
The Role of the Parabrachial Nucleus in the Natural History of Tinnitus and Its Implications

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Abstract: The final common pathway in severe tinnitus is modified to include the parabrachial nucleus, which has been identified by *c-fos* immunocytochemistry as an active, non-auditory site. The parabrachial nucleus acts in conjunction with the amygdala and insula (part of the medial temporal lobe system) to produce a somatic emotional sense that can result in a “bad” feeling. The activation of the final common pathway is rapid, suggesting that early treatment is prudent to prevent neuroplastic changes that would likely lessen affect.

Key Words: insula; parabrachial nucleus; tinnitus; tinnitus pathway

More than a decade ago, Shulman [1] proposed for severe, disabling tinnitus a final common neurological pathway composed of auditory and nonauditory neural sites. Restated, the final common pathway (FCP) for tinnitus [1] is a function of the transformation of an aberrant auditory stimulus into one with a highly affective loading, involving the medial temporal lobe system, with the initial process or processes being the establishment of a paradoxical auditory memory for the aberrant auditory stimulus. Further, the FCP is dynamic in that multiple brain functions that are involved influence conscious perception of tinnitus [2].

Imaging and physiological evidence has been steadily accruing in support of this hypothesis [2,3]. The brain areas involved are in the frontal, temporal, and medial temporal lobes, parietal lobes, basal ganglia, and the cerebellum. Hearing loss, often associated with tinnitus, can lead to neural reprogramming at the levels of the thalamus and cortex [4,5]. Such brain plasticity may act as a trigger to the creation of the FCP, but the assumption was that this took time. Alternatively, the FCP may establish completely very early in the tinnitus process.

If so, the remaining question is what is the time scale for creating and completing the FCP in the initial presence of the aberrant auditory stimulus and its paradoxical memory.

THE PARABRACHIAL NUCLEUS

The expression of the proto-oncogene *c-fos* in auditory brainstem nuclei and its implications for tinnitus have been reported by immunocytochemistry in Mongolian gerbils following salicylate treatment [6]. Evidence supporting very rapid activation of the FCP stems from immunoreactivity in the auditory and nonauditory brain sites after brief (4-hour) high-noise exposure (from 10 kHz to 125–127 dB SPL) induces hearing loss and tinnitus [7]. Support is gleaned from an animal study [8], in which hearing loss was verified by auditory brainstem response and lick-suppression behavioral audiometry. This study was the first report of the use of *c-fos* immunocytochemistry to identify both expected auditory sites, such as the colliculi and the auditory cortices, and non-auditory sites in the medial temporal lobe system. One noncortical site, the parabrachial nucleus (PBN), located near the lateral lemniscus and the inferior colliculus [9], exhibited high *c-fos* immunoreactivity. Electrical stimulation of the cochlea evokes *c-fos* reaction in the lateral PBN [10], suggesting an immediate effect can be induced with just one peripheral exposure. Hence,

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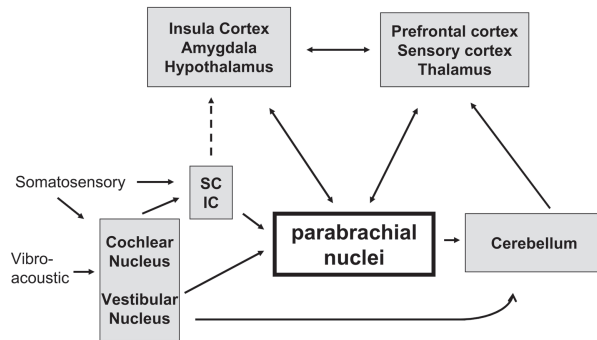


Figure 1. Parabrachial nucleus (PBN) in the final common pathway. The PBN has direct connections to the auditory, vestibular, and somatosensory systems and to the visceral receptors. It also connects to the frontal-temporal cortex, medial temporal lobe system, and the cerebellum. (SC = superior colliculus; IC = inferior colliculus.)

the PBN is a structure interconnected to both the auditory and the medial temporal lobe systems, to the frontal cortices, and to the cerebellum (Fig. 1), and all these brain sites are active in human tinnitus and form components of the FCP. A single 4-hour high-sound exposure (>125 dB SPL) induced changes in the auditory and nonauditory structures sensitive to tinnitus as a consequence of hearing damage. Because all structures identified as key components in the FCP were active, the finding has an immediate clinical impact, as it suggests that early acoustic or medical treatment (or both) may prevent frequency map alteration secondary to hearing loss [11]. The rationale for early medical treatment has been demonstrated in animals exposed to high noise and subsequently treated with high-frequency stimulation, which has resulted in less hearing loss as compared to the loss experienced by similarly exposed animals that were placed in a quiet environment. Despite some hearing loss in the high-frequency-treated animals, the tonotopic map in the primary auditory cortex did not change [11]. The expansion of the tonotopic map has been associated with expansion of the tinnitus frequency in humans with tinnitus [4]. In a replicate study [12], post-noise-exposed cats again exhibited no change in the auditory cortical map and, additionally, exhibited normal spontaneous firing rates in the brainstem neurons after high-frequency sound therapy. Cats reared in quiet or low-frequency sound treatment exhibited high synchronous spontaneous firing rates characteristic of tinnitus. Thus, tinnitus was reduced or prevented by high-frequency stimulation and hearing loss was lessened. Taken together, these studies strongly suggest that waiting for possible spontaneous remission may be ill advised, especially if the FCP is active in mere days after high-noise, tinnitus-inducing exposure.

INTEROCEPTION

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 [13,14]. The amygdala 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* [15]. Interoception is thus the "how I feel" sense, frequently described negatively by tinnitus patients with severe debilitating disease [14]. These patients will often have "bad" days, often 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. Another component of the FCP with direct connection to the PBN is the insula, involved in transforming an aberrant auditory stimulus into an emotionally arousing stimulus (tinnitus) [1].

INSULA CORTEX

Examination of Figure 1 reveals connections of the PBN to both the auditory and the somatosensory periphery. Postauricular muscle vibration is one tinnitus treatment that induces inhabitation in the cochlear nucleus [15] and, as now indicated, it has the potential to alter bodily feeling. The cochlear nucleus inhibitory effect disappears immediately after cessation of the muscle vibration. Vibration plus sound can stimulate multimodal neurons in the superior colliculi, which in turn can activate the insula and the multimodal area of the parietal lobe [16]. Although not systematically studied, the insula was identified as a site of tinnitus sensitivity in our recent positron emission tomography (PET) study [3]. The data from this study, first presented here, are portrayed in Figure 2 as percent change after two imaging studies performed 8 weeks apart after high-frequency acoustic treatment.

At the time, we treated these data as either stable or shifting from one state to another (hypo- or hyperactive) [3]. In light of the quantitative electroencephalography findings [2], we now view PET profiles [3] as dynamic and reflecting the neural substrate changes in voltage over time. The insula plays a dominant role in the conscious awareness of emotional feelings [17]—that is, the insula assists in the transfers of emotional responses of the amygdala into conscious emotional feelings.

Why is tinnitus, for some, so resistant to treatment? In our experience with high-frequency acoustic treatment

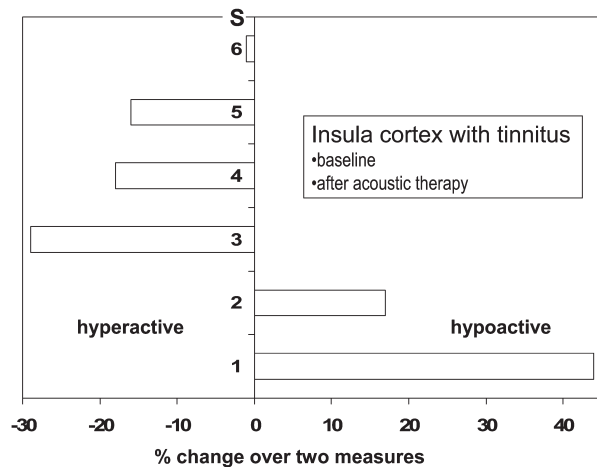


Figure 2. Tinnitus and the insula cortex. The insula cortex is active in tinnitus as indicated by positron emission tomography. The physiological state may not be static or slowly changing but dynamic, reflecting the state of interoception.

of severe, disabling tinnitus [3,13,14], most patients indicate a reduction in severity, but they also report that tinnitus intensity and annoyance are little affected by treatment. Interpreting those findings [14,15] in reference to the PBN, interoception may contribute to patients' lingering feeling of negativity, which may interact with general clinical depression and induce conditioning of fear [18]. In regard to success with antidepressant medications, the PBN may, in fact, be a target.

CONCLUSIONS

Compelling evidence now suggests that the perception of tinnitus is the result of complex and dynamic interactions in a number of auditory and nonauditory neural sites previously termed the FCP in severe tinnitus. This final pathway would seem to be rapidly established in a tinnitus animal model, suggesting that clinicians should consider intervening early. The PBN appears to be a logical but heretofore overlooked component that contributes to the transfer of an aberrant acoustic signal in the amygdala 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, debilitating tinnitus.

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