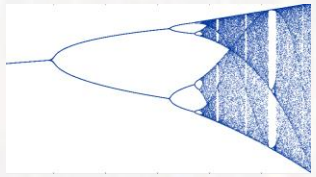
2nda representación cerebro

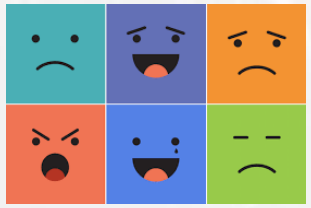
voluntad

emoción

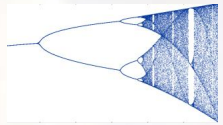
pensamiento

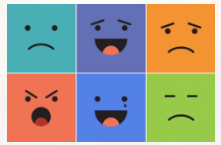
mundo interno



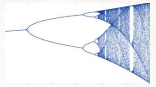


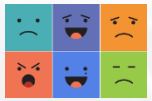
representación directa (cerebro)





representación de la representación





realidad objetiva (fenómeno)
objeto o proceso mental

proceso mental **<u>no</u> manipulable**

procesos mentales **integrables y manipulables**
WORKING MEMORY
LONG TERM MEMORY STORAGE

CONCIENCIA

Acetilcolina → integrabilidad y manipulabilidad de percepción, voluntad, emoción y pensamiento

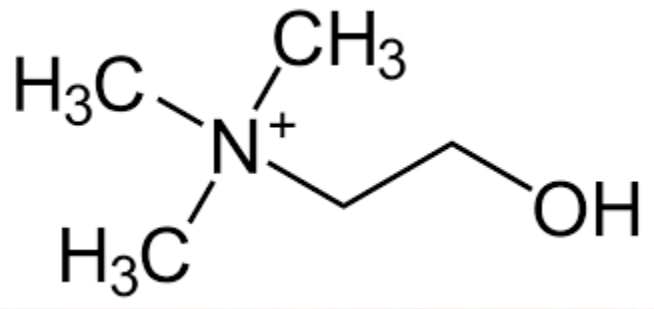
Que es la acetilcolina?

Donde se encuentra?

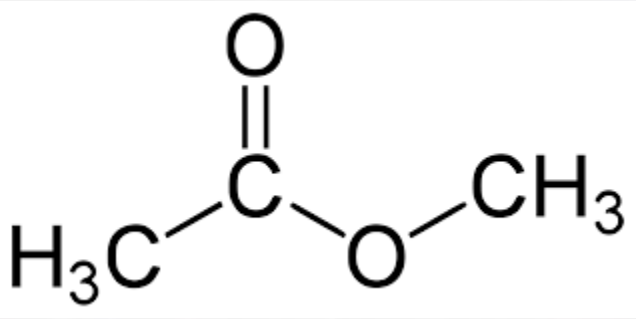
Cuales son sus funciones conocidas?

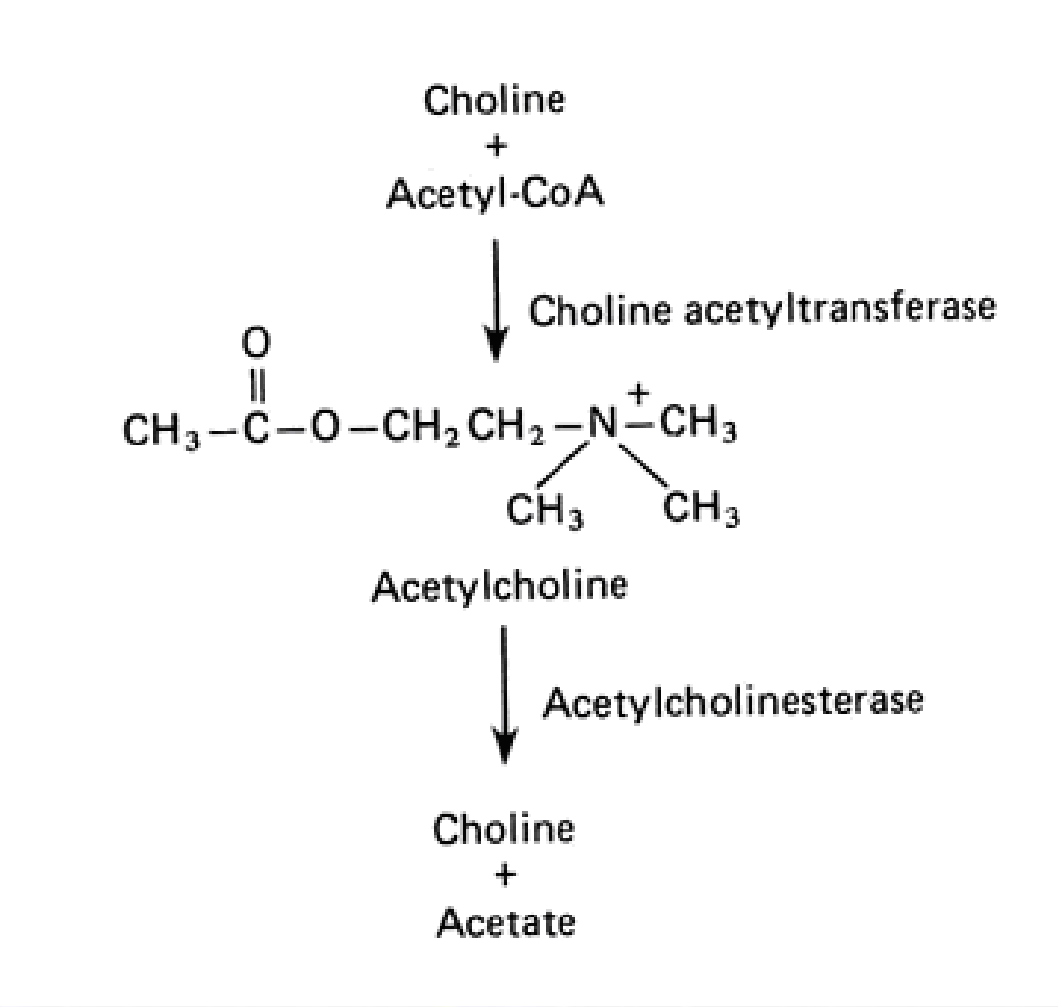
SINTESIS Y DEGRADACION DE LA ACETILCOLINA

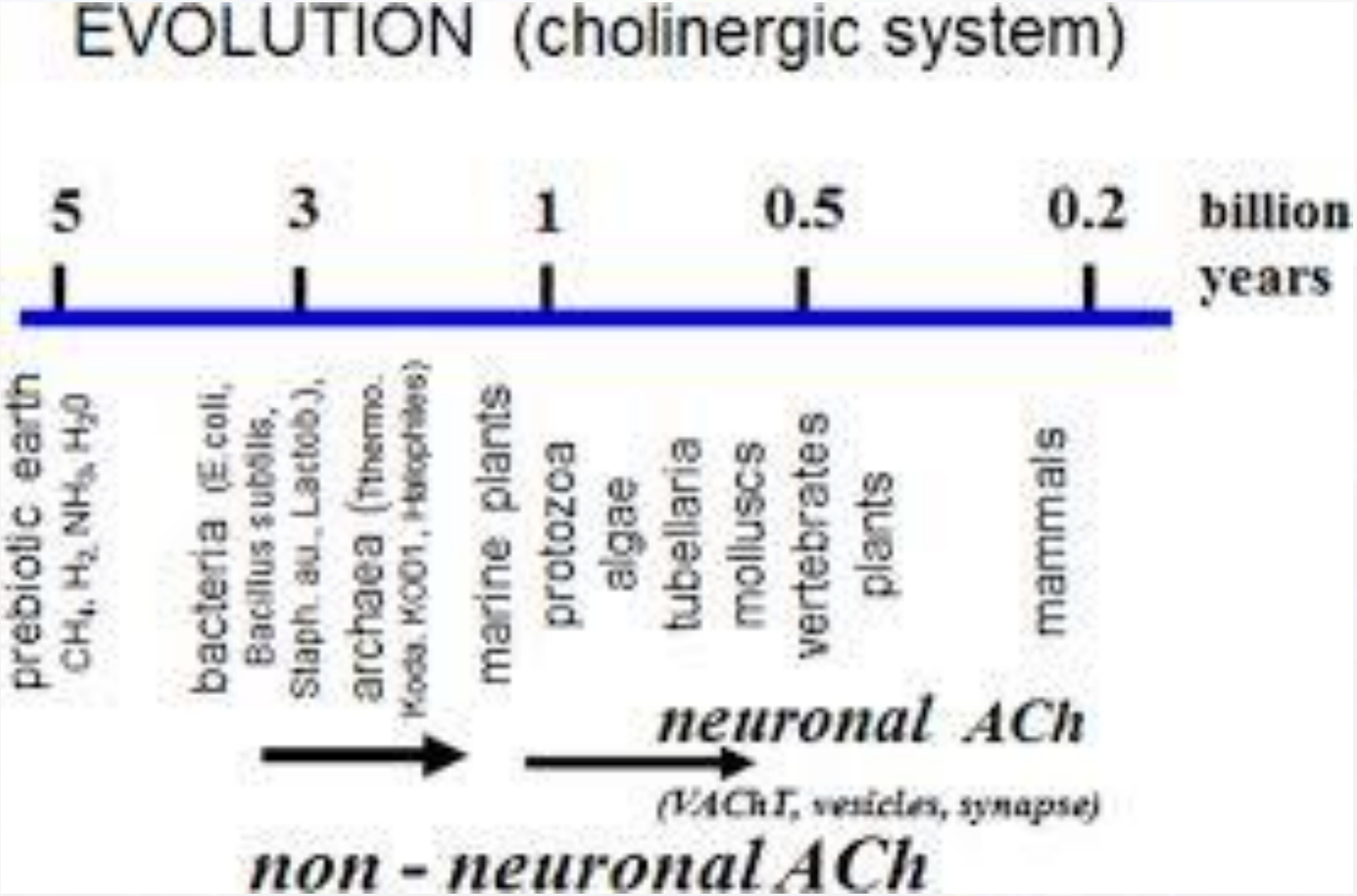
COLINA



ACETATO






EVOLUTION (cholinergic system)
5
3
1
0.5
0.2
billion years
prebiotic earth
CH_4, H_2, NH_3, H_2O
bacteria (E coli, Bacillus subtilis, Staph. au., Lactob.),
archaea (Thermo. Kodo. KOD1, Halophiles)
marine plants
protozoa
algae
tubellaria
molluscs
vertebrates
plants
mammals
neuronal ACh
(VAChT, vesicles, synapse)
non - neuronal ACh

La acetilcolina tiene dos tipos de receptores importantes

Muscarinicos y Nicotinicos

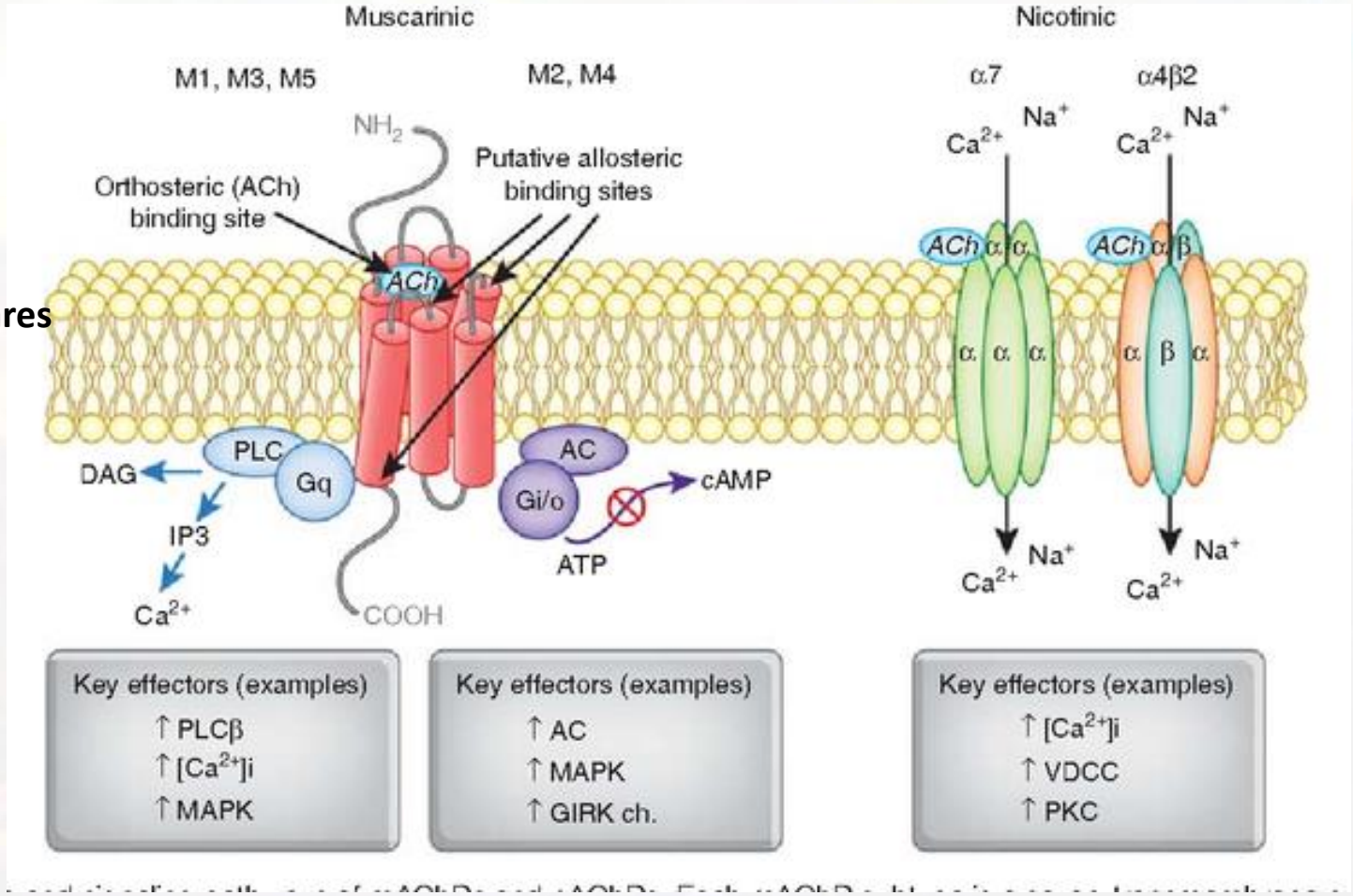
- Muscarinicos: activación lenta de alta afinidad, asociados a cascadas metabólicas:

Proteinas G: $M_{1,2,3,4,5}$:

$M_{1,3,5}$: G_q , liberación de Ca de los almacenes intracelulares con funciones mixtas excitatorias o inhibidoras

$M_{2,4}$: G_I , inhibidora de la adelylyl ciclasa

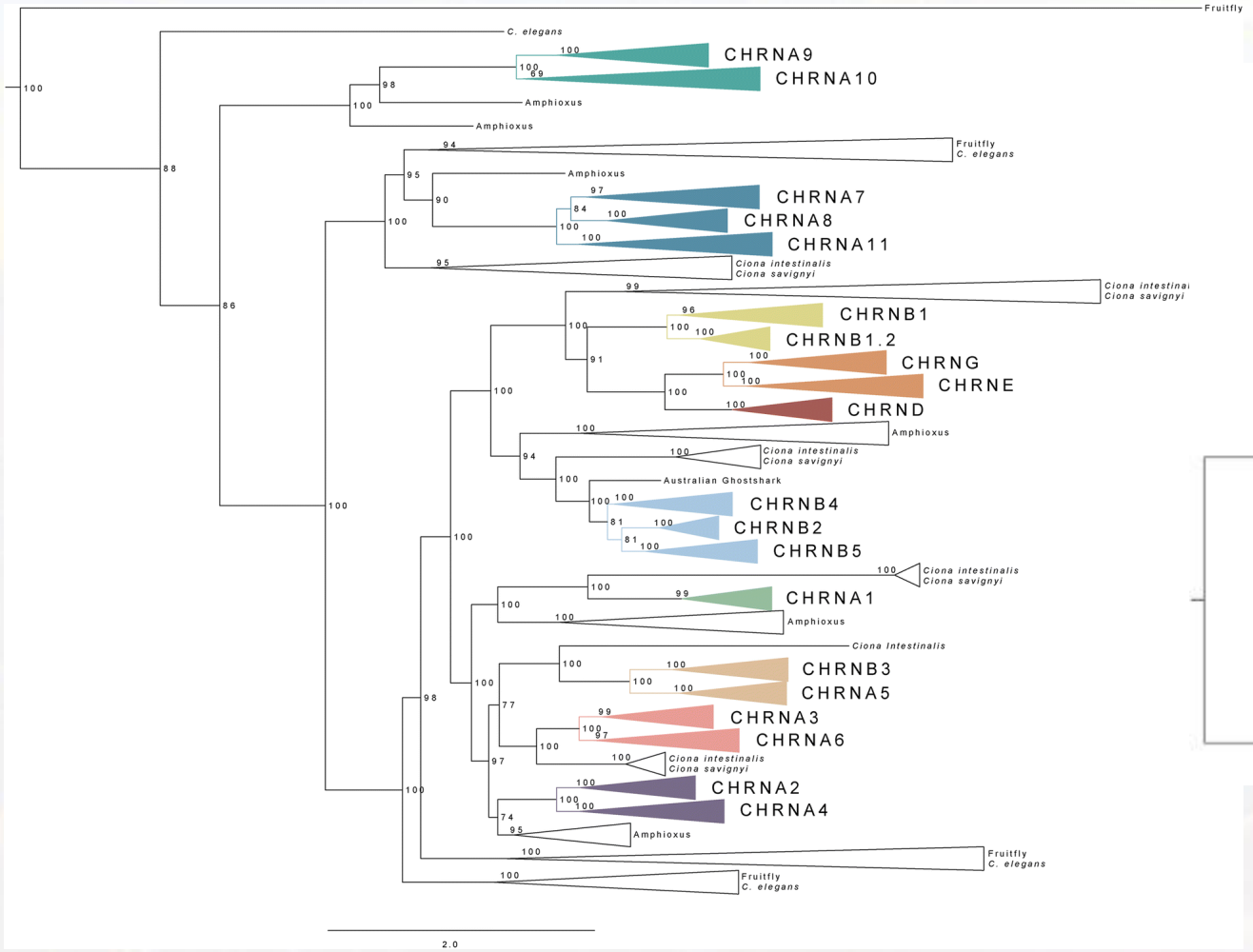
Excitación por cierre de canales de potasio y por reducción de la inhibición sináptica

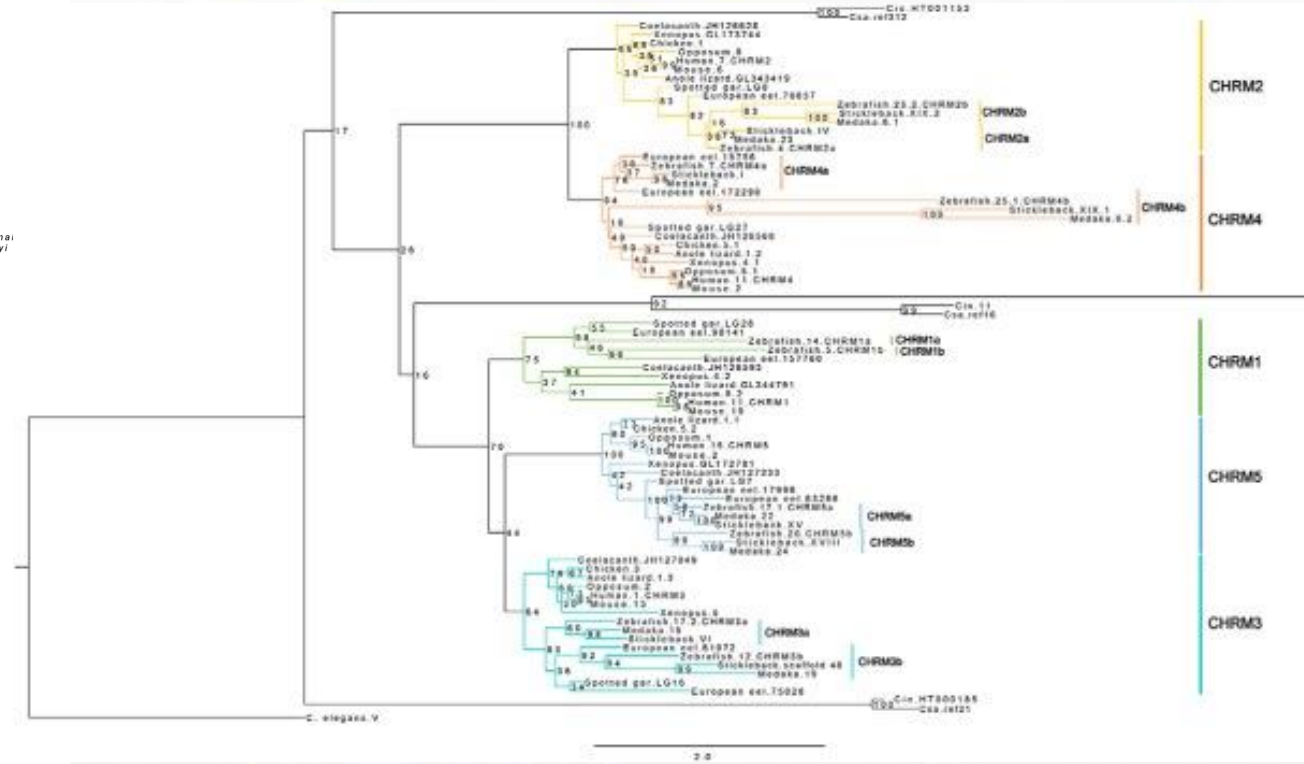


- **Nicotinicos: canales catiónicos (excitatorios)**

despolarizacion
aumento de calcio intracelular (plasticidad)

Evolucion y antigüedad evolutiva de loss receptores colinergicos





2018 Nov 8. Prepublished online 2018 Oct 24.
Evolution of the Muscarinic Acetylcholine Receptors in Vertebrates
Julia E. Pedersen,* Christina A. Bergqvist,* and Dan Larhammar

Evolution of vertebrate nicotinic acetylcholine receptors
•Julia E. Pedersen, Christina A. Bergqvist & Dan Larhammar
BMC Evolutionary Biology **volume 19**, Article number: 38 (2019)

NICOTINIC RECEPTORS
VERSUS
MUSCARINIC RECEPTORS

Nicotinic receptors are a group of cholinergic receptors linked to ion channels in the cell membrane	Muscarinic receptors are a group of G-protein coupled cholinergic receptors that phosphorylate second messengers
Has two types:N1 and N2	Has five types: M1, M2, M3, M4, and M5
Excitatory receptors	M1, M2, and M5 are excitatory receptors while M3 and M4 are inhibitory receptors
N1 receptors are located in neuromuscular junctions; N2 receptors are located in the brain, autonomic and parasympathetic nervous system	Found in the brain, heart, and smooth muscles
Become ion channels upon activation	Phosphorylate various second messengers
A type of ligand-gated ion channels	A type of G-protein coupled receptors
Mediate fast synaptic transmission of nerve impulses	Mediate a slow metabolic response via second messenger cascades
Respond to nicotine	Respond to muscarine

ACh in invertebrates

ACh mediates **fast excitatory cholinergic neurotransmission in the nervous system of all metazoans that use this neurotransmitter**. These actions are conveyed via ACh-induced activation of **pentameric nicotinic receptors**, which are archtypical members of the ligand-activated receptor superfamily that includes 5-HT-, GABA-, and glycine receptors (Sattelle et al., 2005).

ACh is synthesized in nerve terminals from acetyl coenzyme A and choline, by the enzyme choline acetyltransferase (CAT), and broken down by acetylcholine esterase (AChE) after reuptake into neurons and glial cells (Banks et al., 2009) by transporters.

Neuromuscular transmission in invertebrates is both glutamatergic (Hooper et al., 1986; Stein et al., 2006) and cholinergic (Futamachi, 1972; Marder, 1974, 1976; Weiss et al., 1992; Brezina et al., 1995; Katz & Frost, 1996; Kratsios et al., 2012), a trait shared with vertebrates (Vyas & Bradford, 1987; Brunelli et al., 2005; Pizzi et al., 2006; Rinholm et al., 2007).

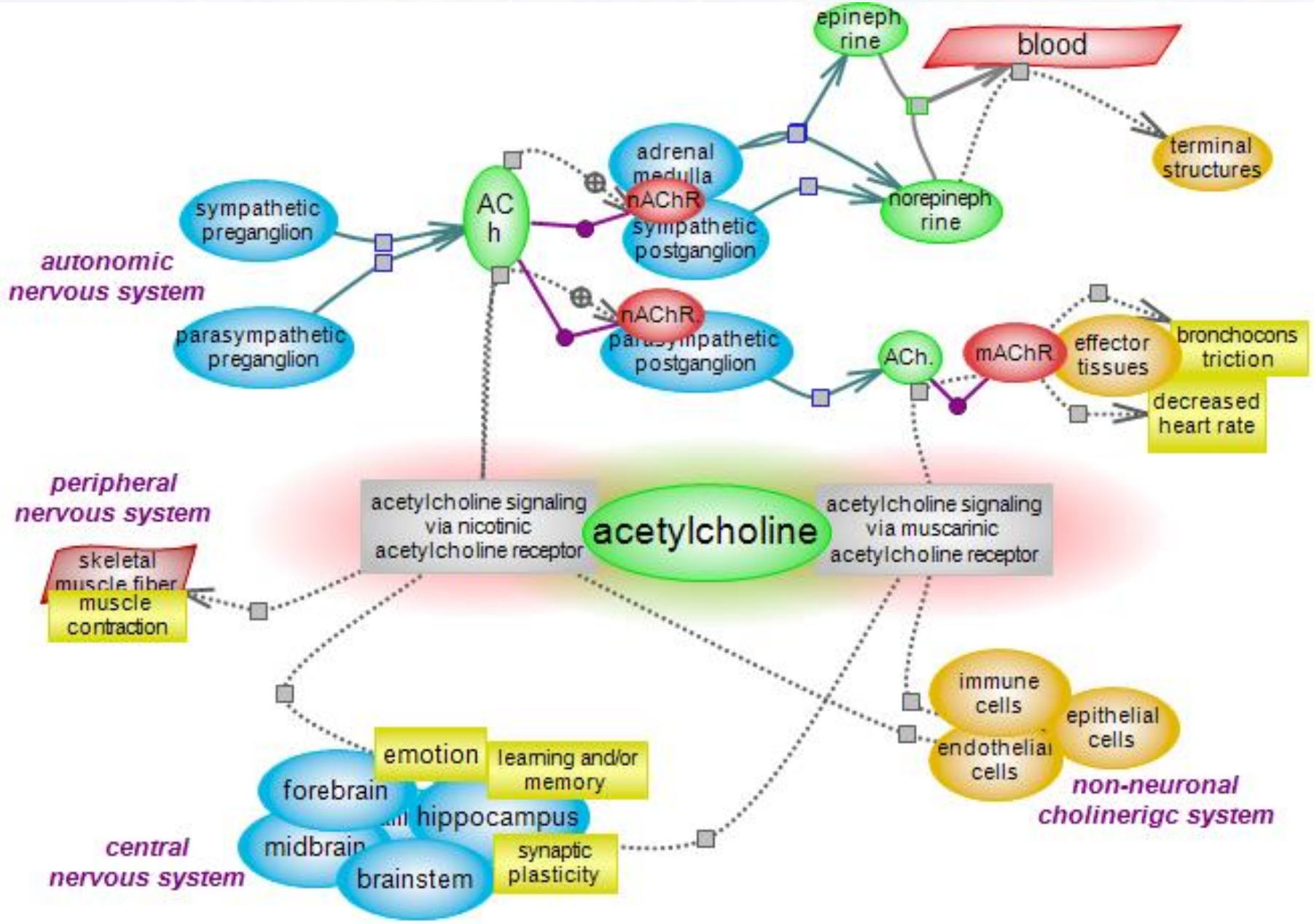
Visceral motor activity in crustaceans is commanded by the stomatogastric ganglion and thus is largely cholinergic (Gallus et al., 2006). Independent confirmation of the cholinergic control of gut motility has been found in molluscs and annelids, although numerous other neurotransmitters and neuropeptides participate (Anctil et al., 1984; Lloyd & Willows, 1988; Ukena et al., 1995).

In nematodes, cholinergic neurotransmission controls the chemosensory nerve output of the amphids, a pair of cephalic sensory organs, and pharangeal pumping is under cholinergic control (Croll, 1977). **Much of cholinergic neurotransmission is inhibitory, increasing Cl or K conductances in postsynaptic neurons**. This has been studied in detail in Aplysia (Kehoe, 1972a,b; Inoue et al., 1994; Kehoe & Vulfius, 2000; and many others).

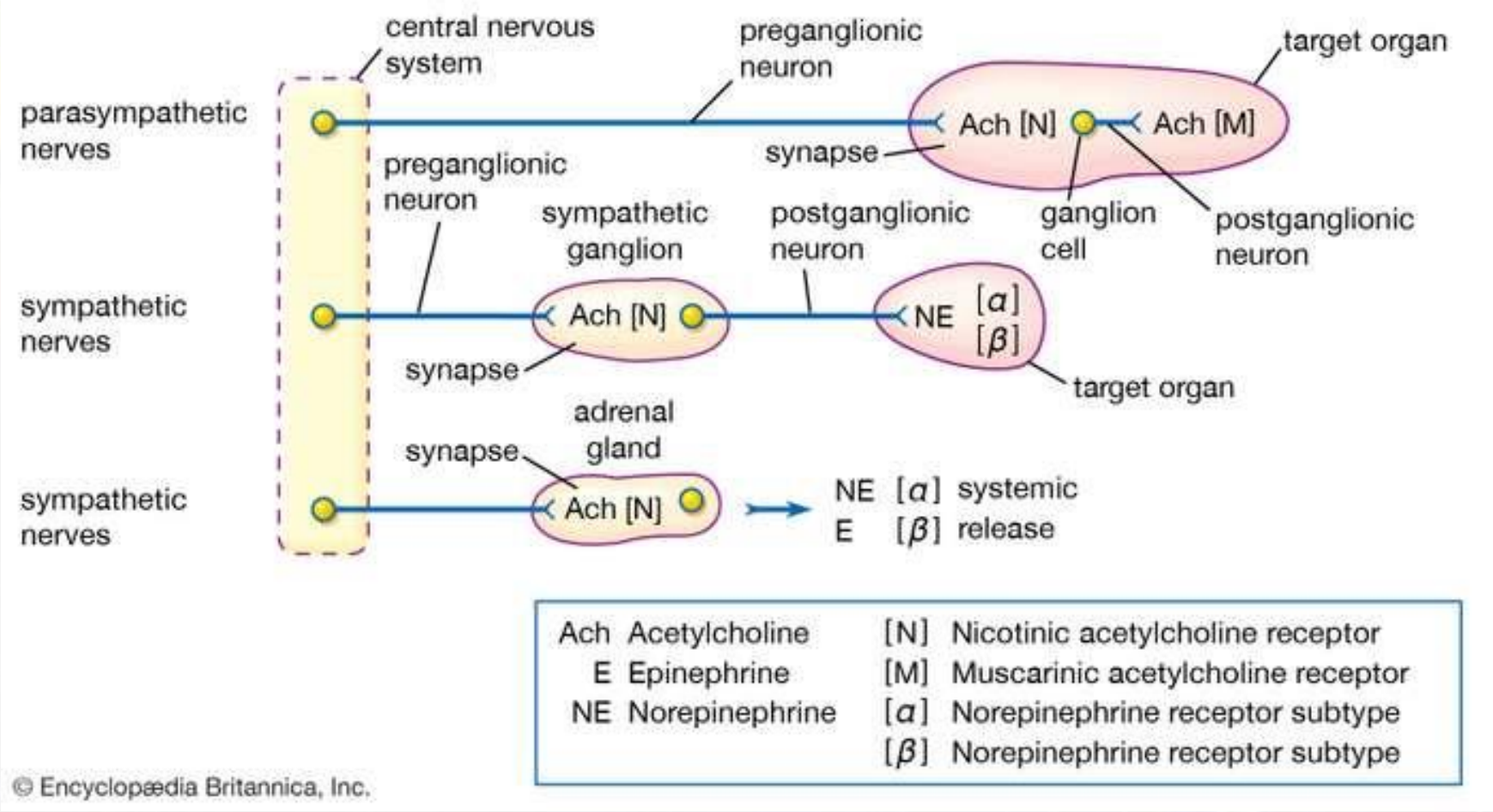
ACh also activates muscarinic receptors associated with G proteins, although these are not well studied in invertebrates (Liu et al., 2016); most studies are in insects. Muscarinic receptors located presynaptically inhibit release of ACh and other neurotransmitters in a form of negative feedback, whereas those located on the postsynaptic membrane induced excitatory responses both centrally and peripherally (Trimmer, 1995; Caulfield & Birdsall, 1998).

Neurotransmitters and Neuropeptides of Invertebrates Lynne A. Fieber The Oxford Handbook of Invertebrate Neurobiology Edited by John H. Byrne Print Publication Date: Apr 2019 Subject: Neuroscience, Invertebrate Neurobiology, Molecular and Cellular Systems Online Publication Date: Feb 2017

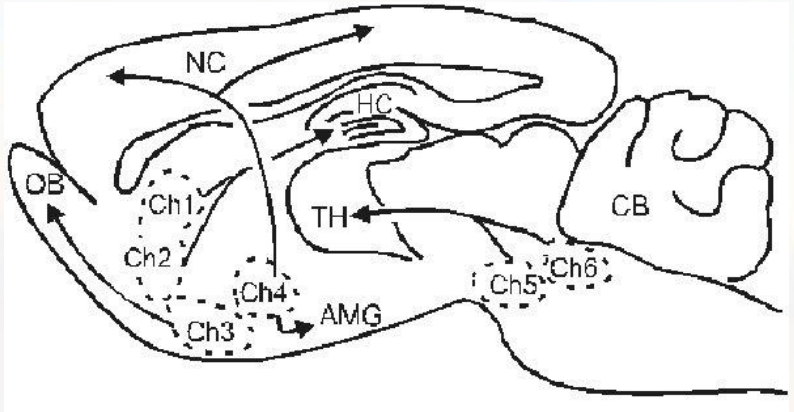
ACh in vertebrates

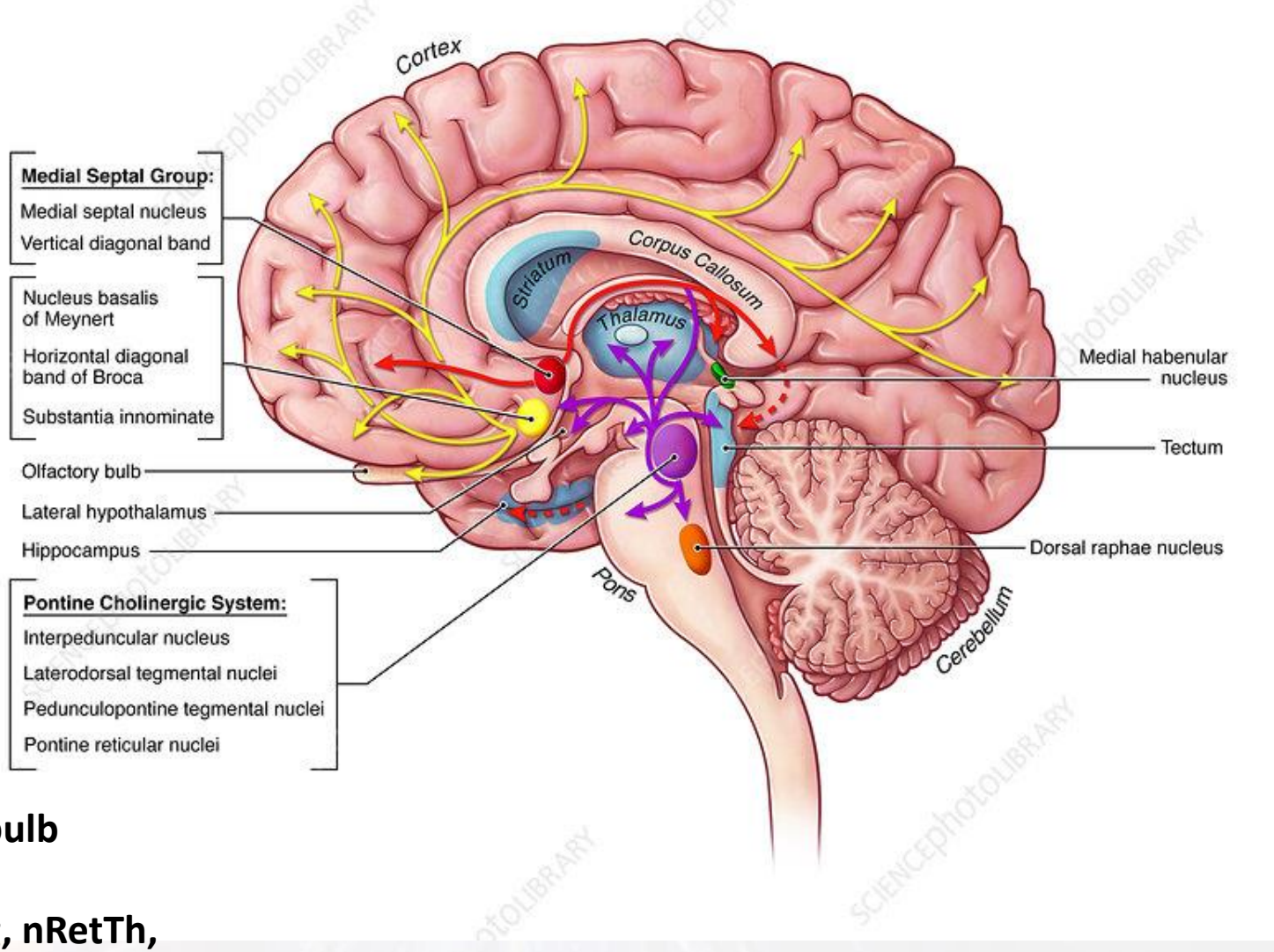


Acetylcholine in the vertebrate autonomic system



Acetylcholine in the mammalian brain: cholinergic nuclei and their projections





Ch1 = medial Medial Septum **to hipp.**

Ch2 = vert. limb of the diag. b. Broca **to hipp.**

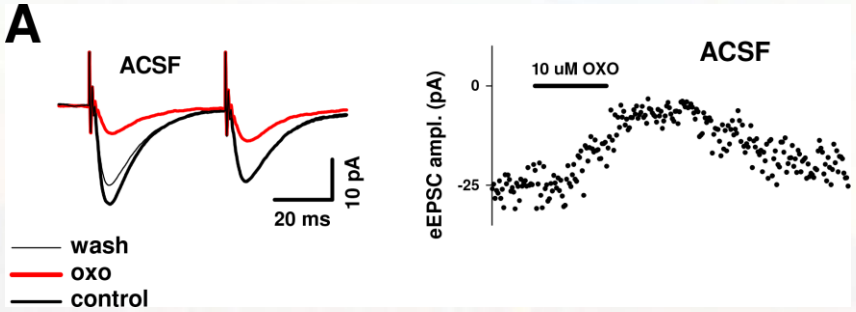
Ch3 = horiz. limb of the diag. b. Broca **to olfactory bulb**

Ch4 = Nucleus Basalis **to NCT, Amyg, nRetTh, InLamTh, bidir with PFCTX**

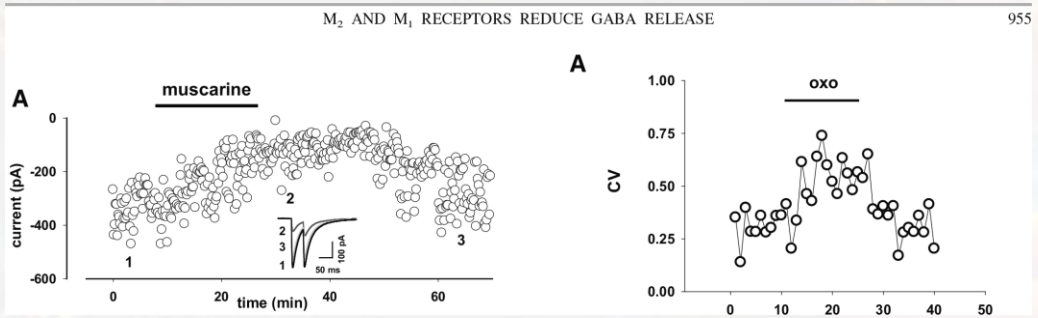
Ch5 = Latero-Dorsal Tegmentum **to whole thalamus, NB**

Ch6 = Pedunculo Pontine Tegmentum **to whole thalamus, NB**

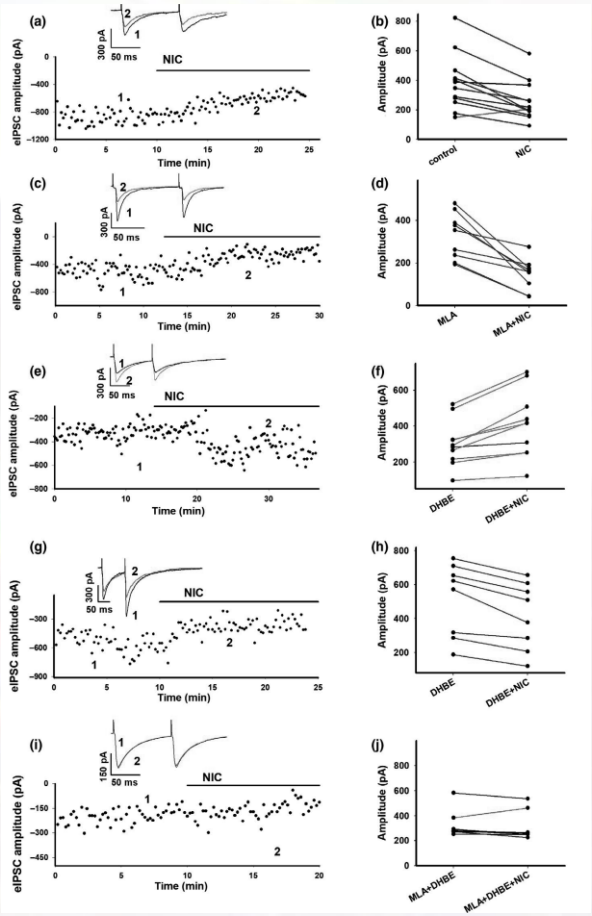
ACh modula las respuestas sinápticas excitadoras e inhibidoras del cerebro



Neuroscience. 2005;134(4):1153-65.
Dopamine prevents muscarinic-induced decrease of glutamate release in the auditory cortex.
Atzori M[1], Kanold PO, Pineda JC, Flores-Hernandez J, Paz RD.

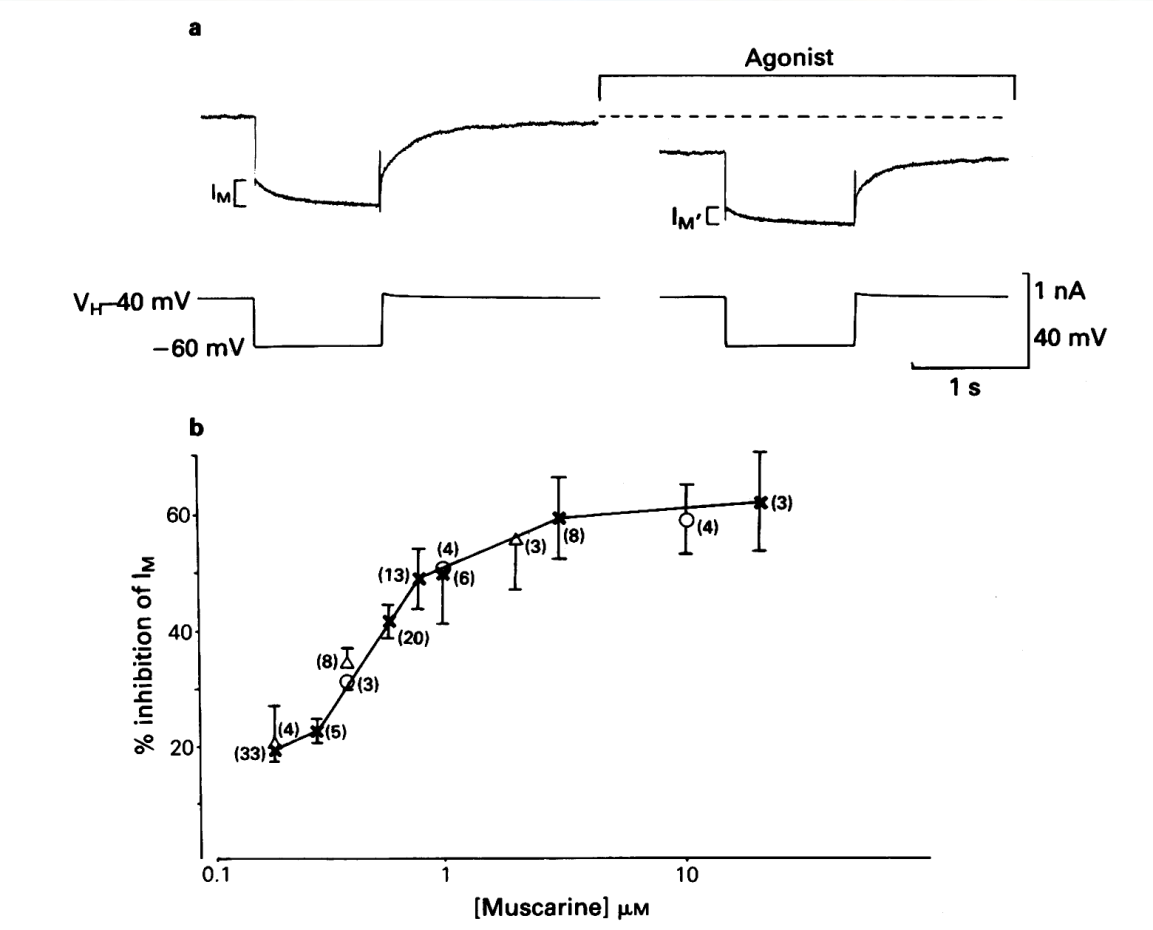


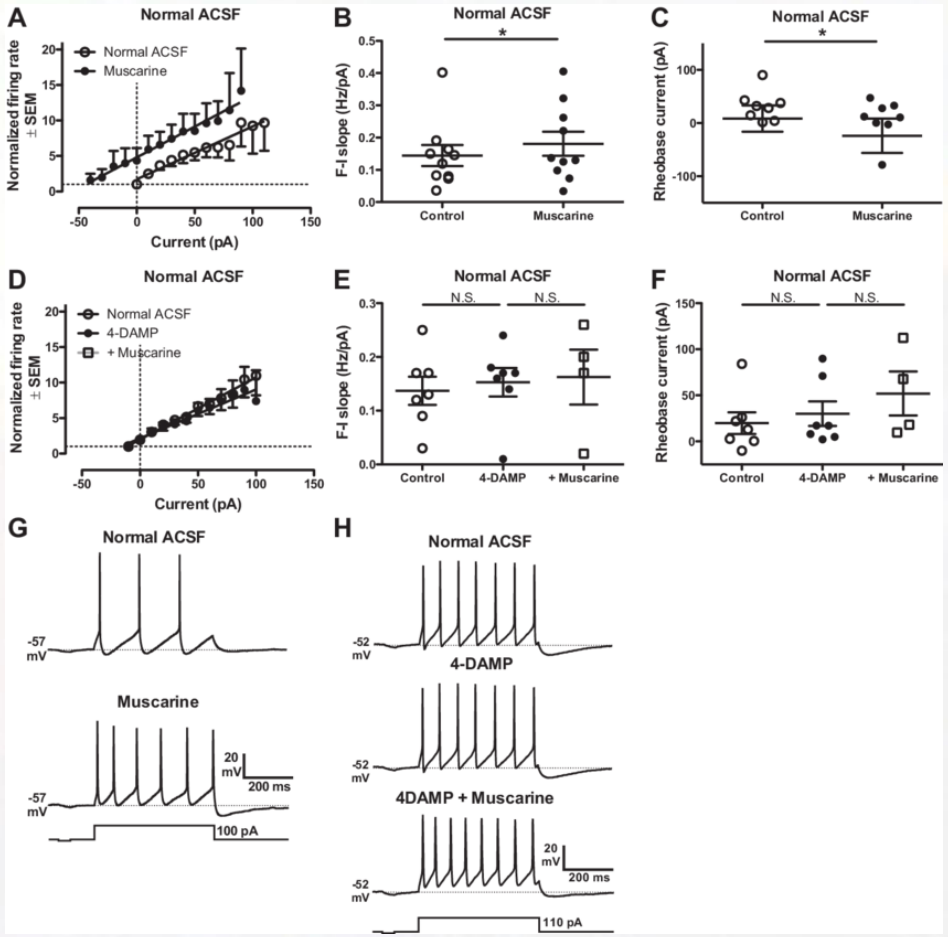
J Neurophysiol. 2007 Aug;98(2):952-65. Epub 2007 Jun 20.
Muscarinic M2 and M1 receptors reduce GABA release by Ca2+ channel modulation through activation of PI3K/Ca2+ -independent and PLC/Ca2+ -dependent PKC.
Salgado H[1], Bellay T, Nichols JA, Bose M, Martinolich L, Perrotti L, Atzori M.



Nicotine smoking concentrations modulate GABAergic synaptic transmission in murine medial prefrontal cortex by activation of α7* and β2* nicotinic receptors.
Cuevas-Olguin R, Esquivel-Rendon E, Vargas-Mireles J, Barajas-López C, Salgado-Delgado R, Saderi N, Arias HR, Atzori M, Miranda-Morales M.
Eur J Neurosci. 2019

ACh aumenta la excitabilidad neuronal bloqueando una corriente de potasio





Br J Pharmacol. 1989 Oct;98(2):557-73.
Muscarinic suppression of the M-current in the rat sympathetic ganglion is mediated by receptors of the M1-subtype.
Marrion NV[1], Smart TG, Marsh SJ, Brown DA.

J Appl Physiol (1985). 2012 Oct;113(7):1024-39. 2012 Aug 2.
Muscarinic acetylcholine receptors enhance neonatal mouse hypoglossal motoneuron e xcitability in vitro. Ireland MF[1], Funk GD, Bellingham MC.

¿Que tiene que ver la acetilcolina con la conciencia?

El bloqueo de los receptores de acetilcolina reduce los estados de conciencia

Receptores muscarinicos:

- escopolamina y zombies
- Extractos de la datura como “rape drug”
- Toluache

Receptores nicotinicos y conciencia

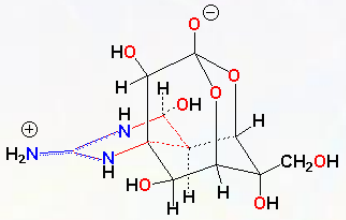
???

“Zombificacion”

Entre los castigos previstos se encontraria, segun los antropologos que estudian la sociedad haitiana, la “zombificacion”.

El acto de “zombificacion” consistiria en utilizar una serie de toxinas para ocasionar una muerte aparente a un individuo reconocido culpable segun las reglas de la sociedad de Bizango, para luego resuscitarlo (en realidad nunca ha estado muerto), para que leve una vida controlada por un amo.

Farmacologia:



Varios antropologos se dieron a la tarea de estudiar y determinar las toxinas utilizadas, entre las toxinas utilizadas, por los “bokors”

Es controversial el uso de la tetrodotoxina, proveniente del pez globo, muy comun en los oceanos Atlantico y Pacifico y en las costas de Africa y Haiti.

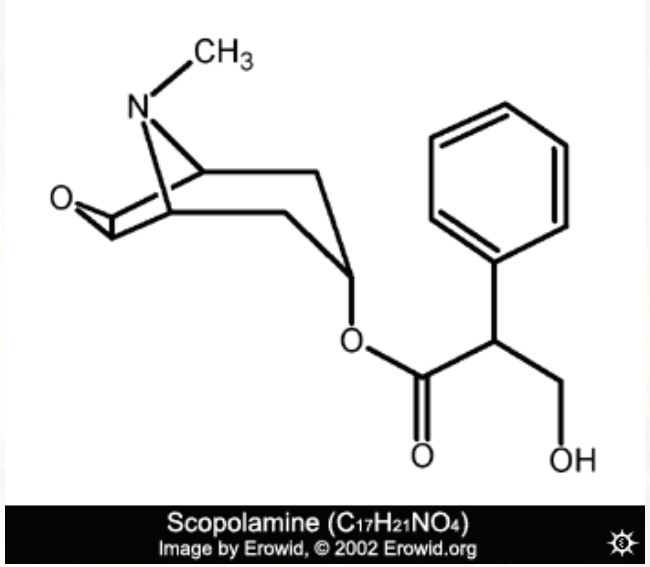
El efecto de la TTX es paralizar, en dosis especificas sin matar al intoxicado, reduciendo el latido cardiaco a niveles imperceptibles, pero suficientes para sobrevivir hasta uno o dos dias.

Farmacologia cont.:

El segundo estadio de la "zombificacion" consistiria en utilizar otra toxina, la escopolamina, un bloqueador de los receptores colinergicos muscarinicos, tambien muy facil de conseguir, que –en dosis apropiadas- induce

- **Perdida de la experiencia consciente:**
- **Perdida de la capacidad de memorizar**
- **Estados semihipnoticos**
- **Perdida de la voluntad**
- **Preserva la capacidad para algunas conductas:**
  caminar, dialogar, acordarse memorias previas

La escopolamina es la version permeable permeable a la barrera hematoencefalica de la atropina, la mas poderosa de las toxinas bloqueadora de los receptores muscarinicos



Jimson Weed
Datura Stramonium

Angels trumpets
Datura Ferox

Datura y zombies

From Wade Davis, a Harvard scholar who studied and identified the nature of the process of zombification (University of North Carolina press, 1988):

"… a strong and timely dose of *Datura Stramonium* –also called Concombre zombie (zombie cucumber) – would undoubtly be instrumental in inducing and mantaining the zombie state.

For if tetrodotoxin provides the physiological background upon which [zombification works] , Datura amplifies those processes one thousand times.

Alone, its intoxication has been characterized as an induced state of psychotic delirium marked by disorientation, acute confusion, and complete amnesia.

Administered to an individual who has already passed through the ground, and who may actually have been conscious the entire time, the devastating psychological effects would be staggering. It is in the course of the datura intoxication that the zombie is baptized with a new name and led away to be socialized in a new existence."

***La Datura stramonium* contiene antagonistas muscarinicos:**
atropina y escopolamina.

BURUNDANGA (Colombia)

BOGOTA, Colombia (Reuters) - The last thing Andrea Fernandez recalls before being drugged is holding her newborn baby on a Bogota city bus.
Police found her three days later, muttering to herself and wandering topless along the median strip of a busy highway. Her face was badly beaten and her son was gone.

Fernandez is just one of hundreds of victims every month who, according to Colombian hospitals, are temporarily turned into zombies by a home-grown drug called scopolamine which has been embraced by thieves and rapists. "When I woke up in the hospital, I asked for my baby and nobody said anything. They just looked at me," Fernandez said, weeping. Police believe her son Diego was taken by a gang which traffics in infants.

Colorless, odorless and tasteless, scopolamine is slipped into drinks and sprinkled onto food. Victims become so docile that they have been known to help thieves rob their homes and empty their bank accounts. Women have been drugged repeatedly over days and gang-raped or rented out as prostitutes.

In the case of Fernandez, the mother of three was rendered submissive enough to surrender her youngest child.

articulo escrito por Phil Stewart, un reportero de la agencia Reuters, desde Bogota', Colombia

Intoxicacion por toloache

trompeta de ángel, hierba del diablo, higuera loca (borrachero), maleza de Jamestown, chamico, campanilla tropical americana

Scopolamine has a long, dark history in Colombia dating back to before the Spanish conquest. Legend has it that Colombian Indian tribes used the drug to bury alive the wives and slaves of fallen chiefs, so that they would quietly accompany their masters into the afterworld.

Nazi "angel of death" Joseph Mengele experimented on scopolamine as an interrogation drug. And scopolamine's sedative and amnesia-producing qualities were used by mothers in the early 20th century to help them through childbirth.

Finding the drug in Colombia these days is not hard.
The tree which naturally produces scopolamine grows wild around the capital and is so famous in the countryside that mothers warn their children not to fall asleep below its yellow and white flowers. The tree is popularly known as the "borrachero," or "get-you-drunk," and the pollen alone is said to conjure up strange dreams.

There are so many scopolamine cases that they usually don't make the news unless particularly bizarre. One such incident involved three young Bogota women who preyed on men by smearing the drug on their breasts and luring their victims to take a lick. Losing all willpower, the men readily gave up their bank access codes. The breast-temptress thieves then held them hostage for days while draining their accounts.

¿Qué es el toloache?

Se trata de una **planta de origen prehispánico**, a la cual los mexicas llamaban ***tolohuaxíhuitl o toloatzin.*** Pertenece al género *datura*, es originaria del Continente Americano y en algunas regiones también se le conoce como 'hierba del diablo' o 'cardo cuco'. Hasta el momento se conocen 12 especies y todas ellas crecen en México.

Uno de los principales activos del toloache son los **alcaloides tropánicos**, una sustancia que si se consume en dosis altas (se calcula que más de 2 gramos) provoca **desorientación**, taquicardia, falta de concentración, **pensamiento incoherente**, aumento de la presión sanguínea, angustia, **psicosis**, vómito, dificultad para respirar y **demencia**. En algunos casos puede causar **alucinaciones** visuales y auditivas e incluso la **muerte**.

Estos efectos negativos puede durar desde unas horas hasta varios días, dependiendo la dosis que se administre. Entre más larga sea la duración, hay mayores probabilidades de que exista un **daño neurológico permanente.**

Robert Bye, investigador del Instituto de Biología de la UNAM, : «Técnicamente, es un **delirógeno**, es decir, causa **delirios**; la persona está aquí, pero no puede medir su relación con un objeto u otra persona. Parece que el efecto no es reversible si se llega a ciertas dosis, en **muchos casos las consecuencias son permanentes**». De ahí que las personas confundan sus efectos y piensen que quien lo consume está muy enamorado, cuando en realidad su mente está confundida y no funciona de manera normal.

La intoxicacion por antimuscarinicos induce alteraciones de

- **percepcion (alucinaciones)**
- **voluntad**
- **capacidad de memorizar nuevos eventos (manteniendo la capacidad de recuperar memorias viejas (retrivial)**
- **estado de conciencia (pensamiento y emocion)**

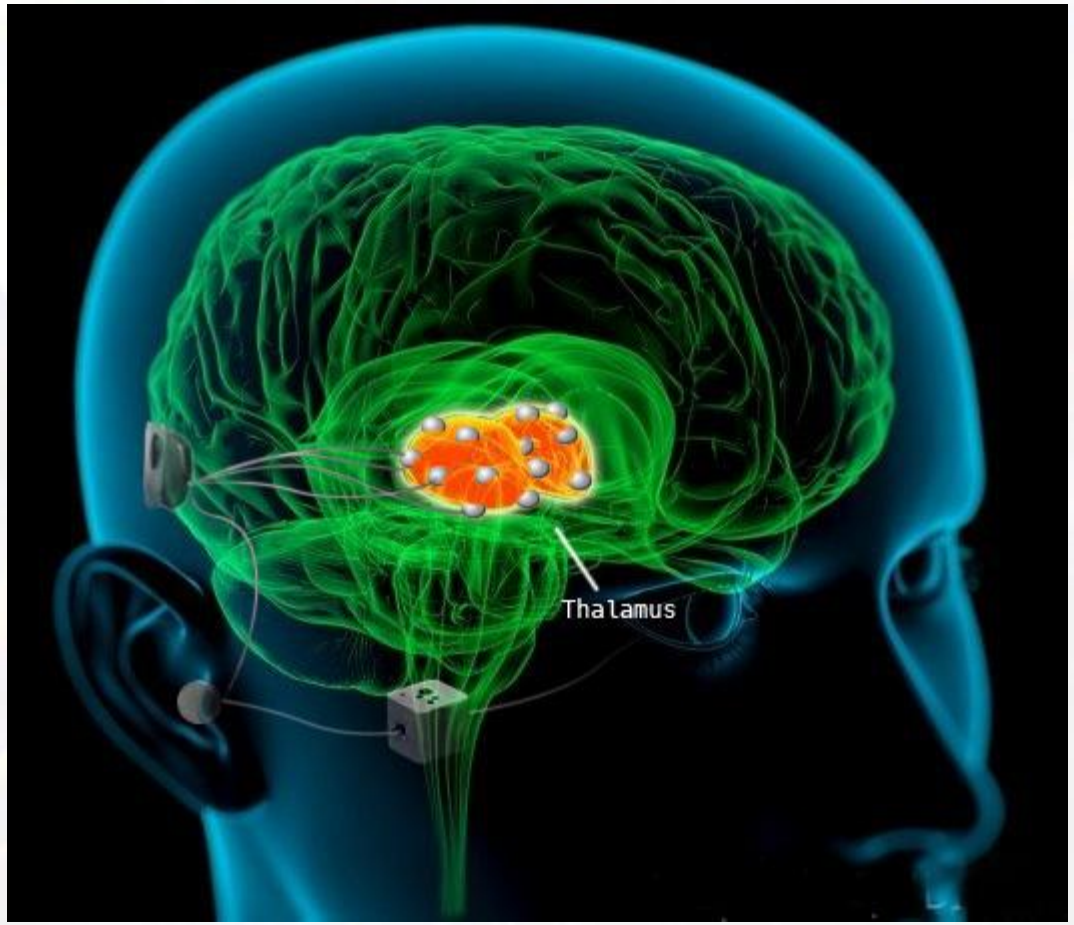
La activacion de receptors muscarinicos es necesaria para mantener un estado de conciencia apropiado

Como?
Porque?

Funciones del talamo

Thalamus Physiology (Overview)

- Primarily - a relay station that modulates and coordinates the function of various systems
- Locus for integration, modulation, and intercommunication between various systems
- Has important motor, sensory, arousal, memory, behavioral, limbic, and cognitive functions
- The largest source of afferent fibers to thalamus is cerebral cortex and cortex is the primary destination for projection fibres from the Thalamus
- Characteristically, thalamic connections are reciprocal, that is, the target of the axonal projection of any given thalamic nucleus sends back fibers to that nucleus. Nevertheless, thalamocortical projections are often larger than their corticothalamic counterparts

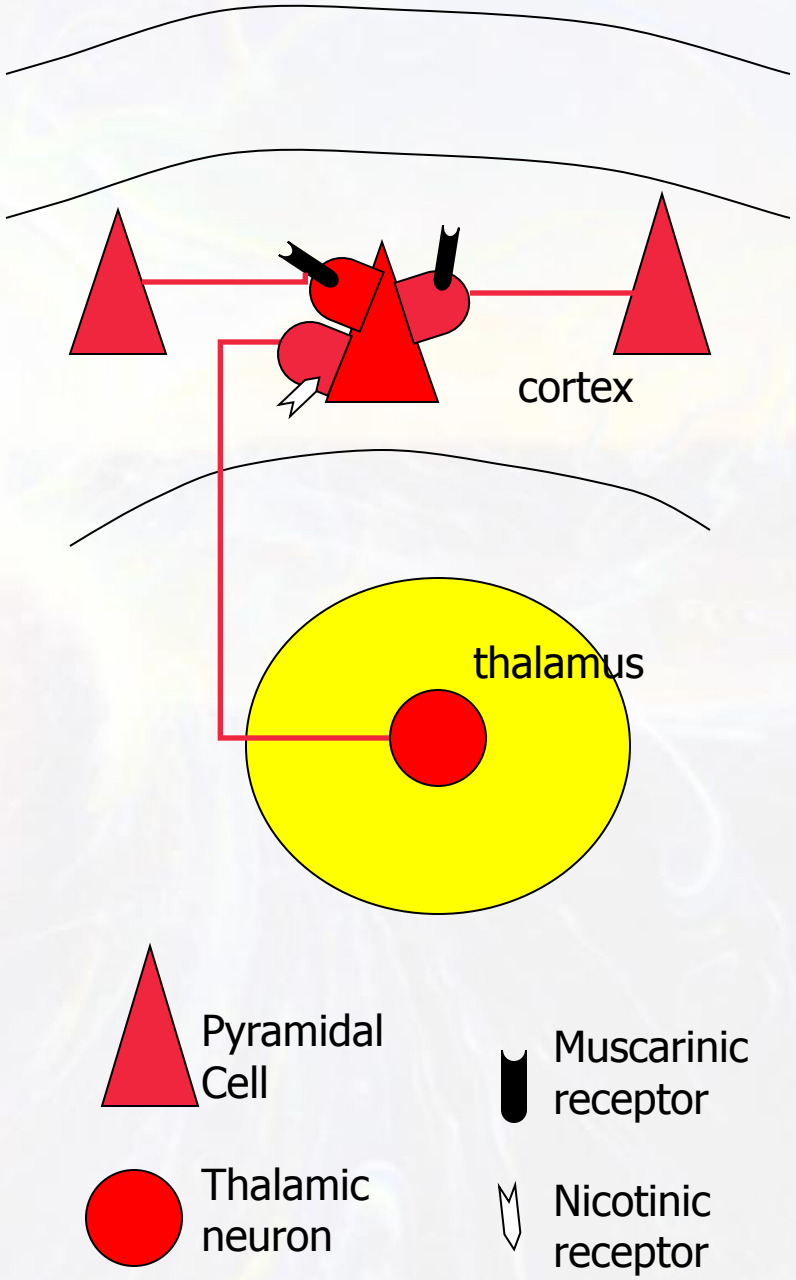


Efectos de la acetilcolina en el funcionamiento

1) del loop intracortical

2) del loop cortico-talamo-cortical

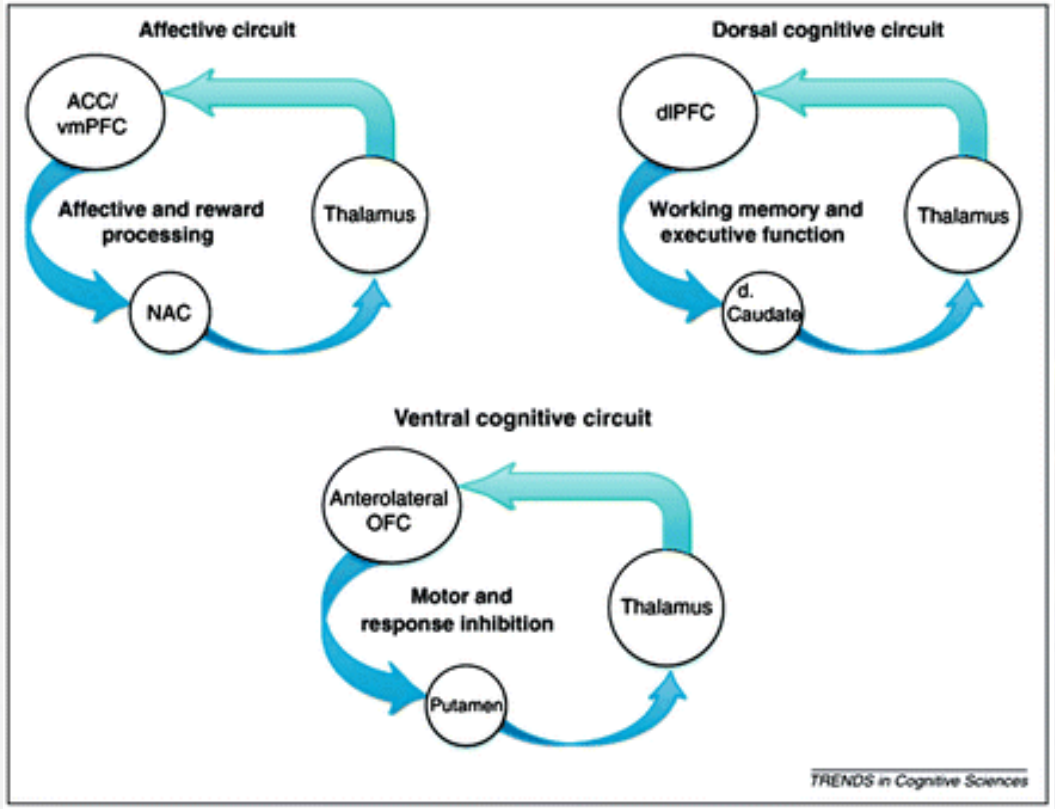
Input source	Effect	Dynamics	Receptor type
Intracortical	Suppression	Slow	Muscarinic
Afferent	Facilitation	Fast	Nicotinic

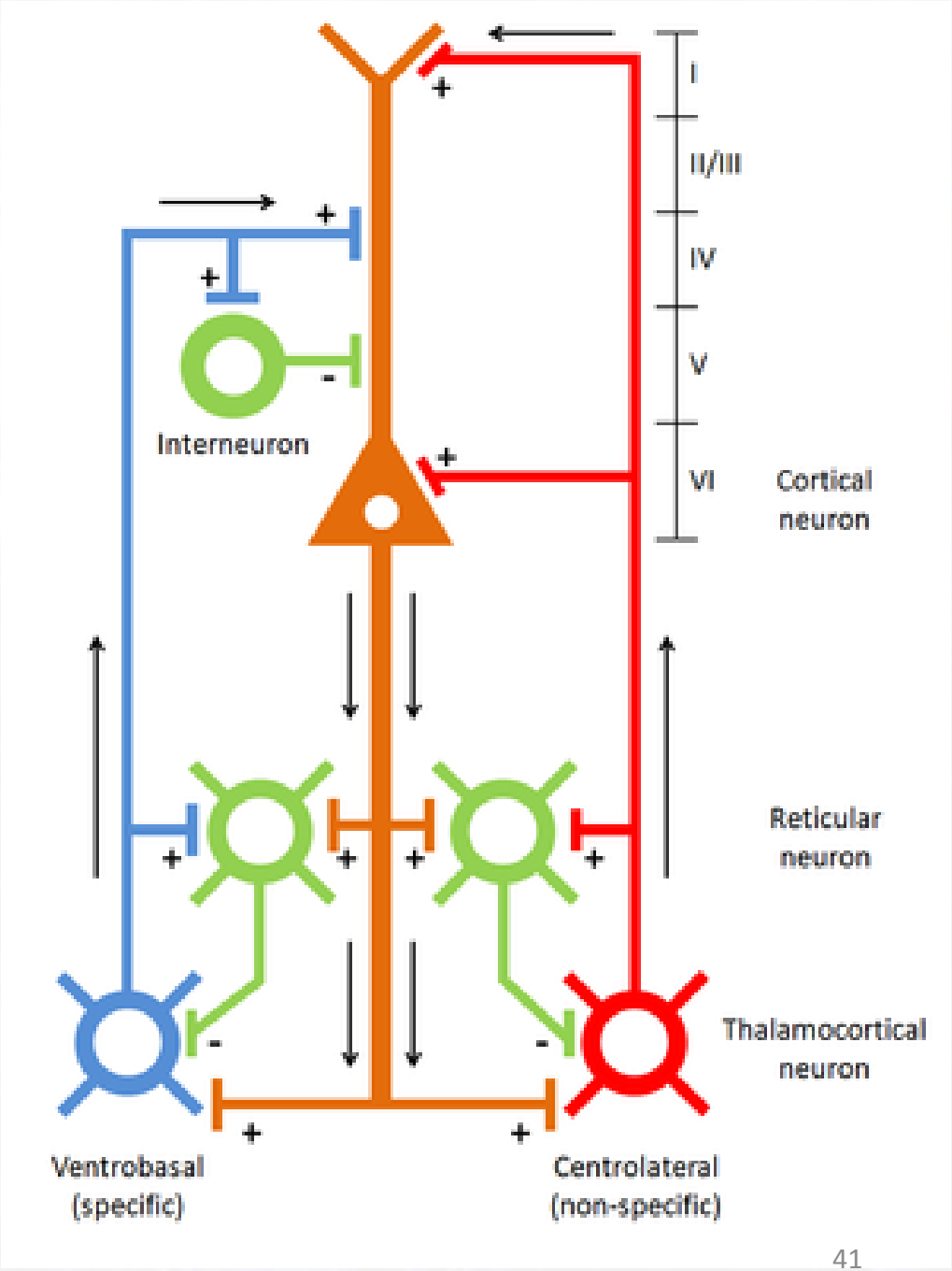


Modified from Kimura F (2000)
Cholinergic modulation of cortical function: a hypothetical role in shifting the dynamics in cortical network. Neurosci Res 38: 19-26

El talamo es un nucleo del cerebro FUNDAMENTAL para todas las funciones de la conciencia

El circuito talamo-cortico-talamico está en el centro de la función de la conciencia





POSSIBLE HALLUCINOGENIC MECHANISM

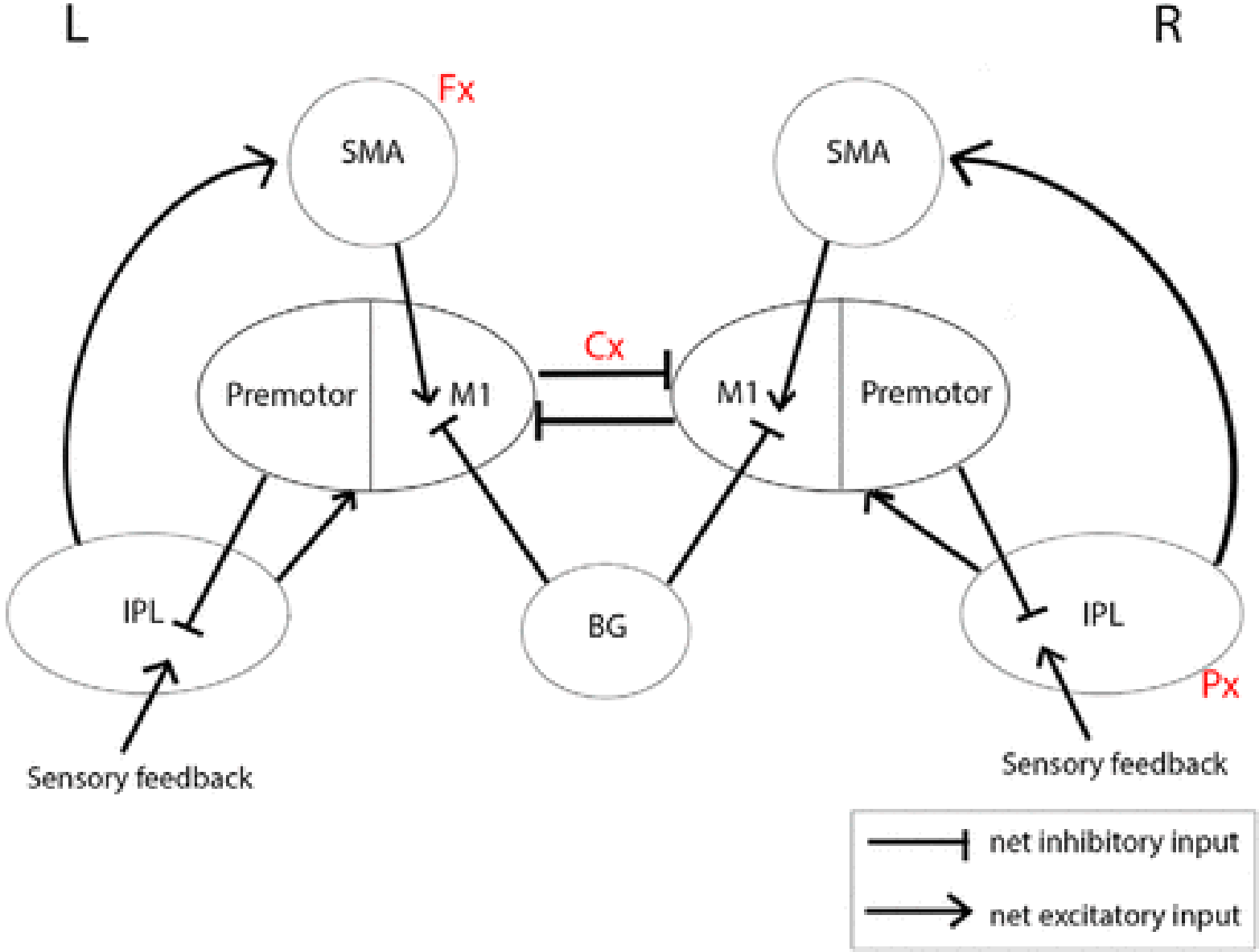
In a normal wake state, the bulk of the cortico-cortical glutamatergic transmission is greatly suppressed by the activation of muscarinic receptors.

In this situation, sensory input -possibly enhanced by presynaptic nicotinic receptors- produces the creation of neuronal ensembles in the sensory cortex, and, in turn, a riverberation of thalamo-cortico-thalamic activity associated with physiological perception.

The presence of muscarinic antagonists prevents the physiological depression of glutamate release, boosting cortico-cortical synapses. The increase in cortical excitability unconstrained by sensory activity may activate the thalamo-cortical-thalamic loop in a similar way to perception, creating an hallucination.

Why do muscarinic antagonist decrease volition?

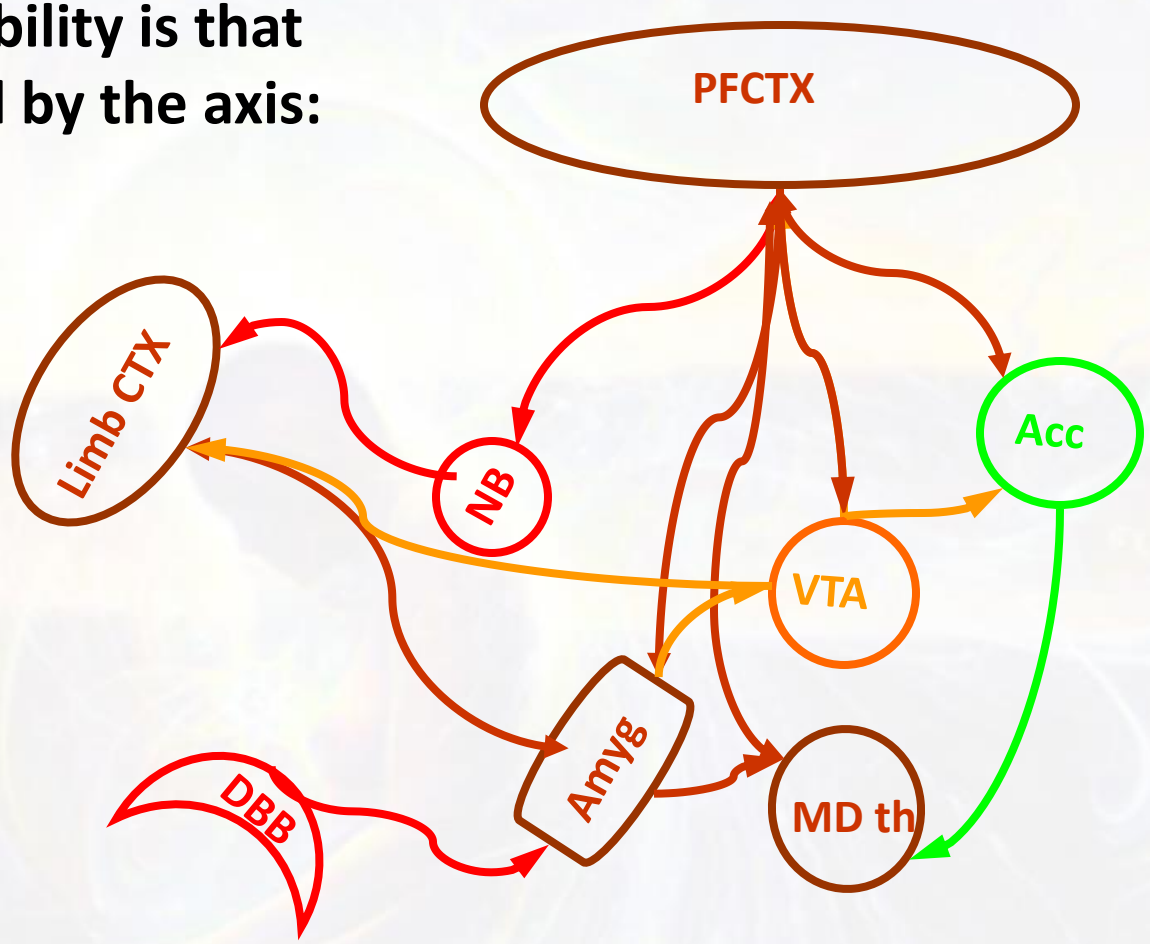
Volition may be triggered by a parietal cortical function



Volition and Action in the Human Brain: Processes, Pathologies, and Reasons
Itzhak Fried, Patrick Haggard, Biyu J. He and Aaron Schurger
Journal of Neuroscience 8 November 2017

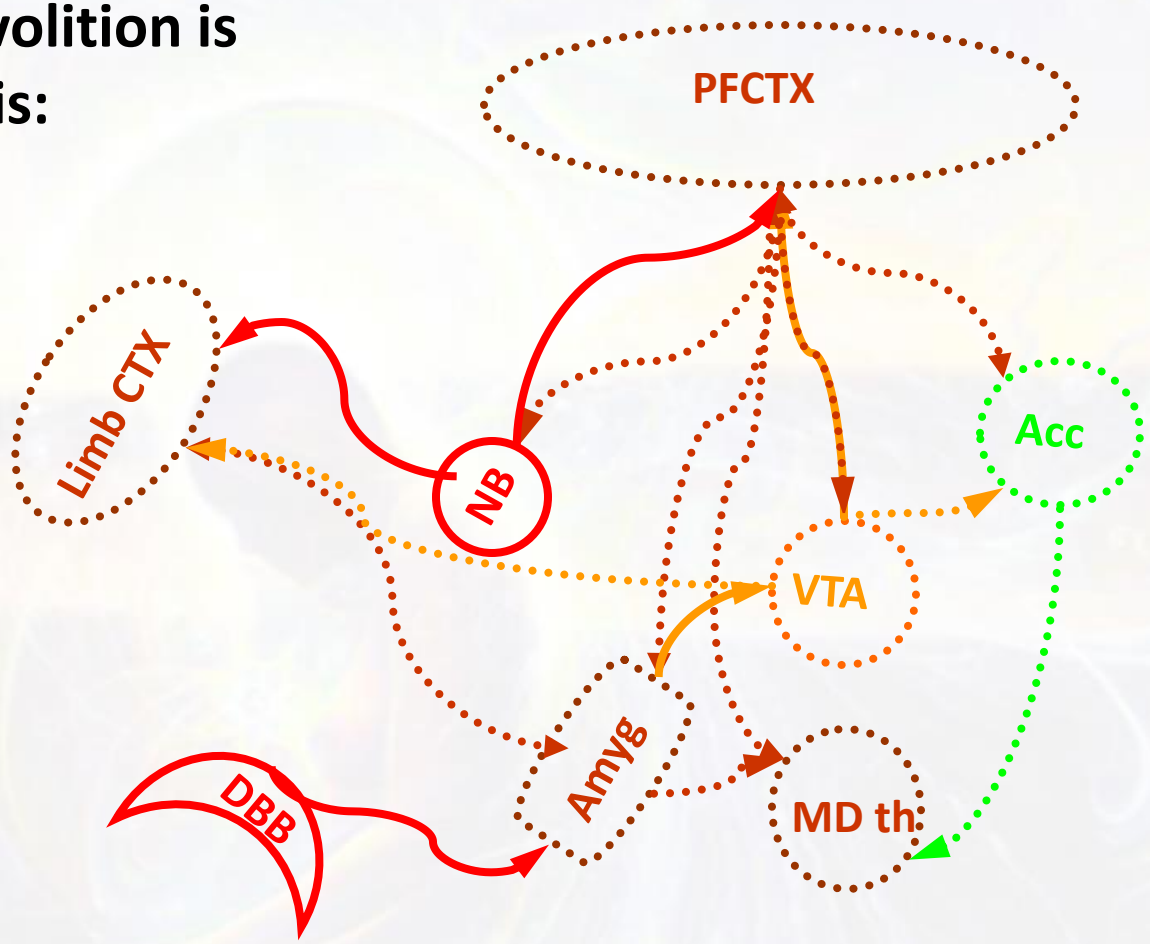
An alternative possibility is that volition is controlled by the axis:

Limbic cortex
Prefrontal cortex
Amygdala



A possibility is that volition is controlled by the axis:

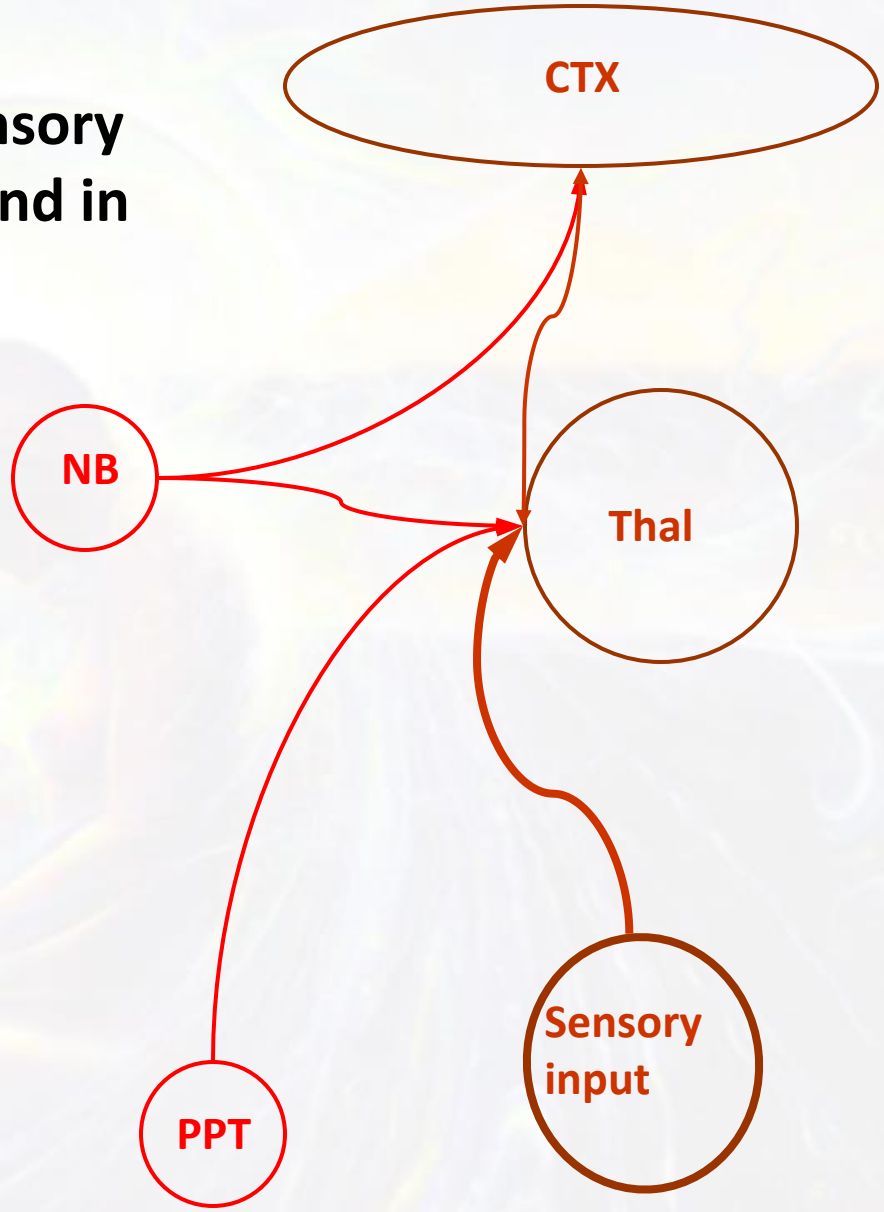
Limbic cortex
Prefrontal cortex
Amygdala



Cholinergic inhibition would decrease the excitability of amygdala, receiving chol input from the DBB and/or of the PFCTX (from NB), weakening the activity in the Acc, VTA and MedioDorsal nucleus of the thalamus, all of them involved in motivation and volition

Do nicotinic receptors have a role in consciousness?

Nicotinic receptors seem to be involved in enhancement of sensory processing, both in the cortex and in the thalamus



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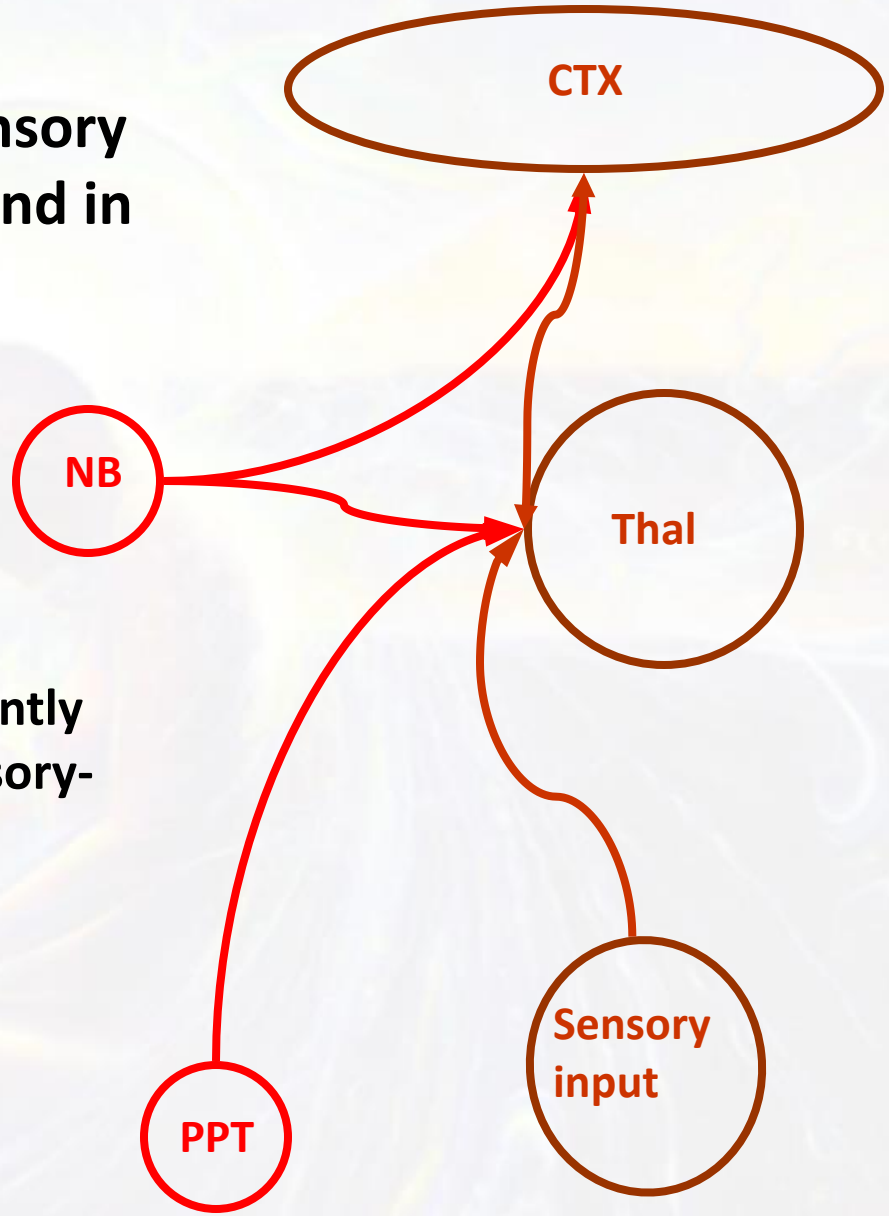
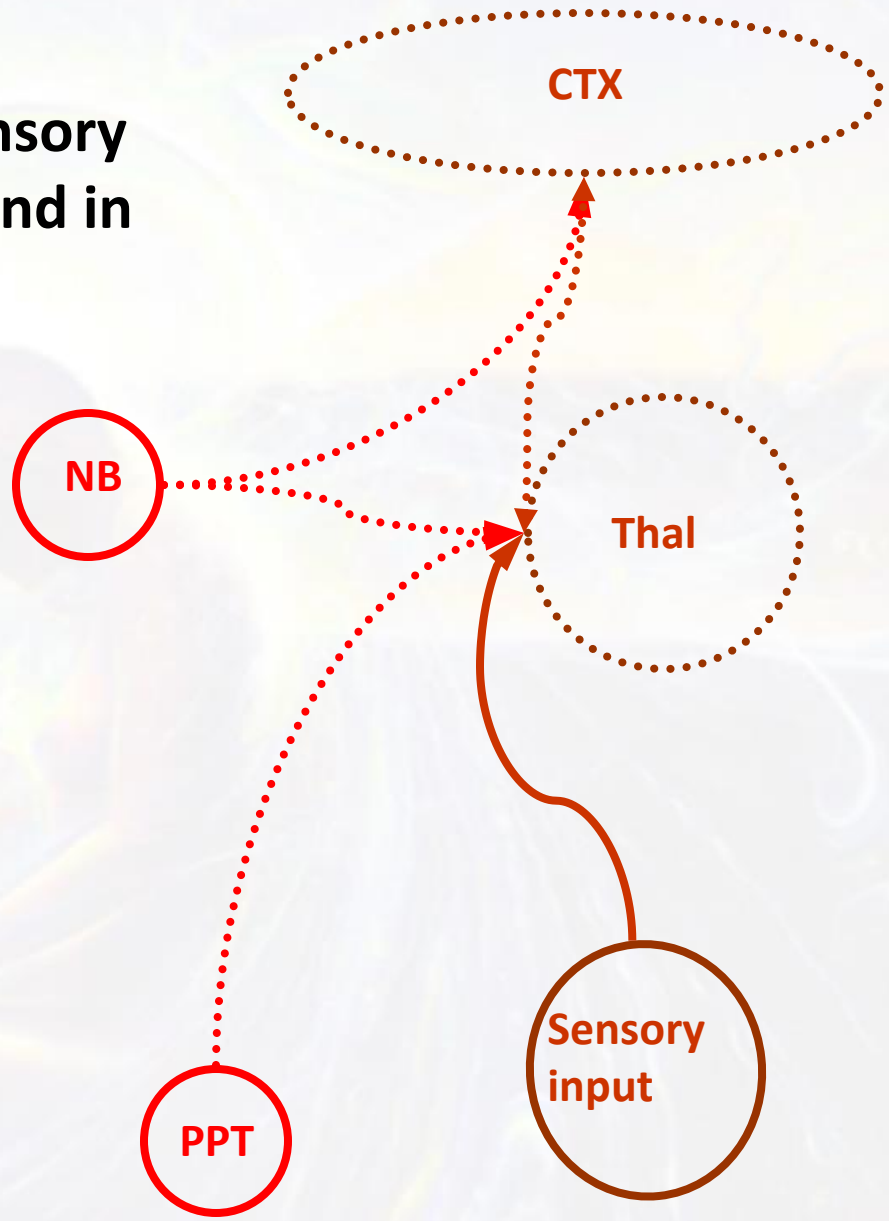


If this hypothesis is correct nicotine should increase alertness by persistently increasing the excitability of the sensory-thalamo-cortical pathway

Nicotinic receptors seem to be involved in enhancement of sensory processing, both in the cortex and in the thalamus



On the contrary, a nicotinic receptor deficit, like in autism should prevent sensory information to be properly processed.

Nicotinic but also muscarinic receptors might be also be involved in selective attention. The involvement of ACh in selective attention is still a matter of debate.

The presence of a level of sensory responsiveness during muscarinic antagonist intoxication suggests that muscarinic receptors are not indispensable for sensory-motor coordination of simple motor tasks.

Two functions for acetylcholine in consciousness:

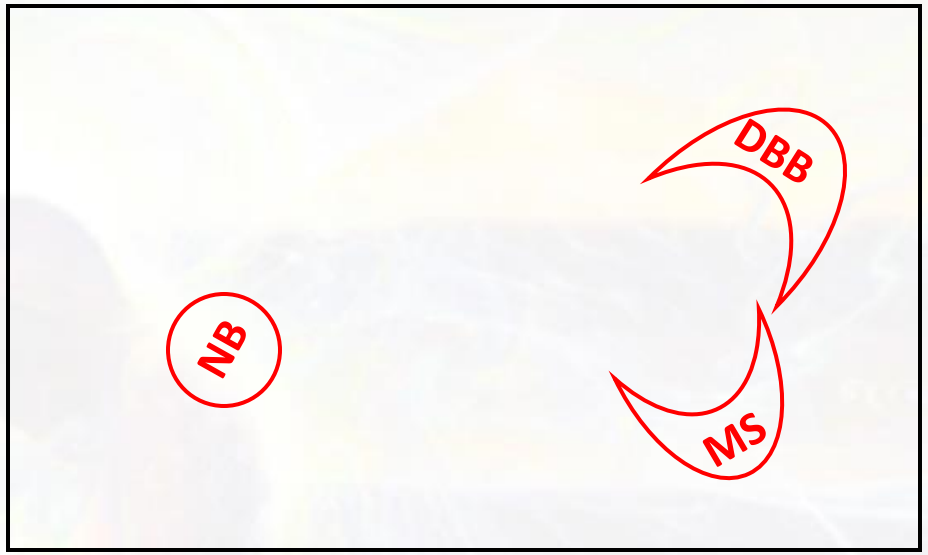
1)Switch (on-off)

2) Modulation

Schematic Anatomy of Cholinergic nuclei

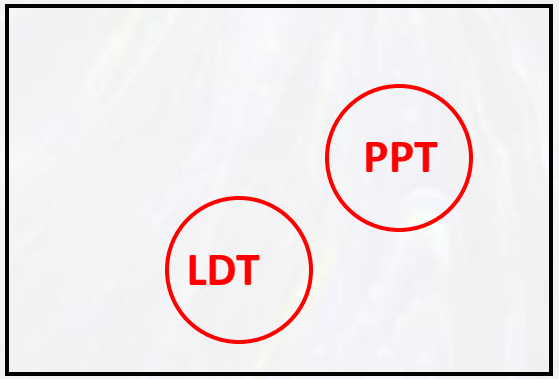
NB	Nucleus Basalis of Meynert
DBB	Diagonal band of Broca
MS	Medial Septum

Rostral cholinergic nuclei

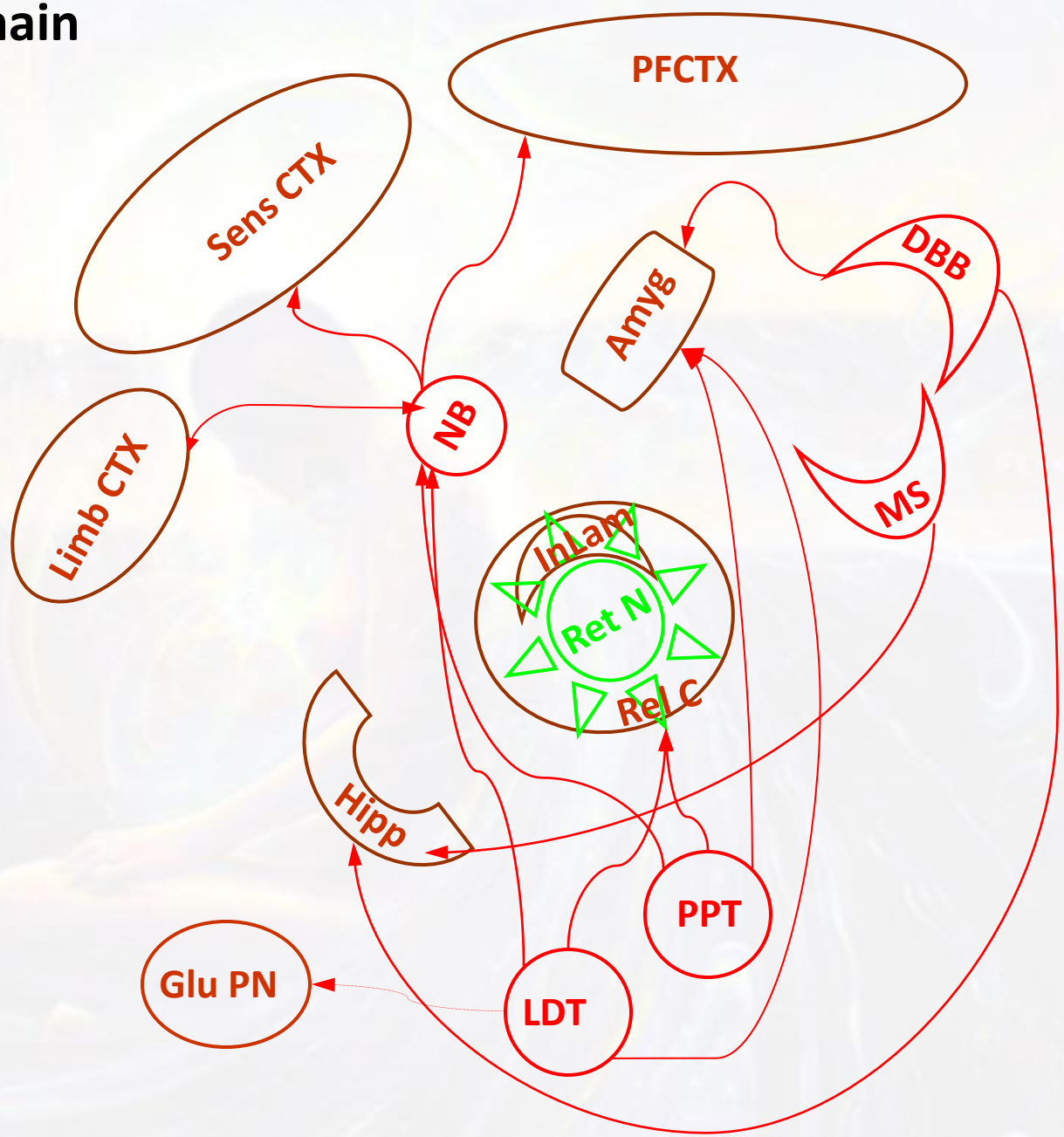


PPT	Pedunculo Pontine Tegmentum
LDT	Latero Dorsal Tegmentum

Caudal cholinergic nuclei



Cholinergic nuclei main outputs



Cellular effects of Ach:

Mediated by muscarinic receptors
(M1-5R, high density in most brain areas)

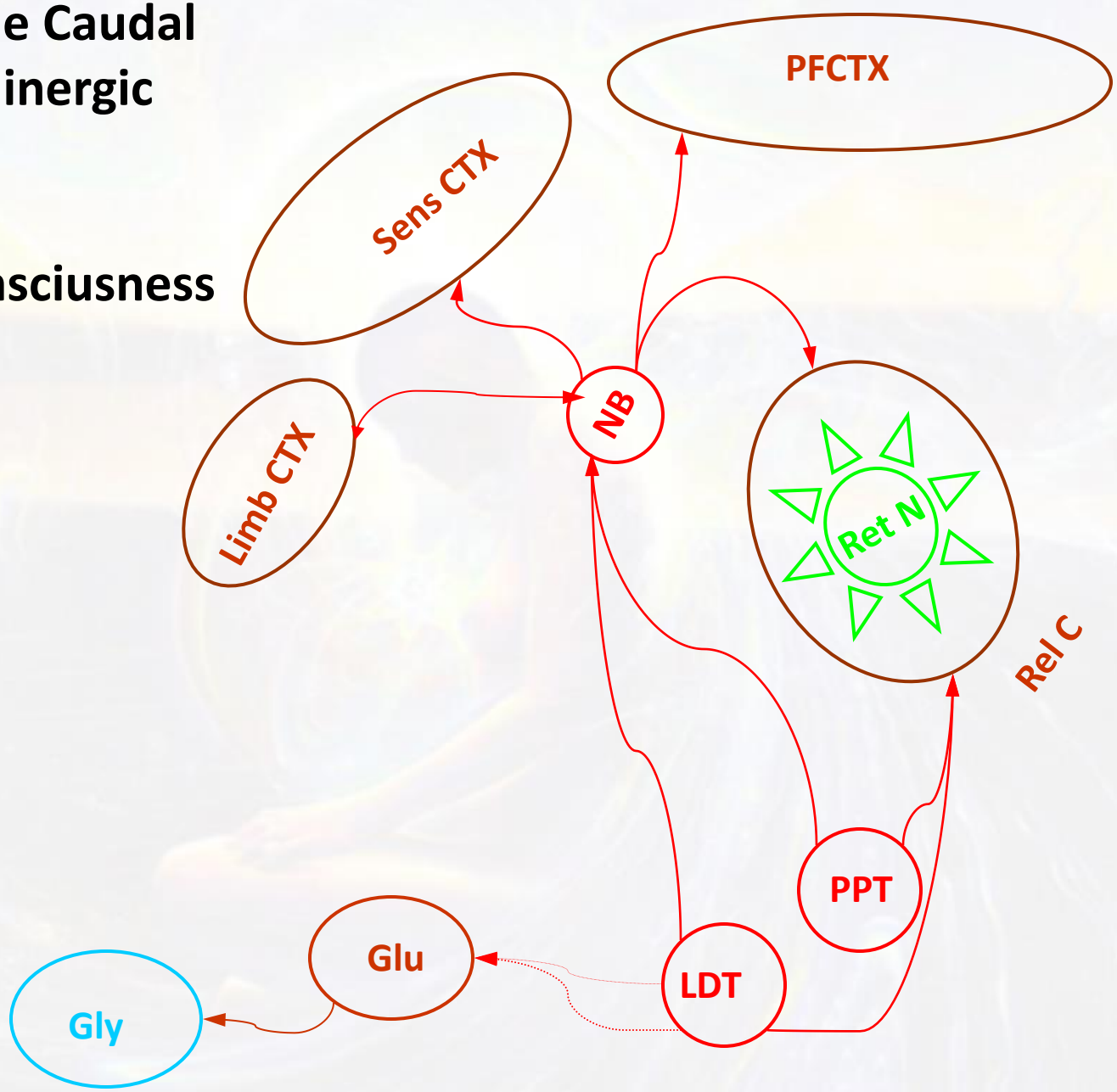
-Depression of Glutamatergic synaptic transmission (↑ inhibition)
-Depression of GABAergic synaptic transmission (↑ excitation)
-Block of AHP (block of accomodation, ↑ excitation)
-Induction of synaptic plasticity

Mediated by nicotinic receptors
($\alpha_4\beta_2$ and α_7 ,high density specifically in the sensory thalamo-cortical pathway)

-Increase in glutamate release
-Promotion of synaptic plasticity

Function of the Caudal group of Cholinergic nuclei:

Switch for consciousness



Different consciousness states are associated with -perhaps triggered by- changes in the activation state of cholinergic nuclei and their targets:

-Wake state

-Slow-wave sleep

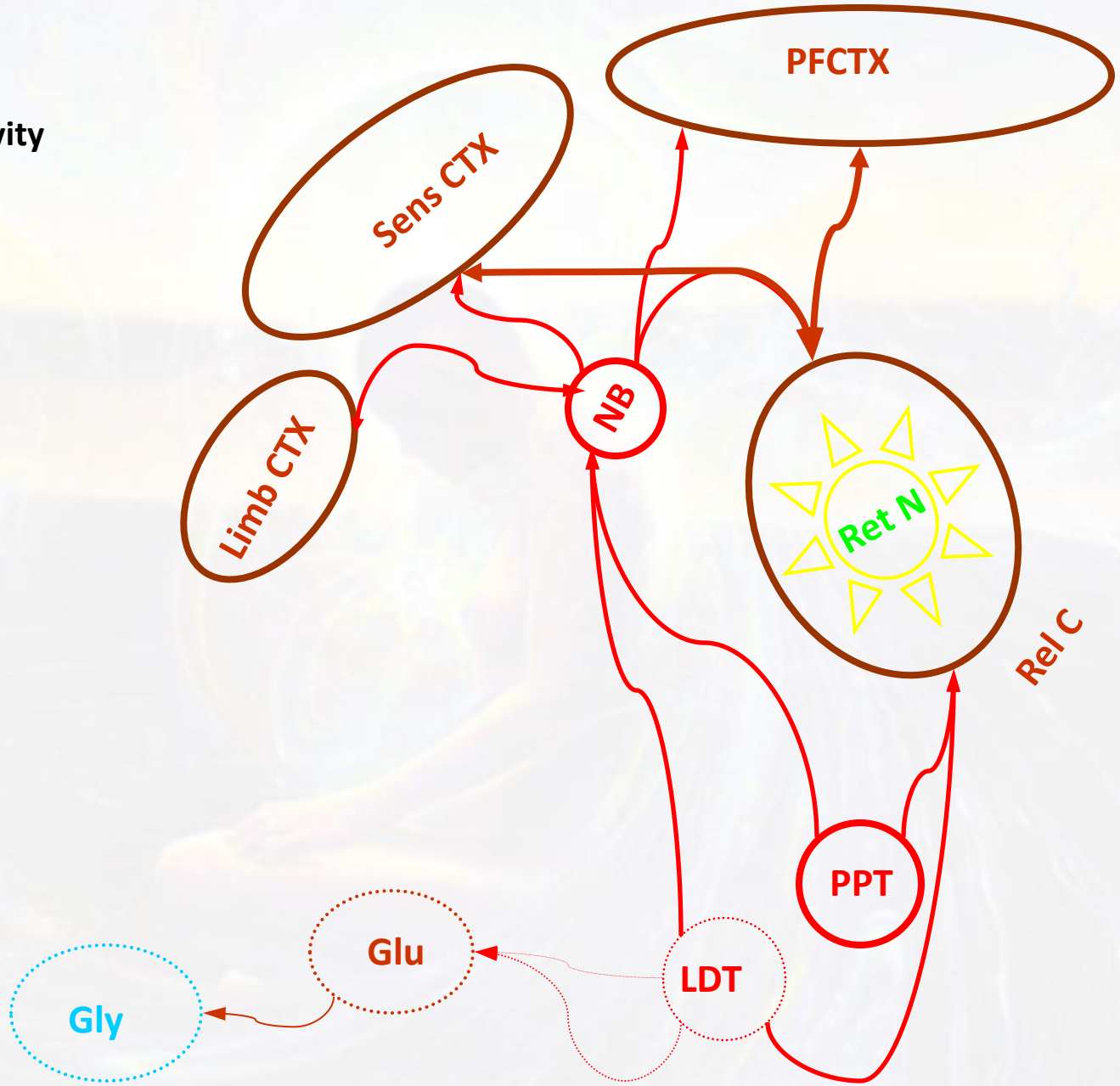
-REM sleep

-Hypnagogic hallucinations

-REM behavior disorder

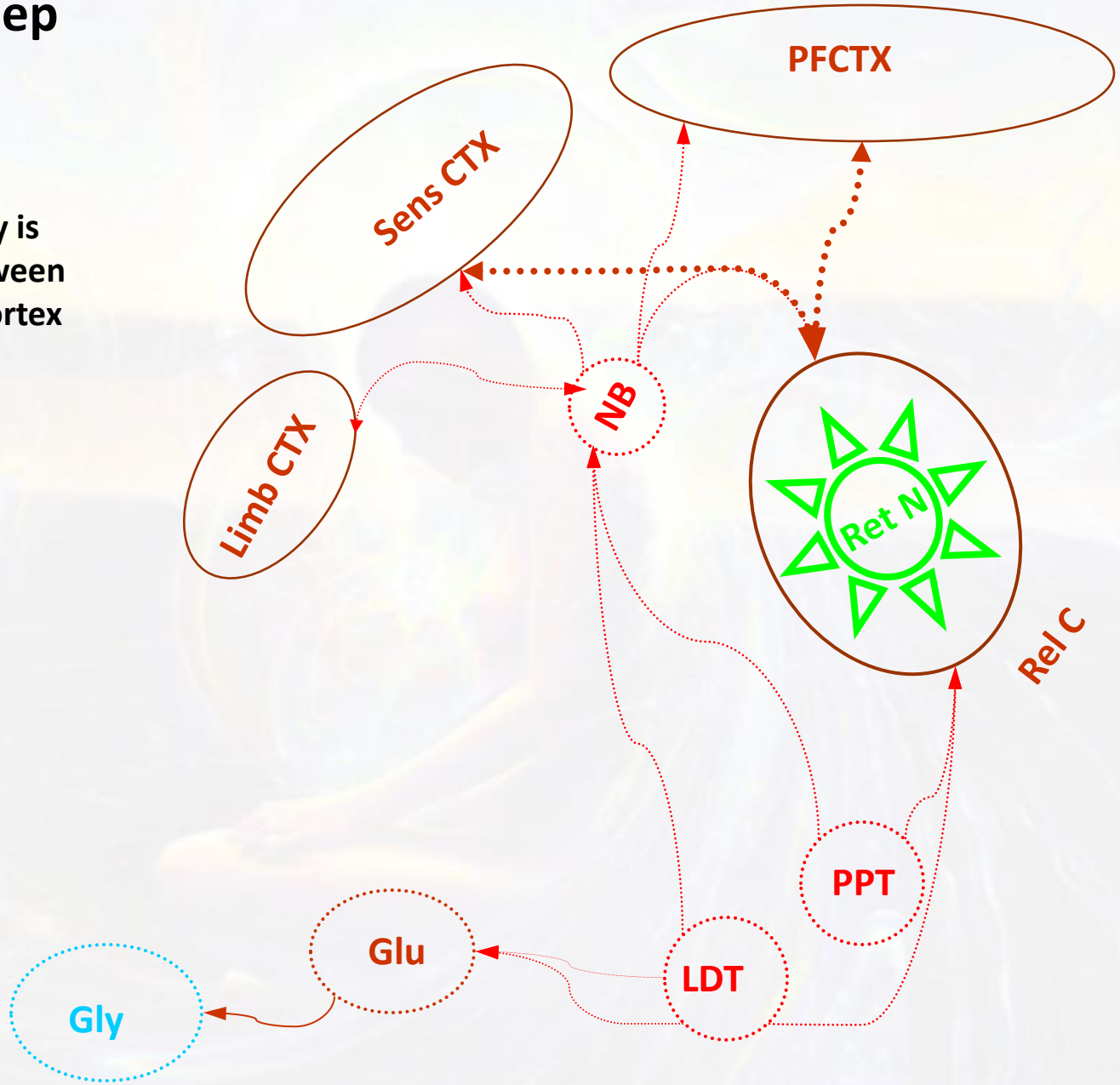
Wake state

Desynchronized activity between thalamus and cortex



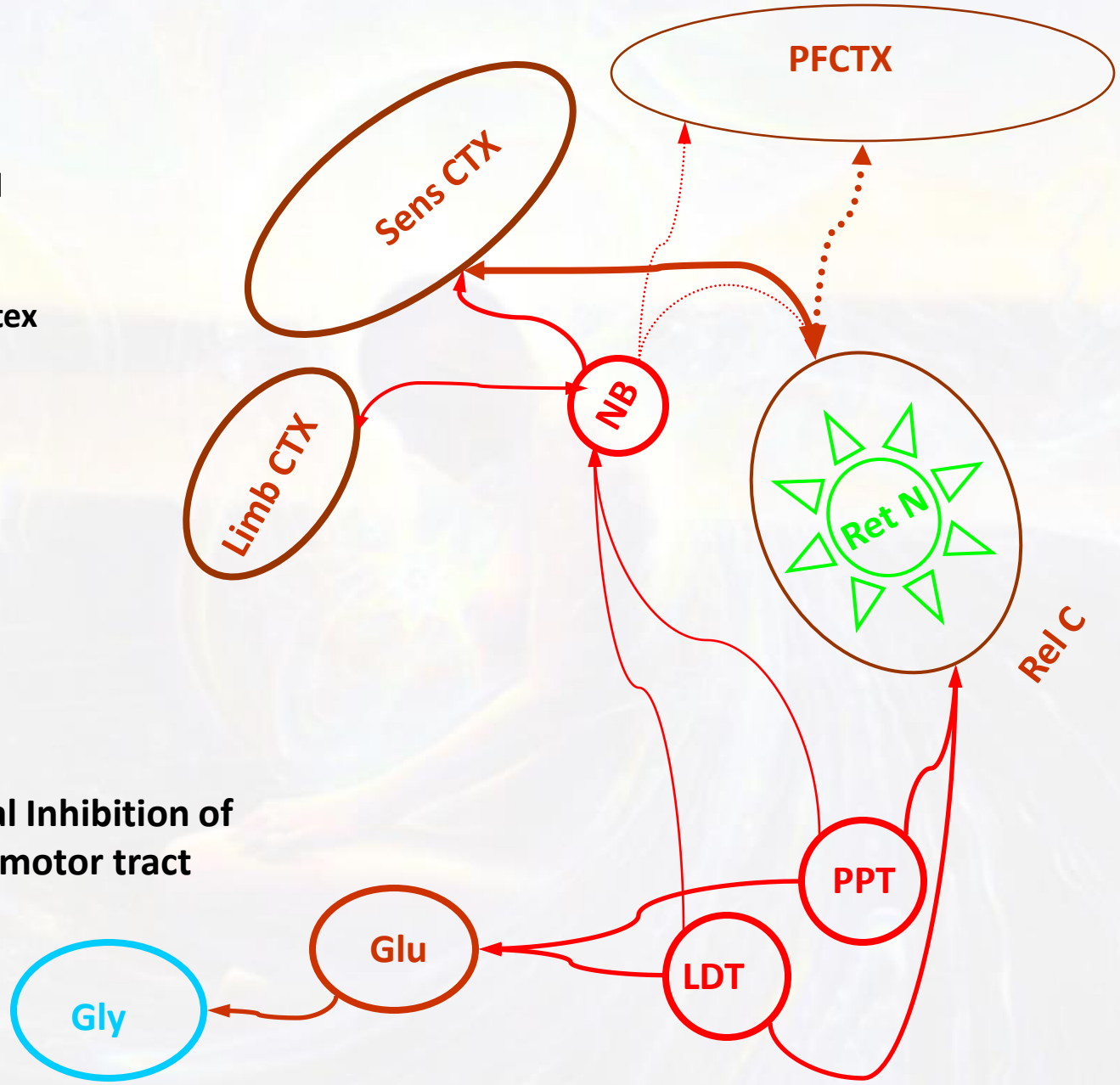
Slow wave sleep

Spindle activity is propagated between thalamus and cortex



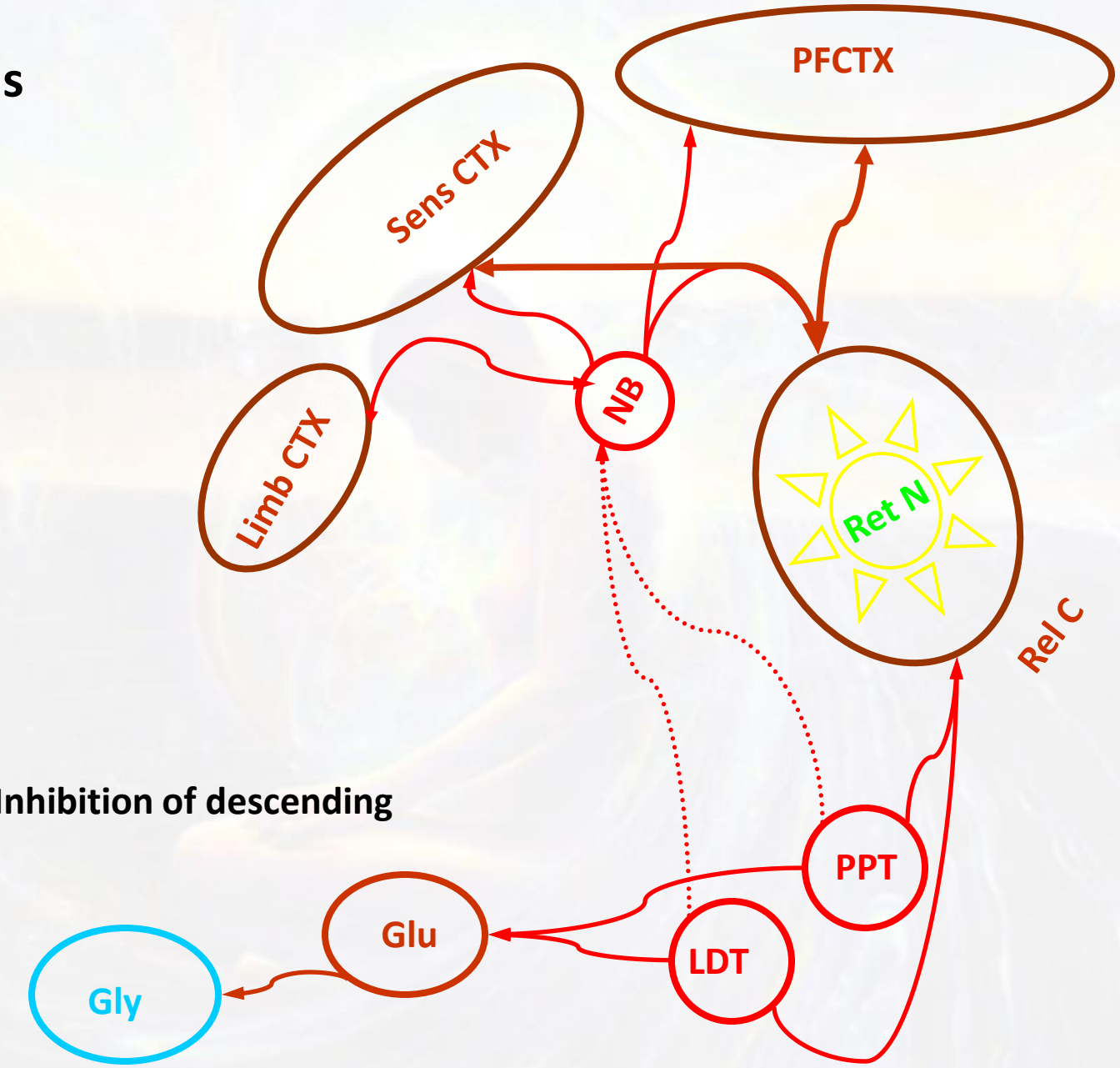
REM sleep

Desynchronized activity between thalamus and cortex



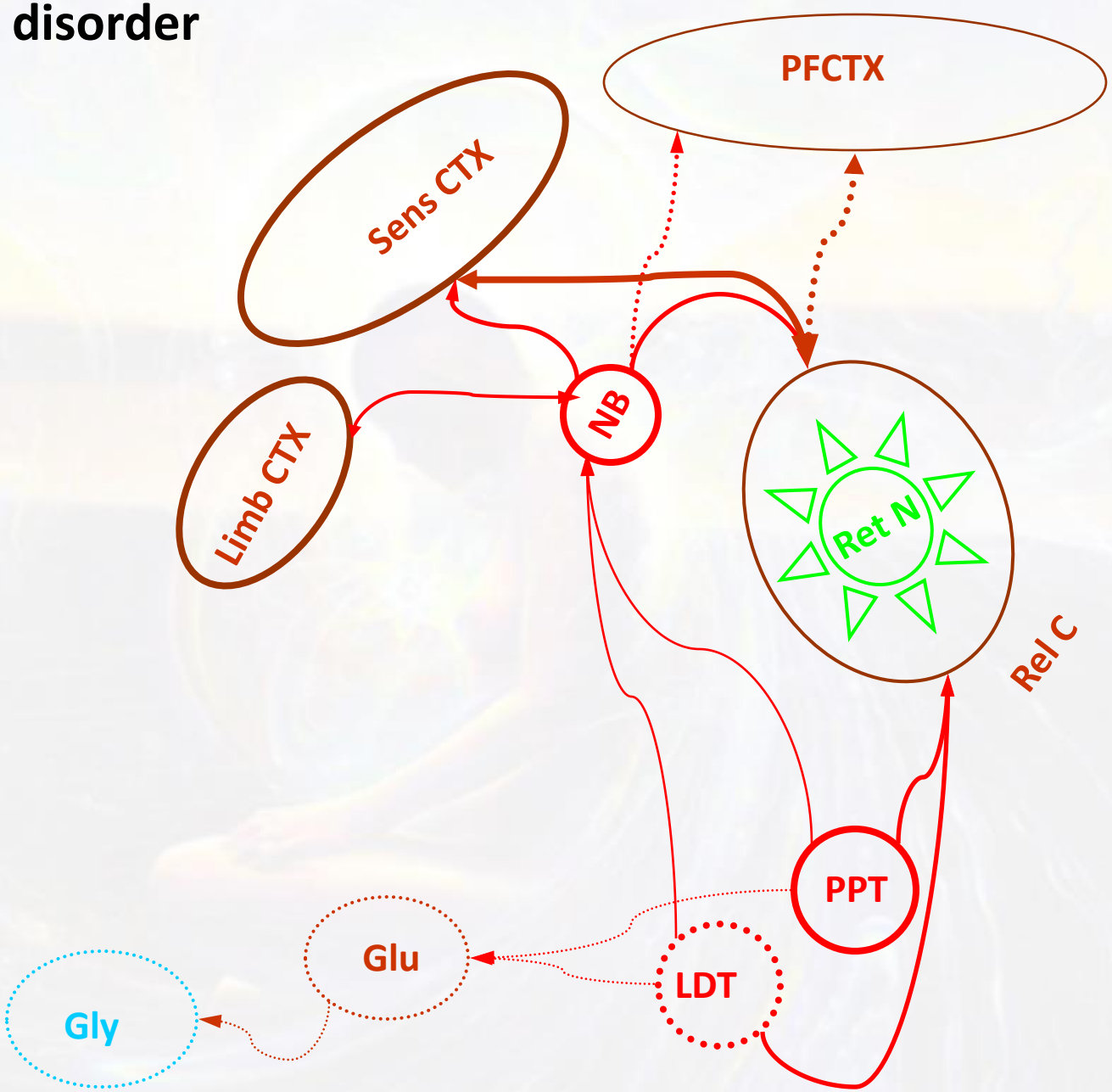
Physiological Inhibition of descending motor tract

Hypnagocic hallucinations

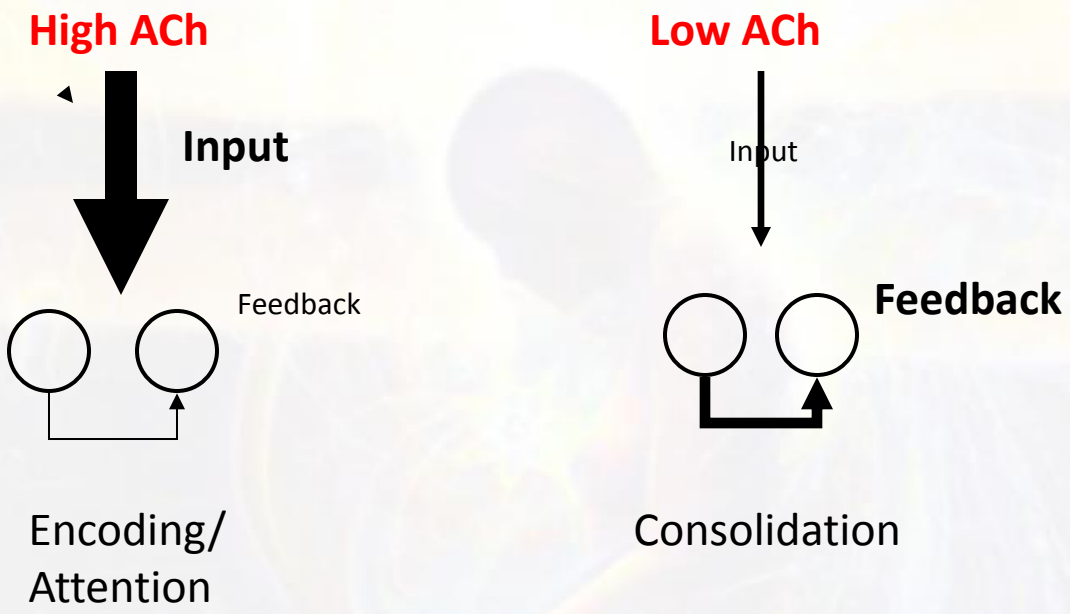


Pathological Inhibition of descending motor tract

REM behavior disorder

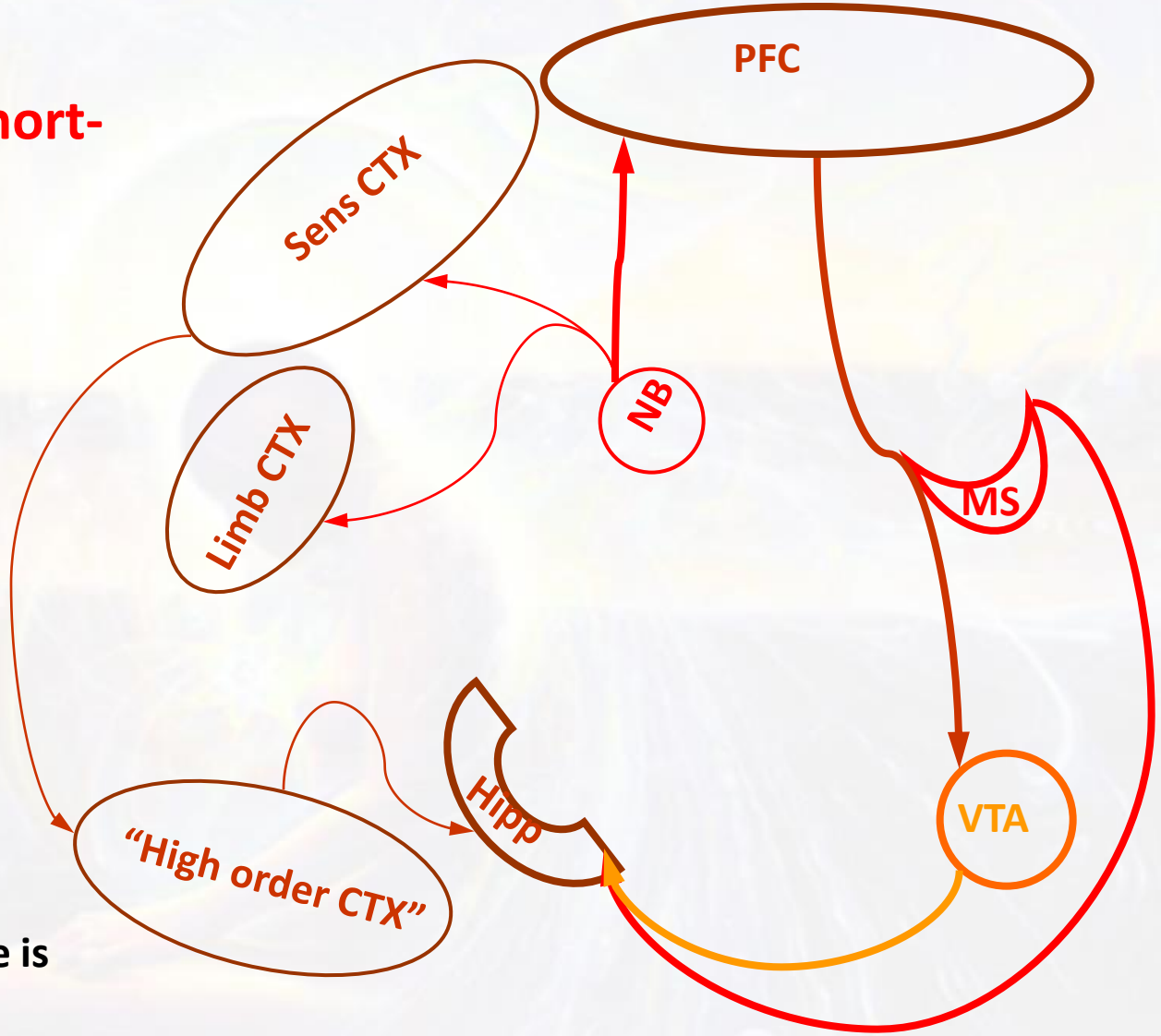


POSSIBLE ROLE OF ACh IN THE CORTEX



modified from: Hasselmo and McGaughy, (2004) Prog Br Res, 145, 207-231

Why do muscarinic antagonists induce short-term memory loss ?



Role of Ach in short term memory:

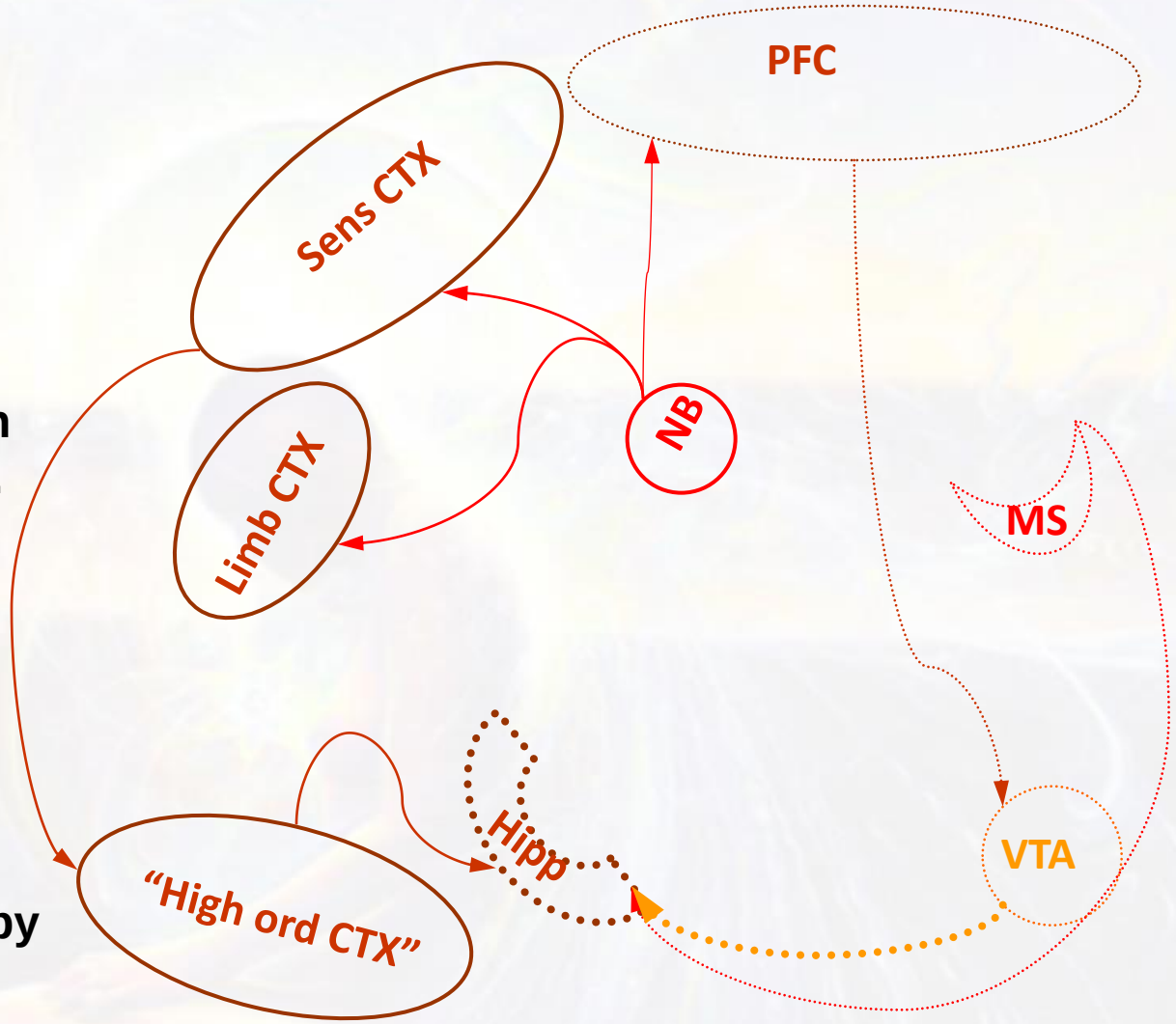
Short-term memory storage is carried out by the hippocampal and parahippocampal complex

Muscarinic antagonists induce impairment of short-term memory storage (but not of retrieval).

Several mechanisms can be impaired by musc. antagonists:

1) **Cholinergic modulation from medial septum**

2) **Activation of dopaminergic fibers by hypofrontal function**



It is unlikely that impairment of muscarinic function in non-frontal cortices impairs short-term memory, since subjects intoxicated with antimuscarinic have unimpaired retrivial and unimpaired sensory discrimination

Conclusiones:

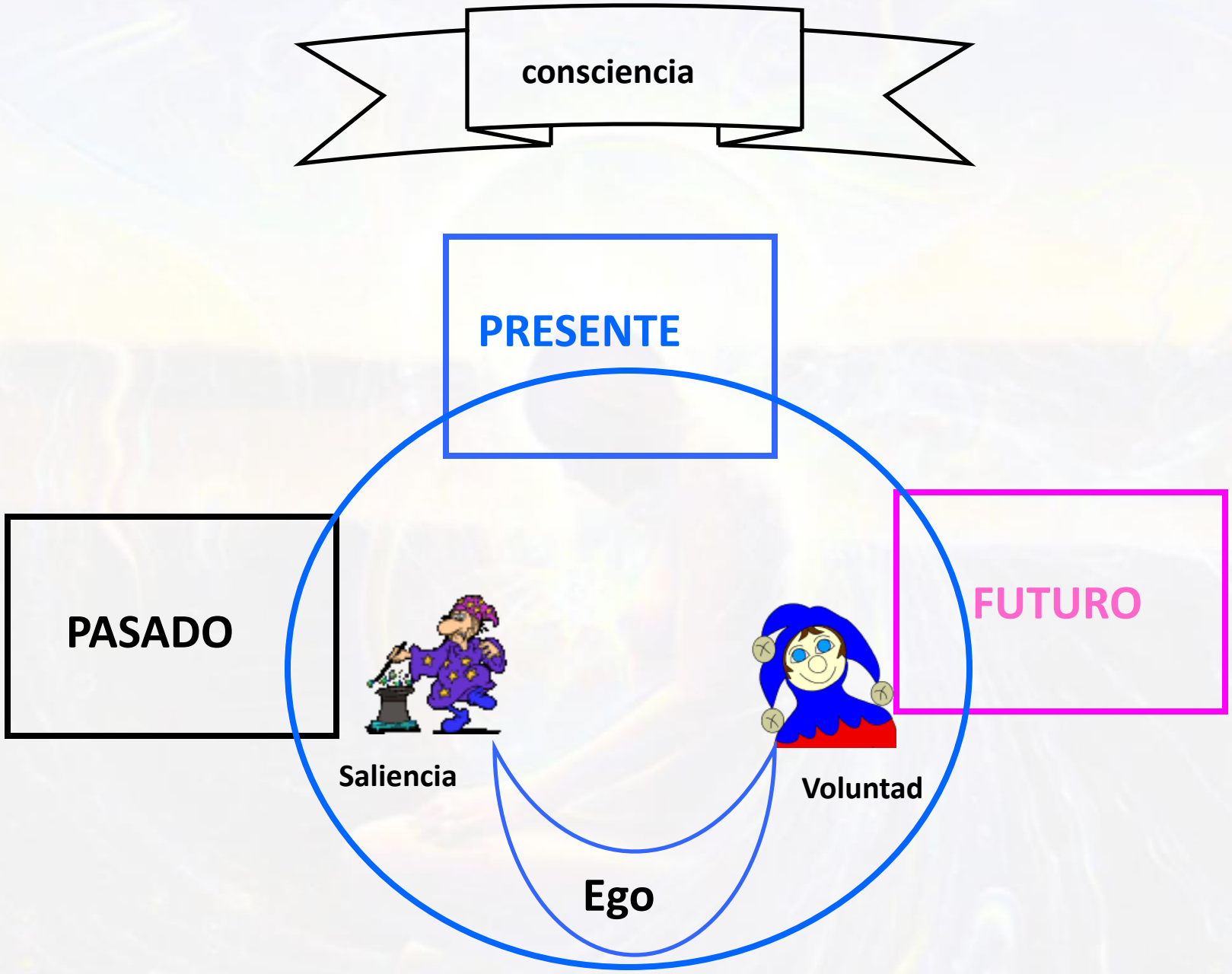
0) La conciencia es una función del sistema nervioso central, y como tal puede ser estudiada, en sus varios niveles y expresiones, en animales y en humanos

1) Diferentes propiedades de la consciencia están asociadas con el funcionamiento de varias areas cerebrales:

- tallo cerebral
- Talamo
- Corteza, sobre todo posteriores

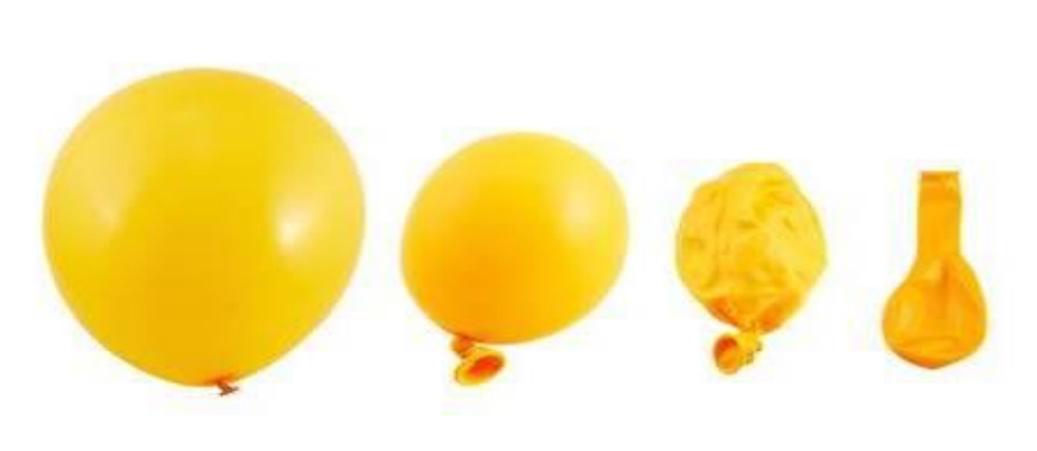
2) El circuito talamo-cortico-talamico es responsable de la consciencia, como percepción inmediata de la realidad

3) El funcionamiento correcto de los circuitos de la conciencia puede ser alterado por lesiones, drogas, fármacos o toxinas, llevando a estados alterados de conciencia, por falta de algunos de sus componentes esenciales. La ocurrencia de estos estados de conciencia alterados brinda información útil para entender los sustratos organicos de la conciencia.


consciencia
PRESENTE
PASADO
FUTURO
Saliencia
Voluntad
Ego

GRACIAS

Para entender que es se puede investigar que pasa cuando no lo hay



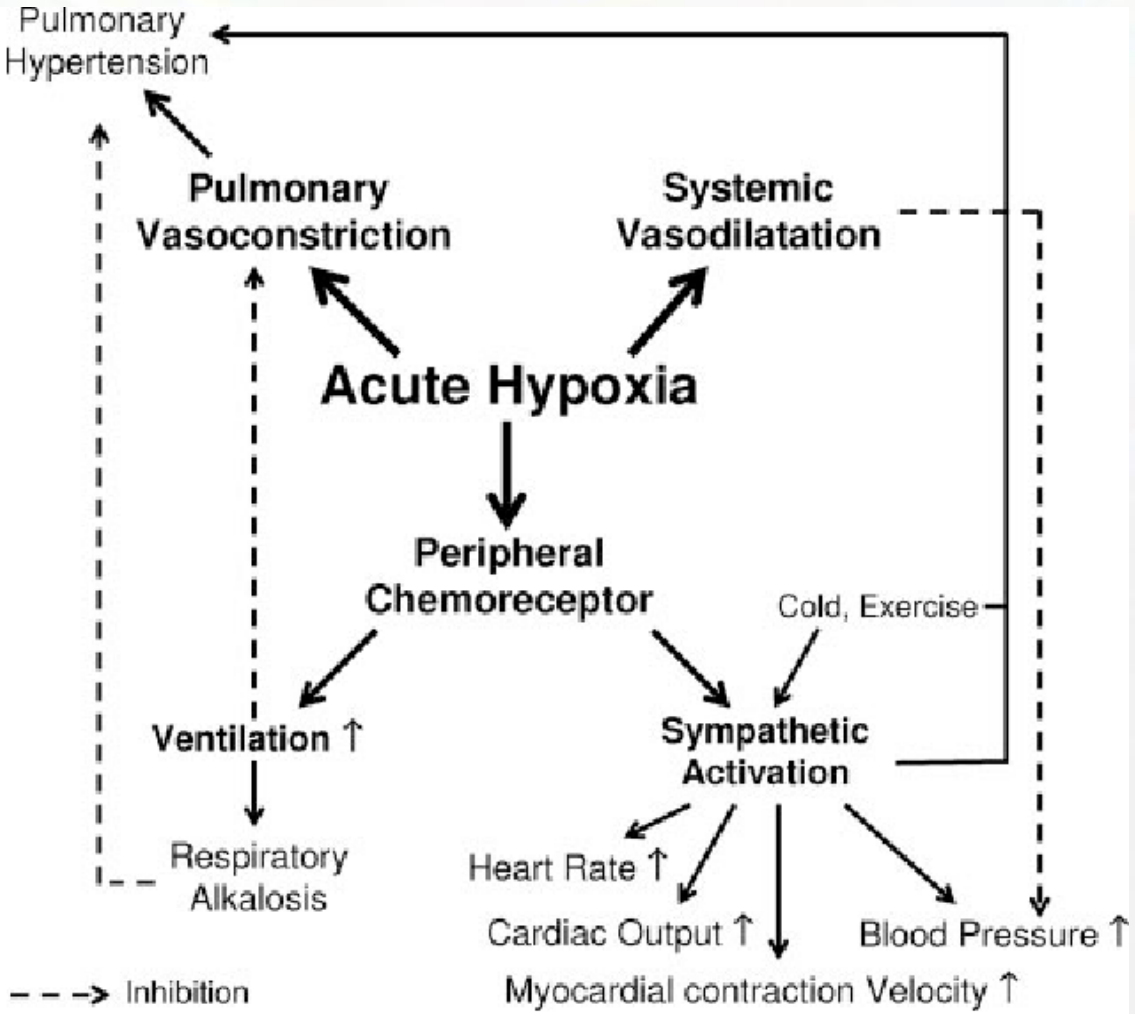
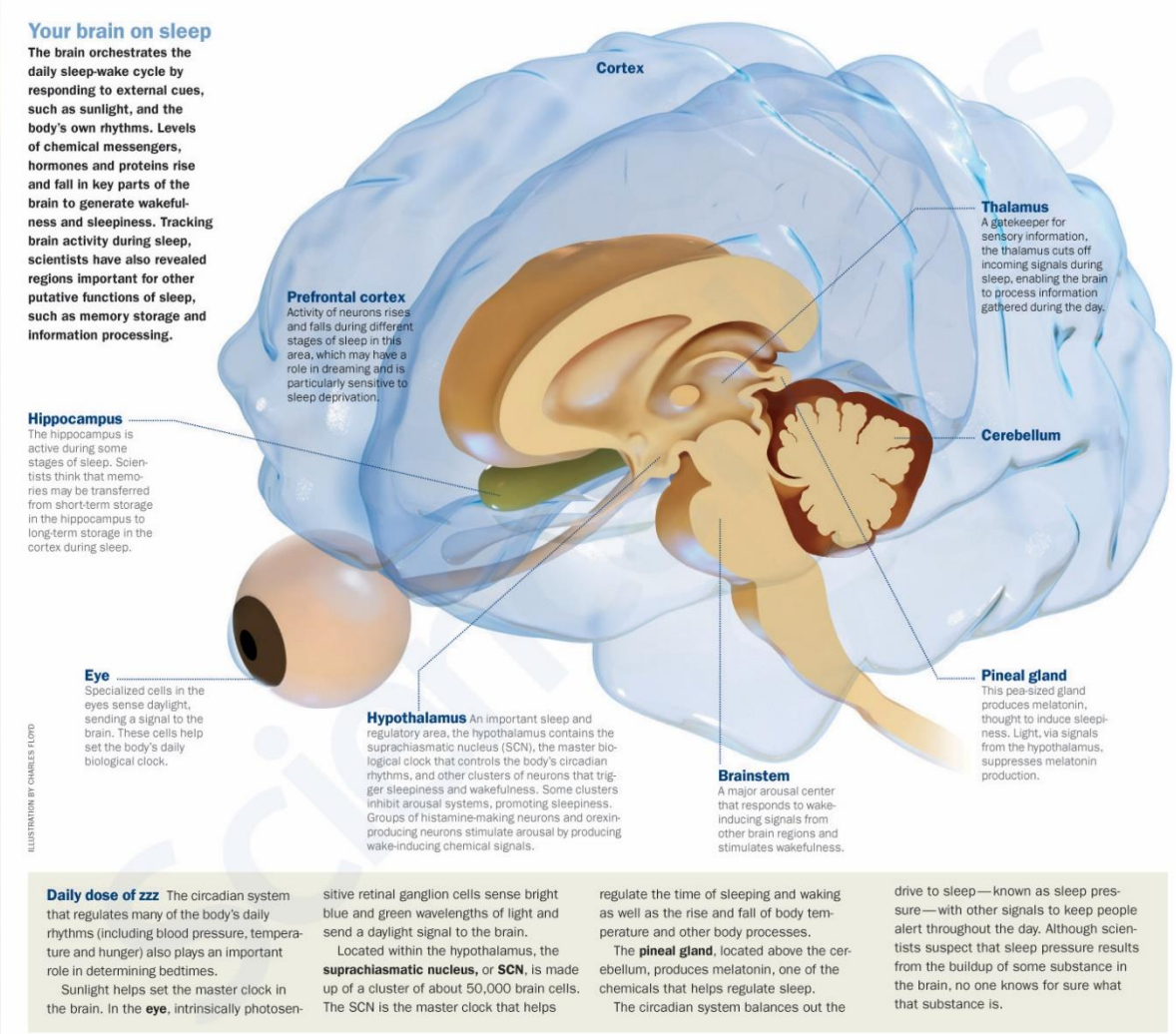
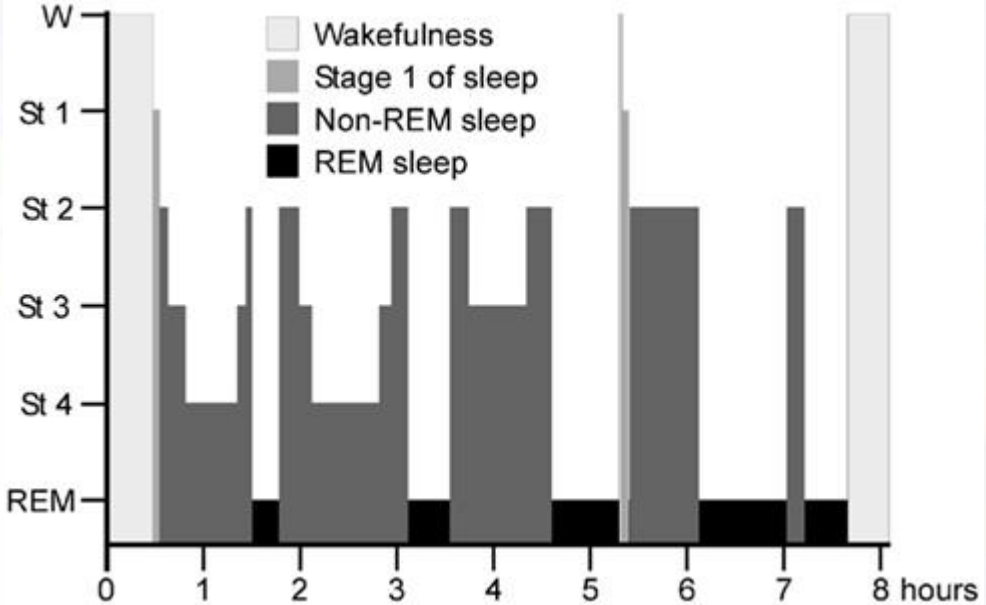


Figure 1. Effects of hypoxia on systemic and pulmonary

Anatomia fisiológica del sueño

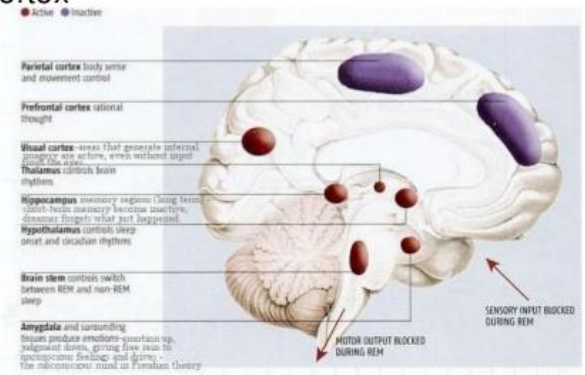




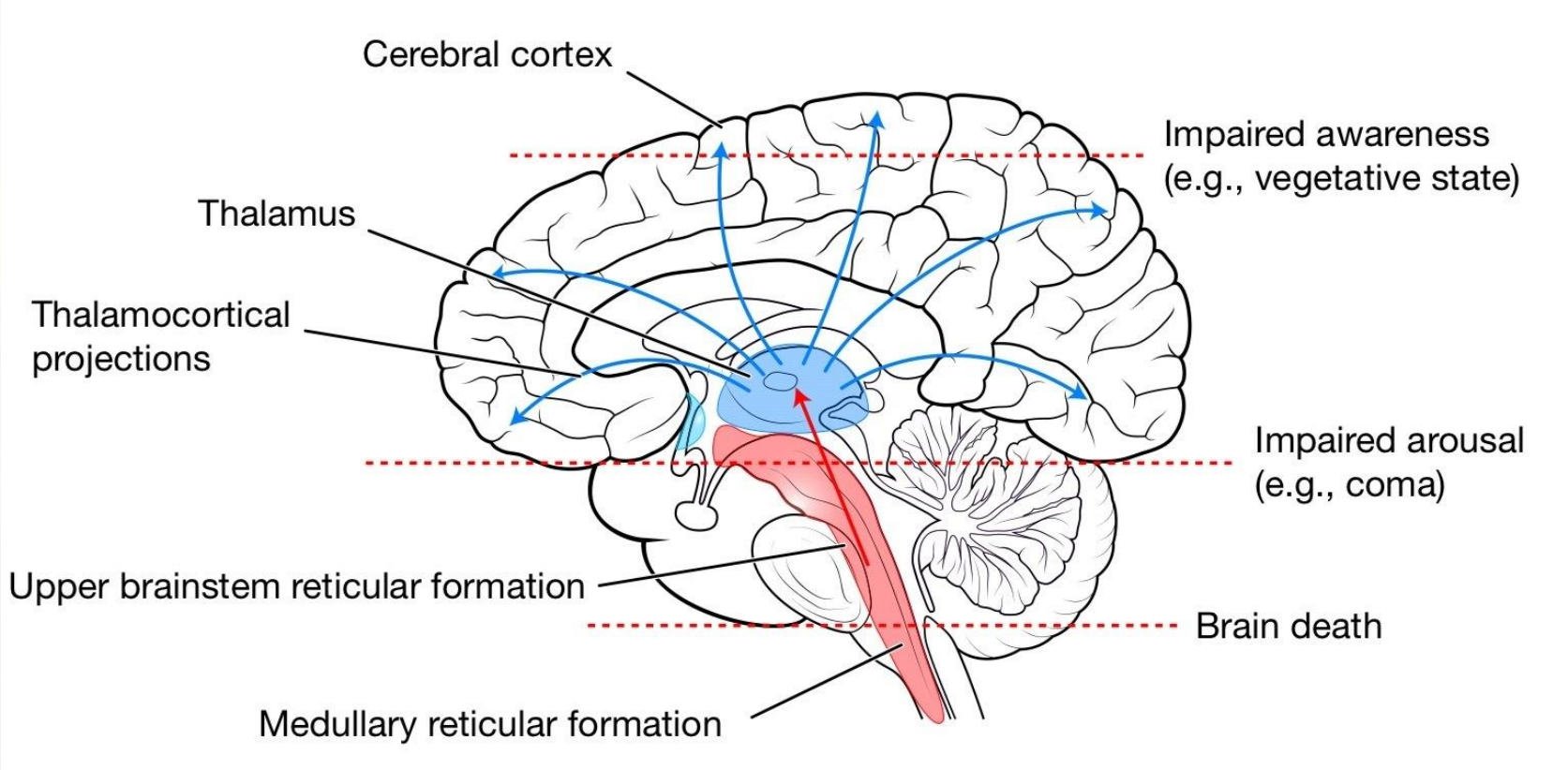
ANATOMY OF DREAMING

During REM Sleep

- ACTIVE
  - Reticular formation
  - Thalamus
  - Hypothalamus
  - Amygdala & Hippocampus
  - Visual Cortex
- INACTIVE
  - Parietal Cortex
  - Prefrontal Cortex



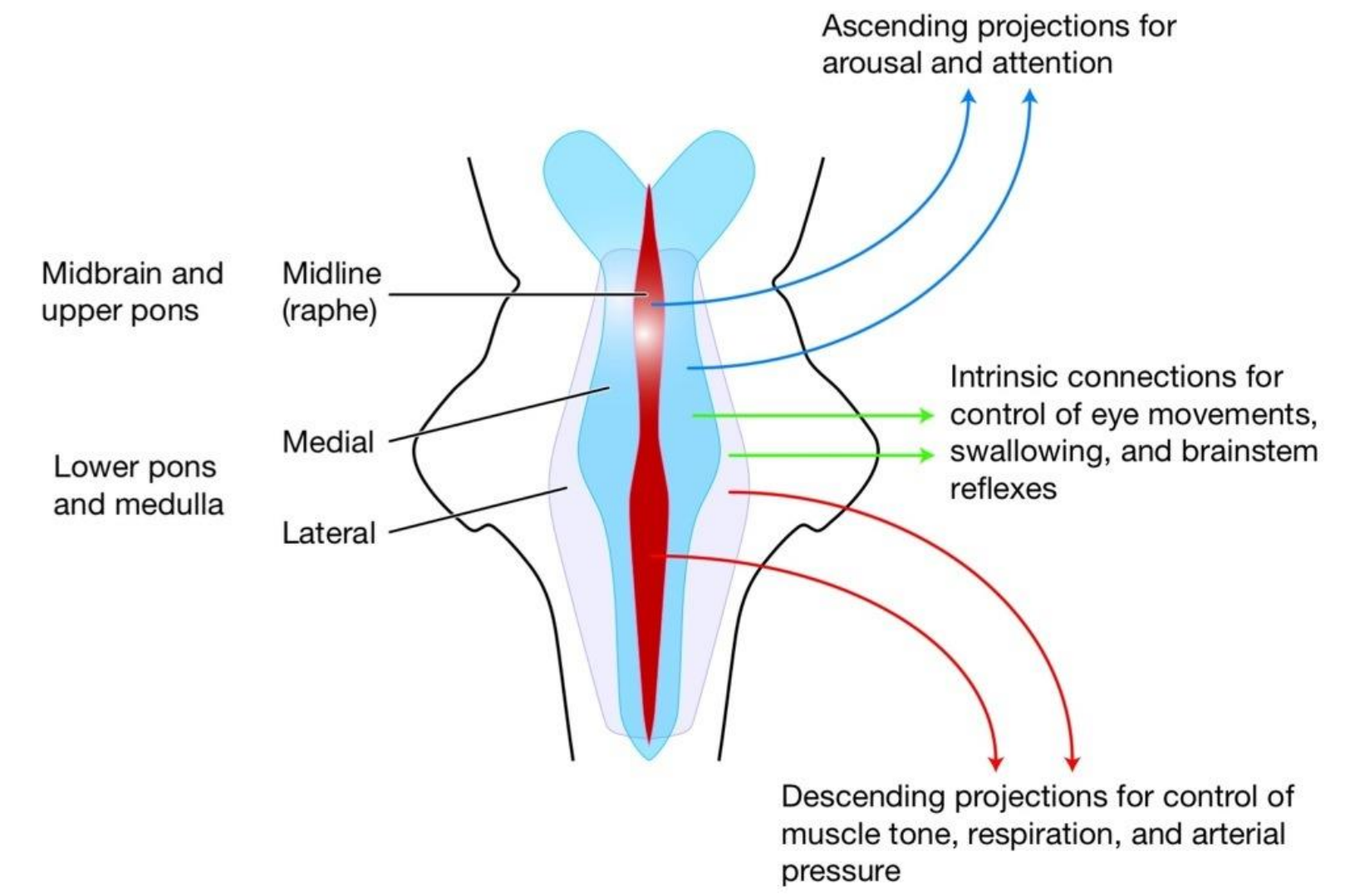
¿Porqué hay diferentes tipos de perdida de consciencia?

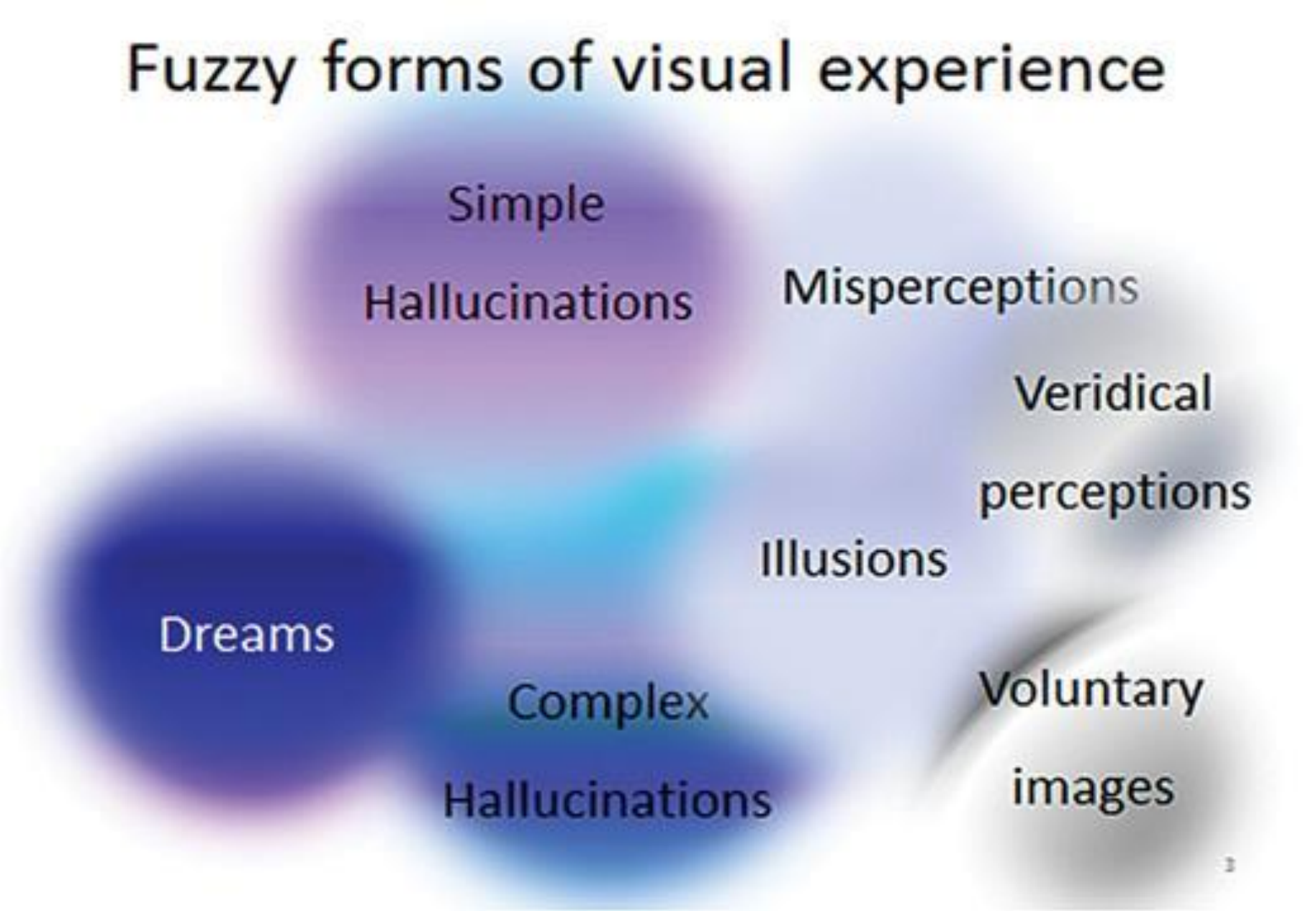


Diferentes niveles de consciencia dependen del nivel de la interrupcion de comunicación entre:

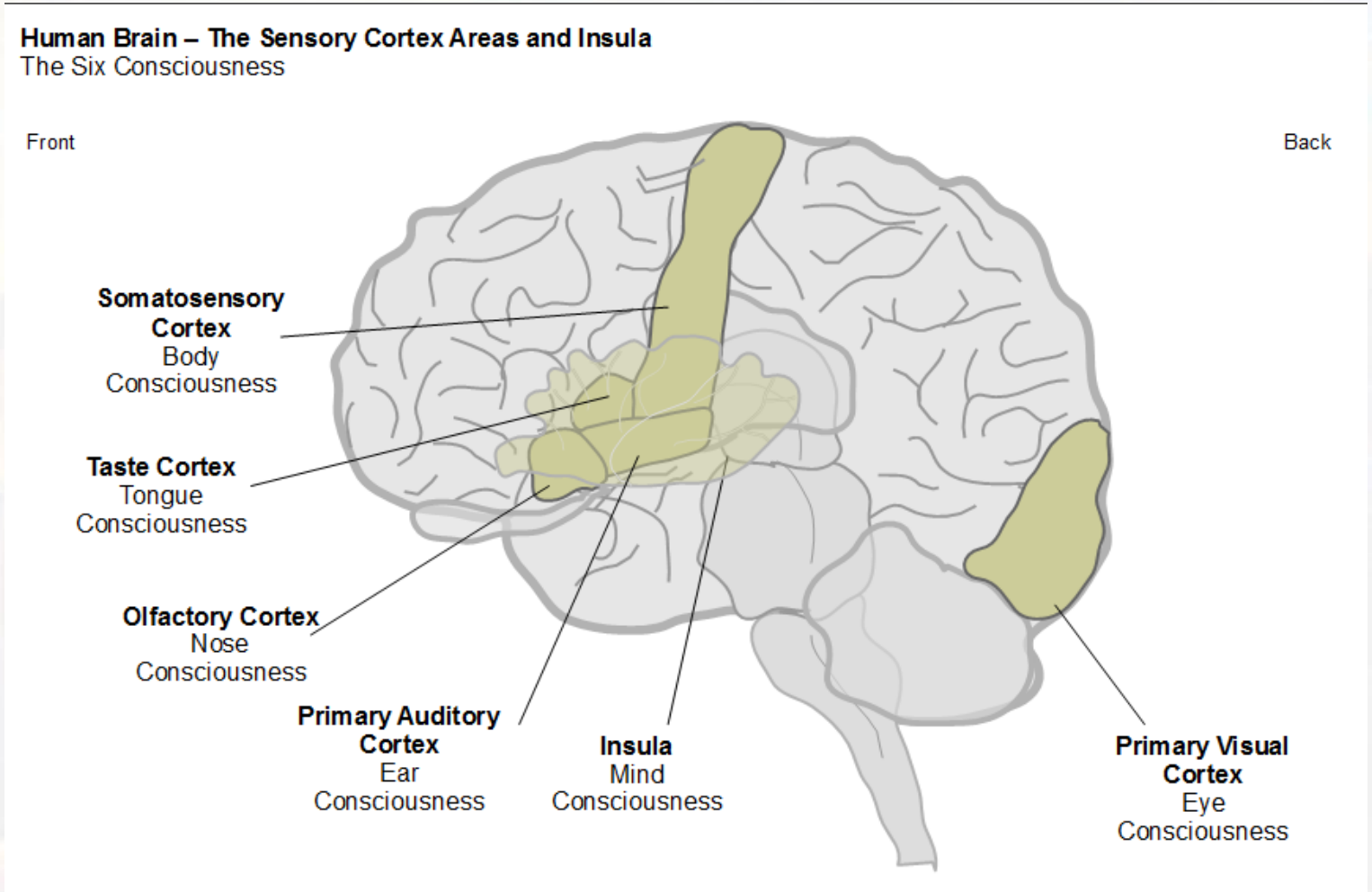
- **Tallo cerebral**
- **Talamo**
- **Corteza anterior (frontal, motora)**
- **Cortezas posteriores (sensoriales)**

Funciones del tallo cerebral



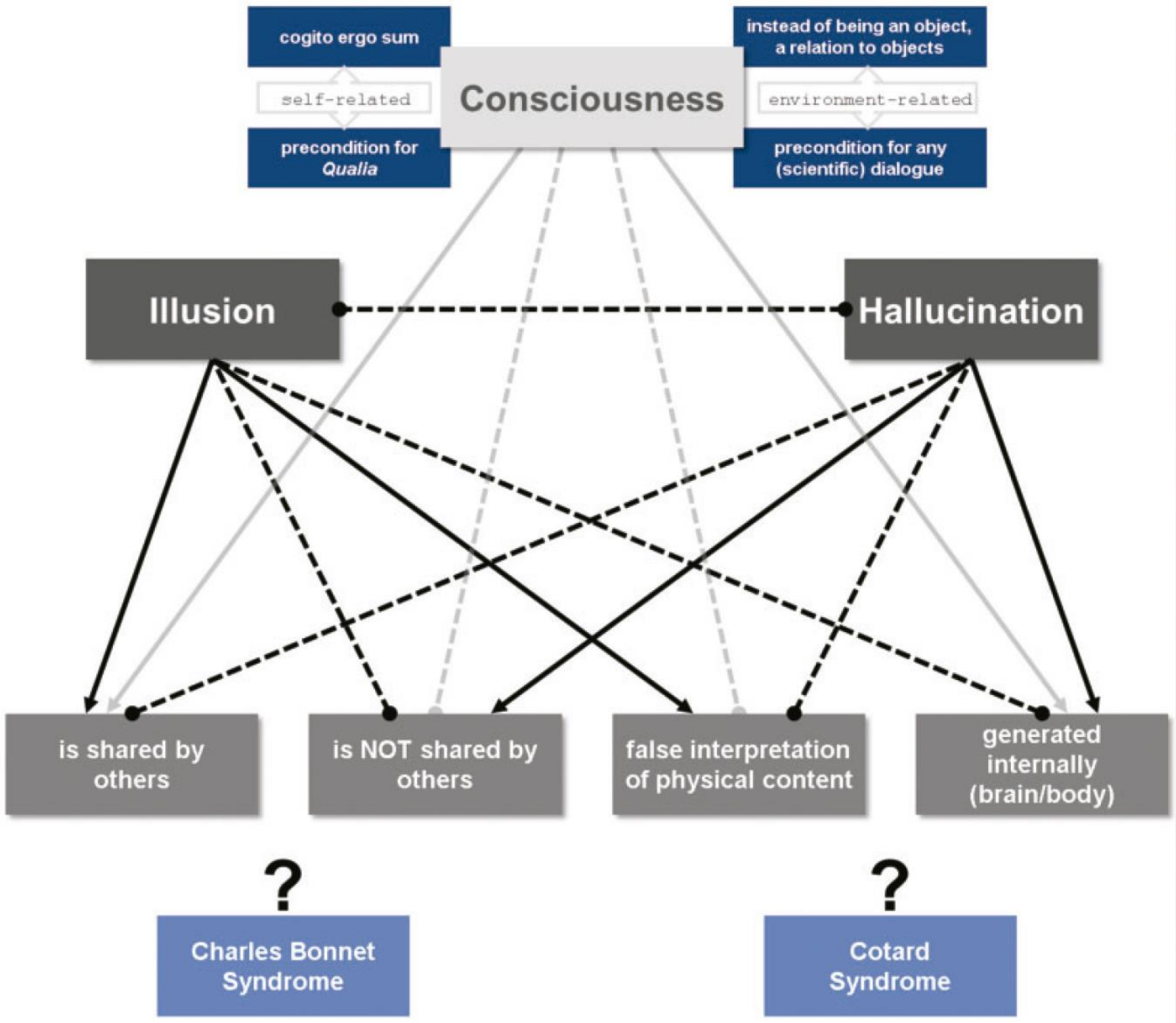

Fuzzy forms of visual experience
Simple
Hallucinations
Misperceptions
Veridical
perceptions
Illusions
Dreams
Complex
Hallucinations
Voluntary
images

A través del circuito talamo-cortico-talamico se desarrollan las percepciones de la realidad y sus multiples representaciones sensoriales, emocionales, y cognitivas



¿De donde viene la sensación de realidad?

La activación del loop cortico-talamico-cortical da lugar a las “realidades” de perceptcion consciente, sueños, alucinaciones, y el sentido inmediato de realidad que destaca la percepción de realidad, verdadera, o imaginaria



CUADRO 1: SINTOMAS PSIQUIATRICOS ENCONTRADOS EN LA INTOXICACION POR FLORICUNDA.

Síntomas psiquiátricos	N°	%
Desesperación	4	57.0
Agitación psicomotriz	4	57.0
Lenguaje incoherente	4	57.0
Agresividad	3	42.8
Alucinaciones visuales	2	28.5
Euforia	2	28.5
Sensación de flotar	2	28.5
Alucinaciones auditivas	1	14.2

CUADRO 2: OTROS SINTOMAS Y SIGNOS ENCONTRADOS EN LA INTOXICACION POR FLORICUNDA.

Otros síntomas y signos	Nº	%
Amnesia Lacunar	7	100.0
Rubor	7	100.0
Resequedad de mucosa oral	7	100.0
Midriasis	7	100.0
Hipertermia	7	100.0
Cianosis peribucal	4	57.0
Ataxia	3	42.8
Vómitos	2	28.5
Taquipnea	2	28.5
Taquicardia	1	14.2