

Contributions of the Brainstem to the auditory and non-auditory components of Tinnitus

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Outline of this presentation

Part 1- The brainstem as a tinnitus generator

Part 2-The brainstem as a tinnitus modulator

Part 3-The brainstem's role in tinnitus comorbidities

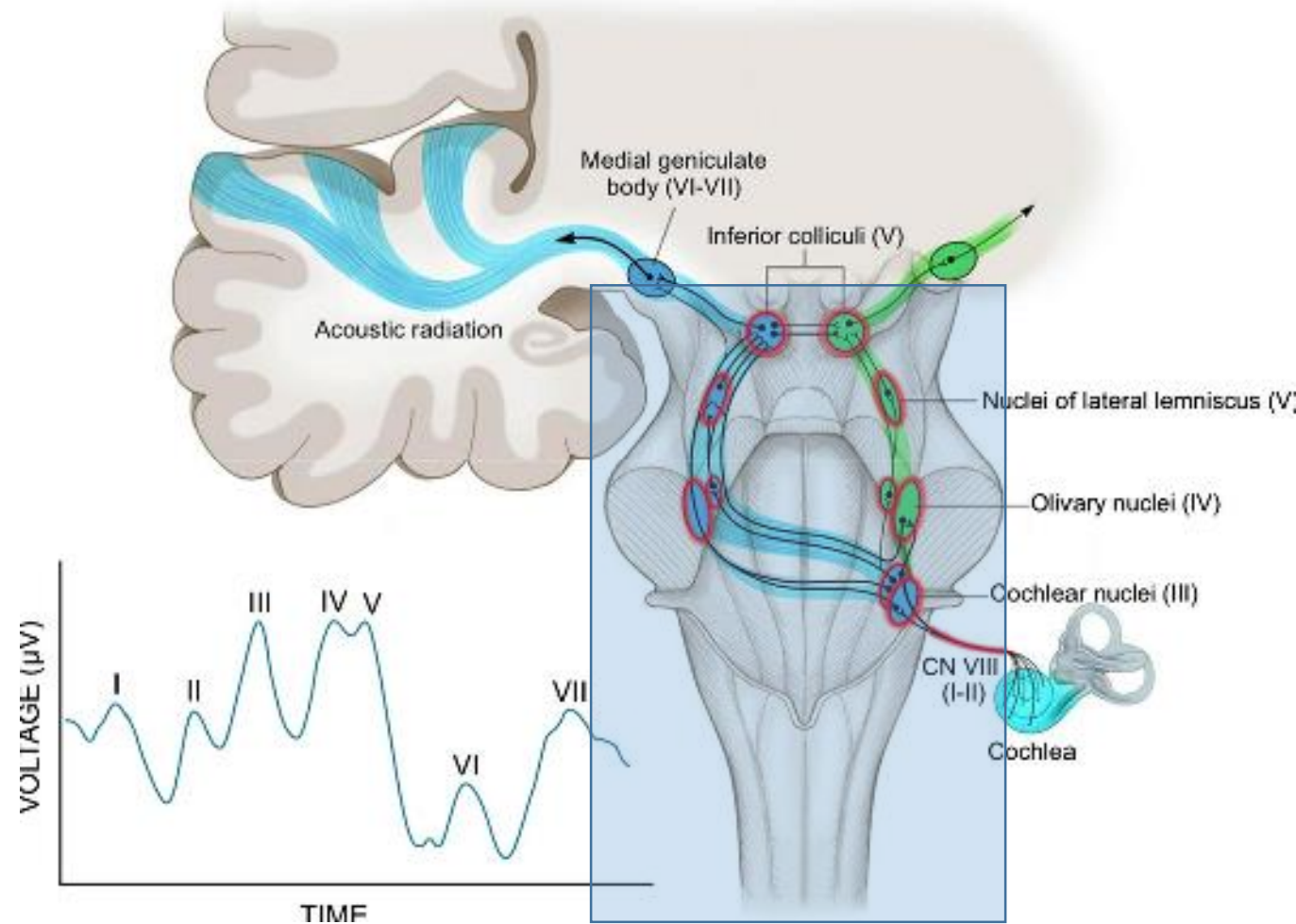
Brief Review of brainstem anatomy

The portion of the brain that includes the medulla, pons, midbrain, and cerebellum.

What structures does the brainstem include?

Auditory nuclei:

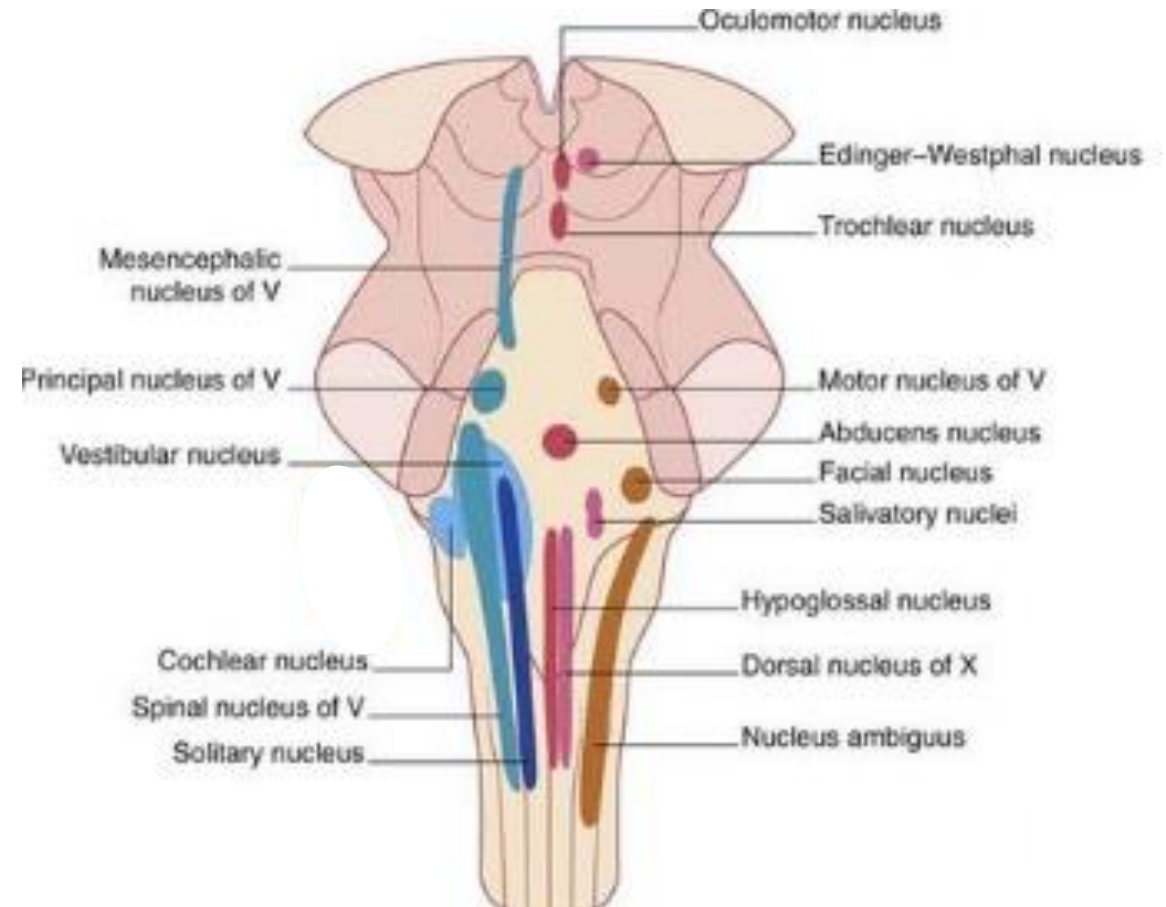
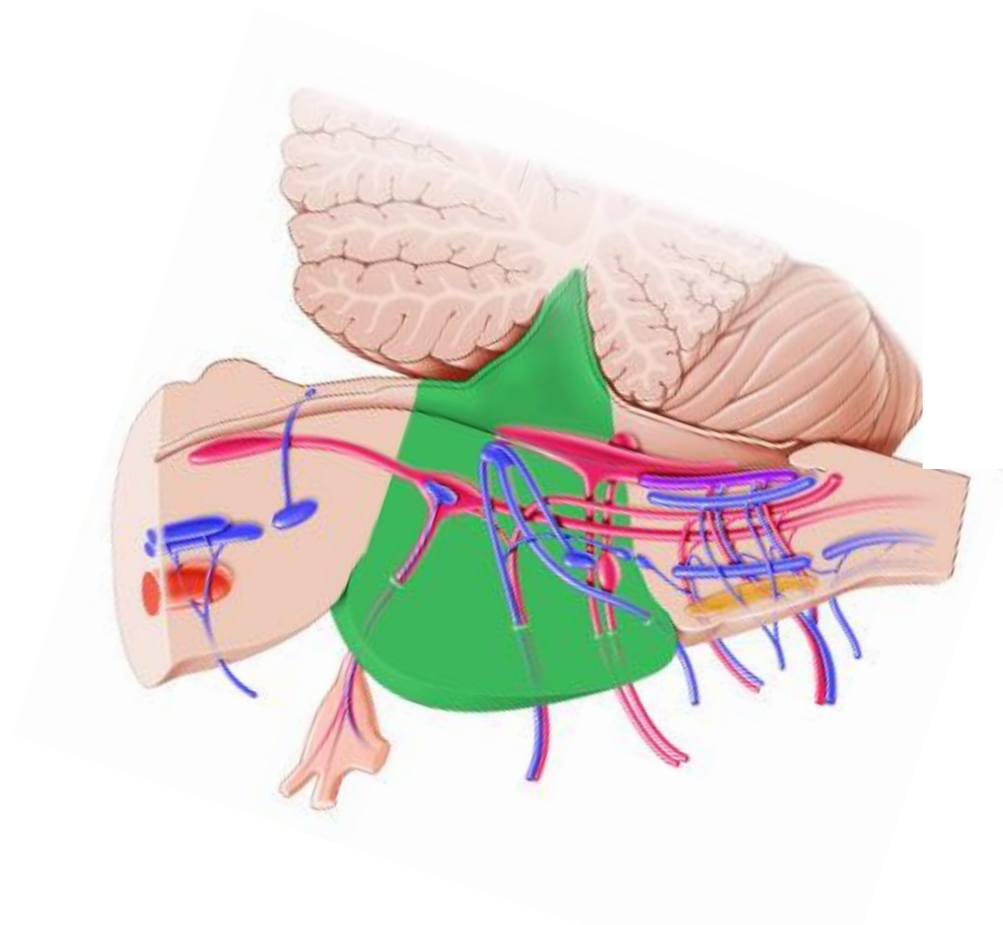
- Cochlear nuclei
- Inferior colliculi
- Nuclei of the lateral lemniscus
- Superior olivary complex



What structures does the brainstem include?

Cranial Nerve nuclei

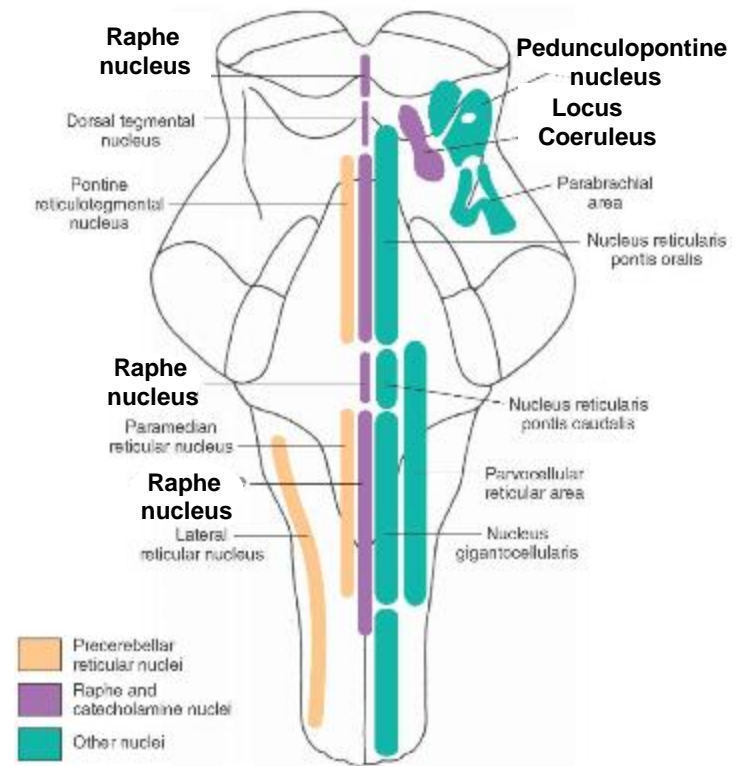
Cranial nerve nuclei



What structures does the brainstem include?

Nuclei of the Reticular Activating System

- Locus coeruleus (arousal, wakefulness)
- Pedunculopontine nucleus (PPN)(attention)
- Raphe nuclei (mood)



What structures does the brainstem include?

--Somatosensory nucleus (cuneate) from the neck and trunk

--Numerous other nuclei involved in the control of:
homeostatic and autonomic functions:

sleep

wakefulness

control of heart

breathing

visceral functions

Part 1: The brainstem as a tinnitus generator

Animal studies continually show disturbances in the level and pattern of resting (spontaneous) neural activity of brainstem auditory nuclei following manipulations that cause tinnitus:

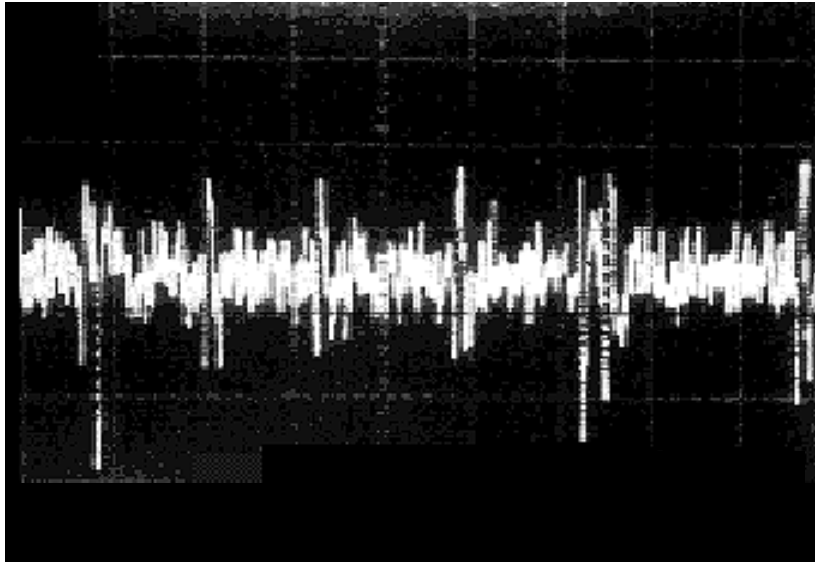
- **Increased firing rates (hyperactivity)**
 - **Increased bursting activity**
 - **Increased neural synchrony**

Features of abnormal spontaneous activity:

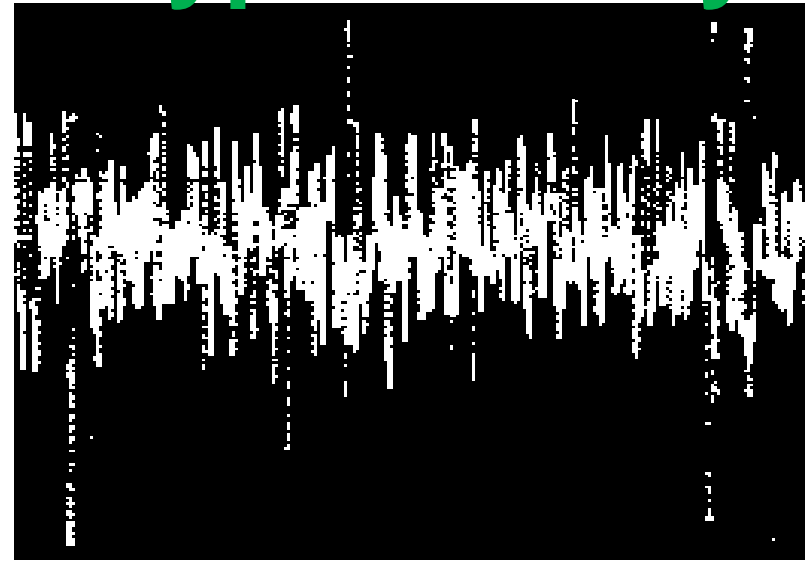
- Originates in the Cochlear Nucleus (CN) and Inferior Colliculus (IC)
 - Is relayed to higher levels of the pathway
 - It is a chronic condition
 - Correlates with behavioral evidence of tinnitus
- Widely believed to contribute to the percepts of tinnitus

What does this tinnitus-producing hyperactivity look like?

Hyperactivity

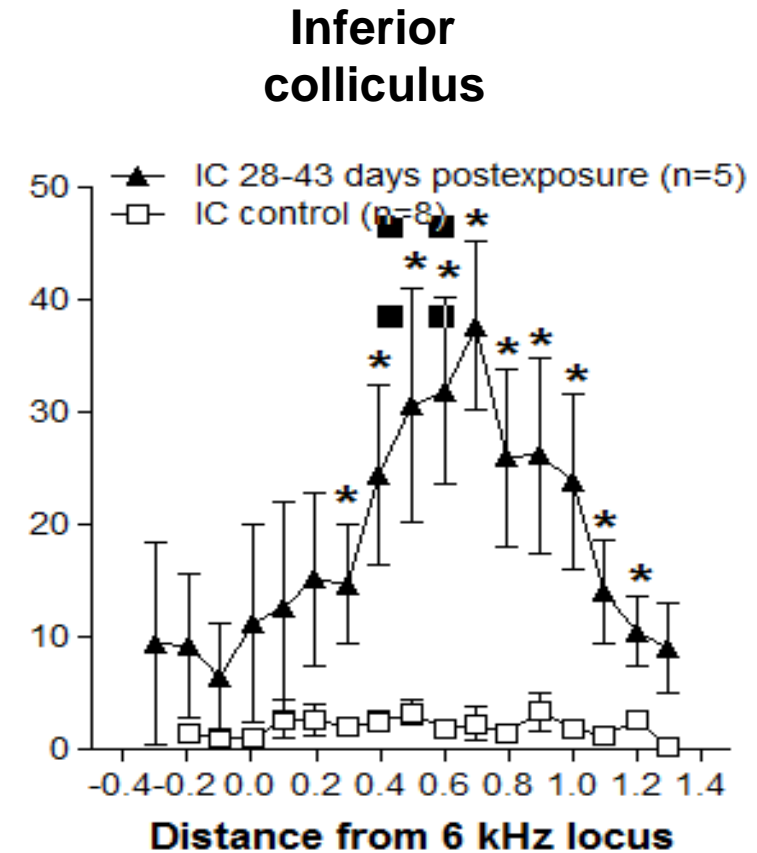
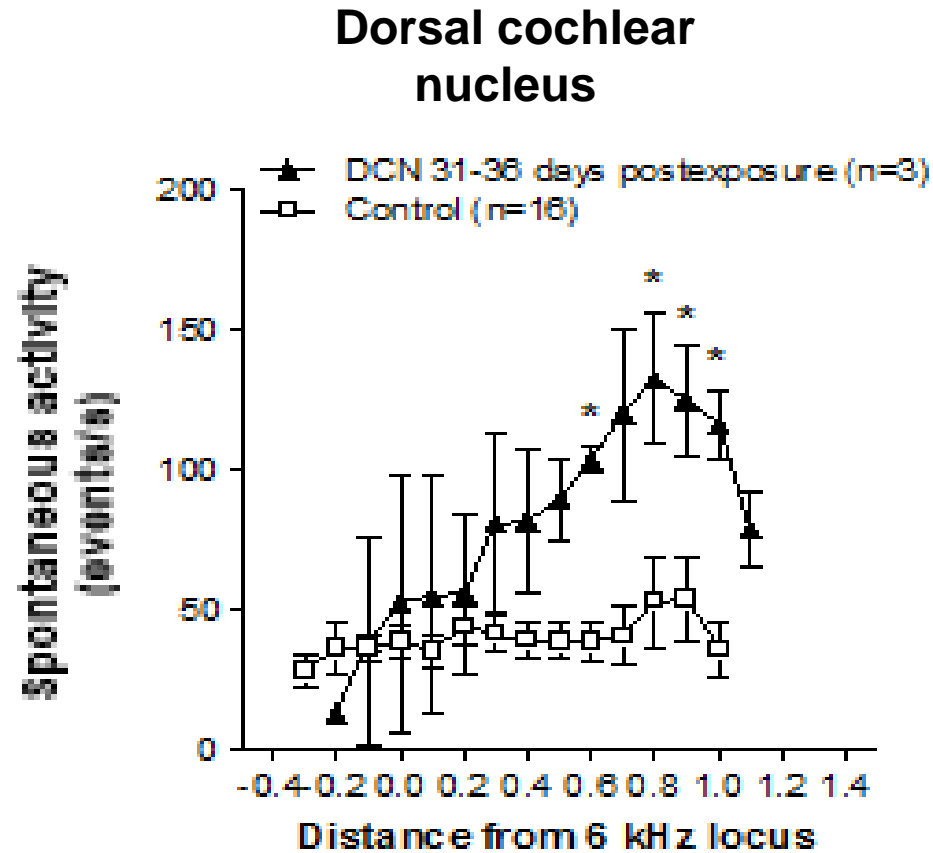


normal spontaneous activity



activity after noise exposure

Mapping studies of hyperactivity reveal a distinct peak in the high frequency part of the tonotopic range



**Increased resting state activity
(hyperactivity) is also found in brainstem
auditory nuclei of humans with tinnitus**

Development/Plasticity/Repair

The Relation between Perception and Brain Activity in Gaze-Evoked Tinnitus

Margriet J. van Gendt,^{1*} Kris Boyen,^{1,2*} Emile de Kleine,^{1,2} Dave R.M. Langers,^{1,2} and Pim van Dijk^{1,2}

¹Department of Otorhinolaryngology/Head and Neck Surgery, University of Groningen, University Medical Center Groningen, 9700 RB Groningen, The Netherlands and ²Graduate School of Medical Sciences, Research School of Behavioural and Cognitive Neurosciences, University of Groningen, 9700 RB Groningen, The Netherlands.

Tinnitus is a phantom sound percept that can be severely disabling. Its pathophysiology is poorly understood, partly due to the inability to objectively measure neural correlates of tinnitus. Gaze-evoked tinnitus (GET) is a rare form of tinnitus that may arise after vestibular schwannoma removal. Subjects typically describe tinnitus in the deaf ear on the side of the surgery that can be modulated by peripheral eye gaze. This phenomenon offers a unique opportunity to study the relation between tinnitus and brain activity. We used functional magnetic resonance imaging in humans to show that in normal-hearing control subjects, peripheral gaze results in inhibition of the auditory cortex, but no detectable response in the medial geniculate body (MGB) and inferior colliculus (IC). In patients with GET, peripheral gaze (1) reduced the cortical inhibition, (2) inhibited the MGB, and (3) activated the IC. Furthermore, **increased tinnitus loudness is represented by increased activity in the cochlear nucleus (CN) and IC** and reduced inhibition in the auditory cortex (AC). The increase of CN and IC activity with peripheral gaze is consistent with models of plastic reorganization in the brainstem following vestibular schwannoma removal. The activity decrease in the MGB and the reduced inhibition of the AC support a model that attributes tinnitus to a dysrhythmia of the thalamocortical loop, leading to hypometabolic theta activity in the MGB. Our data offer the first support of this loop hypothesis of tinnitus, independent of the initial experiments that led to its formulation.

ORIGINAL ARTICLE

Functional imaging of unilateral tinnitus using fMRI

C.P. LANTING^{1,2}, E. DE KLEINE^{1,2}, H. BARTELS^{1,2} & P. VAN DIJK^{1,2}

¹*Department of Otorhinolaryngology/Head and Neck Surgery, University Medical Center Groningen and* ²*Faculty of Medical Sciences, School of Behavioral and Cognitive Neurosciences, University of Groningen, Groningen, The Netherlands*

Abstract

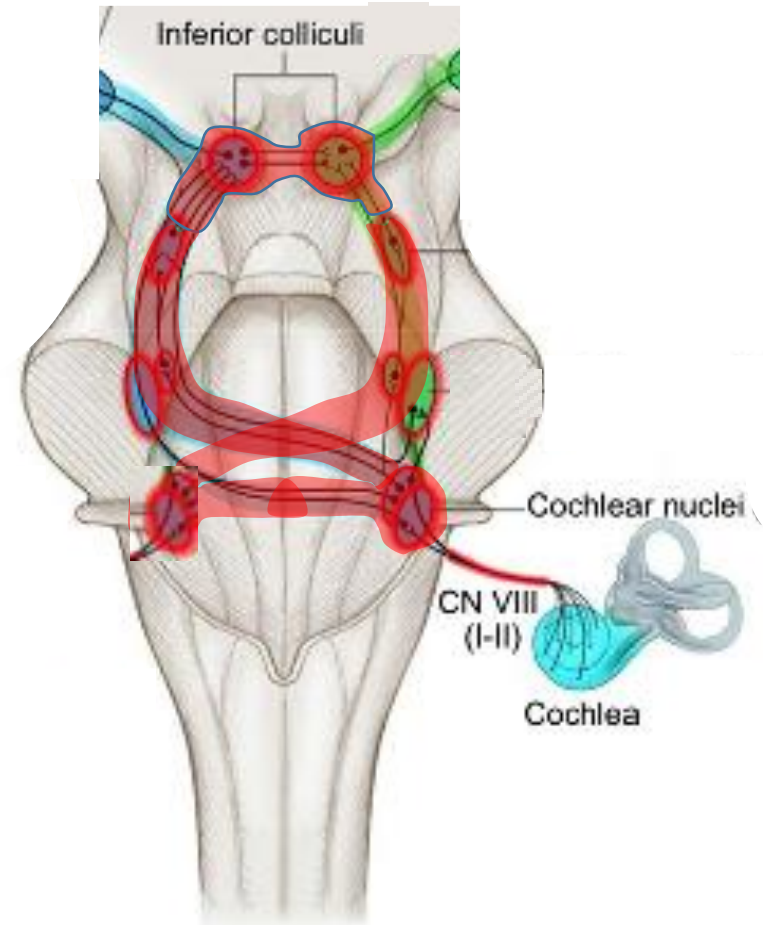
Conclusions. This article shows that the inferior colliculus plays a key role in unilateral subjective tinnitus. **Objectives.** The major aim of this study was to determine tinnitus-related neural activity in the central auditory system of unilateral tinnitus subjects and compare this to control subjects without tinnitus. **Subjects and methods.** Functional MRI (fMRI) was performed in 10 patients (5 males) with unilateral tinnitus (5 left-sided, 5 right-sided) and 12 healthy subjects (6 males); both groups had normal hearing or mild hearing loss. fMRI experiments were performed using a 3T Philips Intera Scanner. Auditory stimuli were presented left or right and consisted of dynamically rippled broadband noise with a sound pressure level of 40 or 70 dB SPL. The responses of the inferior colliculus and the auditory cortex to the stimuli were measured. **Results.** The response to sound in the inferior colliculus was elevated in tinnitus patients compared with controls without tinnitus.

Keywords: fMRI, tinnitus, central auditory system, auditory cortex, inferior colliculus

Brainstem tinnitus core

Auditory nuclei:

- Cochlear nuclei
- Inferior colliculi

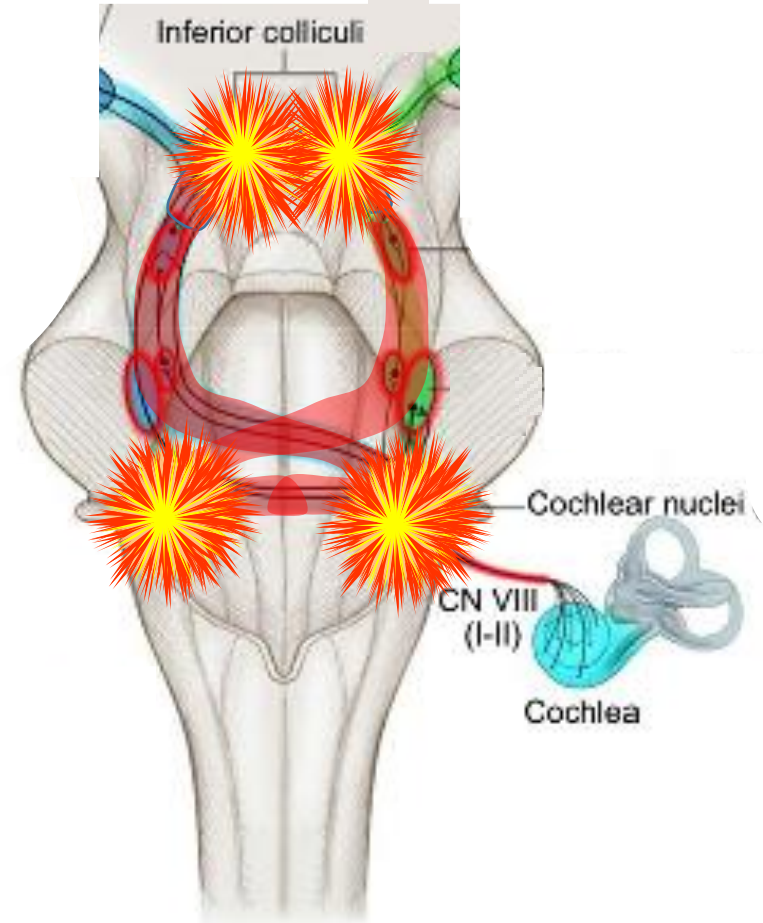


Tinnitus Generators (red)

Brainstem tinnitus core

Auditory nuclei:

- Cochlear nuclei
- Inferior colliculi



Tinnitus Generators (red)

Part 2: The brainstem as a tinnitus modulator

What is meant by tinnitus modulation?

Tinnitus modulation: The process by which the perceptual attributes of tinnitus can be actively regulated or varied over time.

What controls these modulations?

Modulations are under the control of neural pathways that feed back and provide input to the core tinnitus generators.

Origins of these modulatory pathways:

AUDITORY

- Superior olivary complex
- Inferior colliculi
- Nuclei of the lateral lemniscus

NON-AUDITORY

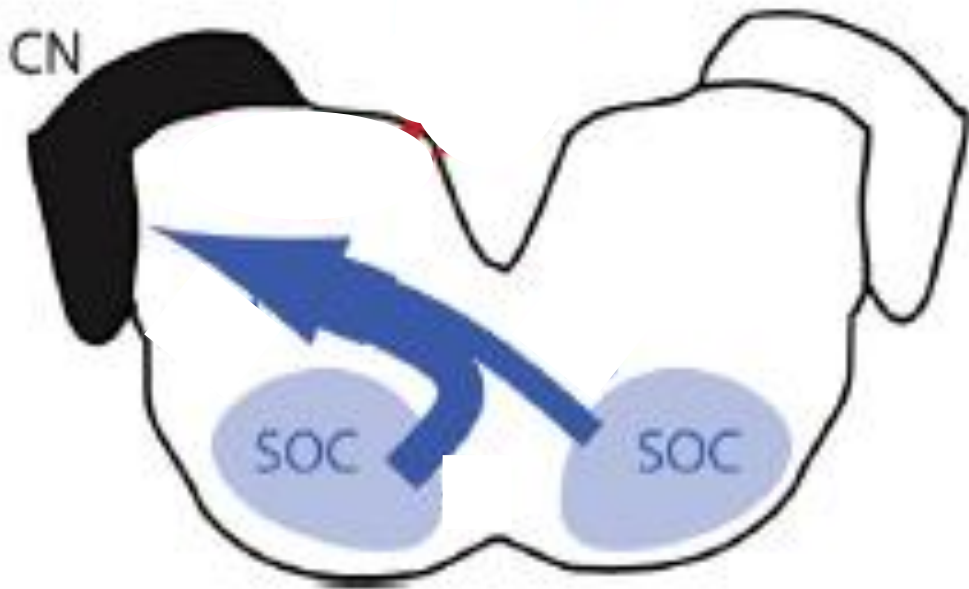
- Somatosensory nerve & nuclei
- Locus coeruleus
- PMT (in midbrain)
- Raphe nucleus

Examples of tinnitus modulations by auditory brainstem centers

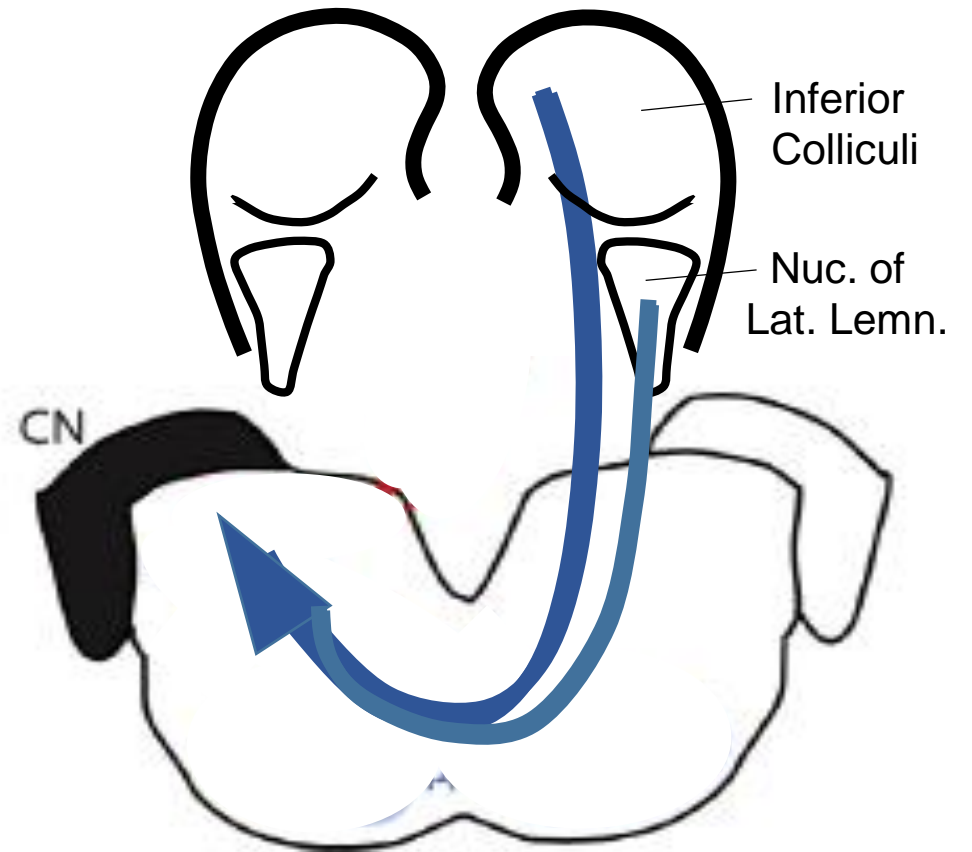
- **Contralateral masking** of tinnitus with noise (Feldman, 1981)
- **Day to day fluctuations** of tinnitus loudness and pitch (Penner, 1983)
- **Residual inhibition:** transient suppression of tinnitus following presentation of sound (Feldman, 1971)

Auditory brainstem pathways that likely play a role in the modulation of tinnitus

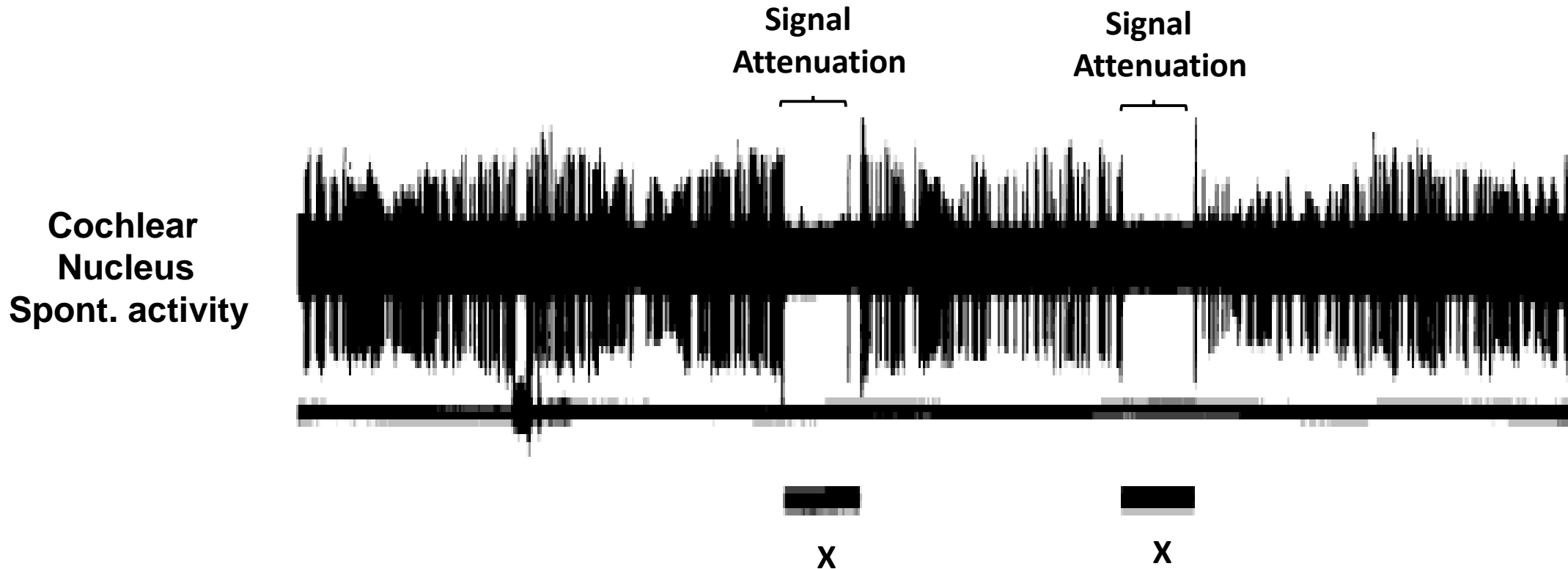
Olivocochlear pathway



Colliculo-cochlear and Lemnisco-cochlear pathways

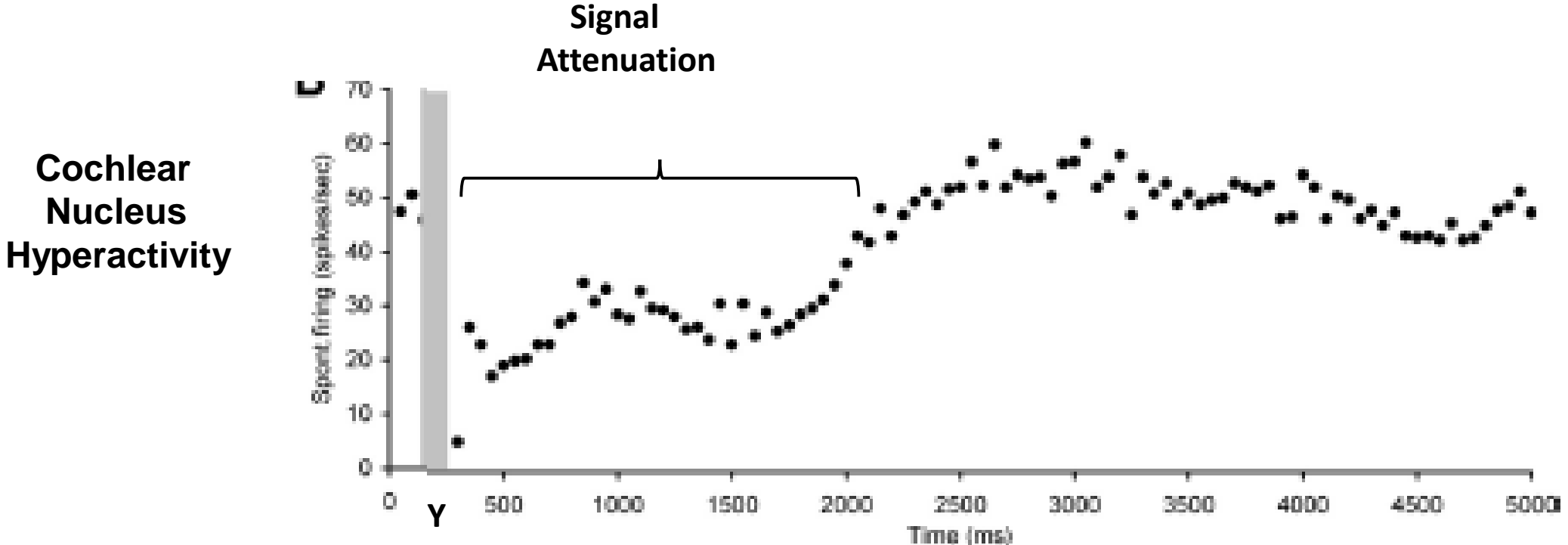


Modulation of spontaneous activity by lemnisco-cochlear pathway



X= Stimulation of contralateral nucleus of lateral lemniscus

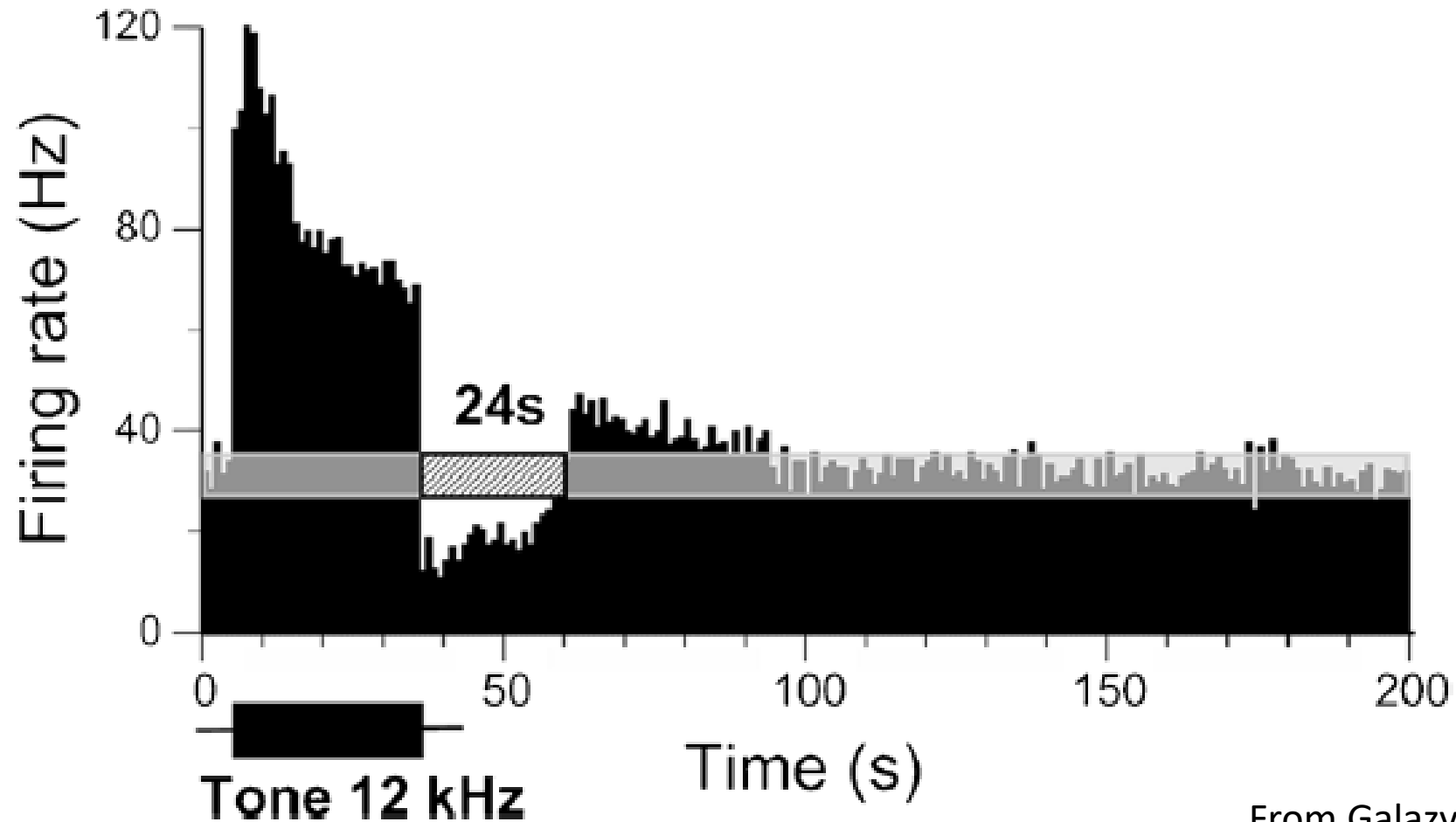
Modulation of hyperactivity by olivocochlear pathway could underlie day to day fluctuations of tinnitus:



Y= Stimulation of olivocochlear bundle

From Mulders et al., 2010

Neural correlate of residual-inhibition in the inferior colliculus



From Galazyuk et al. (2017)

Examples of tinnitus modulations by non-auditory brainstem centers:

1. Somatically-induced changes in tinnitus (Somatic tinnitus)
2. Attention-induced changes in tinnitus
3. Tinnitus fluctuations with change in affective state (emotion/mood)

Somatically-induced tinnitus modulations (Somatic tinnitus):

A form of tinnitus whose attributes (pitch, loudness, etc.) can be varied by manipulations of muscles in the head and upper neck

- **Incidence: 68-79% of patients with tinnitus.**
- **Effective manipulations: Neck muscle contractions, jaw clenching, sliding of jaw to one side.**
- **Laterality: When tinnitus is unilateral, the most effective manipulations are on the side ipsilateral to the tinnitus.**

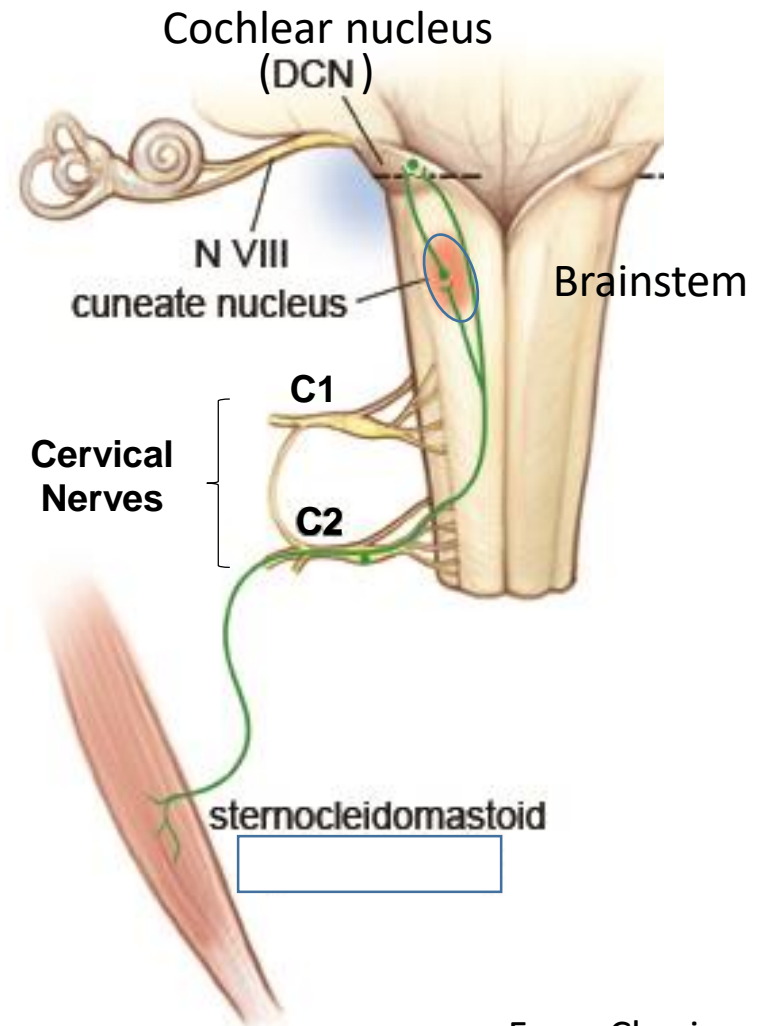
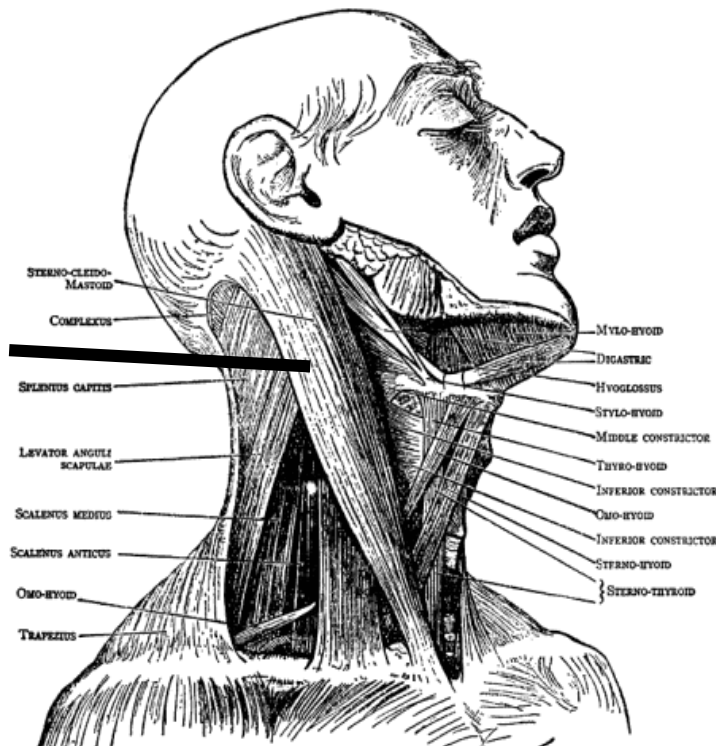
Brainstem pathways implicated in somatic modulations of tinnitus

- Cervical nerves and nucleus
- Trigeminal nerve and nucleus

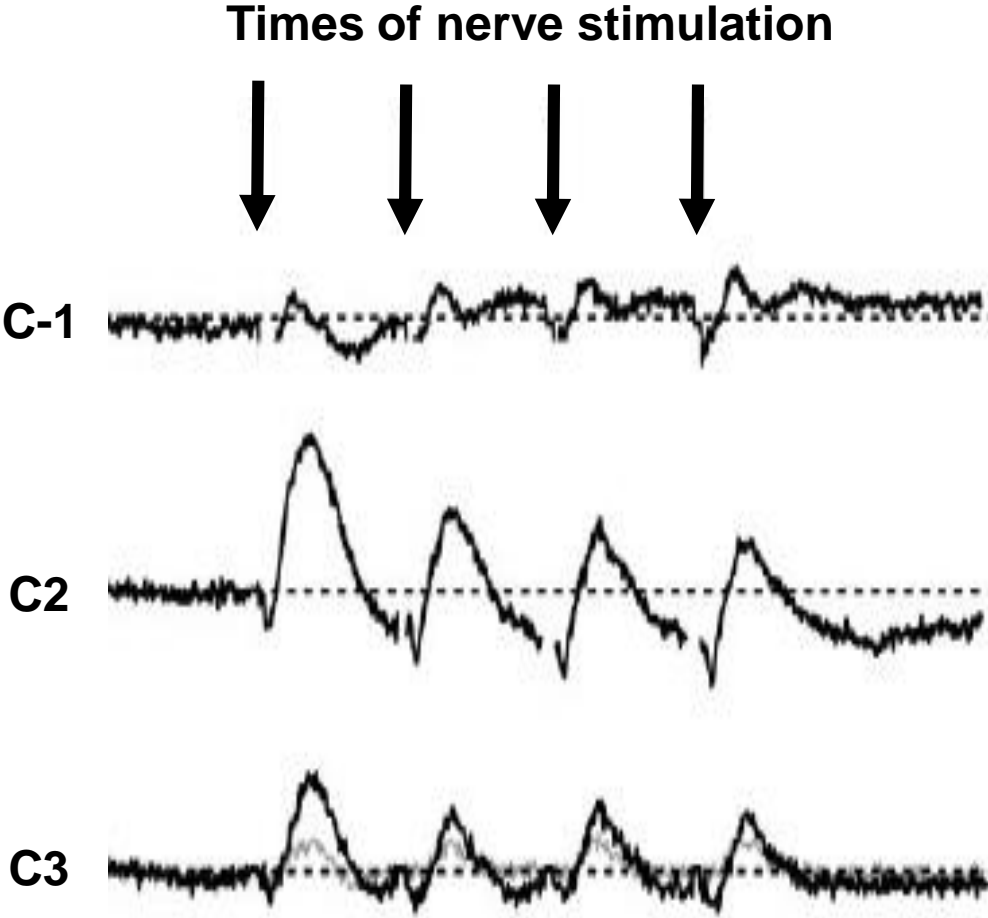
Modulatory pathways to the cochlear nucleus from the cervical nerve (C2)

Neck muscles

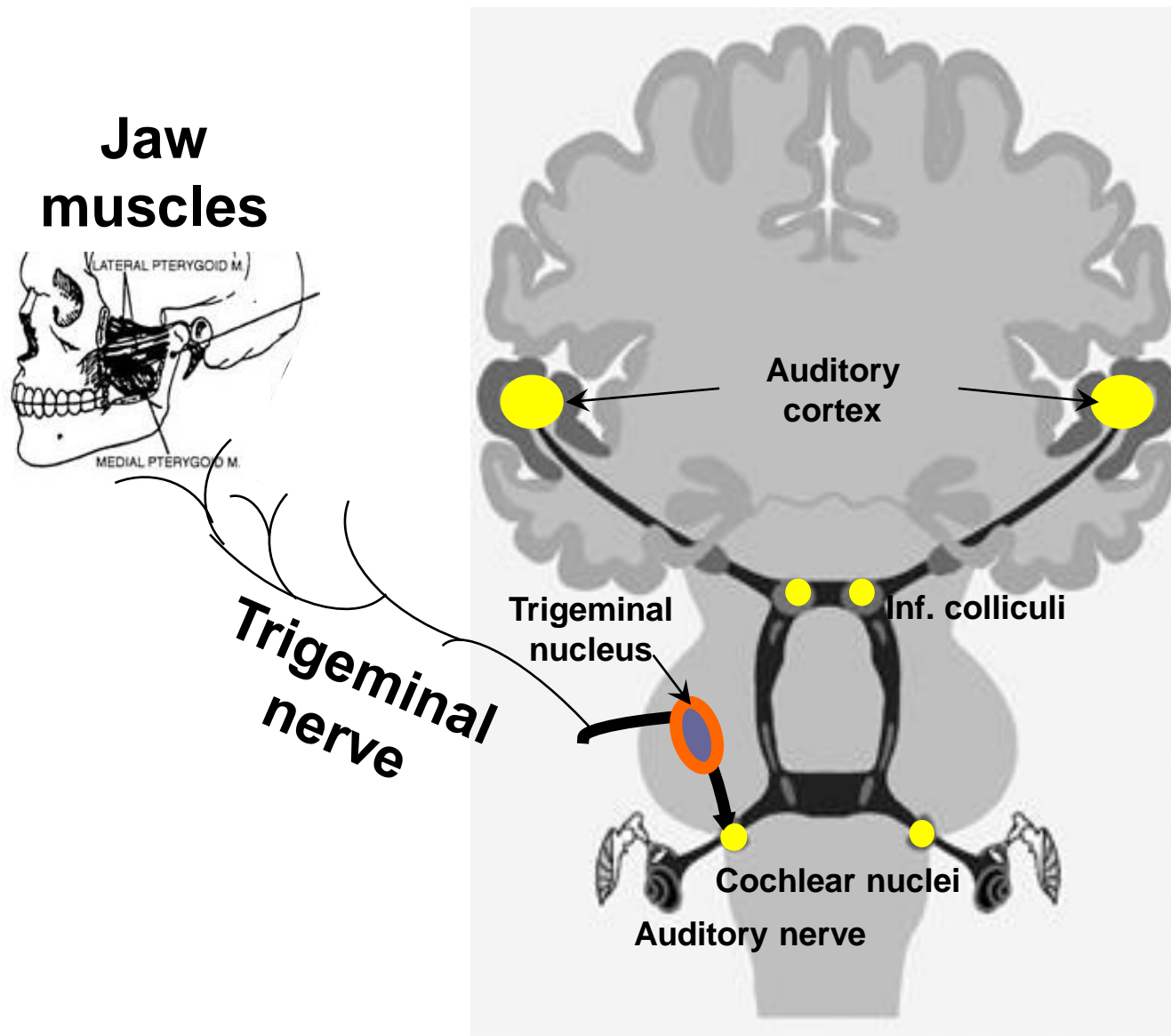
Sternocleidomastoid muscle



Cochlear nucleus responses to cervical nerve stimulation

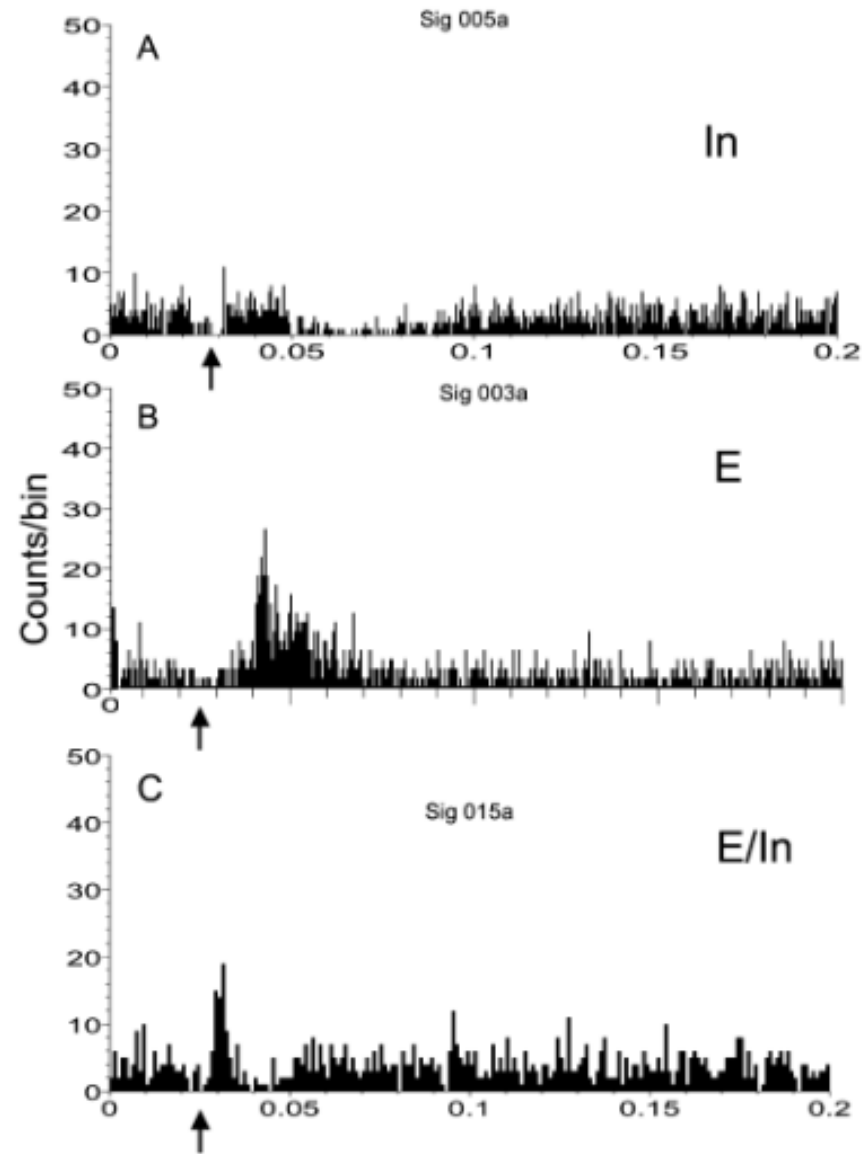


Modulatory pathways to the cochlear nucleus from the trigeminal nerve and nucleus



Modified after sketch from
Eaton-Peabody Laboratory

Cochlear nucleus responses to trigeminal nerve stimulation



From Shore (2005)

2. Attention-induced modulations of tinnitus

Variations in the perceived severity of tinnitus that accompany shifts in the focus of attention

Clinical findings:

Awareness of tinnitus decreases when focus of attention is on activities that are absorbing (Roberts et al., 2013).

Tinnitus severity/annoyance can be reduced with attentional training (Searchfield et al., 2007; Eysel-Gosepath et al., 2004; Spiegel et al., 2015).

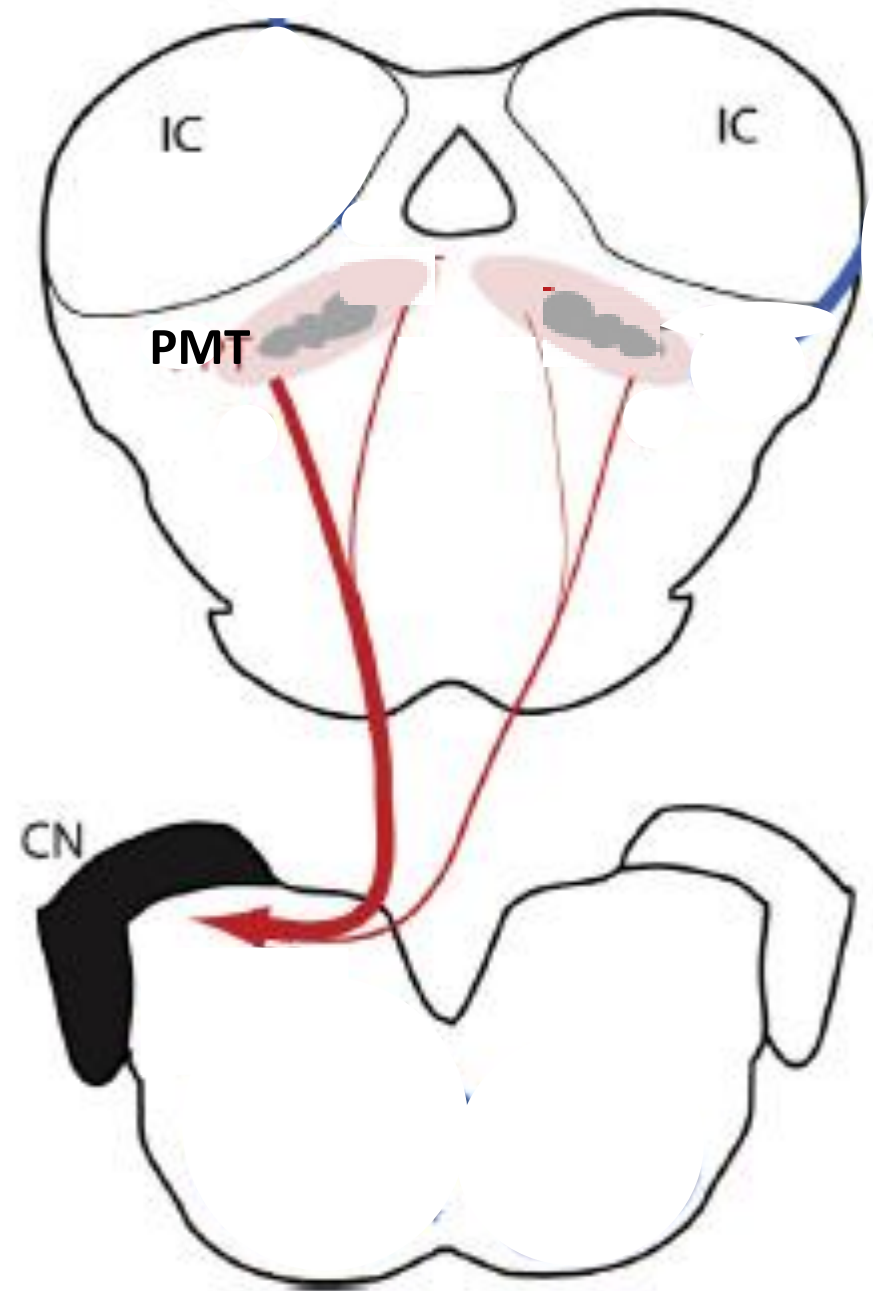
Brainstem areas that may participate in attention-induced modulations of tinnitus

PMT in midbrain

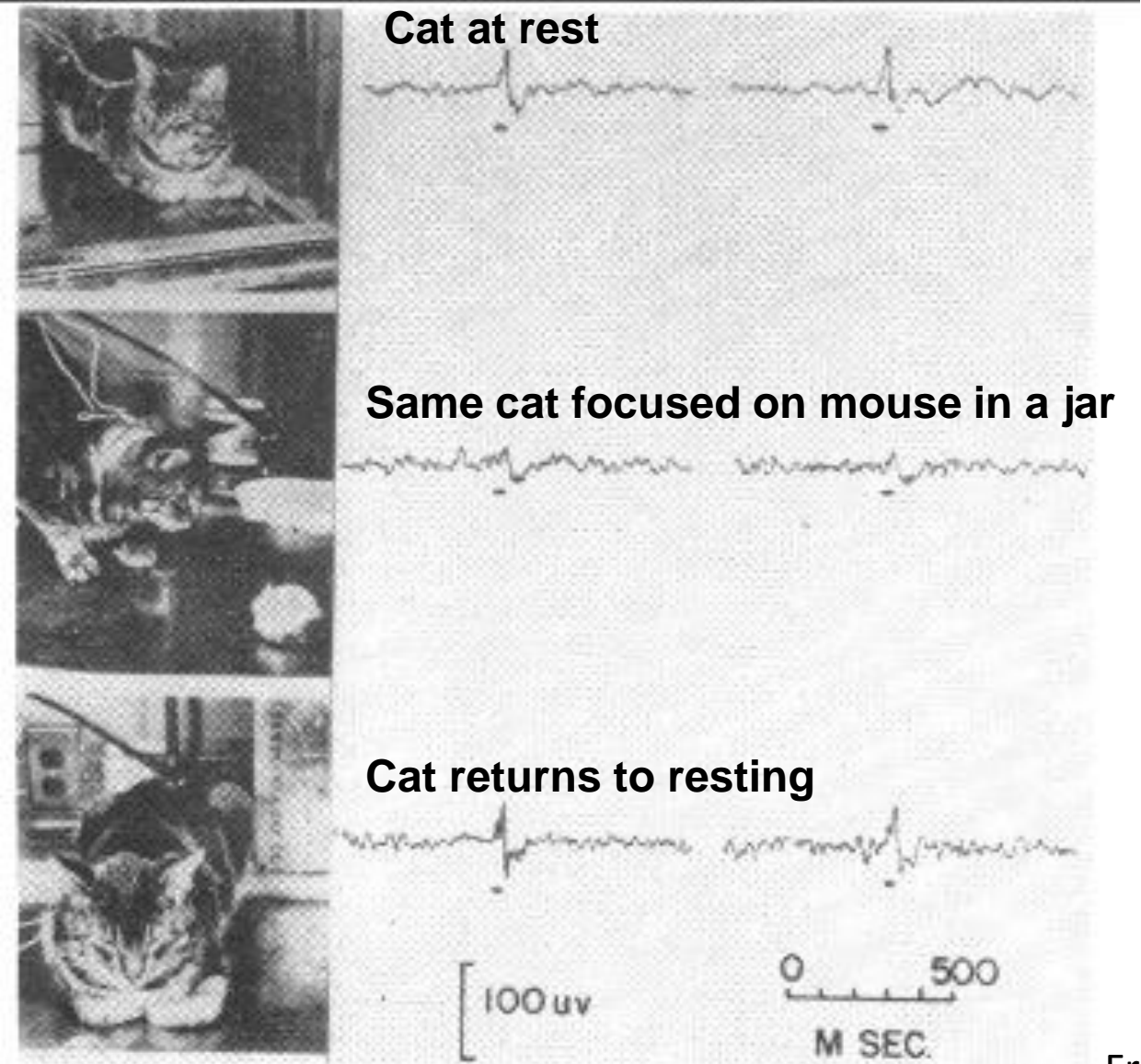
Locus coeruleus (LC)

Brainstem pathways participating in attention gating that connect with tinnitus generators

IC-inferior colliculi
CN-cochlear nucleus
PMT-pontomesencephalic tegmentum



Cochlear nucleus activity is modulated during changes in attentional state



From Hernandez-Peon et al. (1956)

3. Emotional state-induced tinnitus modulation

Variations in the severity of tinnitus associated with changes in levels of stress, anxiety, and depression

- **The severity of chronic tinnitus is highly correlated with anxiety, depression, stress, and emotional exhaustion (Folmer et al., 2001; Langguth et al., 2011, Hebert et al., 2012; Mazurek et al., 2015)**
- **Depressive symptoms play a key role in facilitating the chronic nature of tinnitus and may underpin the onset and continued reinforcement of the two pathways of a 'vicious cycle' (Trevis et al. (2016).**

Tinnitus Severity Is Reduced with Reduction of Depressive Mood – a Prospective Population Study in Sweden

Sylvie Hébert^{1*}, Barbara Canlon⁴, Dan Hasson^{2,4}, Linda L. Magnusson Hanson², Hugo Westerlund², Töres Theorell^{2,3}

1 École d'orthophonie et d'audiologie, Faculté de médecine, Université de Montréal, BRAMS, International Laboratory for Brain, Music, and Sound Research, and Centre de recherche de l'Institut universitaire de gériatrie de Montréal, Montréal, Québec, Canada, **2** Stress Research Institute, Stockholm University, Stockholm, Sweden, **3** Department of Public Health, Karolinska Institute, Stockholm, Sweden, **4** Department of Physiology and Pharmacology, Karolinska Institute, Stockholm, Sweden

Abstract

Tinnitus, the perception of sound without external source, is a highly prevalent public health problem with about 8% of the population having frequently occurring tinnitus, and about 1–2% experiencing significant distress from it. Population studies, as well as studies on self-selected samples, have reported poor psychological well-being in individuals with tinnitus. However, no study has examined the long-term co-variation between mood and tinnitus prevalence or tinnitus severity. In this study, the relationship between depression and tinnitus prevalence and severity over a 2-year period was examined in a representative sample of the general Swedish working population. **Results show that a decrease in depression is associated with a decrease in tinnitus prevalence, and even more markedly with tinnitus severity.** Hearing loss was a more potent predictor than depression for tinnitus prevalence, but was a weaker predictor than depression for tinnitus severity. In addition, there were sex differences for tinnitus prevalence, but not for tinnitus severity. This study shows a direct and long-term association between tinnitus severity and depression.

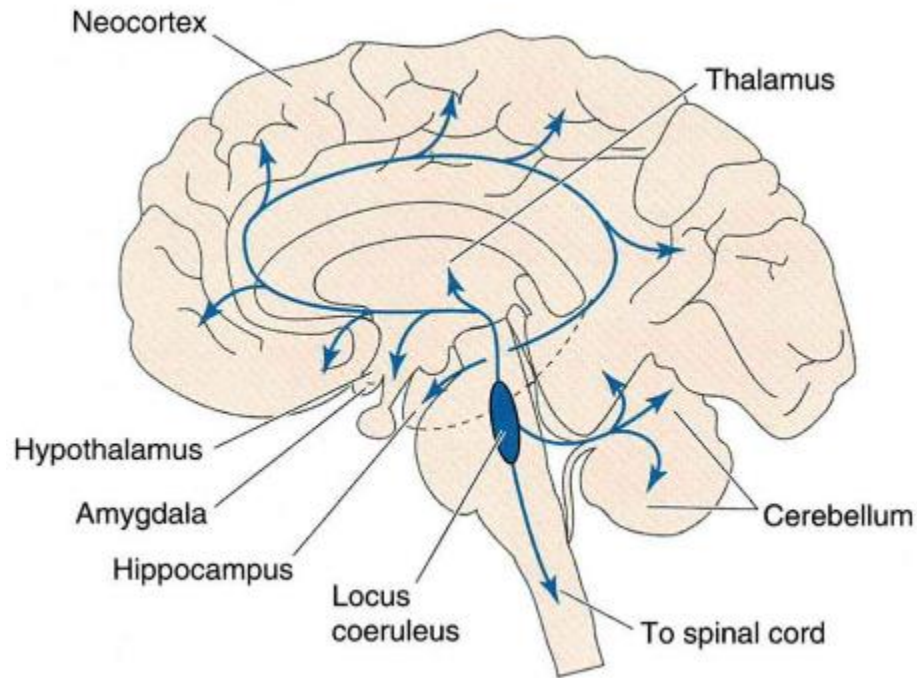
Brainstem centers that may participate in emotional state-induced modulations of tinnitus

Locus coeruleus (LC)

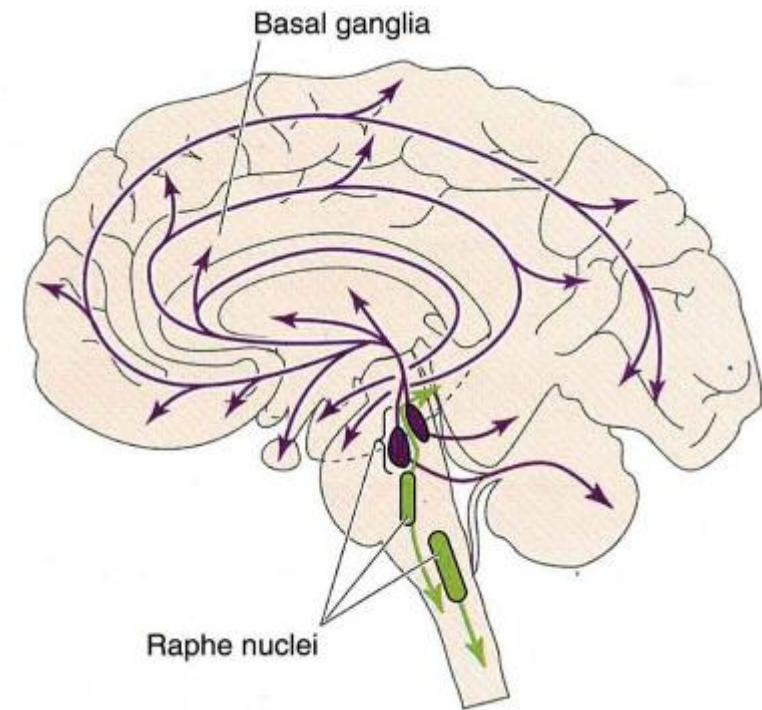
Dorsal Raphe Nucleus

Brainstem centers that participate in signaling changes in emotional state:

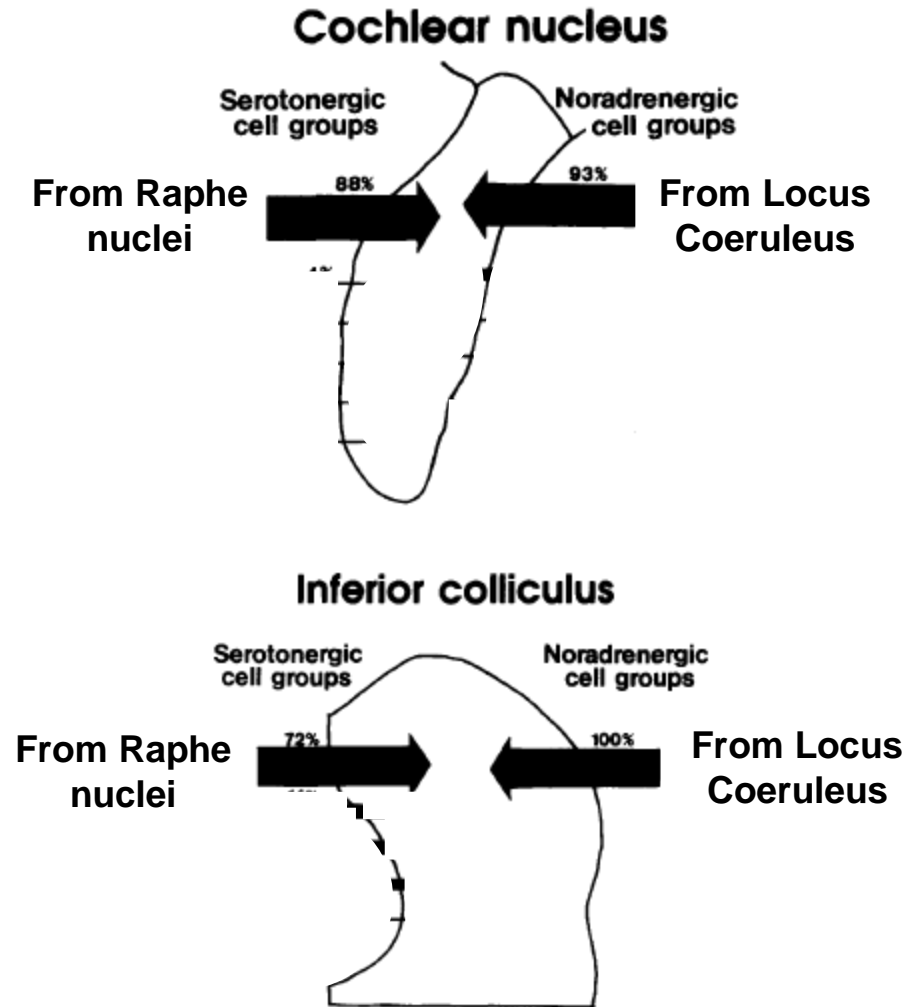
Locus coeruleus



Raphe nuclei



Inputs from Locus Coeruleus and Raphe Nuclei to the tinnitus generator sites



Main features of the Locus Coeruleus (LC) related to tinnitus modulation

- The LC is the brain's principal source of noradrenalin
- It releases noradrenalin in response to stressful stimuli
- Boosts the level of activation of other brain areas
- Increases the level of alertness and wakefulness
- Enhances attentional focus and orientation to sensory stimuli
- Overactivation leads to anxiety and stress reactions
- Projects to all levels of the auditory system, including the tinnitus generator cells in the cochlear nucleus
- This projection suggests a possible role in amplification of tinnitus signals during periods of stress.

Main features of Dorsal Raphe Nucleus related to tinnitus modulation

- The brain's principal source of serotonin
- Role in depression
- Projects to the cochlear nucleus and inferior colliculus tinnitus generators
- Serotonin administered to the cochlear nucleus increases neural (spontaneous) activity
- This projection suggests a possible role in amplification of tinnitus signals during periods of stress
- Antidepressants often reduce the severity of tinnitus (Robinson, 2004, 2007).

Part 3-Brainstem's role in tinnitus comorbidities

What are the most common non-auditory comorbidities associated with tinnitus?

HEAD AND NECK DISORDERS (Folmer and Greist, 2003)

ANXIETY (Pattyn et al., 2016; Durai and Searchfield, 2016)

SLEEP DISORDERS (Izuhara et al., 2013; Hebert and Carrier, 2007)

DIFFICULTY CONCENTRATING (Newman et al., 1997; Tyler & Baker, 1983)

DEPRESSION (Temugan et al., 2016; Langguth et al., 2011)

**Why are these comorbidities so common
in tinnitus patients?**

The prevalence of comorbidities reflects, in part, underlying brainstem connections between generator and modulator sites

Comorbidities associated with tinnitus generally reflect interconnections between generator sites and modulator sites

Examples:

COMORBID DISORDER	BRAINSTEM NUCLEI	PRIMARY FUNCTION	DIRECT CONNECTIONS WITH CN-IC?
Head and neck disorders	somatosensory nuclei and cervical nerves	Sensations and motor control of head/neck muscles	Yes
Anxiety and stress related disorders Sleep disorders	Locus coeruleus	Anxiety/stress Control of sleep cycle	Yes
Difficulty concentrating	Cholinergic part of the Midbrain tegmentum	Arousal, Attention Sleep induction	Yes
Depression	Dorsal Raphe nucleus	Main source of serotonin, which controls mood	Yes

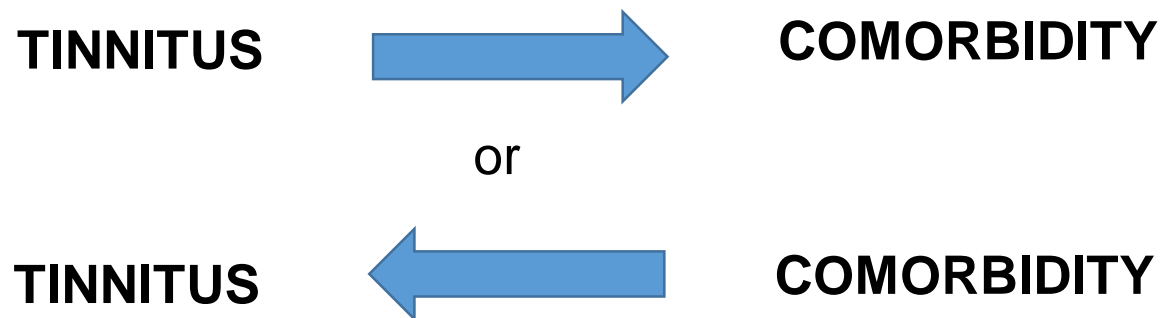
Tinnitus is not usually associated with disorders arising from brainstem nuclei not connected to tinnitus generators

Examples:

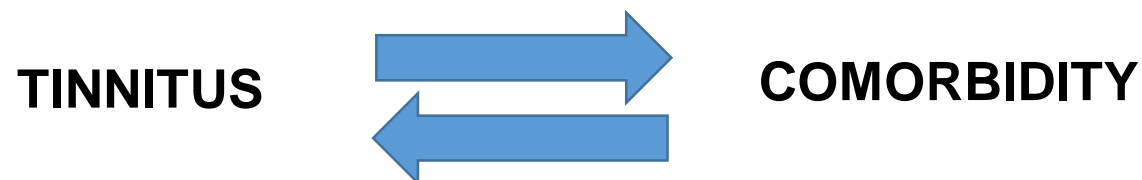
NON-COMORBID DISORDER	BRAINSTEM NUCLEI	PRIMARY FUNCTION	DIRECT CONNECTIONS WITH CN-IC?
Breathing abnormalities Heart Arrhythmias Gastroparesis	Nuclei of the vagus nerve	Control of visceral functions	No
Dysgeusia (taste abnormalities)	Solitary nucleus	Taste	No
Disorders of nasal mucosa, lacrima and salivary glands	Salivatory nucleus	Glandular secretions	No
Tongue movement disorders	Hypoglossal nucleus	Muscular control of tongue	No
Skin and muscle disorders below the neck	Gracile nucleus	Sensations/motor control of muscles of the trunk	No

Types of cause and effect relationships between tinnitus and its comorbidities

1. One way relationship:



2. Two-way relationship:



**Example of a comorbidity that has a one-way
cause and effect relationship with tinnitus:
Head or neck injury**

Chronic tinnitus resulting from head or neck injuries.

Folmer RL¹, Griest SE.

⊕ Author information

Abstract

OBJECTIVES: The main objectives were 1) to determine the percentage of cases of chronic tinnitus in a specialized clinic that resulted from head or neck injuries; 2) to describe the characteristics of this population; and 3) to compare patients with head or neck trauma with patients whose tinnitus onset was not associated with head or neck injuries.

STUDY DESIGN: Retrospective analysis of tinnitus clinic patient data.

METHODS: Detailed questionnaires were mailed to 2400 patients before their initial appointment at the Oregon Health and Science University Tinnitus Clinic (Portland, OR). All of the patients experienced and received treatment for chronic tinnitus. Patient data were entered into a database and later analyzed.

RESULTS: Two hundred ninety-seven patients (214 male and 83 female patients) reported that their chronic tinnitus started as a result of head or neck injuries. Compared with patients whose tinnitus onset was not associated with trauma, patients with tinnitus associated with head or neck trauma were younger; had better hearing thresholds; experienced headaches more frequently; reported greater difficulties with concentration, memory, and thinking clearly; were more likely to experience current depression, but not lifetime depression; rated their tinnitus as louder on a 1-to-10 scale; matched their tinnitus to louder sounds on the right side; and had higher Tinnitus Severity Index scores.

CONCLUSIONS: Tinnitus is a significant symptom that commonly occurs as a result of head or neck trauma. The fact that tinnitus resulting from head or neck injuries tends to be more severe (and is often accompanied by a greater number of co-symptoms) than tinnitus resulting from other causes should be taken into account by clinicians treating these patients.

PMID: 12792317 DOI: [10.1097/00005537-200305000-00010](https://doi.org/10.1097/00005537-200305000-00010)

[Indexed for MEDLINE]



TABLE I.

Types of Injuries and Associated Symptoms Reported by Head or Neck Trauma Patients.

Motor vehicle accidents	166 (56%)
Head injuries (with or without whiplash/neck injuries)	202 (68%)
Whiplash/neck injuries only	95 (32%)
Concussions	144 (48%)
Additional hearing loss (as a result of accident)	103 (35%)
Dizziness	175 (59%)
Skull fractures	37 (12%)
Vertebral fractures	22 (7%)

Only a one way cause and effect relationship between tinnitus and head and neck disorders

Tinnitus develops secondarily after the neck trauma



But, neither tinnitus nor its inducers cause or worsen the neck trauma



*Tinnitus generator sites (CN/IC) receive one way
input from modulator sites (cuneate nucleus)*

**HEAD OR
NECK INJURY**

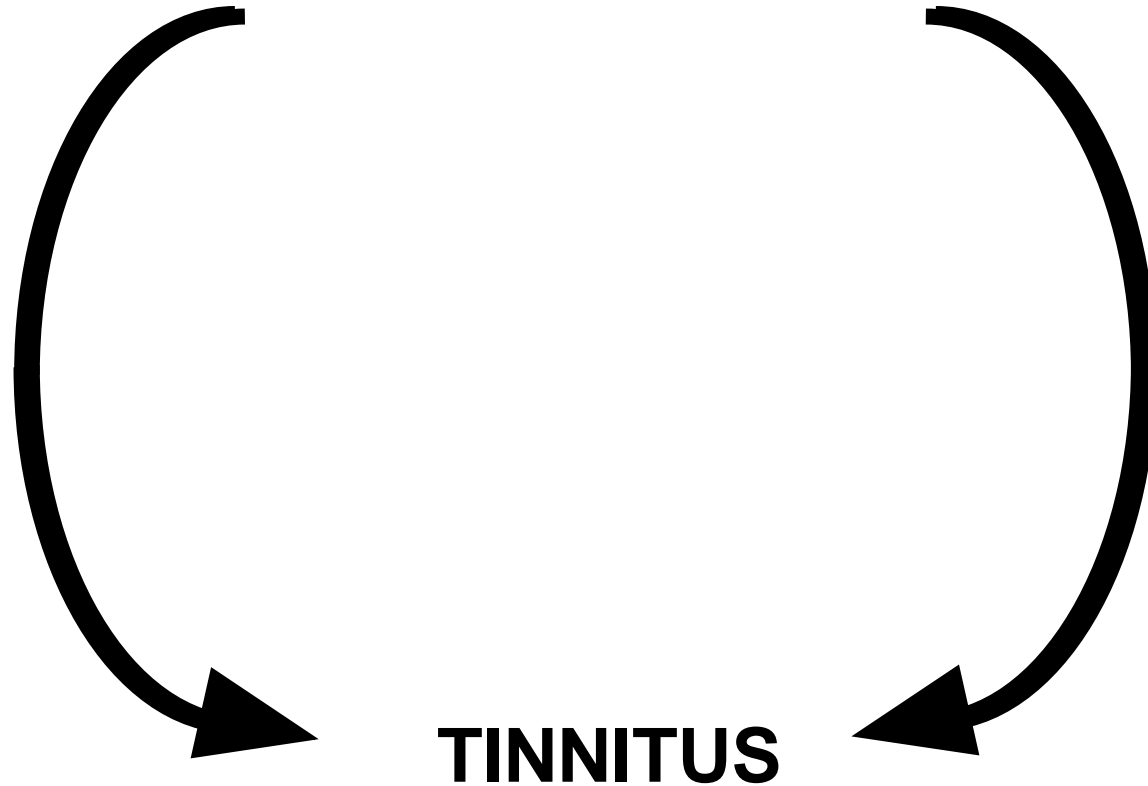
*Tinnitus generator sites (CN/IC) receive one way
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NECK INJURY**

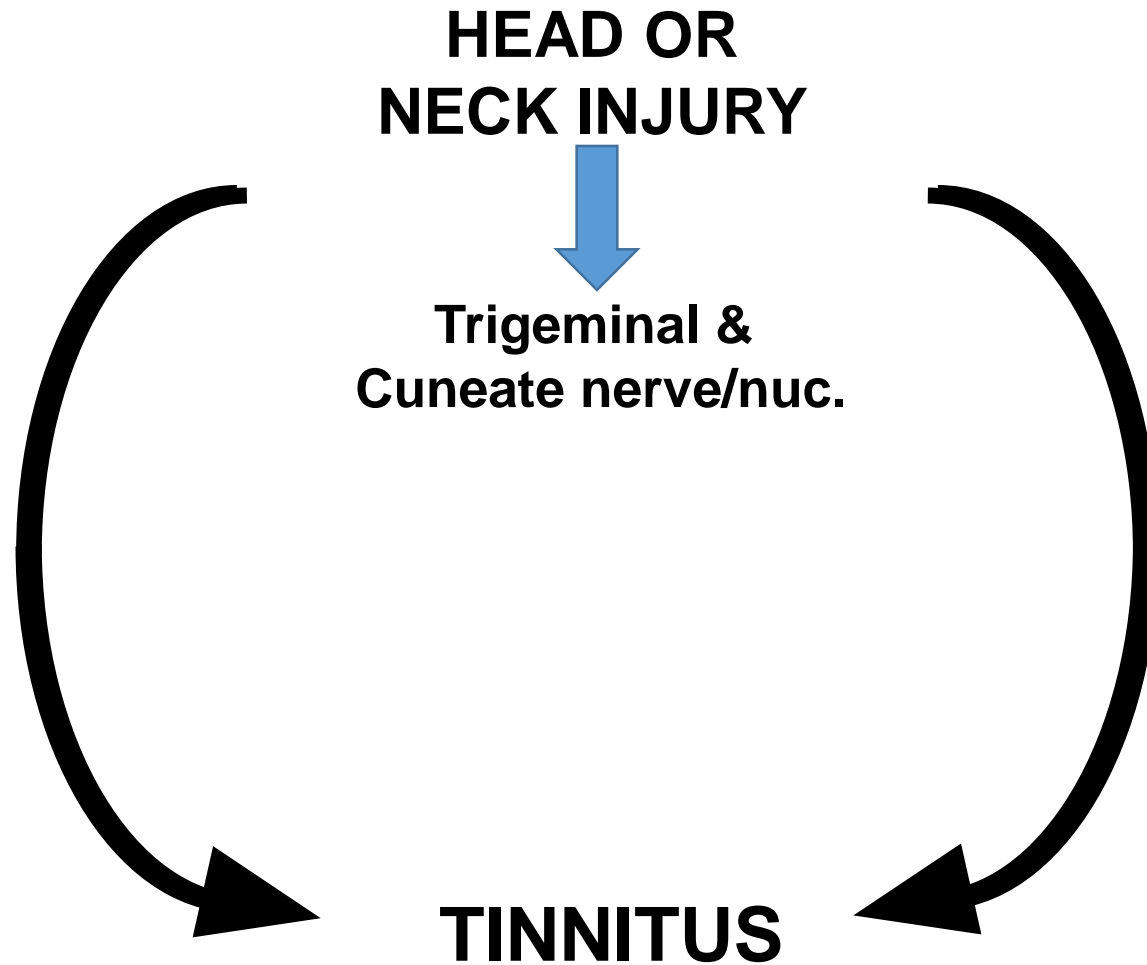
TINNITUS

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input from modulator sites (cuneate nucleus)*

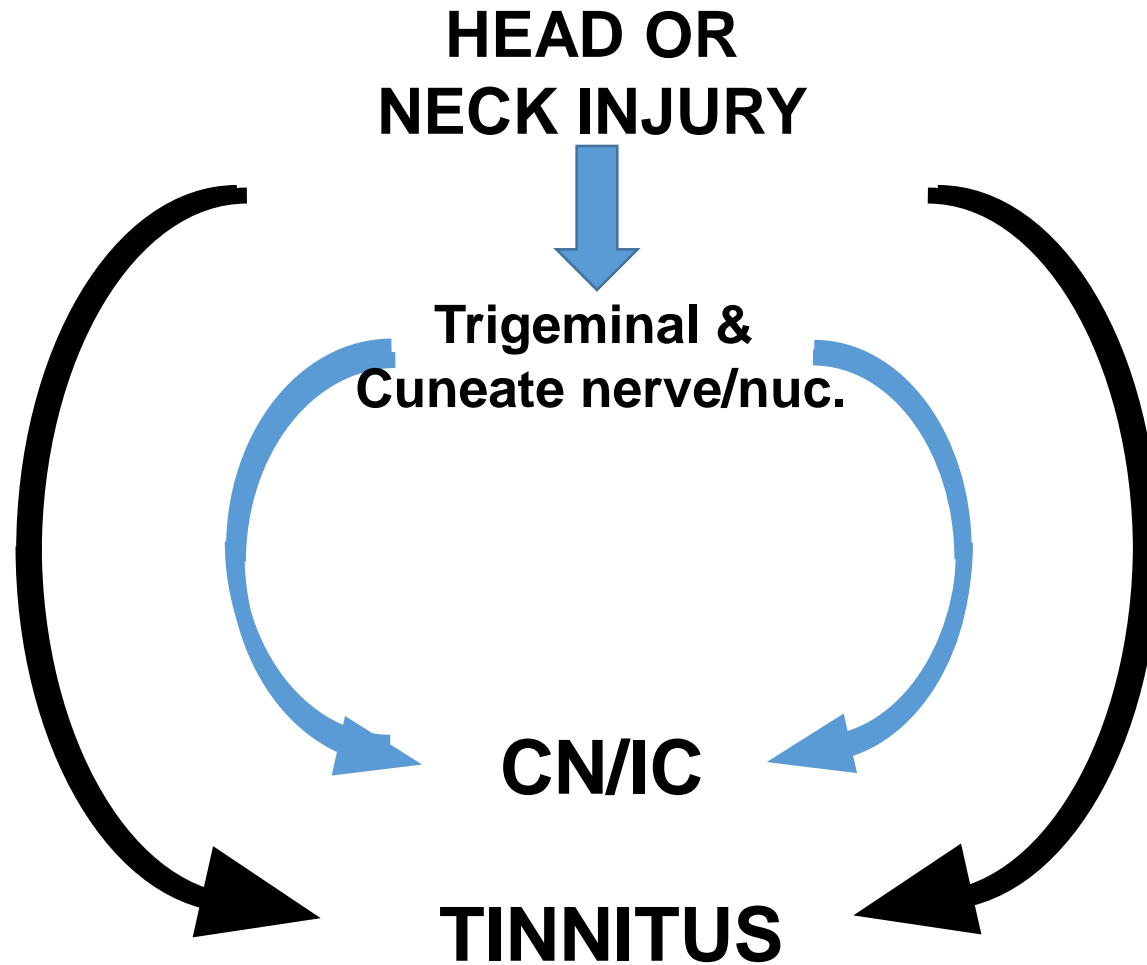
**HEAD OR
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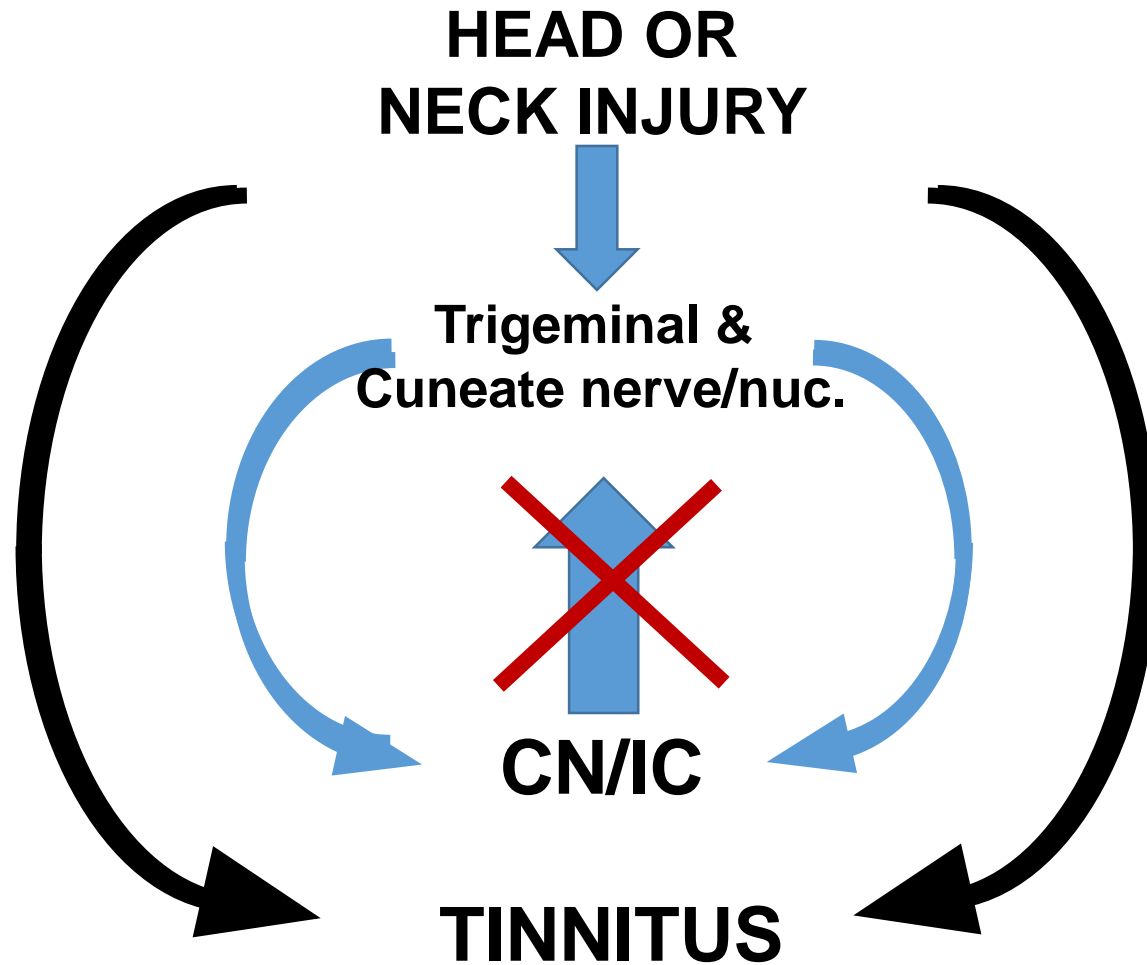
Tinnitus generator sites (CN/IC) receive one way input from modulator sites (cuneate nucleus)



Tinnitus generator sites (CN/IC) receive one way input from modulator sites (cuneate nucleus)

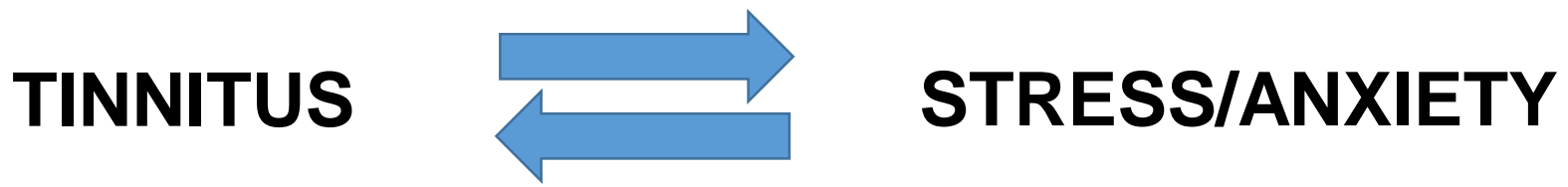


Tinnitus generator sites (CN/IC) receive one way input from modulator sites (cuneate nucleus)

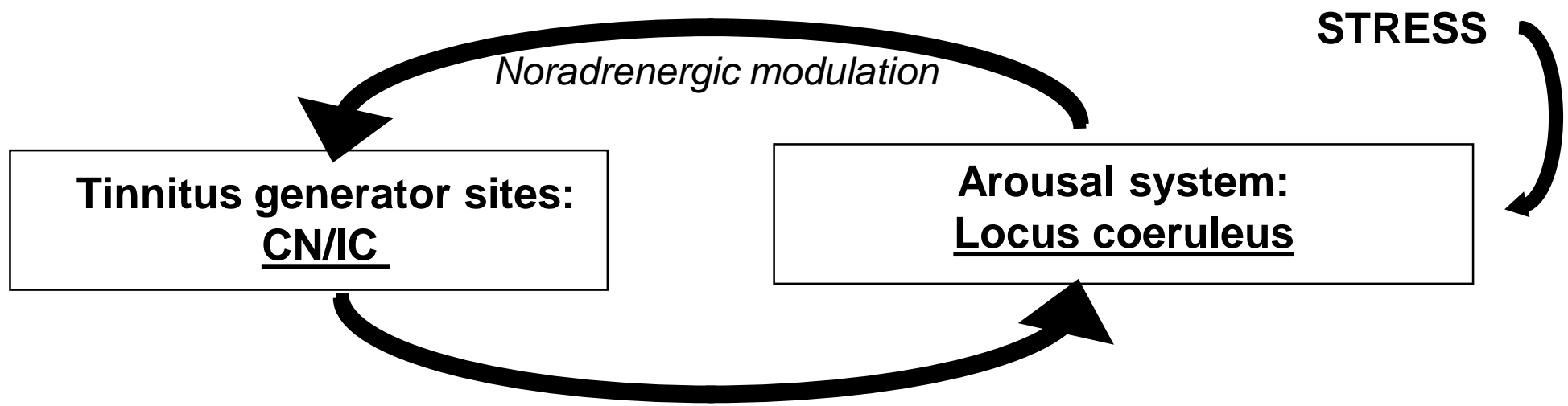


**Other comorbidities have a two-way
cause and effect relationships with tinnitus:**

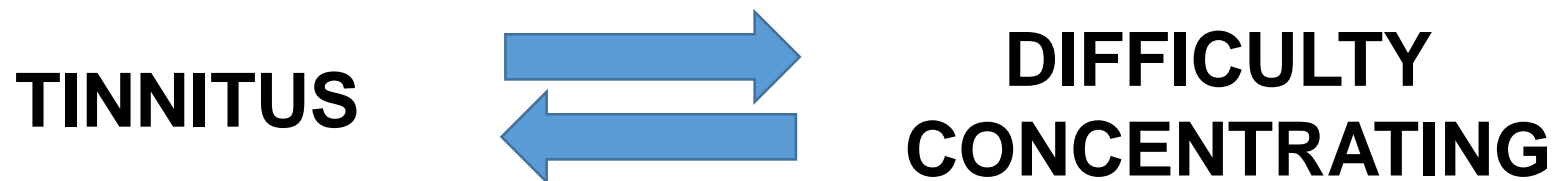
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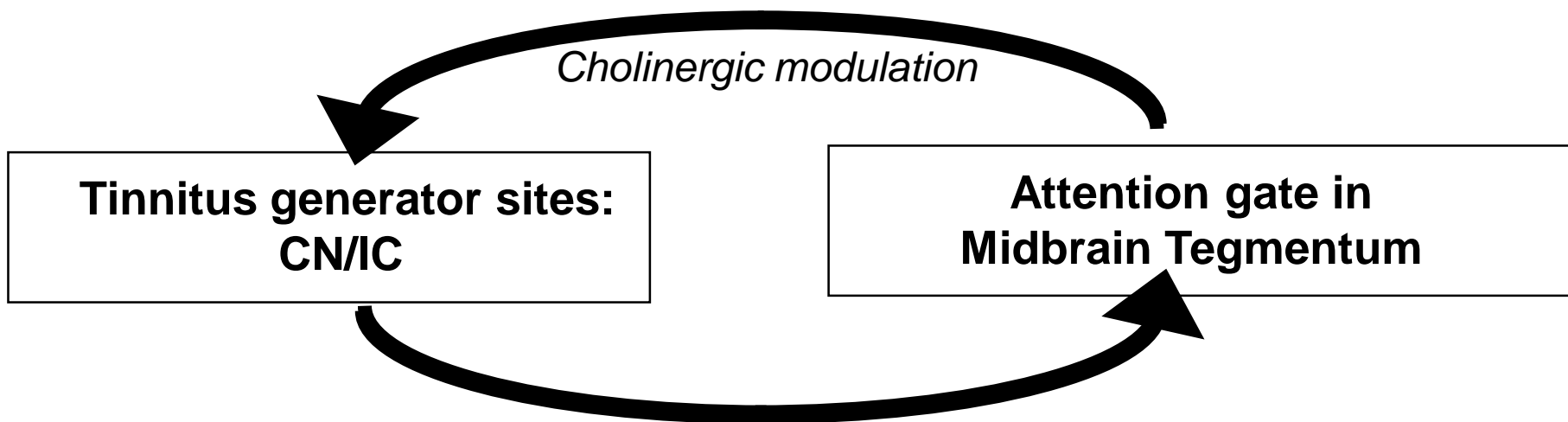
ANATOMICAL CORRELATE:



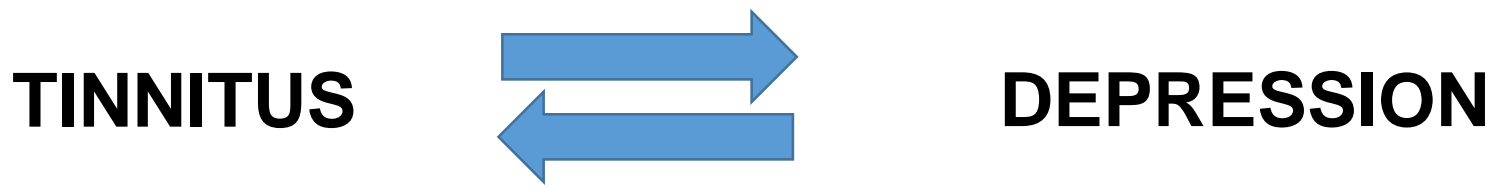
Other comorbidities have a two-way cause and effect relationships with tinnitus:



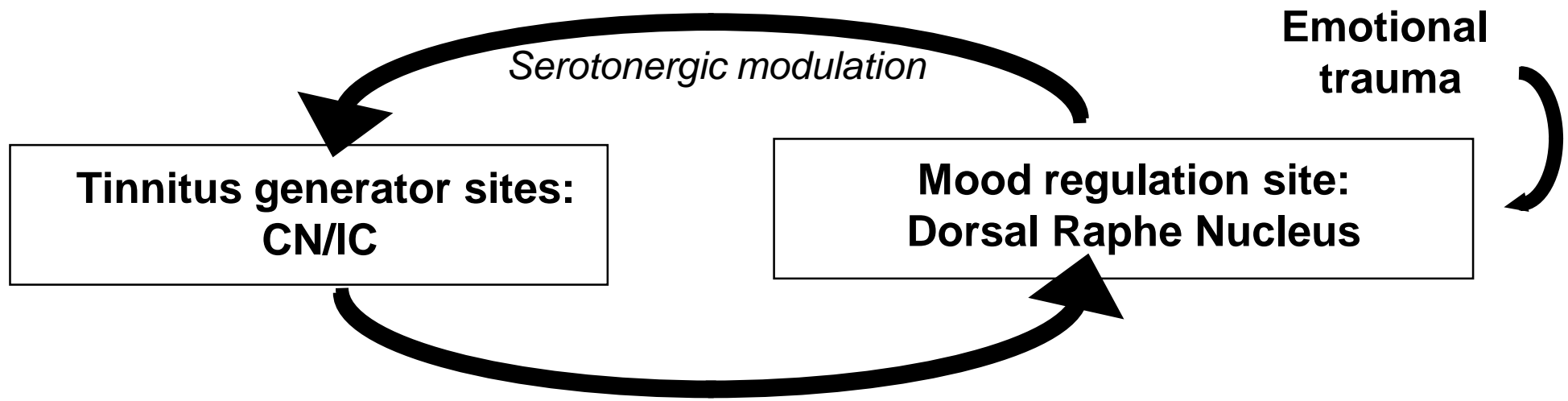
ANATOMICAL CORRELATE:



Other comorbidities have a two-way cause and effect relationships with tinnitus:



ANATOMICAL CORRELATE:



Where does this lead us in terms of clinical translation?

Tinnitus treatment needs to be guided by an understanding of the connections between the generator sites and the modulatory sites

*Given that somatic tinnitus is comorbid with head and neck disorders, and that the relationship is top down only, treatment plan
Needs to target the head and neck disorder rather than the tinnitus itself.*

Improving tinnitus with mechanical treatment of the cervical spine and jaw.

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Abstract

BACKGROUND: Tinnitus affects approximately 30-50 million Americans. In approximately 0.5-1.0% of the population, tinnitus has a moderate to severe impact on their quality of life. Musculature and joint pathologies of the head and neck are frequently associated with tinnitus and have been hypothesized to play a contributing role in its etiology. However, specific physical therapy interventions to assist in improving tinnitus have not yet been reported.

PURPOSE: To describe the examination and treatment intervention of a patient with subjective tinnitus.

PATIENT DESCRIPTION: The patient was a 42-yr-old male experiencing intermittent bilateral tinnitus, headaches, blurred vision, and neck tightness. His occupation required long-term positioning into neck protraction. Examination found limitations in cervical extension, bilateral rotation, and side bending. Asymmetry was also noted with temporomandibular joint (TMJ) movements. Upon initial evaluation the patient demonstrated functional, physical, and emotional deficits per neck, headache, and dizziness self-report scales and a score on the Tinnitus Handicap Inventory (THI) of 62. Resisted muscle contractions of the cervical spine in flexion, extension, and rotation increased his tinnitus.

INTERVENTION: Treatment focused on normalizing cervical spine mobility through repetitive movements, joint mobilization, and soft tissue massage.

RESULTS: At 2.5 mo, the patient demonstrated a complete reversal of his tinnitus after 10 physical therapy sessions as noted by his score of 0 on the THI upon discharge. He also demonstrated objective improvements in his cervical motion. This case reflected treatment targeted at cervical and TMJ impairments and notable improvements to tinnitus. Future studies should further explore the direct and indirect treatment of tinnitus by physical therapists through clinical trials.

Tinnitus that is comorbid with emotional, mood, or cognitive disorders, are more likely to improve with a multimodal management plan that treats both the tinnitus and the comorbidity

DUAL APPROACH SHOULD COMBINE TREATMENT OF BOTH THE TINNITUS AND THE COMORBID CONDITIONS

Targeting the tinnitus

Acoustic therapy

maskers

hearing aids

CRNM

Electrical stimulation

Anti-oxidant therapy

Targeting the comorbidity

CBT/desensitization

Antidepressants

Anti-anxiety (anxiolytics)

Stress management

Sleep aids

Counseling/Education

**Attentional retraining
(e.g., TRT)**

Clinical importance of knowing the brainstem components of tinnitus

- 1. Provides a framework for understanding the relationships between tinnitus and its associated comorbidities*
- 2. Provides a guiding framework for improving therapeutic approaches for the treatment of tinnitus*

The future of tinnitus therapy

- New treatments will be based on activation of modulatory pathways
- Will seek to restore balance in levels of activation among modulatory pathways
- Will Multidisciplinary team-based approach that treats tinnitus and/or its comorbidities
- Will use new patterns of stimulation (electrical and acoustic that simulate activation of modulatory pathways and/or reset the pattern and level of activity in the tinnitus generator sites
- Will increase emphasis on the psychological aspect of tinnitus with focus on attentional, mood, and emotional reconditioning