

Tinnitus: A New Model of Pharmacological Therapy

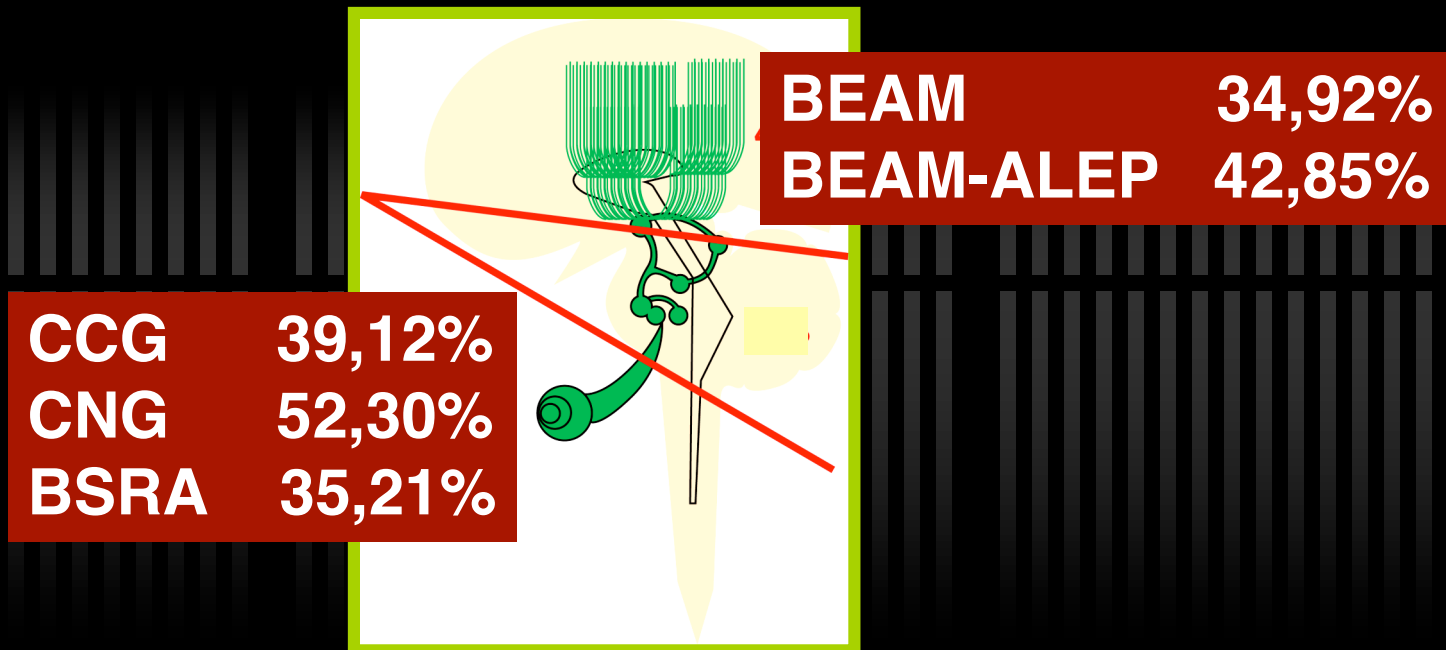


Otoophthalmological Neurophysiology

Buenos Aires - Argentina

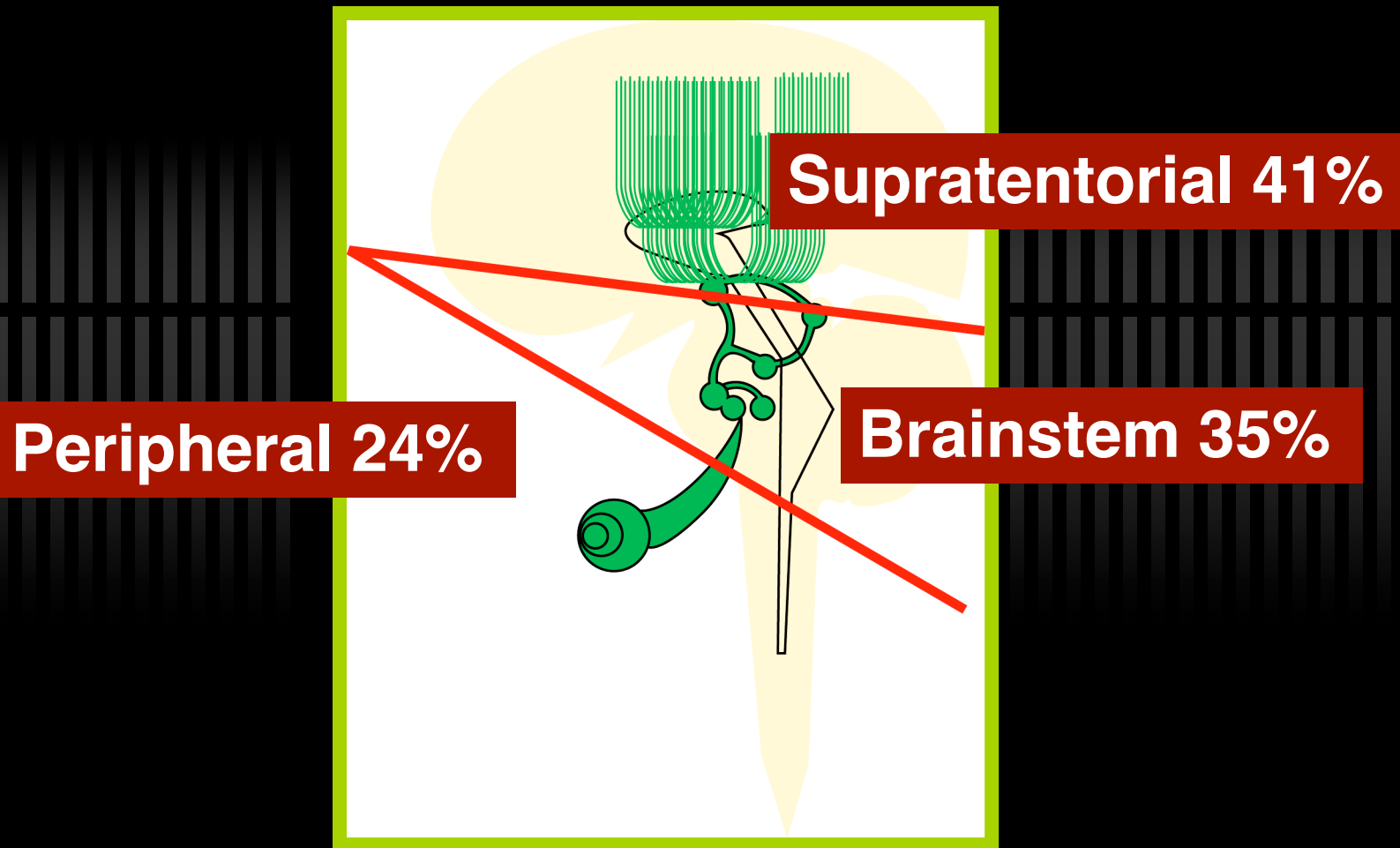
Guillermo O. Bertora – Julia M. Bergmann

In 1996, we introduced the topodiagnostic study of tinnitus from inner ear up to cerebral cortex using the different neurotometric methods (BSER, CNG, CCG, etc.) together with BEAM

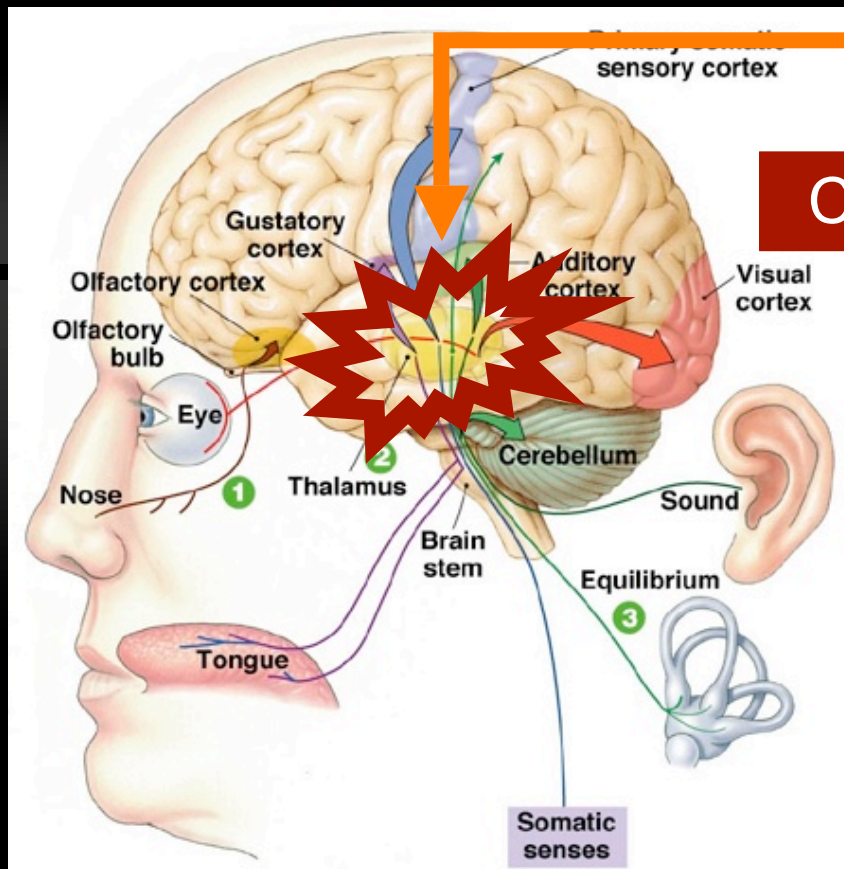


Tinnitus : Statistical results neurotometric tests

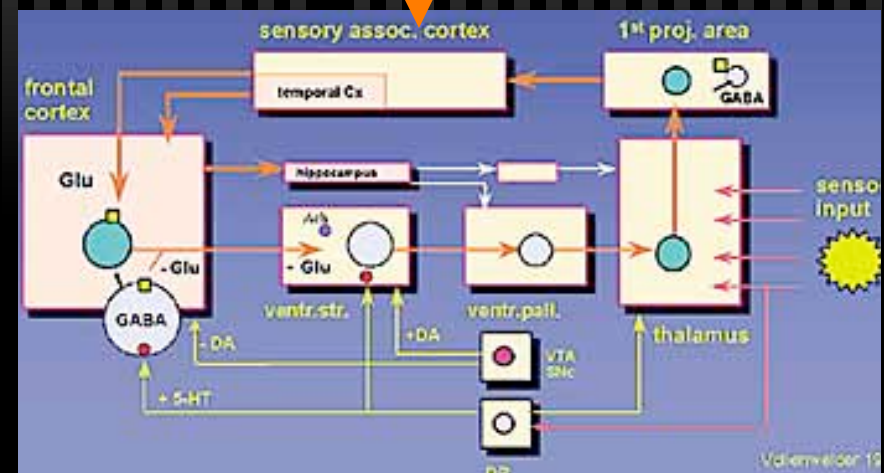
These discoveries indicate the numerous and different locations of the symptom, and enable us to prove that in around 24% of the patients, tinnitus has a peripheral origin, in 35% it is originated in the brainstem and in 41% at a supratentorial level.



Until now the tinnitus symptom at the supratentorial level. was explained like a phantom symptom or sensorial deprivation related to the pain pathway.
 It has been described that every sensorial afferentia to the brain is modulated by the cortico-striatum-thalamus-cortical loop. The auditory via is a sensorial one, therefore, it is involved in this circuit.
 In the **topographic diagnosis** and treatment of the supratentorial tinnitus, we have proved through our investigations carried out during the last 5 years, that the cortico-striatum-thalamus-cortical loop was the key to understand the mechanism of the tinnitus symptom at this level.



Cortico-striato-thalamo-cortical loop



During the last ten years, by working on experimental models on animals the explanation of tinnitus phenomenon has been started.

Studies carried out by Jastreboff (1988) and Lobarinas (2004), have reliably demonstrated that the agents producing

tinnitus on human beings such as sodium salicylate, acoustic trauma, quinine and others, produce on experimental animals an hyperexcitability which is characteristic of an increase of the spontaneous neuronal activity.

This hyperactivity has been observed at different levels of the auditory pathway, starting at the Dorsal Cochlear Nucleus (DCN), following at the Inferior Colliculo level and reaching the Auditory Cortex.

Kaltenbach and col. have demonstrated that the lowest point in auditory via, where the hyperactivity provoked by tinnitus can be checked is at the Dorsal Cochlear Nucleus (DCN) level. This structure is related with the sound spatial location, also receiving multiple synapsis particularly from the somatosensitive system.

The Dorsal Cochlear Nucleus (NCD) is particularly sensitive to any variation of the information received from auditory nerve and the cochlea, particularly when this one is affected.

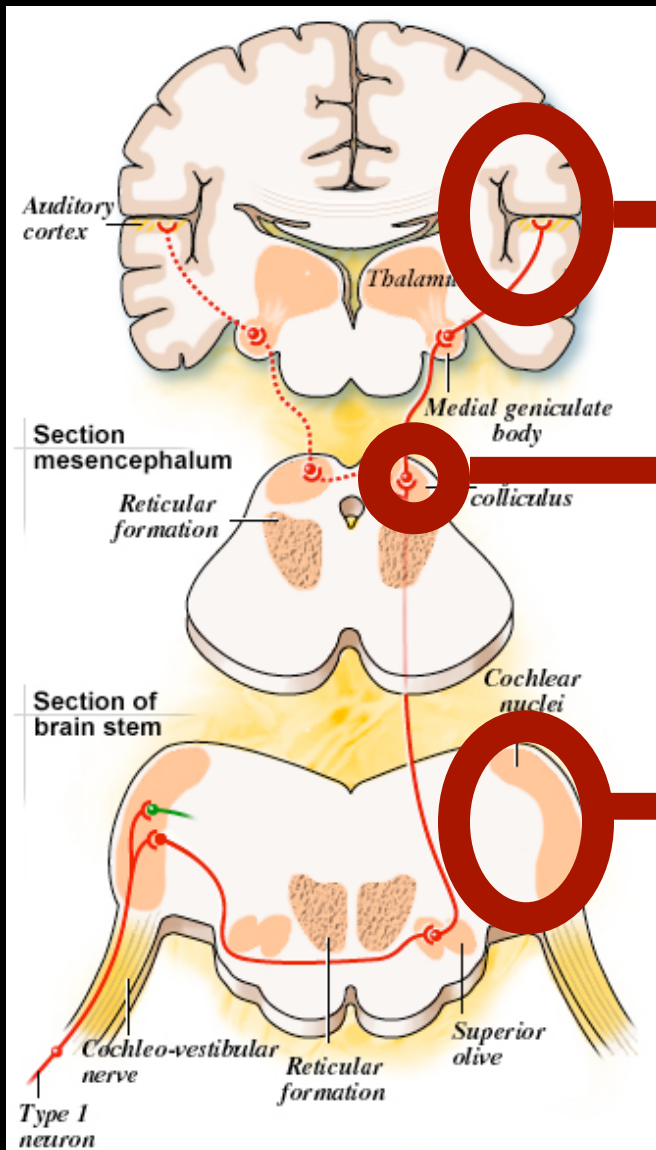
The NCD is also involved in somatic type tinnitus by means of the multiple vias by which it is connected to the cervical spine and some other cranial nerves.

Tinnitus could be modulated stimulating medianum nerve or as it has been demonstrated by Shulmann, by stimulation of cervical spine at C2 and C3 level by means of electric current.

80% of tinnitus modify its tone realizing chewing, swallowing movements or massaging and stretching the neck muscles.

Collicus Inferior (CI) hyperactivity has been largely demonstrated on animals of experimentation by Jastreboff by influence of sodium salicylate action.

Studies carried out by Melcher and col. in human beings show in fMNR (Functional Magnetic Nuclear Resonance), the Collicus Inferior (CI) hyperactivity in tinnitus.



Auditory Cortex

Inferior Colliculus

Dorsal Cochlear Nucleus

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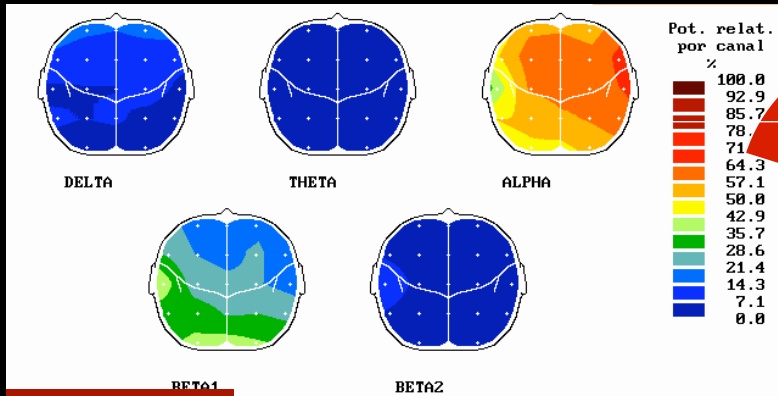
Irritability of auditory cortex has been demonstrated on cats by Kimura and Eggermont affecting the cochlea with noise.

The advance in radioimaging techniques such as PET shows in tinnitus patients a pattern of metabolic hypercaption, indicating an increase of the cerebral activity. (Shulman, Lockwood and others).

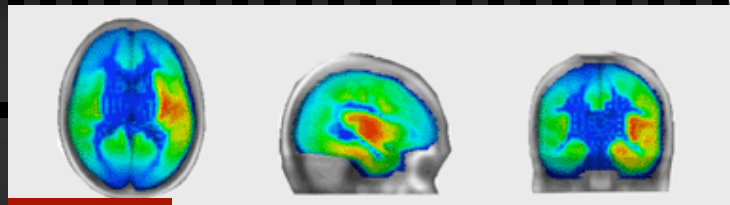
The recent introduction of programs in 3D, applied to Electroencephalogram (EEG) inverse solution and Magnetoencephalogram (MEG), allow us the using of these techniques in our daily practice, being them much simpler and less expensive.

We have described in 1995, working on brain mapping the presence of fast rhythms in the EEG of β type on derivations C3, C4, T3, T4 on tinnitus patients.

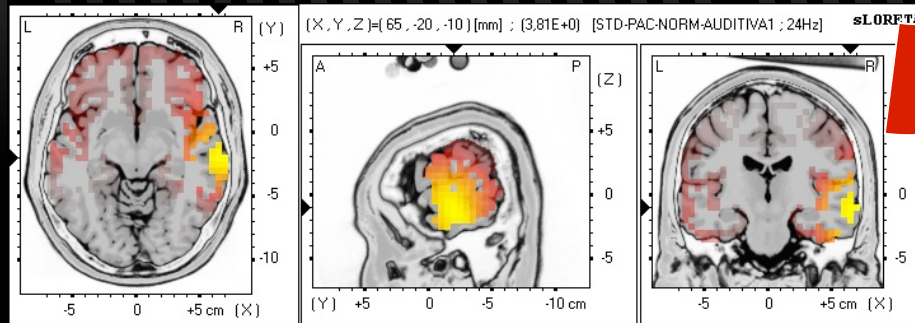
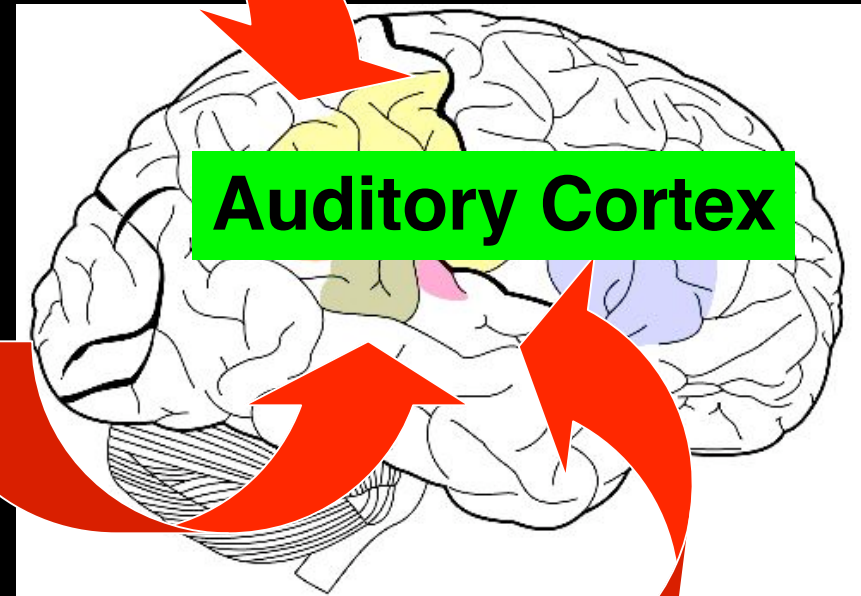
As from 2002, working through Brain Electric Tomography (LORETA – Pascual Marqui and col.) we were able to demonstrate the aforementioned patterns on cranial surface and to selectively locate the origin of the electric dipoles provoking them in the different brainslices from Talairach Atlas.



BEAM

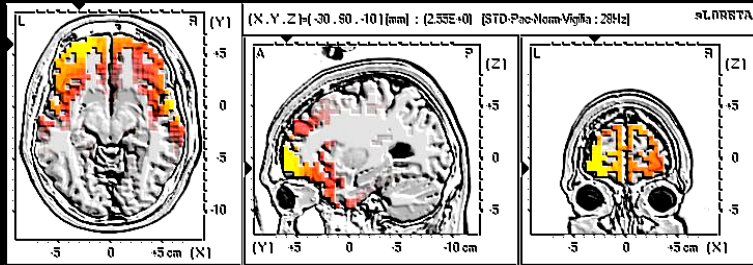


PET

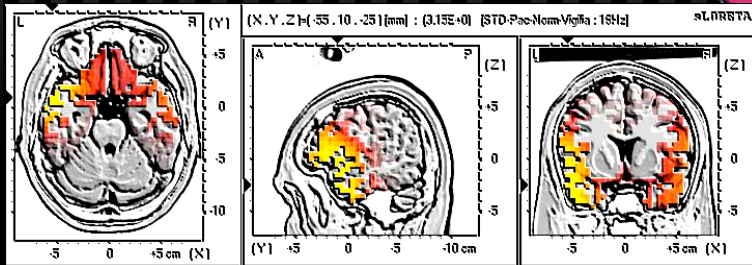
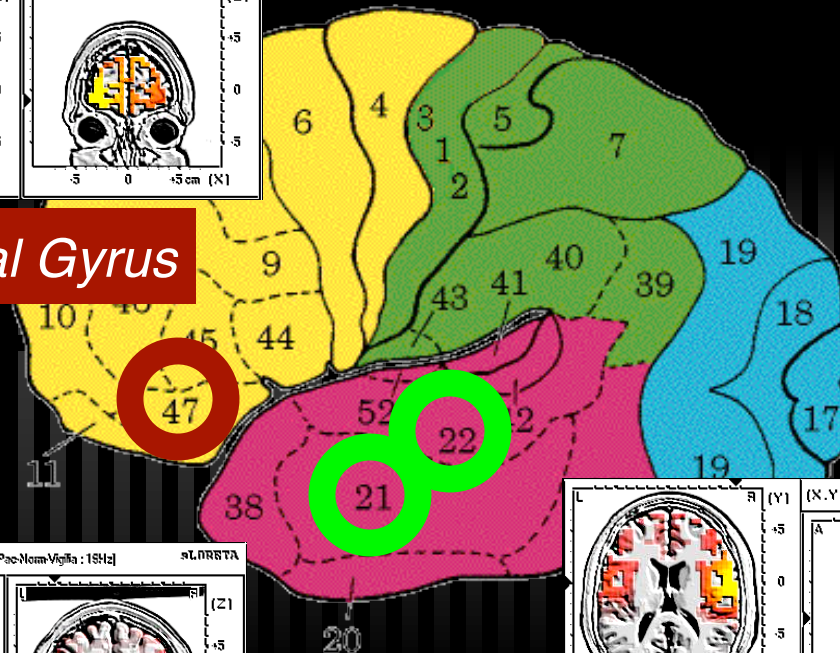


LORETA

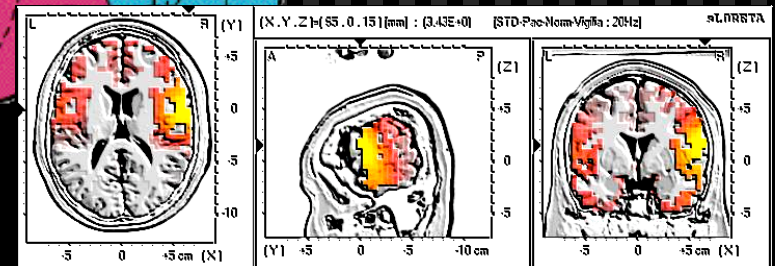
In year 2008, studying 200 tinnitus patients, without stimulation, in rest condition. and comparing the results vs. 50 normal patients, we have obtained 3 characteristic areas of hyperexcitability in tinnitus at cortical level:



BA 47 - Inf. Frontal Gyrus

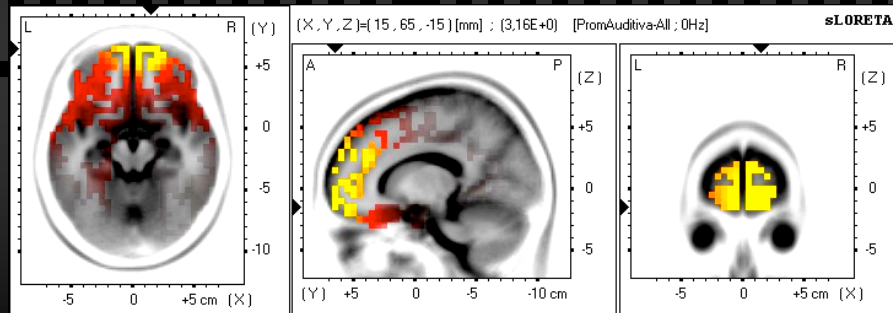


BA 21 - Middle Temporal Gyrus

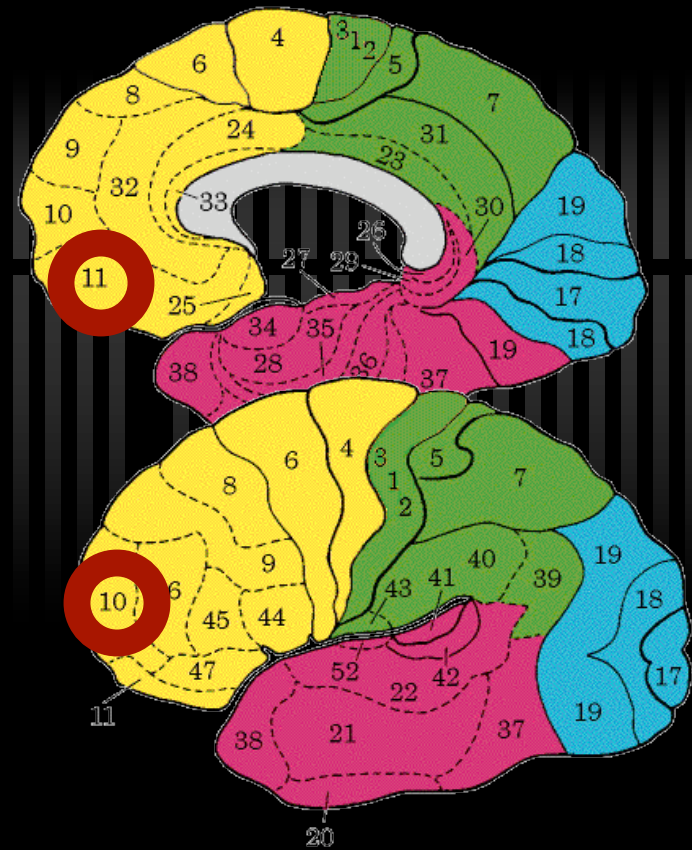


BA 22- Sup. Temporal Gyrus

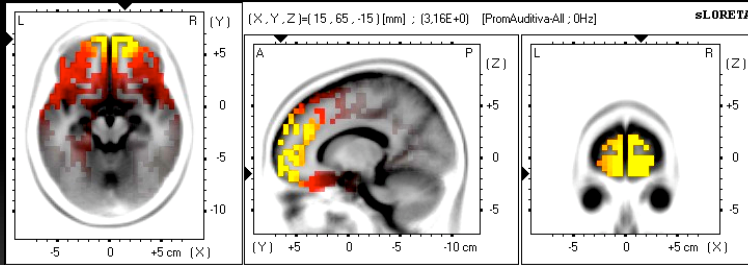
And 2 areas of hipoexcitability at the prefrontal cortex



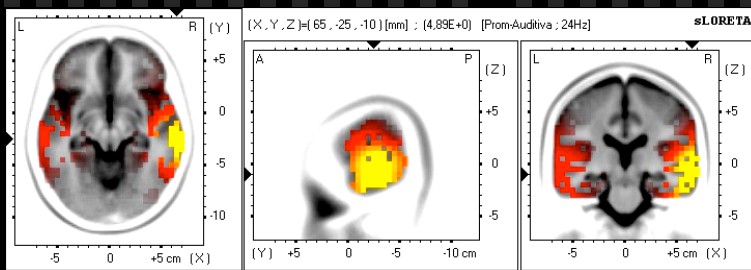
BA 10 - 11 - Middle Frontal Gyrus



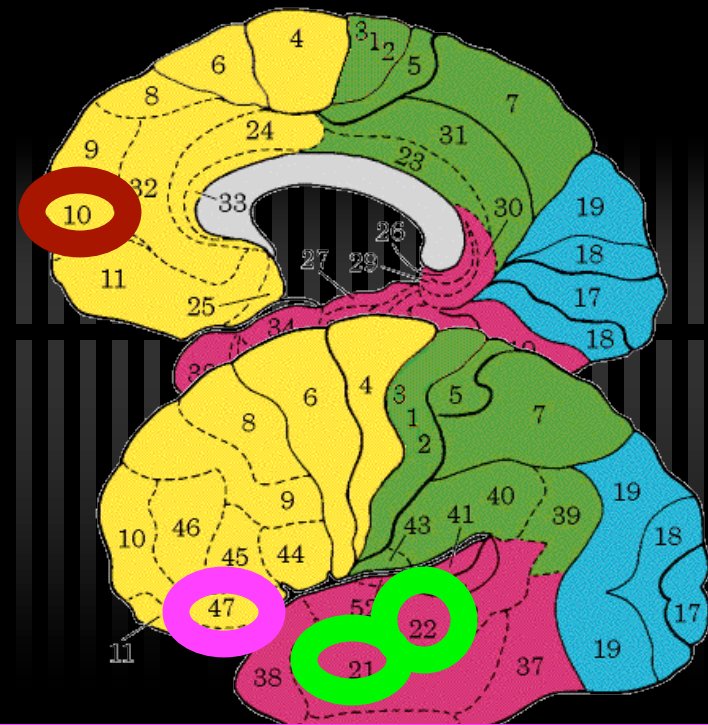
This same group of patients studied under auditory stimulation showed the following results:




Alpha Rhythm
 BA 10 - *Middle Frontal Gyrus*



Beta Rhythm
 BA 21 - *Middle Temporal Gyrus*
 BA 22 - *Sup. Temporal Gyrus*



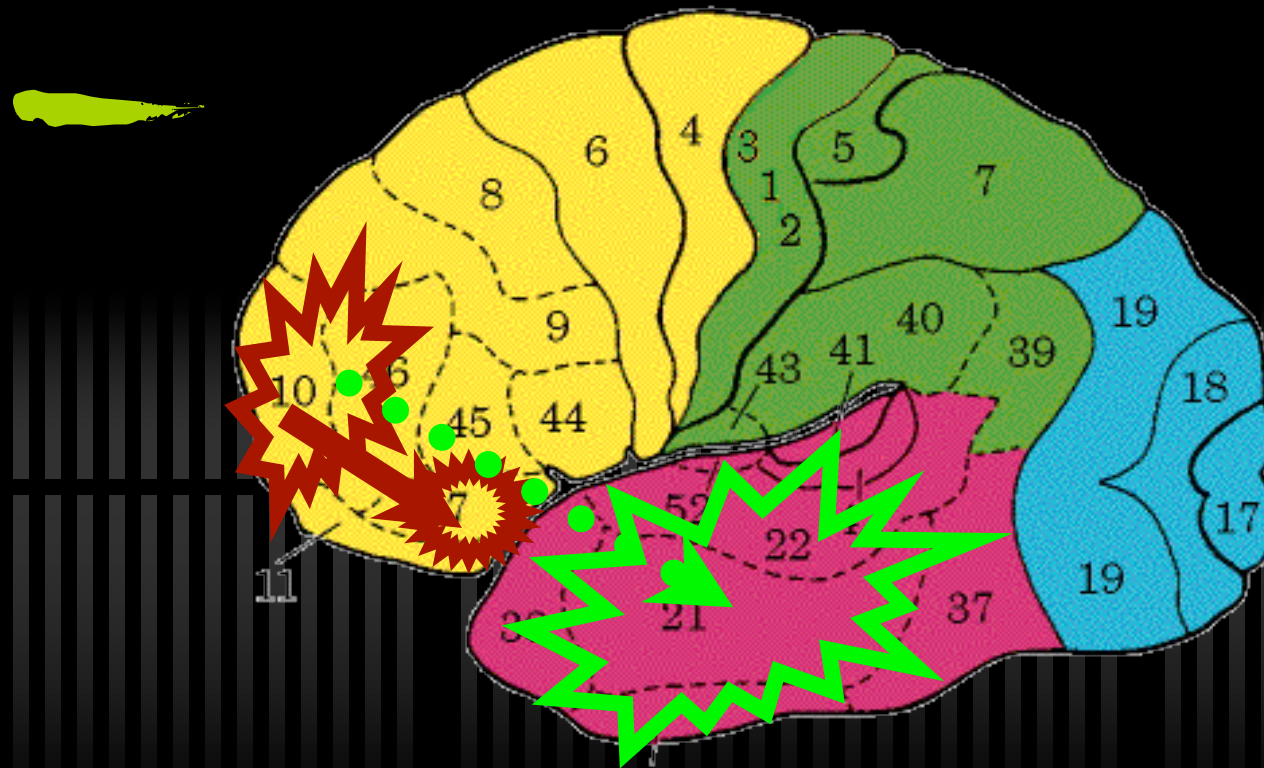
Hyperactivity disappears
 BA 47 - *Inf. Frontal Gyrus*



These highly significant results, show that tinnitus modulation and plasticity, are regulated by frontal areas, particularly by Brodmann area 10, removing the hyperactivity observed in BA 47, present in every tinnitus forms.

This modulation is not enough to depress the hyperactivity observed in BA 21 and 22, which on the contrary, in many patients the irritation is increased.

Our Data Bank show that 56,6% of the patients are correlated with hipoactivity in BA 10 and 11 but exist a 30% of the cases related with hyperactivity of these areas.



These highly significant results, show that tinnitus modulation and plasticity, are regulated by frontal areas, particularly by Brodmann area 10, removing the hyperactivity observed in BA 47, present in every tinnitus forms. This modulation is not enough to depress the hyperactivity observed in BA 21 and 22, which on the contrary, in many patients the irritation is increased.

Our Data Bank show that 56,6% of the patients are correlated with hipoactivity in BA 10 and 11 but exist a 30% of the cases related with hyperactivity of these areas.

We have explained that Modulation of all sensorial afferentias which reach cerebral cortex are regulated by the cortico-striato-thalamo-cortical feedback loop.

The thalamic reticular nucleus receives collateral axons of the thalamus-cortical ascending fibers and of the cortical-thalamo descending ones.

Our tinnitus physiopathological schema, obtained after several years of experiencing and pharmacological working allow us to say that in 80% of the cases, the starting point for producing tinnitus is a pathology of cochlear type. Afterwards, the unbalance between information of afferent and efferent fibers between cochlea and the dorsal cochler nucleus (DCN), produces irritation of this nucleus.

Once the irritation of this nucleus is produced, the cochlear pathology jumps to a secondary level, as it is demonstrated by the different studies on which cochlear destruction or neurectomy has been produced, obtaining no result at all on tinnitus.

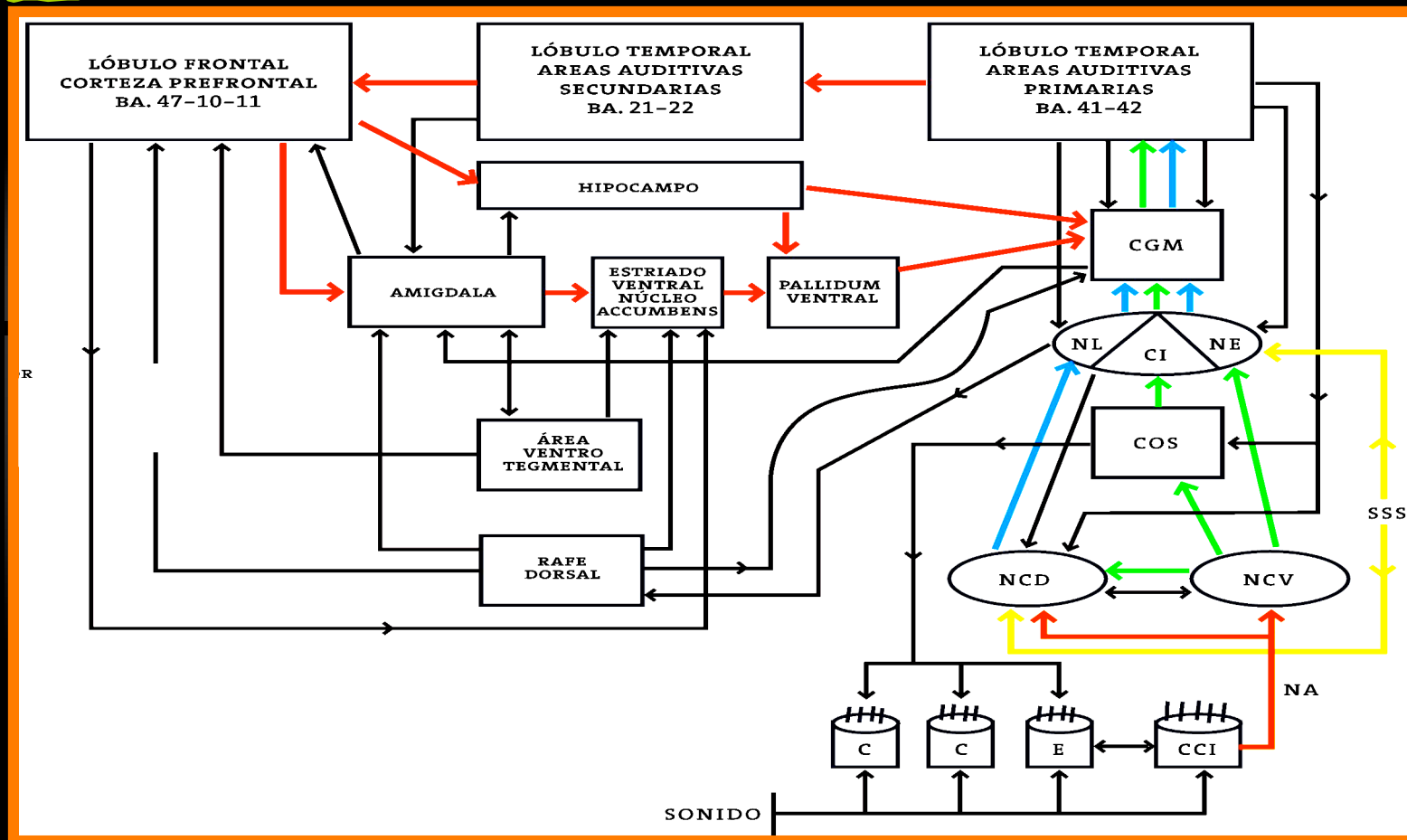
In effect, tinnitus is a reflex circle of central origin.

Under normal conditions of this circuit of cortical control, tinnitus is modulated by the cortico-striatum-thalamus-cortical loop

When this modulation controlled by the above loop is regularly working, tinnitus phenomenon does not imply any alteration in the patient's daily routine or social life.

Patients suffering on tinnitus under this situation, referred to it as listening it only in a silent environment, having no difficulty for a quiet sleeping.

Tinnitus Pathway





In our model, thalamus acts as a selective filter for the inter and exteroceptive information reaching the brain. Any modification of this function produces a sensorial overcharge, blocking the respective brain areas.

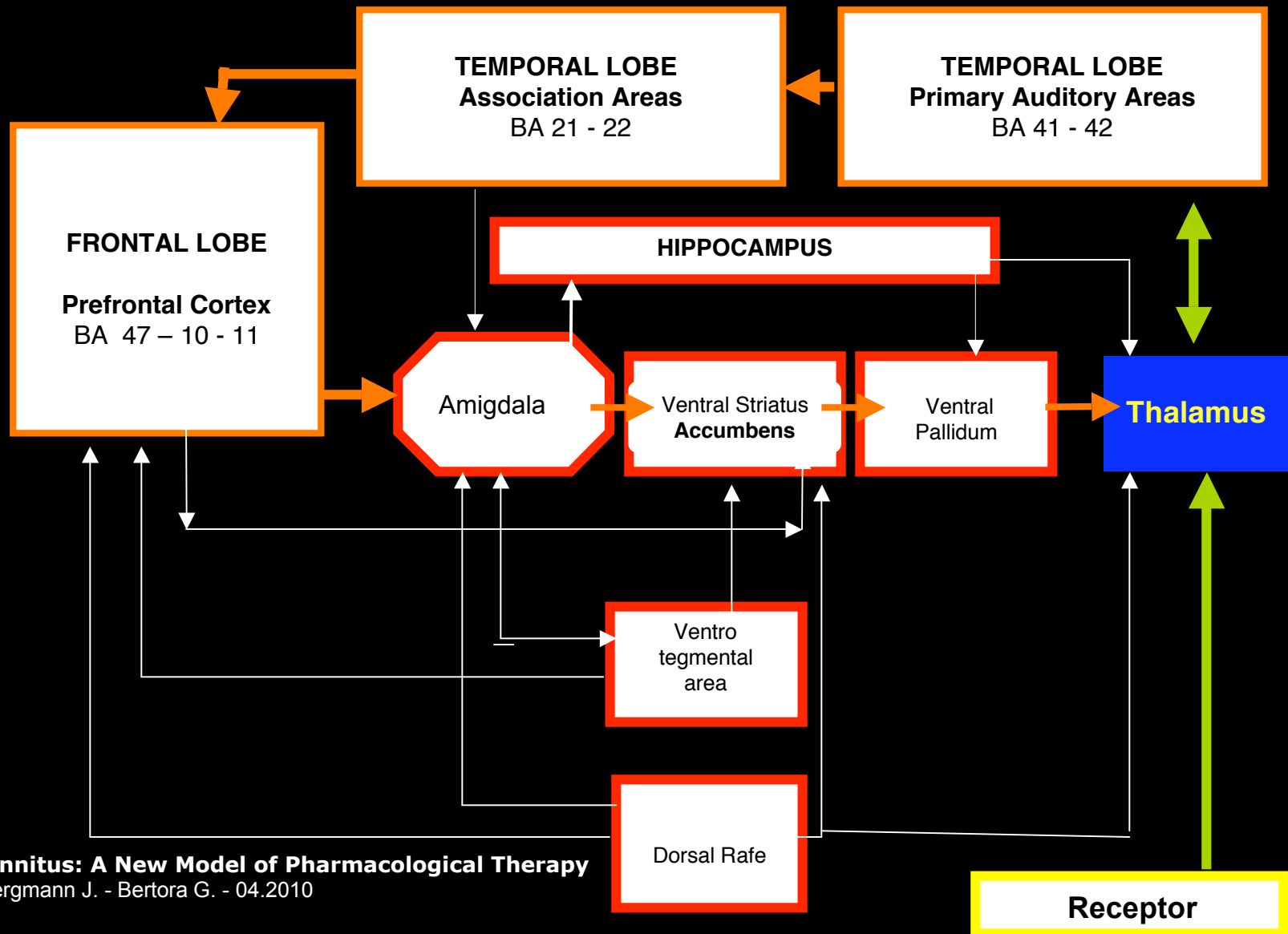
Control of the thalamic filter is under the influence of the cortico-striato-thalamo-cortical loop. Auditory information reaches the thalamo, there from it is projected towards the brain primary auditory areas BA 41 and 42.

Once the information has been elaborated, the pathway projects towards the associated auditory areas BA 21 and 22, for finally projecting towards the associated areas located at the prefrontal cortex BA 47, 10, 11.


The prefrontal cortex projects towards subcortical emotional areas, particularly the striated one, stretching towards dorsal and ventral parts, including the accumbens nucleus, amygdala and the dorsal and ventral pallidum. These areas are in charge of thalamic control and of closing this filter.

Thalamus inhibition results in a decrease of the sensorial afferentia to the cortex, lowering the attention and protecting the cortex from the sensorial overcharge.

Tinnitus Pathway



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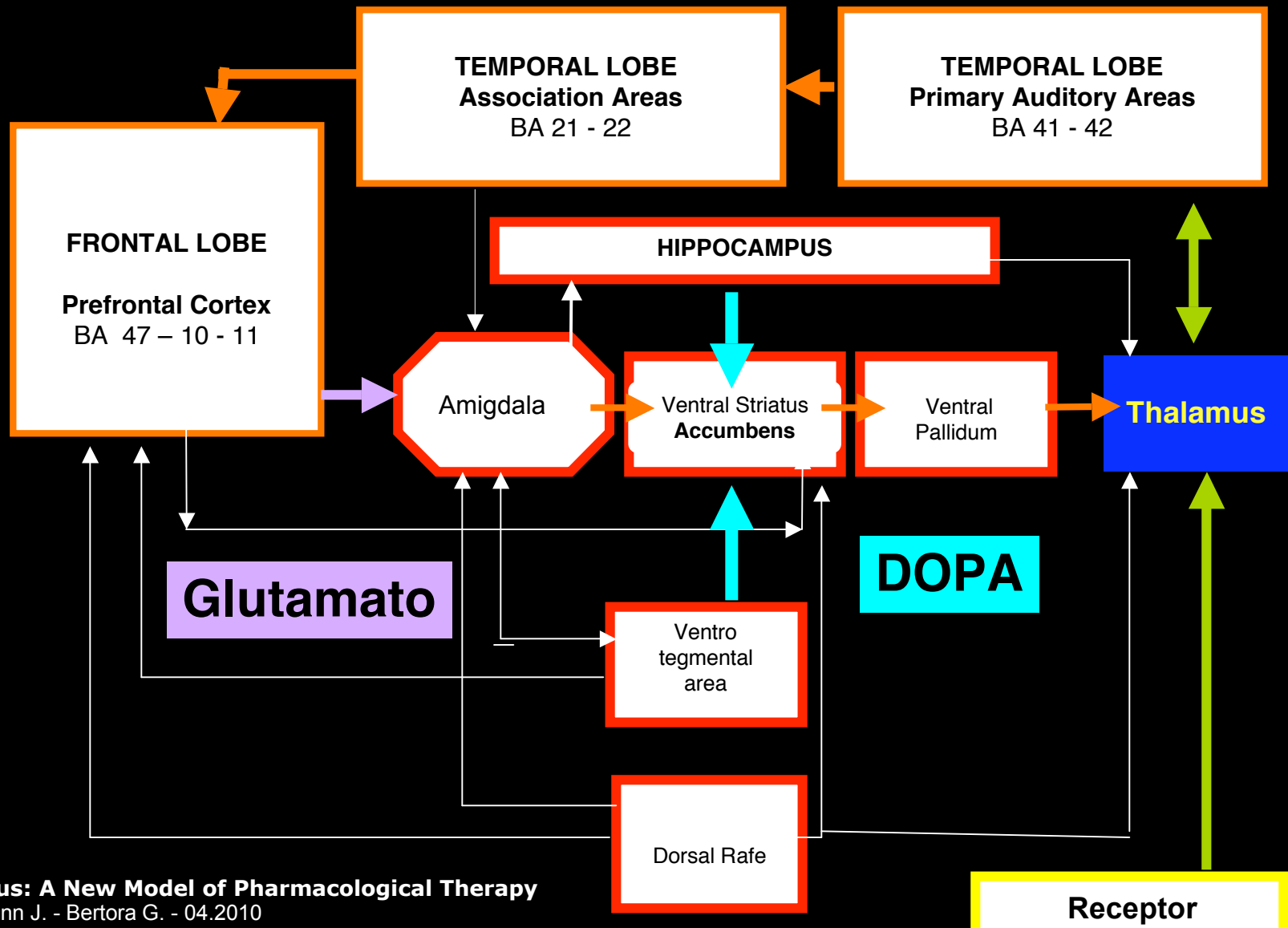


Striatal activity is modulated by other subsidiary circuits with their respective neurotransmitters. Thus, the projections of the mesostriated and the limbic area act by means of dopaminergic inhibitory pathway on the striatum including the accumbens nucleus. Under normal conditions the dopaminergic inhibitory action is counterbalanced by the exciting glutamatoergic pathway coming from the cortex.

In fact, an increase of the dopaminergic action or a decrease of the glutamatoergic action leads to a reduction of the striatal inhibitory action on the thalamus, with the opening of the thalamus filter and an overcharge of information towards cortex.


This simple model has been tested by us and other authors as Vollenweider with different drugs, given us very good results.

Tinnitus Pathway



Same as in the case of dizziness treatment, tinnitus pharmacological treatment is our choice.
We planning a rational therapy in line with tinnitus topodiagnosis considering the following neurootological tests:

- **Typified Anamnesis**
- **Tonal, Verbal Audiometry and Supraliminal tests**
- **Impedanciometry**
- **Otoacoustic Emissions**
- **Fast Evoked Potentials of Brain Stem – BSER**
- **Slow Auditory Evoked Potentials of Brain Cortex – ALEP**
- **Cognitive Potentials – P 300**
- **Brain Mapping and Evoked Potential Mapping – BEAM**
- **Brain Electric Tomography – LORETA**



In tinnitus therapy schedule developed by us, we based on the schema of the auditory via and on the cortico -striato- thalamo -cortical control system.

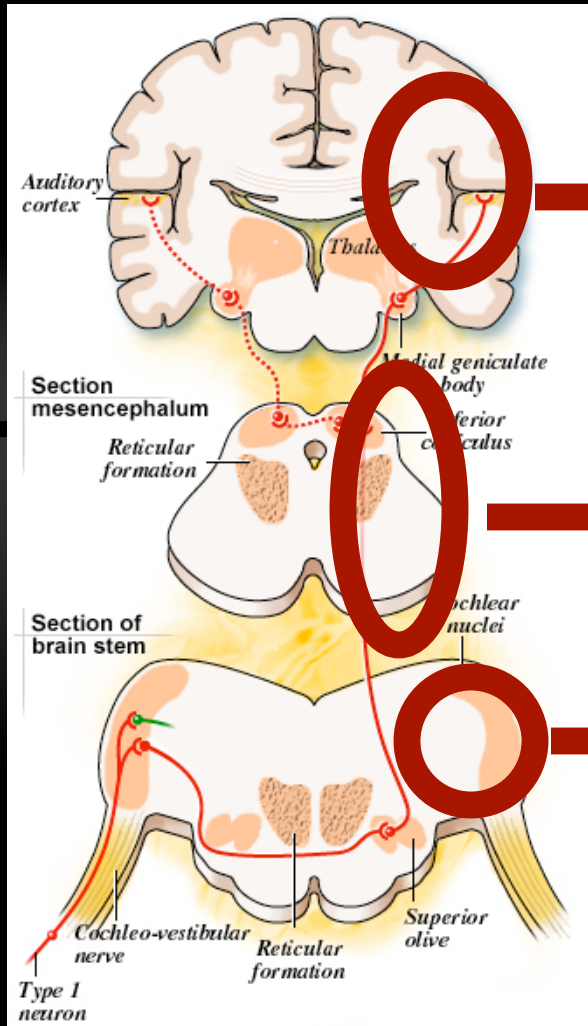
The selected medicine or neurotransmitter will be directed to regulating the neuronal hyperactivity or hypoactivity functions, depending on the topographical location of tinnitus.

The functions of control and depression of auditory nucleus, particularly that of the dorsal and ventral cochlear nucleus (DCN) are controled by the cerebellum through a mechanism such as GABA-minergetic type as it is present in the case of equilibriometric disorders.

In tinnitus cases with hyperactivity of the dorsal and ventral cochlear nucleus (DCN) we indicate medicines with GABA-minergetic functions such as piracetam, piridoxin, or clobazan with excellent results.

As from the cochlea and up to the middle geniculated corp (CGM), the specific function of cellular activation is assisted by the acetylcholine. In cases of slowness syndrome of the brainstem, where this neurotransmitter is depressed, showed in the neurootological tests, particularly in brainstem potentials by an extension in latency times and a decrease in amplitude of BSER waves, we use acetylcholinic precursors as CDP-choline, naphtyhydrophuril and cocculus and conium as phytotherapeutic.

In cortical brain disorders, where we have proved a neuronal hyperactivity. (BA 21, 22) we prescribe regulators of the brain rhythm such as benzodiazepinic derivatives as the clonazepan, GABA-minergetic precursors as gabapentin and its derivatives. Without disregarding as alternative therapy regular antiepileptic products as carbamazepines, topiramate and derivatives of the valproic acid.



**Brain regulators
Bzd precursors
GABA precursors**

Ach precursors

GABA precursors

In frontal dysfunctions we observe hyperactivity or hypoactivity phenomena in certain areas, (BA 10, 11, 47)

En cases of prefrontal hyperactivity we prescribe precursors of the GABA-minergetic system.

In frontal hypofunctions we prescribe glutamatergic antagonist acting on the glutamatergic system by blocking NMDA glutamate receptors and the inhibitors of serotonin reuptake

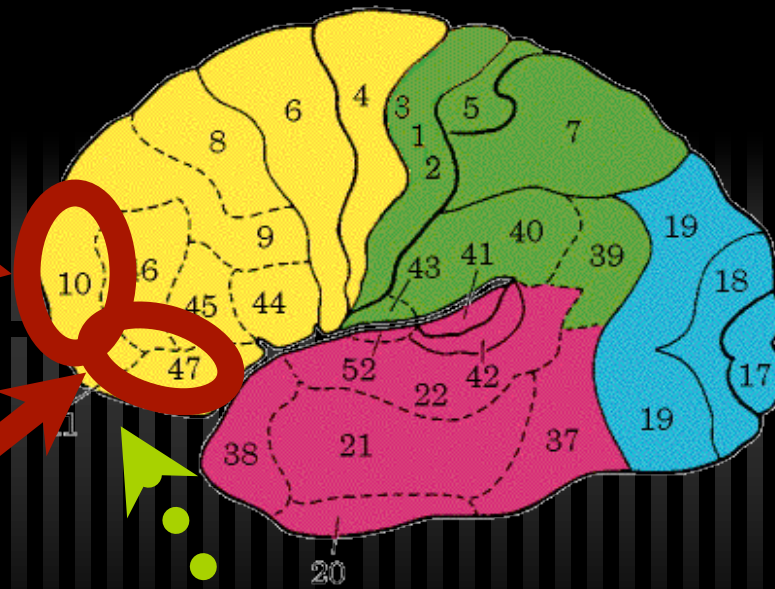
It should be taken into account that control on prefrontal cortex of serotoninergic pathways comes from dorsal rafe and the dopaminergic pathways from the ventro tegmental area.

Many tinnitus cases are related to psychiatric pathologies of prefrontal cortex known as bipolarity, depression and schizophrenia where the aforementioned pathways play a fundamental role, thus they should be considered in the therapy schema.

Tinnitus Treatment

Hiperactivity
GABA precursors

Hipoactivity
NMDA antagonist
Serotonin reuptake



Bipolarity
Depression
Schizophreny

Control of prefrontal cortex is projected over the ventral striatum particularly over the amygdala and the nucleus accumbens, being both structures altered in severe tinnitus process.

These also being trigger areas of panic, anxiety and phobias.

Action on the amygdala is done by means of serotonergic precursors or dopamine antagonist.

But on the nucleus accumbens we work specifically with benzodiazepinic mediators.

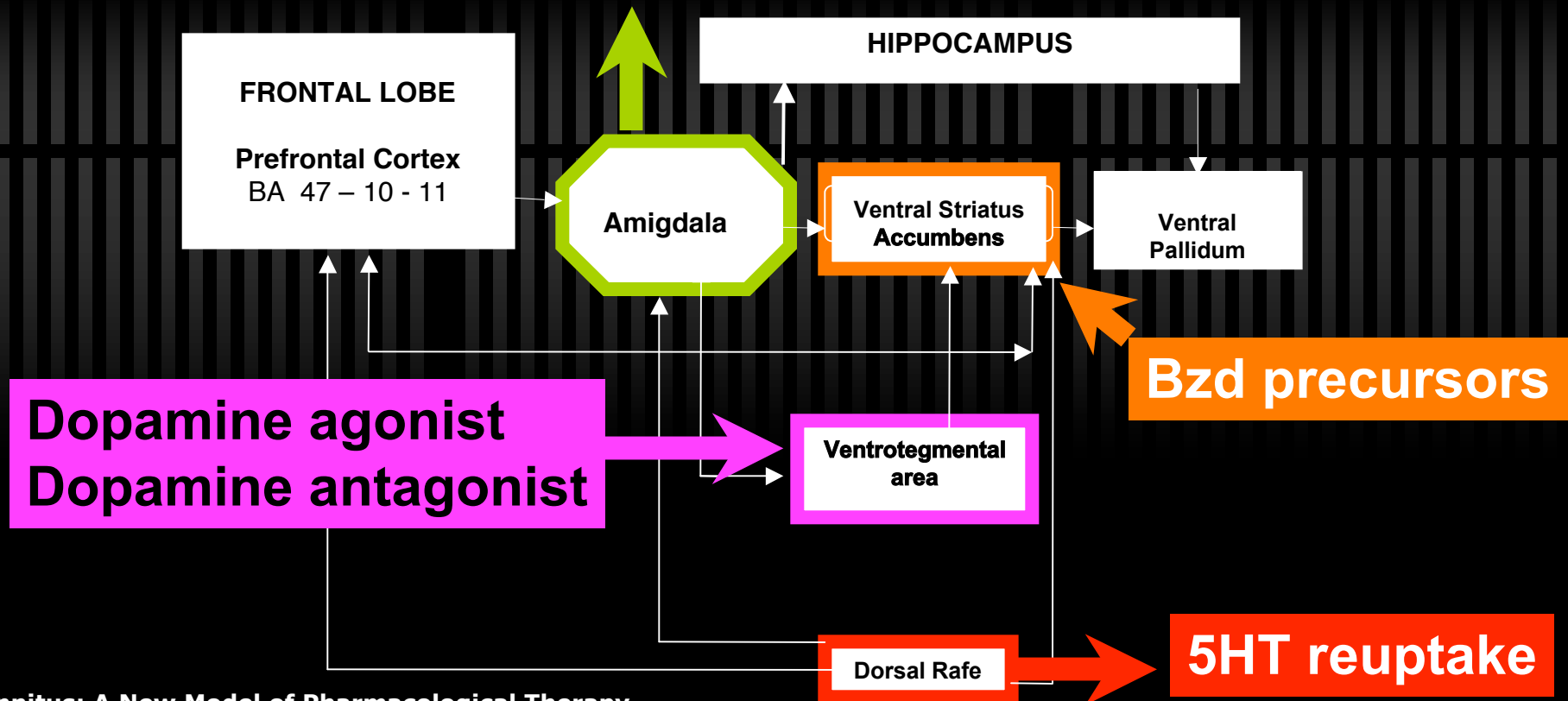
The rubro-nigro-striated system predominantly controlled by dopamine provokes a depressive action on the ventral striatum at mesencephalic level.

Dopamine acts as inhibiting transmitter, opening the thalamic filter.

In Tinnitus treatment vasoactive drugs, should be complementary prescribed as in the equilibriometric disorders.

Tinnitus Treatment

**5HT reuptake
Dopamine antagonist**



Tinnitus Treatment



In view of the above said, it is easy to understand that it is impossible to treat tinnitus by a monodrug, but it is necessary to use a combination of numerous neurotransmitters capable of regulating the hyper / hypofunction phenomena in line with the different topographical locations.

~~No monodrug~~

Our tinnitus therapy results

An statistical evaluation of patients under study, (Bergmann-Bertora) quantitatively before and after treatment, allows us to state that:

- **61% complete restitution of tinnitus**
- **30% an important decrease of tinnitus**
- **9% no modifications of tinnitus**

Tinnitus and dizziness of central origin represent those symptoms which are of chronic type in a very high percentage.

Thus, as it is the case of some other pathologies – diabetes, hypertension, hyperthyroidism – the treatment should be supporting and permanent.

