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Tinnitus Dyssynchrony-Synchrony Theory: A Translational Concept for Diagnosis and Treatment

Abraham Shulman and Barbara Goldstein

Martha Entenmann Tinnitus Research Center, Forest Hills, New York, and Department of Otolaryngology, Health Science Center at Brooklyn, State University of New York, Downstate Medical Center, Brooklyn, New York

Abstract: The tinnitus dyssynchrony-synchrony theory (TDST) is a hypothesis that considers tinnitus to be an abnormal, conscious, auditory percept. It is believed to originate as an initial dyssynchrony in pre- or postsynaptic neuronal transmission within the peripheral or central nervous system (cortical or subcortical). It interferes in the excitatory and inhibitory process or processes involved in maintaining homeostasis for brain neurofunction, in multiple neural substrates, and acts as an aberrant auditory stimulus to express this dysfunction via the auditory system. The conscious auditory percept for tinnitus is hypothesized to reflect clinically a summation of synchronous activities of neuronal activity recordable from multiple neural substrates at the brain cortex. The transformation from the dyssynchrony of the aberrant auditory stimulus to one of synchrony and individual brain function of affect, somatosensory response, and consciousness is clinically considered to be a final common pathway for tinnitus. The clinical application of the TDST has increased the accuracy of tinnitus diagnosis and improved the efficacy of treatment modalities attempting tinnitus relief.

Key Words: consciousness; dyssynchrony; final common pathway for tinnitus; paradoxical auditory memory; perception; synchrony

The tinnitus dyssynchrony-synchrony theory (TDST) is a hypothesis and concept that is dynamic. It has evolved since 1979, providing an understanding of the mechanisms of tinnitus production, and has made possible clinical application in tinnitus diagnosis and treatment, which are individual for each affected patient. It reflects the translational application and clinical integration of advances in auditory science and neuroscience and in brain function to an aberrant auditory stimulus (i.e., tinnitus). The clinical application of the TDST has increased the accuracy of tinnitus diagnosis and improved the efficacy of treatment modalities attempting tinnitus relief.

Reprint requests: Abraham Shulman, MD, FACS, Department of Clinical Otolaryngology, Health Science Center at Brooklyn, State University of New York, Downstate Medical Center, 450 Clarkson Avenue, Box 1239, Brooklyn, NY 11203-2098. Phone: 718-773-8888; Fax: 718-465-3669; E-mail: metrc@inch.com

Tinnitus in this hypothesis refers to subjective idiopathic tinnitus of the severe disabling type. This type is reported to have an incidence in the United States of 12 million [1] and is differentiated from that in tinnitus patients who can ignore, or at least cope with, their tinnitus.

We present the TDST at this time because of the clinical, basic science, and neuroscience objective evidence thought to support it. First, we point to nuclear medicine imaging in the form of single-photon emission computed tomography (SPECT), positron emission tomography (PET) identification of multiple neural substrates involved in sensory-affect transformations in tinnitus patients [2,3], and electrophysiological recording data obtained with quantitative electroencephalography (QEEG) of brain oscillations reflective of brain function. Second, we rely on neuroscientific advances that have identified underlying processes involved in the sensory physiology and brain function of perception and consciousness, presented in the past as a hypothesis. We submit both sources of data for clinical consid-

eration in supporting our hypotheses of the TDST and a final common pathway (FCP) for tinnitus (i.e., sensory-affect transformation). Our hypothesis is highlighted in the brain by the functions of perception, consciousness, memory, and emotional-behavioral response to an aberrant auditory stimulus (i.e., tinnitus).

Hypotheses of mechanisms of tinnitus production in the past included changes in temporal firing patterns of neuronal activity [4–6]; analogy to pain perception [7]; damage to the temporal dysfunction of the inner or outer hair cells [8–11]; imbalanced activity in the eighth nerve, resulting in tinnitus [8,9]; the efferent system [12,13]; and partial interruption of the eighth nerve [14,15].

The TDST at this time focuses on dyssynchrony-synchrony within the peripheral or central cochleovestibular system, not on the underlying processes involved. There is a need to differentiate between the dyssynchronous signal hypothesized to be tinnitus and the synchrony of neuronal activity at the brain cortex, which is the function of the perception and conscious awareness of tinnitus.

Clinical experience with tinnitus evaluation and attempts for control (i.e., relief), ongoing since 1979 in more than 10,000 patients who completed a medical-audiological tinnitus patient protocol (MATPP), has been highlighted by the heterogeneity of the complaint, its individuality for each patient, the clinical identification of clinical types of tinnitus (individual for each patient), the identification of factors influencing the clinical course of the tinnitus, and the predominance of the behavioral and emotional component of the complaint in its clinical manifestation. Tinnitus has clinically been found to be a symptom of neurotological disease and not to be a unitary complaint [16,17].

The efficacy of attempts for tinnitus relief with existing modalities—instrumentation, medication, and surgery—has been influenced by the accuracy of the tinnitus diagnosis, treatment of underlying factors identified in patients' clinical history, and physical examination influencing the clinical course of the tinnitus (e.g., fluctuation in aeration of the middle ear, secondary endolymphatic hydrops) [18–20].

This publication presents (1) the TDST; (2) its historical background; (3) concepts of basic sensory physiology considered to underlie the hypothesis of the TDST, the FCP for tinnitus, and their link; (4) a model for the TDST that includes an integration of processes identified by neuroscience to be involved in brain function of perception and consciousness and found to support a theory of perception and consciousness and a FCP; (5) the clinical application of the TDST for tinnitus diagnosis and treatment for the benefit of tinnitus patients; and (6) clinical consideration of a paradigm shift in clinical thinking from a focus on the brain response to psychophysical and psychoacoustic aspects of tinnitus to that of specific brain function responses to tinnitus, with a focus on perception, consciousness, concentration, and the like.

HISTORICAL CONTEXT: TDST

The historical evolution of the TDST evolved in stages reflective of our clinical experiences since 1975.

Stage 1: Auditory Physiology and Auditory Evoked Potentials (1960)

The hypothesis of the TDST, in retrospect, had its origin in my initial interest in auditory physiology, stimulated by presentations by Georg v. Bekesy, Dorothy Wolf, and E.G. Wever, which I attended in Julius Lempert's 1960 postgraduate course in temporal bone surgery. Clinically, this led to my investigations in auditory-evoked response testing in adults in the late 1960s and early hearing screening in newborns and children in the early 1970s.

Stage 2: Auditory Evoked Potentials and Attempts at Identifying an Electrophysiological Correlate

The first objective demonstration of dyssynchrony in the electrical response to an auditory stimulus was observed in our initial experience in the late 1970s with the clinical application of auditory-evoked potentials testing, the auditory brainstem response (ABR) in tinnitus patients. Simultaneous brainstem responses with monaural stimulation in tinnitus patients revealed patterns of the early responses for the metrics of latency and amplitude [21]. The "noise" in the tracing, interpreted as dyssynchrony, was clinically considered to be tinnitus, and patterns of response were described. The subsequent introduction of ABR techniques to "smooth" the response is considered to have interfered in the observations reported.

ABR testing in tinnitus patients was an attempt to objectify a subjective complaint by the identification of an electrophysiological correlate for tinnitus [21–25]. The application of this technique was based on the hypothesis that tinnitus, a neurotological disorder, was a reflection of dyssynchrony in the neuronal firing and transmission in the pathways of the auditory system (peripheral, central, or both).

Stage 3: Clinical Attempt at Objectifying Tinnitus and MATPP (1975)

From the start in 1975, our clinical goals have been establishing accuracy for diagnosing tinnitus, objectify-

ing a subjective aberrant sensory complaint, identifying factors influencing the clinical course of the tinnitus and determining its medical significance, and attempting tinnitus relief. We have been impressed by the heterogeneity of the complaint, the predominance in the clinical complaint of the demonstration of the emotional and behavioral response of affected patients to the presence of the tinnitus, and the influence of noise and exposure and resultant stress on the clinical course of the tinnitus complaint. The dilemma presented to the basic scientist and clinician emerged as how to explain the transposition of a sensory complaint to one of affect and how the affect and emotional state of affected patients influenced the sensory complaint. Attempts to find answers to these questions were not new. Descartes attempted to answer these questions in his writing [26].

Our approach to find answers to these complicated questions has been to recognize the need to consider the entire cochleovestibular system (peripheral and central) and brain function. Initially, starting in 1975, a clinical approach for tinnitus patient evaluation followed a protocol, the MATPP [17–21], which included testing of the entire cochleovestibular system (peripheral and central), central speech testing when appropriate, and short-latency ABR testing. The MATPP provided a basis for clinically attempting to objectify the subjective tinnitus complaint. This led to the clinical identification of different clinical types of tinnitus by the extrapolation of the cochleovestibular test findings as electrophysiological correlates of cochleovestibular function and dysfunction and its integration with the clinical history and neurotological physical examination for an accurate tinnitus diagnosis. The hypothesis that tinnitus could have its origin in the central or peripheral cochleovestibular system was clinically considered to be supported by the cochleovestibular test findings highlighted by the ABR results [21–28]. Treatment was clinically recommended from a menu-based selection process, including instrumentation and medication.

Stage 4: Translation of Basic Sensory Physiology for Clinical Tinnitus Diagnosis and Treatment (1981)

Electrophysiological and metabolic correlates can, when identified, provide objectivity to subjective sensory perceptions. Basic science in sensory physiology has identified components of a sensation (i.e., the sensory, the affect, and the psychomotor) [29]. The clinical findings derived from patient medical history, physical examination, cochleovestibular testing, diagnosis, and treatment are differentiated for each component of the aberrant tinnitus sensory complaint. The sensory component is the tinnitus sensation itself, the affect component is the behavioral response to the presence of the aberrant auditory sensory stimulus, and the psychomotor component is the somatomotor response to the behavioral affective component of the tinnitus. Treatment was clinically recommended for tinnitus, differentiating between its components in a menu-based selection process that included instrumentation and medication. The basic science of sensory physiology and the underlying processes involved has been (since 1981), and continues to be, translated clinically into the MATPP for tinnitus diagnosis and treatment.

Stage 5: SPECT (1989), QEEG (1999), PET (2000), and Magnetoencephalography (2002)

The introduction of nuclear medicine imaging and QEEG and magnetoencephalography (MEG) has, since 1989, been an attempt to improve the accuracy of tinnitus diagnosis, establish its medical significance, objectify a subjective complaint, and monitor the clinical course of the complaint and the efficacy of therapy modalities attempting tinnitus relief.

In 1989, SPECT was introduced into the MATPP first as an investigative tool in an attempt to objectify tinnitus [30]. Since that time, in excess of 275 SPECT examinations have been performed under the supervision and direction of Arnold M. Strashun, MD, Director of Nuclear Medicine, State University of New York, Downstate Medical Center, Brooklyn.

Since 1999, imaging with SPECT has been introduced into the MATPP for tinnitus patients in whom neurodegenerative disease is considered in the tinnitus diagnosis. PET imaging has been used clinically since 2000 in selected tinnitus patients.

We consider nuclear medicine imaging to be the single most significant contribution to tinnitus diagnosis: first, for identifying in the brain multiple neural substrates [2,3]; second, for identifying patterns of metabolic function that we consider to be metabolic correlates for tinnitus; third, for objective demonstration of patterns of metabolic response in multiple neural substrates in the brain, supporting the TDST; fourth, for identifying a biochemical marker, the GABA-A receptor, for a particular, predominantly central-type tinnitus, which has clinically been translated into a tinnitus therapy [31]; fifth, for suggesting the hypothesis of an FCP for tinnitus based on the identification of multiple neural substrates and highlighted by the medial temporal lobe system [32]; and sixth, as a basis for a clinical paradigm shift from focusing on brain function response to psychophysical and psychoacoustic characteristics of the tinnitus to that of multiple brain function responses (e.g., perception, consciousness, concentration, cognition, learning, memory, affect-emotion, attention, and psychomotor activity) [33].

Highlights of this PET/SPECT experience (1995–2006) include identification of the FCP for tinnitus, the stress diathesis model for tinnitus, tinnitogenesis, the cerebellum involvement as an expression of interference in the system for tinnitus of the acousticomotor system, and the development of neuroprotective drug protocols focusing on treatment of not only tinnitus but myoclonus, auditory hallucinations, and cerebrovascular disease, all reflecting tinnitogenesis, an epileptogenic auditory process. A biochemical marker for predominantly central-type tinnitus has been identified to be the GABA-A benzodiazepine-chloride receptor. A benzodiazepine deficiency syndrome has been identified, meaning that some patients with stress require benzodiazepines to reestablish the homeostasis within the system. A receptor-targeted therapy directed to the GABA-A receptor (RTT-GABA) and influencing its activity by increasing or decreasing inhibition is resulting in significant long-term tinnitus relief in predominantly central-type tinnitus patients [31].

QEEG and tinnitus, reported originally by Weiler et al. [34,35] and introduced into the MATPP since 2000, has provided insight into the underlying cellular, neuronal, and interneuronal substrates involved in brain rhythms and their role in mechanisms producing tinnitus. The neuroscience of brain function has identified various rhythms of different frequencies in the brain. Different rhythms (frequencies) have been correlated with behavioral and mental functions. Rhythmicity implies organization and function.

QEEG is a significant addition to the MATPP for improvement in accuracy of tinnitus diagnosis via identification of a predominantly central-type tinnitus. It has supported the hypothesis that a significant role is played by the temporal and temporal-frontal regions in patients with tinnitus of the severe disabling type [33,36].

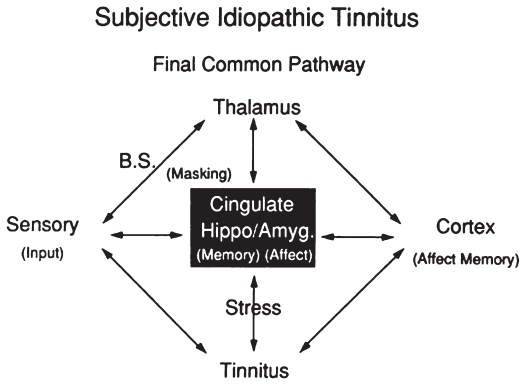

Figure 1. Final common pathway for tinnitus, 1995. A reciprocal, innervating, interneuronal network transforming a sensory aberrant stimulus, tinnitus, to one of affect and emotion. The factor of stress and the biophysiological processes involved modulate the severity of the tinnitus. (*Hippo*, hippocampus; *Amyg*, amygdala; *B.S.*, brainstem.)

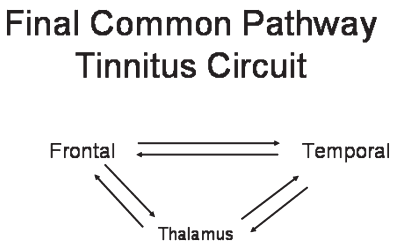

Figure 2. Tinnitus circuit, brain cortex, and quantitative electroencephalography. The interneuronal, reciprocal, innervating circuit involves the frontal and temporal lobes and is modulated by the thalamus [33].

An interneuronal circuit has been identified and hypothesized to be an FCP for tinnitus (Fig. 1) [32]. QEEG recording data of the power distribution by frequency bands and electrode sites correlate with neural substrates identified with SPECT of brain imaging and support the FCP for tinnitus, to be highlighted by a reciprocal innervating interneuronal circuit involving the frontal temporal neural substrates and the thalamus (see Figs. 1 and 2) [32]. A pattern of electrophysiological response in tinnitus patients has been identified and is considered to be an electrophysiological correlate, individual for each tinnitus patient and reflecting brain function, as hypothesized by the TDST [33].

MEG [37] provided a method for objectifying the magnetic component of the electrical activity of the brain in a masking paradigm for a tinnitus patient. The findings reported are considered support for the TDST and an alteration in the tinnitus clinical paradigm to a focus on the brain function of consciousness.

Stage 6: Brain Function, Consciousness, and Tinnitus

The integrative theory of consciousness [38–40] has provided a basis for clinical interpretation and understanding of the QEEG data recorded in tinnitus patients, for clinical translation for tinnitus diagnosis and treatment, and for its integration in support of the TDST model.

Summary

Historically, the evolution of the TDST has been one of integration of neurotological clinical observations with advances reported from neuroscience in auditory physiology, sensory physiology, and brain function. It is satisfying to report such scientific support for the TDST and its translation into tinnitus diagnosis and treatment.

TINNITUS DYSSYNCHRONY AND SYNCHRONY THEORY (2006)

Hypothesis

The TDST is a hypothesis considering tinnitus to be an abnormal, conscious, auditory percept originating as an initial dyssynchrony in pre- or postsynaptic neuronal transmission within the peripheral or central nervous system (cortical or subcortical). This dyssynchronous transmission interferes in the excitatory and inhibitory process or processes involved in maintaining homeostasis for brain neurofunction, in multiple neural substrates, and acts as an aberrant auditory stimulus to express this dysfunction via the auditory system.

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. The conscious auditory percept for tinnitus is hypothesized clinically to reflect a summation of synchronous activities of neuronal activity recordable from multiple neural substrates at the brain cortex. The transformation of the dyssynchrony of the aberrant auditory stimulus to one of synchrony and individual brain function of affect, somatosensory response, and consciousness is clinically considered to be an FCP for tinnitus.

Dyssynchronization: Mechanism for Tinnitus Production

The basic, initial, underlying mechanism for all clinical types of tinnitus is hypothesized to be a dyssynchronization within neuronal ensembles of the peripheral or central cochleovestibular system or the peripheral or central nervous system and becoming clinically manifest in the cochleovestibular system. *Dyssynchronization* is a lack of synchrony or timing of the discharge rate and phase locking of the auditory signal (peripheral, central, or a combination)—"noise" or spontaneous neural activity. Failure to establish a synchrony of activity in response to the dyssynchronous stimulus may become clinically manifest by seizure activity, behavioral abnormalities, and other neuropsychiatric symptoms. It is hypothesized that the balance between dyssynchrony and synchrony in neuronal firing is clinically reflected in the severity of the tinnitus complaint (i.e., perception and consciousness).

The degree of homeostasis in neuroanatomical substrates is hypothesized to be associated with an increasing synchrony in neuronal transmission at the cortex and clinically signifies development of a paradoxical auditory memory and conscious awareness for a dyssynchronous aberrant auditory percept: tinnitus.

The clinical application of the TDST has also provided a scientific basis to understand clinical types of tinnitus and the concepts of auditory and nonauditory clinical and subclinical types of tinnitus [27,28,41,42]. Clinical types of tinnitus—auditory or nonauditory, clinical or subclinical—have been identified and all reflect the degree of ability of a dyssynchronous signal to become synchronous and to establish itself as a conscious awareness of memory: in other words, a paradoxical auditory memory established for an aberrant auditory signal [3,32].

Concepts

Definition of Tinnitus

The definition of tinnitus must be dynamic to reflect what has been in the past, is at present, and will be in the future known of sensory biophysiology, the cochleovestibular system (peripheral and central), and the brain (both structure and function). The definitions of tinnitus that we have published have reflected our clinical experiences with tinnitus. These definitions are highlighted at this time by a clinical paradigm focus on the brain function of consciousness and the translation for tinnitus diagnosis and treatment of reported advances in underlying neurobiology, neurobiophysiology, and neurochemistry of synaptic neurotransmission.

In 1979, tinnitus was defined as an aberrant perception of sound unrelated to an external auditory stimulus. This definition reflected the limited understanding of the cochleovestibular system, of auditory biophysiology, and of brain function [16,24].

In 1992, tinnitus was defined as a sensory disorder of auditory perception reflecting an aberrant auditory signal produced by interference in the excitatory or inhibitory process involved in neurotransmission. This definition reflected the integration of clinical efforts of observation with neuroscience and nuclear medicine to identify underlying mechanisms of tinnitus production and to establish the disorder's medical significance.

Today (2006), tinnitus is a clinically conscious awareness, varying in degrees of consolidation, of an aberrant auditory paradoxical auditory memory, originating in response to an interference in the homeostasis between dyssynchrony and synchrony occurring within the synaptic circuitry of the neural substrates involved, thus interfering in the precision, specificity, and complexity involved in synaptic transmission for normal neuronal and interneuronal function [43]. Initially, tinnitus may be clinically manifest as an aberrant auditory perception. Development and increasing consolidation of the paradoxical auditory memory is accompanied by an increased conscious awareness and tinnitus of the severe disabling type. This definition demonstrates the

clinical application of the TDST for tinnitus diagnosis and treatment.

Synchrony and Brain Function

Synchrony in neurotransmission is the coincidence of timing of the discharge rate and locking of the signal. Brain function is reflected in synchrony at the brain cortex. The establishment of learning and memory has been reported to mirror synchrony in neurotransmission [43–45].

Synaptic Activity, TDST, Stochastic Noise and Resonance, and Tinnitus

What happens at the synapse (i.e., level of activity) in the peripheral or central cochleovestibular system and brain in a tinnitus patient is hypothesized to determine the clinical course of the tinnitus and will influence the efficacy of future treatment modalities attempting its treatment and control.

Synaptic activity has demonstrated excitatory inhibitory and modulatory neurotransmitter functions. The processes of long-term potentiation and long-term depression strengthen and reduce, respectively, synaptic transmission. Both are initial processes involved in establishing learning and memory and are influenced by lateral inhibition, the confluence of excitatory pathways of neurotransmission, lateral to which is inhibition mediated by GABA [46–49].

Final locking-in at pre- and postsynaptic membranes occurs by excellent guidance with path finding of a gross target that is selected for recognition. There is an attempt made to find the target or the receptor (or both). The elaboration of synaptic context onto appropriate cellular domains determines whether the signal transmission is one of synchrony or dyssynchrony [39].

The concept of dyssynchrony and synchrony extends beyond what we traditionally know of auditory function at this time. The concept is hypothesized to provide a new basic understanding of tinnitus and its relationship to sensorineural hearing loss.

The word *stochastic* is a term for random noise activity. Stochastic resonance (SR) is a phenomenon that occurs in a nonlinear system when a weak periodic signal—too weak to be detected—becomes detectable in response to an increase in ambient noise intensity and signal-noise ratio. The signal becomes detectable owing to a resonance that has been established between a weak deterministic signal and the stochastic noise. SR is commonly involved when noise and nonlinearity concur to determine an increase in order of the system response [50,51].

Spontaneous random noise, synaptic noise, and channel noise are variables influencing cellular metabolism and resultant neural response to a given stimulus in neuronal systems [52]. Noise has been demonstrated to be masked with the electrical stimulation cochlear implant [53]. The complexity of the processes involved in stochastic and channel noise will significantly influence the understanding of dyssynchrony-synchrony in neuronal systems, the functional manifestations, and its translation into tinnitus diagnosis and treatment.

Spontaneous neural activity input has been hypothesized to contribute to tinnitus [54]. Lack of spontaneous activity has also been considered as a factor that may contribute to tinnitus. Spontaneous activity is reduced or absent in deafened cochleas. The TDST posits that the spontaneous neural activity (i.e., "stochastic noise") of the cochleovestibular system—peripheral or central (or both)—is the dyssynchronous aberrant auditory stimulus (i.e., tinnitus) in a subclinical masked state: the underlying synaptic-channel processes to be identified. The degree of conscious awareness of the tinnitus is a reflection of the degree of synchronization at the cortex of multiple interneuronal ensembles of activity in response to the tinnitus. The masking phenomenon is considered to be a central cortical function of perception and consciousness.

The SR phenomenon contributes to an increased awareness of the tinnitus. The SR may be the primary process in the periphery of the cochleovestibular system resulting in the clinical manifestation of the tinnitus (i.e., the increased detection of the signal). In the peripheral cochleovestibular system, it is hypothesized that SR determines the efficacy of the central masking effect (i.e., a peripheral factor in the central auditory masking mechanism). The presence of sensorineural hearing loss establishes a condition that results in interference in the homeostasis between dyssynchrony and synchrony: Dyssynchrony is increased and predominates. The integrity of brain function will ultimately determine, or at least influence, the ability for plastic change at the cortex; when successful, it will result physiologically in the transformation of the dyssynchronous signal to one of synchrony with no perception of the tinnitus. This is essentially a central masking phenomenon involving the frontal and temporal lobes and modulated by the thalamus (see Fig. 1) [55].

The establishment of a synchrony of activity at the cortex is manifested clinically by establishment of a paradoxical auditory memory in response to the aberrant auditory sensory stimulus. Affected patients have a conscious awareness of the tinnitus, the severity of which is reflected clinically in varying degrees of a disabling tinnitus. The TDST provides a basis for understanding that the masking phenomenon for tinnitus has peripheral and central components. This masking phenomenon is suggested to be a sign of predominance of synchrony in neuronal activity within the cochleovesti-

bular system, which establishes a resonance in sound transmission. This masking of tinnitus provides a basic understanding of one of the functions of the auditory system: masking. Experiments that attempt tinnitus relief in animals and humans and focus on SR and exclude the factors of residual auditory neuronal function and brain integrity function may produce results that conflict with the underlying hypothesis of the experiment. In general, it is suggested that one of the failures of hypotheses attempting tinnitus relief in the past has been trying to explain a central perceptive function (masking) in terms of a peripheral process (e.g., electrical stimulation) [53,56–58].

The biophysiological processes involved in acoustic masking are considered related to those of brain functions of sensory perception, consciousness, memory, and affect-emotion in tinnitus patients. SR may be the process that explains the increase of tinnitus intensity in patients after noise exposure. Whether the clinically manifest tinnitus is maskable depends on the extent of the sensorineural hearing loss and the integrity of the cortex. Clinical evidence originally of the significance of the sensorineural hearing loss was established by the Feldmann masking curves [59].

Recently, PET of brain imaging attempting tinnitus relief in patients via ultra-high-frequency acoustic stimulation demonstrated clear correlation of the resultant relief with the residual peripheral, acoustic, neuronal function and cortical integrity [55]. QEEG data in tinnitus patients is the basis for a hypothesis that the development of an alpha rhythm may correlate with central masking. Development of the theta-beta rhythm may correlate clinically with interference in central masking and increased consolidation of a paradoxical auditory memory for tinnitus, clinically demonstrating varying degrees of tinnitus severity.

Acoustic masking and the identification of the underlying processes involved are the twenty-first century's challenge to the discipline of tinnitology and will be directly related to any or all attempts for tinnitus control and treatment. Masking may highlight a homeostasis in neuronal activity regulated by multiple neurotransmitters regulating dyssynchrony and synchrony in cochleovestibular function in the peripheral or central cochleovestibular system; in this outcome, synchrony in neuronal activity predominates, and the spontaneous dyssynchronous noise (tinnitus) is not perceived.

Thalamocortical Oscillation and Tinnitus

A reciprocal corticothalamic feedback mechanism is significant in the oscillatory effect between thalamus and cortex [60–64]. The classic sensory transfer of input to the thalamocortical cells is highlighted by bottom-up or top-down innervation. Synaptic background activity controls spike transfer from thalamus to cortex [65]. Depolarized potentials are manifested by single-action neuronal discharges. Hyperpolarized potentials result in activation of low-threshold calcium T-type channels, which trigger high-frequency bursts of action potentials. In the cortex, the result is an activation of the symptoms that are indications of the underlying neural substrate [64].

A unifying theory, the TDST, based on dyssynchrony can then be proposed for attempting tinnitus relief and understanding the symptom of tinnitus when grasped in terms of neurotransmitter systems highlighted by the GABA and the glutamate systems. The identification of a biochemical marker, the GABA-A receptor, and of a deficiency in the benzodiazepine receptor in tinnitus patients—translated for treatment of a predominantly central-type tinnitus—is one such clinical application of the TDST [31,66,67].

Specifically, imbalance in the homeostasis of normal function between the glutamate-GABA systems, at single or multiple neural substrates or at any particular level of the cochleovestibular system or within the central nervous system (peripheral or central in location), can establish a dyssynchrony in neural discharge. Attempts of the homeostatic system to reestablish synchrony is reflected at a subcortical or cortical level. When the dyssynchrony is at the cortex, QEEG can provide a system whereby it attempts to objectify a tinnitus complaint that has now been reported [33]. The nuclear medicine metabolic correlates have been identified in establishing and reflecting attempts of the brain to restore homeostasis and synchrony for firing and beginning a learning process.

Neuroanatomical Homeostatic System, Brain Function, Integrative Theory of Consciousness, TDST, and Tinnitus

Our experience has highlighted the brain functions of consciousness, perception, concentration, sleep, attention, memory, information processing, learning, behavior, speech expression, affect-emotion, and somatomotor activity in the history and clinical course of tinnitus patients.

The TDST is clinically considered to be supported by QEEG results in tinnitus patients and the integrative theory of consciousness [39,40]. These results have provided a basis for clinical interpretation in terms of brain function highlighted by consciousness, the clinical course of the tinnitus, and clinical translation into tinnitus diagnosis and treatment [33].

It is hypothesized that the spontaneous electroencephalographic (EEG) rhythmic synchronous oscillations in several broad frequency bands reflect brain function. A periodic sampling of local-global networks occurs.

Interaction occurs at the brainstem and at the medial temporal lobe system (i.e., limbus), thalamus, and cortex. The TDST maintains that the spontaneous EEG-rhythmic synchronous oscillations in several broad frequency bands represent degrees of consolidation of a conscious awareness for the tinnitus complaint. A neuroanatomical homeostatic system is hypothesized to regulate baseline levels of local synchrony and global interactions among regions [38,68–70].

Definitions and identification of processes involved in perception and consciousness are a work in progress. Clinically, we define perception as a physical awareness of a sensory stimulus. Consciousness is the awareness of a memory activated by a stimulus in the environment, reflecting a summation of synchronous neuronal activity in multiple neural ensembles and in multiple neural substrates.

John [39] and John and Prichep [40] described perception as an active process that specifies the content of consciousness. It is the embodiment of a combination of activities in neural substrates involved in the establishment of a "ground state" of activity of brain function, allowing the normal brain to achieve adaptive and normal behavior. Alterations in the homeostatic regulation of the ground state is a reflection of a brain response, a "sensory exogenous system," to multiple stimuli originating within or outside the brain. Interaction and stimulation of an "endogenous system" provide the establishment of continuous episodic and short-term memories and emotional content to the signal. The signal of neuronal activity received from neuronal assemblies and to be applied for the brain's adaptive response is separated from the spontaneous neural activity, or noise, to restore the ground state. Failures in this self-organizing system for the encoding of the signal results in a deviation of brain activity in reestablishing the ground state of brain activity and may become clinically manifest in seizure activity, inappropriate behavior, misperceptions, delusions, or other psychiatric symptoms. Consciousness is an inherent property of an electric field resonating in a critical mass of coherently coupled cells.

TDST, FCP for Tinnitus, Tinnitus Circuit, and Consciousness

Since 1995, an FCP for tinnitus has been hypothesized for transformation of a sensory aberrant auditory stimulus to one of affect. It involves the medial temporal lobe system, the initial processes being the establishment of a paradoxical auditory memory for the aberrant auditory stimulus (see Fig. 1). "The chief function is the transition of a dyssynchronous auditory sensory signal to affective behavioral response. It is hypothesized that for all sensory systems the sensory and affect components are linked by memory" [32]. A reciprocal, interneuronal, interconnecting innervation system exists between the source of the aberrant dyssynchronous sensory stimulus, peripheral or central in origin, and brain cortex. It ascends bottom-up in the brainstem when arising in the periphery and top-down when arising in the cortex. Modulation of the input is controlled by the thalamus and highlighted at the cortex by the function of affect-emotion and memory in response to the tinnitus. The cingulate and medial temporal lobe system, highlighted by the amygdala and hippocampus, reciprocally interacts with the thalamus in establishing for the tinnitus a memory and affect-emotional response. Stress is a factor influencing the clinical course of the aberrant auditory sensory to that of a severe disabling-type tinnitus.

In 2006, identification of neural substrates in brain and advances in neuroscience for brain function (as referenced) have identified processes involved in the bottom-up and top-down interneuronal reciprocally activating networks. The integration of the theory of consciousness [39,40] with the FCP is considered to support the TDST, highlighted clinically in an understanding of the clinical course of tinnitus based on the brain functions of perception and consciousness. The conscious auditory percept for tinnitus is hypothesized clinically to reflect a summation of synchronous activities of neuronal activity recordable from multiple neural substrates at brain cortex. The transformation of the dyssynchrony of the aberrant auditory stimulus to one of synchrony and individual brain function of affect-emotion, memory, somatosensory response, and consciousness is clinically considered to be an FCP for tinnitus. The QEEG data gathered from tinnitus patients clinically are considered to have objectively identified, electrophysiologically, a tinnitus circuit—the frontotemporal thalamus—hypothesized in the FCP model and algorithm of 1995 (see Fig. 2).

Tinnitus: TDST, Phantom Phenomenon, Function of Neural Substrates

Tinnitus has been characterized as an auditory phantom disorder [64,71]. In the past, the term *phantom* has been applied in the absence of known neural substrate or underlying processes involved in sensory coding. Tinnitus is considered to embody the basic problem in sensory physiology: sensory coding. "True code" has been defined as a parameter of the signal that actually carries behaviorally useful information [72]. The TDST refutes the characterization of the past supported by advances in clinical and basic science understanding of sensory physiology and brain function. The foregoing reports have established or identified underlying neural substrates that clinically represent patterns of information processing in the transition of a dyssynchronous aberrant auditory sensory stimulus to one of synchrony in multiple neuro-

nal ensembles and a transformation of an aberrant sensory stimulus to one of affect-emotion [2,3,32,73].

Tinnitus is not a phantom but an active physical process(es) or phenomenon(a) occurring in multiple neural substrates in response to a peripheral or central stimulus. This stimulus is identifiable both in electrophysiological recordings (cortical and subcortical) and in metabolic activated neural substrates reflecting a synchrony-dyssynchrony in homeostatic mechanisms involved in maintenance of "normal" individual brain function. The identification of neural substrates in the brain with nuclear medicine imaging and QEEG electrophysiological patterns of response at the cortex supports the recommendation that tinnitus is not to be considered a phantom phenomenon [33,36].

The TDST Model

We propose a model for the TDST (Fig. 3). The common mechanism underlying all clinical types of tinnitus production is a dyssynchrony in neuronal activity arising within the peripheral or central nervous system and using the cochleovestibular system to express its dysfunction. The model provides an understanding of the clinical course and propagation of tinnitus severity. Theories of consciousness and the FCP, integrated into the TDST, and processes reported to underlie brain functions of consciousness and the FCP find clinical application for tinnitus diagnosis and treatment.

The theory of homeostatically regulated thresholds for every neuronal population in the brain and how this activity is transformed into a subjective experience is the problem of consciousness [39,40].

At the cortex, QEEG data demonstrate rhythmic voltage oscillations derived from the electrical activity of the subjacent neuronal populations [74], reflecting the nonrandom synchronization of postsynaptic potentials. They are regulated by interactions of a homeostatic system mediated by different neurotransmitters consisting of rhythmic oscillations in broad frequency bands: delta (1.5–3.5 Hz), theta (3.5–7.5 Hz), alpha (7.5–12.5 Hz), beta (12.5–25 Hz), and gamma (25–50 Hz) [38,68].

The homeostatic system, hypothesized to generate and regulate the electroencephalographic power spectrum, depends on a complex of ionic currents causing a sequence of hyperpolarizations followed by depolarizations. They influence the thalamocortical circuits to act as pacemakers in response to network interactions [60–62,75].

Sensory input received by the relay nuclei in the thal-

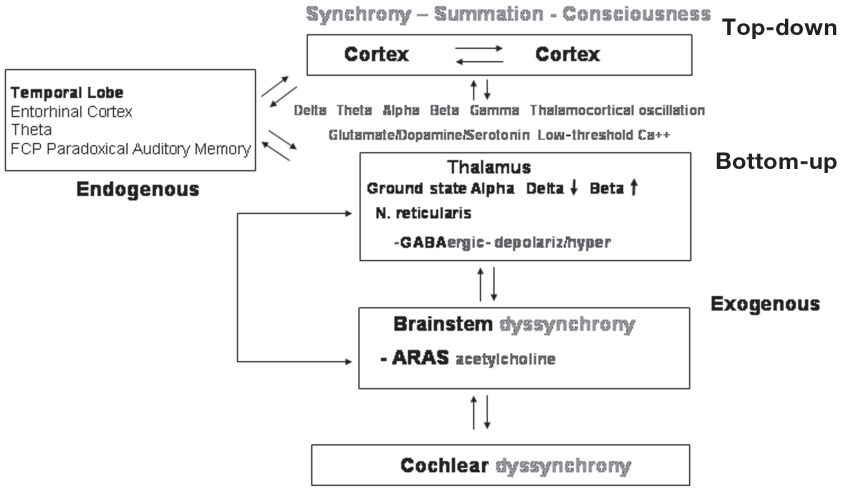

Figure 3. Integrated model for the tinnitus dyssynchrony-synchrony theory: tinnitus development, propagation, brain function, final common pathway for tinnitus (*FCP*). It is hypothesized that a homeostasis of neuroanatomical substrates and neurotransmitters regulate dyssynchrony and synchrony for sensory input received at the brain cortex from the peripheral or central nervous system (CNS). Rhythmic oscillations modulated by the thalamus are recorded at the cortex and reflect brain function (i.e., delta, theta, alpha, beta, gamma). The sensory information ascends via the ascending reticular activating system (*ARAS*) to the thalamus, part of an exogenous system of the CNS for receipt of sensory information arising from the environment or the peripheral or central CNS. Hyperpolarization and depolarization of a GABA-influenced thalamic neuron activity results in thalamocortical oscillations that displace a theoretical ground state of brain activity from the alpha down to a theta or delta rhythm or up to a beta rhythm. Input from the thalamus to the temporal lobe and the entorhinal cortex, an endogenous system of the CNS, is hypothesized to result in the establishment of a "memory" for the sensory stimulus, which has a reciprocal influence on the thalamus. The summation of synchronous neural discharges from multiple neural ensembles of neurons at cortex results in a gamma rhythm associated with a conscious awareness of the sensory stimulus. Synchronized neural activity in multiple neuronal ensembles is hypothesized to be the basis of perception and consciousness.

amus are pacemaker neurons that oscillate in the frequency range of alpha (8–12 Hz) and synchronize the excitability of cells in the thalamocortical pathways. This modulation is further distributed throughout the cortex by corticocortical interactions. The alpha rhythm dominates the resting QEEG. The alpha activity arises from interaction between the neurons on the thalamus and areas of the cortex. The intrinsic property of these thalamic cells has oscillatory activity in the alpha range (7.5–12.5 Hz). The reticular nucleus of the thalamus mediates GABA influences, which can hyperpolarize cell membranes of these cells and result in a slowing of the alpha rhythm to that of the theta range (3.5–7.5 Hz) and further reduction to the delta range (1.5–3.5 Hz) with increasing GABA activity. The theta activity is generated in the limbic system by pacemakers in the septal nuclei. They are inhibited by collaterals from the mesolimbic system's entorhinal and hippocampal influences [63] and are propagated to the cortex by the anterior cingulate and medialis dorsalis. Delta activity (0.5–4 Hz) is generated in the cortex when cortical neurons are deprived of input (i.e., extreme depression of thalamic gates) together with decreased activity of the brainstem reticular formation, also called the *ascending reticular activating system* (ARAS). Significant is the inhibition of ARAS by descending pathways from the cortex via the striatum. Beta activity largely reflects intracortical interactions. which receive collaterals from all afferent sensory pathways and exert cholinergic influences, resulting in a diminution of the GABAergic influence of the reticular nucleus neurons. They can be initiated by glutaminergic influences from the cortex, resulting in a depolarizing effect on the thalamic cells and an increased rhythm in the beta range. The beta band reflects corticocortical and thalamocortical oscillations related to specific information processing. Gamma activity (25–39 Hz) reflects corticocortical and corticothalamic transactions. Its significance is suggested to reflect perceptual processes and consciousness [39,40]. Normal conscious function is proposed to require activation among the ARAS, intralaminar nuclei of the thalamus, and cortex. The binding together of fragments of perception from dispersed neuronal assemblies into a unifying reverberating system comprises the perceptual content of consciousness [39,40].

A characteristic low-frequency brain wave (i.e., theta) has been reported to modulate ultra-high-frequency oscillations. This high gamma power thereby allows communication between corticocortical regions that support behavior [76].

CLINICAL APPLICATION

Clinical correlation with the TDST has been reported between the QEEG and SPECT of brain [2,3,33,36,73]. The clinical application of the theory of homeostasis of brain activity and consciousness provides a basis for translation to tinnitus diagnosis and treatment.

The exogenous system of the central nervous system for sensory information processing [39] is hypothesized to receive sensory input from sensory receptors either peripheral or central in origin. The endogenous system [39], including the limbic system, is hypothesized to process the sensory input in the exogenous system by establishing a "memory" and thereby contributing to consciousness.

The QEEG analysis of power in tinnitus patients has identified delta and beta band predominance in frontal and temporal recording sites [33], hypothesized to reflect thalamic response to the aberrant dyssynchronous auditory sensory stimulus within the exogenous system.

Specifically, patients with delta band responses—hyperpolarization at the level of the thalamus—mediated by an increased GABA response experience a reduction of the activity of the alpha band to that of the delta band. In patients exhibiting the beta band of activity, the GABA response is reduced; the result is an increase of the alpha band of activity to that of the beta band. Thalamocortical and corticocortical oscillations of each have been identified with recordings from multiple electrical sites, highlighted by frontal and temporal readings [33,36]. In both cases, correlation of the incidence of the different band frequencies in the recording electrical sites has been hypothesized to reflect the degree of severity of the tinnitus complaint, the ability or attempt of the brain to reestablish the ground state of brain activity, and homeostasis of brain activity in multiple neuroanatomical substrates.

The beta activity is clinically considered to exhibit reverberating activity at the cortex and may signal seizure-type activity, misperceptions, and alterations in affect. The theta band of activity is clinically considered to be generated by the endogenous system; clinically, it reflects attempts to establish a paradoxical auditory memory. The theta band of activity is clinically hypothesized to reflect an increased synchrony of activity of cortical neurons not involved in informational processing but rather involved in the sensory-affect transformation, receiving collateral inputs from multiple neuroanatomical electrical recording sites and highlighted by frontal and temporal electrical recording sites. In the cohort of tinnitus patients cited, the establishment of a paradoxical memory is considered to be in progress. It is hypothesized that successful attempts for tinnitus relief may be increased by demonstration in a tinnitus patient of low (not high) theta band activity. This activity may embody the consolidation of a conscious awareness of a memory that is difficult to influence or erase.

Factors in the environment (e.g., noise, stress) in the

cochleovestibular system, such as aeration of the middle ear, secondary endolymphatic hydrops, and systemic disease (e.g., cardiovascular, metabolic, central nervous system), all have the potential—alone or in combination—to "trigger" the dyssynchrony, with resultant initiation of or increase in the synchronous cortical perception and conscious awareness of the tinnitus.

A rationale for treatment options of medication and instrumentation attempting tinnitus relief based on a theory of homeostasis of brain activity finds support for biofeedback attempts to increase the alpha band activity and for receptor-targeted therapy directed toward the GABA receptor [31,34–36].

TDST SUPPORTIVE DATA

Nuclear medicine imaging and QEEG are considered to be the predominant sources of support for the TDST. Nuclear medicine imaging in tinnitus patients, ongoing since 1989 and with SPECT of brain since 1989, has been completed in excess of 250 examinations. Imaging with PET of brain since 2000 stands in excess of 35 examinations. Both techniques have demonstrated perfusion asymmetries in multiple neural substrates, highlighted by hypoperfusion in the medial temporal lobe system and in decreasing instances of occurrence of the frontal, primary auditory, cerebellum, basal ganglia, and parietal cortices. The data clinically point to a tinnitus metabolic correlate for 4-FDG and a basis for correlation of structure and function [2,3,32,73]. QEEG is providing an electrophysiological correlate for tinnitus that is individual for each tinnitus patient. The distribution of the frequency bands recorded with QEEG when analyzed for the metric of power has been reported to have been heterogeneous and to demonstrate patterns of brain activities responding to an aberrant auditory stimulus (i.e., variations in a common pattern) [33].

Clinical applications of the results based on the TDST and the integrative theory of consciousness have provided an understanding of the heterogeneity of the tinnitus symptom in terms of brain function responses to an aberrant auditory stimulus. The electrophysiological QEEG results demonstrated a definite pattern of electrophysiological responses at specific electrode sites, with a pattern of distribution of frequency bands (i.e., not a single electrophysiological correlate) [33]. The pattern of delta greater than beta greater than alpha greater than theta in frontal greater than temporal greater than occipital, and equal in occipital, parietal, and central recording sites is clinically considered to mirror multiple neuroanatomical ensembles of activity in a predominantly central-type, severe disabling tinnitus.

The TDST hypothesizes that tinnitus patients will have variations in the general pattern of the electrophysiological response as manifested in the distribution of the frequencies (i.e., different or multiple electrophysiological correlates for different clinical types of tinnitus) and may signal the degree of severity of the tinnitus complaint. QEEG is an objective method to record this pattern of the electrophysiological response. Significantly, the QEEG recording site results of distribution of power response and correlation of EEG frequency band with recording area correlate with the nuclear medicine neural substrate results and the TDST.

TDST AND FUTURE APPLICATIONS

The TDST is foreseen to be dynamic, portending advances in sensory physiology, auditory science, and understanding of brain function. The ultimate clinical application of the TDST model is for tinnitus treatment. The identification of neural substrates and the biochemical marker, the GABA-A receptor, is considered but a start in the direction of identifying underlying processes involved and translation to drug development [30,31]. The identification of specific neural substrate sites and processes involved in the dyssynchrony and synchrony of activity in tinnitus patients will be followed by the implementation of biomolecular applications for clinical diagnosis and treatment.

The generation of seizures is associated with abnormal synchronization of neurons [77]. Nonlinear time series analysis of brain electrical activity in epilepsy patients has been identified in epileptogenic areas resembling linear stochastic dynamics [78]. This is considered to be clinical evidence supporting innovative application of recommended antiseizure drugs for a particular type of central tinnitus, the underlying mechanism of which is considered to be tinnitogenesis [30,32,79].

Translational medicine will include application of advances in sensory physiology, auditory science, and brain function for tinnitus treatment to include instrumentation, medication, and surgery. The new field of tinnitopharmaco-proteogenomics—the development of tinnitus drugs based on the identification of proteins involved, their function, and genetic control already in place—will be followed by additional drug options of increased efficacy to the practitioner and tinnitus patient for tinnitus relief.

Surgeons will use the TDST for improvement in the selection process for a procedure, the location of the procedure, and as a monitor for its efficacy. The TDST will increase the incidence of its recommendation for attempting tinnitus relief parallel to advances in the understanding of advances in sensory physiology, auditory science, and brain function.

The TDST contributes to the understanding of acoustic masking [59,80,81] and the brain function response

to an aberrant auditory stimulus, tinnitus. It contributes also to the increased clinical significance of the reintroduction of masking, in 1978, as a modality for attempting tinnitus relief [82]. Identification of the underlying processes involved in acoustic masking will significantly influence and underlie any and all future modalities of treatment attempting tinnitus relief.

CONCLUSIONS

The TDST is a hypothesis that considers tinnitus to be an abnormal, auditory, conscious percept reflecting a dyssynchrony in pre- and postsynaptic neural transmission within the peripheral or central nervous system. It interferes in the excitatory and inhibitory process or processes involved in maintaining homeostasis for brain neurofunction, acting as a stimulus to express this dysfunction via the auditory system. The dyssynchrony expressed at the brain cortex and involving multiple neural substrates becomes one of synchrony, reflecting multiple brain functions that include consciousness, memory, cognition, information processing, perception, learning, emotion-affect, and attention. The auditory conscious percept of a memory of tinnitus reflects a transformation in brain function of the sensory component of the aberrant auditory stimulus to one of affect and somatosensory response for an aberrant auditory sensory stimulus (i.e., an FCP for tinnitus).

The TDST provides a theoretical basis for integration of the components of sensory physiology with brain function for translation to clinical diagnosis and treatment for severe disabling tinnitus. Objective metabolic and electrophysiological data support the theory of TDST and the integrative theory of consciousness in tinnitus patients and a tinnitus circuit.

The TDST calls for a paradigm switch in clinical thinking to concentrate on brain function responses to an aberrant dyssynchronous auditory sensory input, particularly consciousness, with continued respect for the psychophysical and psychoacoustic characteristics of the tinnitus. The TDST is supported by identification of objective metabolic and electrophysiological correlates of tinnitus in multiple neural substrates for the symptom of tinnitus. The clinical application for the TDST has translated itself into significant increased modalities, efficacy, or modalities of therapy attempting tinnitus relief.

The TDST suggests that the severity of the tinnitus complaint may be a clinical correlate of the degree of dyssynchrony or lack of synchrony in the establishment of a paradoxical auditory memory for the tinnitus complaint. It is identified objectively in slow-wave brain oscillations recorded with QEEG and with nuclear medicine imaging techniques.

The TDST provides a model for understanding acoustic masking and the biophysiological processes involved as they relate to brain function of perception, consciousness, memory, emotion, and affect in tinnitus patients.

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