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A Final Common Pathway for Tinnitus - The Medial Temporal Lobe System

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Abstract: A final common pathway for tinnitus is hypothesized to exist for all patients with tinnitus. Its function is the transition of the sensory to the affect component of the symptom of tinnitus.

Single Photon Emission Computerized Tomography (SPECT) with the radio isotope TC99-HMPAO has identified side to side perfusion asymmetries highlighted by that of the amygdala - hippocampal complex. Adjacent perfusion asymmetries involving the frontal, temporal and parietal lobes suggest a interneuronal network resulting in the transition of the sensory to the affect components of the symptom of tinnitus.

It is hypothesized that a fundamental function of the amygdala - hippocampal structures is the establishment of a paradoxical auditory memory for tinnitus. It is a result of alteration in auditory masking found in all tinnitus patients. A paradoxical memory for an aberrant auditory signal i.e., tinnitus, is considered to be the initial process in the transition of the sensory to the affect component. Underlying mechanisms are hypothesized to exist and to be highlighted by a diminution of inhibition mediated by gamma aminobutyric acid (GABA) due to disconnection from excitatory (glutamate) inputs. Blockage of GABA mediated inhibition results in Tinnitogenesis, a epileptiform auditory phenomena.

The overall hypothesis of a final common pathway for tinnitus; the role of the MTLS; and clinical support for this hypothesis is presented.

Key Words: Final Common Pathway; Sensory; Affect; Tinnitogenesis; Paradoxical Auditory Memory; Medial Temporal Lobe System; Tinnitology.

INTRODUCTION

A Final Common Pathway (FCP) is hypothesized to exist for all patients with tinnitus, particularly of the severe disabling type (SIT). Its function is the transition of the sensory to the affect component of the symptom of tinnitus and the interaction between the two.[1,2]

All sensory systems involve a sensory stimulus input and behavioral response output. Tinnitus - a sensory disorder of the auditory system is compelling professionals, regardless of discipline, to address the issue of how a auditory sensory stimulus results in a particular behavioral response; or conversely, does a antecedent behavioral pattern of response, influence the sensory perception of an auditory sensory input, particularly if and when the sensory stimulus is considered aberrant, which is what tinnitus is, i.e. an aberrant auditory signal.[3] Such a interaction/transformation/translation/interaction reflects brain action and brings up the age old question of how to differentiate between brain action and the mind. The symptom of tinnitus is compelling otology/neurotology, and other disciplines who are involved in its understanding and attempts for medical audiologic diagnosis and treatment, to become knowledgeable to what is and is not known of brain action; and what is the mind. Tinnitology, a discipline involving professionals dedicated to the science of sound perception unrelated to an external source of sound, reflects this effort.[3]

Historically, this search for understanding how the transition from sensory to affect occurs in the brain is not new. Descartes regarded the mind as something immaterial, separate from brain but interacting with it in some manner.

Kandel divides behavioral brain action into simple e.g.,

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motor behaviors, and complex affective and cognitive behaviors e.g., feeling, learning.[4] For tinnitus, attributes of tinnitus are postulated with associated brain regions of interest e.g., masking, intensity, annoyance, anxiety, depression and interference in communication capabilities.[5] A corollary can be that a disorder of affect i.e., feelings can be seen as a disturbance of brain function. Mind can be considered a range of functions performed by the brain. Localization of brain action is now possible and is being investigated with both Positron Emission Tomography (PET) and Single Photon Emission Computer Tomography (SPECT) brain imaging.

The concept of William James, the Father of American Psychology is suggested to find application to a FCP for tinnitus. He observed that consciousness is not a thing but a process.[6] Specifically when applied to tinnitus, a FCP can be considered to include different processes - all of which are directed to the primary function of transition of a sensory stimulus to conscious manifestations of affect i.e., mood, emotion, paradoxical memory, sleep, stress, fear, interference in communication and behavior. The transition is acknowledged to be complex, involving an integration of multiple neuronal networks within the brain. The ultimate end result i.e., FCP is a correlation of structure/function, and mind and brain. The clinical manifestations of the affective behavior of the tinnitus patient can be considered to be components of the FCP for tinnitus. In the future, as the clinical experience of multiple disciplines increases for the symptom of tinnitus, it is predicted that additional components will be identified.

Our efforts for tinnitus diagnosis and treatment have been ongoing since 1977. A Medical Audiologic Tinnitus Patient Protocol (MATPP) has been applied to an excess of 4,000 patients with tinnitus, particularly of the severe disabling type, at the Tinnitus Clinic of the Health Science Center at Brooklyn, State University of New York.[3] Clinical investigation has identified the following highlights to be significant for tinnitus diagnosis and efficacy for its treatment and control[3]:

a. Clinical types of tinnitus - a symptom of neurotologic disease.
b. Components of the symptom of tinnitus i.e.,sensory, affect, psychomotor.
c. Masking characteristic of each tinnitus patient is individual.
d. SPECT imaging of brain has identified for the first time in-vivo differences in blood flow in several regions of brain of patients with a predominantly central type tinnitus.[2,5,7-11]
e. Fear and stress in tinnitus patients particularly of the severe disabling type are a result of a paradoxical auditory memory of an aberrant dysynchronous auditory signal.

Our definition of tinnitus is dynamic and reflects an integration of what is known of the basic science of tinnitus; and our clinical experience.[3] Initially we defined tinnitus to be an aberrant perception of sound unrelated to an external source of auditory stimulation. Most recent, and at this time, we define tinnitus as a disorder of auditory perception due to an altered state of excitation/inhibition in neuronal networks resulting in a dysynchrony of neuronal signalling. The underlying mechanism is that of dysynchronization, that is, a lack of synchrony or interference in timing of the discharge rate and phase locking of the auditory signal having a location peripheral, central or both. Since 1977 different clinical types of tinnitus have been identified.[12-14] One such clinical type is a central type tinnitus speculated to have a tinnitus site of lesion in brain reflecting brain dysfunction.[13]

Clinical investigations at the Tinnitus Clinic of the HSCB-SUNY to identify a tinnitus site of lesion(s); mechanisms of tinnitus production, particularly of a central type and subtypes of tinnitus; have been performed in the 1980's, continue up to and include the present, and have been reported.[3] To accomplish such goals, the auditory brain stem response, that is the ABR, was introduced in the 1970's; and in 1981 we reported an electrophysiologic correlate for tinnitus.[15] The initial motivation as a physician has been to attempt to objectivize a subjective complaint; and continues to be a need, as a physician, to identify the medical significance of tinnitus; and to identify a metabolic and electrophysiologic correlate for the subjective complaint of tinnitus. Such information is believed to provide a basis for accurate, objective tinnitus diagnosis; and treatment/cure for tinnitus.

Single Photon Emission Computerized Tomography (SPECT) with the radioisotope Tc-99 HMPAO is a detection method which provides information of cerebral perfusion in brain. Its introduction to our Medical Audiologic Tinnitus Patient Protocol since 1989 has increased our accuracy for tinnitus diagnosis and provided a basis to monitor the efficacy of treatment.[2] Our clinical experience and reports to date consistently have demonstrated side-to-side perfusion asymmetries involving the medial temporal lobe system; frontal, temporal, and parietal areas of the brain. To date 48 patients were selected for SPECT imaging of the brain identified with the MATPP to have severe disabling tinnitus of the central type. Common to all has been an incidence of perfusion asymmetries involving the medial temporal lobe system (MTLS) in greater than 90% with a p less than 0.05.[1,2,5,7-11] Coregistration of SPECT and MRI of brain data has become a reality in our laboratory and is being investigated to confirm our past reports of involvement of the medial temporal lobe system; and to identify neurotransmitter receptor systems involved.

Based on clinical experience with tinnitus particularly of the severe disabling type and supported by SPECT imaging of the brain, the medial temporal lobe system is speculated to be a key site of action of processing of an aberrant auditory signal resulting in a paradoxical auditory memory; and an accompanying parallel transition in processing of the sensory to the affect component of the symptom of tinnitus. The establishment of a paradoxical auditory memory for tinnitus is hypothesized to be the initial process localized in the medial temporal lobe. The resultant affect components become clinically manifest by complaints in alteration in mood, i.e., anxiety, depression, increasing attention to tinnitus, annoyance, interference in communication, fear, and the negative effects of stress.

In other words, the heterogeneity of the symptom of tinnitus is reflected in a FCP for tinnitus. Such a pathway includes the integration of multiple neuronal circuits, which are utilized by multiple reciprocal processes included in the transition/interaction between the sensory and affect components of tinnitus. The origin and localization of sensory/affect processing is hypothesized to be in a key area of the brain, i.e., the MTLS.

It is hypothesized that the transition from perception to memory i.e., sensory to affect/memory as reported by Squire et al. in 1991 has a direct application to tinnitus particularly of the severe disabling type.[16] The Medial Temporal Lobe System (MTLS) has been identified for the function of memory[16,17] and stress.[18] Both are clinically significant for tinnitus (SIT).

The FCP is presented as a hypothesis focusing on a process within the MTLS of a paradoxical auditory memory with speculations as to its clinical applications for both diagnosis and treatment. Demonstrations of SPECT imaging of brain in patients are presented to support this hypothesis. The clinical application of this hypothesis for present and future tinnitus diagnosis and treatment is considered significant. It is considered to transcend the classical thinking of tinnitus as an auditory signal restricted to the auditory pathway.

HYPOTHESIS

A. General:

Clinical evidence suggests that mechanisms involved in the transition of sensory to affect interchange processing include: a) the medial temporal lobe system (MTLS); and b) the limbic lobe.[2,5]

The concept of a FCP for tinnitus (FCP) has evolved from a clinical experience that all patients with tinnitus, particularly of the severe disabling type, have as a common denominator a disorder in affect.[2,3] Specifically, a behavioral disorder which may reflect a response to or an accompaniment of a aberrant auditory sensory stimulus, i.e., tinnitus. The heterogeneity of response both for sensory and affect has been reported by professionals of all disciplines who are involved in tinnitus diagnosis and attempts for its control. A FCP for tinnitus must by definition, demonstrate a integration of clinical experience with basic science of brain function; explain and identify the site of transition of the sensory to affect components of the symptom of tinnitus and the anatomical substrate(s) involved; and the physiological mechanism(s) underlying the processes that result in such change. This suggests anatomic-physiological components of a FCP. At this time, the medial temporal lobe system (MTLS), and the limbic lobe are hypothesized to represent the primary cortical anatomic sites of brain action in a FCP wherein the sensory/affect transition is initiated by a process of establishment of a paradoxical auditory memory with resultant alterations in mood.

B. Medial Temporal Lobe System (MTLS) and the limbic lobe:

The MTLS is part of the limbic lobe.[19] The limbic lobe is considered a "synthetic lobe." It encircles the upper brain stem. It includes the most medial margin of frontal, parietal and temporal hemispheres. It includes the subcallosal, cingulate, and parahippocampal gyri, the hippocampal formation, and the dentate gyrus. The limbic system is a term used to include the limbic lobe and associated subcortical nuclei (amygdaloid complex, septal nuclei, hypothalamus, epithalamus and other thalamic nuclei). Physiologic evidence suggests functional differences between the various components although most are related to visceral or behavioral activities (Fig. 1).

James Papez (1937) suggested that certain rhinencephalic and limbic pathways provided an anatomical basis for emotions and their expression through visceral and instinctual actions such as those involving feeding, mating, mothering, and aggression.[20] The "Papez circuit" consists of feed in/feed out pathways between cortical and subcortical centers with a major connecting bundle in the cerebral white matter and the **cingulum**. The Papez circuit proposed the anatomical basis of emotion to consist of the **cingulate gyrus** which connects with the parahippocampal gyrus and peripheral area of the temporal lobe. The temporal lobe connects with the **hippocampus** (AMMONS horn) via the **temporo-ammonic tract.** The hippocampus connects with the **mamillary body** via the **fornix**. The mamillary body connects with the **anterior nucleus of the thalamus** via the **mamillothalamic tract**. The anterior nucleus of the **thalamus** connects with the **cingulate gyrus** via the **superior thalamic peduncle**, thus completing the circuit. Additional feeding pathways to the circuit were described to include the septal and olfactory regions and amygdala.

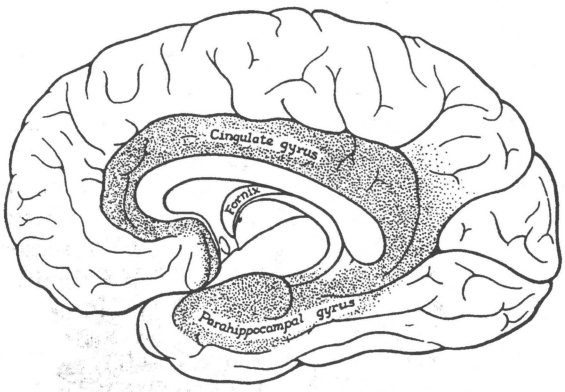

Fig 1. Drawing of the medial surface of the hemisphere. Shading indicates the limbic lobe which encircles the upper brain stem. This cortex lies on the most medial margin of the hemisphere (i.e., the limbic) and includes archicortex, paleocortex and juxtallocortex. (From Carpenter and Sutin, Human Neuroanatomy, 1983; courtesy of Williams and Wilkins).

C. Medial Temporal Lobe System (MTLS) and Memory:

The MTLS has been identified in humans and monkeys for the function of memory.[16] The anatomical components consist of the hippocampal formation; amygdaloid complex and adjacent cortical areas i.e., perirhinal cortex (areas 35, 36); periamygdaloid cortex (area 51); entorhinal cortex (area 28); and parahippocampal (areas TH, TF). The anatomical components are best seen by a saggital section of the medial surface of the brain; and ventral views of the base of brain. The entorhinal cortex is a major source of projections at the hippocampus and in turn receives input from adjacent perirhinal, parahippocampal cortices. The frontal, temporal, parietal lobes project to the perirhinal, parahippocampal cortices from unimodal and polymodal areas. Additional direct inputs to the entorhinal cortex originate in the orbital frontal cortex; cingulate cortex; insular cortex; and superior temporal gyrus. All projections are considered to be reciprocal (Fig. 2).

Squire and Zola Morgan in 1991 summarized recent and past investigations of the MTLS and memory; differentiated between investigations for declarative and non-declarative memory; and discussed the function of the hippocampal formation and the amygdala for declarative memory.[16] Memory was reported to be not a single faculty but composed instead of separate systems, only one of which is impaired in amnesia i.e., declarative memory.[21] Declarative memory is the ability to acquire information about facts and events. Non-declarative memory, also called implicit memory, includes all abilities which are unconscious and expressed through

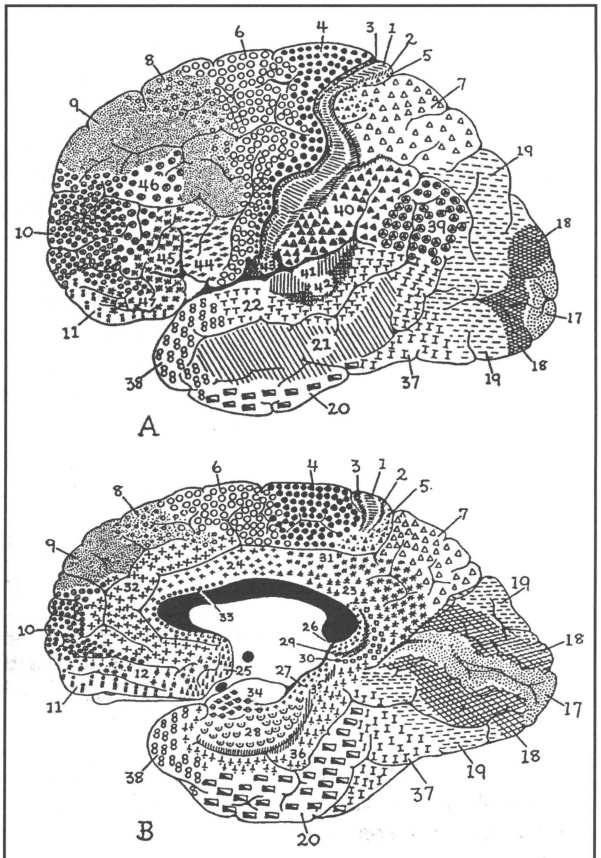

Fig. 2. Cytoarchiectural map of the human cerebral cortex. (A) Convex surface; (B) medial surface (after Brodmann, '09). (From Carpenter and Sutin, Human Neuroanatomy, 1983; courtest of Williams & Wilkins).

performance.[16] Such abilities provide for cumulative changes in perceptual and response systems of new skills and habits, priming, simple classical conditioning, and non-associative learning. Non-associative learning includes habituation and sensitization. Limbic lesions have selective and specific effects on memory. Severe memory impairment associated with hippocampal and amygdala lesions were attributed not to the addition of the amygdala to the hippocampal lesion but instead to the addition of cortical regions that lie adjacent to the amygdala and that are necessarily damaged when the amygdala is removed or impaired. The entorhinal cortex was suggested to be the principle route by which information from the neocortex reaches the hippocampus. For declarative memory, lesions in the perirhinal cortex, and not damage to the amygdala, contributed to severe memory impairment associated with hippocampal/ amygdala lesions.

Le Doux[22,23] has identified a neuroanatomical subcortical emotional processing circuit (i.e., thalamo-amygdala), in which the emotional significance of a auditory stimulus

can be learned, stored in memory, and expressed in body physiology by the autonomic nervous system or behavior by the somatomotor system. Thalamic and cortical sensory projections to the amygdala are compared i.e., thalamo-cortical-amygdala emotional pathway.

D. Hypothesis:

It is hypothesized that a FCP for tinnitus exists in the brain of all patients. Its chief function is the transition of a aberrant dysynchronous auditory sensory signal to a affective behavioral response (Fig. 3).

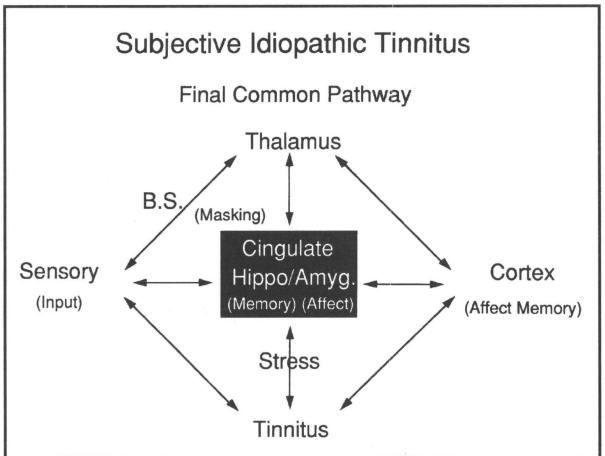

Fig. 3. Final Common Pathway for Tinnitus - The Medial Temporal Lobe System (Presentation at the Charles Univ. Prague, Czech Republic January/95).

It is hypothesized that for all sensory systems the sensory and affect components are linked by memory.[2] The experience of the sensation is a perceptual image of the stimulus. This conceptualization is a basic tenet of the FCP for tinnitus of the cochleovestibular system.

It is hypothesized based on our tinnitus experience that in the normal auditory system a sequence of auditory images, results first in establishment of an auditory memory for a sensory input , both short and long term; and secondarily a positive affective behavioral response. Both the sensory stimulus and affect response reflect an interaction of neuronal networks. This sequence of events is hypothesized to exist in general for other sensory systems and specifically for the cocheovestibular system. Other aberrant sensations experienced by patients include hyperacusis, dysacusis, vertigo, etc.

For tinnitus it is hypothesized that first, a primary physiologic process is the transition of the sensory auditory aberrant signal i.e., tinnitus, to a paradoxical auditory memory which secondarily, results in a significant negative alteration in affect i.e., behavior. Paradoxically, the memory of the aberrant sound, i.e., tinnitus, if it becomes chronic, is hypothesized to result in tinnitus of the severe disabling type.

Psychology and neuroscience evidence have differentiated between long term and short term memory. Long term memory consists of two functionally independent systems i.e., an explicit system for facts and events and an implicit system for learning of perceptual motor skills and habits. Short term memory systems appear to reflect the parallel operation of two mechanisms. One being automatic and the other active.[21,24]

The basic transition from sensory to affect is considered to have at least three essential components at this time: a) sensory; b) affect and c) memory. The sensory and affect components are considered to be in a constant state of reciprocal interaction. The establishment of a paradoxical memory provides a linkage i.e., "a bridge" between the sensory and affect components. A paradoxical memory modulates the transition between the sensory and behavioral component of tinnitus.

It is speculated that the interpretation of the findings reported by Squire and Zola Morgan[16] of transition from perception to memory in the MTLS can be modified for tinnitus based on a correlation with the perfusion asymmetries identified by SPECT in regions of interest of the brain in tinnitus patients examined to date.[2,5,7-11] The MTLS is reported to be essential for establishing long term memory for facts and events i.e., declarative memory.[16,17] The role of MTLS was reported to be temporary. With time memory stored in neocortex gradually becomes independent of MTLS structures. Distinction is made between the role of the hippocampus, and that of the amygdala. It is speculated that for tinnitus the amygdala is significant for the alteration in emotional behavior described by the patient. The amygdala is reported to be involved in the behavioral response reflected in non-declarative explicit memory i.e., unconscious and expressed by interference in communication ability, sleep etc. For tinnitus such abilities may reflect cumulative changes in perceptual and response systems and for the development of new skills and habits personified by increasing attention to tinnitus and inability to "cope" with tinnitus. Increasing attention and a probable relationship to sleep phenomena also is considered to be a reflection or projection from the amygdala to sleep areas in cortex. The influence of sleep on tinnitus has been reported.[3] The sensory input from the primary and secondary auditory cortex; and secondary auditory cortex to the amygdaloid complex is also speculated to reflect and to be modulated by the influence of stress.[18] This is the basis for our stress model for tinnitus[25] (Fig.4). Young (1991) considered for depression that the location of cortisol control to be not in the hypothalamus but rather in the hippocampus.[26] It is proposed for tinnitus that a cycle can be established wherein reciprocal projections between hippocampus,

amygdala, entorhinal cortex and hypothalamus vary in the degree of control of cortisol levels resulting in further strengthening of an already established paradoxical memory with resultant additional negative affect behavioral manifestations of emotion, fear, anxiety, depression, etc.

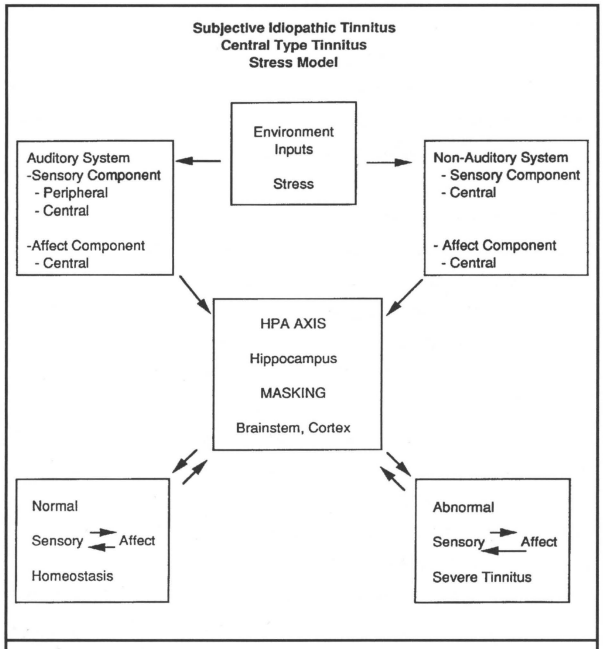

Fig. 4. Model Central Tinnitus/Stress. From Shulman A: A Stress Model for Tinnitus. Presentation International Tinnitus Study Group, Washington, D.C. 9/92.

The modulator of the sensory component is considered to be the efferent system and the process of masking.[3] The modulator of the afferent component is considered to be stress. Modulation of both tinnitus components reflect single or multiple neurotransmitters/neuromodulators, acting alone and/or in combination.

In the patient with tinnitus, particularly of the severe disabling type it is hypothesized that both the hippocampus and amygdala of the MTLS are significant for the transition of the sensory to the affect component. For memory, alterations occur in the hippocampal formation with the establishment of a paradoxical memory for an aberrant dysynchronous signal. Inputs to the hippocampus include temporal, orbital frontal, and parietal areas. It is speculated that the primary auditory cortex projects to the hippocampus and amygdaloid complex. The medial temporal lobe establishes a paradoxical memory function. The reciprocal projections between the entorhinal cortex, hippocampus and amygdala result in an emotional response.

In summary, the FCP model for tinnitus involving the medial temporal lobe system is initiated in the MTLS by the process of establishment of a paradoxical memory. The thalamus is speculated to be a primary site for integration of sensory/affect interaction which projects to the MTLS and cortex for initiation of the auditory sensory memory and affect behavioral response.[22,23] The paradoxical memory for tinnitus is considered a non-declarative or implicit memory. It involves not only the hippocampus but also the amygdala. The transition from perception to memory involves reciprocal interconnections between the hippocampus, entorhinal cortex, and adjacent neocortical inputs i.e., temporal, parietal, frontal. The central efferent system at a cortical and subcortical level at brainstem is speculated to control the masking capability of the auditory system. The degree of inhibition regulated by GABA function is hypothesized to be reflected in the degree of development of the paradoxical memory for tinnitus. It also modulates the sensory component. The reciprocal interconnections between primary and secondary associated auditory cortices and vestibular cortices of the cochleovestibular system reflect multiple neuronal networks which have the capability to adapt to changes reflecting alteration in sensory input and output due to different factors influencing neuronal activity of the cochleovestibular system and other systems at a cortical and subcortical levels. Claussen already has demonstrated in a tinnitus patient the influence of a rotary stimulus on cortical hyperactivity.[27] The symptom of tinnitus may reflect the adaptation of multiple neural networks at cortical and subcortical levels to aberrant sensory stimuli; which may demonstrate in the future a molecular and functional distribution to be identified as tinnitus types and subtypes. Neuronal networks are hypothesized to exist which in the past were identified as primary and secondary areas. An initial interaction between the sensory and affect components is reflected by function/dysfunction within the peripheral and/or central cochleovestibular system.

It has been hypothesized that one mechanism for the translation/integration /transition from sensory to affect includes the neurotransmitters glutamate, GABA and alterations in calcium homeostasis. It is conceived that the excitatory action of the amino acid glutamate may result in more than one physiological function. Different attributes of tinnitus may be the clinical reflection of a multiplicity of function of a particular protein e.g., glutamate.[5,10] Such a protein may demonstrate a degree of adaptability of different function. An imbalance in protein activity may contribute to neuronal damage. A diminution of inhibition by gamma-amino butyric acid (GABA) results in altered function. The decrease in GABA function can arise because of a disconnect of GABA ergic interneurons from excitatory inputs e.g., glutamate. It is speculated that the GABA ergic inhibition and resultant glutamate excess produces a disruption in

calcium homeostasis. Such a sequence of events, called glutamate neuroexcitotoxicity can result in a hyperexcitability of "epileptic" characteristics i.e., epileptogenesis.[28,29] It is speculated that any system or mechanism or drug that blocks GABA mediated inhibition can produce a seizure type activity.[30]

For tinnitus, one can speculate on a tinnitogenesis i.e., a seizure type activity resulting in the perception of an aberrant auditory stimulus. In such a manner tinnitus of a central type may arise due to a seizure type activity, for example at a cortical level; and via mechanisms of deficient central masking capability and/or reduced efferent function have as a FCP the development of a paradoxical auditory memory with a resultant cascade of events reflecting a heterogeneity of behavioral/emotional change highlighted by anxiety, depression, and interference with sleep and communication.

DISCUSSION

Most neuroscientists now believe that all aspects of mind including consciousness or awareness can more likely be explained in a materialistic way as behavior of large sets of interacting neurons.[22,23,29,6,30] James stated that consciousness is not a thing but a process.[6,31] The problem at this time is to identify what is the process or processes.[31]

Our approach is clinical and attempts to identify not all components of the FCP but rather to focus on one aspect, specifically memory which is considered at present to be clinically most significant; and is explainable by what has been reported for understanding brain function specifically memory. I consider the experimental and theoretical work of consciousness as reflected in memory, to be a starting point to explain our SPECT findings to date.[4,6,16,17,21,22,23,29, 31,32]

The activity in the brain that corresponds to memory can be found in the medial temporal lobe system. The reports of Squire et al. have focused primarily upon declaritive memory.[16,17.24] Tinnitus is a sensory perceptual phenomena believed to be reflected in the implicit memory.

Crick's comments on the problem of visual awareness I believe can be applied to that of tinnitus - an auditory perceptual phenomenon.[6,31] Specifically, investigations for tinnitus are necessary from a psychological and a neuro-science perspective for the issues of attention and very short term memory. Neurobiological theories of tinnitus awareness need to be developed and tested using a combination of molecular, neurobiological and clinical imaging studies. The interaction which we have called a transformation/integration/translation of sensory to affect is but another way that tinnitus reminds us of the age old question of centuries namely how the brain relates to the mind.

The MTLS can be considered an information processing pathway for the integration of sensory and affect components of all sensory inputs. It is possible that there is a localization in the MTLS for all sensory inputs similar to that which exists in the motor cortex. It is possible that there may be further or additional localization for a particular sensation.

We have clinically identified three components to exist for the symptom of tinnitus i.e., sensory, affect, and psychomotor.[3] Tinnitus is a multidimensional symptom disorder with sensory, affect, and psychomotor components. In 1991 we speculated that information for normal auditory function was processed along two different pathways i.e., one for sensory and other other for affect.[33] In the ascending auditory system an integration occurred at the thalamus level which progressed for final integration at the cortex and MTLS. At this time a hypothesis is proposed that normal auditory function depends on multiple routes of integration, transformation, translation which can be selectively/individually damaged at any level. Specifically, the anatomic substrate where integration of sensory and affect components occurs for the auditory system, is suggested at this time to be in the MTLS.

Feedback loops produce a dynamic characteristic into a system. A feedback loop is considered to be the process of masking. Feldmann reported the difference in interaction of signal and masker in patients with and without tinnitus by masking curves. The masking curves "can be thought of as contour lines of the neural elements involved in processing signal and masker."[34] Tinnitus is believed to produce or reflect a instability or interruption in auditory masking function.

The perception of a auditory image, considered to be "normal", is hypothesized to be determined by a normal masking function. Interference in masking within brain, initially at brain stem is hypothesized to set in motion a cascade of events wherein the sensory component is overwhelmed by that of the affect due to the establishment of a paradoxical auditory memory. In the case of tinnitus, the end result is tinnitus of the severe disabling type.

The total cochleovestibular system provides a network not only for the sensory signal but rather a multi-dimensional flow pattern of information whose coordinates are defined by all the auditory features i.e., sensory, affect, sensorimotor, that the network can represent. Hinton et al.[35] have described such neuronal networking in investigations simulating brain damage.

The FCP is hypothesized at present to rely on the properties of a neural network that transforms one representation i.e., sensory into another i.e., affect. This creates an error in pattern recognition of the normal auditory signal. SPECT findings at this time suggest a

common neural pathway and not an abstract algorithmic description. The future is to identify neural networks and to create idealized computer simulates of groups of neurons.

One can, for tinnitus at this time speculate on six layers of such a network. Initially the periphery i.e., Organ of Corti; second the brain stem, third the ascending auditory system to the level of the inferior colliculus; fourthly between the inferior colliculus and thalamus; fifthly brain between thalamus and auditory cortex; and sixth - multiple neuronal circuits within the brain. Feedback loops exist at brain stem, thalamus, temporal lobe, and the MTLS. The feedback loop is a cleanup layer. Such layers attempt to re-establish a homeostasis within the sensory system. Tinnitus can be considered to be an auditory error i.e., a defect in the ability of the masking neurons to function normally. It is speculated that a reversal or repair of the processing would/can result in elimination of tinnitus.

It has become apparent to us from our clinical experience with SPECT since 1989, that the manner in which the brain processes auditory sensory information is radically different with or without the presence of tinnitus. The FCP reflects this experience. The FCP is a biological model which is an outgrowth of our ongoing attempts to integrate the basic sciences with our clinical experience for the diagnosis and treatment of all types and subtypes of tinnitus.

Recent findings using SPECT suggest that in some patients tinnitus may be a sign of organicity of the brain.[5,9] SPECT investigations in tinnitus patients and the identification of mechanisms of transduction in the cochlea lend support to the hypothesis that tinnitus is not a unitary symptom but that the clinical manifestation and differentiation of types of tinnitus can be further

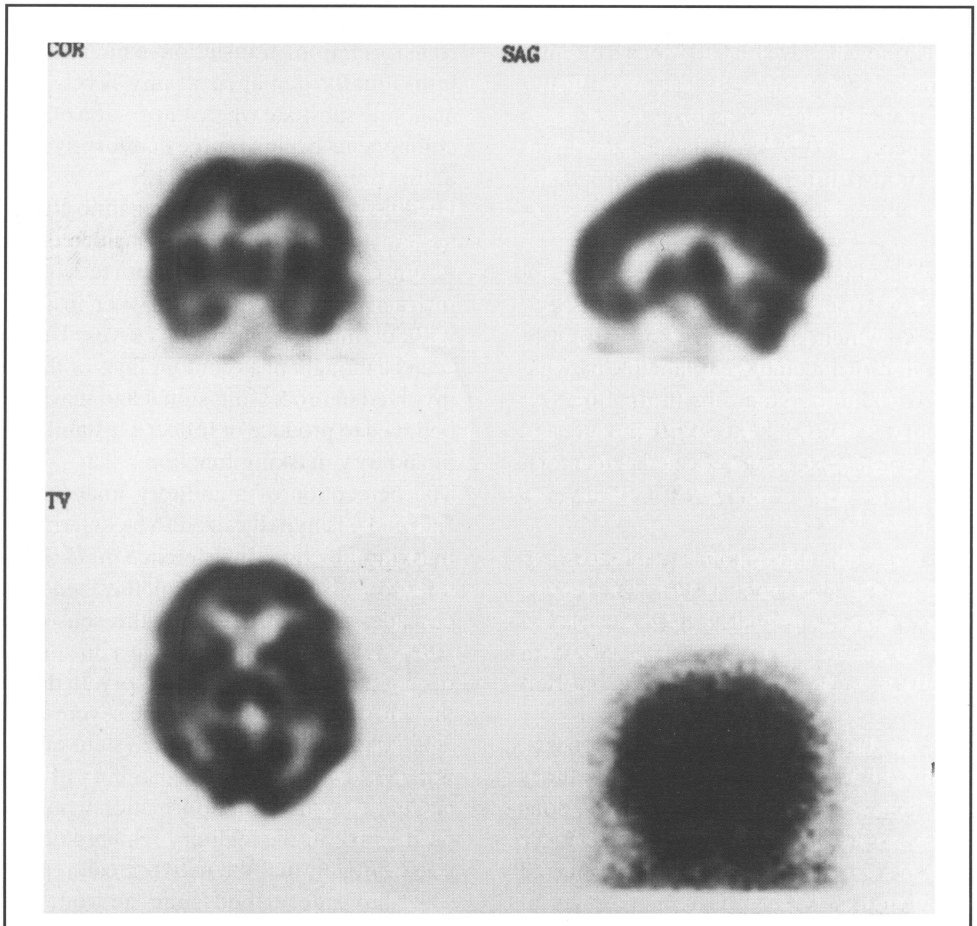

Fig. 5. Normal SPECT/brain[10]
Three orthogonal imaging planes coronal (upper left), sagittal (upper right), transaxial (lower left), raw data (lower right).

differentiated by subtypes.[3,13-15]

The consequences of the identification of a FCP for tinnitus and the role of the MTLS are considered significant. For the first time, here is a model which may differentiate tinnitus between its sensory and affect components both from its clinical and basic science perspectives. It provides a basis for the development of a neuropharmacology for tinnitus.

The heterogeneity of tinnitus both for its sensory and affect components, can for the first time be investigated with respect to a site of lesion(s); mechanisms for tinnitus production; and have a practical application for its diagnosis and treatment.

The following SPECT images of the brain demonstrate multiple perfusion asymmetries, highlighted by the MTLS (Fig. 5-8).

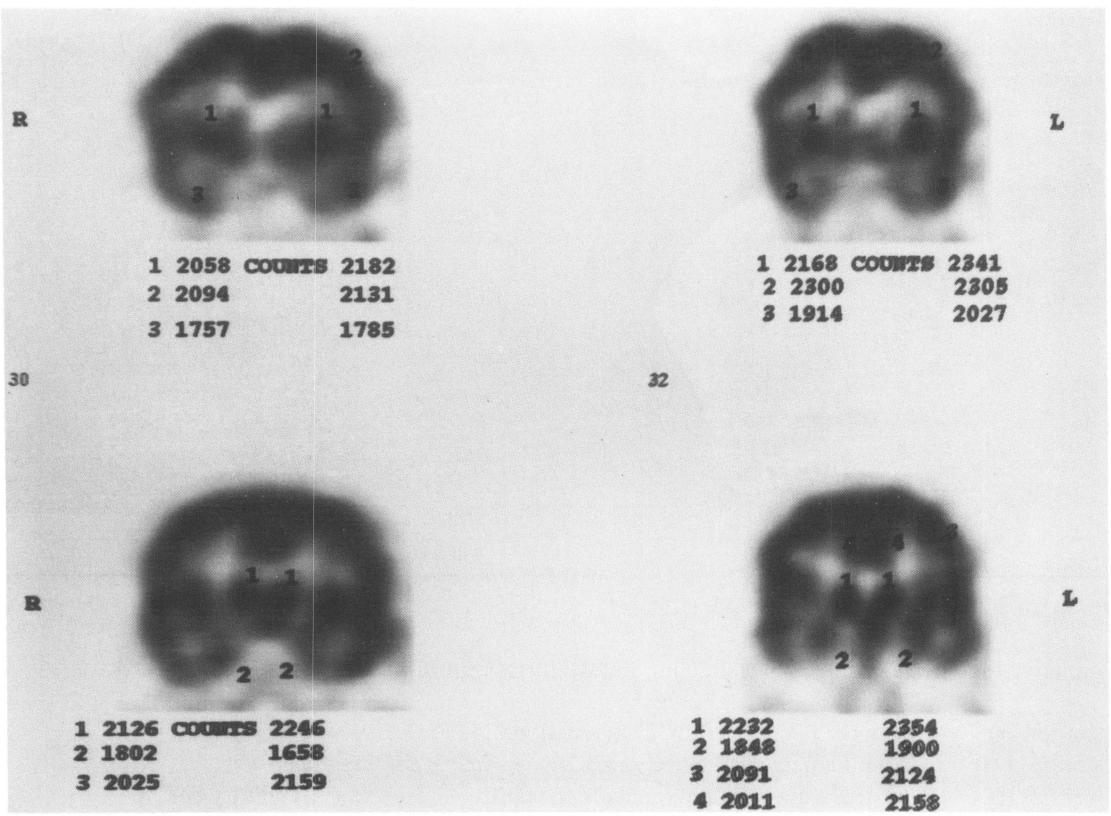

Fig. 6. Normal SPECT/brain - coronal images. Right (r), left (l)[10]

upper left (r): 1 - putamen 2 - frontal 3 - temporal lobe
upper right (l): 1 - putamen/caudate 2 - frontal 3 - temporal/amygdala
lower left (r): 1 - thalamus 2 - amygdala/hippocampus 3 - primary auditory cortex
lower right (1): 1 - thalamus 2 - hippocampus/parahippocampus 3 - parietal 4 - cingulate

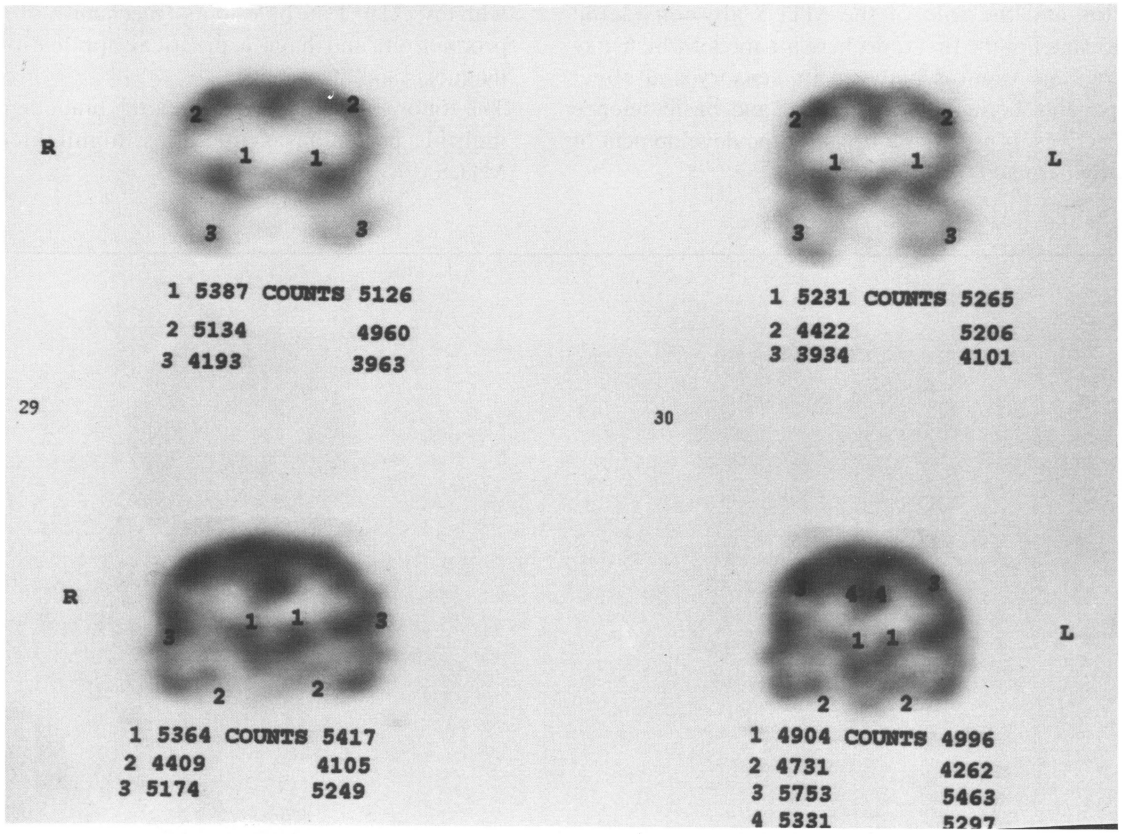

Fig. 7. Case 1 coronal images right (r), left (l)[10]

1 - relative high perfusion 2 - 4 asymmetry (r) (l), hypoperfusion

upper left (r)	1 - putamen 2 - frontal 3 - temporal lobe
upper right (l)	1 - putamen/caudate 2 - frontal 3 - temporal/amygdala
lower left (r)	1 - thalamus 2 - amygdala/hippocampus 3 - primary auditory cortex
lower right (l)	1 - thalamus 2 - hippocampus/parahippocampus 3 - parietal 4 - cingulate

CONCLUSIONS

The FCP for tinnitus provides a rationale and model for understanding the integration, interaction, translation, and transformation of the sensory auditory signal to the affect behavioral response.

An initial process, in the MTLS, is hypothesized to be the establishment of a paradoxical auditory memory for tinnitus.

The FCP for tinnitus/MTLS for the first time provides a model which explains the heterogeneity of the symptom of tinnitus. The MTLS in this model provides a rationale to understand how and where a transformation/transition occurs between sensory auditory perception and behavior response.

SPECT imaging of brain provides an ability to identify regions of interest in the brain which demonstrate perfusion asymmetries frequently found in patients with tinnitus of the severe disabling type. Clinical applications include an improvement in the accuracy of tinnitus diagnosis; identification of its medical significance; selection of medication to attempt tinnitus control; and a monitoring method to establish the efficacy of therapy.

Perception of images in general is initiated by psychochemical events. For auditory perception this includes the inner ear and Organ of Corti; transmission within the

ascending auditory system to registration of impulses within the auditory cortex. Such message transfer is a complex function. Kassirer stated it well in discussing a visual image in clinical medicine that "often we are creating mental models of physical models. Nevertheless, such models, whether once or even twice removed from reality are invaluable aids to perception and interpretation functions which are critical to the performance of the doctor."[36]

The processes involved in the establishment of the symptom of tinnitus particularly of the severe disabling type and the problems encountered, relate to the overall problem and question over centuries of what is the relationship of mind and brain and what are the processes involved in such identification. The problem is not only scientific but also philosophical. This is the reason for the complexity encountered in tinnitus diagnosis and treatment.

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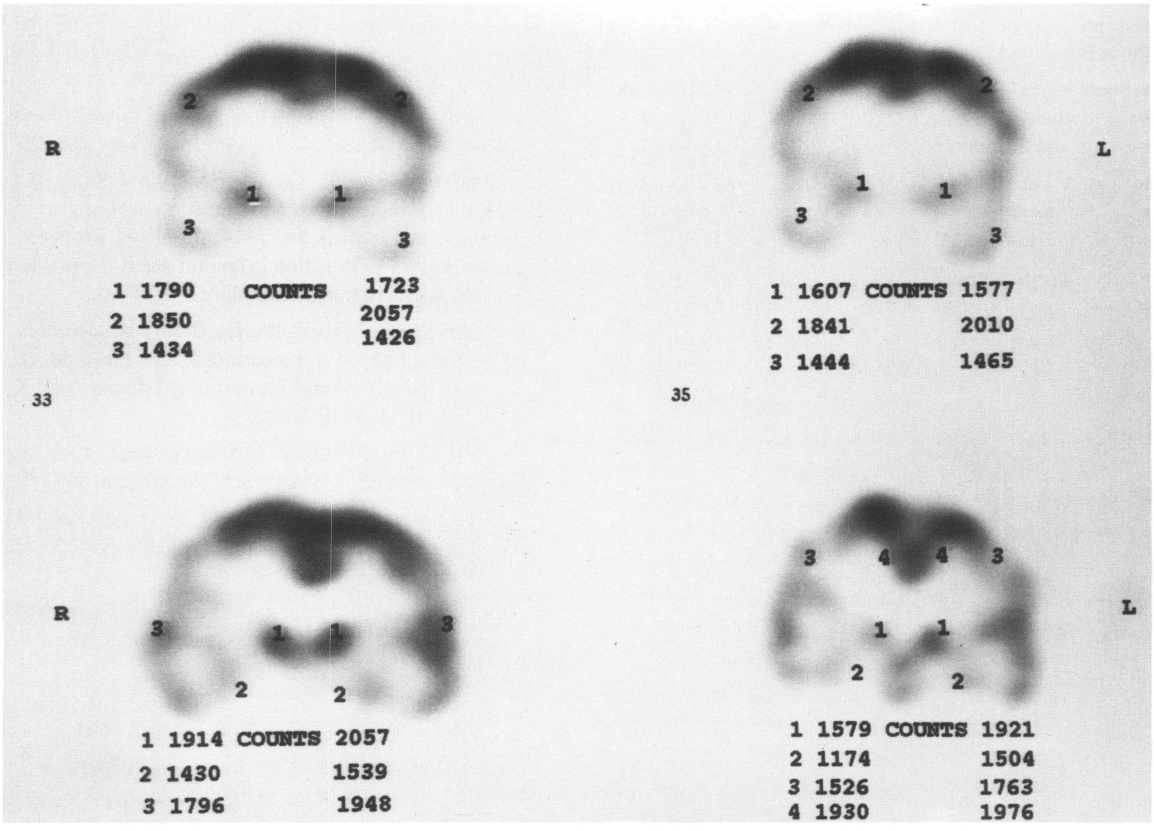

Fig. 8. Case 2 coronal images right (r), left (l)[10]

1-4 asymmetry (r) (l), hypoperfusion

upper left (r)	1 - putamen 2 - frontal 3 - temporal lobe
upper right (l)	1 - putamen/caudate 2 - frontal 3 - temporal/amygdala
lower left (r)	1 - thalamus 2 - amygdala/hippocampus 3 - primary auditory cortex
lower right (l)	1 - thalamus 2 - hippocampus/parahippocampus 3 - parietal 4 - cingulate

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