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Expanding the biological basis of tinnitus: crossmodal origins and the role of neuroplasticity

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Abstract

Tinnitus is most often initiated by modality specific otopathologic disturbances affecting peripheral and central auditory pathways. However, there is growing evidence indicating that the anatomical location generating tinnitus occurs at sites different from the initial pathology. Support for this notion is found in individuals where tinnitus can be triggered or modulated by inputs from other sensory modalities or sensorimotor systems (somatosensory, somatomotor, visual-motor). The use of functional imaging methods combined with psychophysics, detailed physical examinations and questionnaire-based assessments has reinforced and validated these observations. Available data suggest that tinnitus-related crossmodal interactions are more common than previously anticipated. This communication reviews these advancements and suggests that a relatively broad *multimodal* network of neurons is involved in generating and sustaining the tinnitus perception in some forms of the disorder. Also implicated as part of the tinnitus experience are interactions within large-scale neural networks subserving attention, cognition, and emotion. Incorporating this knowledge into contemporary psychophysiological models will help facilitate the conceptualization of this phantom perception in a more comprehensive manner.

Key words: Tinnitus; Gaze-evoked tinnitus; Cranio-cervical tinnitus; Cutaneous-evoked tinnitus; Somatomotor-evoked tinnitus; Plasticity; Crossmodal plasticity; Limbic system; Trigeminal ganglion; Amygdala; Phantom perception; Pain

1. Introduction

Tinnitus is the phantom perception of sound in the absence of overt acoustic stimulation (Jastreboff, 1990)[1]. Because tinnitus is most often triggered by modality specific otopathologic conditions, it has traditionally been viewed as having a purely auditory etiology[2]. However, evidence is accumulating to suggest that neural activity underlying this condition is a much more complex entity involving abnormal interactions between multiple sensory modalities, sensorimotor systems, neuro-cognitive networks, and brain pathways involved in processing emotional reactions. Below, our present knowledge of abnormal crossmodal information processing is reviewed and consideration is given to how these relatively new findings can be incorporated into

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Abbreviations: *f*MRI, functional magnetic resonance imaging; PET, positron emission tomography; TMS, transcranial magnetic stimulation; TNS, transcutaneous electric nerve stimulation; CNS, central nervous system; OFM, oral–facial maneuver; US, unconditioned stimulus; CS, conditioned stimulus; 2-DG, deoxyfluoro-D-glucose; SPECT, single photon emission computed tomography; i.v., intravenous

[1] Nomenclature used herein follows concepts proposed by Jastreboff (1990, 1995). By definition, tinnitus is a subjective phantom perception (Jastreboff, 1990). All other acoustic events generated within the head or neck regions, resulting from blood flow, myogenic activity or other factors (i.e., vascular pulsations, jugular outflow syndrome, palatal and intra-tympanic myoclonus, patulous Eustachian tube, cervical crepitus, etc.), are considered 'somatosounds' (Jastreboff, 1990, 1995; Hazell, 1995). To unify the codification of this condition, avoiding or abandoning terms such as 'objective tinnitus' and 'subjective tinnitus' has been advocated.

[2] Exceptions include tinnitus associated with whiplash injury, closed head injury, lightning hits, etc. (Claussen and Constantinescu, 1955).

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psychophysiological models concerned with the cause of tinnitus.

1.1. Evidence for crossmodal interactions

1.1.1. Gaze-evoked tinnitus

Initially described as a medical curiosity and reported as brief communications within a specialty medical journal (i.e., Whittaker, 1982a,b, 1983; House, 1982), gaze-evoked tinnitus is becoming recognized as a distinct clinical entity. Codification is based on phenomenological aspects of this condition because tinnitus can be switched on and off (triggered) by static deviation of horizontal or vertical eye position from an egocentric reference. Gaze-evoked tinnitus has most often been reported following complete and acute unilateral deafferentation of the auditory periphery after surgical extirpation of space occupying lesions from the base of the skull (i.e., Whittaker, 1982a,b, 1983; House, 1982). Subsequently, more detailed accounts of this phenomenon have appeared in the literature (Wall et al., 1987; Cacace et al., 1994a,b) and it has now been confirmed and studied by many other teams of investigators worldwide (Giraud et al., 1999; Herraiz et al., 1999; Caraceni et al., 1999; Lockwood et al., 2001; Biggs and Ramsden, 2002). Whereas exact mechanisms remain unknown and because peripheral deafferentation has been cited as the most common event initiating this phenomenon, several hypotheses have been put forth to explain this condition. These include crossmodal reactive sprouting of neurons to unoccupied (denervated) synaptic sites, unmasking of silent synapses and ephaptic interactions (Wall et al., 1987; Cacace et al., 1994a). Moreover, the time from deafferentation to the onset of symptoms may provide cues about potential mechanisms. Rapid onset of tinnitus suggests unmasking of silent synapses whereas longer delays may be consistent with sprouting, ephaptic interactions, changes in strength of existing neural connections, or a combination of processes (Lockwood et al., 2001).

In its pure form, gaze-evoked tinnitus is absent in certain eye positions (i.e., 0° gaze, from a neutral head-referenced condition) but can be activated when static deviation of eye gaze exceeds a certain displacement in the horizontal or vertical direction. Based on visual planimetry assessments, Cacace et al. (1994b) showed that tinnitus could be activated by as little 3–10° gaze deviation in the horizontal or vertical direction. Reports from individual patients also indicate that pitch and loudness perceptions can remain constant as long as the same horizontal or vertical eye gaze position is maintained, but these psychophysical dimensions can change, as eye gaze locations are altered. Moreover, in individuals capable of sustaining the tinnitus perception with static deviation of eye position, computer-controlled adaptive tracking methodology can quantify the psychophysical (pitch and loudness) dimensions of these activations in high resolution (Cacace et al., 1994b). When fine grained adaptive tracking methods are used or when other matching procedures are combined with visual planimetry studies, detailed quantification of the visual–spatial coordinates underlying this condition can be ascertained (Cacace et al., 1994a,b; Giraud et al., 1999).

Transient, i.e., short duration auditory perceptions have also been reported with changes in eye position but this variant has not received much attention. In addition to these unique crossmodal interactions, features that make gaze-evoked tinnitus both important and interesting from a scientific standpoint, is the ability to internally generate on and off states (Cacace et al., 1994a; Giraud et al., 1999) or to *modulate* a constant background tinnitus (Lockwood et al., 2001). The ability to evoke and/or to modulate tinnitus by static change in eye position provides the conditions necessary to apply functional imaging methods as a means to gain insight into brain areas involved in generating and/or processing this phantom perception (Cacace et al., 1994a, 1996a,b; Cacace, 1999; Cacace et al., 2000). Initial studies using functional magnetic resonance imaging (*f*MRI) showed activations in superior colliculus and frontal eye fields (Cacace et al., 1996a,b). Other subsequent imaging investigations using positron emission tomography (PET) have provided additional insight into this condition. Giraud et al. (1999) studied four adults that developed the pure form of gaze-evoked tinnitus which became manifest after unilateral acoustic tumor removal. In these individuals, profound hearing loss preceded tumor removal because tumor size was large (>3 cm). When change in eye gaze evoked tinnitus during PET studies, localized sites within temporo-parietal association areas, but not in primary auditory cortex were activated bilaterally. Lockwood et al. (2001) used PET to study individuals that could modulate a constant background tinnitus with eye gaze. In this investigation, all participants underwent surgery for excision of unilateral acoustic tumors, all developed severe or profound hearing loss in the affected ear after surgery (unilateral deafferentation) and thereafter, all individuals were able to modulate a constant background tinnitus with eye gaze. During PET scanning, background tinnitus was modulated by right or left lateral gaze deviations $>60°$. When data were analyzed either in individual participants (where each patient served as his own control), or in groups, activation of brainstem (lateral pontine tegmentum, vermis of the cerebellum, cuneus) and auditory cortical areas were observed. Lockwood and colleagues suggest three possible mechanisms that might generate this form of gaze-evoked tinnitus: abnormal interactions

between brainstem system controlling eye movement and central auditory system, abnormal neural activity in auditory cortical sites and failure of lateral gaze to suppress/inhibit auditory cortical activity. Wall et al. (1987) were first to hypothesize that damage to the neural integrator for eye movement could underlie this phenomenon. They speculated that neurons with eye position dependent firing rates in the vestibular nucleus interacted with neurons in the auditory system, thereby causing eye movements to evoke or modulate an auditory percept. Data from Lockwood and colleagues are consistent with this hypothesis. In addition to modifying tinnitus perceptions, extreme lateral gaze can also induce co-activation of transverse auricular muscles and activate neural pathways subserving these functions (so-called ocular–auricular phenomenon; Urban et al., 1993).

Further descriptive information concerning individuals with gaze-evoked tinnitus has been provided by questionnaire research based on solicitations to several national organizations (Newsletter, Acoustic Neuroma Association; Tinnitus Today, magazine of the American Tinnitus Association) (Coad et al., 2001). In their survey, 91 respondents reported they could 'modulate their tinnitus with eye movement' following posterior fossa surgery. Based on this sample, the vast majority of respondents (95.6%; 87/91) had unilateral acoustic tumors; of the remaining individuals, two had bilateral acoustic tumors, one had a glomus jugulare tumor and one had cholesteotoma. With respect to psychophysical dimensions, most individuals (98.9%; 86/87) indicated that eye movement increased tinnitus loudness. In those that responded to whether pitch changed, 88.9% (64/72) indicated that pitch increased, 6.9% (5/72) indicated that pitch decreased, and 4.2% (3/72) indicated that pitch increased and decreased. In response to whether gaze-evoked tinnitus was present prior to surgery, the majority (71.2%; 52/73) indicated it was not present prior to surgery, 27.4% (20/73) did not know, 1.4% (1/73) indicated it was present prior to surgery. With respect to onset of symptoms, 4.1% (3/73) reported onset within 24 h, 11.0% (8/73) reported onset from 1 to 7 days, 16.4% (12/73) reported onset from 1 week to 1 month, 17.8% (13/73) reported onset from 1 to 6 months, 37% (27/73) reported onset greater than 6 months, 11% (8/73) did not know when gaze-evoked tinnitus started and the remaining 2.7% (2/73) were unaware they had gaze-evoked tinnitus until reading the notice in the newsletter/magazine. Interestingly, 17 additional respondents reported having gaze-evoked tinnitus, but their condition was unrelated to surgery.

Given a mailing circulation of ~5000 members (Newsletter, Acoustic Neuroma Association) and based on actual returned questionnaires, a prevalence rate of ~1.8% (91/5000) was estimated for individuals having gaze-evoked tinnitus after unilateral acoustic tumor surgery.

1.1.2. Somatosensory system interactions

Møller et al. (1992) provide clinical evidence and a neuroanatomical framework for incorporating auditory/somatosensory system interactions in the generation and/or modulation of some forms of tinnitus. In adults whose tinnitus magnitude ranged from mild to severe, Møller and colleagues showed that low-level electrical stimulation to the median nerve near the hand region could modify perceptual characteristics (loudness or pitch) of a continuous background tinnitus. Based on their series, over 38% (10/26) of subjects reported that tinnitus perceptions were altered, sometimes in very complex ways. In 15.4% (4/26) of subjects, low-level electrical stimulation increased tinnitus loudness, in 23.1% (6/26) tinnitus loudness decreased, but in 61.2% (16/26) no apparent change was reported. By contrast, in adult control subjects *without* tinnitus, median nerve stimulation during acoustic activation either had *no* effect on sound perception or produced only slight increases in loudness. These unique experimental findings led to the hypothesis that some forms of tinnitus might be generated in 'extralemniscal' or non-classical auditory pathways (i.e., in neuroanatomical areas where auditory and non-auditory (somatosensory) information could interact). As a follow-up to this initial investigation, Møller and Rollins (2002) provide additional insight into auditory/somatosensory system interactions in normal subjects by showing that changes in loudness perception to acoustic events by concurrent low-level electrical stimulation were differentially affected by age. They showed that electrical stimulation at the periphery had the greatest effect in children (7–8 years) and relatively little effect in adults (20–40 years). The authors interpret these findings from an ontogenetic/neuromaturational perspective: 'The change in function of the auditory system that we observed may be an example of specialization where auditory processing is shifted from the phylogenetically older non-classical system, towards the phylogenetically newer classical auditory system that performs finer analysis of sounds'; '... the results of the present study have led us to hypothesize that the efficiency of synapses that connect auditory input to the non-classical pathways decreases during ontogeny and that these synapses become ineffective at the time of adulthood'. In adults with tinnitus, the authors speculate that non-classical auditory pathways become *re*activated as an expression of neuroplasticity. The unmasking of silent (ineffective) synapses, a mechanism put forth by Wall (1977) to account for certain types of neuropathic pain, may be involved in this process (reviewed by Møller, 1997). Accordingly, *re*activation of the non-classical (extralem-

niscal) pathway in tinnitus may involve connections between dorsal thalamus and basal lateral amygdala. Møller and Rollins suggest that functional interactions between extralemniscal pathways and the amygdala may also contribute to certain pathological features associated with tinnitus, such as abnormal loudness perceptions (hyperacusis) and phonophobia.

In relation to the studies noted above, transcutaneous electrical nerve stimulation (TNS) has also been used as a means to treat tinnitus[3]. With respect to treatment applications noted below, TNS was based on the premise that electrical stimulation at the periphery could suppress tinnitus in the same way that pain is thought to be modified in the central nervous system (CNS) based on 'gate control theory' (Melzack and Wall, 1965; Tonndorf, 1987). For example, Kaada et al. (1989) applied TNS to the hand region (i.e., at the dorsal web region between the first and second metacarpal bones and at the ulnar edge of the same hand) and reported that tinnitus was reduced or eliminated temporarily in over 31% (9/29) of individuals tested. This reduction in tinnitus magnitude was concordant with modifications to tinnitus perceptions induced by peripheral electrical stimulation reported by Møller et al. (1992). The remaining 20 subjects reported no change in tinnitus magnitude. Interestingly, in some individuals (7/9), hearing sensitivity also improved (mean 13.3 dB, range 5.0–30.0 dB). Kaada and colleagues concluded that TNS could provide relief from tinnitus and may be a viable treatment option in some individuals. Rahko and Kotti (1997) also applied TNS at the periphery in 26 individuals with tinnitus (i.e., at the metacarpal fold between the first and second finger) to study whether this technique is a viable treatment. Based on telephone interviews at 1 month post treatment, it was found that 26.9% of affected individuals received benefit in terms of a reduction in the loudness of tinnitus. Because tinnitus was not eliminated in any of their patients, these authors were less enthusiastic for using this approach as a clinical treatment. Nevertheless, a theme that emerges from these studies is the analogy between tinnitus and pain, a topic that will be developed in a later section. It is also noteworthy that Chouard et al. (1981) suggested that low-level electrical stimulation at several sites on the head and near the external ear region might alter tinnitus perceptions by direct action on 'sensitive cutaneous fibers' rather than by electrical stimulation of the cochlea.

By suggesting parallels between tinnitus and pain and by invoking 'gate control theory', the tacit assumption is that central mechanisms are involved which filter and modulate aversive inputs through the delicate interplay between excitation and inhibition. In its classical representation, the proposed gating mechanism for pain is thought to reside in the spinal cord at the level of the substantia gelatinosa. In response to normal stimulation of fast conducting touch fibers on the skin (no-pain condition), it is hypothesized that the gating mechanism is closed; the gate is opened when slow conducting 'pain' fibers transmit high volume/intense sensory signals through somatosensory pathways. In tinnitus, the site of the gating mechanism is unspecified, but it is thought to be located centrally. In this context, an equally plausible alternative explanation holds that modifications to tinnitus perceptions by electrical stimulation at the periphery result from crossmodal interactions between auditory and somatosensory activity in extralemniscal pathways (Møller et al., 1992; Møller and Rollins, 2002). Both heuristics (gate control theory and the extralemniscal pathway hypothesis) offer the possibility that tinnitus can be modulated by means of crossmodal interactions.

1.1.3. *Modulation of tinnitus with oral–facial movements (jaw clenching)*

Lockwood et al. (1998) studied a group of individuals that could alter (increase or decrease) tinnitus loudness by oral–facial maneuvers (OFMs; jaw clenching). Using PET and a between group experimental design, two groups were scanned separately during OFMs, a tinnitus group and a normal control group without tinnitus or hearing loss, that also performed jaw clenching. Normal controls showed bilateral activation of sensorimotor cortex and supplemental motor area in response to jaw clenching. In two patients where OFMs *increased* tinnitus loudness (i.e., where tinnitus was localized to the right ear in one patient and in the left ear in the other), increases in cerebral blood flow were observed in sensorimotor cortex, primary auditory cortex in the left superior temporal gyrus and in a region near the medial geniculate nuclei. To separate changes in cerebral blood flow due to increases in tinnitus loudness, group subtractions were performed between PET results obtained during jaw clenching in controls and OFM in tinnitus patients. The group subtractions showed residual activation in the left thalamic region (left medial geniculate nucleus) in the tinnitus group. This was interpreted as indicating that the post subtraction increase in neural activity was due to the increase in tinnitus loudness. In two other patients where OFMs *decreased* tinnitus

[3] As a potential treatment option, low-level electrical stimulation has been applied to sites on the round window of the inner ear (e.g., Cazals et al., 1978; Aran and Cazals, 1981), at or around the external ear at the mastoid process, tragus, ear canal, etc. (e.g., Shulman et al., 1985; Lyttkens et al., 1986) and via cochlear or brainstem implants (e.g., Soussi and Otto, 1994; Ruckenstein et al., 2001; see Dauman, 2000 for a comprehensive review). However, in keeping with the topic of the present paper, discussion of tinnitus suppression by electrical stimulation will be limited to studies involving crossmodal somatosensory system interactions.

loudness, a decrease in cerebral blood flow was observed in the posterior and mid portion of the left middle temporal gyrus. Here, the subtraction procedure showed a region of reduced cerebral blood flow in the temporal lobe and hippocampus of the left hemisphere. The hypoactivity localized to the hippocampus has been used as evidence for limbic system linkage to OFM-related tinnitus activity. The authors emphasize that unilateral changes in neural activity in auditory cortical regions paralleled changes in the loudness of tinnitus in individuals who were able to alter loudness of their tinnitus by jaw clench. Based on these findings, it was argued that the unilateral nature of blood flow patterns suggests that tinnitus originated in the central auditory system and not in the cochlea. In those individuals with temporomandibular joint dysfunction and tinnitus, approximately one third can modulate their tinnitus with oral–facial movements (Rubinstein et al., 1990; Rubinstein, 1993; also see Levine, 1999b).

1.1.4. Cutaneous-evoked tinnitus

A previously unrecognized, or at least unreported phenomenon, is one in which individuals can evoke tinnitus directly by cutaneous stimulation of skin on the hand region in the periphery (Cacace et al., 1999a,b). This phenomenon was reported in two adult human subjects in which cutaneous-evoked tinnitus occurred following neurosurgery for space occupying lesions at the base of the skull and posterior craniofossa. In these individuals, hearing and vestibular functions were lost completely and acutely in one ear (unilateral deafferentation) and facial nerve paralysis (unilateral de-efferentation) was present either immediately following neurosurgery or had occurred as a delayed-onset event. In one individual, tonal tinnitus was elicited and could be reliably measured by adaptive psychophysical tests by stroking a region on the backside of one hand. In another individual, a transient tinnitus could be elicited by touching the fingertip regions on one hand. In this case, magnitude estimation was used to estimate loudness. Either alone or in combination, psychophysical correlates and *f*MRI data were used to validate these perceptions. In this latter individual, when the trigger zones of the fingertips on the right hand were activated by a repetitive finger opposition tapping task (i.e., a condition which evoked tinnitus perceptions), areas of localized brain activity were observed in the contralateral temporal–parietal junction, i.e., in the superior portion of the Sylvian fissure and the inferior aspect of the parietal operculum. Activation was also noted in the ipsilateral caudate and a small area in the contralateral orbital–frontal cortex. In addition, finger tapping produced activations in the contralateral motor, pre-motor areas and pre-Rolandic sulcus. A control finger opposition tapping task using the opposite (left) hand also elicited activity in the contralateral motor cortex. Activation of motor cortex was seen in the Rolandic sulcus and extended to pre-motor cortex. Significantly, there were no foci of activation in contralateral auditory areas (superior temporal and/or inferior parietal regions).

Thus, in an individual with cutaneous-evoked tinnitus, repetitive tapping of the fingertip region elicited activation in brain regions associated with motor movement of the fingers in addition to activations of the auditory cortex. In contrast, finger tapping using the opposite hand, which did not induce tinnitus, only produced activation in motor cortex. These functional imaging data dissociated tinnitus from non-tinnitus conditions, demonstrating both the specificity of the task and the modality associated with the phantom auditory perception.

1.1.5. Somatomotor-evoked tinnitus

Cullington (2001) reported a case of a 78-year-old male with moderate to profound bilateral hearing loss who experienced tinnitus evoked by 'finger movement'. This case is distinguished from cutaneous-evoked tinnitus because it involved motor movement of a digit and was not induced by an acute or abrupt unilateral deafferentation at the periphery. Moreover, the age of the individual studied was also of interest. This aspect of the investigation suggests that damage to the auditory periphery can produce cortical reorganization even in the elderly.

1.1.6. Craniocervical modulation of tinnitus

Levine (1999a) reported that craniocervical manipulations, using cephalo-cervical isometric maneuvers or extremity contractions, could modulate tinnitus perceptions in a clinical population of individuals *without* overt otologic pathology and developed a working model (Levine, 1999b) to facilitate an understanding of these effects. Until recently, somatic interactions fell under the rubric of 'anecdotal reports'; the attributes associated with these maneuvers were never thoroughly explored and their prevalence was not known. In fact, it is reasonable to suggest that these types of interactions have been known for some time but have been ignored/dismissed by clinicians for unknown reasons.

Based on assessment of 70 consecutive tinnitus patients, Levine (2000) found that regardless of etiology or underlying audiometric data, 71% could modify their tinnitus with a variety of cephalo-cervical isometric maneuvers or extremity contractions. These maneuvers had the effect of changing the loudness (42% increased, 17% decreased), pitch (10% increased, 17% decreased) and location (6%). He also noted that head/neck versus isometric maneuvers of the extremities were much more

likely to result in detectable perceptual modifications by patients; decreased loudness was more likely for monaural than binaural tinnitus. It was suggested that the unilateral nature of somatic tinnitus might occur by modulation of a central neural pathway from medullary somatosensory nuclei to ipsilateral dorsal cochlear nucleus with no involvement from the auditory periphery. Levine and Abel (2001) studied 44 non-clinical patients (24 with some noticeable tinnitus; 20 individuals without tinnitus), with normal or near normal hearing that could modulate a background tinnitus or induce tinnitus by methods described above. They found that with at least one of the isometric cephalo-cervical or extremity contraction procedures, 79% of the tinnitus group could modulate their tinnitus and that 40% of individuals without tinnitus were able to induce tinnitus. Levine and Cheng (2002) extended their observations to profoundly deaf subjects, where roughly similar results have emerged. These additional studies are consistent with the view that the somatic modulation is a fundamental attribute of tinnitus not due to specific otologic pathology (Levine, 1999a).

1.1.7. Trigeminal interactions

Other evidence is emerging from animal experiments which demonstrates direct sensory innervation from ophthalmic and mandibular divisions of the trigeminal ganglion to the vasculature supply of the cochlear, to structures within the middle ear and to specific sites within cochlear nucleus and superior olivary complex, where auditory and somatosensory systems could interact (e.g., Itoh et al., 1987; Vass et al., 1997, 1998a,b, 2001; Shore et al., 2000; Haenggeli et al., 2002). Vass and colleagues suggest that trigeminal nerve/cochlear blood vessel interactions may contribute to a range of related symptoms including fluctuating hearing loss, increased sensitivity to noise, phonophobia, tinnitus, prodromal auditory symptoms associated with basilar artery migraine, as well as other associations linked to endolymphatic hydrops (Vass et al., 1997, 1998b, 2001). Presumably, it is the neuroanatomical projections from trigeminal ganglion to auditory brainstem areas that may contribute to modulating certain forms of tinnitus.

Recent physiologic investigations using guinea pig suggest that electrical stimulation to the trigeminal ganglion provides excitatory input to the cochlear and primary auditory nerve fibers (Shore and Lu, 2002). This excitatory input also results in an asymmetric increase in metabolic activity in afferent auditory pathways with greater effects occurring in the cochlear nucleus ipsilateral to the trigeminal ganglion stimulated (El-Kashlan and Shore, 2002). Additionally, when the fluorescent tracer Fast Blue is injected into the 'granular cell domain' of dorsal cochlear nucleus in rats, retrograde transport of labeling was found in cells of trigeminal nucleus complex (ipsilateral to the injection site) and in vestibular, gracile, cuneate and pontine nuclei (Haenggeli et al., 2002). In cat, proprioceptive input from pinna movement can also activate areas in dorsal cochlear nucleus (Young et al., 1995; Kanold and Young, 2001). This observation is thought to represent part of a complex multimodal network of auditory, somatosensory, and visual neurons involved in localizing objects in space (e.g., Stein et al., 1976; Stein and Clamann, 1981; Hyde and Knudsen, 2001).

As neuroanatomical and neurophysiological relationships between trigeminal and auditory brainstem sites are being clarified, differences that exist within areas of cochlear nucleus between small laboratory animals (rat, guinea pig, cat), primates and humans are also highlighted. In small mammals, such as cat, somata of inhibitory neurons are concentrated in granular cell domains of dorsal cochlear nucleus. However, in primates, regions of cochlear nucleus that contain granular cells and cartwheel cell types (interneurons) are markedly reduced/depopulated in number, the presumption being that phylogenetic changes have influenced the location of these cell domains (Heiman-Patterson and Strominger, 1985; Moore et al., 1996). When further comparisons are made between primate and humans, available autopsy data suggest that humans lack a granular cell layer in the dorsal cochlear nucleus region (Heiman-Patterson and Strominger, 1985). It has been postulated that early in development, these cells either die off or migrate to the cerebellum. Other evidence cited by Levine (1999b, p. 360) suggests that granular and molecular cell layers in dorsal cochlear nucleus might be vestigial in adult humans (i.e., Moore and Osen, 1979; Moore, 1987; Adams, 1986). Thus, whereas trigeminal projections to auditory brainstem structures have relevance to modulating or generating 'somatic' forms of tinnitus, actual circuits between small laboratory animals (rodents), cats, primates and humans may differ.

In addition to well-established neuroanatomical interactions known to occur between auditory and somatosensory systems throughout the neuroaxis (Wepsic, 1966; Aikin et al., 1981; also see Møller et al., 1992 and Cacace et al., 1999b for reviews), association areas in frontal, parietal and temporal cortex are known to be responsive to a combination of auditory, somatosensory and/or visual stimuli. In several mammalian species (guinea pigs and primates), polysensory areas in the cortex are located in or near the superior temporal sulcus (Benevento et al., 1977; Bruce et al., 1981; Pandya et al., 1988; Hikosaka et al., 1988), dorsal rostral areas of secondary auditory cortex (Wallace et al., 2000) and caudal medial areas of secondary auditory cortex (Schroeder et al., 2001). Other brain sites such as pre-

frontal cortex, hippocampus and amygdala, which either integrate or deal with highly processed multimodal information, may also contribute to these effects.

1.1.8. Expanding the neuromatrix of tinnitus: crossmodal interactions

The observation that tinnitus can be evoked or modulated by muscle activity, by somatosensory stimulation, and/or by somatomotor activation provides strong evidence for the multimodal nature of the tinnitus experience. To date, it has been shown that static change in eye position (Whittaker, 1982a,b, 1983; House, 1982; Wall et al., 1987; Cacace et al., 1994b; Giraud et al., 1999; Caraceni et al., 1999; Herraiz et al., 1999; Lockwood et al., 2001; Biggs and Ramsden, 2002), cutaneous stimulation of the hand or fingertip region (Cacace et al., 1999a), movement of a digit (Cullington, 2001), electrical stimulation of the median nerve and hand region (Kaada et al., 1989; Rahko and Kotti, 1997; Møller et al., 1992), craniocervical manipulations and extremity contractions (Levine, 1999a,b, 2000; Levine and Abel, 2001; Levine and Cheng, 2002) and OFMs (Lockwood et al., 1998) can cause or alter the perception of tinnitus in many individuals. Indeed, none of the available hypotheses, models, or theories that attempt to account for tinnitus as a modality specific anomaly (e.g., Sasaki et al., 1980; Kemp, 1981; Salvi and Ahroon, 1983; Jastreboff, 1990; Hazell and Jastreboff, 1990; Jastreboff and Hazell, 1993; Lenartz et al., 1993; Zenner and Ernst, 1993; Møller, 1984; Hazell, 1995) emphasize the notion that tinnitus could result from, or could be modified by crossmodal neural interactions occurring somewhere in the brainstem or cortex to the extent that this concept deserves. In this regard, these important and highly relevant contributions noted above serve as a reference point from which to expand our current understanding of the many different forms of tinnitus that may exist. Consequently, this also means that there is a need to reformulate the concept of crossmodal integration in sensory and motor systems (Stein and Meredith, 1993).

Several authors have discussed crossmodal plasticity, either in the context of tinnitus or from a more general biological perspective (Cacace et al., 1994a,b, 1999b; Salvi et al., 2000; Shimojo and Shams, 2001). When considering the more general biological viewpoint, a growing number of studies have focused on auditory, visual and somatosensory systems whereby abnormal or novel aspects of crossmodal information processing have been reported. Below, an expanded and updated review of this topic considers advancements from basic science experiments and relevant clinical investigations. Neuroplasticity (reorganization or re-mapping) appears to be a normal consequence of the brain's response to injury (Chen et al., 2002). However, it is not always possible to predict a priori whether injury-induced plasticity will be compensatory or pathologic. Plastic changes may be limited to modality specific brain areas and/or crossmodal effects may be involved. In this regard, neuroplasticity can be construed as a 'dual-edged sword' (Mattson, 1991).

1.2. Crossmodal neuroplasticity

1.2.1. Compensatory or pathologic changes

Symptoms associated with neuroplasticity include hyperactivity, hypersensitivity, spread of activity (i.e., expansion of subcortical and/or cortical receptive fields into deafferentated modality specific or multimodal areas) and compensatory adjustments (Harrison et al., 1996; Rajan and Irvine, 1996; Grafman and Litvan, 1999; Grafman, 2000; Salvi et al., 2000; Møller, 2001). Modality specific and crossmodal plasticity have been the source of intense investigation (see Sur and Leamey, 2001; Bavelier and Neville, 2002; Calford, 2002, for reviews). It is generally acknowledged that neuroplasticity is most robust in early stages of development, but continues throughout the life span. In the neonatal period, evidence that functional crossmodal circuits can be induced experimentally between central visual and central auditory areas has been used as evidence that one sensory system may be substituted for another (e.g., Frost, 1990; Sur et al., 1990; Rauschecker and Korte, 1993; Rauschecker, 1995, 1997). Recent experimental studies in ferret have shown that when retinal projections are redirected to auditory cortex in early life by novel experimental lesions (i.e., removal of retinal targets by partial ablation of the lateral geniculate nucleus or superior colliculus, and removal of auditory afferents by deafferentation of medial geniculate nucleus) reactive sprouting of retinal axons into medial geniculate nucleus can occur (Angelucci et al., 1998). When combined with behavioral data, the striking observation that higher order architectonic features found in normal visual cortex (visual space maps, orientation modules, etc.) can emerge in the rewired auditory cortex (Sharma et al., 2000) indicates that these new synapses can mediate visual processing and influence behavior (von Melchner et al., 2000). From these and other related studies (i.e., Frost et al., 2000), it is apparent that patterns of extrinsic driven activity from thalamocortical afferents play a significant role in the functional and structural alterations observed during neocortical development and those intrinsic mechanisms, such as differential genetic regulation, are *not* solely responsible for these outcomes. Merzenich (2000) commented: 'The studies by Sur and collaborators present a direct challenge to the increasing number of claims that the development of visual orientation columns and topography of the VI region is not dependent on input activity.

From the new papers, we can see that retinal inputs into the auditory thalamus are sufficient to account for the VI pattern of development. It would be a peculiar world indeed if this remarkable emergence of VI structure in AI cortex does not also underlie the development of visual cortex under normal conditions.' Furthermore, these findings support the idea that 'different cortical areas are not restricted in terms of the types of computations they can carry out ... it appears that percepts are determined by the type of cortical processing that sensory inputs receive, ... rather than by the specific piece of neural tissue that does the analysis' (Swindale, 2000). Clearly, these aforementioned crossmodal phenomena have important implications for brain development, neuroplasticity, and evolution (Pallas, 2001; Kahn and Krubitzer, 2002).

In developmentally based neurodegenerative conditions, exquisite documentation is available showing that anomalous crossmodal circuits can occur naturally. An example of this phenomenon is found in the blind mole rat, *Spalax ehrenbergi*. In this micro-ophthalmic mammal, striate cortex of the visual system changes its mode of input and becomes vigorously activated by acoustic stimulation (Heil et al., 1991; Cooper et al., 1993; Doron and Wollberg, 1994). It is hypothesized that during development, crossmodal plasticity occurs when retinofugal projections, which normally project to the dorsal lateral geniculate nucleus, degenerate and subsequently become occupied by projections from the inferior colliculus. Likewise, in congenitally blind mice and in short tailed opossum, *Monodelphis domestica*, enucleated binocularly early in life, cortical areas normally involved in visual processing can completely change their mode of input and become 'captured' by auditory and somatosensory systems (Asanuma and Stanfield, 1990; Kahn and Krubitzer, 2002). Even more remarkable is the finding that a new cortical area could emerge as a result of early enucleation (Kahn and Krubitzer, 2002). In cats deafened bilaterally in the first postnatal week, Rebillard et al. (1977) showed that electric field potentials evoked by flashes of light could be recorded in the primary auditory cortex. When the same experiment was performed at 2 months of age or with monaural cochleotomy, visual responses could not be recorded in the primary auditory cortex. However, in congenitally deaf cats, crossmodal reorganization does not occur at least in the AI field (Kral et al., 2002). Additionally, when fetal tissue from visual cortex is transplanted into parietal (somatosensory) cortex in early life, this primary visual tissue can develop functional and cytoarchitectural features of the somatosensory cortex (Schlaggar and O'Leary, 1991). Based on extensive background knowledge derived from innovative animal experiments, the ability to extend these observations to humans is being aided by functional imaging technology and other contemporary investigative techniques.

In congenitally blind adult humans or in individuals with blindness of early onset, data suggest that primary visual cortex can be co-activated by somatosensory and auditory systems by tasks involving sensory discriminations (Kujala et al., 1995; Sadato et al., 1996; Cohen et al., 1997; see Kujala et al., 2000 for review). When there is a shift in function of the primary visual cortex, such that tactile discrimination or Braille reading is processed in this area, there also appears to be an age dependence to this effect (Sadato et al., 2002). Crossmodal plasticity can be demonstrated before 16 years of age but is suppressed after this time. Interestingly, crossmodal auditory–somatosensory interactions reported by Møller and Rollins (2002) follow a similar age dependence.

By transiently inducing current flow in specific brain areas and temporarily exciting or inhibiting electric activity, transcranial magnetic stimulation (TMS) has been used as a non-invasive tool for studying brain function in vivo. In experiments where TMS is applied to the occipital cortex when blind individuals are reading Braille, distortions and omissions of letters frequently can occur (Cohen et al., 1997). In contrast, when similar occipital stimulation is applied during tactile tasks in normal sighted individuals, no significant performance decrements were evident. The authors interpret these findings to suggest that blindness at an early age can cause visual cortex to be recruited for processing somatosensory input. The implication is that somatosensory information is being encoded by primary visual areas; a view that is concordant with functional imaging studies in which primary visual cortex can be activated by Braille reading and other tactile discrimination tasks in individuals blind from an early age. In a study that is particularly relevant to the phenomenon of cutaneous-evoked tinnitus, Levänen et al. (1998) and Levänen and Hamdorf (2001) showed that vibrotactile stimuli applied to the palm and finger region of a congenitally deaf human adult activated both somatosensory and auditory cortical areas. These authors speculate that human cortical areas normally subserving hearing can change its typical mode of input and be transformed/substituted to process vibrotactile information.

The functional consequences of crossmodal plasticity take on greater significance when considered in the context of remediating sensory disorders early in life. When PET was used to study *prelingually* deaf children (mean age 6 years, range 2.2–20.3 years) selected for cochlear implantation, analysis of group data showed a positive correlation ($r = 0.81$, $P < 0.005$) between performance on speech perception tests after cochlear implantation and the degree of glucose utilization measured prior to

implantation. Poor performance on speech tasks was associated with hypometabolic activity in the primary auditory cortex and in auditory association areas of both hemispheres (Lee et al., 2000). Lee et al. speculated that if hypometabolism in auditory cortex was restored by input from another sensory modality prior to cochlear implantation, such as visual activity associated with hand, body, face or lip motion (i.e., through signed language or lip reading; Nishimura et al., 1999 and Calvert et al., 1997), then speech perception through the auditory channel could be limited and overall success of the implant would be compromised. The hypometabolic glucose utilization hypothesis of central auditory structures secondary to early onset deafness is supported by the work of Antonelli et al. (2002). However, these authors showed that hypometabolism in inferior colliculus of fetal sheep deafened by gentamicin could be restored to levels associated with normal hearing controls by electrical stimulation from a cochlear implant, if stimulation occurred early in life (Antonelli et al., 2002). In contrast to findings from Lee et al. (2000) and Antonelli et al. (2002), PET results in older subjects with deafness of early onset (mean 26.3 years, range 18–37 years), showed *higher* glucose metabolism in primary and association cortex compared to normal hearing subjects (Catalán-Ahumada et al., 1993). Similar effects have also been found in the visual cortex in adults with early onset blindness (Veraart et al., 1990). While data on this topic are limited, it appears that in cases of sensory deprivation, including deafness and blindness, differences in glucose utilization and potential restoration of cortical function may be age and experience dependent.

Areas in the temporal lobe in or near the superior temporal sulcus appear to be important for processes associated with social communication, including motion perception of eyes, mouth, hands and body (Allison et al., 2000; Grossman and Blake, 2002; Bernstein et al., 2002). Using PET in the case of a deaf adult proficient in visual communication, Nishimura et al. (1999) reported that secondary auditory cortex could be activated by signed language. In a group of deaf native signers studied with PET, Petitto et al. (2000) found that secondary auditory cortex and the surrounding superior temporal regions were activated bilaterally while perceiving single signs (American Sign Language) and nonsense signs composed of hand movements. These authors speculate that the auditory cortex within the superior temporal gyrus including the planum temporale '... may entail polymodal neural tissue that has evolved unique sensitivity to aspects of the patterning of natural language (p. 13961)'. Other studies using *f*MRI show that early-deafened humans exhibit high activation in primary auditory cortex and in Brodman's area (right > left hemisphere) in response to *visual motion* stimuli (Finney et al., 2001). With similar imaging methodology, Bavelier et al. (2001) compared visual motion perception in individuals with early onset deafness and early exposure of sign language, to hearing controls and hearing signers. In contrast to the hearing controls and hearing signers, when deaf signers attended to different patterns of moving flow fields, cortical activation was observed in polysensory areas of the posterior superior temporal sulcus and in posterior parietal cortex. Moreover, in congenitally deaf individuals proficient in British sign language, MacSweeney et al. (2002) showed with *f*MRI, that specific regions in the temporal lobe of the left hemisphere could be recruited for processing visual information. Taken together, these findings suggest that both non-linguistic and linguistic *visual* input can activate auditory areas in individuals that were deaf from an early age and may form the basis of crossmodal interactions in these unique groups. Interestingly, stimuli involving perception of *auditory motion* have been shown to activate *visual cortex* (right -> left hemisphere) of the blind (Weeks et al., 2000).

In *postlingually* deafened adults studied with PET after cochlear implantation, stimulus specific engagement and growth of activation occurred in auditory and visual cortical areas during auditory activation (Giraud et al., 2000, 2001). These authors speculate that the progressive activation of visual cortex in response to sound after cochlear implantation parallels an improvement in sound discrimination. Although counterintuitive to the prevailing view that the visual modality would compensate for deterioration of hearing, Giraud and colleagues suggest that after implantation, the brain's response becomes more highly tuned to meaningful sounds and that this process is associated with improvement in lipreading proficiency. Clearly, this fascinating and evolving area of crossmodal plasticity in cochlear implant recipients raises many important issues that require further investigation (Zatorre, 2001).

1.2.2. Crossmodal phantom perceptions

Other examples of abnormal crossmodal processing have been reported in which *acoustic* stimulation can evoke phantom perceptions in the *visual* modality. These crossmodal phenomena fall under the rubric of 'sound-evoked phosphenes' or 'sound-induced photisms'. Whereas phosphenes are defined as self-generated visual perceptions in the absence of visible/luminous stimuli, in individuals with optic nerve disease, phosphenes can also be induced by acoustic stimulation (Lessell and Cohen, 1979; Page et al., 1982). Sound-evoked phosphenes reportedly occur secondary to *unilateral* visual loss and have been associated with other abnormalities in the visual system, such as optic disk swelling and visual field defects. In partial contrast, the

term 'photism' (considered a form of synesthesia and discussed in more detail below) is used to describe the evocation of visual images or color sensations induced by acoustic, olfactory, gustatory or tactile stimuli. Jacobs et al. (1981) describe nine patients who experienced 'photisms' induced by sound; all individuals had visual loss due to lesions of the optic nerve or optic chiasm. The photisms ranged from simple flashes of white light to complicated colorful events likened to a flame, a petal of oscillating lines, a kaleidoscope, or an ameba, and these phantom experiences always appeared in a defective area of the visual field demonstrated by planimetry. According to the authors, acoustic stimuli that evoke these phantom perceptions were those usually encountered in activities of daily life; ranging in intensity from soft to loud and always seemed to be heard by the ear ipsilateral to the eye in which the photism was seen. Moreover, in individuals without overt sensory or neurologic deficits, crossmodal phantom perceptions are typically classified under the rubric of synesthesia (Cytowic, 2002). Synesthetes can be described as those individuals in whom sensory stimulation in one modality can lead to concurrent sensory perceptual experiences in another unstimulated sensory modality[4]. An example is where words in the auditory modality can induce consistent color perceptions in the visual modality, a phenomena known as color–word synesthesia. Using PET in synesthetes vs. controls, Paulesu et al. (1995) found that words activated areas in posterior inferior temporal cortex, in the parietal–occipital junction (i.e., visual association areas) and in language areas in the perisylvian area. No significant activity was detected in early stages of visual information processing (V1, V2 or V4). Using *f*MRI, Nunn et al. (2002) also showed that in individuals with color–word synesthesia, words activated visual association cortex and color-selective brain regions, V4 and V8. In non-synesthetic controls, neither V4 nor V8 was activated to words or to explicit instructions to use imagery. The authors argued 'the synesthetic color experience was closer to that of a true color percept than to color imagery, resembling hallucinations of color in patients with Charles Bonnet syndrome'. One important difference between activations observed in synesthetes experiencing color in response to words versus stimulation induced by specific colored visual stimuli, lies in the absence of primary visual cortex activation in the former case. However, an exception to this hypothesis was reported in a single case report by Aleman et al. (2001) in which primary visual cortex was reportedly activated.

[4] A sensory stimulus that triggers a crossmodal synesthetic event has been termed the 'inducer'; the perceptual attribute induced in another unstimulated sensory modality has been termed the 'concurrent' (Grossenbacher and Lovelace, 2001).

Phantom perceptions like synesthesia are thought to arise early in life and persist throughout adulthood (Grossenbacher and Lovelace, 2001; Rich and Mattingley, 2002). However, if synesthetic-like phenomena are acquired later in life, as a result of brain injury or sensory deafferentation (i.e., Jacobs et al., 1981; Vike et al., 1984; Armel and Ramachandran, 1999), then it is reasonable to suggest that these unique perceptual experiences are more consistent with crossmodal plasticity than with synesthesia, vis-à-vis, Cytowic (2002). Consequently, it would not be a leap of logic to suggest that auditory–visual synesthetic perceptions, such as those described above, share certain phenomenological features and possible mechanisms in common with somatic, cutaneous and gaze-evoked tinnitus. Indeed, similarities are found in both the nature and quality of the perceptual events experienced. In these examples, tinnitus and synesthesia are involuntary perceptual experiences that are induced automatically. Inducers are unidirectional and the inducer and concurrent typically belong to separate sensory modalities. After induction, the concurrent experience is often characterized by simple sensory events (such as the evocation of color, tones, noises, buzzing, etc.) rather than by highly integrated percepts like an image of a face or the organized sequence of a musical melody. Accordingly, the limited range of concurrent phenomena experienced may indicate particular stages of cortical processing activated (Grossenbacher and Lovelace, 2001). Moreover, from a theoretical orientation, disinhibition of feedback connections from a polysensory convergence area within an inducer/concurrent pathway has been suggested as a mechanism for synesthesia (Grossenbacher, 1997). Levine (1999a,b) speculated that reduced auditory nerve input to the CNS leads to disinhibition in dorsal cochlear nucleus, resulting in increased spontaneous activity which might be perceived as tinnitus. Lockwood et al. (2001) also put forth the hypothesis that gaze-evoked tinnitus could result from failure of crossmodal inhibition.

The two previous sections serve to illustrate that crossmodal plasticity occurs under many different circumstances. Likewise, if pathologic forms of crossmodal plasticity, such as tinnitus modulated by eye gaze, are more common than previously anticipated (Coad et al., 2001) and if cranio-cervical modulations represent a 'fundamental' property of certain forms of tinnitus (Levine, 1999a), then in order to provide a more comprehensive account of the tinnitus experience, these and other previously underrecognized phenomena need to be incorporated into contemporary psychophysiological models. Indeed, the manifestation and multimodal nature of the tinnitus experience may also help to explain why, in some individuals, tinnitus can be so resistant to various forms of treatment (Lockwood et al., 2001).

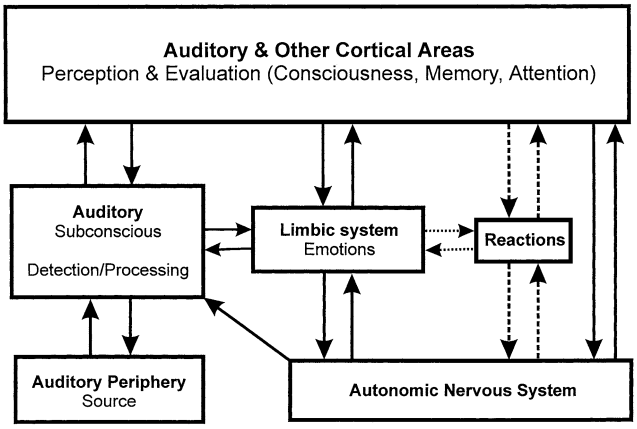

Fig. 1. Block diagram of the neurophysiological model of tinnitus. Adapted from Jastreboff (1999) and reproduced with permission of the author.

1.3. Expanding the biologic basis of tinnitus

1.3.1. Models

Over the last decade, a generalized framework has evolved for conceptualizing tinnitus in the context of known neuroanatomic relationships and psychophysiologic reactions, termed 'the neurophysiological model' (Jastreboff, 1990, 1999, 2000; Hazell and Jastreboff, 1990; Jastreboff and Hazell, 1993)[5]. Whereas more specific mechanistic models are available for consideration (see Eggermont, 2000 for a review), the 'neurophysiological model' is relevant to the present discussion because it is based on contemporary principles of CNS function and is sufficiently broad in scope to accommodate new information as it develops. As shown in the box diagram (Fig. 1), the model encompasses a network of interconnected serial and parallel pathways including feedforward (bottom up) and feedback (top down) connections, containing sensory, limbic and autonomic nervous system components. Included therein is a neural generator mechanism, central mechanisms mediating neural pattern detection, and an affect elaboration network, which is reactive to the phantom percept (Levine, 1994). It is hypothesized that fear conditioning plays a major role in sustaining the tinnitus perception. This concept is appealing because fear conditioning has strong underpinnings in psychological theory and is linked to a wide range of affective traits/conditions known to have an effect on individuals with tinnitus, including anxiety disorders and phobias. Based on the neurophysiological model, fear conditioning is initiated when an abnormal pattern of neural activity (tinnitus) is detected and consciously interpreted as a harbinger of a serious medical condition (e.g., a brain tumor) or as a constituent precursor of a potentially distressful event (i.e., a sign of progressive hearing loss that may lead to total deafness, etc.) (Jastreboff, 2000). This conceptualization is consistent with prevailing views that fear learning is a product of evolution, which serves as a defense mechanism to promote survival of the organism from impending or future threats (Fanselow, 1994). It has been emphasized, 'Emotions evolved not as conscious feelings, linguistically differentiated or otherwise, but as brain states and bodily responses' (LeDoux, 1996). When viewed in terms of conditioning theory, the neurophysiological model considers tinnitus as the *stimulus* and the aversive reaction to the stimulus as a *negative reinforcer*. Although exact temporal relationships between stimulus and reinforcer are not specified, pairing the phantom stimulus with negative reactions can engage limbic[6] and associated autonomic nervous system components. Consequently, if left untreated, tinnitus can become pervasive and evolve into a life altering experience, disturbing sleep, disrupting concentration and potentially contributing to depression (e.g., Simpson and Davies, 1999; Erlandsson, 2000; McKenna, 2000). At the extreme, there have been reports linking tinnitus to suicide, although available data are not sufficiently compelling to form convincing cause and effect relationships, suggesting that other intervening factors are also involved (Jacobson and McCaslin,

[5] The neurophysiological model also provides theoretical justification for non-invasive treatment options; however, this aspect of the model is not the focus of this report and will not receive further discussion.

[6] Whereas the term 'limbic system' is thought to be synonymous with brain areas or circuits that subserve emotion, it also represents a topic that does not have universal acceptance in contemporary views of neuroscience. Therefore, applying this controversial term loosely in the area of tinnitus research may be counterproductive. For example, LeDoux (2000) has elaborated on several issues that limit the broad designation implied by this term: (1) there are no widely accepted criteria for deciding what *is* and what is *not* a limbic area, and (2) limbic system theory does not explain how the brain 'makes' emotions. It points to broad forebrain areas located roughly between neocortex and hypothalamus. Horel (1988) has also expressed reservations with this term and points to the fact that it has created confusion, because of its 'continual state of evolution'. Indeed, this state of affairs can be appreciated by considering this topic from a broader historical perspective (see Mega et al., 1997, for a phylogenetic/anatomic/clinical review). Consequently, as more and more anatomical areas were added arbitrarily to the limbic system by different investigators, justification for this amalgam has become questionable and remains open to discussion. Indeed, several prominent neuroscientists have recommended eliminating the term entirely (e.g., Brodal, 1982; Blessing, 1997). Without elaboration, the downside of using a generalized and vaguely defined neuroanatomical construct is directly related to the limitations it imposes on accepting or rejecting specific hypotheses, models or theories. The rationale given for the survival of the term 'limbic system' was articulated by LeDoux (2000): 'This in part is attributable to the fact that both the anatomical concept and the emotional function it was thought to mediate were so vaguely defined as to be irrefutable'. Thus, the appeal made herein is for individuals involved in tinnitus research to specify neuroanatomical relationships during tinnitus processing rather than to invoke the general term 'limbic system' and assume it conveys information that is part of the common language.

2001). The amygdala is thought to be an essential link in the expression of emotion and motivational responses by processing inputs from various sensory modalities (auditory, somatosensory, visual, olfactory, gustatory) and directing output to specific pathways involved in regulating body homeostasis and behavior (hypothalamus, brainstem, striatum, endocrine system, basal forebrain, trigeminal and facial motor nuclei, etc.). Indeed, designating the amygdala as the 'sensory gateway to the emotions' (Aggleton and Mishkin, 1986) is well supported by clinical studies and experimental work in animals[7].

Contemporary neuroanatomical studies also show clear linkage between auditory projections from both thalamus and cortex to the amygdala, which are essential for fear conditioning to occur (Herzog and Van Hoesen, 1976; Turner et al., 1980; Aggleton et al., 1980; Van Hoesen, 1981; Pandya and Yeterian, 1985; Ledoux et al., 1986; Romanski and LeDoux, 1992; Romanski et al., 1993; McCabe et al., 1993; Campeau and Davis, 1995). Highly processed polysensory inputs also have access to lateral and basal areas of the amygdala through prefrontal cortex and the perirhinal and entorhinal cortex of the hippocampus. When complex stimulus representations exist, such as those associated with arousal and attention to biologically relevant stimuli, it has been suggested that these representations have a greater propensity to be mediated by cortico-amygdalar interactions than by thalamo-amygdalar pathways (Aggleton and Mishkin, 1986; Kapp et al., 1992; Gallagher and Chiba, 1996; McDonald, 1998; LeDoux, 2000).

Whereas fear conditioning has become a powerful tool for studying processes involved in learning and memory, what makes this approach both appealing and important, is that neuroanatomical input and output pathways are relatively well known. In the neuroscience literature, fear conditioning is based on classical or *Pavlovian* associations, whereby the response to an unconditioned stimulus (US), such as a noxious shock, can activate intrinsic system responses that alter body homeostasis and result in a range of overt behaviors (freezing, arousal, startle, etc.) (Davis, 1997). When the US is paired with a neutral stimulus like a tone, light, or odor and if conditioning is successful, then the neutral stimulus acquires the ability to elicit these defensive responses, thereby becoming a conditioned stimulus (CS). Work focusing on cellular and molecular mechanisms underlying memory consolidation, storage, and plasticity links fear conditioning to the medial and lateral nuclei of the amygdala as a likely site of US–CS convergence (Schafe et al., 2001; Maren, 2001). In this context, '... the fear system has been treated as a set of processing circuits that detect and respond to danger, rather than as a mechanism through which subjective states of fear are experienced. With this approach, fear is operationalized, or made experimentally tractable.' (LeDoux, 2000). The fear conditioning paradigm also allows for questions to be asked about how the brain processes emotional information (i.e., detects and responds to danger) without necessarily solving the more vexing problem of how or where conscious feelings arise in the CNS (i.e., issues related to consciousness). Thus, from a theoretical vantage point, this paradigm is advantageous because it allows one to escape from the confines of the so-called 'mind–body problem', a long-standing philosophical debate/quagmire concerning independence of brain–body relationships. With respect to issues dealing with emotion and cognition, the classical view of mind–body independence has been effectively challenged (Damasio, 1994). In summary, it is reasonable to assume that conditioned fear induced by aversive stimuli is mediated in large part by transmission of information about the CS and US to the amygdala and that fear expression occurs though a cascade of reactions involving the lateral and central nucleus of this structure. As the principal output pathway of the fear system, the central nucleus sends projections to areas of the hypothalamus and brainstem that control specific behavioral, endocrine and autonomic nervous system responses (arousal, freezing, startle, facial expressions of fear; changes in respiration, blood pressure, electroencephalographic activity, etc.) (Davis, 1997; LeDoux, 2000; Maren, 2001).

1.3.2. *Linking tinnitus to the amygdala and other non-auditory brain areas: animal studies*

Involvement of certain brain areas associated with fear conditioning, fear learning and plasticity has direct relevance to non-auditory brain systems involved in tinnitus. Conceptually, unfamiliar sounds and discrepant or novel input tend to produce arousal, increase attention, and potentially initiate fear reactions in those individuals affected. Indeed, neurophysiological data suggest that when monkeys are presented with a range of biologically relevant auditory stimuli, neurons in the lateral nucleus of the amygdala respond to *unfamiliar* sounds, but not to familiar sounds associated, for example, with food reward (Ono and Nishijo, 1992). In the development of an animal model for tinnitus, activation sites in auditory and non-auditory brain areas have been elucidated by metabolic mapping techniques

[7] Although the discussion of tinnitus has focused on a particular aspect of emotional behavior, i.e., one that generates *negative* affect, it is recognized that an alternative goal-oriented system also exists. The alternative system is one which facilitates appetitive behavior and generates positive affect, such as enthusiasm and pride, etc. (Davidson and Irwin, 1999). Moreover, it is believed that these two systems can involve reciprocal and overlapping brain circuits, which include prefrontal cortex and amygdala.

such as ^{14}C-2-deoxyfluoro-D-glucose (2-DG), which infer neural activity or c-*fos* immunocytochemistry, which identifies gene expression associated with activated neurons (e.g., Sasaki et al., 1980; Wallhäusser-Franke et al., 1996; Wallhäusser-Franke, 1997). *Non*-auditory activation sites initially identified such as locus coeruleus, midbrain periaqueductal gray, and the lateral parabranchial nucleus, correlate with behavioral states associated with arousal, anxiety, stress and pain. Further insight into auditory and non-auditory brain areas involved in tinnitus use awake gerbils, *Meriones unguiculatus*, inducing agents such as salicylate or noise exposure and a combination of 2-DG and c-*fos* labeling as detection methods (Langner and Wallhäusser-Franke, 1999). Previous to this time, Jastreboff and Jastreboff (1996) showed that c-*fos* expression was related to salicylate-induced tinnitus activity and validated the presence of tinnitus by behavioral methods. Anatomical sites evaluated by Langner and Wallhäusser-Franke included dorsal cochlear nucleus, inferior colliculus, primary auditory cortex, anterior auditory cortical field, lateral, medial and central nuclei of the amygdala. Counts of immunoreactive c-*fos*-labeled neurons from various brainstem and cortical sites were used to establish a correlation matrix using data from their noise exposure experiment. Based on these data, modest pairwise correlations were found for c-*fos*-labeled cells between primary auditory cortex and the anterior auditory cortical field ($r = 0.70$). However, much higher correlations were found for c-*fos* activity between each auditory cortical area and specific parts of the amygdala. For example, strong pairwise positive correlations were found between primary auditory cortex and the lateral nucleus of the amygdala ($r = 0.99$); modest positive correlations were also found between anterior auditory cortical field and the central ($r = 0.92$) and medial ($r = 0.85$) nuclei of the amygdala. Principal component analysis and multidimensional scaling were used to explore the structural composition, dimensionality and spatial representation of these relationships. Based on principal component analysis, three factors explained 83% of the variance in their data. Component 1 accounted for 36% of the variance and involved primary auditory cortex, lateral and medial amygdala; component 2 accounted for 30% of the variance and involved anterior auditory cortical field, central and medial nuclei of the amygdala; and component 3 accounted for 17% of the variance and was limited to dorsal cochlear nucleus. The multidimensional scaling procedure showed a prominent role for c-*fos* expression in auditory cortex after noise exposure. Using a circumplex graphics plot to characterize these relationships, it was shown that auditory brainstem and cortical areas (dorsal cochlear nucleus, inferior colliculus, and anterior auditory field) group together along one side of an auditory cortex center point, whereas medial, lateral and central amygdala nuclei group together on the other side. Accordingly, this spatial representation suggests that auditory cortex is interacting in a similar way with all observed auditory and non-auditory areas and may be the center of the observed tinnitus-related activity. The novel aspect of this study was the combination of contemporary neurobiological investigative techniques coupled with inferences derived from multivariate statistical analyses. The limitation of this study was that tinnitus was not independently confirmed by behavioral testing. Indeed, there is growing consensus emphasizing that the success and generalizability of any animal model will ultimately depend on validating the tinnitus perception by behavioral methodology, a line of investigation which is both complex and important (e.g., Jastreboff et al., 1988a,b; Jastreboff and Brennan, 1994; Jastreboff and Sasaki, 1994; Bauer et al., 1999; Bauer and Brozoski, 2001; Brozoski et al., 2002; Heffner and Harrington, 2002).

1.3.3. Corollaries to pain

In a rather contemporaneous manner, neuroanatomical frameworks proposed for understanding certain forms of pain have paralleled models used for gaining insight into tinnitus or vice versa (Melzack, 1990; Jastreboff, 1990). In theory, the 'neuromatrix for pain' (Melzack, 1990; 1999), was proposed as a way to understand continuously unwanted aversive sensations associated with loss of a body part (i.e., 'phantom limb pain'), a condition thought to arise following deafferentation-induced changes to a central neural representation of an underlying body schema[8]. In this formulation, pain processing is thought to include a network of neurons that respond to sensory stimulation while at the same time continuously generating a characteristic pattern of impulses that the body or part of the body is intact. Within the pain neuromatrix, three major processing circuits have been implicated: classical somatosensory pathways, neural pathways through brainstem to limbic system areas and parietal association areas. Partial validation of the pain neuromatrix has been aided by empirical evidence obtained from functional imaging studies (see Derbyshire, 2000 for a review). Because pain can be induced on a regular temporal basis by applying and removing various types of aversive stimuli to different body areas, including temperature (heat, cold), visceral, gastric, rectal, and esophageal distensions, and/or other manipulations including application of pain inducing substances (capsaicin, subcutaneous ascorbic acid injections, etc.), functional

[8] Sensations like phantom limb pain may be more complex, since they can occur in individuals with congenitally *absent* limbs (Brugger et al., 2000). This suggests that genetic and other factors may also be involved.

imaging techniques are well suited for determining those brain structures involved in processing the noxious or painful input. In a recent review of functional imaging studies associated with pain induced from various forms of aversive/noxious stimuli, Derbyshire (2000) showed consistent patterns of activation within a large and broadly distributed network of brain areas. Activated areas include thalamus, primary and secondary somatosensory cortices, midbrain region of the periaqueductal gray and the lenticular complex, as well as the insula, orbital frontal cortex, prefrontal cortex, motor and inferior parietal areas. Interestingly, the most consistently activated area across all studies was the anterior cingulate region of the brain.

Over the years, the analogy between tinnitus and pain has received increased attention (e.g., Aran and Cazals, 1981; Vernon and Meikle, 1985; Tonndorf, 1987; Møller, 1997, 1999, 2000; Vincey et al., 1999; Folmer et al., 2001). A common feature shared by tinnitus and pain is the belief that both conditions are often triggered by peripheral injury and result in plastic changes at more central locations in the nervous system (Meikle, 1995; Salvi et al., 2000; Møller, 2001). This conceptualization is consistent with the premise of gate control theory and recent theorizing by Wall (2000) that *central* mechanisms are critical for modulating and sustaining pain perceptions. Activation 'triggers' for tinnitus such as eye gaze, somatosensory stimulation, somatomotor events, etc., also have analogs in the pain literature (e.g., Wyant, 1979; Sola and Bonica, 1990; Alvarez and Rockwell, 2002). With respect to pain, the implication is that relationships exist between two different topographic areas on or in the body (a trigger and a target); or in the case of tinnitus, two different sensory modalities or sensorimotor systems. In myofacial pain syndromes for example, trigger points on the head and neck region can also be manifested as temporomandibular joint pain, tension headache, torticollis, eye symptoms, and tinnitus. Analogous to pulling the trigger of a gun, somatosensory stimulation like direct pressure or muscle contraction produces effects at another place in the body.

Moreover, studies of pain and tinnitus are following similar paths. This observation is particularly true with respect to contemporary functional imaging methodology used to gain insight into brain areas or pathways involved in processing aversive events. Take the work of Hsieh et al. (1995), in which a group of neuropathic pain sufferers were studied with PET. In this example, PET scans were obtained on two occasions: first when patients were experiencing continuous burning pain, as a result of a nerve injury to a body part (arm) and again after injecting the injury zone with a local anesthetic (lidocaine) to induce a pain free period. When the pain free image was subtracted from the pain present image, the difference image showed brain areas which were presumably involved in the pain processing network. Moreover, when compared to pain induced in normal volunteers by intramuscular injections in the arm, activity occurred in similar brain areas (frontal lobes, motor and sensory areas, anterior cingulate, hypothalamus, midbrain and cerebellum). Similarly, lidocaine has been used to temporarily deactivate tinnitus and functional imaging modalities have been applied to study brain areas involved in tinnitus processing under these conditions. The basic tenet is similar to the approach used by Hsieh et al. (1995), to perform functional imaging studies under conditions where tinnitus is present and tinnitus is absent after lidocaine administration. When possible, image subtraction is used as a means to gain insight into brain areas contributing to the tinnitus perception. Using PET and labeled ^{15}O-H_2O to map regional cerebral blood flow, Mirz et al. (1999) studied conditions of tinnitus suppression using narrow band acoustic masking, intravenous (i.v.) lidocaine and combined conditions of masking plus lidocaine administration. Based on image subtraction in the lidocaine condition, activation was localized to the right prefrontal (middle and superior) and right posterior (middle temporal and precuneous) gyri. Deactivations were observed in the left transverse temporal gyrus. However, interpretation of these activation patterns is tempered by the fact that statistical significance was not always obtained (see Reyes et al., 2002, for a more detailed discussion). Staffen et al. (1999) studied effects of lidocaine in a 55-year-old woman with severe bilateral disabling tinnitus and left-sided hearing loss using single photon emission computed tomography (SPECT) with xenon^{133} inhalation. In this case study, cerebral perfusion was measured in the presence of tinnitus and after tinnitus was suppressed by i.v. lidocaine. In the tinnitus present condition, there was slightly increased perfusion in right versus left hemisphere with a greater asymmetry in perfusion found in primary auditory cortex (right > left). In the lidocaine condition, an overall reduction in global perfusion was observed and the right/left asymmetry in primary auditory cortex disappeared. Rigorous statistical interrogation, however, was not performed and the authors emphasized they could not delineate a peripheral from a central effect of the medication. Melcher et al. (1999) used *f*MRI to study the effects of i.v. lidocaine on neural activity in the inferior colliculus in an individual with normal hearing sensitivity and tinnitus lateralized to one ear. Using a binaural masking paradigm, this study found that activity in the inferior colliculus was highly asymmetric prior to i.v. lidocaine injection, a pattern of results found in patients with lateralized tinnitus (Melcher et al., 2000). However, after lidocaine administration, the asymmetric activity tinnitus normalized. Over time,

the asymmetry increased approaching the initial baseline (tinnitus present) condition. These results imply that the method used for detecting lateralized tinnitus was sensitive to the effects of lidocaine. Andersson et al. (2000) reported a PET study using i.v. lidocaine in a middle-aged woman with bilateral intractable tinnitus and mild hearing loss. In conditions contrasting tinnitus versus tinnitus suppression with lidocaine, increased blood flow was found in primary and secondary auditory cortical areas; decreased blood flow was found in frontal, temporal and occipital areas. Reyes et al. (2002) used i.v. lidocaine in two groups of patients using labeled ^{15}O-H_2O and PET to map regional cerebral blood flow. These authors showed that the effect of lidocaine was not always predictable; either lidocaine administration had no effect on tinnitus, produced decreased loudness (expected result), or, in others, produced a paradoxical increase in loudness (unexpected result). In those individuals where lidocaine reduced tinnitus loudness, this effect was accompanied by a significant change in neural activity found only in auditory association cortex of the right hemisphere.

In retrospect, studies demonstrating effects of lidocaine on tinnitus have been limited to small sample sizes and in some instances based on experimental designs that were not optimal. Reyes et al. (2002) point out that none of the previous studies provided adequate controls for placebo effects or other non-tinnitus side effects of lidocaine, such as perioral numbness. Nevertheless, trends emerging from these endeavors suggest that several neuroimaging modalities (SPECT, PET and *f*MRI) are sensitive to short-term effects of i.v. lidocaine on tinnitus-related activity (i.e., decreased loudness or complete suppression of the tinnitus percept which correlated with decreased blood flow or a reduced blood oxygenation level dependent response). This information is encouraging because it suggests that with further refinements, functional imaging can play a role in monitoring various treatment options in a more objective manner. Moreover, there was a trend for unilateral right hemisphere involvement of the auditory association cortex. Reyes et al. (2002) argues that a unilateral activation pattern suggests a central generator site for tinnitus. Indeed, localizing tinnitus activity to auditory association cortex also suggests extralemniscal pathway involvement, which is consistent with other experimental data (e.g., Eggermont and Kenmochi, 1998; Giraud et al., 1999).

Another approach for studying relationships between tinnitus and pain compares and contrasts brain areas activated by aversive auditory and aversive somatosensory stimuli. In a PET study designed to study brain areas associated with different classes of aversive auditory stimuli that mimicked tinnitus, Mirz et al. (2000) found activation sites localized to prefrontal cortex and frontal lobe areas, parahippocampal and amygdaloid bodies, which were in addition to expected bilateral activations of the primary auditory cortex in response to the acoustic input. Whereas superior frontal, medial frontal gyri and inferior parietal lobe showed increased activation, *no* significant activations were found in cingulate gyrus. These data, albeit limited to a single study, suggest that brain areas associated with aversive auditory stimuli are in partial contrast to brain activation sites induced by aversive painful somatosensory stimuli. Blood et al. (1999) explored the relationships between musical consonance and dissonance and brain activation associated with these dichotomous inputs. In this study, musical dissonance was correlated with activation in right parahippocampal and precuneus regions. Whereas music may recruit neural mechanisms associated with pleasant or unpleasant emotional states, it appears that these responses also differ from those underlying auditory perceptual representations and those induced by fear.

1.3.4. Other potential relations between tinnitus and pain

An intriguing and alternative approach for understanding the complexity as well as mechanisms underlying different forms of pain posits that 'glial' activation is involved in creating and amplifying pain (Watkins et al., 2001). These authors suggest that other (unnamed) sensory phenomena may also be subsumed under this framework. It is speculated that tinnitus could easily be included therein. Arguments to support this notion are based on the observations that glia express characteristics in common with immune cells in that they respond to viruses, bacteria, sensory damage, etc., and can release 'proinflammatory cytokines'. In addition to a direct role in creating pathological pain, cytokines may also act as immune system modulators involved in neuroplasticity (e.g., Vikman et al., 2001). For example, in relation to pain perception in the somatosensory system, peripheral damage and secondary inflammatory reactions can contribute to so-called 'windup' and 'sensitization' effects, both phenomena being distinct forms of synaptic plasticity (Woolf, 1996). Windup represents a change in excitability of central neurons, whereas sensitization, in addition to representing increased neural responsiveness of novel inputs, can also contribute to changes in receptive field properties and reductions in threshold. The behavioral expression of this effect can be seen as an abnormally heightened sensitivity, which can potentially spread to uninjured sites and be associated with other pain-related processes such as hyperalgesia and allodynia. Whereas windup, *hyper*sensitivity, and receptive field expansion are often discussed in relation to pain (e.g., Woolf and Thompson, 1991; Coderre et al., 1993), these effects also have clear analogies to tinnitus (Møller, 1997; Mühlnickel et al., 1998). As

proposed by Sahley and Nodar (2001) and in conjunction with pain processes noted above (Woolf and Thompson, 1991), mechanisms associated with tinnitus might also occur as part of a cascade of reactions through an excitatory facilitation of glutamate on central *N*-methyl-D-aspartate receptors.

2. Summary and conclusions

Evidence from basic research and clinical studies shows that tinnitus can be evoked directly or modulated by inputs from somatosensory, somatomotor, and visual-motor systems in a proportion of individuals. Such crossmodal interactions have been demonstrated by static change in eye position (gaze), applying electrical stimulation to the median nerve and hand region, oral–facial maneuvers, cutaneous stimulation of the hand or finger regions, isometric cranio-cervical manipulations of the head, neck or extremities and finger movement. The validity of these observations is supported by functional imaging studies combined with psychophysics, detailed physical examinations and questionnaire-based assessments. Speculation that trigeminal activation of cochlear vasculature and/or neural interactions within specific brainstem auditory sites is also involved in tinnitus generation/modulation represents another area of keen interest and ongoing investigation.

Furthermore, gaze-evoked, somatosensory-evoked and somatomotor-evoked tinnitus are of particular value to auditory neuroscience research because they: (1) represent variants of continuous tinnitus whose mechanisms are incompletely understood, (2) can be considered examples of crossmodal plasticity (another poorly understood physiological property of the nervous system), (3) have potential to provide insight into the physiology of human auditory perceptions, which do not involve direct external input to the auditory receptor mechanism, and (4) provide a means, with contemporary functional imaging modalities, to localize tinnitus-related neural activity and identify processing networks in the CNS.

Increasing the knowledge base of phantom auditory perceptions, to include abnormal crossmodal information processing, clearly expands the biological basis of tinnitus in humans. Inclusion of this knowledge into contemporary psychophysiological models will help researchers and clinicians conceptualize tinnitus in a more comprehensive manner.

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