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Electrical stimulation and tinnitus: neuroplasticity, neuromodulation, neuroprotection

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Abstract

Neuroplasticity (NPL), neuromodulation (NM), and neuroprotection (NPT) are ongoing biophysiological processes that are linked together in sensory systems, the goal being the maintenance of a homeostasis of normal sensory function in the central nervous system. It is hypothesized that when the balance between excitatory - inhibitory action is broken in sensory systems, predominantly due to neuromodulatory activity with reduced induced inhibition and excitation predominates, sensory circuits become plastic with adaptation at synaptic levels to environmental inputs[1]. Tinnitus an aberrant auditory sensation, for all clinical types, is clinically considered to reflect a failure of NPL, NM, and NPT to maintain normal auditory function at synaptic levels in sensory cortex and projected to downstream levels in the central auditory system in brain and sensorineural elements in ear. Clinically, the tinnitus sensation becomes behaviorally manifest with varying degrees of annoyance, reflecting a principle of sensory physiology that each sensation has components, i.e. sensory, affect/behavior, psychomotor and memory. Modalities of tinnitus therapies, eg instrumentation, pharmacology, surgery, target a particular component of tinnitus, with resultant activation of neuromodulators at multiple neuromodulatory centers in brain and ear. Effective neuromodulation at sensory neuronal synaptic levels results in NPL in sensory cortex, NPT and tinnitus relief. Functional brain imaging, metabolic (PET brain) and electrophysiology quantitative electroencephalography (QEEG) data in a cochlear implant soft failure patient demonstrates what is clinically considered to reflect NPL, NM, NPT. The reader is provided with a rationale for tinnitus diagnosis and treatment, with a focus on ES, reflecting the biology underlying NPL, NM, NPT.

Keywords: tinnitus, neuroplasticity, neuromodulation, neuroprotection, electrical stimulation, inhibition, auditory and somatosensory cortex.

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I INTRODUCTION

In general, neuroplasticity (NPL), neuromodulation (NM) and neuroprotection (NPT) are biophysiological processes linked together to maintain a homeostasis of function:

a) structural for life forms at a molecular genetic, synaptic, cellular, tissue, organ, and system levels; and
b) functional as clinically manifested by sensory, behavior, learning memory, and motor activity in the central nervous system.

The biophysiological processes of NPL, NM, NPT are considered in our experience to provide a "bridge for continuity of function" between both a sensation and its transformation into one of behavior and affective and somatomotor response. The cognitive brain function of "memory" is the predominant brain function that is hypothesized to bind the two together[2].

It is hypothesized that when the balance between excitatory-inhibitory action is broken in sensory systems, predominantly due to neuromodulatory activity with reduced induced inhibition and excitation predominates, sensory circuits become plastic with adaptation at synaptic levels to environmental inputs. The resulting alterations in synaptic transmission and neuronal network function depend on the extent of calcium signaling and NMDA activation in response to different patterns of stimulation[1,3,4].

Clinically, this hypothesis has relevance for tinnitus:

1. The roles of excitatory amino acids, specifically glutamate, and calcium as mediators of excitotoxicity has been reported with resultant cellular neuronal death. The rapid activity of NMDA receptors to trigger cell death was suggested to reflect its increased ability to induce calcium influx and resultant calcium overload[5];
2. A particular cohort of a predominately central type subjective idiopathic tinnitus of the severe disabling type patients in who the medical significance of the tinnitus was identified to be CNS neurodegeneration[6]; and
3. The reported role of NMDA receptors as the predominant molecular mechanism for the control of synaptic plasticity and memory function[7].
4. Clinically, the excitatory hypothesis is considered significant for the development of an auditory memory, hypothesized to be "paradoxical" for tinnitus[8].

In this manuscript, tinnitus refers to a predominantly central type subjective idiopathic tinnitus of the severe disabling type (SIT).Tinnitus an aberrant auditory sensation, for all clinical types, is clinically considered to reflect a failure of NPL, NM, and NPT to maintain normal auditory function at synaptic levels in sensory cortex and projected downstream to levels in the central auditory system and sensorineural elements in ear.

Clinically, the tinnitus sensation becomes behaviorally manifest with varying degrees of annoyance, reflecting a principle of sensory physiology that each sensation has components, i.e. sensory, affect/ behavior, psychomotor and memory. Modalities of tinnitus therapies, eg instrumentation, pharmacology, surgery, target a particular component of tinnitus, with resultant activation of neuromodulators at multiple neuromodulatory centers in brain and ear. Effective neuromodulation at sensory neuronal synaptic levels results in NPL in sensory cortex, NPT and tinnitus relief.

Sensory inputs to brain are considered to have resulted in the phylogenetic development of multiple brain functions for survival of the species. The biophysiological processes of NPL, NM, NPT are ongoing and considered to have been and are critical in this development.

A global arousal system (GA) has been proposed that involves the activation of all vertebrate behaviors in response to all brain inputs. It has also been hypothesized that the neuroanatomical, neurophysiological and molecular properties of reticular neurons within the nucleus gigantocellularis (NGC) of the mammalian medulla, have a major role in GA. The neuronal circuits of control and regulation of the GA are considered central to understanding the origin and motivated behaviors e.g. hunger and thirst. The GA hypothesis is recommended to be considered for translation of the affect behavioral component of all clinical types of tinnitus[9].

A summary of the highlights of functional changes identified for tinnitus in animal models in the central auditory system at levels of brainstem, mid brain and cortex include:

1. increased spontaneous firing rates of neurons;
2. increase in burst firing;
3. alteration of the tonotopic organization and involvement of non auditory brain areas. These findings provide the beginning of an understanding of a biology for tinnitus[10].

A physiological process of significance for NPL and NPT is hypothesized to be inhibition and as reflected in pharmacological and approaches attempting tinnitus relief[1,11-15].

Both the somatosensory and auditory systems demonstrate "plasticity" changes with respect to behavior. When a stimulus is cognitively associated with reinforcement, its cortical strength is strengthened and enlarged. The changes are caused by both the sensation and "learning of the sensory experience, particularly when associated with reward and classical conditioning behaviors[16]".

This report is found to support a hypothesis based on clinical observations with nuclear medicine functional brain imaging (SPECT/PET) in tinnitus patients of a final common pathway for tinnitus. Specifically, a hypothesis that attempts to explain how an aberrant auditory sensory stimulus becomes transformed into one of affect and somatosensory (motor) response(s). The hypothesis of the FCP for tinnitus and the identified neuroanatomical substrates, highlighted by hypometabolism in the medial temporal lobe, and structures in the pontomesencephalic region of brain including the nucleus accumbens, when viewed in terms of the physiology of sensory processing, is considered to be expanded and broader in its application for all sensations, normal or aberrant[2].

Clinically the translation of sensory physiology for tinnitus has resulted in the identification of a discipline tinnitology, principles of tinnitology, a theory for all clinical types of tinnitus, an accuracy for the tinnitus diagnosis and a combined tinnitus targeted therapy (TTT) approach for attempting tinnitus relief[17-20].

This publication will:

1. review the biophysiological processes of neuroplasticity (NPL), neuromodulation (NM) and neuroprotection (NPT) in the context of tinnitus;
2. demonstrate with functional brain imaging, metabolic, i.e. PET CT brain and electrophysiology with quantitative electroencephalography (QEEG) what are clinically considered to be the bio physiologic processes of neural synchrony/dysynchrony, NPL, NM, NPT, thalamocortical oscillation (TCO) and thalamocortical dysrhythmia (TCD) in a subjective idiopathic predominantly central type tinnitus patient of the severe disabling type (SIT) who experienced an exacerbation of tinnitus with an initial cochlear implant and subsequent tinnitus relief when replaced with a new cochlear implant implant electrical stimulation; i.e. a soft cochlear implant failure.
3. present future projections of NPL NM NPT for tinnitus diagnosis and treatment.

II. HISTORICAL REVIEW BRAIN FUNCTION SENSATION AND TINNITUS SUNY DOWNSTATE; RELEVANCE NPL, NM, NPT:

Brain function and Sensation

Clinically fundamental for all sensory systems is the relationship between structure and function and the identification in neuroanatomic substrates of the underlying involved processes and mechanisms.

The significance and intimacy of brain function and sensation was recognized as early as the first century AD by the Roman philosopher and politician Lucius Aenneus Seneca (*c. 4 BC - + AD 65) who said: "*Nihil in intellectu, quod non erat ante in sensu!*" (i.e. "Nothing is to come into our mind if it not has passed through the gates of our senses before!"). This concept of the intimacy of the sensory environment and brain function lives on today since its reintroduction to neurotology in the 1970s by Claus F Claussen, M.D., PhD, Prof. Extraordinarius Neurotology, University Wurzburg, Germany[21].

The dilemma which faces both the tinnitus patient and professionals attempting tinnitus relief is the one posed originally by Descartes R, i.e. how a sensory phenomenon is transformed into affect behavior and *vice versa*[22]. Investigations for tinnitus, both clinical and basic science, attempting to answer this question for tinnitus are resulting in advances in the understanding of the ear and brain function, of the peripheral and central cochleovestibular system, translated for tinnitus diagnosis and treatment. Specifically for tinnitus this has resulted clinically in an alteration in the definition of tinnitus, theories of hearing and balance, introduction of new concepts of central auditory function, relationship between tinnitus and hearing loss, expansion of existing teachings in neurotology to include principles of sensory physiology for complaints of hearing loss, tinnitus and vertigo; and the translation of concepts of heterogeneity, homeostasis of function for tinnitus diagnosis and treatment.

The terminologies of NPL, NM, NPT have increasingly been introduced into the tinnitus lexicon as advances in understanding the physiology of normal brain function and pathophysiology underlying brain function for specific diagnostic categories is being investigated. Initially the focus was on the sensorineural approach to understand tinnitus, limited predominantly to the ear, reflective of what was known of the cochleovestibular system. Advances in sensory physiology, auditory science, neuroscience of brain function, results of functional brain imaging technology all have dramatically shifted the focus for tinnitus to the brain. This focus has resulted in an emerging neurobiology for tinnitus reflective of which brain function(s) are elicited in the presence of the tinnitus signal. In this case the neurobiology for tinnitus that is being identified in brain is "top down".

However to not forget:

1. the "bottom up" neurobiology from the ear, ascending levels in the central auditory system (CAS) starting at brainstem;
2. clinical types of tinnitus and;
3. the heterogeneity of tinnitus highlighted clinically by its etiology, and clinical types of tinnitus, and response to modalities of treatment attempting tinnitus relief.

Historical Review Brain function Sensation and Tinnitus SUNY Downstate; Relevance NPL, NM, NPT:

Our ongoing clinical experiences with SIT at SUNY Downstate since 1979 has an increased relevance for

tinnitus diagnosis and treatment when integrated with evidence connecting synaptic plasticity to functional plasticity, perceptual learning and memory, and the emergence of a neurobiology for sensation and perception.

Since 1979 and ongoing in the Tinnitus Clinic Department of Otolaryngology SUNY/Downstate, tinnitus has been identified as a neurotologic disorder[23]. Basic science investigations and clinical efforts for the diagnosis and treatment of all clinical types of tinnitus have been and continue to be grounded in translation of principles of sensory physiology for tinnitus. Specifically the fundamental principle that every sensation has components, i.e. sensory, affect behavior psychomotor and memory it be translated for tinnitus theory, diagnosis and treatment[17,18].

The focus specifically on neural plasticity and tinnitus was initially presented from the perspective of a basic science sensorineural approach with animal physiology studies of normal and abnormal predominantly peripheral and central auditory function[24-26].

Increasingly, and ongoing since mid 1980s, advances in sensory physiology, neuroscience and auditory science, have included evidence for understanding that a linkage exists between sensory biophysiological processes of neural synchrony, dysynchrony, neural plasticity, neuromodulation, thalamocortical oscillation, thalamocortical dysrhythmia and neuroprotection, all of which underlies and results in central auditory and nonauditory brain function. These advances have been integrated into expansion and supplementation of the predominant peripheral and original sensorineural theoretical approach for tinnitus based predominantly on the ear and brain to a focus on both brain and ear, which has found translation for tinnitus theory, diagnosis and treatment[18,27-29].

Tinnitus, a neurotologic complaint, originally was defined as the perception of an aberrant auditory sensation, unrelated to an external auditory stimulus, which can arise at any level of the peripheral and/or central auditory system[23].

Our definition of tinnitus in general has changed:

a) 1981-1989 - reflective of understandings of biophysiological processes underlying sensory physiology and
b) specifically since 1989 of biophysiological processes underlying brain functions associated with tinnitus.

Since 2006 tinnitus is defined as a clinically conscious awareness of an aberrant auditory paradoxical memory, varying in degrees of consolidation, originating in response to an interference in the homeostasis between dysynchrony and synchrony occurring within the synaptic circuitry of the involved peripheral neural and/or central subcortical cortical neural substrates thus interfering in the precision, specificity, and complexity involved in synaptic transmission for normal neuronal and interneuronal function[19].

Tinnitus is marked clinically by its heterogeneity for etiolgy, clinical type and subtype, factors influencing its clinical course, and response to treatment. Interference in the precision, specificity involved in synaptic transmission for normal and interneuronal function reflects the complexity of the tinnitus symptom. Neurotologic complaints of hearing loss, tinnitus, vertigo, ear blockage, hypercusis, alone or in combination, are a reflection of and associated with a damaged hearing system, but not tinnitus severity. The incidence of occurrence and severity of tinnitus is not associated with the degree/extent of the damaged hearing system. This is another example of two of the three components of the aberrant tinnitus sensation, i.e. sensory and affective/behavior[30].

In our clinical experience, subjective tinnitus is not a unitary complaint. Clinical types and subtypes of tinnitus have been reported since[31]. Neuroanatomic substrates associated with tinnitus have been identified in brain with nuclear medicine single photon emission computerized tomography (SPECT) since 1989, which precludes by definition consideration of subjective idiopathic tinnitus to be a "phantom phenomenon[2,6,8,32-34]".

The functional interactions demonstrated with nuclear medicine brain imaging (SPECT/PET/PET CT) between auditory and non auditory regions of interest in brain cortex reflect activation of multiple brain functions in the presence of the tinnitus signal and not the tinnitus signal[6,8,32-34].

The evidence presented of the connection between synaptic plasticity and functional activity finds clinical support for the original clinical reports of nuclear medicine brain SPECT/PET tinnitus patient imaging.

The underlying biophysiology, originally reported in 1991, is considered to be epileptiform activity in auditory and nonauditory multiple regions of interest in brain[2,32].

III. SENSORY SYSTEMS: COMMONALITIES AND DIFFERENCES; HETEROGENEITY:

Commonalities and differences have been identified.[33,34]

It has been hypothesized that commonalities and differences in both developmental and adult plasticity exist in sensory cortices. Common to both is considered to be a "transient" imbalance between inhibition and excitation. Differences between the two are considered greater than the commonalities[35,36]. Whereas alterations during the early development of sensory cortices are very long lasting and frequently permanent[37] plasticity in the adult sensory cortex is frequently transient[38].

Significant to be considered as demonstration of a commonality in sensory systems are inhibitory plasticity experiences reported in the visual and auditory systems with deprivation. In the visual system inhibitory plasticity has been considered to be important in circuit refinement that can contribute both to the compensatory forms of circuit plasticity in the early stages of development and to the pathological loss of function induced by visual deprivation during the critical period. Inhibitory plasticity as an important player in circuit refinement can contribute both to the compensatory forms of circuit plasticity in the early stages of development and to the pathological loss of function induced by visual deprivation during the critical period[39].

In the auditory system an auditory deprivation effect for the unfitted ears of the subjects with monaural hearing aids has been reported[40].

The term "deprivation" is used in its everyday sense to refer to the bilateral absence of acoustic stimulation. Outcomes from implantation reveal consistent effects of deprivation, evidenced by significant negative correlations between accuracy of speech perception and the duration of profound/total deafness before implantation. Outcomes also show acclimatization in the form of significant improvements in performance over time after implantation[41].

In early deafness a "pronounced" reduction has been reported in synaptic plasticity in. auditory cortex. Developmental abnormalities in synaptic plasticity result in abnormal connectivity, functional disintegration and immaturity of auditory cortical areas, the smearing of feature representations in the auditory system, cross-modal recruitment of some auditory areas for non-auditory functions, and the reorganization of cognitive functions due to absence of auditory input[42].

Increased sensory cortical plasticity and improvement in perception and the behavioral response are hypothesized to result by targeting the cortical interneurons and neuromodulatory centers[43].

This hypothesis is supported by reports demonstrating control over cognititive and emotional behavioral performance by optogenetic and pharmacogenetic targeting of different types of inhibitory and excitatory interneurons or neuromodulatory neurons and for different aspects of auditory perception by targeting the cholinergic system[44-46].

In our clinical experiences since 1979 the commonalities and differences are reflected in the clinical heterogeneity of different clinical types of tinnitus.

IV. CORTICAL PLASTICITY- BASIC SCIENCE

The cited publication by Carcea & Froemke is recommended reading to tinnitus professionals and patients for understanding the complexity of tinnitus and projection to the future for tinnitus diagnosis and treatment[1].

The following is a brief edited summary of what the authors of this manuscript consider in their tinnitus experience to be fundamental and essential of what is known at this time for cortical plasticity and for its translation to tinnitus diagnosis and treatment.

1. The multiple biophysiological processes of NPL, NM, NPT reflect adaptation in neuroanatomic brain substrates and interconnectivities between neural circuits internal and external environments. Adjustment is primarily to excitatory and inhibitory synapses.
2. Neural plasticity, NM, NP are biophysiological processes, linked together to assure structural maintenance and modification of neuronal ensembles with their synapses and circuitries, in response to internal and external sensory stimulation. The goal is functional maintenance of an ongoing homeostasis of normal function to assure survival.
3. The sensory cortex responds to behavioral stimuli by different neuromodulators which control plasticity in the human brain by coordination of modifications at selected sets of neuronal synapses[45]. Synaptic transmission and network function is dependent on which neuromodulatory systems are activated and on the extent to which intracellular Ca^{2+} signaling and NMDA receptor activation are engaged in stimulus patterns. This is basic for development and design of modalities of treatment.
4. Synaptic transmission and network function are dependent on which neuromodulatory systems are activated and on the extent to which intracellular Ca^{2+} signaling and NMDA receptor activation are engaged in stimulus patterns[1]. This is basic for development and design of modalities of tinnitus treatment.
5. The correlation between excitatory and inhibitory inputs may dictate the stability of synaptic fields in the developing auditory cortex. Unbalanced excitation allows for rapid activity induce retuning of synaptic inputs. Patterned stimulation increased the correlation between excitatory and inhibitory inputs nonspecifically, with improvement in the overall balance[47].
6. The relationship between the strength and timing of excitatory and inhibitory currents control input integration[48].
7. Sensory maps reflect the development of synaptic and spiking receptive fields at a neuronal population level[49].

8. Developmental windows called critical periods, are characteristic for most sensory cortices and structures important for emotion, eg Amygdala[50]. The critical window is considered to exist not only for different modalities of treatment but for different functions of the same sensory system.
9. The relationship between synaptic plasticity and excitatory-inhibitory balance is consistent in the adult sensory cortex. When neuromodulatory forces of excitation predominate, i.e. become unbalanced by inhibition, sensory circuits become plastic and adapt to best represent environmental inputs[51].
10. Activation of various modulatory systems can alter excitatory- inhibitory balance and enable experience -dependent modifications. Neuromodulatory systems can differ one from the other with significant effects on functional maps and sensory performance[52].
11. Neuromodulators, single or multiple including - acetylcholine, dopamine, serotonin or peptide modulators eg oxytocin result in activation different behavioral states, i.e. a multidimensionality of behavioral states. Sensory cortices are linked to and between neuromodulatory centers e.g. brainstem, basal forebrain (cholinergic, gabaergic, glutamatergic) with projection neurons, local Gabergic interneurons, and hypothalamus[1].
12. Neuroanatomic substrates/neuromodulators;
    • Basal forebrain- cholinergic, gabaergic and glutaminergic projection neurons and local GABAergic interneurons.
    • Locus Coeruleus-noradrenergic neurons innervate forebrain including sensory cortices. A unified theory is lacking to explain how the locus coeruleus modulates synaptic activity in the neocortex.
    • Ventral tegmental area or substantia nigra-dopamine release innervates the striatum and regions of prefrontal cortex[53].
    • Raphe nuclei: midbrain secretion serotonin; projection to forebrain via medial frontal bundle[54].
13. Two disinhibitory network mechanisms in auditory cortex:
    1) Activation muscarinic receptors in mid and deep cortical layers, resulting in rapid depression of stimulus evoked inhibitory inputs on pyramidal neurons;
    2) cholinergic inputs trigger disinhibition in the upper cortical layers by activation of nicotinic receptors on layer 1 inhibitory neurons[51].
14. N-methyl-D- aspartate receptor, a glutamate receptor, is the predominant molecular device to control synaptic plasticity and memory function[7].

V. BIOPHYSIOLOGICAL PROCESSES AND TINNITUS

Synchrony/Dysynchrony of neural activity describes a coincidence of timing or lack of timing of the discharge rate and phase locking of a sensory auditory signal (peripheral, central, or a combination) "noise" or spontaneous neural activity. Failure to establish a synchrony of activity in response to the dysynchronous auditory stimulus may become clinically manifest by seizure activity, other neuropsychiatric symptoms, behavioral abnormalities, and tinnitus. The dyssynchrony of spontaneous activity (i.e. "noise") arising in and involving multiple neural substrates is synchronized and expressed at the brain cortex as brain functions (i.e. rhythms), including cognition, consciousness, perception, memory, information processing, learning, affect and emotion, and attention. There is a need to differentiate between the dysynchronous signal hypothesized to be tinnitus and the synchrony of neuronal activity at the brain cortex, which is expressed as the function of perception and conscious awareness of tinnitus[19].

Thalamo cortical oscillation describes the synchronous firing and interaction that occurs between thalamic and cortical neurons at specific brain frequencies, delta 5-4 Hz, theta 3.5-7.5 Hz, Alpha 8-12 Hz, Beta 12-24 Hz, and Gamma 25-39 Hz in the thalamocortical system[55].

Thalamo cortical dysrhythmia - a pathophysiologic model of brain wave activity of brain function is proposed for neurogenic pain, tinnitus, abnormal movements, epilepsy, and neuropsychiatric disorders.

A lesion results in deafferentation of excitatory inputs on thalamic relay cells which initiates tinnitus.

It is hypothesized for tinnitus that the spontaneous and constant gamma band of hyperactivity causes tinnitus.

"In a dafferented state the thalamocortical columns fire in a burst mode of 4-7 Hz which results in a decrease of lateral inhibition in adjacent areas and a halo activity in the gamma band (> 30Hz) called the edge effect[55]".

Neural plasticity, clinically, is a reorganization in brain structure and or function in response to constant, single or repetitive, internal and or external stimulation e.g. physical, sensory, emotional. Multiple ongoing processes and levels of activity are involved at organ, tissue, cellular, synaptic and molecular genetic locations. The result of the reorganization is a positive or negative alteration in structure and or function from the normal, i.e. "positive plasticity or negative plasticity". The goal is to attempt to restore and or to maintain a homeostasis of normal neural function in the peripheral and or central nervous system[56].

Brain plasticity has been defined by "the father of sensory substitution and brain plasticity as the adaptive capacities of the central nervous system - its ability to modify its own structural organization and functioning[57]".

Neuromodulation in neuroscience, is considered to be a complex biology of physiological process(es) which exerts a positive or negative influence on an existing neural signal input or output, but does not eliminate the existing neural signal. It is conceptualized to be a process which can alter the circuitry in brain wave activity associated with tinnitus

At a synaptic level one presynaptic neuron directly influences a postsynaptic partner (one neuron reaching one other neuron), neuromodulatory transmitters secreted by a small group of neurons diffuse through large areas of the nervous system, having an effect on multiple neurons

In our tinnitus experience, neural plasticity can result in or be accompanied by neuromodulation and neuroprotection. An increase/decrease of tinnitus intensity can be considered to be a clinical reflection of an underlying neuromodulation of the existing tinnitus signal by a single and or/combination of different neurotransmitters. It involves and reflects adaptive and maladaptive changes in neuronal activity at cortical and subcortical levels of neuronal activity.

Different neurotransmitters regulate brain function at synaptic levels of activity. They are not absorbed, but remain in the CSF and influence/modulate different neurotransmittor activity with associated alterations in brain wave activity. Included are the neurotransmitters dopamine, serotonin, acetylcholine, histamine

Neuroprotection: refers to processes that protect neuronal function from injury or that improve such function after injury. It is hypothesized that common etiological agents that cause injury to the CNS have similar effects on the inner ear It is hypothesized that common etiological agents that cause injury to the CNS have similar effects on the inner ear. The chief etiologies to be considered include ischemia, trauma, or hemorrhage, and neurodegenerative disease.

Pharmacological agents that are considered to be neuroprotective have been identified and include calcium channel blockers, free radical scavengers, corticosteroids, antagonists of glutamate at N-methyl-D-aspartate (NMDA) and non-NMDA receptors, and various thrombolytic agents. An innovative application of such drug therapy is to provide neuroprotection[29,58].

VI. CLINICAL EVIDENCE IN SUPPORT OF NPL, NM, NPT

A review of the NPL NM NPT literature finds translation and significance for tinnitus of all clinical types for basic science, clinical medicine, diagnosis and treatment. The following are a few of many references cited to support translation of NPL, NM, NPT for the reported experiences for tinnitus:

1. Spontaneous activity and reorganization of the cortical map, i.e. neuronal; plasticity) are two significant biophysiological phenomena which have been identified to be associated with tinnitus[59,60].
2. Neocortical circuitry can alter throughout life with experience. Alterations in local excitatory circuitry increase the spread of spared representations into deprived cortical regions[61].
3. Neural plasticity is reported to be "considerable" in healthy individuals across life spans. The mechanisms involved are reported to support cognition and are influenced by normal ageing, particularly in the medial temporal lobe and prefrontal cortex, changes in which can clinically demonstrate interference in behavior[62-67].
4. Aging is associated with progressive losses in function across multiple systems, including sensation, cognition, memory, motor control, and affect. Studies of adult brain plasticity have shown that substantial improvement in function and/or recovery from losses in sensation, cognition, memory, motor control, and affect should be possible, using appropriately designed behavioral training paradigms. A brain-plasticity-based intervention targeting normal age-related cognitive decline may potentially offer benefit to a broad population of older adults[68].
5. Behavioral training has been demonstrated in a reliable training gain for (intra modal) auditory but not for the (across-modal) visual transfer task. Training-induced activation decreases in the auditory transfer task were found in two regions in the right inferior frontal gyrus. The right inferior frontal gyrus is frequently found in maintaining modality-specific auditory information. These results might reflect increased neural efficiency in auditory working memory processes. In addition, with tasks of less auditory specificity, i.e. task -unspecific activation, decreases in the visual and auditory transfer task were found in the right inferior parietal lobule and the superior portion of the right middle frontal gyrus reflecting less demand on general attentional control processes[67]. Clinically the reported behavioral changes are considered reflective of NPL, NM.
6. Neural plasticity and neuromodulation are reflected in the report of:
   a) The potential modifiability of cognitive function. Cognitive training was reported to be to be a potential tool for investigation of basic mechanisms of adaptive behavior, neuronal functioning, and design training[69-72].

b) In tinnitus patients with magnetoencephalography (MEG), the cortical representation of the tinnitus frequency was shifted into an area adjacent to the expected tonotopic location. Significantly in this study patients with impaired hearing identified with audiometry were excluded from this study[73].

c) Chronic subjective tinnitus patients demonstrate an increase of power in particular frequency bands In tinnitus patients as measured with magnetoencephalography (MEG). Alpha band power was significantly reduced, whereas delta and gamma band power was significantly increased in the temporal regions[74].

Varied changes in spectral content in the EEG of patients were reported with tinnitus throughout the frontal and temporal lobes. The most common significant changes were seen in frontal lobes. Given the heterogeneity reported apparently other conditions must modify the EEG content in these tinnitus patients[75,76].

Tinnitus related distress was correlated with an abnormal pattern of spontaneous activity in particular in right temporal and left frontal brain areas[77].

With the electroencephalogram (EEG), an increase of band power and local field potential (LFP) signals is typically interpreted as an increase in neuronal synchronization in terms of coincident firing within a neuronal population[78].

d) Vascular dementia patients underwent quantitative EEG recording and F18 PET. Correlation was found between slow frequency band power and glucose metabolism. A widespread inverse relationship of delta power to metabolism was found between various regions; additionally, delta power was negatively correlated to cerebral glucose metabolism in individual regions. Frontal theta power correlated especially with rostral thalamic central medial nucleus (CMR). Alpha power correlated directly with metabolism in the occipital lobe. No significant relationships were found between beta power and metabolism[79].

e) Some EEG descriptors correlated linearly with the magnitude of the cerebral metabolic reduction caused by propofol and isoflurane anesthesia. These data suggest that a physiologic link exists between the EEG and cerebral metabolism during anesthesia that is mathematically quantifiable[80].

An inverse relationship has been reported with PET between thalamic activity and EEG alpha power in depressed and healthy patients, i.e. greater thalamic activity with decreased alpha power[81].

f) Pathological neural synchronization has consistently been confirmed in electrophysiological epidural recordings from the secondary auditory cortex. Gamma band activity highly correlated with tinnitus loudness[82]. Clinically this is considered to reflect NPL and NM.

g) The suppression of behavioral evidence of tinnitus with auditory cortex electrical stimulation (ES), identified in a rat model, is cited for clinical evidence of the underlying biophysiologic processes of NPL, NM, and NPT, associated with ES[83].

h) Neuromodulation may be accompanied by but not result in a reorganization in brain at a organ, tissue systems, cellular, synaptic and molecular genetic levels of activity. Clinically, to illustrate this point, are the reports of significant tinnitus relief with instrumentation, i.e. C-R neuromodulation, a potential significant advance for all clinical types of tinnitus treatment objective electrophysiological evidence is demonstrated of improvement in particular neural circuitry(ies) neuroanatomical substrates of brain functions, and resultant reported tinnitus[84].

i) Depression is frequently associated with subjective idiopathic tinnitus of the severe disabling type. The mesolimbic dopamine system has been linked with reward and motivation. In rodents, an increase in dopamine neurons in the nucleus accumbens modulated the neural encoding of depression related behaviors, suggesting that processes affecting depression symptoms may involve alterations in neural encoding action in the limbic system[85].

Clinically, this paper is cited for future neuromodulatory pharmacological approaches attempting treatment of the affect component of tinnitus.

j) The positive neuroprotective results in brain of instrumentation and/or pharmacological agents clinically can be considered to underlie and to be linked to the processes in brain of neural plasticity and neuromodulation. The long term effects for tinnitus relief reported with tinnitus retraining therapy (TRT)[86] and receptor targeted therapy with gabapentin/Klonopin 2002(RTT-GABA)[87] clinically are considered to reflect NPL and NM.

7. Summary: The positive and negative subjective results reported with multimodalities attempting tinnitus relief are clinically considered to reflect degree of success or failure of underlying

biophysiological processes of NPL, NM, NPT. targeting the components of the aberrant auditory stimulus, i.e. tinnitus.

VII. FUNCTIONAL BRAIN IMAGING-CLINICAL OBJECTIVE EVIDENCE ELECTRICAL STIMULATION-NEUROPLASTICITY, NEUROMODULATION; NEUROPROTECTION

Functional brain imaging, metabolic with Cerebral F-18 2-deoxy-fluoroglucose (FDG) Positron Emission Tomography (PET) and electrophysiologic with quantitative electroencephalography (QEEG) was recommended to a cochlear implant patient (CI) age 74, who reported in 2008 an increase in tinnitus intensity and decreased hearing function with the CI ON of 6 months duration. The suspected working diagnosis was a cochlear implant soft failure[92].

The original insertion of the CI was ear rt 3/25/99.

The CI was evaluated and reported by the manufacturer to demonstrate normal function. The clinical impressions included the following:

1. predominantly central type tinnitus of the severe disabling type ear rt;
2. Subclinical tinnitus ear lt
3. hearing loss sensorineural profound type rt lt
4. RO Cochlear implant soft failure ear rt.

The goals included:

a) to improve the accuracy of the tinnitus diagnosis;
b) to provide a rationale for a tinnitus plan of treatment for tinnitus relief and;
c) to provide objective evidence to support recommendation for removal/replacement of the original CI original insertion ear rt 3/25/99.

A. MATERIALS AND METHODS

1. Cerebral F18-FDG Positron Tomography (Figure 1-5) (Table 1)

PET data was acquired in 3D mode with a Siemens Exact 47 HR + after administration of weight adjusted doses of F-18 2-deoxy-fluoroglucose. Routine PET processed standard uptake value data (SUV) was in turn analyzed by the NeuroQ program which provided a comparative three dimensional quantitative normative data base with statistical analysis of 240 neurologically appropriate ROIs normalized to whole brain counts after spatial morphing of subject data to the standardized 3D template. Individual patient data was compared for both hypometabolic and hypermetabolic activity. Patient ROI count data falling more than 1.65 STD beyond the mean value for a longitudinally validated control group ROI is flagged as abnormal by the NeuroQ analysis. Variation from expected symmetrical ROI activity was expressed in an

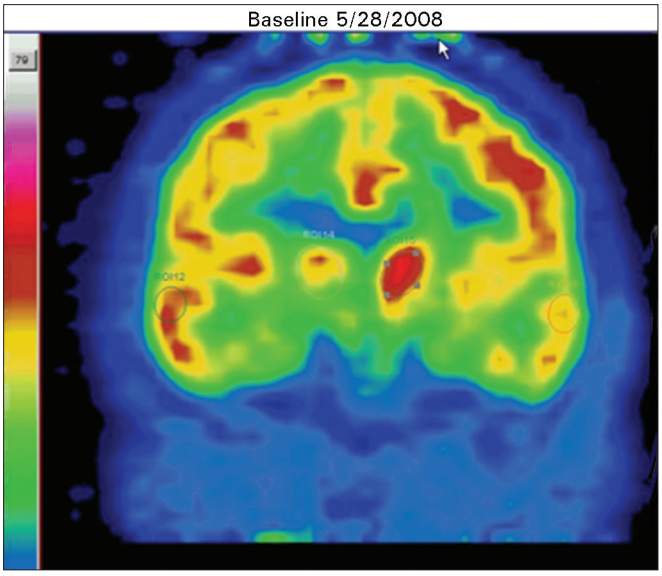

Figure 1. 5/28/09 baseline FDG PET scan in coronal orientation identified bilateral medial temporal lobe hypometabolism, mildly increased right primary auditory cortex activity (ROI 12), decreased activity right thalamus (ROI 14) and right frontal, at a level of severe tinnitus.

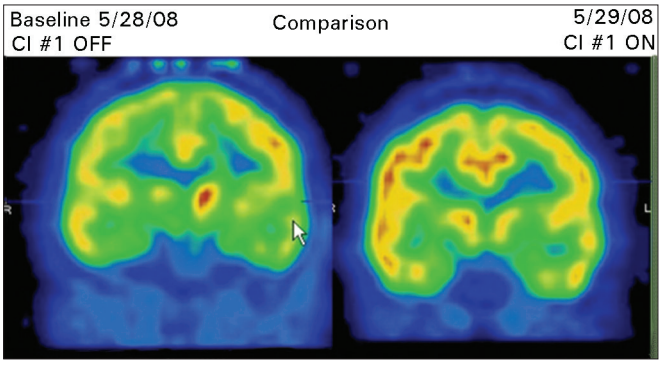

Figure 2. 5/28/08; 5/29/08. Before and after activation of cochlear implant sequential FDG scan coronal images reveal that following activation of cochlear implant which produced greater tinnitus especially of the right side (R), FDG activity is markedly elevated in ipsilateral right thalamus and primary auditory cortex. There is persistent medial temporal lobe hypometabolism, now worse on the left (L). The primary auditory cortex is identified (arrow Lt).

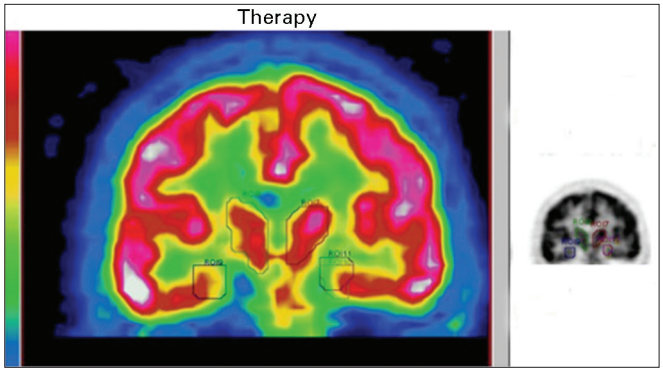

Figure 3. 10/30/08 Cochlear Implant #1 OFF and Therapy. Following Klonopin/Gabapentin therapy and after D/C of cochlear implant,#1, there is a dramatic reduction in right and left primary auditory cortex asymmetry and right thalamic hypermetabolism (ROI 18) with subjective reported improvement in the tinnitus complaint.

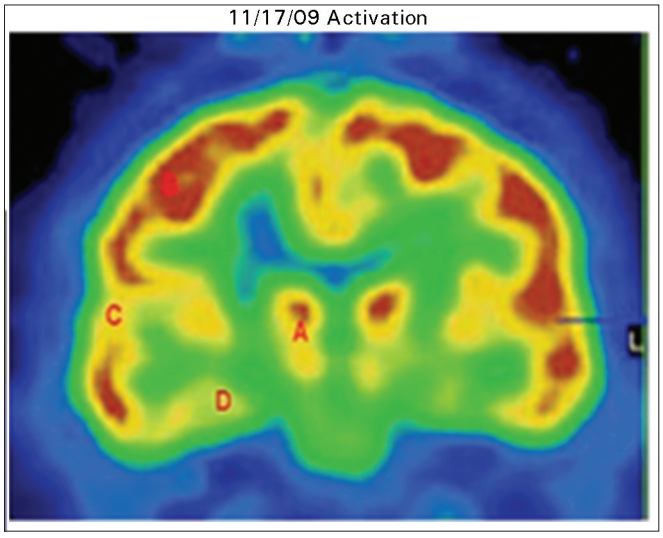

Figure 4. 11/17/09 Activation Cochlear Implant #2 Cerebral F-18-FDG PET SUV values A: Thalamus Rt; B: Frontal right; C: Primary Cortex Rt; D: Medial temporal lobe Rt; Table 1.

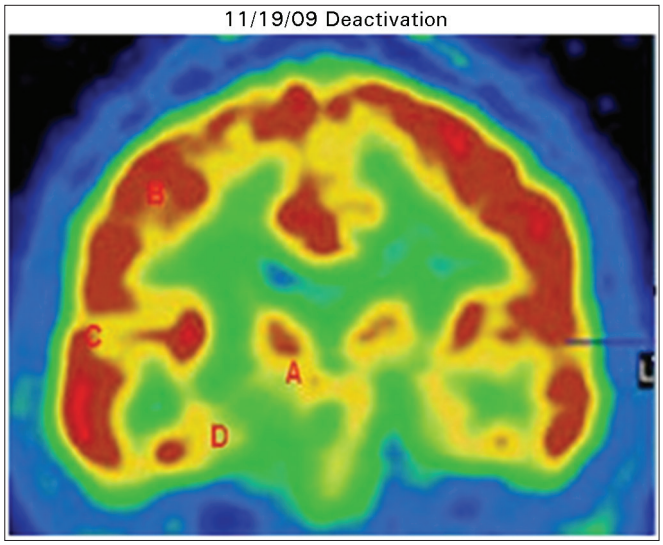

Figure 5. 11/19/09 Deactivation Cochlear Implant #2 Cerebral F-18 FDG - PET SUV values A: Thalamus Rt; B: Frontal right: C: Primary Cortex Rt; D: Medial temporal lobe Rt; Table 1.

asymmetric index of relative side-to-side percentage of R/L% normalized to whole brain activity.

The F-18 FDG PET Standard uptake values and an asymmetry index were calculated at 5 different intervals of time:

1. Baseline cochlear implant #1 off 5/28/08 (Figure 1)
2. Comparison 5/28/08 cochlear implant #1 ON AND OFF 5/29/08 (Figure 2)
3. Cochlear implant #1off and therapy (Figure 3)
4. Cochlear implant #2 On and therapy 11/17/09 (Figure 4)
5. Cochlear Implant#2 off deactivation and therapy 11/19/09 (Figure 5).

The clinical goals of functional brain imaging included:

1. To establish an accurate diagnosis for the tinnitus ear rt.
2. To obtain objective evidence of activation of regions of inters(ROIs)t in brain by electrical stimulation with the implanted cochlear implant ear rt reported by the patient to result in an increased tinnitus severity.
3. To monitor treatment efficacy with the implanted cochlear implant ear rt On and Off.

Preselected regions of interest (ROIs) in this report include medial temporal lobe, frontal, primary auditory cortex and thalamus. Sequential PET CT studies were performed at five intervals of time:

Coronal ROIs were preselected for this report to evaluate the association between the sensory and affect components of the tinnitus complaint reported by all tinnitus patients These ROIs highlight our ongoing SPECT/PET brain imaging experience since 1989.

In addition it is hypothesized that the activated ROIs reflect metabolic correlates of the underlying biophysiological processes in brain of NPL, NM and NP. Visual interpretation of the PET images and QEEG data demonstrate a significant association between the thalamus and frontal lobes. A future study is planned for the significance of this association.

2. QEEG: Materials and Methods (Table 2)

The QEEG is a spectral analysis of the raw EEG data, which was performed at the following intervals of time:

1. Baseline cochlear implant #1 off 5/27/08;
2. Cochlear implant #1 off and therapy 10/28/08;
3. Cochlear implant #2 off and therapy 11/18/09.

The Neurosearch (Lexicor Company, Boulder, CO) QEEG equipment was used for the recording. Nineteen (19) electrodes were placed on the patients' scalp using the international 10/20 montage (a montage being a standardized array of electrode sites used to ensure consistent results). The impedance measured at each electrode site with respect to the reference was less than 5,000 Ohms. The filter bandpass was set between 0.5 Hz and 32 Hz. Three hundred (300) epochs were recorded; twenty five (25) were selected as being representative and artifact-free, processed and compared with the normative database. The gain was 32,000, with a sampling rate of 128,000. The raw data EEG results were submitted to the Lexicor Company for analysis, and that firm generated a report called the Datalex report for clinical application (Lexicor Medical Technology, Inc. "Datalex

Table 1. F18-FDG Pet Standard Uptake values.

	Thalamus			Primary Auditory Cortex			Medical Temporal Lobe		
	R	L	R/L%	R	L	R/L%	R	L	R/L%
5/28/08 Baseline	9	10.4	- 14	12	9.9	+ 21	7	10	-30
5/29/08 Activation	5.1	4.5	+ 13	5.7	4.0	+ 42	3.8	4.7	-19
10/30/08 D/C Activation & Therapy	2.3	2.5	-8	2.7	2.5	+ 8	2.5	2.3	+ 8
11/17/09 Activation & Therapy	3.7	4.2	- 12	4.4	4.3	0	2.9	3.5	- 17
11/19/09 D/C Activation & Therapy	3.6	3.3	+ 11	3.6	3.6	0	2.5	2.8	- 11

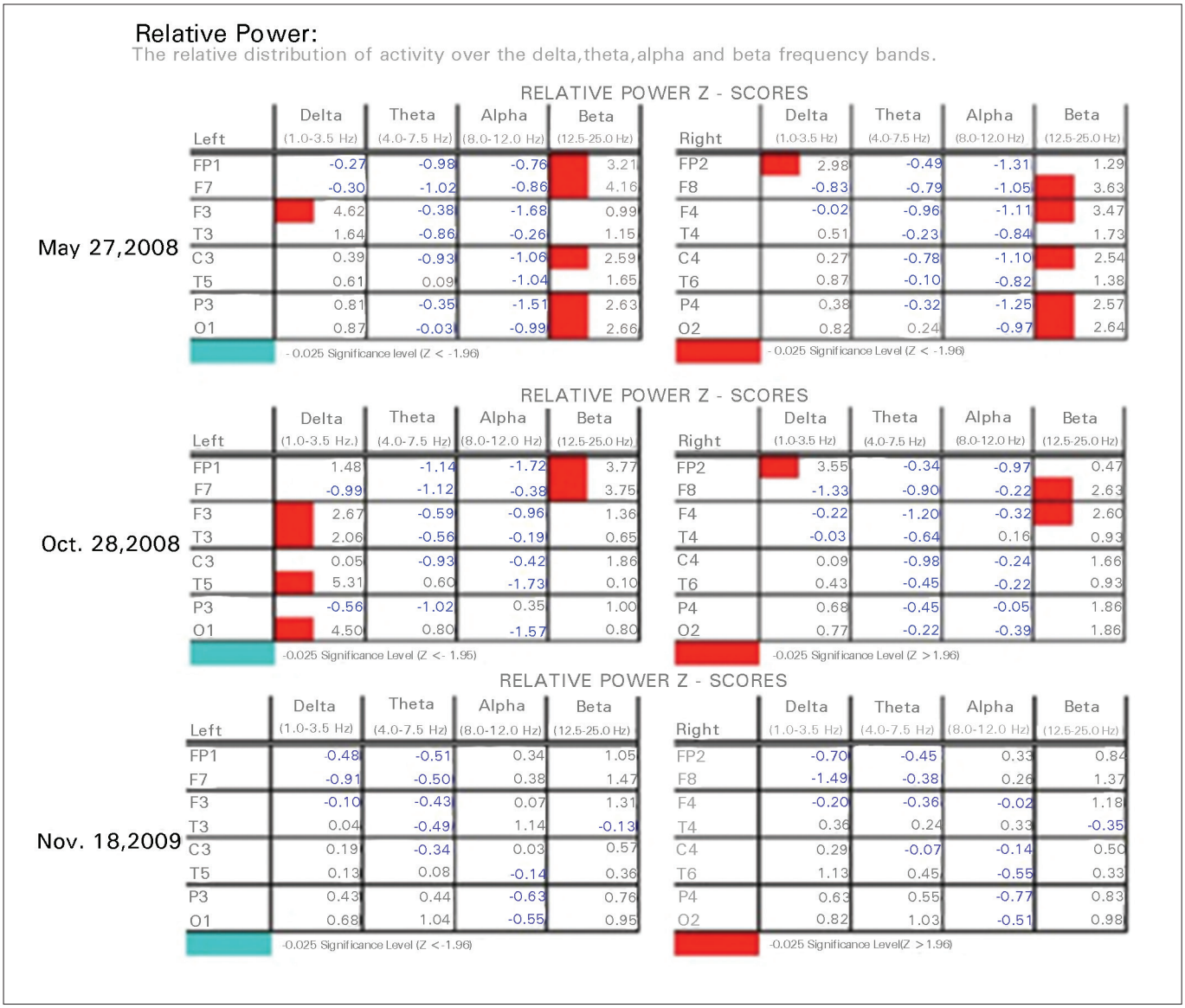

Table 2. Normative Reference database comparisons.

On Line EEG Analysis-The Future of Mental Health Diagnosis". Training Seminar, New York City, April 21, 2001

Electroencephalographic functional brain imaging provides a quantitative demonstration of the spectral analysis of the raw EEG brain wave activities (QEEG)73 c): Low resolution brain electromagnetic tomography (LORETA) is a family of analyses which provides a 3D demonstration of the distribution of the generating electric neuronal activity. i.e. standardized with no bias in the presence of measurement and biological noise (s LORETA)

and exact low resolution and zero error localization s-e LORETA. LORETA is not merely a linear imaging method. (Pasqual-Marqui et al 1994), (Pasqual-Marqui 1999). Its translation for tinnitus diagnosis, i.e. electroencehalotinnitograph (ETG), is considered analogous to the advent of the electrocardiograph (EKG) in the 1930s for cardiology. It is considered to provide a clinical objective demonstration of neural electrical activity, neural plasticity, neuromodulation with and without tinnitus treatment e.g. pharmacologic, acoustic, electrical, instrumentation, neurofeedback-individual for each tinnitus patient.

B. RESULTS

1. Cerebral F-18 FDG Positron - CT brain Tomography color images represent greater to lesser relative ROI metabolic activity reconstructed from red (greater SUV) to blue (lesser SUV) multicolor display. Multicolor display for each study is designed to maximize visualization of relative functional ROI asymmetry and not absolute activity as expressed in standard uptake value (SUV).

Quantitative F-18 FDG PET data is expressed in standard uptake values (SUV) Table 1. A relative asymmetry of activity is expressed as percentage of metabolic activity normalized to whole brain activity (R/L%) for ROIs thalamus, primary auditory cortex, and medial temporal lobes, at baseline cochlear implant #1 off 5/28/08, cochlear implant #1 on 5/29/08; cochlear implant #1 off and therapy 10/30/08; and cochlear implant #2 on 11/17/09 and off 11/19/09.

a) F-18 FDG PET SUV values 5/28/08, 5 29 08 -11/17/09, 11/19/09

Thalamus: The SUV% asymmetry between rt and lt metabolic activity of the thalamus with the new cochlear implant CI #2 reveals a reduction but persistence of SUV asymmetry. Original SUV asymmetry 5/28/08 lt > rt; reduction SUV asymmetry lt 11/17/09, and a persistent reduction but SUV asymmetry rt > lt.

CI #2 11/17/09 activation lt > rt/ = SUV -12; deactivation rt > lt SUV + 11.

CI #1 5/28/08 deactivation Baseline lt > rt -SUV -14; activation rt > lt SUV = + 13.

Primary auditory cortex (PAC): The SUV% asymmetry between rt and lt metabolic activity of the primary auditory cortex reveals with the new cochlear implant CI #2 a significant reduction and absence of SUV% asymmetry compared to CI #1 baseline Off deactivation 5/28/08 and On activation.

CI #1 5/29/08: CI #2 11/17/09 activation = SUV 0; 11/19/09 deactivation SUV 0 No asymmetry CI #1 Off Deactivation Baseline rt > lt = SUV + 21, On activation rt > lt SUV = + 42. Significant asymmetry rt > lt.

Medial temporal lobe: the SUV% asymmetry between rt and lt metabolic activity of the medial temporal lobe reveals with the new cochlear implant CI #2 ON a reduction of SUV% asymmetry compared to CI #1 baseline Off deactivation 5/28/08 and activation On CI #1 5/29/08: CI #2 On activation and therapy 11/17/09 lt > rt = SUV -17; OFF deactivation and therapy lt > rt SUV -11. CI #1 Off 5/28/08 deactivation Baseline rt > lt = SUV -30; On 5/29/08 activation rt > lt SUV = -19

b) F-18 FDG PET SUV values 5/28/08-10/30/08 Table1

The F18 FDG PET brain and the Standard uptake values 10/30/08 reflect an attempt to provide tinnitus relief with discontinuation use of CI #1. Treatment recommendations included diuretic therapy for presumed secondary endolymphatic hydrops lt; Gabapentin 300 mg bid, and Klonopin 5 mg hs for control.

QEEG reported excess brain wave activity. Subjectively a 10-20% tinnitus relief was reported.

Comparison of the F-18 FDG PET SUV values 5/28/08-10/30/08 demonstrate a significant reduction SUV asymmetry lt > rt of the thalamus, primary auditory cortex and medial temporal lobes with the activation and deactivation the CI #1 and therapy (Table 1).

Thalamus: 5/28/08 = - 14 10/30/08 = -8 **primary auditory cortex (PAC)** 5/28/08 = + 21 10/30/08 = + 8 **Medial Temporal lobe:** 5/28/08 = -30 10/30/08 = + 8

c) Comparison F-18 FDG PET SUV values 10/30/08-11/17/09; 11/19/09 Table 1

Comparison F-18 FDG PET SUV values 10/30/08 - and 11/17/09, 11/19/09 with CI #2 activation ON and therapy, demonstrate in **thalamus** an increase in SUV asymmetry lt > rt 11/17/09 and SUV asymmetry rt > lt 11/19/09; in the **primary auditory cortex (PAC)** SUV asymmetry initial rt > lt 10/30/08, SUV absence asymmetry with CI #2 On activation 11/17/09 and Off deactivation 11/19/09, and in **medial temporal lobe** an initial SUV asymmetry rt > lt with CI #1 off and therapy 10/30/08 and increased SUV asymmetry lt > rt.

The significant reduction, 10/30/08, and 11/17/09, 11/19/09 in the F-18 FDG PET SUV values compared to 5/28/08 and 5/29/08 was maintained for thalamus, primary auditory cortex and medial temporal lobe. **Thalamus**: 10/30/08 = -8 11/17/09 = -12 11/19/09 = + 11 **primary auditory cortex (PAC)** 10/30/08 = + 8 11/17/09 = 0 11/19/09 = 0 **medial Temporal lobe:** 10/30/08 = + 811/17/09 = -17 11/19/09 = -11

d). Comparison 5/28/08 and 5/29/08 to 11/17/09, 11/19/09:

Thalamus 5/28/08 = -14 11/17/09 = -12 5/29/08 = + 13 11/19/09 = +11 **primary auditory cortex (PAC)** 5/28/08 = + 21 11/17/09 = 05/29/08 = + 42 11/19/09 = 0 **medial temporal lobe** 5/28/08 = -30 11/17/09 = -17 5/29/08 = -19 11/19/09 = -11

Coronal images on left with replacement cochlear implant right activated (11/17/09) and with replacement cochlear implant on right deactivated (11/19/09). Color images identify clinically critical regions of thalamus (A), posterior frontal cortex (B), primary auditory cortex (C), and medial temporal lobe (D).

With activation asymmetries reduced thalamus lt > rt, primary auditory cortex absent asymmetry rt lt, reduced asymmetry medial temporal lobes lt > rt.

With deactivation asymmetries reduced thalamus rt > lt, primary auditory cortex absent asymmetry rt lt, medial temporal lobe increased reduction asymmetry lt > rt.

2. Quantitative electroencephalography (QEEG) relative power Z-Scores (Table 2)

The QEEG is a spectral analysis of the raw EEG data.

The results of the QEEG include reference database comparisons for relative power Z scores at 1-Hz intervals in the frequency domain, in a numerical table from which topographical maps are derived. All results reported are based on an analysis of the data referenced to Z scores in the database described[88,89].

The relative power Z score distribution of brain wave activity over the delta (1.0-3.5 Hz), theta (4.0-7.5 Hz), alpha (8.0-12.0 Hz) and beta (12.5-25.0 Hz) frequency bands were obtained at different time intervals:

1. Baseline cochlear implant #1 off 5/27/08;
2. Cochlear implant #1 off and therapy;
3. Cochlear implant #2 off and therapy 11/18/09.

Initially a high beta with was recorded bilateral essentially equal from all recording electrodes. With Cochlear implant #1 OFF deactivation and therapy the reported tinnitus relief 10/28/08 is reflected in a reduction in Beta and increase in delta. With removal of cochlear implant #1 and reimplantation with cochlear implant #2 the brain wave activities for all frequencies returned within the normal range.

The sequential QEEG recordings when reviewed in reverse order starting with 11/18/09-5/27/08 are considered to support the hypothesis of alterations in relative power reflective of development of an increasing chronicity for a tinnitus from initial onset that starts with alterations in delta which progress to predominant beta.

Is the consciousness awareness of the tinnitus a reflection the gamma range (> 25 Hz)? The QEEG clinically provides an electrophysiological correlate of brain wave of activity of multiple brain functions in the presence of the tinnitus signal.

The neural plasticity process is dramatically demonstrated in the alteration in activity between the thalamus and frontal cortex in the PET CT images with CI #1 on and off.

The neuromodulation process, both positive and negative is clinically considered to be reflected in the sequential QEEG relative power Z scores.

The neuroprotective process is clinically demonstrated by the efficacy of cochlear implant #2 in the both PETCT images and QEEG recordings. Specifically, demonstration of a correlation between metabolic reduction in asymmetries in and between regions of interest in brain and electrophysiologic reduction in relative power Z-scores with cochlear implant #2 compared to cochlear implant #1.

IX. DISCUSSION

The focus of this manuscript has been on biophysiological processes in brain of NPL, NM, and NPT and their translation for tinnitus.

The role of NPL, NM, NPT for all clinical types of tinnitus is discussed under the following headings:

1. NPL, NM, NPT and tinnitus

Evidence has been presented linking synaptic plasticity, functional activity and learning[1].

The neuroscience evidence underlying NPL NM PNPT is contributing to an evolving neurobiology for the diagnosis and treatment of all clinical types of tinnitus by linking synaptic plasticity, not only with functional activity, and learning but also memory, sensory perception and behavior. The complexities involved in NPL, NM, NPT are hypothesized to be reflected clinically in the heterogeneity of all clinical types and subtypes of tinnitus, and to underlie an ongoing attempt to maintain a normal homeostasis of function in underlying neuroanatomical substrates in brain.

The clinically identified principles of tinnitology for tinnitus diagnosis and treatment[20] are considered to find support from neuroscience and sensory physiology evidence of NPL, NM, and NPT[1]

The original sensorineural approach for understanding tinnitus with a focus predominantly on the ear and also brain reflected what had been known in the past of auditory and brain function. Advances in sensory physiology, auditory science, neuroscience of brain function, results of functional brain imaging technology all have dramatically shifted the focus for tinnitus to the brain. Tinnitus is a symptom of neurotologic disease in which ear and brain functions are of equal significance.

A final common pathway for tinnitus (FCP), hypothesized for transformation of an aberrant auditory sensation to one of affect/behavior and vice versa[8], is suggested to be regulated by NPL, NM, and NPT, which attempts to establish learning and memory, functional activity, sensory perception and behavior for the diagnosis and treatment of all clinical types of tinnitus. The FCP is suggested to be expanded for and to have clinical application for all sensations.

2. Functional brain imaging- F-18 FDG PET CT brain; QEEG

a. Correlations PET CT brain; QEEG with NPL, NM, NPT:

The results of nuclear medicine brain imaging (PET CT) and electrophysiology quantitative electroencephalography (QEEG) provide objective evidence of:

1. An increased clinical accuracy for the diagnosis of a soft failure of CI #1 electrical stimulation for tinnitus suppression;
2. Activation of multiple brain functions in multiple ROIs for the metric of metabolism with PET CT and for brain wave activity for the metric of relative power with QEEG;
3. A monitor for treatment efficacy, i.e. tinnitus suppression, with electrical stimulation (ES);
4. A therapy hypothesized to target the GABA-A receptor, i.e. RTT-GABA[87];
5. F-18-FDG PET SUV clinically hypothesized to reflect the metabolic activity associated with the biophysiological processes of neural plasticity, neuromodulation and neuroprotection in thalamus, primary auditory cortex, and medial temporal lobe; and
6. Demonstration of evidence of tinnitus suppression in multiple brain ROIs with ES and pharmacological therapy.
7. Positive and negatives effects of electrical stimulation (ES) clinically are demonstrated with functional brain imaging.

Significant is considered the correlation of the data between nuclear medicine brain imaging (PET CT) and electrophysiology quantitative electroencephalography (QEEG). These are two different metrics which demonstrate and support the recommendation of clinical translation of these technologies particularly for SIT for improvement of accuracy for the tinnitus diagnosis and a monitor for treatment efficacy.

Specifically, the metabolic activity in ROIs of thalamus and primary auditory cortex with the ES CI #1 and CI #2, is hypothesized to reflect a reorganization in both with ES On and OFF i.e. NPL and NM. The metabolic activity between thalamus and frontal cortex clinically is hypothesized to reflect a thalamocortical oscillation and dysrhythmia. The hypometabolism in the medial temporal lobes is hypothesized clinically to reflect the affect/behavioral component of the tinnitus, learning and establishment of a memory, “paradoxical” for the tinnitus. The SUV for thalamus, primary auditory cortex, medial temporal lobes with CI #1 and CI #2 provide objective data reflective of a reduction in metabolic activation in all three ROIs which correlates with the reduction in the relative power Z scores.

b. Cerebral Positron Tomography-Clinical relevance CI #1; CI #2

Comparison F-18 FDG PET SUV values 5/28/08, 5/29/08-11/17/09, 11/19/08 with the CI #1 and #2 demonstrate:

1. Reversal in the pattern of for activation and deactivation of the thalamus with activation and deactivation the CI #1 and CI #2. Specifically with the new CI #2, the patient reported significant subjective tinnitus relief ear rt and improvement hearing. The SUV% asymmetry between rt and lt thalamic metabolic activity is decreased bilateral with activation and deactivation, but reversed asymmetry compared to the old CI #1. With CI #1, Off, 5/28/08, the SUV% asymmetry metabolic activity of the thalamus was reduced rt and lt, rt > lt with the CI #1 ON. With CI #2 ON, 5/29/08, the SUV% asymmetry metabolic activity of the thalamus was reduced lt, and reduced rt, lt > rt, with the CI #1 OFF.

Significant metabolic improvement in the thalamus, primary auditory cortex and medial temporal lobe with both conservative therapy and new CI #2 electrical stimulation.

2. Correlation of the subjective tinnitus complaint with the alteration in SUV values is greatest in the order of the primary auditory cortex > thalamus, > medial temporal lobe.
3. The difference in SUV uptake values between the therapy and no ES CI #1 and CI #2 is highest in the significant reduction in the primary auditory cortex.
4. The significant reduction, 10/30/08, in the F-18 FDG PET SUV values compared to 5/28/08 and 5/29/08 was maintained.

It is hypothesized that the SUV result in the primary auditory cortex clinically reflects the neuroprotective effect of the ES CI #2 for the sensory component of the SIT. The medial lobe temporal lobe is clinically considered to reflect the affect/behavioral component to the SIT. Significant is considered the absence of asymmetry with ES CI #2 in the primary auditory cortex. This predominance of the ES effect in the primary auditory cortex clinically supports the observation of the high association of “tinnitus” with sensorineural hearing loss but not with severity. The severity is the affect/behavioral response of the tinnitus patient to the presence of the tinnitus.

5. Comparison of the F-18 FDG PET CT brain SUV values show significant reduction in the asymmetry index R/L% for the thalamus, primary auditory cortex and medial temporal lobes. Clinically the PET SUV values are

considered to reflect the metabolic effects of neuroplasticity (NPL), neuromodulation (NM), and neuroprotection (NPT) associated with electrical stimulation.

6. The mild FDG-18 PET SUV asymmetry % in the thalamus with CI #2 on and off is clinically hypothesized to reflect a lack of total tinnitus suppression at the level of the thalamus - But-total tinnitus suppression at the level of the primary auditory cortex. Clinically to consider that the result may reflect a metabolic F-18 PET response in the brain to the residual clinically manifest tinnitus signal, and/or a subclinical tinnitus signal at the level of the thalamus.
7. The Inter-connectivity between thalamus and primary auditory cortex, are clinically considered to reflect the process (es) underlying neuromodulation and reflected in the FDG -18 PET SUV% asymmetry indices. Clinically, the thalamo cortical interconnectivity may have a dynamic range of activity greater for overall sensory function than that between the temporal and frontal lobes. The "plasticity" may be of a higher order reflecting an "older "origin of brain structure and function in the hierarchy of phylogenetic development of the brain. This is suggested by the correlation of improvement with CI #2 compared to CI #1 i.e. the change in asymmetry index is greater between the thalamus and primary auditory cortex than for the medial temporal lobe. It is hypothesized that this is reflected clinically in the high incidence of association between sensorineural hearing loss and tinnitus - but - not in the tinnitus severity and auditory brain function of memory.
8. Visual inspection of the coronal images with a focus on the activation pattern between the thalamus and frontal lobe is clinically considered to support:

a) The hypothesis and theories of the thalamocortical oscillation/dysrhythmia[55] and the tinnitus dysynchrony/synchrony for tinnitus[19].
b) The biophysiological processes of NPL and NM are clinically hypothesized to be reflected in the alteration of activity between the thalamus and frontal cortex. In the F-18 FDG PET -CT images comparing the ROIs with CI #1 on and off.

The interconnectivity between medial temporal lobe and frontal lobes are clinically considered to reflect process(es) underlying neuromodulation. It is hypothesized that the brain functions of affect, behavioral response and memory functions, are in response to the presence of the tinnitus signal in brain and are reflected to the limits of this examination by the interconnectivity between medial temporal and frontal lobes. The affect, behavioral response to the presence of the tinnitus and memory functions are individual for each tinnitus patient for all clinical types of tinnitus. Significantly, the functional brain imaging with FDG -18 PET and the SUV% asymmetry indices correlate with the electrophysiology quantitative electroencephalography (QEEG) relative power scores (Tables 1 and 2).

9. The tinnitus relief reported with the activation and use of CI #2 is an example of the neuroprotective function of electrical stimulation (ES). The tinnitus relief is a clinical manifestation of the linkage between the biophysiological processes of NPL, NM, NPT.

The clinical recommendation of functional brain imaging, metabolic with F-18 PET brain, and electrophysiology quantitative electroencephalography (QEEG) provide an objectivity for improvement of the accuracy of the tinnitus diagnosis and provide a rationale for treatment.

10. The hypo metabolic function in the medial temporal lobe is a reflection of the low level of metabolism associated with the low frequency brain wave activity. This is correlated with the delta frequency of brain wave activity demonstrated in the QEEG.

The significant elimination of asymmetry with CI #2 in primary auditory cortex is not reflected in the degree of change in the F-18 FDG PET SUV hypometabolic activity in the medial temporal lobe.

Clinically this suggests:

1) The ES neuroprotective effect is greater for the sensory component of the tinnitus in the primary auditory cortex than the affect behavior component in the medial temporal lobe;
2) The multifunctionality e.g. memory function, of the medial temporal lobe; and
3) The neuronal interconnectivity between thalamus, primary auditory cortex and medial temporal lobe reflect a medical significance other than limited to tinnitus.

11. The striking feature in the FDG -18 PET SUV% asymmetry indices is the absence of asymmetry in the primary auditory cortex with the CI #2 on and off, and the marked reduction in asymmetry in the thalamus, primary auditory cortex, and medial temporal lobe with CI #2 and therapy including elimination CI #1 electrical stimulation.

Clinically the correlation of tinnitus relief with the reduction in SUV asymmetry between the F-18 FDG PET and QEEG reduction in excess brain activity in delta and beta demonstrate the NM and NPT function of CI #2 ES.

12. The F-18 FDG PET and QEEG brain data provide objective evidence that CI #1 was a cochlear implant soft failure in this patient.

c. QEEG

The sequential QEEG recordings when reviewed in reverse order starting with 11/18/09-5/27/08 are considered to support the hypothesis of alterations in relative power reflective of development of an increasing chronicity for a tinnitus from initial onset that starts with alterations in delta which progress to predominant beta.

Is consciousness an awareness of sensation reflected in the gamma range (> 25 Hz)? The QEEG clinically provides an electrophysiological correlate of multiple brain wave activities accompanying multiple brain functions in the presence of the tinnitus signal.

The neuromodulation process, both positive and negative is clinically considered to be reflected in the sequential QEEG relative power Z scores.

The neuroprotective process is clinically demonstrated by the efficacy of cochlear implant #2 in the both F18- FDG PET CT images, SUV, and QEEG recordings.

Clinically significant is considered the correlation between the metabolic F18 FDG PET PET SUV in the thalamus, primary auditory cortex, mesial temporal lobes and the relative power Z-scores from the recording sites of the QEEG.

3. Phantom perceptions and tinnitus

The perception of tinnitus has clinically been considered to be a "phantom sensory phenomenon[90]", i.e. the conscious awareness of an auditory percept in the absence of an external stimulus.

A phantom symptom is physiologically defined as the lack of or inability to identify a underlying neural substrate.

Clinically the authors of this manuscript have recommended since 1989 that subjective idiopathic tinnitus of all clinical types and subtypes no longer be considered a "phantom" sensory auditory percept.

The recommendation is based on our reported and ongoing experience with identification of neuroanatomic substrates in SIT patients with:

a) Functional brain imaging, SPECT/PET in SIT patients- ongoing since 1989[32].
b) QEEG analysis since 1999[75]; and Low resolution brain electromagnetic tomography (Loreta) since 2006.

Evidence has been accumulating since 2004 that an imbalance between excitation and inhibition in multiple neuroanatomic substrates in brain underlies NPL NM NPT[1,4,41]. All sensations have components i.e. sensory, affect behavior, psychomotor[17]. At synaptic levels in brain, for each component of all sensations, there is an attempt to connect synaptic neuronal plasticity with functional plasticity, affect behavior, somatomotor response, learning and memory. NPL, NM, NPT are not phantom phenomena. *The increasing identification of neuroanatomic substrates in subjective idiopathic tinnitus (SIT) for all clinical types and subtypes of SIT supports consideration that tinnitus no longer be considered to be a "phantom" sensory auditory percept.*

4. Synaptic Plasticity: Developmental/Adult brain differences

Synaptic plasticity has been reported to be reduced in adult brain compared to developmental brain[1]. Clinically this is significant for existing modalities of treatment. In general, preexisting anatomical, physiological alterations at brain stem, ascending descending levels of the central auditory system and at auditory sensory cortex and in white/grey matter is hypothesized to interfere in the goal of any/all modalities of tinnitus therapies, i.e. tinnitus relief. Specifically,

a) In the geriatric population, when considered for cochlear implantation for hearing improvement it is hypothesized that positive tinnitus suppression is reflective of a reset of balance between excitatory and inhibitory inputs for synaptic plasticity at sensory cortex associated with biophysiological processes of ND and NPT. Initiation of a tinnitus, or increase in preexisting tinnitus and activation of associated non auditory ROIs with affect and behavioral and motor symptoms is hypothesized to reflect an imbalance between excitatory and inhibitory processes at sensory cortex. When due to the ES, clinically this reflects an interference in synaptic plasticity and accompanying NM and NPT, and
b) Reports of initiation and/or increase in preexisting tinnitus associated with acoustic tumor removal is hypothesized to reflect a interference in synaptic plasticity at sensory cortex with a similar cascade of change described following cochlear implant at brainstem level ES.

In summary it is hypothesized that anatomical morphological alterations and or biophysiological alterations associated with normal/aberrant auditory function, e.g. tinnitus, result in an interference in the

maintenance of synaptic plasticity, its connection to functional plasticity learning, auditory perception and memory and interference in modalities of therapy attempting tinnitus relief.

5. Identification and treatment of factors influencing the clinical course of tinnitus and tinnitus treatment efficacy

Identification in the clinical history of factors influencing the clinical course of the tinnitus, and treatment as appropriate, can result in tinnitus relief in individual tinnitus patients[23,86,90].

The responses to modalities of treatment are clinically oreflective of positive NPL, NM and NPT.

The elimination of the negative effect of the ES of CI #1 and the positive effect ES of CI #2 is a clinical manifestation of NPL NM NPT underlying the reported subjective tinnitus relief.

Functional brain imaging results reported,10/30/08, F18-FDG brain PET and QEEG, correlated with subjective tinnitus improvement. Therapy 5/29/08-10/30/08 included treatment of factors identified in the clinical history to be contributing to the clinical course of the tinnitus as described and elimination of the ES CI #1. Clinically this provides objective evidence in support of the recommendation for attempting tinnitus relief by identification and treatment of factors influencing the clinical course of all clinical types of tinnitus, individual for each tinnitus patient.

X. FUTURE

The future for tinnitus diagnosis and treatment is positive and expected to include:

1. The identification of the biophysiology underlying NPL NM NPT for all tinnitus types and subtypes.
2. Identification of similarities and differences, based on etiologies of tinnitus, in the neurobiology underlying the biophysiological processes of NPL, SD, NPT, and its linkage with functional plasticity, affect behavior, learning auditory perception and memory.

The ultimate goal is to identify multiple targets of tinnitus activity and develop multimodal tinnitus treatment approaches for all clinical types and subtypes of tinnitus, eg. pharmacologic, instrumentation, surgery, alone or in combination. The recommendations to specify, alone or in combination, which component(s) of the aberrant tinnitus sensation, is being targeted by a particular modality of tinnitus treatment.

Functional brain imaging results presented in this manuscript provided clinical objective demonstration of the positive and negative effects of ES.

Morphological, physiological, and molecular alterations and reorganization in the cerebral cortex and ear, individual for each tinnitus patient, will determine the extent and/or the degree of efficacy for tinnitus control and or cure for a particular type and subtype of tinnitus.

The biophysiological evidence underlying synaptic plasticity and the processes NPL, NM, NPT are expected to provide targets for the development of:

a) *A pharmacology for tinnitus, personalized and individual for each tinnitus patient. Specifically, the development of a tinnitopharmacology reflective of the molecular genetic code of the individual tinnitus patient, i.e. tinnitopharmacoproteogenomics.*
b) Surgical approaches to specific single/multiple targets in brain for specific components of the tinnitus.
c) Sound therapy instrumentation - external/internal.

Questions to be answered for the future include how to increase the accuracy of the tinnitus diagnosis and efficacy for treatment of all clinical types and subtypes of tinnitus include the following:

1. What is 'common' and shared for all clinical types of tinnitus in sensory auditory and non auditory for NPL NM NPT cortices and what is different, "special" for a particular clinical type of tinnitus, with "top down" or "bottom up" processing?
2. What are the determinants for the outcomes of the biophysiological processes NPL, NM, and NPT at sensory auditory cortex and in nonauditory cortices for a normal auditory stimulus and/or a aberrant auditory sensation, i.e. a particular type/subtype of tinnitus?
3. What significance is the etiology of the tinnitus in the activation of neuromodulator(s) at different neuromodulatory centers?
4. Is the neurobiology underlying each of the four components of a particular type of tinnitus the same or different for the processes of NPL, NM, and NPT?
5. How can the present evidence connecting synaptic plasticity to functional plasticity, perceptual learning and memory be translated to an increased accuracy for tinnitus diagnosis and efficacy for treatment for all clinical types and subtypes of tinnitus?
6. Is the neurobiology the same for each of the four components of a particular type of tinnitus?

X. CONCLUSIONS

1. Evidence has been presented connecting synaptic plasticity with functional plasticity, affect behavior, learning, auditory

memory and perception and the underlying biophysiological processes of NPL, NSD, NPT.

2. It is hypothesized that an imbalance between excitatory and inhibitory inputs at synaptic neuronal circuits in brain triggers synaptic plasticity, functional plasticity and the biophysiological processes of NPL ND and NPT.
3. Neural plasticity, NM, NPT are biophysiological processes, linked together to maintain structure, maintain a homeostasis of normal function and reflect modification of selected neuronal ensembles with their synapses and circuitries, in response to internal and external sensory stimulation. The goal short and long term is functional maintenance of an ongoing homeostasis of normal function for survival.
4. The degree of efficacy of modalities of treatment attempting tinnitus relief are clinically considered to reflect varying degrees of activity of the biophysiological processes of NPL, NM, and NP.
5. The evidence for the hypothesis of synaptic activity and its connection with functional plasticity, affect behavior, learning, auditory memory and perception, is considered to support the clinical translation of the principle of sensory physiology of components of a sensation and its perception for normal and/or aberrant auditory stimuli, i.e. tinnitus components sensory, affect/behavior, psychomotor and memory.
6. Functional brain imaging F-18 FDG Pet Ct brain and quantitative electroencephalography (QEEG) clinically demonstrated a) Objective metabolic and electrophysiologic evidence to improve the diagnostic accuracy, provide a rationale for a treatment modality for a particular type of tinnitus, eg ES CI #2; b) A monitor for treatment efficacy and; c) clinically demonstrate the biophysiological processes of NPL, NM and NPT.
7. The clinical implications of Cerebral F-18 FDG PET CT SUV are multiple and highlighted by the significant absence of asymmetry at primary auditory cortex and reduction in the asymmetries for the non auditory thalamus and medial temporal lobes with CI #2. Clinically, this result is demonstration of the specificity of ES for the sensory component of the tinnitus as well as the affect behavior, i.e. medial temporal lobe. The asymmetries and brain location of the PET SUVs for the thalamus clinically are considered to support the thalamocortical and thalamocortical dysrhythmia hypothesis translated for tinnitus.
8. Functional brain imaging is recommended to be considered for the clinical identification of a cochlear implant soft failure (CISF) in a predominantly central type subjective idiopathic tinnitus of the severe disabling type[92].
9. A final common pathway for tinnitus (FCP), hypothesized for transformation of a aberrant auditory sensation to one of affect/behavior and vice versa, is suggested to be regulated by NPL, NM, and NPT, which attempts to establish learning and memory, functional activity, sensory perception and behavior for the diagnosis and treatment of all clinical types of tinnitus and all sensations[8].
10. It is hypothesized that the input and output from the Olivary System in brain has a significant influence on normal and aberrant auditory function and maintenance of a balance between excitation and inhibition at sensory auditory cortex and the resulting biophysiological processes of NPL, NM and NPT[93].

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