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Unintended Consequences of White Noise Therapy for Tinnitus—Otolaryngology's Cobra Effect
A Review

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IMPORTANCE Critical to the success of many medical therapeutics is a consideration of the brain's miraculous ability to dynamically rewire itself anatomically and neurochemically on the basis of incoming information. We argue that white noise exposure, a commonly recommended therapy for patients with tinnitus, engages these plastic processes in a way that induces maladaptive changes in the brain that degrade neurological health and compromise cognition.

OBSERVATIONS The pathophysiologic mechanisms commonly associated with hearing loss and tinnitus reflect cortical dedifferentiation and widespread loss of inhibitory tone throughout the central auditory pathway. Importantly, these same changes are also induced by exposure to unstructured noise, even at nontraumatic levels in the adult nervous system. Not by coincidence, the same changes appear in age-related decline of central auditory function, suggesting that both tinnitus and white noise accelerate the aging of the brain.

CONCLUSIONS AND RELEVANCE Noise exposure therapies offer a seductive short-term solution for relief but, in the long term, undermine the functional and structural integrity of the central auditory system and the brain more generally. Sound therapies using unstructured, random ("white") noise should be avoided as a treatment for tinnitus. Alternative therapeutics that drive positive, adaptive plastic changes are discussed.

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There are many historical stories of how the best of intentions can backfire. In an apocryphal anecdote set in the 1800s, the British Raj in India recognized usually fatal cobra bites as a major public health issue. The solution seemed simple and intuitive. Citizens were paid for every dead cobra delivered to government authorities under the irrefutable logic that fewer cobras must translate into fewer cobra-bite deaths. Officials failed to anticipate that their payments for dead snakes would be rapidly exploited by entrepreneurs who began breeding cobras in large numbers. The incentive program was abruptly discontinued when officials became aware of the scheme and breeders consequently freed their cobras, driving the wild cobra population to unprecedented numbers. The intended solution made the original problem worse. Medical practice, past and present, is replete with "cobra effects": treatments that worsen the symptoms they were intended to relieve. Herein, we cast light on a cobra effect that appears to be in play in the treatment of tinnitus.

Tinnitus degrades the quality of life of approximately 50 million US adults and profoundly disables and precludes a normal life in an estimated 2 million.[1,2] Few medical conditions are as personally disruptive or as continuously distressing as the squeals or noises continuously "roaring from the ears" of the patient with severe tinnitus. In many, excessive noise exposure with associated sensorineural hearing loss, ear and nerve disease conditions, high stress, hypertension, traumatic brain injury, cumulative concussions, and drug and chemical exposures are accumulating causes of their primary or secondary tinnitus.[3] Age-related neurophysiological changes and subclinical neurodegeneration are other identified contributors.[4] At the same time, tinnitus has no obvious or immediately identifiable cause in 65% to 98% of cases.[5] With frequent confusions about etiology, patients are commonly referred to a variety of specialists and health care clinics, which often address their tinnitus in unstructured ways.[6]

There is currently no cure for tinnitus, and approaches to treating symptoms have not been standardized across clinical practice.[2,6,7] Sound therapy is a common approach for managing tinnitus symptoms[8] and was recently included among a small handful of options for addressing bothersome tinnitus in a clinical practice guideline published by the American Academy of Otolaryngology–Head and Neck Surgery.[7] A variety of sound therapies have been deployed with the common goal of masking the tinnitus percept, many of which implement random, broadband noise as the masking stimulus. Although some evidence suggests that noise-based sound therapy provides relief from intrusive tinnitus percepts via auditory masking,[9] we discuss a large and growing body of literature documenting that unstructured, random acoustic input is capable

of inducing maladaptive neuroplastic change throughout the central auditory system that ultimately undermines that system's structural and functional integrity.

In the present review, we argue that the potential adverse effects of noise-masking strategies outweigh their therapeutic potential. We further suggest that noise exposure may eventually compound the maladaptive plasticity thought to underlie tinnitus, which could worsen the neurological expressions of the tinnitus over time: a cobra effect. We recommend against sound therapies using unstructured acoustic noise, and consider several possible alternatives.

Pathophysiologic Mechanism

Over the past 50 years, the emergent science of brain plasticity has documented that the brain is capable of continuous, large-scale anatomical, neurochemical, and functional change—in either an adaptive or maladaptive direction—across the lifespan.[10] Neuroscientists have reached better understanding of tinnitus within this framework, characterizing the phantom sounds as a product of plastic auditory system distortions that competitively exaggerate neurological representations of tinnitus percepts.

Although the pathophysiologic mechanism underlying tinnitus remains incompletely understood, substantial progress has been made within the past several decades in establishing neurobiological hallmarks of tinnitus in animal models, with an encouraging degree of agreement in the available human studies.[11,12] Although most tinnitus cases are believed to reflect peripheral hearing loss, tinnitus is known to persist even after lesions of the cochlear nucleus or auditory nerve transection,[13] implicating the involvement of downstream central structures. Extensive evidence now documents widespread changes associated with tinnitus throughout the central auditory pathway—from cochlear nucleus to cortex. Convergent evidence from anatomical, physiological, and neurochemical studies suggests that the most common pathophysiologic mechanism in animals with hearing loss and behavioral evidence of tinnitus is net loss of inhibition.[14-17] As reviewed elsewhere,[18,19] this reduction in inhibitory strength reflects reduced inhibitory neurotransmitter release, altered subunit composition of inhibitory neurotransmitter receptors, downregulation of inhibitory synapses, and strengthened excitatory synapses, which result in elevated spontaneous firing rates and neural synchrony, cortical hyperexcitability, reduced spectral and temporal inhibition, and increased receptive field bandwidth. Clinical studies in human patients are largely consistent with these outcomes, reflecting increased gain in central pathways,[20,21] including reduced auditory cortical inhibition,[22] often with evidence of cortical tonotopic reorganization.[11,15,23]

Temporal response precision throughout the auditory pathway, which critically depends on excitation-inhibition balance,[24] is also compromised by diminished inhibitory tone associated with hearing loss and tinnitus.[15,25] These degraded temporal processing capabilities severely undermine central processing of complex amplitude-modulated signals including conspecific vocalizations and speech, as well as discrimination of signals in noise. Behavioral studies in both animal and human subjects suggest that these central processing deficits translate into impaired ability to discriminate temporal patterns and communication signals, especially when embedded in noise.[26-28]

Exposure to traumatic noise, resulting in permanent elevated peripheral tone thresholds, has long been recognized as a prevalent cause of central auditory dysfunction associated with tinnitus. However, a rapidly growing body of literature, largely conducted in animal models within the last decade, has now established that long-term exposure to nontraumatic noise—in which peripheral tone thresholds remain unchanged—is capable of inducing maladaptive plastic reorganization of the central auditory nervous system in ways that bear striking phenomenological overlap with the persistent, widespread disinhibition of the auditory system thought to underlie tinnitus in humans.[29,30] Specific putative physiopathologic conditions associated with tinnitus that are also induced by nontraumatic noise exposure, even in the absence of hearing loss, include loss of inhibitory tone through decreased expression of inhibitory interneuron protein[31] and inhibitory neurotransmitter receptor subunits,[32] increase in neural spontaneous firing, increase in spontaneous neural firing synchrony,[30,33] tonotopic reorganization,[33] increased auditory cortical receptive field bandwidth and overlap,[33] as well as degraded auditory cortical temporal processing and impaired behavioral performance in temporal rate discrimination tasks.[33] Notably, these changes have been observed following exposure to noise levels in the 60 to 70 dB sound pressure level range, typical of commercially available noise generators[34] and considered "safe" by the US Occupational Safety and Health Administration[35] on the basis of preserved peripheral thresholds. They have moreover been documented as developing in both young[32] and adult subjects,[31,33] following exposures spanning as little as a couple of months,[36,37] and may persist for at least several weeks to months after noise exposure discontinuation.[31]

It has been convincingly established in multiple experimental preparations and sensory modalities that downregulation of inhibition observed following sensory deprivation, peripheral damage, or deafferentation reflects a loss of statistically meaningful input from the sensory periphery.[18,31] Compromised peripheral inhibition initiates cascading consequences that propagate to the cortex, which in turn exacerbate rather than compensate for reduced subcortical inhibition.[19] The recent discovery that nontraumatic noise exposure similarly compromises the functional integrity of the central auditory pathway through net loss of inhibition fits neatly within this general paradigm, considering that noise is statistically random by definition. Physiological outcomes such as increased synchrony in spontaneous firing rates and reduced spectral and temporal selectivity are believed to reflect mechanisms of Hebbian plasticity recruited during simultaneous, equivalent activation of central auditory neurons, which occurs in both sensory deafferentation and nontraumatic noise exposure. To the extent that these neurons "fire together," they "wire together," resulting in progressive increase in coactivation and loss of selectivity for specific spectral frequencies and other acoustic features.[32,33,38] Auditory perceptual impairments observed at the behavioral level can be interpreted within the context of degraded spectral and temporal selectivity in the auditory nervous system, especially at the level of cortex.[33,39]

Controlled neurobiological experiments investigating nontraumatic noise exposure thus suggest that sound therapies implementing broadband noise may be driving patients' brains further toward, rather than away from, the pathological disinhibitory state that has long been associated with tinnitus. Nevertheless, only a handful of studies have specifically examined links

between nontraumatic noise exposure and tinnitus, likely because the deleterious consequences of nontraumatic noise have only recently been documented and because of ethical concerns about exposing human subjects to potentially harmful noise.[40] The results of these studies have yielded only partial agreement and are in some cases difficult to interpret for lack of ideally suited dependent measures or experimental controls. In 1 study, animals exposed to nontraumatic noise but without evidence of peripheral hearing loss exhibited all of the major putative neural correlates of tinnitus, including increased cortical spontaneous firing rates and neural synchrony.[30] Although the authors speculated that these physiological correlates might translate into behavioral manifestations of tinnitus, a recent follow-up study by the same group failed to identify significant behavioral signs of tinnitus in subjects exposed to nontraumatic noise (50-70 dB), as assessed by the acoustic startle reflex.[41] On the other hand, another group of researchers exposing animals to borderline-traumatic noise (97 dB) observed significant behavioral signs of tinnitus using the same behavioral paradigm, even though the exposure protocol preserved cochlear integrity.[42] Studies in human subjects have similarly yielded only partially consistent results and, moreover, carry caveats regarding lack of rigorous experimental control over noise exposure parameters. Thus, 1 study of patients with tinnitus but no evidence of peripheral hearing loss found that estimates of lifetime exposure to noise (>80 dB) obtained through interview were significantly higher than closely matched controls.[43] Another study, however, reported that tinnitus prevalence was significantly associated with noise exposure only in participants with peripheral hearing loss—not in participants with normal audiograms.[44]

In summary, the recent experimental efforts to understand the consequences of nontraumatic noise exposure reviewed herein cast doubt on the therapeutic merits of sound therapies implementing unstructured masking noise, which are problematic for 2 fundamental reasons. First, long-term exposure to nontraumatic noise is now known to produce the same anatomical, physiological, and behavioral symptoms of hearing loss associated with tinnitus. These outcomes raise the disconcerting possibility that broadband noise exposure may be sufficient to unmask, exacerbate, or prolong tinnitus symptoms, even without damaging the cochlea. Second, aside from tinnitus, hyperactivity in the central auditory pathway induced by nontraumatic noise exposure has a known causal role in the emergence of a host of auditory perceptual problems, especially those reflecting compromised temporal processing ability, which is critical for speech comprehension and perception of signals in noise. Concerns about the potential for nontraumatic noise to worsen tinnitus symptoms call for detailed investigation of key relationships among noise exposure level and duration, physiological changes in the auditory central pathway, and behavioral symptoms of tinnitus. For instance, it is not yet clear whether long-term exposure to very low noise levels used in some sound therapies (<50 dB) might be sufficient to produce the hallmark disinhibitory syndrome resulting from levels used in existing studies (60-70 dB). At present, however, the available evidence reviewed herein suggests that sound therapies implementing noise, while providing temporary relief by masking tinnitus percepts in the short term, may be adding fuel to the fire in the long term.

Treatment: Neuroplasticity-Based Therapeutics

Fortunately, many alternative strategies are available for treating tinnitus that do not carry known risks for exacerbating symptoms in the long term and are free from adverse effects known to be induced by long-term exposure to unstructured noise. Herein, we focus on several recently developed approaches for tinnitus treatment that harness its adaptive potential in the service of restoring the structural and functional integrity of the central auditory system. Thus, whereas noise pathologically undermines inhibitory control throughout the central auditory pathway, each of the treatment options considered in this section are associated with restoration of lost compromised inhibitory transmission long believed to underlie hearing loss associated with tinnitus. Although not all of these strategies have yet been tested in large human clinical trials, there is enough supportive evidence to justify their investigation.

Sound Therapy Using Structured Acoustic Signals

Perhaps the most straightforward alternative to sound therapy with unstructured noise is to simply replace the masking stimulus with a structured (nonrandom) acoustic signal, such as music or speech.[11,45] As noted herein, the simultaneous, random activation of the auditory system by broadband stimuli results in neurons firing together and thus wiring together. In the long term, spectral and temporal receptive fields broaden as a result of the increased capacity of one neuron to activate another. From this perspective, it follows that exposure to sounds with rich spectrotemporal structure such as music and speech might instantiate changes in the central auditory pathway opposite to noise, preserving or enhancing receptive field selectivity. This hypothesis has been largely confirmed in animal studies of enriched acoustic environments featuring dynamic changes in spectral and temporal modulation, which have reported sharpened receptive fields,[45] as well as facilitated recovery from and protection against the deleterious consequences of noise,[46] including reduced behavioral signs of tinnitus.[47]

Additional studies in humans have obtained promising results using music that has been filtered to match an individual patient's tinnitus percept profile. For example, music that has been altered or "notched" to exclude frequencies neighboring the tinnitus[48] have suppressed tinnitus-related hyperactivity via synaptic lateral inhibition across the notched region.[49] Another example includes acoustic coordinated reset neuromodulation, which randomly presents brief tones both above and below the pitch of the tinnitus to improve desynchronization and cortical map differentiation (ie, abnormal frequency couplings). Under this method, participants reported perceived reductions of tinnitus loudness and annoyance, and reduced oscillatory activity as measured by electroencephalogram mirrored these improved clinical outcomes.[50] Note that such therapies carry additional costs to develop personalized programs for the individual's tinnitus symptoms. For patients who cannot afford such programs, clinicians may recommend exposure to unmodified music or speech.

Computerized Brain Training

It is now recognized that the neuroplastic processes responsible for initiating, perpetuating, and elaborating deficits associated with

many neurological conditions can be redirected to drive changes in a corrective trajectory, potentially ameliorating rather than exacerbating symptoms.[10] From this perspective, abnormally organized auditory and nonauditory systems, and their associated perceptual and cognitive deficits, should also be amenable to intensive training-based remediation. Indeed, many promising examples of training-induced rehabilitation have recently been reported for partially restoring pathological auditory cortical function associated with traumatic hearing loss, presbycusis, or tinnitus in both animal models[51,52] and humans.[53]

In an initial demonstration of the potential for positively affecting tinnitus by intensive training, Kallogjeri and colleagues[54] applied BrainHQ's validated progressively adaptive computerized exercises targeted at auditory speed of processing, accuracy, sequencing, working memory, and attentional control in an open-label, intent-to-treat randomized clinical trial in emergency workers with severe bothersome tinnitus. Participants with tinnitus were randomized to either auditory training exercises or treatment-as-usual. Magnetic resonance neuroimaging, as well as a number of neuropsychological and self-report measures, including the Tinnitus Handicap Inventory (THI), were taken before and after an epoch of approximately 40 hours of training. There was a numerical, although not significant, reduction in THI scores in the trained group over controls, with more than twice the number of trained participants showing a clinically meaningful reduction in THI scores (35% vs 15%), and self-reporting an improvement in their tinnitus (50%) or in their ability to learn and remember (70%). That is, for approximately half of trainees, tinnitus was brought under effective attentional control (the percepts could be "put out of mind" at will), enabling a restoration of normal sleep and an amelioration of tinnitus disruptions affecting sustained employment and more normal everyday functioning. Resting-state functional connectivity in neural networks largely responsible for attention and cognitive control mirrored the behavioral gains and reliably improved at post-test in the tinnitus trained group only.

Although a small set of tinnitus-nonspecific auditory training programs demonstrated a benefit for some patients with tinnitus in this independent study, the mechanism of action was not through remediation of the tinnitus itself but rather through secondarily affected networks, most notably those involved in attentional control. Auditory exercises strengthened functional connectivity so that the tinnitus percept was easier to ignore but did not necessarily modify the tinnitus percept itself, thus helping individuals control their attention to the tinnitus "from the top down."

Stimulus Timing–Dependent Plasticity

Attentional-based brain training may be insufficient to remediate tinnitus for many patients. Additional computerized training exercises may be needed, specifically designed to drive corrective changes across the auditory nervous system in ways designed to weaken or override the neurological distortions giving rise to the tinnitus percept, thus approaching remediation "from the bottom up."[55]

If tinnitus is perpetuated by abnormally enlarged, system-wide, cortical and subcortical representational assemblies amplifying the power of tinnitus-associated sounds, then reducing the neural real estate maintaining the tinnitus should lead to a reduction in the tinnitus percepts. Research has shown that representation of any arbitrary frequency can be sharply reduced by applying conditioning strategies that produce long-term synaptic depression (LTD).[56] In a recent study, Marks and colleagues[57] significantly reduced symptoms in humans with chronic somatic tinnitus using the principles of LTD. In a double-blind, placebo-controlled crossover study, repeated presentation of auditory and somatosensory bimodal stimulation (targeting the fusiform cell circuit in the dorsal cochlear nucleus at an interval shown to produce LTD in guinea pig models of tinnitus) significantly and cumulatively decreased perceived tinnitus loudness and intrusiveness as assessed by the Tinnitus Functional Index in humans. Relief from tinnitus may have been mediated by LTD of strengthened somatosensory inputs to deafferented auditory pathways. This approach of stimulus timing–dependent plasticity differs significantly from existing neurosensory rehabilitation approaches in that its goal is to restore auditory mapping rather than simply compensate for negative plastic reorganization.

Vagus Nerve Stimulation

Another, albeit invasive and experimental, neuroplasticity-based therapy is vagus nerve stimulation (VNS). Vagus nerve stimulation eventuates in the release of acetylcholine which, when paired with a stimulus such as a tone, increases cortical representation of that stimulus through neuroplastic processes. In animal models, the general strategy of the VNS approach has been to induce tinnitus, map the tonotopic organization of auditory cortex, and pair VNS with tones other than the tinnitus-match frequencies to normalize tonotopic map organization.[58] Through competitive reorganization, the nontinnitus maps increase in size and representation while the tinnitus maps decrease, ultimately extinguishing the tinnitus percept. In human studies that use these same principles of paired brief electrical stimulation of the vagus nerve with nontinnitus sounds, participants with severe chronic tinnitus benefited from VNS as measured by the THI.[59] Notable exceptions to this form of therapy were those who were taking medications known to interfere with instantiation of neural plasticity. A noninvasive form VNS may well be feasible in the near future.[60]

Association of Tinnitus With Progressive Downstream Cognitive Consequences

Although pathophysiologic conditions of the central auditory pathway reviewed herein seem to be the sine qua non of tinnitus,[61] both human and animal studies reveal that the auditory system distortions extend, in time, to distort nonauditory areas in the frontal lobe, limbic and paralimbic systems, basal ganglion, and cerebellum.[61-65] Importantly, Burton and colleagues[66] documented striking abnormalities in the connectivities of networks controlling attention and mood, strong within-system and significantly weakened cross-modal connectivities between auditory and visual or somatomotor networks, and a complex combination of positive and abnormal connectivities with specific limbic and basal ganglia areas. These studies richly manifest the neurological bases of the neurobehavioral havoc that can degrade the quality of life and welfare of patients with tinnitus.

Chronic tinnitus is further known to degrade processing speed, working memory, learning, selective attention, recognition, cross-modal switching, successive signal masking, verbal

learning, phonemic verbal fluency, memory recording and retrieval, and sustained auditory and nonauditory attention.[67-72] These impacts on brain speed, attentional control, and cross-modal integration contribute to behavioral deficits that extend far beyond hearing and language. Tinnitus sharply increases the risks of suicide, major depressive and anxiety disorders, intractable insomnia, social avoidance, unemployment, and other fundamental contributors to a negative quality of life.[73,74] It also may foretell a premature passage to age-related dementia onset.[4,75] Tinnitus, as well as noise-masking treatments, may thus not only undermine the organic health status of the brain but also undermine cognition more broadly.

Conclusions

A noisy environment produces a noisy brain. Yet current clinical practice includes the use of random-noise generators as a therapeutic treatment for tinnitus. Such signals are known to dedifferentiate cells comprising the auditory pathway and thus maximize the likelihood of continuance or recurrence of neurological dysfunction and cognitive impairment.

Effective, long-term therapeutic solutions for tinnitus will ultimately depend on a clear understanding of neuroplasticity in the central auditory system. At present, we suggest that such neuroplasticity-based interventions will include (1) restrengthening of central inhibitory processes in ways that restore normal, healthy auditory function, (2) reorganization of the auditory pathway in ways that de-exaggerate neurological representations of tinnitus percept frequencies, and (3) strengthened general cognitive resources to facilitate the voluntary attentional suppression of tinnitus. With exciting developments currently under way, we envisage a new era in medicine in which disease is understood in the context of brain health and treatment is guided by well-established principles of neuroplasticity. Only then shall we do no harm.

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