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Final Common Pathway for Tinnitus: Theoretical and Clinical Implications of Neuroanatomical Substrates

Abraham Shulman,[1,2] Barbara Goldstein,[1,2] and Arnold M. Strashun[3]

[1] *Martha Entenmann Tinnitus Research Center, Forest Hills, and Departments of* [2] *Otolaryngology and* [3] *Radiology and Nuclear Medicine, Health Science Center at Brooklyn, State University of New York, Downstate Medical Center, Brooklyn, New York*

Abstract: A final common pathway (FCP) for tinnitus has been hypothesized since 1989 for all clinical types of tinnitus, particularly subjective idiopathic tinnitus (SIT) of the severe disabling type. This was intended to explain the transformation-transition of the sensation of an aberrant auditory sensation—tinnitus (i.e., the sensory component)—to one of affect (i.e., the emotional-behavioral component) or, conversely, that an emotional-behavioral stimulus (affect) can result in the clinical manifestation of a sensation (a sensory stimulus). Understanding the pathophysiology of this transformation is fundamental for the diagnosis of tinnitus and the treatment of the patient, and it presents a dilemma to basic science, neuroscience, and clinical medicine. Clinically, tinnitus is not a unitary symptom; it constitutes many clinical types; can have its origin in the auditory or nonauditory systems and in the peripheral or central nervous system; and may be clinically manifest or subclinical. Accumulating evidence is presented to support the original hypothesis of an FCP. The resolution of this dilemma involves sensory processing (i.e., the integration, identification, and understanding of the ongoing, underlying, simultaneous, multiple associated brain function processes not only from one sensory modality but from multiple sensory modalities accompanying and associated with an FCP). In the FCP, the predominant brain function process is that of the sensory–affect transformation of a sensation and its conscious awareness by the affected patient. The neuroanatomical substrates identified in 1989 in tinnitus patients (reported originally in 1991 and published in 1995) are presented as a common framework for the hypothesis of an FCP. They further the understanding of the clinical heterogeneity of the tinnitus symptom, clinically manifest as multiple brain functions associated with the clinical course of tinnitus patients, particularly those with SIT. The FCP provides a model for tinnitus theory, diagnosis, and treatment.

The FCP is not a tinnitus theory. Specifically, it is a hypothesis that attempts to explain how an aberrant auditory sensory stimulus becomes transformed into one of affect and somatomotor response. The neuroanatomical substrates of the FCP provide a basis for the identification of the involved neurocircuitries and neurochemistries. The physiology and biochemistry underlying the neuroanatomical substrates of the FCP provide a basis for translation for tinnitus diagnosis and treatment.

The neuroanatomical substrates of the FCP are presented as algorithms of (1) components of a sensation (i.e., sensory, affect, and psychomotor), a translation from basic sensory physiology for tinnitus; (2) clinically manifest biophysiological brain functions and underlying processes associated with the tinnitus; (3) a model for investigation of metabolic-electrophysiological

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

correlates for tinnitus; (4) the basis for an integrated theory of tinnitus and brain function (i.e., tinnitus dyssynchrony-synchrony theory; (5) a model for the identification of underlying neurocircuitries and neurochemistries involved in brain for the sensory–affect transformation of an aberrant auditory stimulus (tinnitus); (6) a model for the selection-introduction of innovative therapies attempting tinnitus relief; and (7) its clinical translation for objective monitoring systems for the determination of the efficacy of modalities of therapy attempting tinnitus relief. The hypothesis of the FCP for tinnitus and the identified neuroanatomical substrates, when viewed in terms of the physiology of sensory processing, is considered to be expanded and broader in its application for all sensations, normal or aberrant.

Key Words: affect; attention; consciousness; cross-modal integration brain function; final common pathway; medial temporal lobe; neuroanatomical substrates; paradoxical auditory memory

A final common pathway for tinnitus (FCP) has been hypothesized to exist in brain for all tinnitus patients and all clinical types of tinnitus, particularly tinnitus of the severe disabling type, such as subjective idiopathic tinnitus (SIT), to explain the transformation-transition of an aberrant auditory sensation—tinnitus (i.e., the sensory component)—to one of affect (i.e., the emotional-behavioral component [1–4]. It is not a tinnitus theory.

In general, the medical concept of an FCP for a given clinical manifestation of a symptom or disease process implies the identification of involvement of identical anatomical substrates and the involved underlying processes of biochemistry and physiology, expressed in specific multiple anatomical tissue pathologies. Anatomy provides a structural basis for understanding function. Physiology is the basic science of identifying the *physical* factors and processes involved in the functions of a living organism; biochemistry identifies the *biochemical* elements involved in the functions of a living organism.

The FCP hypothesis is considered to be dynamic, reflecting an integration of advances in our evolving understanding of sensory physiology: what is and is not known of the cochleovestibular system and associated brain functions, highlighted and translated for tinnitus by the development of a paradoxical auditory memory, perception, and consciousness. The update on the neuroanatomical substrates of the FCP is considered to reflect the growth and development of the discipline of tinnitology, a practice involving professionals dedicated to the science of perceiving sound unrelated to an external source [5].

The neuroanatomical substrates identified in tinnitus patients on which the hypothesis of an FCP is based are presented in a neuroscience framework for understanding the underlying multiple mechanisms and processes associated with the multiple brain functions ongoing in a patient during the clinical course of tinnitus. The FCP, when viewed in terms of sensory physiology and a neuroscience framework of brain function, is considered to be expanded and broader in its application for all sensations, normal or aberrant (or both).

The neuroanatomical substrates of the FCP are proposed to be neural correlates of sensory processing for tinnitus and for its interconnections in brain with regions of cortex that receive inputs from more than one sensory modality (i.e., cross-modal integration of brain function). The initial process and brain function in the FCP have been hypothesized to be the establishment of a "paradoxical" auditory memory for the tinnitus. Brain functions associated with tinnitus are perception, consciousness, concentration, cognitive functions of memory and learning, auditory masking, attention, sleep, affect and behavior or mood (emotion), fear, stress, communication, "paradoxical reward," and autonomic functions.

This article is an update from 1991 on neuroanatomical substrates of the FCP for tinnitus patients, particularly those with SIT, in the context of advances in neuroscience and sensory physiology and an ongoing translation of basic sensory physiology and neuroscience for the tinnitus symptom. The update on the neuroanatomical substrates for the FCP reflect increased understanding of the mechanisms and processes underlying brain functions, specifically the complexities involved in and accompanying the sensory–affect transformation. The focus of the FCP is on the predominant brain function of sensory–affect transformation and that of perception, memory, and consciousness in response to the initial tinnitus stimulus; its clinical translation and application for tinnitus theory, diagnosis, and treatment; and its clinical translation as neuroanatomical correlates for tinnitus, particularly SIT. Our understanding of tinnitus and associated brain functions is ongoing and based on multiple theories and hypotheses. The FCP has provided the basis for an integrated theory of tinnitus and brain function (i.e., the tinnitus dyssynchrony-synchrony theory [6]; and a model for the clinical diagnosis of different clinical types of tinnitus [7–9]. The establishment of an accurate diagnosis for physical-sensory complaints and

the identification of the anatomical, physiological, and biochemical processes involved form the basis for successful treatment.

This article is an update of the original hypothesis of the FCP and the involved neuroanatomical substrates identified with the technologies of nuclear medicine imaging and quantitative electroencephalography (QEEG). It focuses on the neuroanatomical substrates in brain, integrating recent advances in sensory physiology and neurosciences to provide the following:

1. An update of the ongoing dilemma for sensory physiology and the symptom of tinnitus (i.e., the answer to the question of how a sensory stimulus is transformed into one of affect)
2. An update on the support of the original hypothesis of an FCP for tinnitus with neuroanatomical substrates in brain that have been identified since 1991 with nuclear medicine imaging and correlated since 2000 with QEEG—both of which support and expand the original FCP hypothesis to include the psychomotor component of the tinnitus —as QEEG has provided the identification of an electrophysiological correlate for a predominantly central-type tinnitus
3. An update and integration into the FCP of recent advances in sensory physiology and neuroscience for perception, consciousness, memory, and affect
4. An update of algorithms for the FCP, integrated with neuroanatomical substrates and basic sensory physiology, that differentiate between components of a sensation (i.e., sensory, affect, and psychomotor)
5. An update of the role of the FCP in an integrated theory of tinnitus (i.e., tinnitus dyssynchrony-synchrony theory)
6. An update of the clinical application of the FCP for establishing accuracy in tinnitus diagnosis (i.e., identifying clinical types of tinnitus), factors influencing the clinical course of the tinnitus, and treatment (i.e., a medical-audiological tinnitus patient protocol [MATPP]) [10], and a combined treatment protocol of instrumentation and medication (i.e., tinnitus-targeted treatment to increase the efficacy of modalities of therapy attempting tinnitus relief).

HISTORY: A FINAL COMMON PATHWAY FOR TINNITUS

General

An update on the neuroanatomical substrates for the FCP gains significance when reviewed historically both in the context of attempts to understand the transition-transformation in brain of a sensation to one of affect and ongoing attempts to understand and identify the pathophysiology underlying brain function.

In our clinical experience, originating in 1979 at the tinnitus clinic of the State University of New York, Downstate Medical Center (SUNY/DMC), and continuing today, the predominant brain function of sensory–affect transformation has been highlighted in the history and clinical course in more than 10,000 tinnitus patients. This has been accomplished by monitoring simultaneous the ongoing brain function processes as previously listed (perception, consciousness, etc.).

The approach for understanding the basic science of tinnitus production and attempts for its diagnosis and treatment has been limited to date by what is and is not known of the cochleovestibular system and brain functions, highlighted by perception and consciousness. The tinnitus experience of professionals prior to 1989 was a sensorineural approach focusing predominantly on the peripheral auditory system (i.e., cochlea) and its projection to and within the brainstem. The introduction of nuclear medicine brain imaging (1989) and the identification of multiple neuroanatomical substrates in SIT patients provided (1) support for the original clinical concept of a predominantly central-type tinnitus [7–9] and (2) focus on central brain functions (listed previously) associated with tinnitus, particularly SIT.

Originally, and to date, the nuclear medicine imaging of brain by single-photon emission computed tomography (SPECT) identified and reported multiple neuroanatomical substrates on which the hypothesis of the FCP was based. SPECT was considered to reflect not a modular concept of brain function and particular processes limited to specific neuroanatomical substrates but rather reciprocal, simultaneous, activated, interactive interneuronal networks highlighting multiple similar and dissimilar, simultaneously activated biophysiological processes underlying multiple brain functions. Clinically, the heterogeneity of tinnitus is a reflection of ongoing multiple brain function processes. The solutions to the clinical dilemma of the sensory–affect transformation are evolving in advances in our understanding of the heterogeneity of multiple brain functions. The ultimate challenge presented by the symptom of tinnitus to basic science and medicine is to find answers to the dilemma presented initially by Descartes [11,12] (i.e., how a sensation is transformed to affect).

Hypothesis: FCP for Tinnitus

SUNY/DMC: Background and Experience 1989

The FCP hypothesis (evolved and ongoing since 1989) was formally presented in 1993 and originally published

in 1995 [2]. The FCP hypothesis is considered to be dynamic, requiring updates demonstrating, in general, what is and is not known of the neuroscience of brain function and the basic science of sensory biophysiology —specifically of the peripheral and central cochleovestibular system.

The original concept of an FCP evolved from brain SPECT identification (1989) in SIT patients of perfusion asymmetries in multiple neuroanatomical substrates in the brain, frontal, parietal, and temporal lobes and highlighted by the medial temporal lobe system (MTLS) [1–4,13–17].

Nuclear medicine brain SPECT with the radioisotope TC 99-HMPAO was introduced in 1989 into an MATPP for SIT patients in an attempt to improve the diagnostic accuracy of tinnitus diagnosis and to identify its medical significance [10]. SPECT of brain imaging has been ongoing since that time (in excess of 250 examinations to date). Brain positron emission tomography (PET) has been recommended since 2000 (more than 35 examinations to date). Nuclear medicine brain imaging has been recommended, initially and to date, in selected patients with predominantly central-type severe disabling tinnitus of more than 1 year's duration and resistant to protocols attempting control and relief with medication and instrumentation.

Perfusion asymmetries are seen in multiple regions of interest in brain, highlighted by the MTLS, the amygdala-hippocampal complex, and adjacent frontal, temporal, and parietal lobes. The original concept of an FCP evolved from SPECT identification of perfusion asymmetries varying in degree in multiple neuroanatomical substrates in brain, highlighted by the MTLS. The incidence of perfusion asymmetries involving the MTLS has been greater than 90%, with a p factor of less than .05 [1–4,13–17]. SPECT of brain asymmetries in the cerebellum were demonstrated in 60–70% of patients with tinnitus of the central type and were reported in 1999 [18].

More recently, PET [19–22] and electrophysiology (i.e., QEEG) [23–32] and functional magnetic resonance imaging (fMRI) support the originally identified multiple neuroanatomical substrates in brain in SIT patients [25,30–35].

A reciprocal, innervating, interneuronal network within and between the multiple neuroanatomical substrates is suggested to result in transition of a sensory stimulus (i.e., a sensation) into an affect (i.e., emotion-behavior) and vice versa. Since 1995, the FCP has found support in reports of significant advances in neuroscience and sensory physiology [25,36–42].

The diagnostic tools of SPECT brain imaging since 1989 and brain fluorodeoxyglucose (FDG) and PET (FDG PET) since 2000 have continued to provide objective evidence of brain perfusion asymmetries of hyper- and hypoactivity, extrapolated to demonstrate metabolic activity in multiple neural substrates (i.e., a metabolic correlate for tinnitus). Both provide an integration of structure and function, a technology that can monitor the efficacy of modalities of therapy attempting tinnitus relief and can provide an insight into the medical significance of tinnitus symptoms for tinnitus patients. The clinical application of QEEG for tinnitus diagnosis since 2000 has provided an objective recording of electrical brain activity and an electrophysiological correlate for tinnitus [23,24]. Together, the metabolic and electrophysiological data co-register with each other in identifying involved neuroanatomical substrates in SIT patients [22].

The clinical translation of the FCP to SIT patients has found application for (1) basic science conceptualization of an integrated theory of tinnitus and brain function [6] and (2) clinical improvement in the accuracy of tinnitus diagnosis [43–45], a basis for introducing innovative drug therapies attempting tinnitus relief [46,47] and an objective method for monitoring their efficacy [23,24]. The key to successful treatment is the establishment of an accurate diagnosis for a symptom or disease. Long-term tinnitus relief has been reflected in an increased efficacy of tinnitus treatment protocols of combined instrumentation and medication, in excess of 85% since 2004 [43].

FCP: Hypothesis and Concept

The FCP is not a theory for the origin and generation of an aberrant auditory stimulus (i.e., tinnitus) but is a hypothesis that posits an FCP existing in the brain for all clinical types of tinnitus, an aberrant auditory sensory stimulus marked by a sensory–affect transformation in brain and reflecting multiple brain function processes. Conversely, an antecedent emotional-behavioral pattern of response can initiate or influence the perception of an aberrant auditory sensory stimulus (i.e., tinnitus) by activation of the same common pathway in the brain [2]. Lack of understanding of the need to differentiate between the theory of tinnitus and neuroscience of brain function involved in the sensory–affect transformation is considered by the authors to present a dilemma to tinnitus patients and tinnitus professionals for the theory, diagnosis, and treatment of all clinical types of tinnitus.

The original concept of an FCP evolved from identifying (in 1989) via brain SPECT varying degrees of perfusion asymmetries in multiple neuroanatomical substrates highlighted by the MTLS. The original 1995 FCP algorithm focused on the neuroanatomical substrates of the cochlea, the thalamus, the MTLS, and the brain cortex. Stress was considered to be a modulator of the tinnitus. Increased stress resulted in an increase in tinnitus

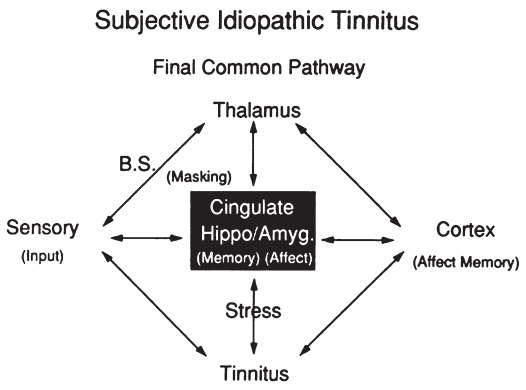

Figure 1. Final common pathway for tinnitus, 1995. A reciprocal, innervating, interneuronal network transforming a sensory aberrant stimulus, tinnitus, to one of affect and emotion. The factor of stress and the biophysiological processes involved modulate the severity of the tinnitus. (*Hippo* = hippocampus;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

intensity and the development of the clinical course of SIT (Fig. 1) [2, p. 119].

The FCP neuroanatomical substrates provide a location in the brain for the sensory–affect transformation of an aberrant auditory stimulus—tinnitus—and a "target " for identifying the underlying biophysiological neurocircuitries and neurochemistries involved in the associated brain functions.

The FCP is based on the identification of neuroanatomical substrates and the underlying neuronal-interneuronal brain function processes involved in this reciprocal activating sensory–affect transformation. Inherent in this reciprocal interaction-transformation are basic questions of the underlying biophysiological processes of the brain functions involved (as previously listed). The neuroanatomical substrates of the FCP, identified in SIT with nuclear medicine brain imaging, are hypothesized to reflect not the tinnitus signal but rather the simultaneous ongoing activation of multiple regions of interest in the brain, with resultant clinical and subclinical manifestations of multiple brain functions in the presence of the tinnitus signal.

Ultimately, the questions to be answered are whether the brain functions and underlying processes are clinically manifest or subclinical in tinnitus patients and how to differentiate between the selectivity of brain action and the mind for particular brain function processes. The neuroanatomical substrates of the FCP to date suggest that the brain has a mind of its own.

The hypothesis or concept of an FCP for tinnitus evolved from our clinical experience since 1975 that demonstrates that all patients with tinnitus, particularly of the severe disabling type (SIT), have as a common denominator an alteration in affect (i.e., emotion-behavior) [2,3]. Specifically, the alteration in emotion-behavior (e.g., anxiety, depression, a central brain function) is an accompaniment of the aberrant auditory sensory stimulus (i.e., tinnitus) or may reflect an initial or supplemental affect response to a preexisting condition of affect.

Such an association of brain function response for both the sensory and the affect components has been reported by professionals of other disciplines involved in tinnitus diagnosis and attempts at its control [25,48–52]. This experience supported the original hypothesis presented in 1983: that tinnitus is not a unitary symptom but clinically can be differentiated as different clinical types, particularly of a predominantly central-type, severe, disabling tinnitus [7]. In 1995, Shulman [2] stated: "For tinnitus, attributes are postulated with associated brain regions of interest [i.e., masking, intensity, annoyance, anxiety, depression and interference in communication ability(ies)]. A corollary can be that a disorder of affect (i.e., feelings) can be seen as a disturbance of brain function."

The FCP neuroanatomical substrates provide a neuroscience framework for understanding the clinical heterogeneity of tinnitus and particularly SIT (i.e., the clinical manifestation of multiple brain functions cited previously, highlighted by perception and consciousness). The initial brain function and underlying processes in the FCP were and continue to be hypothesized as the establishment of a paradoxical auditory memory for the tinnitus with a secondary alteration in affect (i.e., emotion-behavior) [2]. It is paradoxical in the sense that the tinnitus patient does not desire to retain such a memory. The original algorithm hypothesized that the tinnitus was modulated by stress, increase of which contributed to the clinical course of SIT. Consolidation of the paradoxical memory in the clinical course of tinnitus, varying in degree, was further hypothesized to "trigger" activation of additional central nervous system (CNS) brain function processes as previously outlined [6]. Specifically, for the tinnitus patient, an increase in attention and concentration for the tinnitus stimulus results in an increasing conscious awareness of the tinnitus. The conscious awareness is considered to be a reflection of multiple, simultaneous, ongoing brain function processes, highlighted by perception, attention, and so on, as previously cited. Consciousness has been defined as the clinical awareness of multiple simultaneous ongoing brain function processes [53,54].

EVIDENCE SUPPORTING THE FCP HYPOTHESIS

Numerous references in the literature are considered to provide supportive evidence for the hypothesis of the FCP.

Basic Science

Neuroanatomical-Physiological Reports

Frontal Lobe Traditional reports of the anatomy of the frontal lobe describe it as the largest of all lobes of the brain; it constitutes some one-third of hemispheric surface. The convexity of the frontal lobe has four principal convolutions: the precentral gyrus and three horizontally oriented convolutions—the superior, the middle, and the inferior gyri [55].

Elaborate neural mechanisms underlie complex correlations, sensory discriminations, and use of former experiences and reactions. These mechanisms involve associative memory and mnemonic reactions [56].

Frontal lobe functioning has been associated with reasoning, planning, parts of motor-expressive speech function, movement, emotions, problem solving, recent memory, attention, behavior, and executive and cognitive functions [57]. In addition, prefrontal cortex (PFC) function is for executive function and categorization of auditory objects [58].

Recent anatomical-physiological reports of the prefrontal, orbital frontal, and dorsolateral prefrontal cortices and their projections in brain, together with reports of affect-emotional-motivation-reward-memory systems in the brain, provide an anatomicophysiological framework for identifying the location of the clinical sensory–affect transformation as posited in the FCP and the hypothesized initial brain function processes (i.e., the development of a paradoxical auditory memory to the aberrant tinnitus sensation) and are considered to be highlighted by the following entities.

Prefrontal and Orbitofrontal Cortices The prefrontal gyrus is the region of the frontal lobe anterior to the primary and association motor cortices and divided into the dorsolateral, the orbitofrontal, and the mesial prefrontal areas. Function includes the domains of cognition and memory, which are overlapping. Impairment in one type of processing can affect the other. In rhesus monkeys, the basal surface of the PFC of the frontal lobe includes BA13, the orbital part of BA12, rostrally area 11, and basal part BA10.

Historically, the characterization of variants of frontal lobe syndrome and differentiation of damage to the medial-basal and the orbitofrontal cortex (OFC) was reported in 1980 [59]. It was pointed out that lesions of the syndrome profile involving the OFC shift toward the affective disturbance, leading to a disturbance of character and personality. This historical observation is particularly significant for tinnitus patients, particularly those with SIT (i.e., the predominance of the affect [emotional] component of the tinnitus with the clinical manifestation of anxiety or depression).

The dorsolateral PFC (DLPFC) has been identified as a focal region in a network that modulates the activity of the network and the associated function of presence (i.e., the fact of being present). Presence is associated with a network, including the dorsal and ventral visual stream, the parietal cortex, the premotor cortex, the MTLS, the brainstem, and the thalamus [60]. This article finds clinical application to tinnitus patients who occasionally report localization of their tinnitus as "outside their body." The inclusion into the FCP of this circuit can establish a diagnosis of tinnitus, its medical significance, and a basis for treatment.

The term *orbitofrontal cortex* has been used increasingly frequently and has been associated with identification of similarities in orbitofrontal function that exist across species, recognition that the OFC plays a significant role in behaviors that are interrupted in neurological and neuropsychiatric diseases. Different laboratories have studied the OFC from different perspectives (e.g., olfactory association cortex, prefrontal working memory system, system for controlling emotions) [42,61].

The OFC is considered a nexus link in the FCP of the circuitries of prefrontal working memory and control of emotions. Disruption in the OFC is clinically considered to be a key neuroanatomical substrate in the sensory–affect transformation of the tinnitus symptom. Information about the circuitry of the primate PFC and its role in regulating behavior is reading recommended to tinnitus professionals [62,63].

Orbitofrontal Cortex Advances in sensory physiology and the neuroscience of brain function associated with sensation, focusing on the OFC, lend further support to the original FCP hypothesis of sensory–affect transformation and transition, particularly in SIT patients. In general, the primate OFC is associated with encoding the significance of stimuli with an emotional context. In the macaque monkey, the OFC is prefrontal in location, with heterogeneous connections to adjacent prefrontal, limbic, sensory, and motor areas. Limbic cortical connections are highlighted by the hippocampus and parahippocampus. Sensory cortical connections include olfactory, gustatory, somatosensory, auditory, and visual processing. Subcortical structure connections include the amygdala (AG), multiple thalamic nuclei, the striatum, the hypothalamus, and periaqueductal gray matter.

Architectonic separation of the OFC has an identified medial sector and a lateral sector. The medial sector is selectively connected to the hippocampus, the parahippocampus, the posterior cingulate, and the retrosplenial areas and area prostriata. The lateral orbitofrontal sector is highlighted by connections with gustatory, somatic, premotor, and visual modalities and the AG [64].

In rhesus monkeys, the basal surface of the PFC includes BA13, the orbital part of BA12, rostrally area 11, and basal part BA10. The OFC areas are distinct from areas on the medial wall of the PFC (mPFC). The mPFC is divided into an anterior sector (i.e., BA10, 9, 14) and a posterior sector, which includes anterior cingulate areas (i.e., BA32, 24, 25, and MPA 11). Distinct features of the OFC include its bidirectional connections to cortices from every sensory modality, each of which projects to the AG. The posterior OFC has significant bidirectional connections with the AG. The connections to the intercalated masses of the AG inhibit hypothalamic autonomic centers, which in turn innervate the brainstem and peripheral organs. Activation of this pathway is expected to disinhibit the hypothalamus, thus allowing its activation in emotional arousal. A pathway from the posterior OFC to the central nucleus of the AG is expected to return the system to autonomic homeostasis. Although the OFC is architectonically heterogeneous, its connections and functions are grouped by cortical type into anterior and posterior sectors. The posterior OFC is the primary region for the perception of emotions. The posterior mPFC areas in the anterior cingulate areas are not multimodal but have strong connections with auditory association areas, brainstem vocalization, and autonomic structures in pathways that may mediate emotional communication and autonomic activation in emotional arousal. A sequence of information processing for emotions is suggested by the communication of posterior and anterior OFC areas by feedback projections with lateral PFC and other cortices [65,66].

Attention, Emotion, and the Orbitofrontal Cortex The role of the OFC for the brain function of attention for emotional events as hypothesized in the FCP and TDST is supported by the following:

- Identification of the innervation of the OFC by the AG with a high density of inhibitory fibers spread projections to the thalamus [67].
- Attentional focus on stimuli with emotional content has been demonstrated by identification of the pathway from the AG to the OFC [67,68].
- Activation of PFC inhibitory neurons is associated with focusing attention on relevant features for a task and on suppressing distracters [69].

The interaction of the PFC and the inhibitory thalamic reticular nucleus (TRN) reveals a circuitry suggestive of a mechanism through which behaviorally relevant stimuli can be selected and distracters filtered out early in information processing through the thalamus. Orbital frontal area BA13 is one of the prefrontal areas with widespread projections to the TRN, which provides another pathway to facilitate and focus attention on motivationally relevant stimuli [70].

Connections: OFC, Anterior Cingulate Gyrus, and Limbic Lobe The interrelationships between the OFC and the anterior cingulate gyrus (ACG) to the limbic lobe, part of the temporal lobe system, provides neuroanatomical support for the significance of the MTLS and the autonomic function as hypothesized in the FCP. The prefrontal limbic system includes contributions to the great limbic lobe. The posterior OFC areas are called the *orbital part* of the prefrontal limbic region (i.e., BA OPA11, OPro, and 13) and the anterior cingulate areas from the posterior medial PFC (i.e., MPA11, 25, 32, and 24). The division of the OFC and medial prefrontal regions into anterior and posterior sectors is based on cortical type. Both components share strong connections with cortical and subcortical limbic structures, the thalamic nuclei, the AG, the hypothalamus, and memory-related medial temporal cortices. The medial prefrontal cortices differ from the OFC by their stronger projections to hypothalamic autonomic centers, spinal cord, and brainstem autonomic centers. The ACG has been called the emotional motor system [66,71]. Significant for the FCP is the hypothesized interaction between the cerebellum-acousticomotor system and the ACG (FCP algorithm, Fig. 2).

OFC and Memory Neuroanatomical reports have identified strong connections between the OFC and brain cortices involved with the brain function of memory formation. The following reports provide a framework to understand the SPECT/PET neuroimaging findings and the hypothesized establishment of a paradoxical auditory memory as the initial brain function process in the FCP.

Anatomical data of the OFC and its connections with the limbic areas of the medial temporal lobe (MTL) have established the critical involvement of both in the processing of novel information, breaches of expectation, and memory—specifically, for declarative memory, the neuroanatomical substrates (entorhinal, perirhinal, and hippocampal cortices) and, for emotion and motivation, the AG and the hypothalamus. The role of the AG is in the emotional processing of the affective component of the mnemonic experience. Significantly, the caudal region of the OFC has architectonic characteristics similar to those of the limbic areas of the MTL. Major bidirectional connections via the uncinate fasciculus link the OFC with the entorhinal, perirhinal, hippocampal, and parahippocampal cortices. A direct connection exists between the OFC and the AG and the temporopolar cortex, the hippocampus, and the anterior nucleus of the thalamus, which has connections with the mamillary bodies, which in turn project to the ACG and subcallosal gyri. In

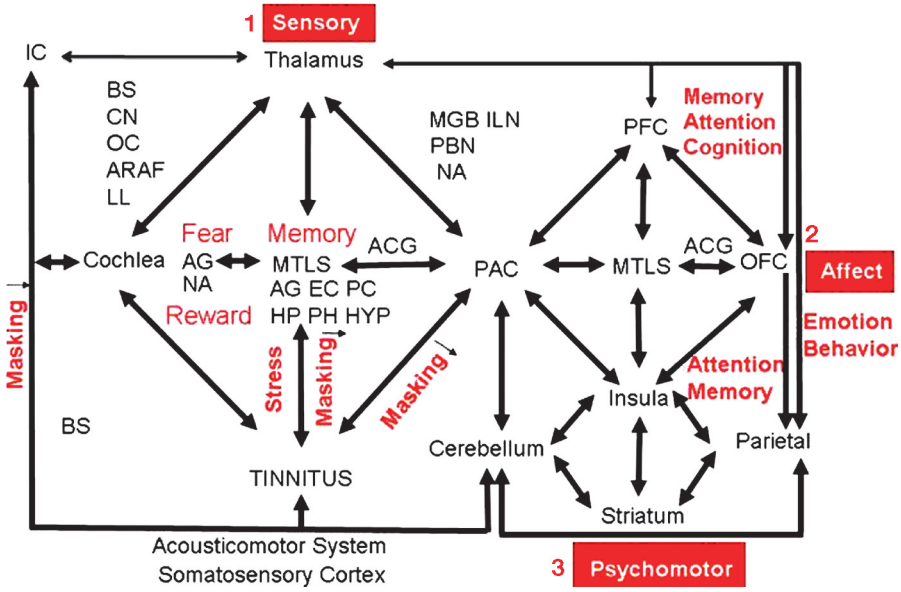

Figure 2. Three final common pathway algorithms reflect the neuroanatomical substrates of the sensory, affect, and psychomotor components of a sensation (i.e., the aberrant auditory sensory stimulus—tinnitus). The brain functions associated with each component of the aberrant auditory sensory stimulus (tinnitus) are integrated in each algorithm with the involved neuroanatomical substrates. The reciprocal interacting neuroanatomical substrates of the three components complete a circuit—the final common pathway sensory–affect transformation. **Algorithm 1, Sensory Component:** It is hypothesized that for the sensory component, the sensory information (i.e., dyssynchronous aberrant auditory signal) arising from the peripheral cochlea or central nervous system (CNS) ascends via (1) the brainstem (*BS*), cochlear nucleus (*CN*), and olivocochlear bundle (*OC*) to the inferior colliculus (*IC*) and on to the medial geniculate body (*MGB*), intralaminar nuclei (*ILN*) of the thalamus, and the parabrachial nucleus (*PBN*) and nucleus accumbens (*NA*) and (2) the primary ascending reticular activating formation (*ARAF*) of the lemniscal system to the thalamus—both as part of the exogenous system of the CNS [53,54] for the receipt of sensory information arising from the environment or peripheral or central nervous system that projects to the primary auditory cortex (*PAC*), which in turn projects to the prefrontal cortex (*PFC*), orbitofrontal cortex (*OFC*), anterior cingulate gyrus (*ACG*), and insula. The cerebellum, via the acousticomotor system, has reciprocal projections to and from the somatosensory cortex, IC, thalamus, PAC, and parietal lobe [18]. Hyperpolarization and depolarization of GABA-influenced thalamic neuron activity results in thalamocortical oscillations in a synchronous signal at brain cortex [204,254]. Reciprocal innervation from the thalamus to the medial temporal lobe system (*MTLS*), including the amygdala (*AG*), hippocampus (*HP*), paparahippocampal formation (*PH*), entorhinal cortex (*EC*), perirhinal cortex (*PC*), ACG, and hypothalamus (*HYP*), comprise an endogenous system of the CNS as hypothesized for sensory processing [53,54]. For tinnitus, the endogenous system is hypothesized to result in the establishment of a "paradoxical memory" for the aberrant auditory sensory stimulus (tinnitus) and has a reciprocal interaction with the thalamus [16]. The associated brain function processes within the neuroanatomical substrates of the sensory component include memory, stress, masking, fear, reward, and autonomic functions. Stress is considered to be a modulator of the clinical course of the tinnitus with the accompanying reduction and alteration in auditory masking [2,230–232]. **Algorithm 2, Affect (Emotional-Behavioral) Component:** The neuroanatomical substrates of the affect (emotional) component are highlighted by the OFC, PFC of the frontal lobe, PAC, MTLS of the temporal lobe, and insula. Reciprocal innervation is hypothesized to occur between the PAC of the sensory component and the OFC, ACG, PFC, MTLS, and insula. The insula, by its central location, is hypothesized to exert a modulating effect among the sensory, affect, and psychomotor components. The thalamic activity is ongoing with reciprocal projections to the PFC, OFC, and parietal lobe. The associated brain function processes within the neuroanatomical substrates of the affect (emotional-behavioral) component include attention and cognition (i.e., learning and memory). **Algorithm 3, Psychomotor Component:** The neuroanatomical substrates of the psychomotor component include the insula, parietal lobe, striatum, and cerebellum. Reciprocal interaction is hypothesized between each of the neuroanatomical substrates. The thalamic activity is ongoing with reciprocal innervation of the parietal lobe, OFC, and PFC. Significant for the sensory–affect transformation is considered to be the interaction between the striatum, parietal lobe, and OFC via the insula. The associated brain function processes within the neuroanatomical substrates of the psychomotor component include attention and cognition (i.e., learning and memory) and their influence on the affect (emotional-behavioral) component. (*LL* = lateral lemniscus.)

short, a massive direct interaction occurs between the caudal medial frontal cortex that surrounds the rostral portion of the corpus callosum (BA24), the limbic medial region temporal lobe system, and the septal nuclei for establishment of new declarative memories (i.e., a septohippocampal system). Lesions of the septal region reduce cholinergic inputs to the hippocampus, with resultant memory loss. Evidence from the monkey indicates that the orbital region does play a direct role in memory processing [72].

The entorhinal, perirhinal, hippocampal, and parahippocampal cortices and the AG are critical in forming

declarative memory [73]. The hippocampal and parahippocampal cortex are involved in spatial memory and perhaps the contextual aspects [74,75].

OFC and Basal Ganglia Neuroanatomical substrates of the OFC and the basal ganglia (BG) are integrated into the FCP for the translation of the normal brain function of motivation-reward control in response to a sensation—namely, tinnitus, an aberrant auditory sensation (i.e., the establishment in tinnitus patients of the brain function of a paradoxical motivation-reward). The following reports are considered to support the concept of a "paradoxical" motivation-reward in tinnitus patients, particularly those with SIT.

- The OFC is involved in the motivational control of goal-directed behavior [76].
- Rewards may constitute basic goals of behavior [77].
- Reward processing in the primate OFC and BG has been interpreted and reviewed in comparison to discharging neurons in the striatum (i.e., caudate, putamen, and ventral striatum, including nucleus accumbens) [78]. Significant for tinnitus are the reported multiple, heterogeneous, partly simultaneous activations related to specific aspects of rewards in response to activation of OFC neurons and BG response (i.e., activation in the striatum in relation to both the expectation and detection of rewards and activities related to the preparation, initiation, and execution of movements reflecting an expected reward).
- Mechanisms of inhibitory response control in frontostriatal systems are organized according to distinct levels of abstraction. The ventral striatum, which projects to the OFC and the medial PFC, is restricted to the transformation of concrete stimulus exemplar information into motor responses. The adaptive function of the lateral PFC extends to the transformation of abstract task-rule representations into actions [79]. The translation of this finding is suggested for explanation of the psychomotor component of the tinnitus in the FCP (i.e., a potential neural circuit mechanism).

Significantly translated for the FCP and tinnitus are the reports that (1) lesions of the OFC impair decision making about the expected outcome of actions [80]; (2) monkeys with OFC lesions respond abnormally to changes in reward contingencies [81]; (3) altered reward references have been demonstrated [82]; (4) OFC neurons respond selectively to rewards or aversive stimuli [83]; (5) OFC neurons process a relative preference for rewards [84]; and (6) the motivational functions of the OFC may involve the BG via frontostriatal projections [85–87].

It is hypothesized for the FCP that the motivation-reward response of the OFC to the input of the tinnitus signal is analogous to that with a lesion in the OFC (i.e., an aversive response). The tinnitus signal triggers in the OFC and striatum an activation of aversive brain function processes of reward and behavior (i.e., a paradoxical reward) with resultant altered reward preference (e.g., fear). This is similar to the activation in the MTLS —in response to normal auditory sensation—of the brain function processes of auditory memory. The tinnitus signal triggers activation of a paradoxical auditory memory. Both the motivational and memory brain functions are paradoxical (i.e., the patient does not want either of these aversive brain functions [reward and memory], which have been activated in response to the tinnitus). The tinnitus stimulus, paradoxically, activates the normal motivation-reward response to a sensory stimulus (i.e., sense of well-being, emotion of joy, and memory of the sensation).

OFC and Hippocampus The hippocampus is a brain region frequently studied in the context of plasticity. It has been demonstrated in rats that acoustic overstimulation resulted in activation of neural plasticity as manifested in alteration in the place field activity (i.e., location-specific firing) in the hippocampus. Acoustic overstimulation is not limited to the auditory nervous system but extends to other parts of the CNS [88].

The interactions between the OFC and hippocampal memory systems and neocortical associated cortices have been proposed as the sources of initial processing of information for long-term memory (i.e., a broader bidirectional hippocampal memory system) [89].

In the long term, declarative memory is mediated by a network of brain structures including the hippocampus and the parahippocampus. The parahippocampus, including the entorhinal, perirhinal, and postrhinal cortices, has been referred to as the *parahippocampal region* [89–91]. Declarative memory, also called *episodic* [92] or *explicit memory* [93], is a memory for facts and events that are stored for future conscious recollection.

In this proposed broader bidirectional hippocampal memory system, the functions of association neocortex are included. All sensory information is initially processed in widespread neocortical association areas and then propagated through the parahippocampus to the hippocampus. Back-projections send memory information from the hippocampus to the parahippocampus and then to the association neocortex for long-term retention of these memories. The OFC is proposed to serve as a high-order association neocortex.

The proposed view of a broader bidirectional hippocampal memory system is based on olfactory experimentation in the rat and includes the OFC neocortical

association cortex. This view is recommended for translation for the hypothesis of the FCP that the initial brain function process in the FCP is the establishment of paradoxical auditory memory for tinnitus. Furthermore, this proposal emphasizes the significance of the initial and ongoing SPECT/PET reports from SUNY/DMC of perfusion asymmetries in multiple regions of interest, highlighted by the MTLS.

In summary, it is hypothesized that in the FCP, the development of the paradoxical auditory memory in the hippocampus is projected from the hippocampus by widespread connections to cortical ensembles in different functionally related areas, reflecting affect processing and higher mental functions of cognition and learning.

OFC and Amygdala The AG and OFC comprise an interactive neural circuitry that contributes to affect–action relations. Damage to fibers passing near or through the AG, rather than neuronal loss in the AG, appears to account for many of the behavioral deficits observed in primates [94].

In primates, three components of the telencephalon contribute to affect–action relations: the AG, the OFC, and the medial frontal cortex. The textbook view of AG-OFC interaction is a model of the working together of the AG and OFC in affective processing, including both emotion and reward (i.e., a common circuitry for both). The implication is that reward processing and emotion are the same thing; that the AG is necessary for both and that the OFC represents values of expected outcomes (i.e., a cost-benefit analysis).

In the new model, the AG and OFC make distinct contributions to emotional responses and reward processing, which are distinctly different neuronal responses. The AG provides the information needed for it to make value comparisons. Two routes are proposed to the OFC: one for visual information and the other for affective information (which subserve emotional responses and reward-driven responses). For visual stimuli, interactions between the OFC and the inferotemporal and perirhinal cortex, rather than interactions between the OFC and AG, would allow the visual cues to elicit the long-term value of the affective signal (e.g., food) [94].

The new model is based on research in primates of the contributions of the AG and the OFC to affect–action. The view is presented that the AG and OFC make distinct contributions to emotional responses and reward processing. Interconnections between the lateral and medial parts of the OFC and the OFC and medial frontal cortex may reflect the interactions of these systems.

The interaction of the AG with sensory cortex influences sensory perception. It is suggested that the AG cortical pathways provide for increased perceptual processing of biologically significant stimuli. The AG is considered to be essential for a top-down influence of emotion on perceptual processing, a kind of "emotional processing." The OFC and AG are suggested to process affect together to mediate the relationship between memory and advantageous actions.

This view is recommended for translation to the hypothesis of the FCP for affect–emotion interaction. Furthermore, this proposal emphasizes the SUNY/DMC reports of perfusion asymmetries in multiple regions of interest, highlighted by the MTLS.

Dorsolateral Prefrontal Cortex The DLPFC is described as equivalent to BA9 and 46 [95,96]. A broader definition of the DLPFC consists of the lateral portions of BA9–12, 45, 46 and the superior part of 47. The DLPFC is connected to the OFC, the thalamus, the dorsal caudate nucleus, the hippocampus, and primary and secondary neocortex association areas, including posterior temporal, parietal, and occipital areas [97].

The function of the DLPFC is as the highest cortical area responsible for motor planning, organization, and regulation. In addition, integration of sensory and mnemonic information, working memory, cognitive and emotional aspects of memory, and regulation of intellectual functioning and action, all complex mental activities, requires the additional cortical and subcortical circuits with which the DLPFC is connected [97,98]. Two pathways of complex information processing have been reported in the brain: the emotional brain pathway, which attaches values to incoming information via the AG, ACG, ventromedial prefrontal cortex (VMPFC), and OFC, and the cognitive pathway, which provides a detailed feature analysis of the incoming information via the hippocampus, the posterior cingulate, and the parietal and occipital temporal cortices. The DLPFC provides an integration of emotion and cognitive information [25].

The integrative function of the DLPFC for emotion, cognition, and attention is significant for the FCP. The literature discussed next is considered to have clinical application for tinnitus theory, diagnosis, and treatment.

The DLPFC is identified as a key location of a network that modulates the activity of the associated experience of presence. *Presence* is understood as referring to the subjective feeling of being in a virtual environment while remaining transiently unaware of one's real location and surroundings and of the technology that delivers the stream of virtual input to the senses. The use of transcranial direct current stimulation while participants were exposed to the virtual roller coaster ride and the influence on presence-related measures were evaluated. The findings were discussed in the context of current models, explaining the experience of presence and out-of-body experiences. The right-sided DLPFC plays a pivotal role in the activation and control of a network

that generates or modulates the presence experience. The network mentioned is not exclusively associated with the modulation of presence experience. Rather, it is a network involved in the control of many other psychological functions, including top-down and bottom-up control of attention, spatial orientation, egocentric orientation, and motor behavior. The studies demonstrate that a particular network is involved in many functions, and the psychological specificity cannot be inferred simply by identifying the activated brain structures. This study emphasizes the key role of DLPFC in controlling several behavioral aspects. The DLPFC acts as a modulator of the network and also as a modulator of the concomitant psychological experiences [60].

In the context of the FCP, this article has implications for tinnitus diagnosis and treatment and the brain function processes of attention. For tinnitus diagnosis, implications are for tinnitus patients who report the location of the tinnitus to be "outside my body." For treatment, it applies to site selection for transcranial magnetic stimulation for attempting tinnitus relief for unilateral tinnitus [25].

Recent analysis of fMRI brain data in patients being tested in hypothesis generation tasks that involve set shifts (i.e., successful solutions for match problems requiring determination of a number of possible solutions) implicated the right PFC. The results identified the ventral lateral (BA47) aspect of the right PFC as a critical component of neural systems underlying set shifts and demonstrated a dissociation between the right ventrolateral PFC and DLPFC in the generation of hypotheses and maintenance [99]. This article emphasizes the ongoing multiple functions in neuroanatomical substrates and the role of the DLPFC in controlling several behavioral aspects. The DLPFC acts as a modulator of the network and also as a modulator of the concomitant psychological experiences that is to be considered in the FCP and for clinical translation for tinnitus theory, diagnosis, and treatment.

Temporal Lobe The temporal lobe lies ventral to the lateral sulcus and displays three convolutions: the gyri superior (BA38, 22), middle (BA21), and inferior (BA20). The rostral part of the superior gyrus participates in Wernicke's area. The anterior temporal lobe is BA15. The superior temporal sulcus (STS) runs parallel to the lateral sulcus and terminates in the angular gyrus. On the posterior third of the superior plane of the superior temporal gyrus (STG) are several convolutions that form the transverse gyri of the primary ACG (BA41, 42). The inferior surface of the temporal lobe contains part of the inferior temporal gyrus (BA20), the occipitotemporal gyrus (BA36), the parahippocampal gyrus (BA27, 28, 34, 35, 36), and the fusiform gyrus (BA37). The fusiform gyrus is separated from the inferior temporal gyrus by the inferior temporal sulcus. The collateral sulcus separates the parahippocampal gyrus and its medial protrusion, called the *uncus*. The rostral part of the parahippocampal gyrus, the uncus, and the lateral olfactory stria form the pyriform lobe, part of which constitutes the primary olfactory cortex [100,101].

The MTLS is part of the limbic lobe [2,102]. The limbic lobe is considered a "synthetic lobe"; it encircles the upper brainstem and includes the most medial margins of the 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). Physiological evidence suggests functional differences between the various components, although most are related to visceral or behavioral activities [17].

Modification of the synaptic connection strengths (or weights) between neurons results in useful neuronal information processors for most brain functions, including perception, emotion, motivation, and motor function [103]. The role of the MTLS is considered to be crucial for tinnitus for the brain function processes of memory and emotion. The MTLS is a nexus of activity in the FCP.

Temporal lobe functions are highlighted by perception and recognition of auditory stimuli, memory, and speech. The STG, which includes the primary auditory gyrus, is involved in reception of auditory signals (BA41, 42). The ventral part of the temporal cortex is involved in visual processing of complex stimuli as faces (fusiform gyrus BA37) and scenes (parahippocampal gyrus BA27, 28, 34–36).

The following are summaries of research relating to the role of the temporal lobe that supports the significance of the temporal lobe and the MTLS for the FCP.

Primary Auditory Cortex Magnetic source imaging showing reorganization of the primary auditory cortex (PAC) in tinnitus has been reported. A high positive association was reported between the strength of the tinnitus and the amount of shift of the tinnitus frequency in the PAC. The evidence lends support to the belief that cortical reorganization has functional significance for the experience of an organism [104]. The reorganization of the PAC is clinically considered to be reflected in the reported patterns of the QEEG in SIT patients and as hypothesized in the TDST [6,23,24]. Such brain plasticity may act as a trigger to the creation of the FCP, which may vary in time of onset [105].

The anatomicophysiological investigations of the mammalian PAC are considered basic for the neuroscience of

tinnitus and the FCP (i.e., identification of "maps" of projections in the sensory auditory neurons across the cortical surface) [106], identification of the thalamocortical and corticothalamic connections in the cat [107], the concept of neuroplasticity in the PAC [108], and that cortical population coding could, in principle, rely on either the mean rate of neuronal action potentials or the timing of action potentials, or both [109].

Limbic Lobe and MTLS An anatomical circuit focusing the limbic system as a basis for emotion was proposed in 1937 [110]. It was hypothesized that certain rhinencephalic and limbic pathways provided an anatomical basis for emotions and their expression through such visceral and instinctual actions as those involving feeding, mating, mothering, and aggression. 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 cingulum. The cingulate gyrus connects to the parahippocampal gyrus and peripheral area of the temporal lobe; the temporal lobe connects to the hippocampus (Ammons horn) via the temporoammonic tract; the hippocampus connects to the mamillary body via the fornix; the mamillary body connects to the anterior nucleus of the thalamus via the mammillothalamic tract; and the anterior nucleus of the thalamus connects to the cingulate gyrus via the superior thalamic peduncle, thus completing the circuit. Additional feeding pathways to the circuit are described to include the septal and olfactory regions and the AG. Significant for the FCP for tinnitus since 1989 has been the Papez circuit, which was referenced in our initial publication in 1995. The neuroanatomical substrates of the hypothesized FCP for tinnitus found support in the Papez circuit, particularly in its emphasis on the MTLS, and was and still is considered significant for tinnitus patients, particularly those with SIT [3,4,17].

The MTLS, including the AG-hippocampal complex, was reported in 1995 to demonstrate with SPECT of brain a greater than 90% incidence of occurrence of perfusion asymmetries involving the MTLS, with a p value of less than .05 in 48 tinnitus patients. The MTLS is part of the limbic lobe. In addition, multiple perfusion asymmetries were demonstrated in adjacent frontal, temporal, and parietal lobes. It was hypothesized that the transition from perception to memory (i.e., from sensory to affect to memory) as reported by Squire et al. [111] in 1991 had a direct application to tinnitus, particularly of the severe disabling type. The MTLS had been identified for the function of memory [3,4,17,75] and stress [112].

Significantly, the perfusion asymmetries in multiple neural substrates, highlighted by the MTLS, described originally with brain SPECT from 1991 to 1995, has continued with brain FDG PET for approximately 300 examinations to date. Since 1995, the clinical impression has evolved that the functional significance for the temporal lobe is for multiple sensory input analogous to that for motor function in the precentral motor cortex.

PET–mapped brain regions were reported in four patients who were responding to changes in tinnitus loudness and could alter tinnitus loudness by performing voluntary orofacial movements (OFMs). Cerebral blood flow was measured in four patients and six controls at rest, during the OFM, and during stimulation with pure tones. OFM-induced loudness changes affected the PAC contralateral to the ear in which tinnitus was perceived, whereas unilateral cochlear stimulation caused bilateral effects, suggesting a retrocochlear origin for these patients' tinnitus. Patients compared with controls showed evidence for more widespread activation by the tones and aberrant links between the limbic and auditory systems. These abnormal patterns provide evidence for cortical plasticity that may account for tinnitus and associated symptoms. Although audiological symptoms and examination results of these patients were typical, the unusual ability to modulate tinnitus loudness with an OFM suggested some caution may be warranted in generalizing these findings [113]. This report confirmed the significance in tinnitus patients of the limbic lobe and the MTLS, reported originally with SPECT of brain in 1989, and provided the basis for the FCP, published in 1995 [1,3,4,13–17].

The significance of the MTLS for sensory stimulation and its translation for tinnitus is considered to be supported additionally by the reports summarized here.

Cellular Basis for the FCP and Working Memory The entorhinal cortex is a major contributor of afferents to the hippocampus and the dentate gyrus. Regions of both the frontal and temporal lobes contribute afferents to this region of the brain. These afferents form probable multisynaptic links in pathways connecting the classic sensory areas of the cortex and the limbic system [114]. This article projects future significance of the entorhinal cortex for sensory afferent input, which has since been established for sensory input in general and specifically for tinnitus (i.e., FCP paradoxical auditory memory).

Ablations of the perirhinal cortex alone for visual recognition produced a deficit nearly as severe as that found after rhinal cortex lesions, whereas ablations of the entorhinal cortex alone produced only a mild deficit. The damage limited to the rhinal cortex is sufficient to produce a severe loss in visual recognition, but also such damage leads to a far greater loss than damage to any other single structure in the medial part of the temporal lobe [75].

Recent efforts to define the functions of the primate rhinal (entorhinal and perirhinal) cortical areas have

focused on their interaction with the hippocampus in the mediation of normal memory. Less is known of the functional meaning of their strong connections to the AG, a key substrate for emotion. A previous study showed evidence that complete rhinal ablations yield changes in monkeys' behavioral responses to affectively salient stimuli. The two separate lesions in entorhinal or perirhinal cortex produced similar changes, and each replicated the effects of complete rhinal lesions (i.e., attenuated affiliation and enhanced defense). Failure to modulate responses based on previous experience (i.e., memory difficulties) may explain these affective changes [115]. This is considered to support the significance of establishing the paradoxical auditory memory in the FCP.

Working memory represents the ability of the brain to hold externally or internally driven information for relatively short periods. The entorhinal cortex in the parahippocampal region is crucially involved in the acquisition, consolidation, and retrieval of long-term memory traces for which working memory operations are essential. Neurons from layer V of the entorhinal cortex link the hippocampus to extensive cortical regions; it is linked to cholinergic muscarinic receptor activation and relies on activity-dependent changes of a Ca^{2+}-sensitive cationic current. An intrinsic neuronal ability to generate graded persistent activity constitutes an elementary mechanism for working memory [116]. This article provides a significant pathophysiological cellular basis for working memory and its translation for the FCP and potential future tinnitus treatment with medication.

QEEG, Tinnitus, and the FCP The significance of QEEG for tinnitus was introduced in 2000 (i.e., tinnitus-typical electroencephalography features can be extracted from the electroencephalogram) [26]. A descriptive analysis-interpretation of QEEG data for the metric of power in patients with tinnitus of the severe disabling type (N = 61) revealed statistically significant abnormalities in frontal greater than temporal electrode recording sites. The results suggested multiple central electrophysiological correlates for different clinical types of tinnitus identifiable with QEEG, for the metric of power, by frequencies of brain activity of delta greater than beta greater than alpha greater than theta bands (delta > beta > alpha > theta), reflecting physiologically the individuality of brain function and clinically the heterogeneity of the symptom of tinnitus for tinnitus patients. Clinical interpretation of the QEEG data in terms of brain function in a tinnitus patient—with a focus on theories of a neuroanatomical homeostatic system that regulates baseline levels of local synchrony in multiple neuronal assemblies and on theories of consciousness—introduces a paradigm switch in our clinical understanding of the symptom of tinnitus and an application for tinnitus diagnosis and treatment. The pattern of brain rhythm activity of delta > beta > alpha > theta in frontal greater than temporal greater than occipital recording sites and occipital equal to parietal and central recording sites is clinically considered to reflect multiple neuroanatomical ensembles of activity in patients with predominantly central-type SIT. Specifically, an electrophysiological correlate is seen for a predominantly central-type tinnitus of the severe disabling type (i.e., the thalamo-fronto-temporal circuit) [23,24].

Tinnitus Masking and FCP In a masking paradigm, magnetoencephalographic (MEG) recordings from tinnitus patients revealed responses in the MTL [117]. A neurophysiological approach to tinnitus was proposed in 1993. It is a significant contribution to the theory and clinical course of tinnitus, with application for tinnitus treatment [118]. The original article is considered to be a translation from the Papez circuit with an emphasis on the limbic system and the affect behavioral component of tinnitus. It provides a focus on the philosophy of perception, the affect behavioral response of the tinnitus patient, and the concept of tinnitus as a phantom perception. To be considered is that, in physiology, the term of a phantom perception for a sensation is reserved for sensations lacking identifiable neural substrates. Since 1989, multiple neural substrates have been identified in brain in SIT patients via nuclear medicine imaging (SPECT/FDG PET) and, since 2000, with electrophysiological identification of low-frequency brain rhythms from multiple scalp recording sites with QEEG. This is the basis for our recommendation that clinically tinnitus *not* be considered a phantom sensation.

Magnetic resonance imaging (MRI) diffusion tensor tracking has reported a new amygdalo-fusiform and hippocampal-fusiform pathway. This pathway has been hypothesized to have possible significance for recognition, memory consolidation, and emotional processing of visual and lexical information [119]. The fusiform gyrus may have significance for the brain function of attention and consolidation of the paradoxical memory in the FCP.

Parietal Lobe The parietal lobe is identified as having three parts: postcentral gyrus, superior parietal lobule, (BA7), and the inferior parietal lobule (BA40). The primary somatesthetic area includes the posterior bank of the central sulcus and the postcentral gyrus, which receive inputs for tactile and kinesthetic sensations and are somatotopically oriented. The superior (BA71) and inferior parietal lobules (BA40) are caudal to the postcentral gyrus. The inferior parietal lobule consists of two gyri, the supramarginal part of Wernicke's area and the angular gyrus part of Wernicke's area (BA39). The inferior parietal lobule represents a cortical association area

for inputs from multisensory perceptions that are received from adjacent and parietal, temporo-occipital regions. The parietal lobe functions are classically associated with movement, orientation, recognition, visuospatial processing, integration, and perception of stimuli (i.e., visual, auditory, vestibular, somatosensory) [55]. The posterior parietal cortex is referred to by visual scientists as the dorsal stream of vision. The ventral stream of vision is in the temporal lobe. The following reports are considered significant to support the role of the parietal cortex in the FCP.

Neuroanatomical tracers were injected into two functionally distinct areas in the lateral sulcus of macaque monkeys: the parietal ventral (PV) area and the second somatosensory (S2) area. Our results indicate that the PV receives substantial input from the inferior division of the ventral posterior nucleus (VPi), the anterior pulvinar (Pla), and the ventral portion of the magnocellular division of the mediodorsal nucleus (MDm), which also is interconnected with the PFC, the entorhinal cortex, and the AG. The S2 receives input predominantly from VPi, the ventral posterior superior nucleus (VPs), and the Pla. These results indicate that the PV and the S2 are involved in processing inputs from deep receptors in the muscles and joints. Because the PV and the S2 receive little, if any, cutaneous input from the thalamus, cutaneous input to these fields must arise mainly through cortical connections. Connectional data support the proposition that the PV and the S2 integrate motor and somatic information necessary for proprioception, goal-directed reaching and grasping, and tactile object identification. Further, the PV may play a role in tactile learning and memory [120]. This article is considered to demonstrate the integrative function of the parietal lobe for the components of tinnitus in the FCP (i.e., sensory, affect, and psychomotor), with a focus on brain function processes of emotion and memory.

The parietal lobe has been suggested to be part of a "global workspace." The concept is that the formation of a conscious percept involves a coupling between neuronal activity in a sensory cortex with other neurons widely distributed in brain frontal, cingulate and, in particular, parietal lobes: a frontal-parietal-cingulate network for a conscious perception that is clinically manifest to an individual. Lack of such coupling would not be clinically manifest (i.e., a subliminal nonconscious stimulus) [121]. This concept is significant for its support of (1) what has clinically been identified since 1983 to be subclinical tinnitus and (2) the multiple neuroanatomical substrates reported with nuclear medicine and QEEG to be involved in the FCP. It is recommended to be considered in context of reports of consciousness and global brain function theories (see the section Neuroscience and Brain Function).

Cerebellum The cerebellum lies in the posterior cranial fossa and consists of a midline portion, the vermis, and two lateral lobes, the hemispheres. Its surfaces are superior (covered by the tentorium), inferior (overlying the fourth ventricle), and posterior (in the suboccipital region). Structurally, it consists of the gray cerebellar cortex, a medullary core of white matter, and four pairs of intrinsic nuclei. The cerebellum connects to three lower segments of the brainstem by three paired cerebellar peduncles: superior, middle, and inferior. The hemispheres are divided into the anterior and posterior lobes of the cerebellum. The function of the cerebellum is one of processing, organizing, and integrating sensory inputs. Output function contributes to control of somatic motor function and arises from the deep cerebellar nuclei to exert major influences on brainstem nuclei at multiple levels [122]. The following reports are considered to support the role of the cerebellum in the FCP.

Classically, the cerebellum has been associated with motor function. New anatomical labeling techniques have led to new concepts for the function of the cerebellum, which include identification of corticocerebellar loops and their involvement in motor and nonmotor aspects of behavior. Associations between stimuli involved in cognitive function generate new context-dependent and adaptive responses via cerebellar signaling to nonmotor areas of cortex [123,124].

Functional imaging studies report the cerebellum to be involved in working memory, implicit and explicit working memory, and language [125]. A specific neurological condition called *cerebellar cognitive affective syndrome* is proposed; in it, cerebellar damage leads to a dysmetria of thought. Cerebellar influence on cognitive thought is considered to be analogous to its influence on motor function [126,127].

The cerebellum and descending auditory system (DAS) are clinically considered to be significant for influencing the development of the clinical course of tinnitus, particularly SIT. Brain SPECT demonstration since 1993 of perfusion asymmetries in the cerebellum in 60–70% of patients with central-type tinnitus was reported to clinically reflect the influence of an aberrant auditory stimulus—tinnitus—on the activity and function of the DAS highlighted by the cerebellum and the acousticomotor systems. Abnormalities in cerebellar function identified with brain SPECT correlated with abnormal visual vestibular interaction, prolongation, and interference in the vestibuloocular reflex and craniocorpography and are considered to reflect the psychomotor component of tinnitus [18].

An auditory cortical-cerebellar-thalamic loop has been hypothesized and is supported by the following reports. Regional cerebral blood flow and PET have demonstrated an increase in cortical synaptic activity with

40-Hz stimulation in the PAC, posterior STG, and STS and in bilateral activation of the cerebellar hemispheres. The cerebellum, driven by the auditory STG-STS, fulfills the role of an epicenter within the attentional network that may modulate ongoing corticothalamic oscillatory activity, in this case the generation of the steady-state auditory response. In humans, 40-Hz auditory input engages the coupling between auditory area–STG-STS and Crus II in a selective fashion [128].

There is increasing evidence that the steady-state auditory response at 40 Hz represents an induced oscillatory brain activity rather than an evoked response [129]. The anatomical substrate comprises the cortico-ponto-cerebellar projections, part of a closed loop with the cerebral cortex, in which the cerebellum returns projections to the cerebral cortex via the thalamus. The systems interacting with the cerebellum are not just somatosensory and motor but include visual and auditory loops [130].

The participation of corticothalamic loops in stimulus-induced oscillatory brain activity has been described previously [131]. The mechanism of oscillatory thalamocortical activity is manifested at cortex in a 40-Hz synchrony of brain rhythm.

An event-related fMRI experiment suggested that input from the PAC to the cerebellar hemisphere through cerebropontine pathways is conveyed, preferentially, at gamma-band frequencies. In other words, the cerebellum gates cortical output in the cortical-cerebellar-thalamic loop to preferentially boost 40-Hz responses [132].

Activated areas have been reported in the posterolateral portion of both cerebellar hemispheres, lateral to the paravermian region, Crus II [133]. The cerebellum receives monaural auditory input, processes it bilaterally in the lateral hemispheres, and integrates visual signals in neighboring hemispheric areas [134].

Connectivity studies in the cat have shown that the bulk of afferents to Crus II originate in the temporal lobe with a relay in the pontine nuclei, before reaching the cerebellar cortex. Primates demonstrate no direct projections from the primary auditory area; instead, corticopontine auditory fibers originate in the secondary auditory area A2 and adjacent association areas, although the most important cortico-ponto-cerebellar afferents are from multimodal areas in the upper bank of the STS [135].

The inferior parietal lobule (IPL) is a functionally and anatomically heterogeneous region that is concerned with multiple aspects of sensory processing and sensorimotor integration. Subcortical inputs to this cortical region are not known. To examine this issue, retrograde transneuronal transport of the McIntyre-B strain of herpes simplex virus type 1 were injected into four monkeys to identify the second-order neurons in subcortical nuclei that project to the IPL. The IPL is known to be involved in oculomotor and attentional mechanisms, the establishment of maps of extrapersonal space, and the adaptive recalibration of eye-hand coordination. The findings suggested that these functions are subserved by distinct subcortical systems from the superior colliculus, the hippocampus, and the cerebellum. Furthermore, the finding that each system appears to target a separate subregion of the IPL provides an anatomical substrate for understanding the functional heterogeneity of the IPL [136].

Neurons from multimodal areas in the upper bank of the STS project to the dorsolateral and lateral nuclei of the pons, which in turn project to the cerebellar area, Crus II [137]. The cerebellum returns connections to the cortex via the thalamus (i.e., an auditory cortical-cerebellar-thalamic loop).

The role of the cerebellum in tinnitus patients is considered to be an integration of functions: motor response to the aberrant auditory stimulus (i.e., acousticomotor system) and cognitive and behavioral response (i.e., auditory cortical-cerebellar-thalamic loop). It is suggested for the FCP that the role of the cerebellum is clinically significant. First, its activity is clinically manifested as the psychomotor component of the aberrant auditory sensation of tinnitus, a brain function analogous to that of the OFC or the affective-emotional-behavioral component of the aberrant auditory sensation—tinnitus—and that of the PAC for the sensory component (i.e., analogous and integrated brain functions) reflecting the components of a sensation—normal or aberrant.

Parabrachial Nucleus The parabrachial nucleus (PBN) is a region in the human brain that is related to the ascending reticular activating formation (ARAF). The PBN is a noncortical site located near the lateral lemniscus and the inferior colliculus, with connections to both the auditory and the somatosensory periphery [138]. The significance of the PBN for integration into the FCP and for the theory of tinnitus is supported by the following reports.

After salicylate treatment in Mongolian gerbils, c-fos expression in auditory brainstem nuclei was as low as after saline treatment (in controls). Pronounced differences between groups were found, however, in areas susceptible to stress, with many immunoreactive cells in the locus ceruleus, the midbrain periaqueductal gray, and the lateral PBN of salicylate-treated animals. These results suggest that salicylate may evoke tinnitus through a combined effect on auditory and nonauditory brain nuclei. Though activity in auditory brainstem nuclei is reduced, stress-susceptible nonauditory areas are activated. It seems possible that the interaction of these effects at particular locations of the brain causes tinnitus [139]. Distributions of arg 3.1 and c-fos immunoreactive

neurons in gerbil PAC and AG showed characteristic differences when comparing systemic application of the tinnitus-eliciting drug salicylate with acoustic stimulation or saline injections. Similarly, in the inferior colliculus, numbers of c-fos immunoreactive neurons were lowest after salicylate injections. In the AG, c-fos and arg 3.1 immunoreactive neurons were increased substantially after salicylate injections as compared to auditory stimulation or saline injections. In particular in its central nucleus, c-fos and arg 3.1 immunoreactive neurons were found exclusively after the tinnitus-inducing treatment, suggesting that coactivation of the PAC and the AG may by an essential feature of tinnitus-related activation [140]. The report of c-fos immunochemistry in the PBN has been integrated as an active nonauditory site into the FCP [105].

The PBN, with projections to the central amygdaloid nucleus and on to the intralaminar thalamic nuclei, contributes to conscious emotional behavior, including stress and anxiety often associated with tinnitus. The AG can further induce autonomic reactions and endocrine stimulation indirectly through the hypothalamus. The PBN has direct connection to the hypothalamus and visceral receptors. As a result, the PBN contributes directly to the sense of the physiological condition of the body's well-being, or interoception. Interoception is thus the "how I feel" sense, frequently described negatively by tinnitus patients with severe debilitative disease. These patients will often have "bad" days, frequently described as just "feeling poorly." These somatic complaints appear to be based on physiological mechanisms involving the PBN as part of the FCP, which contributes to the "emotional feeling" of tinnitus [141].

The PBN appears to be a logical but heretofore overlooked component that contributes to the transfer of an aberrant acoustic signal in the AG to an emotional feeling by the insula. It may be that the somatic aspect of the negative emotional feeling modulated by the PBN accounts for some of the "bad" bodily feelings that seem to define severe, idiopathic, debilitative tinnitus [105].

The relationship of the PBN to the ascending reticular system and the thalamus provides an anatomicophysiological pathway for influence of the oscillatory activity between the thalamus and the cortex, and ultimately on the synchrony of electrical activity at the cortex. This anatomicophysiological pathway has been integrated into the TDST [6].

Insula The insula is an invaginated cortical area buried in the depth of the lateral sulcus and can be seen only when the temporal and frontal lobes are separated. It is also sometimes grouped with limbic structures deep in the brain into a limbic lobe [142]. Parts of the frontal, temporal, and parietal lobes form opercula over the insula. The insular cortex is considered by some authorities to be a separate lobe of the telencephalon. Other sources see the insula as a part of the temporal lobe [143].

The insular cortex, in particular its most anterior portion, is considered a limbic-related cortex [143]. The insula is well situated for the integration of information relating to bodily states into higher-order cognitive and emotional processes. The insula does not act alone; it is part of multiple circuits. The insula receives information from "homeostatic afferent" sensory pathways via the thalamus and sends output to a number of other limbic-related structures, such as the AG, the ventral striatum, and the OFC. The insula plays a dominant role in the conscious awareness of the emotional feelings [144]. The summarized reports that follow are considered to support the role of the insula in the FCP.

The MTL system, including the AG and the hippocampus (involved in processing emotions and memory), is connected into the lemniscal and extralemniscal pathways at both the cortical and subcortical levels. It is hypothesized that the initial process in the transformation of a sensory stimulus to one of affect is the establishment of the aberrant auditory memory in tinnitus. Reciprocal neuronal connections among the MTL system—OFC, PFC, striate, cuneus, and hypothalamus—modulated by the insula transform the sensory component of the aberrant auditory stimulus into one of affect. This process establishes the paradoxical auditory memory and psychomotor and autonomic responses, manifested clinically in the behavior of tinnitus patients [2,41,105,145].

Functionally speaking, the insula is believed to process convergent information and integration of emotion with the sensation: The anatomical location of the insula provides for the integration of information relating to bodily states into cognitive and emotional processes. The anterior insula is related predominantly to olfactory, gustatory, viceroautonomic, and limbic functions. The posterior insula is related more to auditory-somesthetic-skeletomotor function. The insula also receives differential cortical and thalamic input along its length. The anterior insula receives a direct projection from the basal part of the ventral medial nucleus of the thalamus and a particularly large input from the central nucleus of the AG. Additionally, the anterior insula itself projects to the AG. The posterior insula connects reciprocally with the S2 and receives input from spinothalamically activated VPi thalamic nuclei. The VPi receives inputs from the ventromedial nucleus (posterior part) of the thalamus that are highly specialized to convey emotional-homeostatic information such as pain, temperature, itch, local oxygen status, and sensual touch [146].

Functional imaging experiments have revealed that the insula has an important role in pain experience and the experience of a number of basic emotions, including

anger, fear, disgust, happiness, sadness, and conscious desires, such as food and drug cravings. The insula receives information from "homeostatic afferent" sensory pathways via the thalamus and sends output to a number of other limbic-related structures, such as the AG, the ventral striatum, and the OFC [143,147,148].

The insula cortex (Brodmann's 13–16) has distinct auditory and multisensory areas that have been identified through imaging to be active or hypoactive in cases of severe tinnitus. As such, the insula is a candidate for inclusion in the FCP for tinnitus. The insula has connection with the prefrontal and auditory cortices, the AG, the thalamus, the PBN, the OFC, the striate, the cuneus, and the cerebellum. The insula, as part of the MTLS—which also includes the AG and the hippocampus—modulates its metabolic activity after high-frequency stimulation. The FCP is characterized by numerous areas in the lemniscal and extralemniscal pathways, including the auditory regions in the thalamus, the cortex, and the cerebellum. It is suggested that elements of the FCP, formulated into a general model of tinnitus, should be considered in designing treatment strategies. This view is the direct result of our past and recent new experiences using ultra-high-frequency sound therapy in cases of severe disabling tinnitus, presented at this time. The use of multisensory vibration stimulation (somatosensory and high-frequency jointly) should also be explored to maintain or reprogram the auditory cortical map and induce activity in the FCP circuit, including the PBN and the insula, which may be the physiological substrate of tinnitus behavioral tests [149].

A general hypothesis that has been proposed integrates cognitive processing with neuroanatomy to explain anxiety. The anterior insula is suggested to play a key role in this process [150,151]. A somatic marker hypothesis proposes the idea that rational thinking cannot be separated from feelings and emotions. The insula plays a starring role [76].

It receives information from receptors in the skin and internal organs. Such receptors are nerve cells that specialize in different senses. Thus, there are receptors that detect heat, cold, itch, pain, taste, hunger, thirst, muscle ache, visceral sensations, and so-called air hunger, the need to breathe. The sense of touch and the sense of the body's position in space are routed to different brain regions [152].

Basal Ganglia Anatomical classifications of the BG include the following factors. Classically, the BG are identified as subcortical nuclear masses derived for the telencephalon. Structures composing the BG include the caudate nucleus, the putamen, the globus pallidus, and the amygdaloid nuclear complex. Together, they have been considered to constitute the corpus striatum.

The lentiform nucleus refers to the putamen and the globus pallidus. It lies between the internal and external capsules. The putamen is the largest and most lateral of the corpus striatum. The caudate nucleus is related throughout its extent with the lateral wall of the lateral ventricle. It has an enlarged rostral part (i.e., the head) and a narrower body and tail. The body lies dorsolateral to the thalamus. The tail terminates in the region of the amygdaloid nuclear complex. The caudate nucleus and the putamen along with the interposed anterior limb of the internal capsule are collectively known as the *corpus striatum* (i.e., striated body) because of their appearance [153].

Classically, the striatum has been conceived as consisting of a dorsal sensorimotor and a ventral portion processing limbic information. Anatomy and physiology demonstrate that the two striatal areas have the basic structure and lack sharp boundaries. Behaviorally, a distinction between dorsolateral and ventromedial is supported in accordance with a mediolateral functional zonation imposed on the striatum by its excitatory cortical, thalamic, and amygdaloid inputs [154].

The striatum has been known for its role in the modulation of movement pathways. It is also involved in cognitive processes involving executive function. In humans, it is activated by stimuli associated with reward, aversive, and novel unexpected or intense stimuli to which the striatum is reacting. This article is significant for the role of the striatum in the affect and psychomotor components of the FCP and for the interaction of the striatum and the AG for the brain function of fear (see the section Nucleus Accumbens, subsection Fear).

At this time, the BG are referred to as five major subdivisions: a rostral striatum consisting of the putamen and caudate nucleus and the external segment of the globus pallidus and the internal segment of the globus pallidus and a caudal portion, including the subthalamic nucleus and the substantia nigra. Functionally, they control voluntary and establishing postures. In the brain, they are interconnected with the cerebral cortex, the thalamus, and the brainstem. Mammalian BG are associated with a variety of functions: motor control, cognition, emotions, and learning [155].

The following anatomical classification of the BG and related centers is considered clinically relevant for the FCP. The BG consist of the corpus striatum (i.e., the striatum and the globus pallidus). The components of the striatum are the caudate and putamen (the dorsal striatum [DS]) and the nucleus accumbens (the ventral striatum). The globus pallidus is identified by it medial (internal) and lateral (external) segments (the dorsal pallidum and the ventral pallidum). The remaining components include the substantia nigra and the ventral tegmental area [156].

Nucleus Accumbens The nucleus accumbens (NA) forms the floor of the caudal part of the anterior horn of the lateral ventricle, between the head of the caudate nucleus and the anterior perforated substance [157]. Various reports, as summarized here, support the integration of the NA into the FCP.

The NA is included in the "limbic-related" (or paralimbic) ventral striatum and plays a crucial role in the formation of adaptive behavioral responses to environmental stimuli. In humans, the NA is active during instrumental and Pavlovian conditioning [158]. In animal studies, the NA has been shown to be involved in reward-directed and avoidance learning. Lesions of the NA in rats impair the habituation to noise bursts preceded by a warning sound [159].

The NA receives inputs from the AG [160] and brain stem raphe nuclei [161], which are involved in the regulation of sleep and arousal. Interconnected parallel circuits have been identified between the NA and the thalamus, in particular the TRN [162]. Significant for the FCP is the report of structural brain changes in tinnitus. Tinnitus sufferers were compared with healthy controls by using high-resolution MRI and voxel-based morphometry. Within the auditory pathways, gray-matter increases were identified only at the thalamic level. Outside the auditory system, gray-matter decrease was found in the subcallosal region, including the NA. The results suggested that a reciprocal involvement of both sensory and emotional areas is essential in the generation of tinnitus. It is hypothesized that in the area of the TRN, the NA can exert an inhibitory gating influence over the thalamocortical relay. Decreased gray-matter volume in the NA would, therefore, reduce the inhibition normally produced by the NA. The subcallosal area and the posterior thalamus are critical in the pathogenesis of tinnitus. Only the combined changes in both regions seem to bring about the sensation of tinnitus. Long-term habituation mediated by the subcallosal region or, more specifically, the NA normally helps to cancel out the tinnitus signal at the thalamic level (TRN) and prevents the signal from being relayed onto the AC. Thus, in cases in which the subcallosal region becomes impaired or disabled, a chronic tinnitus sensation would be the result [163].

Thalamus The thalamus is the largest subdivision of the diencephalon, positioned between the interventricular foramen and the posterior commissure and extending from the third ventricle to the medial border of the posterior limb of the internal capsule. The lateral and caudal parts of the thalamus are enlarged and overlie midbrain structures. The stria terminalis and the terminal vein are dorsal in position at the junction of the thalamus and caudate nucleus. The subdivisions of the thalamus include the anterior tubercle, the pulvinar, and the medial and lateral geniculate bodies. The medial and lateral geniculate bodies contain relay nuclei, lie ventral to the pulvinar, and are concerned with audition and vision. The internal medullary lamina is a thin layer of myelinated fibers that divides the thalamus into the anterior, lateral, medial, and ventral nuclear groups. The intralaminar thalamic nuclei are a collection of nuclei within the internal medullary lamina [164].

The significance of the role of the thalamus for sensation is well known. The functionality of the thalamus includes (1) distribution of most of the afferent input to the cerebral cortex; (2) control of the electrocortical activity of the cerebral cortex; (3) integration of motor function via relays through which inputs from the corpus striatum and cerebellum reach the motor cortex; (4) parallel processing of sensory signals; (5) parallel processing of sensory signals; (6) integration of inputs that modify motor activities; and (7) input selection, output tuning, high-fidelity impulse transmission, synchronization, and dyssynchronization of cortical activities. The dominant role of the thalamus in the maintenance and regulation of states of consciousness, alertness, and attention has formed the basis of its being regarded as the chief integrating and tuning mechanism of the neuraxis (i.e., the axial unpaired part of the CNS composed of the spinal cord, rhombencephalon, mesencephalon, and diencephalon) [164,165].

The understanding of the anatomical significance of the thalamus to the neuraxis was the basis of its inclusion at the central position of the algorithm of the FCP (see Fig. 1). The FCP, by its integration of the anatomy of the thalamus and its interrelationships with temporal and frontal cortices, the OFC, the BG, and the insula, provides a basis for clinical translation for tinnitus theory, diagnosis, and treatment.

Lemniscal and Extralemniscal Systems The lateral and medial lemniscus are fiber tracts of the tegmentum of the midbrain. Most of the fibers of the lateral lemniscus extend dorsally, rostrally from the lower pontine tegmentum, and surround the nucleus of the inferior colliculus. Some of the fibers end there, and others continue into the medial geniculate body of the thalamus [100,166].

The lateral lemniscus is a major and principal ascending auditory pathway in the brainstem and is also referred to as the *classical auditory pathway*. The extralemniscal system is non-tonotopic and includes the external and pericentral nuclei of the inferior colliculus, the medial division of the medial geniculate body, and a belt of the AC surrounding the tonotopic fields. This system is referred to also as the "lemniscal adjunct" or "diffuse system," provides "nonspecific" auditory input to the cortex, and includes the brainstem reticular formation and the intralaminar nuclei of the thalamus [167–169].

The following reports support the integration into the FCP of the lemniscal-extralemniscal systems and their cortical projections.

The ascending ARAF, part of the extralemniscal system, has been hypothesized to be significant in a theory of consciousness [53]. Sensory input into the CNS ascends via the ARAF to the thalamus and is hypothesized to be part of an exogenous system of the CNS for the receipt of sensory information arising from the environment or the peripheral or central nervous system. When integrated with the theory of consciousness, the FCP provides a model for an integrated theory of tinnitus and brain function—TDST [6]. In 1991, it was speculated that information for normal auditory function was processed along two different pathways, one for sensory and the other for affect [170].

An overview of central auditory processing by Brugge [167] gains particular significance for theories of tinnitus, the FCP, and translation of what is known of the anatomy and physiology of the auditory system for tinnitus diagnosis and treatment. Particularly significant for the FCP and for clinical translation to tinnitus professionals for theory, diagnosis, and treatment of the disorder are the sections on sensory integration and neural encoding, the auditory forebrain, and the extralemniscal pathways. The forebrain of mammals comprises the entire CNS rostral to the midbrain and is divided into a caudal part, the diencephalon, and a rostral part, the telencephalon. The concept of a "code" as applied to the auditory system describes how sound information can be and is represented in neural activity. This concept of code has been translated for identifying via QEEG an electrophysiological correlate for tinnitus, which provides data in support of the FCP [24]. In the original algorithm of the FCP, the identification of the central role of the thalamus, the major portion of the diencephalon, provides a basis for understanding the anatomicophysiological interrelationship of activities between thalamus and the cortex via reciprocal innervating thalamocortical and corticothalamic pathways. The lemniscal system's auditory information processing is limited by the cochleotopic map on which other stimulus attributes may be superimposed. The inclusion into the AC of cortical fields referred to as *polysensory*, *nonspecific*, or *associational areas* that have little or no cochleotopic organization (the extralemniscal pathways) provides tinnitus professionals with a basis for clinically understanding (1) the need to identify components of tinnitus, (2) the heterogeneity of the tinnitus symptom as manifested by the clinical identification of different clinical types of tinnitus (i.e., auditory and nonauditory tinnitus), and (3) the association with tinnitus of the clinical manifestation of multiple brain functions reflecting the processing of acoustical information: attention, learning, memory, and the execution of hearing-related motor tasks, as hypothesized in the FCP [8,168].

Recently, the lemniscal system has been referred to as the *classic* (lemniscal or specific) *pathways* and the extralemniscal system as the *nonclassic* (extralemniscal or diffuse) pathways [171]. These entities provide clinicians with an understanding of the anatomicophysiological basis for attempting tinnitus relief by differentiating recommendations for treatment targeting the components of tinnitus: sensory, affect, and psychomotor [172].

Sensory Physiology Dilemma: Sensory–Affect Transformation

A sensory physiology dilemma in the past and continuing today is an understanding of how a sensory stimulus—a sensation—becomes transformed into affect (emotion-behavior) and vice versa. The clinical translation for tinnitus diagnosis and treatment of the components of tinnitus (sensory, affect, and psychomotor) provides a basis for differentiation of recommendations by tinnitus professionals. This has resulted in an increase in the efficacy of therapy modalities attempting tinnitus relief [43,172]. The reports summarized next are considered significant for sensory–affect transformation and its translation to the FCP.

Historically, attempts to understand the brain's transition-transformation from sensory to affect for a sensation is not new. Descartes regarded the mind as something immaterial, separate from brain but interacting with it in some manner [11,12]. Sensory physiology has identified three components of any and all sensations. They are (1) the sensory component (sensory stimulus), (2) the affect component (behavioral response to the sensory stimulus), and (3) the psychomotor component (the motor response to express the behavioral response to the sensation) [173].

Neural substrates identified in tinnitus patients via nuclear medicine imaging and involving the PAC and associated auditory cortices for the sensory component, OFC for the affect component, and cerebellum and acousticomotor pathway for the psychomotor component have been integrated into the new algorithms for tinnitus [2–4,13–15,18,42] (see Fig. 2).

An FCP for tinnitus proceeds on the basis of identifying these perfusion-based asymmetries in multiple regions of interest in the brain highlighted by the MTLS. This system is a neuroanatomical substrate found to be significant in the sensory–affect transformation wherein the initial process is the establishment of a paradoxical memory for an aberrant auditory stimulus, tinnitus. The hypothesis of the FCP for tinnitus and the identified neuroanatomical substrates, when viewed in terms of the physiology of sensory processing, is considered to be expanded in its significance for

tinnitus by its application for all sensations, normal or aberrant [2].

Computed ultrasonographic craniocorpography for objective recording, documentation, and quantitative evaluation of abnormal psychomotor activity in psychiatric patients has been reported. It is a new version of craniocorpography originally reported in 1968 [174].

Neuroscience and Brain Function

Advances in neuroscience in animals and humans are providing objective data for understanding brain function in general and particularly for the FCP and brain functions associated with tinnitus. In particular, although the sensory–affect transformation in tinnitus patients is the predominant brain function featured in the FCP and the clinical manifestation of the tinnitus symptom, multiple associated brain functions are reflected in the clinical heterogeneity and complexities of the tinnitus symptom (perception, consciousness, etc.).

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 and reflecting a summation of synchronous neuronal activity in many neural ensembles in multiple neural substrates.

It is hypothesized that for all sensory systems, the sensory–affect components of a sensation are linked by memory. The experience of the sensation is a perceptual image of the stimulus. This concept is proposed as a basic tenet of the FCP for tinnitus of the cochleovestibular system. It is hypothesized that an FCP for tinnitus exists in the brain of all tinnitus patients [2].

Various historical references, as summarized next, have significantly influenced our understanding of sensory processing and brain function and have contributed significantly to the initial hypothesis and ongoing development of an FCP for tinnitus.

Perception and Consciousness

Behavioral brain action has been classified into simple (e.g., motor) behaviors and complex affective and cognitive behaviors (e.g., feeding, learning). The mind can be considered a range of functions performed by the brain [175]. The brain function of consciousness is critically important for tinnitus patients, particularly those with the severe, disabling type (such as SIT). The history of the clinical course of tinnitus in each patient reflects a heterogeneity in the conscious awareness of duration and masking characteristics. William James [176] observed that consciousness is not a thing but a behavior process. When applied to the FCP for tinnitus, a patient's conscious awareness of the tinnitus is a process of behavior reflecting a correlation of structure-function, mind, and brain. James proposed that subjective emotional experience (i.e., feelings) arise from our brain's interpretation of bodily states that are elicited by emotional events (i.e., an example of embodied cognition).

A global workspace theory of consciousness was hypothesized in 1988. It suggested that conscious experiences involve widespread distribution of focal information to recruit neuronal resources for problem solving [177]. The global workspace theory suggests that consciousness is needed to recruit unconscious specialized networks that carry out detailed working memory functions. Interactions are suggested between conscious and unconscious aspects of working memory. The minimal assumptions of the global workspace theory may have translation to understanding the clinical course of tinnitus and the brain function process of consciousness in tinnitus patients: (1) the brain is viewed as a collection of distributed specialized networks; (2) consciousness is associated with a global workspace in the brain; (3) a global workspace can integrate competing and cooperating input networks; (4) unconscious networks shape the contents of the conscious (contexts); (5) the contexts tend to limit the conscious events; (6) goals of the contexts are motives and emotions; and (7) executive functions are expressed at levels of the goal contexts [178].

Studies of different levels of consciousness suggest a global workspace (ongoing brain activity in multiple areas). It is suggested that attending to a sensory subliminal stimulus requires a connectivity between the sensory cortex and frontal cortex [25]. A neuroanatomical homeostatic system is hypothesized to regulate baseline levels of local synchrony [179,180], global interactions among regions [181], and periodic sampling of the signal space [182].

It is hypothesized further that a conscious percept clinically reflects a summation of synchronous activities of neuronal activity recordable from multiple neural substrates at the brain cortex. Perception is described as an active process that specifies the content of consciousness. It is a reflection of a combination of a "ground-state" of brain function activity that allows the normal brain to achieve adaptive and normal behavior. Alterations in the homeostatic regulation of the ground-state are a reflection of brain response to a "sensory exogenous system." The sensory exogenous system receives sensory stimulation from the environment or the peripheral or central nervous system. Sensory information received in the brainstem ascends via the ARAF to the thalamus, which is combined within an "endogenous system" in the temporal lobe to provide continuous episodic and short-term memories and emotional content to the sensory signal. The signal of neuronal activity

received from neuronal assemblies and 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 result in a deviation of brain activity for reestablishing the brain activity's ground-state and may become clinically manifest in seizure activity, inappropriate behavior, misperceptions, delusions, or other psychiatric symptoms. Consciousness is an inherent property of an electrical field resonating in a critical mass of coherently coupled cells [53,54].

The theory of homeostatically regulated thresholds for every neuronal population in brain and how this activity is transformed into a subjective experience is the problem of consciousness [179]. Sensory input received by the relay nuclei in the thalamus 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 theta activity (4–8 Hz) 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 [183] and 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 *ARAF*. Significant is the inhibition of ARAF by descending pathways from the cortex via the striatum. Beta activity (12–25 Hz) 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 that can be initiated by glutaminergic influences from the cortex and result in a depolarizing effect on the thalamic cells—an increase of the alpha rhythm, which is expressed on the thalamocortical circuit 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. Normal conscious function is proposed to require activation among the ARAF, the intralaminar nuclei of the thalamus, and the cortex. The binding together of fragments of perception from dispersed neuronal assemblies into a unifying reverberating system comprises the perceptual content of consciousness [53,54].

Consciousness has been considered to be a series of events, not a physiological state, reflected electrophysiologically by a coherence of shared electrical activity at the gamma frequency [6]. A characteristic low-frequency brain wave (i.e., theta) has been reported to modulate ultra-high-frequency oscillations (high gamma power), thereby allowing communication between corticocortical regions that support behavior [184]. Conscious awareness of "joys, sorrows, memories, ambitions, sense of personal identity and free will is the behavior of a vast assembly of nerve cells and their associated molecules" [185]. A "framework for consciousness" has been described in ten aspects and provides "a coherent scheme for explaining the neural correlates of consciousness." A framework offers a point of view, not a set of hypotheses, to guide research for studies of consciousness. Conscious awareness is proposed as a series of static snapshots reflecting activities of shifting neuronal coalitions. Conscious experiences are sustained by coalitions of neurons that need to be above a certain threshold to be conscious. The nature of the threshold is unknown [186].

Over time, an increasing consolidation of the auditory memory for the tinnitus becomes clinically manifest as SIT. The brain functions of perception of the aberrant auditory sensation (i.e., the sensory component) and its transformation to one of affect-behavior (i.e., the affect component) become the focus of tinnitus patients. The motor expression of the affect-emotion is the psychomotor component of the tinnitus.

Thalamocortical Oscillations

Thalamocortical oscillation has been investigated in the past. Synaptic background activity controls spike transfer from the thalamus to the cortex. A corticothalamic feedback mechanism is significant in the oscillatory effect between the thalamus and the cortex [183,187–193]. It has been hypothesized that in a homeostatic system, the generation and regulation of the electroencephalographic power spectrum depends on a complex of ionic currents causing a sequence of hyperpolarizations followed by depolarizations that influence the thalamocortical circuits to act as pacemakers in response to network interactions [194]. Specifically, depolarized potentials received at the thalamus 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 that in cortex result in an activation—the "edge effect"—the symptoms of which reflect the underlying stimulated neural substrate. The identification of this mechanism at cortex is hypothesized to result in the perception of tinnitus [193].

The significance of the central role of the thalamus in the original algorithm of the FCP is reinforced by the clinical translation of efforts in the past (and present) of thalamocortical oscillations for tinnitus theory, diagnosis, and treatment.

Fear

Fear is a neuroanatomical subcortical emotional processing circuit (i.e., thalamo-amygdala) in which the emotional significance of an auditory stimulus can be learned, stored in memory (thalamo-amygdala-frontal), and expressed in body physiology by the autonomic nervous system or in behavior by the somatosensory system [195,196]. This circuitry had been integrated into the original algorithm for the FCP, first theorized in 1991–1995 [2].

Attention

Attention has been defined as the act of keeping one's mind closely on something or the ability to do this [197]. The following summaries of publications reflect initial investigations of the brain function process of attention in clinical psychology and the visual system and are considered significant for identifying the role of attention in the interaction of the sensory and affect components of tinnitus as hypothesized in the FCP.

Attention was described as being closely related to subjective awareness to the world around us. It can be active (voluntary) or passive (involuntary) [198]. Attention is a brain function reflecting a network of anatomical regions and not the specific function of a single center or function of the brain as a whole. In cognitive science, it is viewed as a neural system for the selection of information, similar to the visual, auditory, or motor systems. Separate neural mechanisms or systems mediate different aspects of attention [199,200].

A visual attention mechanism may have a number of basic components: selection of a region of interest in the visual field, selection of feature dimensions and values of interest, control of information processing through the neuronal network of the visual system, and the shift of focus on selected regions of interest from one to the next over time [201]. Visual attentional control neural processing has been suggested to include two pathways: (1) bottom-up, or stimulus-driven (exogenous attention), and (2) top-down, or goal-directed (endogenous attention) [202].

Awareness has been defined by the triangular circuit of attention. Attention is assumed to be a brain event consisting of simultaneous neural activity in three areas interconnected by a triangular circuit. The three activity sites correspond to three aspects of attention: expression (region of cognitive function in the posterior and anterior cortex), enhancement mechanism (thalamic nuclei), and control (frontal cortex). An attentional event occurs when the three sites are simultaneously activated [203].

Categories of attention have been proposed: (1) selective attention and shifting, (2) sustained attention, and (3) divided attention [204]. A model for attention has been proposed—on the basis of studies of visual orienting with behavioral neuroimaging, lesion, and electrophysiological studies—that different attentional operations during sensory orienting are performed by two separate frontoparietal systems: dorsal and ventral attention systems. The dorsal system is bilateral and composed of the intraparietal sulcus and the junction of the precentral and superior frontal sulcus in each hemisphere. It is involved in voluntary top-down orienting. The ventral system is right-lateralized and composed of the right temporoparietal junction and the right ventral frontal cortex. The functional anatomy of the dorsal-ventral model of human attention is inferred from results of conventional task-response studies [205].

An alternative perspective to identifying dorsal and ventral attention systems (other than task-response studies) has been fMRI studies in the absence of a task, stimuli, or explicit attentional demands. The results identified a bilateral dorsal attention system and a right-lateralized ventral attention system on the basis of spontaneous activity. The findings demonstrate that the neuroanatomical substrates of human attention persist in the absence of external events and are reflected in the correlation structure of spontaneous activity. In addition, prefrontal regions correlated with both systems, a mechanism for mediating the functional interaction between the systems [206].

This study applied a systems-based analysis approach for identification of nonselective systems of attention. Comparison was made of activity in the PAC elicited by sounds while rats performed an auditory task (engaged) with activity elicited by identical stimuli while subjects were awake but not performing a task (passive). Engagement was reported to suppress responses in contrast with selective attention. In the auditory thalamus, engagement increased spontaneous firings but did not affect evoked responses. It is proposed that suppression represents the wakeful baseline condition on which other forms of attention and nonattentional modulation are superimposed [207]. This article is significant in general for the brain function of attention and, specifically, for the need to include in the design of an evaluation protocol for tinnitus patients nonselective attention, the sensory–affect transformation—the FCP.

Attentional and executive functions have been identified to significantly influence the regulation of fear and anxiety. Voluntary and involuntary attentional processes on behavioral and neural levels have been implicated in the maintenance of fearful or anxious behaviors. Interference in these processes can result in maladaptive behavior [208]. An engineering control approach that has been attempted sought to improve our understanding of the interaction of emotion and attention [209].

Attempts were made to identify neural correlates of attention at the earliest sensory-processing stage by recording MEG signals while subjects performed detection tasks requiring employment of spatial or nonspatial attention, in auditory or visual modality. Using distributed source analysis of MEG signals, we found that, contrary to previous studies that used equivalent current dipole analysis, spatial attention enhanced the initial feed-forward response in the primary visual cortex (V1) at 55–90 msec. We also found attentional modulation of the putative PAC (A1) activity at 30–50 msec [210].

Individuals with tinnitus of at least 6 months' duration (14 male, 15 female) and healthy controls (14 male, 21 female) were tested for arousal and habituation to repetitive stimulation at the brainstem-thalamus level by measuring the P50 potential, a scalp-recorded, auditory-evoked response, using pairs of click stimuli [211]. Results showed no difference between tinnitus patients and controls in level of arousal or habituation to repetitive sensory stimulation, as measured by the amplitude of the P50 potential and the ability to suppress a second, closely paired stimulus, respectively. However, reaction-time assessments showed that patients with tinnitus have attentional deficits relative to controls ($p = .02$). We found no significant correlation between sleep disturbance or tinnitus severity and reaction-time testing.

The parietal cortex has been proposed as part of the neural network for guiding spatial attention. Behavioral performance and hemodynamic responses were recorded using fMRI from a patient with focal left parietal damage in covert visual orienting tasks requiring detection of targets at the attended or unattended locations. Though the patient's reaction times to left visual-field stimuli were speeded by valid (relative to invalid) cues, attention to left visual-field stimuli was associated with enhanced activities in the right extrastriate cortex, right parietal and cingulate cortices, and bilateral frontal cortices. However, the patient's behavioral and neural responses to right visual-field stimuli were not influenced by cue validity [212].

Attention is reported as consisting of a selective component composed of an increase in responsiveness to an attended sensory stimulus and a nonselective component involving arousal, vigilance, and sustained attention. The neural signature of selective attention consists of an increase in responsiveness to the attended stimulus [213].

Cortical activity elicited in rats engaged in an auditory task was compared to auditory activity elicited by identical stimuli when the rats were passive but awake, the nonselective component. Engaging in an auditory task suppressed responses in the AC. The suppression is proposed to represent the wakeful baseline condition on which other forms of attentional and nonattentional modulation are superimposed. The passive but wakeful condition is reflected in a specific neural signature accompanying the nonspecific components of attention. It is proposed that task-engaged suppression may represent an initial stage in the routing of the projection from the PAC to the visual cortex, the posterior parietal cortex, and the AG, in which activity in neurons irrelevant to the task are reduced. Where no task is defined (passive condition), no well-defined population of neurons is necessary for the task The result may be a propagation of the auditory signal to a wider range of targeted brain regions, with resultant reduction in responses in the PAC. Engagement was reported to suppress responses, in contrast with selective attention. In the auditory thalamus, engagement increased spontaneous firings but did not affect evoked responses. It is proposed that suppression represents the wakeful baseline condition on which other forms of attention and nonattentional modulation are superimposed [207].

This report has clinical translation for tinnitus theory of long duration and particularly SIT; increased attention of the SIT patient, a passive but wakeful condition, is reflected in activity in multiple regions of interest in the brain. The tinnitus signal may not be threshold, and suppression may emerge as the dominant mechanism at the PAC. The activity of response in the PAC varies or may be absent. This is considered clinically to support results of metabolic and electroencephalographic (EEG) recordings in some SIT patients.

In summary, the brain function processes of attention are clinically considered to accompany and influence the hypothesized initial brain process of the FCP (development of a paradoxical auditory memory). The brain function processes of attention are not unitary. It is hypothesized that multiple memory systems develop for different types of attention. Over time, it is suggested that brain function processes of both memory and attention interact and supplement the action of each other. Specifically, brain function processes involved in increasing attention become clinically manifest in the brain function of concentration, reflecting a consolidation of memory. The synchrony of activity between ensembles of neuronal populations in associated brain cortices is hypothesized to result in an increased conscious awareness of the aberrant auditory stimulus (i.e., tinnitus). The neuroanatomical substrates for attention contribute to the neural correlates of the FCP (see the section FCP Algorithms).

Memory

Memory in our clinical experience can be defined as the brain function of processing, storing, and retrieving information. The MTLS has been identified in humans and monkeys for the brain function of memory [74]. Studies

of working memory in monkeys and rats have demonstrated that neurons in the prefrontal and the parietal cortices and the thalamus exhibit ramping activities that linearly correlate with the interval that the animal is trained to memorize [214–216].

The significance of the perirhinal and entorhinal cortices of the MTLS has been reported for memory. Performance on visual delayed nonmatching to sample was assessed in rhesus monkeys with combined and separate ablations of the perirhinal and entorhinal cortices and in unoperated controls. The results demonstrated not only that damage limited to the rhinal cortex is sufficient to produce a severe loss in visual recognition but that such damage leads to a far greater loss than damage to any other single structure in the medial part of the temporal lobe [75].

Memory is reported to be not a single faculty but composed of separate systems, only one of which is impaired in amnesia (i.e., declarative memory) [217]. Long-term declarative memory is mediated by a network of brain structures including the hippocampus; the parahippocampal region, including the entorhinal, perirhinal, and parahippocampal-postrhinal cortex; and extensive neocortical association areas [90].

Declarative memory, also called *episodic* or *explicit* memory, is a memory for facts and events. Nondeclarative memory, also called *implicit* memory, includes all abilities that are unconscious and expressed through performance [74]. It has been proposed that long-term memories are ultimately stored through interactions between the hippocampal memory system and the neocortical association areas that initially processed the to-be-stored information [91]. The OFC is considered to be an association neocortex reciprocally connected with the hippocampal memory system and is important in odor recognition in the rat. It is proposed that sensory information is initially processed in widespread neocortical association areas and propagated through the hippocampal-parahippocampal region. Memory information is sent via back-projections from the hippocampus to the parahippocampus and then to the association neocortex, which serves as the ultimate repository for these memories. The OFC interacts with the hippocampal memory system to store long-term declarative memories (e.g., olfactory memory) [89].

The proposal for establishment of a declarative memory for olfaction is similar to and supportive of the hypothesized initial process in the FCP as establishment of a paradoxical auditory memory for tinnitus.

Stress Thalamus

The stress model for tinnitus proposed that a cycle can be established wherein reciprocal projections between hippocampus, amygdala, entorhinal cortex, and hypothalamus can vary in degree of control of cortisol levels, resulting in further strengthening of an already paradoxical memory with resultant additive negative affect, behavioral manifestations of emotion, fear, anxiety, depression, etc. Stress is considered to be the modulator for the affect component of the tinnitus. The modulator of the sensory component of the tinnitus is considered to be the efferent system and the process of masking [218–220].

Various published reports, as summarized here, are considered to support the stress model for tinnitus and the role of stress in the FCP.

A model is proposed for understanding differentiation between declarative and nondeclarative memory functions in processing trauma-related information in posttraumatic stress syndrome (PTSD). The brain areas cited as involved in memory functioning and the stress response are the hippocampus, the AG, and the PFC. Chronic stress affects the hippocampus, suggesting that hippocampal dysfunction may partly account for the deficits in declarative memory in PTSD patients. Deficits in the mPFC, a structure that normally inhibits the AG, may further enhance the effects of the AG, thereby increasing the frequency and intensity of the traumatic memories [221].

Significantly, in our experience with the PTSD population, the consolidation of the paradoxical memory for the symptom of tinnitus is the basis for resistance to clinical attempts to provide tinnitus relief. The hippocampus provides a feedback regulation of the hypothalamic-pituitary-adrenal cortex axis [112]. This article supports the hypothesis of the paradoxical memory in the FCP as well as the significance of the MTLS in the FCP.

Animal research related to PTSD indicates that acute and chronic stressors, such as restraint or immobilization, are the most relevant stimuli to study how neural and endocrine systems are affected, both immediately and in the long term. Of particular relevance are the onset and duration of stressor effects on brain areas subserving emotional memories, such as the AG, the PFC, and the hippocampus. The hippocampus plays a role in memory and in vegetative functions of the body. The hippocampus receives input from the AG, and its function in spatial memory is altered by AG activity. Repeated stress in the rat suppresses dentate gyrus neurogenesis and causes dendrites of hippocampal and medial prefrontal cortical neurons to shrink. Conversely, it causes basolateral AG neurons to increase in dendritic complexity and sprout new synapses. Repeated stress also increases fear and aggression, reduces spatial memory, and alters contextual fear conditioning [222]. This article supports the role of stress and the significance of the neuroanatomical substrates of the MTLS and cerebellum in the FCP.

Cross-Modal Sensory Brain Integration

Our understanding of sensory processing in the human brain, on the basis of studies of sensory modalities of audition, vision, and somatosensation, is that it is an active process that includes the projection from transduction in receptors to its representation in the brain; integration with brain function processes of experience, attention, and other homeostatic processes; and other multiple sensory modalities.

Cross-modal brain integration refers to processes by which input from one sensory modality (e.g., vision, audition, somatosensation) influences the processing of information from another modality and leads to either increased or decreased neural responses (multisensory integration). *Unimodal* cortex refers to cortical regions that receive input from one sensory modality, whereas *heteromodal* cortex refers to regions of cortex that receive inputs from more than one sensory modality [223].

It has been proposed that cross-modal sensory integration can be divided into integration of cues leading to facilitation of either localization or identification. Specific roles have been proposed for two heteromodal brain regions: intraparietal sulcus in localization and STS in identification [224]. Facilitation of odor detection by visual cues has demonstrated increased activity in the region of the STS and a region of the OFC adjacent to the olfactory association cortex [225].

Resolution of the FCP dilemma involves the basic issue of sensory processing: the integration, identification, and understanding of the ongoing, underlying, simultaneous multiple associated brain function processes from not one sensory modality but from multiple sensory modalities, accompanying and associated with an FCP, of which the predominant brain function process is that of the sensory–affect transformation—that is, translation of a sensation to its conscious awareness by the patient. The FCP algorithms demonstrate integration of the modalities of somatosensation with audition with associated multiple brain functions (see Fig. 2).

The FCP provides a model for tinnitus theory, diagnosis, and treatment. The neuroanatomical substrates of the FCP are proposed to be neural correlates of sensory processing for tinnitus and for its interconnections in brain with regions of cortex that receive inputs from more than one sensory modality (cross-modal integration of brain function). The integration of additional sensory modalities and brain function processes into the FCP awaits future advances in sensory processing (see the section FCP Algorithms and Fig. 2).

Masking

"*Masking* is a term used to refer to the effect of one tone or one sound on another tone or sound or combinations thereof" [226]. The FCP clinically considers auditory masking to be predominantly a brain function with peripheral and central components. The manifestation of the symptom of tinnitus is considered to be a reduction in the normal auditory masking function in the brain: The neuroanatomical substrates are hypothesized to involve the cochlea, the brainstem, the thalamus, and multiple cerebral cortices (see the section FCP Algorithms and Fig. 2).

Brain Imaging

The 1989 introduction of nuclear medicine brain imaging with SPECT by then SUNY/DMC Director Dr. Arnold M. Strashun is considered to have been a singular event for the discipline of tinnitology. The variations in metabolic activity observed on brain PET are considered to be a metabolic correlate for a predominantly central-type tinnitus. SPECT and PET are functional imaging techniques that reveal spatial patterns of neural activity in brain. Functional MRI brain imaging and MRI spectroscopy are additional resources of investigation for identifying in tinnitus patients underlying neurocircuitries and neurotransmitter systems for the translation to tinnitus theory, diagnosis, and treatment. Nuclear medicine imaging has provided insights into the pathophysiology of tinnitus and a basis for its clinical translation to both tinnitus diagnosis and treatment. Increasingly, reports are considered to support the FCP.

SUNY/DMC Experience: SPECT and PET

The published brain SPECT peer-reviewed reports since 1991 focused on identifying perfusion asymmetries with a tracer Tc 99–HMPAO in multiple neuroanatomical substrates associated with the symptom of tinnitus: For the first time, in vivo identification of alterations in brain function in tinnitus patients was possible. Together with the identification of brain structure with MRI, a correlation of structure and function became available to tinnitus patients and professionals. PET brain imaging with FDG has been ongoing since 2000 and has supported the original SPECT brain reports from which evolved the FCP.

The asymmetries in activity in brain in neuroanatomical substrates identified with brain SPECT/FDG PET have been considered a physiological response in the brain cortex reflecting glucose metabolism. Clinically, the reported SPECT/PET anatomical regions of interest in the brain in tinnitus patients are hypothesized to reflect responses to the presence of the aberrant auditory tinnitus signal—but not the specific aberrant auditory tinnitus signal itself.

Initially, the clinical translation of the brain perfusion asymmetries identified with brain SPECT provided an objective measure for a subjective complaint, a basis for

the hypothesis of the FCP and the identification of the medical significance of the tinnitus. The SUNY/DMC nuclear medicine experience to date has been translated to tinnitus theory, diagnosis, and treatment on the basis of the FCP.

The publications cited in this manuscript reflect an evolving clinical experience with nuclear medicine imaging in tinnitus patients, highlighted by the following:

- the FCP in tinnitus, stress diathesis model of tinnitus [2];
- the descending auditory system (DAS), the cerebellum, and tinnitus [18];
- identification of a biochemical marker for a predominantly central-type tinnitus (GABA-A/BZ/C1 receptor) and the FCP [46];
- hypothesis and identification of a benzodiazepine deficiency syndrome in the tinnitus patient [47];
- a receptor-targeted therapy (RTT-GABA);
- a TDST [6];
- identification or demonstration of tinnitogenesis in a predominantly central-type tinnitus and its role in the FCP [4];
- identification of a metabolic correlate for tinnitus [2]; and
- the coregistration of brain PET and QEEG in tinnitus patients [23,24].

PET, brain fMRI, and electrophysiology (QEEG) have confirmed the SUNY/DMC findings of neuroanatomical substrates in brain (reported originally in 1991 and published in 1995) and multiple additional neuroanatomical substrates identified in brain in SIT patients. Numerous publications, as summarized here, are considered to support the original reported neuroanatomical substrates and the FCP.

The identification of activation of the PAC was confirmed by brain PET [19]. Brain PET also confirmed the significance in tinnitus patients of varying degrees of activity in multiple regions in the brain [20] and of the limbic lobe in tinnitus patients [21].

Functional MRI for Tinnitus

The introduction of fMRI for investigation of tinnitus patients has identified alterations in brain activity on the basis of blood oxygen levels in brain tissue, not with a tracer (as with brain PET). Functional MRI has raised the possibility of obtaining objective data of the psychological aspects of tinnitus, such as the associated distress. An fMRI study of individuals with tinnitus lateralized to one ear and normal hearing thresholds revealed asymmetrical activation at the level of the inferior colliculi in response to a binaural masking stimulus [33,34].

Functional MRI investigations of tinnitus-like perception induced by aversive auditory stimuli activated primary and secondary auditory areas bilaterally, the dorsolateral attention area, and structures in the limbic system involved in emotional processing areas. Initial fMRI reports in tinnitus patients reveal support for the FCP. It was hypothesized that the perception of tinnitus may involve a functional linkage of secondary AC and DLPFC and the limbic system [35]. This report focusing on the affect-emotional component of tinnitus supports the FCP.

The neuronal basis for whether the tinnitus experience can be recalled or forgotten is clinically significant. The results of recordings from the MTL in patients with implanted intracranial microelectrodes in the AG, the entorhinal cortex, and the hippocampus, though enabling them to encode and recall word-paired associates at a single neuron level, support—at the single-neuron level for MTL—contributions to encoding and retrieval. They also suggest the existence of possible differences in the level of contribution of MTL regions to these memory processes [227]. This report supports the role of the MTLS in the FCP.

The compact structures of the MTL appear to function as a system of specialized components that synchronously encode declarative memories. Lesion studies have suggested that separate MTL subregions make distinct contributions to memory [228]. This article is significant for future identification of the contribution of the MTL neural substrates to the process of development of a paradoxical memory for tinnitus in the FCP.

Functional neuroimaging has demonstrated that a relationship exists between the intensity of deafferentation pain and the degree of deafferentation-related reorganization of the primary somatosensory cortex. Therefore, to suppress pain, it seems logical to attempt to modify this deafferentation-related somatosensory cortex hyperactivity and reorganization. This can be achieved using neuronavigation-guided transcranial magnetic stimulation (TMS). This clinical experience suggests that somatosensory cortex stimulation may become a new, neurophysiology-based approach for treating deafferentation pain in selected patients [229]. This article supports the role of the somatosensory system in the FCP in some clinical types of tinnitus.

Functional imaging techniques have demonstrated a relationship between the intensity of tinnitus and the degree of reorganization of the PAC. The results in the first patients treated by PAC stimulation demonstrated a statistically significant tinnitus suppression in cases of unilateral pure-tone tinnitus without suppression of white or narrow-band noise. Hence, AC stimulation could become a physiologically guided treatment for a selected category of patients with severe tinnitus [230]. The results of this report suggest that the FCP may assist in the selection of sites for TMS.

It has been hypothesized that altered activity in the AC will be part of the FCP of tinnitus generation [25]. This presentation finds support for the FCP. Recent research suggests that tinnitus is a phantom phenomenon based on hyperactivity of the auditory system, which can be visualized by functional neuroimaging and transiently modulated by TMS. Results of the first implanted electrodes on the primary and secondary AC after unilateral pure-tone tinnitus are good surgical successful TMS suppression suggest that patients with candidates for electrode implantation and permanent electrical stimulation of the AC, provided that the tinnitus is of recent origin and can be suppressed by TMS [231].

Although the role of the hippocampus in tinnitus has not been established, neuroimaging studies have demonstrated increased metabolism in the hippocampus in tinnitus patients. The idea that the AG-hippocampal area is involved in generating a paradoxical auditory memory for tinnitus is to be considered. Support for hippocampal activity is cited by c-fos studies. Further, superselective Amytal injections into the anterior choroidal artery that supplies the AG-hippocampal area and transiently suppresses tinnitus support the idea that some form of tinnitus might be generated in the hippocampus [232].

Activity within the PFC has been identified with functional imaging during tasks requiring memory processing. Activity foci within the mid-dorsolateral prefrontal areas (BA46 and 9/46) have been shown to be related to the monitoring of information in working memory, whereas activity in the mid-ventrolateral PFC is related to activity-controlled retrieval of memory from both short- and long-term memory [233]. Significantly, monkeys with lesions in the OFC do not habituate easily to the presentation of novel stimuli [234].

Electrophysiology

Physiology, the basic science that attempts to understand the function of the living organism and its parts and the physical and chemical factors and processes involved, and electrophysiology, the study of electrical activities in the body, have provided insight to an evolving understanding of brain function and introduction into the pathophysiology of tinnitus. Historically, with respect to tinnitus, the statistical technique called *neurometrics*, which evaluates electrical brain activity quantitatively by extracting a common metric of probability from the different electrophysiological phenomena, is considered significant. It has been applied to the clinical identification of neuropsychiatric diagnoses including cerebral ischemia, depression, schizophrenia, alcoholism, and head injury [180,235].

QEEG power spectral mapping is a simple and relatively inexpensive method for measuring regional brain activity and various EEG abnormalities in the temporal lobe and other areas of the brain. It is a technique that provides a spectral analysis of the raw EEG data bands and frequencies of electrical activity in different metrics of analysis—that is, quantified, for the frequencies of response in brain and displayed in multimetric topographic maps (i.e., QEEG topographic maps of power, asymmetry, relative power, coherence, and phase). The frequencies of response reflect multiple brain functions. QEEG provides an objective measure for display in the brain of the influence of modalities of treatment attempting tinnitus relief. The introduction of QEEG for tinnitus diagnosis and treatment is thought to have been introduced by Weiler and Brill [26–28].

Source localization analysis in the brain of scalp-recorded electrical potentials for the different metrics of analysis has been an ongoing effort for the last few decades. For tinnitus, it allows us to identify spontaneous activity in the brain cortical regions and changes in response to varying conditions (e.g., TMS, cochlear implantation). The contributions of Pascual-Marqui et al. [236] and Bosch-Bayard et al. [237] are considered significant.

The following physiology publications provide a pathophysiological basis for support of the neurocircuitries and processes hypothesized in the FCP.

In a review of the pathophysiology and neuroscience of tinnitus, tinnitus is considered as a percept dependent on activity in the auditory cortices. The significance of central centrifugal cortical activity on peripheral structures is recognized [238]. Neural correlates investigated for tinnitus in animal models include hair cell loss in the cochlea, burst firing in the central inferior colliculus nucleus after salicylate application, and demonstration of neural synchrony in cortical neurons. Synchrony in the affected frequency region increases with time and relates to the reorganization of the cortical tonotopic representation by noise trauma. In the "phantom limb" model, decreased auditory input to the cortex due to deafness may increase local excitability, leading to increased firing of cortical auditory neurons, which causes hallucinations of sound [36]. In cortical neurons, transitory increases in burst firing in the PAC (A1) after noise trauma return to baseline within a few hours [37]. It has been demonstrated in cats that a very high auditory input after noise trauma reduced both the extent of hearing loss and signs of tonotopic map reorganization in the PAC [38].

> The functional role of neural synchrony is reflected in cortical tonotopic map reorganization and in the emergence of pathophysiological phenomena such as tinnitus. Increased neural synchrony and tonotopic map reorganization go hand in hand. Cortical reorganization with hypersynchrony can be considered as an important driving force underlying tinnitus [39].

All references cited are considered to support the FCP and TDST hypotheses and have had clinical translation to tinnitus diagnosis and treatment.

A MEG study has reported an increase and decrease of delta and alpha power in tinnitus patients as compared to healthy controls [239]. It has been hypothesized that synchronous neuronal activity of cell assemblies within the AC could be the underlying neural code of tinnitus. Alterations in central neuronal activity patterns are suggested to contribute to development of tinnitus. The significance of the gamma frequency (>40 Hz) has been reported for tinnitus patients. Specifically, increased gamma activity in tinnitus patients reflects the synchronous firing of neurons in the AC. It is proposed that the gamma activity could be the neurophysiological correlate of basic sound perception [29,30]. MEG and EEG techniques recorded such synchronous activity. The conclusion was that such an "oscillatory model" of tinnitus may explain many of the different observations of tinnitus.

Clinically, the hypothesis of Weisz et al. [29,30] is considered to be supported by the results of an analysis of QEEG data for the metric of power in SIT patients (N = 61). Specifically, statistically significant abnormalities were observed in 41 of 61 patients (67.2%) in frontal greater than temporal electrode recording sites for the frequencies of brain activity delta > beta > alpha > theta, reflecting physiologically the individuality of brain function in tinnitus patients and the heterogeneity of the symptom of tinnitus. Weisz et al. [30] interpreted that the "enhanced gamma activity reflects the synchronous firing of neurons within the AC and could be the neurophysiological correlate of basic sound perception." Our QEEG experience with SIT patients suggests that the correlation of the beta and gamma bands to delta, theta, and alpha may clinically reflect the most severe disabling tinnitus (i.e., preponderance of recording sites frontal greater than temporal of the gamma > beta, or gamma > beta > delta > alpha > theta) [2,16,24]. The hypothesis of Weisz et al. is clinically considered to provide electrophysiological evidence in support of an electrophysiological correlate for tinnitus, the TDST, and the FCP [2,16,24].

Abnormal outer or inner hair cell function is reported to correlate with the presence of tinnitus [40,240]. High-frequency gamma oscillations may be neural correlates of perception and consciousness [31]. MEG and EEG analysis of abnormal thalamocortical oscillations at the cortex have revealed that the thalamocortical loop contributes to the rhythmicity of the scalp EEG and MEG [241,242].

Using QEEG power spectral mapping, a clinical study of otherwise healthy patients with intractable unilateral tinnitus identified discrete localized unilateral foci of high-frequency activity in the gamma range (>40–80 Hz) over the AC in eight patients experiencing tinnitus during recording [32]. The results of the *Z*-score analysis of QEEG recordings—for the metric of power for SIT patients—based on a large normative database were clinically considered to be a global response of interneuronal cortical networks reflecting multiple brain functions to an aberrant sensory, conscious, perceptive auditory disorder. Specifically, a cortical interneuronal network pattern of spontaneous brain function activity was seen (i.e., delta > beta > alpha > theta in frontal > temporal > occipital recording sites and equal in occipital, parietal, and central recording sites). The predominance of frontal and temporal recording sites provided objective evidence to support the clinical consideration of a frontotemporal thalamic circuit in SIT patients, modulated by the thalamus (i.e., a thalamo-fronto-temporal circuit). The QEEG data in tinnitus patients clinically is considered to have objectively identified electrophysiologically the tinnitus circuit—the frontotemporal thalamus—hypothesized originally in the FCP model-algorithm of 1995. The QEEG results were considered to reflect activation of multiple electrode recording sites, providing objective evidence for an interneuronal cortical network highlighted by the frontal and temporal recording sites modulated by the thalamus (i.e., a thalamo-frontotemporal circuit). The pattern of an electrophysiological correlate for SIT was considered to have been identified, highlighting the individuality of brain function for each tinnitus patient and different clinical types of tinnitus. Clinically, the interpretation of QEEG results for the metric of power in relation to the theory of consciousness is considered to demonstrate how the brain, in response to a dyssynchronous auditory signal (tinnitus), is attempting to reestablish homeostasis in multiple neuroanatomical substrates with a synchrony of activity reflected clinically by a subjective awareness or consciousness. The electrophysiological information obtained with a multimetric analysis (including not only absolute power but *Z* scores of relative power, amplitude asymmetry, coherence, and phase) may provide additional measures for objective clinical analysis of the tinnitus complaint.

It was suggested that the reports of QEEG results in tinnitus patients specify the normative database being referenced for the *Z*-score analysis of the data [24]. This 2006 report clinically confirmed a preliminary 2002 report that supported the significance of QEEG for identifying brain function in tinnitus patients. Specifically, in the preliminary report, data from 21 SIT patients were found to support the hypothesis of the significant role of the temporal and frontal regions of the brain in tinnitus patients. Our clinical experiences with QEEG recordings in tinnitus patients were the basis for recommending its routine inclusion into the MATPP, both for

tinnitus diagnosis and as an in-office monitor to establish the efficacy of therapeutic modalities attempting tinnitus relief [23].

Significantly, in both studies (2002 and 2006), the power distribution by frequency bands and electrode sites correlated with a reported clinical experience of identifying neural substrates with nuclear medicine (SPECT) brain imaging in patients with SIT (i.e., alterations in perfusion in multiple regions of interest in the brain—in frontal, temporal, and parietal lobes, the BG, and the cerebellum—and highlighted by hypoperfusion in the MTLS of the brain).

Two hundred tinnitus patients were reported to have been studied with brain electric tomography (Loreta) and compared to those obtained in 40 normal patients. In the tinnitus patients, a common pattern of pathology was reported (i.e., compromised BA21 and 22 and compromised BA47) [243]. The reports of cortical alteration accompanying TMS are providing information for tinnitus theory, diagnosis, and treatment [25].

The basolateral AG mediates the effects of emotions on memory [244]. Its influence has been identified to extend to various types of memories, including striatal-dependent habit formation. An auditory stimulus-response task in rats has demonstrated that coherent gamma oscillations were identified to coordinate amygdalostriatal interactions during learning and might facilitate synaptic plasticity. The basolateral AG projection to the ventral striatum is an important route for emotionally significant stimuli to influence behavior. This article provides objective evidence of the influence of emotional arousal on memory, for which the basolateral AG is responsible, and support for the FCP sensory–affect transformation in tinnitus patients [245] (see the section FCP Algorithms).

The hypothesis was tested with fMRI in humans via a visual discrimination task: that the amplitude of evoked gamma-band responses and BOLD responses covaried intra-individually as a function of stimulation and inter-individually as a function of the gamma trait. The study further supports the notion that neural oscillations in the gamma frequency are involved in the cascade of neural processes that underlie the hemodynamic responses measured with fMRI [245,246]. These articles are significant for future identification of neuroanatomical substrates of the FCP, demonstrating the gamma response hypothesized to reflect a conscious awareness of a sensation.

Functional MRI and electrophysiology have demonstrated that processes related to sensory integration are not restricted to higher association cortices but already occur in early sensory cortices, such as the PAC. Functionally, this was tested on the basis of the hypothesis that the STS is a source of visual input to the PAC. Interactions from the PAC to the STS prevailed below 20 Hz, whereas interactions from the STS to the auditory sulcus prevailed above 20 Hz. The findings suggest that beta frequencies might be important for interareal coupling in the temporal lobe. The STS might provide a major source of visual influences to the PAC [247]. This report is significant for consideration of the role of visual input for tinnitus patients and its influence on the FCP. Significantly, QEEG occipital recordings have occasionally been noted and anecdotally reported (A. Shulman, 2002, 2006).

Clinical Medicine

In our experience since 1989, the introduction of nuclear medicine imaging, initially with brain SPECT in 1989 and brain PET in 2000, has demonstrated relatively consistent asymmetries of activation in multiple neural substrates, highlighted by the MTLS, and continued support for the hypothesis of an FCP, as cited in our publications. Various reports, summarized here, lend support to this hypothesis.

A neurophysiological approach to tinnitus was proposed in 1993 [118]. It is a significant contribution to the theory and clinical course of tinnitus with application for treatment (tinnitus retraining tinnitus [TRT]). TRT is an attempt for tinnitus treatment influencing the FCP by focus on the affect component of the tinnitus—an example of clinical application of the FCP for attempting tinnitus relief. Support for TRT is found in both the past and the present. Perceptual sensitivity to simple sensory stimuli can improve with training [248]. Performance was modeled on the basis of the readout of simulated responses of direction-selective neurons in the middle temporal area of the monkey cortex. A common, feedback-driven mechanism was demonstrated for some forms of associative and perceptual learning [249].

The literature was reviewed to consider the potential for TMS as a therapy in tinnitus [250]. TMS is a noninvasive method of modulating excitability in the cerebral cortex. It uses electromagnetic principles and has been employed successfully in the treatment of other conditions associated with increased activity of the cerebral cortex. Meanwhile, a growing number of studies suggest that repetitive TMS may be effective in the treatment of chronic tinnitus [250]. This article supports the activation of multiple regions in the cerebral cortex as hypothesized in the FCP.

A significant clinical contribution to understanding the affect-emotional component of tinnitus, particularly in SIT, has been the investigation in the tinnitus population of the association of tinnitus severity, depression, and personality traits. The role of "the big five" personality traits—neuroticism, extraversion, openness, agreeableness, and

conscientiousness—have been studied in relation to how the scores in the tinnitus handicap inventory and in the tinnitus questionnaire were affected. The role of trait, anxiety, and depression were confirmed. Low agreeableness was identified as a novel predictor of tinnitus severity on the tinnitus handicap inventory [52].

This study supports the significance of the affective component of the FCP and the need to clinically base treatment for tinnitus by differentiation between its sensory and affective components. The terminology of sensory physiology is recommended for tinnitus (i.e., the components of a sensation). The introduction of the word *distress* for SIT is accepted as a terminology that describes the severity of the affect-emotional response of tinnitus patients. Frequently, distress is associated with the term *fear*. It is suggested that although the term *distress* has a descriptive value (description of the affect-emotional component of the tinnitus), its use complicates the terminology of sensory physiology (i.e., affect). The introduction of TMS in attempting tinnitus relief is providing not only a therapeutic modality but a modality of brain stimulation contributing to the understanding of brain function in general and specifically for the pathophysiology of tinnitus.

Repetitive TMS has been reported to be a noninvasive method used to induce electrical current in the brain via the external application of magnetic fields applied to the scalp. Tinnitus relief has been reported by modulation of excitability of neurons in the AC, considered to cause some forms of tinnitus [251]. The results of the first implanted electrodes on the primary and secondary AC were reported. Twelve patients underwent an AC implantation, ten for unilateral and two for bilateral tinnitus, on the basis of more than 50% suppression on applying TMS. Results were analyzed for pure-tone tinnitus and white-noise tinnitus. Pure-tone tinnitus might be the conscious perception of focal neuronal hyperactivity of the AC. Once visualized, this hyperactivity can be modulated by neurostimulation [230,231]. The preliminary results of the first implantations suggest that patients with unilateral pure-tone tinnitus are good surgical candidates for electrode implantation and permanent electrical stimulation of the AC, provided that the tinnitus is of recent origin and can be suppressed by TMS [231]. It was concluded that AC stimulation could become a physiologically guided treatment for a selected category of patients with severe tinnitus [229].

The initial efforts for attempting tinnitus relief with TMS are considered to support the FCP with a focus on the PAC (i.e., the sensory component). The TMS response, based on the FCP, is predicted to be individual and will be limited, reflecting the brain function associated with and accompanying the sensory–affect transformation.

FCP ALGORITHMS

General

The neuroanatomical substrates of the FCP are presented as three algorithms of components of a sensation—sensory, affect, and psychomotor—a translation from basic sensory physiology to tinnitus. The algorithms are considered to be dynamic in their development, an update from the original FCP algorithm presented in 1995, reflecting what is and is not known of sensory physiology and brain function (see Fig. 1). The algorithms reflect neuroanatomical correlates of the FCP for each of the components of the aberrant auditory sensation (tinnitus).

The algorithms are arranged to provide (1) the neuroanatomical substrates for each of the three components of the tinnitus sensation, (2) a basis for understanding the complexities of the interactions, neurocircuitries, and neurochemistries involved within and between the neuroanatomical substrates, and (3) correlation of the neuroanatomical substrates for each component of the tinnitus with the multiple spontaneous, simultaneous ongoing brain functions. Clinically, the brain functions of the sensory–affect transformation and its conscious awareness by tinnitus patients predominates. The brain functions included in the present algorithms have been previously cited. The neuroanatomical substrates are hypothesized to be reciprocally activated, providing a "closed circuit" of neuroanatomical substrates of the FCP.

The three algorithms reflect an attempt for integrating structure and function for the FCP as hypothesized at this time. Attempts have been made to include in the algorithms recent advances (cited in references in this manuscript) in sensory physiology, auditory science, and neuroscience. The reader is urged, in reviewing the algorithms, to consider the following: (1) identification, initially for orientation, of each algorithm component, followed by (2) identification of the neuroanatomical substrates for each algorithm, and (3) integration of each algorithm with the brain function.

Algorithm 1: Sensory Component

The neuroanatomical substrates of the sensory component include the cochlea, brainstem, cochlear nucleus, olivocochlear bundle, inferior colliculus, thalamus, medial geniculate body, PBN, MTLS, AG, entorhinal cortex, perirhinal cortex, hippocampus, parahippocampus, hypothalamus, nucleus accumbens, PAC, and the cerebellum-acousticomotor system and somatomotor cortex. The brain functions include sensation perception, memory, fear, reward, stress, autonomic functions, and masking.

It is hypothesized that for the sensory component, the sensory information (i.e., the dyssynchronous aberrant auditory signal arising from the peripheral or central nervous system) ascends via the brainstem, the cochlear

nucleus, and the olivocochlear bundle to the inferior colliculus, the medial geniculate body, the thalamus, and the primary ARAF to the thalamus, part of the exogenous system of the CNS for the receipt of sensory information arising from the environment or the peripheral or central nervous system (see Fig. 2). Hyperpolarization and depolarization of a GABA-influenced thalamic neuron activity results in thalamocortical oscillations that results in a synchronous signal at brain cortex. A theoretical ground-state of brain activity from the synchronous alpha frequency is displaced down to a theta or delta rhythm or up to a beta rhythm. Input from the thalamus to the MTLS and entorhinal cortex, an endogenous system of the CNS, is hypothesized to result in the establishment of a "memory" for the sensory stimulus (tinnitus) that has a reciprocal influence on the thalamus. The summation of synchronous neural discharges from multiple neural ensembles of neurons at the cortex results in a gamma rhythm associated with a conscious awareness of the sensory stimulus. Synchronized neural activity in multiple neuronal assemblies is hypothesized to be the basis of perception and consciousness [16,53,54,241].

The brain function of an auditory memory is initially established at the MTLS and entorhinal and perirhinal cortices, receiving input from the thalamus and the PAC. The PAC interacts with the MTLS (hippocampus), the PFC, the cerebellum–parietal cortex, and the OFC. The brain's memory neurocircuitries in the sensory component for tinnitus are hypothesized to include the thalamocortical, the fronto-temporo-thalamic, and the fronto-temporo-cerebello-thalamo-temporo-parietal neuronal circuitries. Long-term memory involves the parahippocampus, secondary association cortices, and OFC. The brain's fear function neurocircuitries in the sensory component for tinnitus are hypothesized to include the fronto-temporo-AG-PAC-PBN-thalamic circuit.

The brain function paradoxical-reward circuit in the sensory component for tinnitus is hypothesized to include the fronto-temporo-MTLS-AG-PAC-thalamic NA circuit. The masking function is hypothesized to be reduced, to have multiple components with contributions from the cochlea, brainstem, cerebellum, MTLS, hypothalamus, PAC, and parietal cortices. The brain's stress and autonomic function neurocircuitries are hypothesized to include the thalamus, MTLS, and hypothalamus.

Algorithm 2: Affect (Emotional and Behavioral) Component

The neuroanatomical substrates of the affect-emotional component include the OFC of the frontal lobe, the PFC, the temporal lobe (PAC-MTLS), and the insula (see Fig. 2). It is hypothesized that for the affect-emotional component, reciprocal input-output interactions occur among the PAC, thalamus, and AG in the MTLS-OFC and the PFC in the frontal lobe, the insula, and the parietal lobe.

The brain function reciprocal neurocircuitries of affect-emotion for tinnitus are hypothesized to include the thalamotemporal (MTLS-AG) and the frontoparietal. By its location, the insula is hypothesized to be a modulator of input-output activities among the frontal (OFC), the temporal (AG), and the parietal lobes' affect-emotion interactions.

The brain function reciprocal neurocircuitries of long-term paradoxical auditory memory for tinnitus are hypothesized to be in the PFC (i.e., the DLPFC) and involve the insula and the hippocampus and parahippocampus. The brain function reciprocal neurocircuitries of attention are hypothesized to include the thalamus and the frontal, temporal, and parietal lobes.

The role of the basolateral AG in the FCP is significant in the facilitation of memory. The basolateral AG is not the storage site of a facilitated memory but is involved transiently during or shortly after training (or both) to facilitate memory formation in the striatum and hippocampal formation. Evidence suggests that multiple parallel mechanisms are involved for the basolateral AG influence, involving basal forebrain and striatum neurons. AG-mediated facilitation of memory depends on the ability of the basolateral AG to generate gamma oscillations that facilitate the induction of activity-dependent synaptic plasticity in target neurons (i.e., the basal forebrain, the striatum, and the hippocampal formation). The ventral striatum consisting of the NA, the olfactory tubercle, and ventral portions of the caudate and putamen are critically important for reward prediction and certain types of appetitive learning [253]. Inputs to the ventral striatum include the hippocampal and rhinal cortices, the frontal and associative cortical areas, and the AG. The AG, important for learning about aversive stimuli, is also important for a range of appetitive behaviors [254]. The ventral striatum can influence motor behavior via projections to the globus pallidus, the substantia nigra, and the ventral pallidum (i.e., mediation of motivational and appetitive influences on behavior).

In the FCP, the perception of tinnitus (the sensory component) initiates the formation of a paradoxical auditory memory, a cognitive "learning" experience, which, influenced by emotion, contributes to the sensory–affect transformation. The interaction of the basolateral AG and the striatum is hypothesized to contribute to and be reflected clinically in the motor response to the affect-emotional component of the sensation (i.e., the sensory–affect transformation).

Algorithm 3: Psychomotor Component

The neuroanatomical substrates of the psychomotor component include the insula, the parietal lobe, the striatum,

and the cerebellum (see Fig. 2). The brain function reciprocal neurocircuitries of the psychomotor component for tinnitus include the thalamus, PBN, frontal lobe (OFC), insula, striatum, temporal lobe (MTLS), and PAC. The brain function reciprocal neurocircuitries for long-term paradoxical auditory memory for tinnitus are hypothesized to be the frontal lobe (OFC), insula, temporal lobe (MTLS), PAC, hippocampus, parahippocampus, BG, and cerebellum. The brain function reciprocal neurocircuitries of attention for tinnitus are hypothesized to be thalamus, the frontal, temporal, and parietal lobes, and the BG (see the section Cross-Modal Sensory Brain Integration).

Neurocircuitries

The following reciprocal activating neurocircuitries are suggested in the algorithms of the FCP based on our clinical experience with nuclear medicine brain imaging (SPECT and PET) and electrophysiological recordings (QEEG) in SIT patients in whom hyper- and hypo-activation of multiple neuroanatomical substrates were identified:

- Sensory component
  - Cochlear brainstem, (lemniscal-extralemniscal), thalamic
  - Thalamocortical (thalamus, PAC)
  - Thalamo-cortical-cortical (PAC, associated auditory cortices)
  - Thalamotemporal (PAC, MTLS, cerebellum)
  - Thalamic (medial geniculate body, PBN, NA)–temporal (MTLS)–frontal (PAC)
    - Thalamic-AG-hippocampal-parahippocampal-frontal-parietal
    - Thalamic-AG-striatum-NA
  - Thalamic-cerebello
  - Thalamic-hypothalamic
- Affect component
  - Thalamic-cortical-temporal (PAC, MTLS)
  - Thalamic-cortical-frontal (PFC, DLPFC, OFC)
  - Thalamic-cortical-parietal
  - Frontal (PFC, OFC)–insular–temporal (MTLS)
  - Temporal (MTLS)–insular–frontal (PFC, DLPFC)
  - Temporal (MTLS, AG)–insular–striatum
- Psychomotor component
  - Thalamic-frontal (PFC, OFC)–temporal (PAC, MTLS)–parietal
  - Cerebellar-thalamic-cortical (temporal PAC, frontal PFC, parietal)
  - Temporal (PAC, MTLS, AG)–insular–striatum
  - Cerebellar-cortical-parietal, frontal, temporal
  - Insular-parietal-striatum-cerebellum
  - Cerebellum-striatum-parietal
  - Insular-cerebellar-parietal

The algorithms of the FCP provide a framework for integrating the components of an aberrant auditory sensation (tinnitus) with multiple neuroanatomical substrates and brain functions (highlighted clinically by the sensory–affect transformation) and a basis for hypotheses of neurocircuitries and future identification of the underlying mechanisms and processes involved. Multiple brain function processes are ongoing simultaneously in tinnitus patients. Although each can be identified individually, the overriding brain function experienced or demonstrated by tinnitus patients is a conscious awareness of the sensory–affect transformation of the tinnitus. There is a "melding" and consolidation of activities between multiple neural networks within each of the neuroanatomical substrates associated with different brain functions, expressed clinically as the sensory–affect transformation (the FCP). The significance of the FCP for tinnitus is considered to be expanded and broader in its application for all sensations, normal or aberrant.

Simultaneous ongoing reciprocal interacting brain function processes in multiple neuroanatomical substrates for each component of the aberrant auditory sensation (tinnitus) are included in each algorithm of the FCP. Synchronized neural activity in multiple neuronal assemblies is hypothesized to be the basis of perception and consciousness [53,54].

In summary, the neuroanatomical substrates of the FCP exemplify sensory processing in the brain of an aberrant auditory sensation representative of and not limited to one sensory modality, the PAC (i.e., a unimodal cortex). Extensive and multiple are the interconnections of the PAC with other sensory cortices, vision, audition, and somatosensation (i.e., heteromodal cortices) and regions of the neocortex concerned with affective processing, memory, and the maintenance of a homeostasis of brain function.

DISCUSSION

The hypothesis of the FCP that evolved in 1989 from our original interpretation of perfusion asymmetries in multiple neuroanatomical substrates, obtained with brain SPECT and PET, has since 1995 found support in efforts from basic science, clinical medicine, neuroscience, auditory science, electrophysiology, and nuclear medicine imaging, as cited. Significant is the correlation of neuroanatomial substrates with metabolic and electrophysiological evidence, which provides an objectivity for a subjective aberrant sensory complaint (i.e., metabolic and electrophysiological correlates for tinnitus).

The update of the FCP in terms of neuroanatomical substrates provides a dynamic framework and model for an evolving pathophysiology of tinnitus. The following considerations are presented for present and future

translation of the FCP to sensory physiology, tinnitus theory, diagnosis, and treatment, and brain function.

General

Sensory Physiology and Pathophysiology of Tinnitus and the FCP

The basic principles of sensory physiology are recommended to be maintained in the course of translation to tinnitus theory, diagnosis, and treatment (i.e., components of sensation-sensory, affect-emotion, and psychomotor) [173]. Specifically, the cross-correlation of the neuroanatomical substrates for each component of the aberrant sensation as a specific algorithm with brain function processes provides a framework for investigating and identifying neurocircuitries, both real and hypothesized, and a basis for investigating underlying mechanisms of processing for particular brain functions—all contributing to an emerging pathophysiology of tinnitus. A pathophysiology of tinnitus based on principles of sensory physiology for the tinnitus symptom of all clinical types provides a continuity between multiple disciplines of terminology, planning of investigations, reporting of observations, and clinical translation for the ultimate benefit of tinnitus patients (i.e., basic science and clinical applications).

Tinnitus Complexities and the FCP

Tinnitus is not a unitary symptom. Clinically different types of tinnitus have been identified [8]. The algorithms of the FCP demonstrate the clinical complexities encountered by tinnitus patients and professionals. Specifically, each tinnitus patient manifests a clinical multiplicity of simultaneously ongoing brain function processes (perception, consciousness, etc.), as previously listed. Among these, the brain function of conscious awareness of the sensory–affect (emotional-behavioral) transformation predominates. The FCP provides basic scientists and clinicians with a unifying framework of tinnitus theory for establishing accuracy in tinnitus diagnosis and attempted relief.

Tinnitus Theory and the FCP

An integrative tinnitus theory has been hypothesized, encapsulating neuroanatomy, sensory physiology, and a theory of brain function (the TDST) [16]. From the start of our experience with tinnitus in 1979, the perception of tinnitus implied the significance of the CNS for tinnitus patients.

Significantly, the TDST originated from the identification in the early 1980s of a dyssynchrony in the short-latency auditory brainstem response, which provided objective evidence of the clinical significance of the CNS in tinnitus patients [9]. Nuclear medicine imaging (brain SPECT) in 1989 provided the first objective in vivo evidence in tinnitus patients of the identification of neuroanatomical substrates highlighted by the MTLS and the basis of the hypothesis of the FCP [2–4]. The power distribution by frequency bands and electrode sites via QEEG in tinnitus patients correlates with the original reported neural substrates identified with brain SPECT and of many other investigators as cited [19–24]. Specifically, QEEG results in tinnitus patients reflect activation at multiple electrode recording sites, providing objective evidence for an interneuronal cortical network highlighted by the frontal and temporal recording sites and hypothesized to be modulated by the thalamus (i.e., a thalamo-frontal temporal circuit) [23,24]. The clinical translation and integration into the TDST of the hypothesis of conscious awareness [53,54] and thalamocortical dysrhythmia [241], induced at the level of the thalamus (reflecting a lack of auditory input) and at the cortex in an increased synchrony provides a pathophysiological basis for understanding tinnitus and the FCP and a clinical relevance to the predominant role of the CNS for all clinical types of tinnitus. The two functional clinical measures—nuclear medicine imaging and electrophysiological data—provide objective evidence of dynamic maps of brain activity in interaction of frontal and temporal lobes and support the FCP for tinnitus [23,24,41]. The FCP and TDST complement each other, the FCP focusing on neuroanatomical substrates and the TDST focusing on underlying mechanisms of tinnitus production and associated brain functions highlighted by the FCP sensory–affect transformation.

It is hypothesized that tinnitus is a phantom phenomenon related to a deafferentation reflecting a lack of auditory input, which induces a reorganization and hyperactivity at the PAC [193]. Gamma band activity (30 Hz and higher) is necessary for the conscious awareness of any perception. It has been suggested that gamma band activity is required for any stimulus to be perceived. Such gamma band activity has been hypothesized and reported via MEG to predominate in the contralateral PAC [25]. Support of this theory is significant for the neuroanatomical substrates of the FCP highlighted by the thalamus and the PAC. To be considered, by definition, is that identifying neuroanatomical substrates for tinnitus precludes considering it a phantom sensation [2,16,24].

Tinnitus Diagnosis and the FCP

The accuracy of a medical diagnosis significantly influences the success of the recommended therapy. The FCP provides the neuroanatomical framework and model for correlation with the clinical history and cochleovestibular testing results to identify the clinical type of tinnitus.

It encompasses conditions in the ear and brain influencing the clinical course of the tinnitus, its medical significance, and a basis of treatment targeting the components of the tinnitus symptom [10,43,172].

Tinnitus Treatment and the FCP

The neuroanatomical substrates of the FCP provide a framework for (1) underlying mechanisms involved in the hypothesized neurocircuitries and (2) selection of modalities attempting treatment (i.e., medication, instrumentation, and surgery, alone or in combination). The clinical application of the FCP for treatment was the basis of the receptor-targeted therapy directed to the $GABA_A$ receptor for severe, disabling, predominantly central-type tinnitus (RTT-GABA) [46]. The identification of increased delta and beta activity via QEEG in predominantly temporal recording sites in that type of tinnitus controlled for factors influencing the clinical course in the patient. Further, the correlation via brain SPECT of the asymmetry in perfusion in the MTLS, a region of interest in the brain with a high density of the $GABA_A$ receptor, was the basis for recommending an innovative therapy attempting tinnitus relief (i.e., antiepileptic drugs). The RTT-GABA continues to provide significant long-term relief from that type of severe disabling tinnitus.

Tinnitus retraining therapy has been a significant translation of the neurophysiological theory of tinnitus for attempting tinnitus relief [118]. Its focus on the limbic system and habituation is considered additional support for the FCP.

TMS has recently been introduced and continues to be applied in attempting to provide tinnitus relief. The selection of sites for stimulation is considered to reflect neuroanatomical substrates hypothesized in the original FCP [25,250–252]. The lemniscal-extralemniscal systems have been reported to differentiate in the mode of transmission of the tinnitus signal—that is, the lemniscal system fires in a regular mode and the extralemniscal system in a "burst" mode. It has been hypothesized that white noise or noise like tinnitus might be generated by hyperactivity in the non-tonotopic extralemniscal system and a "tonal-quality" tinnitus in the lemniscal system. This may be a basis for clinical translation to tinnitus treatment (e.g., instrumentation) [25,252].

Brain Function

It has been hypothesized that for all clinical types of tinnitus, the predominant brain function is the transformation of the sensation to one of affect (emotion-behavior)—the FCP. Neuroanatomical substrates identified in tinnitus patients via nuclear medicine imaging and EEG provide a framework model for locating multiple brain functions (as listed previously) associated and occurring simultaneously with the sensory–affect transformation.

Consciousness

Establishing the concept of the brain's consciousness function is a work in progress. The recent integrative theory of consciousness propounded by Hughes and John [53,179] and John and Prichep [54] hypothesized that a conscious perception clinically reflects a summation of synchronous activities of neuronal activity recordable from multiple neural substrates at the brain cortex. It is considered to be supported by tinnitus QEEG results [24] and has been integrated into the TDST and the FCP. *Perception* is described as an active process that specifies the content of consciousness. *Consciousness* is defined as an inherent property of an electrical field resonating in a critical mass of coherently coupled cells.

A new definition of tinnitus is recommended: that it is a conscious, abnormal, auditory perception reflecting a dyssynchrony in the development of—or neural transmission in—either the peripheral nervous system or the CNS, or both. We have come to realize that the ultimate answer to the question of how a sensory phenomenon is transformed to one of affect will be seen in tinnitus theory, diagnosis, and treatment via the clinical translation of advances in neuroscience to brain function and, specifically, to consciousness.

Sensory–Affect (Emotion-Behavior) Transformation

Significant neuroanatomical substrates in the sensory–affect (emotion-behavior) transformation are the OFC, the MTLS (i.e., the AG), and the striatum (OFC and BG). Of special note is the recent reported influence of the dorsal striatum on the emotional content of behavior. The dorsal striatum is involved in various forms of learning and memory. The AG role in emotional learning is acknowledged. The possible cooperation between the dorsal striatum and AG was investigated for the effects of electrolytic lesions in the dorsal striatum of rats on tone-fear conditioning. The results suggested that the dorsal striatum plays a role in tone-fear conditioning. Specifically, routes other than the well-established projections of the central amygdaloid nucleus to the periaqueductal gray matter may contribute to acquisition-consolidation of the freezing response associated with the tone-fear conditioning. In addition, it is suggested that tone-fear conditioning and contextual fear conditioning are mediated by different anatomical networks [255].

The advances in neuroscience reported for affect-emotion-learning-behavior are intertwined and inter-

related and are demonstrated clinically by tinnitus patients over time. The tinnitus symptom is considered to be a learning process that initially is subclinical. When tinnitus becomes clinically manifest to a patient as a sensory perception, a "paradoxical" memory is established, eliciting emotional and behavioral responses—individual for each tinnitus patient—and reflecting cochleovestibular function-dysfunction and the degree of CNS plasticity. The consolidation of the memory in different "systems," identified and demonstrated in the FCP algorithms by neuroanatomical substrates, results over time in the clinical manifestation of tinnitus of the severe disabling type (e.g., SIT).

The pathways are hypothesized in the FCP algorithms of the sensory and affect components. Reciprocal innervating pathways are hypothesized to exist. The aberrant auditory stimulus, tinnitus, received by the thalamus from the lemniscal and nonlemniscal systems is forwarded to the PAC and the MTLS (i.e., the entorhinal cortex, the perirhinal cortex, the AG, the hippocampus, and the parahippocampus formation). From these multiple locations, there are projections to the PFC and the OFC, insula, anterior cingulate, parietal lobes, and cerebellum. The AG also connects with the reward pathways (NA). Primary and secondary cortices are hypothesized to connect to multisensory association areas and to the PFC. The DLPFC connects to all neuroanatomical substrates in the FCP algorithms. Significant is the participation of the AG in multiple brain functions in the sensory and affect (emotional-behavioral) components of the tinnitus, which is demonstrated in the FCP algorithms. Connections from the thalamus to the hypothalamus involving the insula are hypothesized to influence the autonomic response to an auditory stimulus.

The affect response is hypothesized not to be a separate brain function but rather a simultaneous ongoing brain function accompanying the initial perception of tinnitus in the PAC, initiated by simultaneous input from the thalamus to the PAC and the MTLS, as hypothesized in the original FCP algorithm and set forth in the FCP sensory component algorithm. Two pathways are reported to induce an emotional response. In one, the emotional stimulus is directly received by the thalamus and connects to the AG, providing an immediate response. In the second, the information is received by the PAC and forwarded to the PFC and the hippocampus, which influences the AG. Primary and secondary cortices connect to multisensory association areas and the PFC. The AG is indirectly or directly influenced by the auditory stimulus. Connections are hypothesized from the anterior cingulate to the anterior insula. The end result is integration of cognition and emotion in the DLPFC [25].

Much of our behavior is guided by rules. Although the human PFC and the anterior cingulate cortex are implicated in implementing rule-guided behavior, the crucial contributions made by different regions within these areas are not yet specified. In an attempt to bridge human neuropsychology and nonhuman primate neurophysiology, the effects of circumscribed lesions to the macaque OFC, the principal sulcus, the superior DLPFC, the ventrolateral PFC, or the anterior cingulate cortex sulcus on separable cognitive components of a Wisconsin Card-Sorting Test analog were investigated. Only the principal sulcus lesions impaired maintenance of abstract rules in working memory; only the OFC lesions impaired rapid reward-based updating of representations of rule value; the anterior cingulate cortex sulcus lesions impaired active reference to the value of recent choice-outcomes during rule-based decision making [256].

This article is significant for identifying the brain functions of the PFC in the FCP. The neuroanatomical substrates and brain functions for sleep and concentration associated with the FCP await future updates of the neuroanatomical substrates of the FCP.

Memory

The initial process in the FCP has been hypothesized since 1991 to be the establishment of a paradoxical memory for tinnitus in the MTLS (paradoxical in the sense that the memory for the tinnitus is aversive and noxious for a tinnitus patient). Cited advances of contributions to memory formation from the multiple neuroanatomical substrates in each component of the FCP algorithms makes consideration of memory formation in a single location simplistic. Rather, the translation of contributions to memory from multiple locations for tinnitus suggests different memory systems for tinnitus, individual for each patient. The concept of different memory systems for tinnitus gains understanding for tinnitus when considered in terms of each of the components of the tinnitus symptom as demonstrated in the FCP algorithms. Specifically, the initial establishment of the paradoxical memory in the MTLS reflects the sensory component; in the PFC, insula, and OFC, the affect (emotional-behavioral) component; and in the striatum, cerebellum, and parietal lobe, the psychomotor component (i.e., multiple neuroanatomical substrates reflecting multiple memories, clinical and subclinical in their manifestation, for each component of the brain function of the conscious awareness of the sensory–affect transformation).

The brain's conscious auditory perception for tinnitus is hypothesized, on the basis of a translation from the theory of consciousness, to clinically reflect a summation of synchronous neuronal activity recordable from multiple neural substrates at the brain cortex. A reciprocal interneuronal interconnecting innervation system

exists between the source of the aberrant dyssynchronous sensory input, peripheral or central in origin, and cortex. The dyssynchronous sensory input 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 reflected in cortical functions highlighted in tinnitus patients by the brain functions of affect-emotion and paradoxical auditory memory. The cingulate and the MTLS, highlighted by activity in the entorhinal cortex, the AG, and the hippocampus, reciprocally interact with the thalamus, establishing for the tinnitus an initial paradoxical auditory memory and associated affect-emotional response. Stress is a factor influencing the clinical course of the aberrant auditory stimulus tinnitus, which can progress to SIT. The transformation of the dyssynchrony of the aberrant auditory stimulus to one of synchrony and individual brain functions highlighted by affect, emotion, memory, somatosensory response, and consciousness is clinically considered to be the FCP for tinnitus.

Clinical translation within a framework for consciousness of the neuroanatomical substrates associated with the perception of tinnitus and the hypothesis of the FCP had and continues to have application for tinnitus theory, diagnosis, and treatment. The neuroanatomical substrates of the FCP provide a framework for understanding neural substrates for consciousness [6,43,46]. The identification within the FCP of metabolic and electrophysiological neural activity will contribute to identifying neural correlates for consciousness. The ultimate solution for understanding the theory, diagnosis, and treatment of all clinical types of tinnitus awaits an understanding of the biochemistry and physiology associated with the brain functions of perception and consciousness.

The report of fMRI bold effect in the hippocampus and the parahippocampus rather than in the PAC in patients with chronic tinnitus is suggested to reflect a consolidation of the paradoxical auditory memory system. The demarcation between acute and chronic tinnitus has been empirically set at 4 years. Interestingly, examination of EEG data reported a change in the alpha and gamma rhythms. Specifically, the gamma-band activity and connectivity in the cortex changed over time (i.e., decreased gamma in the PAC and an increase in the ACG and DLPFC cortex and an increase in beta activity in the hippocampus and parahippocampus). The conscious perception of tinnitus is hypothesized to reflect the activity of the hippocampus and the parahippocampus, ACG, and DLPFC, and not the PAC, an expression of a global network of neuronal activity [25]. In terms of the FCP, it is hypothesized that the generator of the initial perception of the aberrant auditory stimulus was the PAC (i.e., acute tinnitus), and the neural network was of the PAC and the MTLS for the sensory component of tinnitus. With chronicity, which is suggested to be variable for each tinnitus patient, the paradoxical memory becomes consolidated in the hippocampal-parahippocampal system, which becomes the generator for the tinnitus rather than the PAC. The chronic tinnitus network becomes the hippocampal-parahippocampal system, the anterior cingulate cortex, and the DLPFC (i.e., a connectivity of neuroanatomical substrates in the FCP for tinnitus chronicity). The establishment of the memory of the stimulus precludes the need for repeated stimulation to experience the sensation. The stored information is processed emotionally and cognitively and integrated in relation to the original stimulus input.

Thalamocortical Oscillations and the FCP

The significance of the thalamus for the FCP is considered to have been further demonstrated in 2005 by the identification of a cortex mechanism that is hypothesized to result in the perception of tinnitus. Specifically, depolarized potentials received at the thalamus 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 that in the cortex result in an activation, "the edge effect," the symptoms of which are reflective of the underlying stimulated neural substrate [193, 195]. This is considered to be a significant contribution to the FCP hypothesis for understanding cortical brain function of tinnitus patients. Whether this finding is a mechanism for understanding the clinical activation and propagation of a tinnitus signal or a theory for tinnitus development awaits future experimentation and clinical verification.

Reward

It is hypothesized for the FCP that the motivation-reward response of the OFC to the input of the tinnitus signal is analogous to that with a lesion in the OFC (i.e., an aversive response). The tinnitus signal triggers in the OFC and the striatum an activation of aversive brain function processes of reward and behavior (i.e., a paradoxical reward) with a resultant altered reward preference (e.g., fear). This is similar to the activation of the brain function processes of auditory memory in the MTLS in response to a normal auditory sensation. The tinnitus signal triggers activation of a paradoxical auditory memory. Both the motivational and memory brain functions are paradoxical: the patient does not want either of these aversive brain functions that have been activated in response to the tinnitus (i.e., reward or memory). The tinnitus stimulus, paradoxically, activates the normal motivation-

reward response to a sensory stimulus: a sense of well-being, emotion of joy, and memory of the sensation.

Attention

The brain function of attention is not a unitary function. Clinically, in our tinnitus experience, the brain function process of attention is considered to be multidimensional. *Attention* is defined as brain function processes resulting in an awareness by an individual of a particular feature in the environment, external to or within the individual, to the exclusion of others (e.g., the symptom of tinnitus). Multiple neuroanatomical substrates in the FCP involve the visual cortex, the nonvisual cortices, the PAC, the posterior parietal cortex, and the MTLS (i.e., the AG).

It is hypothesized for the future FCP that different attention systems will be identified for each of the components of the aberrant auditory perception, tinnitus. Furthermore, one may hypothesize the establishment of individual memory systems for each attention system, adding to the complexity associated with the brain function for both a normal and an aberrant sensation (e.g., tinnitus; see the section Evidence Supporting the FCP Hypothesis, subsection Attention).

"Distress"

The word *distress* is an ambiguous word applied as a response to anything that is negative (e.g., pain, discomfort): specifically, how one perceives negativity. Distress implies mental or physical strain imposed by pain, worry, suffering, agony, or anguish. It suggests a situation that can be relieved [197].

When applied to emotion and behavior, distress is considered to be descriptive of the degree of an individual's emotional-behavioral response. It is a description of the clinically manifest brain function of the affect component of a sensation (e.g., anxiety, depression). The literature of sensory physiology has identified in the brain neuroanatomical substrates and hypothesized neurocircuitries for specific brain functions of affect (emotion-behavior). The introduction of the word *distress* for an already accepted terminology for the brain functions (i.e., affect-emotion and affect-behavior) is considered a distraction and a duplication that has the potential for resultant confusion in the literature. To be considered is the recommendation that the terminology of sensory physiology of affect (emotional-behavioral) brain functions be maintained and that *distress*, if used, should describe the severity of the disturbance in the brain function of affect-emotion and affect-behavior, manifested clinically as anxiety and depression (see the sections Prefrontal Cortex and Orbitofrontal Cortex).

Masking

The integrity of the auditory masking brain function in the FCP is considered critical for the clinical course of tinnitus from its subclinical to its clinical manifestation as an interference in affect (emotion-behavior). Classically, the auditory masking function has been investigated and discussed in terms of its psychophysical and psychoacoustic characteristics. Our evolving experience with tinnitus suggests that both peripheral and central components exist, of which the central brain function is predominant. Multiple reciprocal innervations and connections between multiple neuroanatomical substrates in brain are hypothesized to be involved. Auditory masking is clinically considered to be predominantly a brain function (i.e., an auditory perception). Two factors have been hypothesized to be significant for influencing the brain masking function: integrity of the cochleovestibular system and the plasticity of the brain.

Global Workspace Theory

The global workspace theory has a special place for consciousness. The response in the visual system requires a combination of activity for a supraliminal stimulus in sensory cortex to be attended to with attention (i.e., combination of visual sensory areas and the frontal region). The FCP algorithms reflect the global workspace theory (see the section Perception and Consciousness).

Cross-Modal Sensory Processing and the FCP

The hypothesis of the FCP is considered to reflect cross-modal sensory processing of an aberrant auditory stimulus (tinnitus) in the brain. The cross-modal sensory integration is hypothesized in the FCP and demonstrated in the FCP algorithms by the reciprocal activation and interaction between the psychomotor and affect components of tinnitus. The neuroanatomical substrates of the FCP are proposed as neural correlates of cross-modal integration of brain function (i.e., sensory–affect transformation). Clinically, cross-modal sensory processing is identified by the somatosensory motor response that accompanies the behavioral affective response to the sensory aberrant auditory stimulus, tinnitus [223]. To be considered is that the somatosensory system may provide a sensory cue that can influence the localization or identification of the stimulus. Clinically, this correlates with the clinical history and tinnitus diagnosis of a non-auditory tinnitus (e.g., temporomandibular joint tinnitus and cervical tinnitus) [9]. For the future, the FCP provides a framework for identifying neuroanatomical substrates activated by the input of the visual system to the tinnitus or the influence of the tinnitus on the visual input for the brain function of attention.

Cerebellum and the FCP

The cerebellum is considered significant for its function in the psychomotor component of the FCP. These contributions and connections involve the acousticomotor system, the thalamus, the PAC, the insula and striatum, and the frontal and parietal lobes for motor, modulatory, and cognitive brain functions (see the section Cerebellum).

Tinnitogenesis and the FCP

The concept of tinnitogenesis (i.e., a seizure-type activity resulting in the perception of an aberrant auditory stimulus, tinnitus), originally hypothesized in 1995, has been demonstrated and reported [257].

> 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 deficit 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 [2, p. 121].

Questions

The identification of neuroanatomical substrates for the FCP is considered to be ongoing, reflecting integration of advances in neuroscience and auditory science and clinical medicine. Questions persist for the future:

1. How does a particular neuroanatomical substrate of the brain differentiate between its multiple functions? What are the mechanisms involved?
2. What are the mechanisms that underlie the brain functions associated with the sensory–affect transformation?
3. Is thalamocortical dysrhythmia the pathophysiological mechanism underlying the symptom of tinnitus?
4. What is the evidence for the hypothesized neuromodulatory role of the parietal lobe and cerebellum in the FCP?
5. Is the identification of the gamma frequency the electrophysiological correlate for the conscious perception of tinnitus? If so, what is the significance of its identification in different and multiple neuroanatomical substrates?
6. What additional neuroanatomical substrates will be identified for inclusion into the FCP?
7. What are the cortical generator sites of tinnitus in addition to the PAC? What in the architecture or biology of the networks hypothesized for the FCP is either bringing the tinnitus signal to the networked regions or propagating tinnitus between the networks?
8. How do the different clinical types of tinnitus affect the neural connectivity between the neuroanatomical substrates of the FCP?
9. At the molecular level, what determines the propagation of the tinnitus signal and its consolidation between networked areas, with resultant consciousness?

CONCLUSIONS

The identification of neuroanatomical substrates in tinnitus patients, translated and hypothesized for the FCP, which originated in 1989, was presented in 1989 through 1995 and published in 1995. The FCP is a hypothesis that attempts to explain how an aberrant auditory sensory stimulus becomes transformed into one of affect and somatomotor response. The concept of the FCP, as documented in this publication, finds support from the literature (i.e., basic science, neuroscience, auditory science) and from ongoing reported clinical tinnitus experience. The FCP neuroanatomical substrates provide a framework model for tinnitus theory, an emerging pathophysiology for tinnitus of all clinical types, and its clinical translation for tinnitus diagnosis and treatment. They are proposed to be neural correlates of sensory processing for tinnitus and interconnections in the brain among multiple regions of the cortex that receive inputs from more than one sensory modality (i.e., cross-modal integration of brain function), with resultant associated multiple brain functions.

The three algorithms of the FCP, formulated as components of an aberrant auditory sensation (i.e., sensory, affect, and psychomotor) include hypothesized reciprocal interactions among the neuroanatomical substrates of the FCP, integrated with resultant associated multiple brain functions. The initial brain function process in the FCP was hypothesized in 1995 and persists to date as the establishment in the MTLS of a paradoxical auditory memory for an aversive sensory stimulus (tinnitus), with speculations as to its clinical applications for both diagnosis and treatment. They are plastic and ongoing and provide a basis for identifying and understanding the underlying neurocircuitries and neurochemistries in the brain involved in the sensory–affect transformation. The reciprocal activities of the AG-striatum-frontal circuit, cited in the literature to demonstrate the influence of emotion on behavior, support the interaction of the components of the aberrant sensory stimulus (i.e., sensory, affect, and psychomotor) demonstrated in the algorithms of the FCP.

The FCP neuroanatomical substrates provide the basis for a neural network of connectivity, the identification of

which in molecular genetic mechanisms can provide the basis for drug development and treatment of tinnitus (i.e., tinnito-proteo-genomic pharmacology).

The ultimate solution for understanding the theory, diagnosis, and treatment of all clinical types of tinnitus and the clinical dilemma posed by the question of the sensory–affect transformation awaits identification of the highlighted underlying mechanisms of sensory processing and multiple brain function processes associated with the FCP and focusing on perception, consciousness, and auditory masking.

The hypothesis of the FCP for tinnitus and the identified neuroanatomical substrates, when viewed in terms of sensory physiology, is considered to be expanded and broader in its application for all sensations, normal or aberrant. The neuroanatomical substrates of the FCP to date suggest that the brain has a mind of its own.

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