Deep Brain Stimulation in Area LC Controllably Triggers Auditory Phantom Percepts

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BACKGROUND: Tinnitus is predominantly viewed as the consequence of dysfunctional hyperactivity, plastic change, or synchronized oscillations in the central auditory system. An alternative to the current auditory-centric view of auditory phantom perception is the basal ganglia-centric view. Recent electrical stimulation experiments in area LC, a locus of the caudate nucleus positioned at its anterior body, has shown loudness modulation of existing tinnitus percepts.

OBJECTIVE: To demonstrate that auditory phantoms are gated by the dorsal striatum.

METHODS: Electrical stimulation in area LC via a deep brain stimulation lead was performed in 6 interactive adult subjects (3 with and 3 without chronic tinnitus) undergoing surgery to treat movement disorders. Tinnitus loudness was rated on a 0 to 10 scale, sound quality was described, and localization was referenced to 1 or both ears.

RESULTS: Short-term area LC stimulation triggered new phantom tones, clicks, and frequency modulated sounds in 5 subjects and altered sound quality of an existing tinnitus percept in 1 subject. The results of this study indicate that perceptual awareness of auditory phantoms is contingent on satisfying a permission condition controlled by the dorsal striatum. Potential auditory phantoms are not automatically gated to reach perceptual awareness. A phantom percept gate control model is proposed.

CONCLUSION: Neuromodulation of area LC can trigger temporary gate dysfunction and reversibly release new phantoms for conscious awareness. Restoration of restrictive dorsal striatal gate function to treat problematic phantom percepts may be realized by adopting long-term area LC neuromodulation and choosing optimal stimulation parameters.

KEY WORDS: Auditory perception, Basal ganglia, Caudate nucleus, Deep brain stimulation, Tinnitus.

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Tinnitus, a phantom perception disorder of internal sounds without external correlates, either arises from or is expressed in auditory cortex or subcortical auditory structures projecting to this region. Acoustic trauma,[1-3] inner ear disorders,[4,5] high-dose aspirin,[6] and chemotherapy[7] are some known agents that injure the auditory periphery, cause measurable hearing loss, and initiate the development of phantom auditory percepts. In some patients, specific external conditions trigger or modulate tinnitus.[8-10] In others, tinnitus qualia are mostly invariant. Once tinnitus becomes chronic and continuous, even auditory deafferentation by cochlear nerve excision cannot reliably eliminate constant head noises.[11]

ABBREVIATION: DBS, deep brain stimulation

It follows that the central auditory system maintains neural representations of phantom percepts that are sometimes accessed for conscious awareness. Neural correlates of tinnitus percepts have been hypothesized to be related to hyperactivity of the central auditory system,[12-15] synchronized oscillations,[16-18] and reorganized frequency maps.[19-23] Yet unambiguous neural correlates of tinnitus percepts remain elusive. The close association between hearing loss and tinnitus has created considerable challenge to separate physiological findings attributable to hearing loss from those attributable to tinnitus.[24]

Patients with similar hearing loss profiles report inhomogeneous tinnitus loudness levels. Some are entirely free of tinnitus. Others are

constantly aware of their auditory phantoms. Furthermore, those with matched hearing loss and phantom percept loudness profiles may be affected by tinnitus rather differently. Whereas one merely experiences tinnitus, another suffers from it. This difference stems from motivational and emotional behaviors strongly linked to auditory phantoms tinnitus sufferers and suggests a tight interaction between limbic structures and phantom percepts.[25] Reinforced behavioral responses to auditory phantoms may be mediated by the basal ganglia, which have been shown to execute essential functions in gating, attending, evaluating, learning, and acting on sensorimotor information. Moreover, the basal ganglia are implicated in habits, ritualistic behaviors, and obsessive-compulsive disorder in humans.[26-29]

Area LC, a locus of the caudate positioned at the anterior aspect of the dorsal striatum, was recently identified as a deep brain stimulation (DBS) target to control loudness of tinnitus percepts.[30] In that study, 5 of 6 subjects in whom the DBS lead traversed area LC reported tinnitus loudness suppression to a nadir of level 2 or less on a 0 to 10 rating scale. Depending on the specific parameters of electrical stimulation, tinnitus loudness decreased or increased. This was a surprising result because neuromodulation of a nonauditory, basal ganglia structure modulated auditory perception so dramatically.

A narrow interpretation of those data is that auditory phantom neural representations are automatically gated for perceptual awareness, and area LC acts as an amplitude rheostat to modulate loudness of existing auditory phantoms. Alternatively, auditory phantom neural representations are necessary substrates for perceptual awareness but are not automatically gated, and area LC controls gating of those representations and their perceptual loudness levels. This broader interpretation would imply tinnitus-free hearing loss patients may in fact have latent auditory phantoms that could be triggered into conscious awareness. Evidence to support the latter far-reaching, but unproven supposition would be partially fulfilled by demonstrating that neuromodulation of area LC can controllably gate perception of new auditory phantoms in hearing loss subjects with and without existing tinnitus. Such data interpreted in the context of electrical stimulation in area LC can modulate tinnitus loudness[30] would strengthen the hypothesis that area LC plays an important role within the auditory phantom representation and awareness network.

MATERIALS AND METHODS

Patients

A sample of 7 adult subjects with movement disorders undergoing surgery for Parkinson disease or essential tremor consented to electrical stimulation experiments in area LC via a DBS lead. Hearing loss profiles in all subjects were documented by perioperative audiometry. Before to DBS surgery, subjects were questioned whether they had tinnitus. Those with tinnitus reported on the following attributes of their baseline (before stimulation epoch) phantom auditory percept: (1) sound quality variation (constant or inconsistent), (2) temporal presence (continuous or intermittent), (3) sound quality description (tonal, noiselike, cricket-like, or musical), and (4) loudness rating localized to each ear on a 0 to 10 scale (0, completely quiet; 10, jet engine). One subject without baseline tinnitus did not experience alteration in auditory perception. Results are reported for the other 6 awake and interactive subjects (age range, 50-67 years; 4 men, 2 women) who described changes in auditory perception with area LC stimulation.

Subjects 1, 2, and 3 had constant, continuous tinnitus localized to both ears for at least 2 years. Each subject described his or her single, dominant auditory phantom as tonal, musical, or cricket-like. All endorsed perception of other auditory phantoms was rare, and tinnitus loudness fluctuation within a stable acoustic environment was very uncommon. Subjects 4, 5, and 6 were tinnitus free at the time of experiments. Subject 6 reported brief noiselike tinnitus in both ears about once per month but did not perceive auditory phantoms on the morning of surgery. The study was completed in accordance with an approved protocol by the University of California, San Francisco Committee on Human Research.

Area LC Electrical Stimulation Experiments

During the conduct of experiments in the operating room, the acoustic environment was kept as quiet as possible. Cardiac and pulse oximetry monitors were muted. Only the surgeon's voice was audible. Subjects were prompted to report on sound quality and loudness level of triggered new or altered baseline phantom auditory percepts. Associated stimulation thresholds were determined in 2 or more trials, with subjects blinded to stimulation parameters at all times.

DBS lead implantation was performed using standard techniques. Patients were placed in a Leksell stereotactic head frame (Elekta, Atlanta, Georgia) and underwent preoperative magnetic resonance imaging. The images were then transferred into FrameLink (Medtronic, Minneapolis, Minnesota) software. Medtronic model 3387 leads were used in all cases except subject 3, who received a model 3389 lead. The DBS lead was paused in the caudate to deliver electrical stimulation before implantation of the target nucleus (Table). In all cases, the lead position was verified to be in area LC by postoperative magnetic resonance imaging visualization of the lead trajectory.

Stimulation epochs spanned parameters that ranged from 0 to 10V (amplitude), 10 or 150 to 180 Hz (frequency), 60 to 180 μs (pulse width), and 60 to 120 seconds (duration). A bipolar stimulation configuration of distal electrodes 0, 1, and 2 negative and proximal electrode 3 positive was used in all subjects. Auditory perception response dependency on stimulation voltage was the predominant focus of the experiments. A systematic exploration of the effects of other stimulation parameters was not possible in the time-constrained operating room setting. Subjects 4, 5, and 6 without tinnitus were presented with an external 1-kHz tone at 60-dB sound pressure level via earphones (ER-2 Tubephone; Etymōtic Research, Elk Grove Village, Illinois) to the ear contralateral to the side of area LC stimulation as one of the experimental conditions.

RESULTS

Triggered new auditory phantoms were reported by 5 subjects, and altered baseline tinnitus was reported by 1 subject. Novel phantom auditory percepts persisted for the entire duration (60-120 seconds) of triggering electrical stimuli, whose parameters varied among subjects (Table). Response curves to electrical stimulation in area LC were generally discontinuous, quantal perceptual events marked by appearance, disappearance, and sometimes reappearance of novel auditory phantoms with increasing voltage amplitude.

TABLE. Clinical Details for Study Subjects[a]

Subject	Age, y/Sex	Indication for Surgery	DBS Target	Area LC Stimulation Side	Stimulation Parameters (Frequency, Pulse Width)	DBS-Triggered Phantom Sound Quality Description	
						Baseline Tinnitus, Percept Localization	New Auditory Phantom or Alteration of Baseline Percept
1	57/M	ET	Vim	Right	180 Hz, 90 μs	Cricket chirps, both ears	New high-pitched tone
2	66/M	PD	STN	Right	150 Hz, 180 μs	High-pitched tone, both ears	New distinguishably separate tone
3	67/M	PD	STN	Left	180 Hz, 60 μs	Musical, both ears	Alteration of baseline to a higher pitch
4	61/M	PD	STN	Right	180 Hz, 60 μs	None	New click sequences with 4 elements each
5	50/F	PD	STN	Right	10 Hz, 60 μs	None	New "airplane taking off" sound
6	67/F	PD	STN	Left	10 Hz, 60 μs	None	New medium-pitched "creaking" sound

[a]DBS, deep brain stimulation; ET, essential tremor; Vim, ventral intermediate nucleus; PD, Parkinson disease; STN, subthalamic nucleus.

Subjects 1, 2, and 3 had chronic baseline constant, continuous tinnitus. Area LC stimulation was performed without an external 1-kHz tone. Subject 1 described his baseline tinnitus as cricket chirps and rated loudness at level 5 in both ears. He had bilateral moderate hearing loss. With right area LC stimulation at 8 V, he reported a new high-pitched tone localized to the left ear at level 3 loudness (Figure 1A). Also at 8 V, his baseline cricket chirp auditory phantom decreased to level 3 loudness in both ears (not shown in Figure 1A). Subject 2 described his baseline tinnitus as a high-pitched tone and rated loudness at level 2 in both ears. He had bilateral moderate hearing loss. With right area LC stimulation at 4.5 V, he reported a new, second distinguishable tone localized to the left ear at level 4 loudness (Figure 1B). Also at 4.5 V, his baseline high-pitched auditory phantom increased to level 4 loudness in both ears (not shown in Figure 1B). Subject 3 described his baseline tinnitus as musical and rated loudness at level 3 in the right and level 4 in the left ears. He had bilateral moderate to severe hearing loss. With left area LC stimulation at 4 V and 8 V, he reported alteration of his baseline tinnitus to a higher pitch localized to the right ear at level 3 (4 V) and level 4 (8 V) loudness (Figure 1C). Pitch shift of his existing auditory phantom could have been a new phantom percept that was sufficiently spectrotemporally similar so as to strongly mask his baseline phantom percept. From this perspective, the new auditory phantom was ambiguously reported as a pitch shift of his baseline tinnitus. At both 4 V and 8 V, his baseline musical tinnitus sound quality in the left ear was unaltered and decreased to level 3 loudness (not shown in Figure 1C).

Subjects 4, 5, and 6 were tinnitus free. Area LC stimulation was performed with and without an external 1-kHz tone presented at 60-dB sound pressure level to the ear contralateral to the side of neuromodulation. The goal of the external sound was to simulate constant, continuous tinnitus. Subject 4 had right normal thresholds and left mild hearing loss. He underwent right area LC stimulation. At 4 V, 6 V, and 10 V, he reported a new phantom percept described as click sequences with 4 elements each, localized to the left ear at level 2 loudness. The phantom percept was perceived only in the presence of the external 1-kHz tone and started and stopped by turning the external sound on and off in the presence of area LC stimulation (Figure 1D). Subject 5 had bilateral mild hearing loss. She also underwent right area LC stimulation. At 2 V, she reported a new phantom percept described as low-pitched frequency modulated rumble akin to "an airplane taking off" localized to the left ear at level 6 loudness. Interestingly, the new phantom percept was not perceived in the presence of the external 1-kHz tone (Figure 1E). Subject 6 had left normal thresholds and right mild hearing loss. She underwent left area LC stimulation. At 4 V, 6 V, 8 V, and 10 V, she reported a new phantom percept described as a medium-pitched frequency modulated "creaking" sound localized to both ears at level 1 loudness. The new phantom percept was similarly not perceived in the presence of the external 1-kHz tone (Figure 1F). No subjects reported distortion of the surgeon's voice when auditory phantoms were triggered.

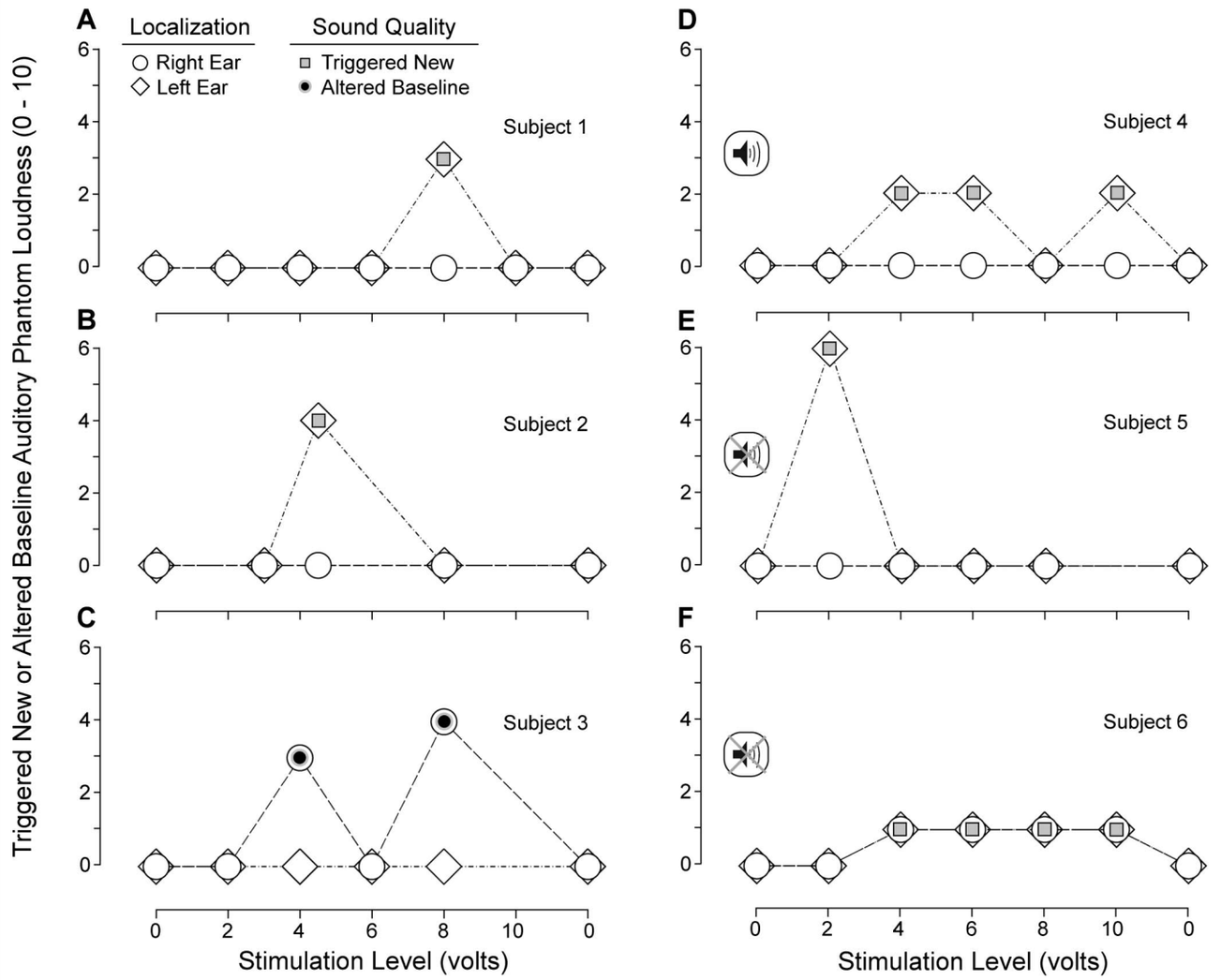

FIGURE 1. *Triggered new or altered baseline auditory phantoms mediated by deep brain stimulatoin neuromodulation of area LC. Phantom auditory percept is localized to a specific ear and loudness is rated on a 0 to 10 scale. Horns without (ON) and with (OFF) crosses indicate presence of an external 1-kHz tone presented to the contralateral ear in subjects 4, 5, and 6.* **A**, **B**, *subjects 1 and 2 reported wholly new auditory phantoms with right area LC stimulation.* **C**, *subject 3 reported sound quality alteration of an existing auditory phantom with left area LC stimulation.* **D**, **E**, *subjects 4 and 5 reported wholly new auditory phantoms with right area LC stimulation under external tone ON and OFF conditions, respectively.* **F**, *subject 6 reported a wholly new auditory phantom with left area LC stimulation under external tone OFF condition.*

DISCUSSION

Area LC neuromodulation under a variety of stimulation parameters and internal and external sound conditions triggered a heterogeneous collection of new auditory phantoms that were typically localized to the ear contralateral to the side of stimulation. Subjects with baseline bilateral tinnitus retained the sound quality of their familiar phantom percept in 1 or both ears, but loudness was modulated. Subjects without baseline tinnitus perceived their triggered auditory phantoms either in the presence or absence of an external 1-kHz tone, but not both. All subjects reported relatively elemental sounds (Table). Triggered tones, clicks, and frequency modulations uniformly terminated when the stimulation amplitude was returned to 0 V.

Electrical stimulation in area LC modulates auditory phantoms in at least 2 ways. First, existing phantom percepts retain their sound qualia, but loudness levels decrease or increase.[30] In that study, tinnitus loudness modulation stimulus-response curves attributable to the electrical stimulation effect were monotonic in 3 and nonmonotonic in 3 stimulation epochs. Nonmonotonic

loudness modulation curves were continuous (no zero crossings), transitioned to neighboring values relatively smoothly, and were localized to both ears. Second, entirely new auditory phantoms are triggered whereby baseline phantom percepts, if present, also retain their sound qualia. In this study, triggered auditory phantom stimulus-response curves in 5 of 6 stimulation epochs were highly nonmonotonic and mostly discontinuous. Triggered phantom percepts were generally localized to the contralateral ear. Taken together, these 2 studies provide evidence that the dorsal striatum acts as a gate to control loudness of existing auditory phantoms and access to new phantoms for conscious awareness.

A comparison of loudness modulation profiles of triggered vs existing auditory phantom effects reveals differences in perceptual spatial specificity and stimulus-response profiles. Ear location specificity is monaural for triggered effects but is binaural for existing phantom effects. The fact that the reported sounds were contralateral to DBS adds strength to the conclusion that the percepts reported were real and not simply a compliance with the task demands of the situation. The basis for spatial segregation of perceptual effects is unknown but may be rooted in network representation differentiation between acute and chronic tinnitus.[31,32] Voltage stimulus-response curves are largely discontinuous for triggered effects but are continuous for existing phantom effects. The quantal nature of triggered effects may reflect inadequate sampling of possible stimulation parameters, a limitation of conducting experiments in the highly time-constrained operating room setting. It is possible that once an auditory phantom is triggered, variation along frequency, pulse width, or some other stimulation parameter dimension could elicit continuous stimulus-response curves. It is also conceivable the quantal response profile may reflect strong bias of basal ganglia circuitry to restore restrictive dorsal striatal gate function. Future studies on subjects with an implanted DBS lead in area LC for long-term neuromodulation will permit a thorough search of the stimulation parameter space to clarify this issue.

Species of Phantom Perception Disorders

Tinnitus may be considered an auditory species of phantom perception disorders related to peripheral deafferentation. Other examples include Charles Bonnet syndrome[33] of variably formed visual images associated with macular degeneration and phantom limb somatosensory perception[34] of variably distorted phantom body images associated with extremity amputation. Tinnitus is a common phantom auditory perception disorder that is prevalent in 10% to 15% of the general adult population.[35,36] Of those with tinnitus, more than 80% adapt well to their auditory phantoms and do not express negative emotional or behavioral reactions.[37,38] Nevertheless, 0.5% to 2% of the population are tinnitus sufferers,[39,40] in whom auditory phantoms can substantially intrude on life activities, drive emotional (depression) and behavioral (anxiety and obsession) distress, disrupt sleep, and impair concentration.

Tinnitus epidemiological features have been well characterized, but its natural history remains poorly defined.[41] Drawing from clinical experience, virtually all new-onset tinnitus patients will find their unfamiliar phantom percepts relatively loud, commanding attention, and annoyingly intrusive. Over the course of 6 to 12 months, most patients will generally report their phantom percepts are much softer and more familiar, no longer commanding attention and by and large easy to ignore. In some patients, tinnitus will have nearly or completely vanished from conscious awareness. This typical course accounts for the vast majority of tinnitus patients who become well adapted to their auditory phantoms. In a select minority, patients suffer because phantom percepts remain as salient as they were at the onset. Despite auditory phantoms having become familiar, they continue to drive attentional, emotional, motivational, and behavioral distress. This atypical course characterizes tinnitus patients who become sufferers. Of interest is that well-adapted tinnitus patients and poorly adapted tinnitus patients cannot be distinguished on the basis of tinnitus loudness, pitch, or maskability.[37,38,41] There is a need to relate typical and atypical clinical courses of new-onset tinnitus with neurophysiological substrates that underlie them. A model centered on striatal gating of auditory phantoms and modulation of gate control by the ventral striatum and related circuits may be appropriate.

Striatal Gate Control of Phantom Percepts

We propose a phantom percept gate control model (Figure 2) with architecture that accounts for recent and current area LC neuromodulation findings in the context of corticostriatal connectivity, basal ganglia neurophysiology, clinical courses of new-onset tinnitus, and limbic circuit involvement in tinnitus. The conceptual framework is inspired by related work on basal ganglia circuitry and function.[27,42] Key assumptions of the proposed model are (1) instruction on details of phantom percepts are represented in the central auditory system[13,19,43-45]; (2) permission to gate candidate phantom percepts for conscious awareness is controlled by the dorsal striatum[46-48]; (3) action to attend, reject, or accept phantom percepts and form perceptual habits is decided by the ventral striatum[26,27,42,47]; and (4) determination of tinnitus distress severity is mediated through the limbic and paralimbic system–nucleus accumbens–ventral striatum loop.[25,49]

Corticostriatal connectivity between the auditory cortex and dorsal striatum is likely the primary avenue to deliver transformed auditory phantom representations to the basal ganglia.[50-52] Those striatal signals are not automatically gated to permit awareness of phantom percepts. Dorsal striatal area LC gate control is normally restrictive (closed position) but can become permissive (open position) by DBS neuromodulation or in pathological states. When the dorsal striatal gate is in an open position, phantom awareness permission is communicated to the auditory cortex for execution of tinnitus neural representations. Conditions that can cause gating permissiveness are principal dorsal striatal gate

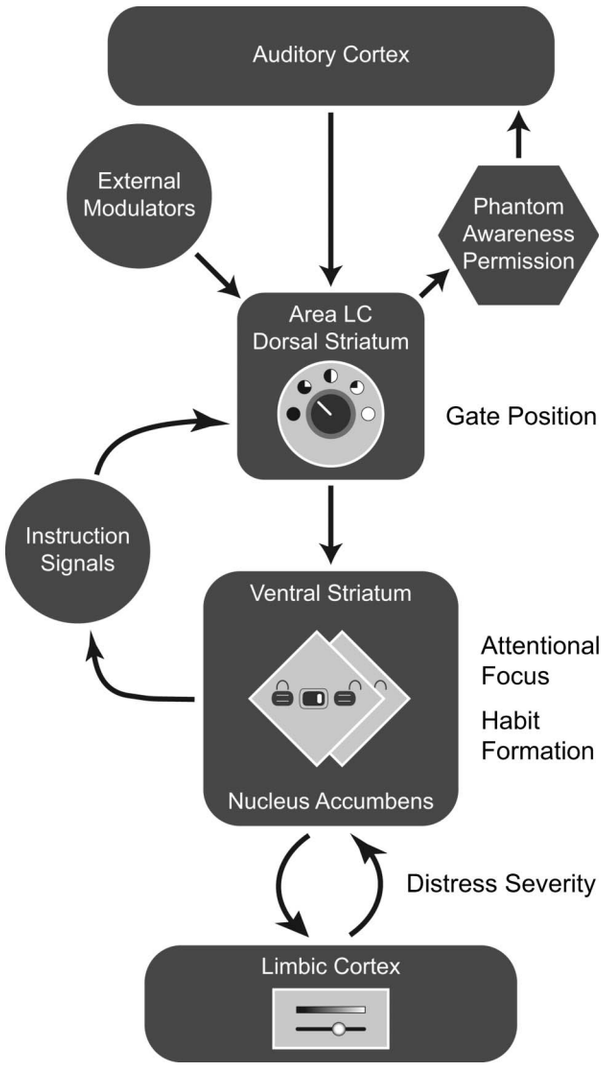

FIGURE 2. *Phantom percept gate control model. Conscious awareness of auditory phantoms is contingent on associated corticostriatal signals passing through area LC of the dorsal striatum. Gate position is determined by restrictive integrity of area LC, strength of phantom percept neural representations, external modulators, and the ventral striatum. Phantom awareness permission is communicated to the auditory cortex for execution of tinnitus neural representations. Attentional focus to and habit formation of auditory phantoms are controlled by the ventral striatum. Instruction signals mediated through intrastriatal and nigrotegmental pathways feedback to the dorsal striatum to modulate gate position. When the limbic cortex, nucleus accumbens, and ventral striatum circuit are engaged, burdensome phantom percept habits elicit varying levels of behavioral and emotional distress.*

dysfunction and exceptionally strong phantom neural representations. Because the basal ganglia are central to sensorimotor integration, area LC gate permissiveness may be modulated by a variety of external factors. Some well-documented tinnitus modulators are somatosensory stimuli,[8,53,54] sensorimotor jaw protrusion,[55,56] and neck contracture[9,57] movements and motor gaze-evoked events.[58-60] Tinnitus may also be modulated by external auditory stimuli,[61-63] as demonstrated by subjects 4, 5, and 6; the triggering of new auditory phantoms depended on presence or absence of an external 1-kHz tone.

With new-onset tinnitus, immediate action by the ventral striatum on the unpredictable auditory phantom is to shift attentional focus to the percept. Later, action by the ventral striatum on an aged, predictable auditory phantom that serves no useful behavioral purpose is to decrease attentional focus and increase gate restrictiveness through feedback instruction signals to area LC.[64] In doing so, a phantom percept may mostly or completely vanish. However, corrective drive to increase gate restrictiveness may be inadequate, thereby enabling a chronic, continuous auditory phantom to become a perceptual habit.[27,65] A phantom percept habit may or may not command attention. In the former, action by the ventral striatum to extinguish attention to a predictable auditory phantom is ineffective.

The limbic cortex loop includes limbic and paralimbic brain structures, nucleus accumbens, and the ventral striatum. This circuit represents a plausible neural substrate for the genesis and maintenance of behavioral and emotional distress associated with burdensome phantom percept habits. Tinnitus distress severity manifests as depression, anxiety, emotional fragility, sleep disturbance, and impairment of daily living activities.[25] Human imaging studies[66,67] have identified structural alterations and atypical activation of limbic and paralimbic structures in tinnitus patients. Recently, an auditory-centric model based on auditory thalamus and limbic structure interactions was proposed to account for chronic tinnitus.[68,69] In contrast, the phantom percept gate control model is basal ganglia centric. Gate permissiveness of the dorsal striatum is modulated by instruction signals from the ventral striatum. Intrastriatal and nigrotegmental pathways connect the dorsal and ventral striatum[70] to effect circuit function modifications.

Basal Ganglia Reach to Intangibles

The operational reach of basal ganglia function extends beyond the domain of measurable and observable sensorimotor events to include the domain of intangible phantom percepts. Striatal gating of phantom percepts may not be specific to audition but also include other sensory modalities. Certainly, basal ganglia neurodegenerative Parkinson disease patients report visual, auditory, olfactory, and tactile hallucinations.[71-74] The genesis of those hallucinations is thought to be multifactorial and may involve disease- and/or treatment-related neurotransmitter changes, sleep disturbance, alterations in sensory systems, and deficits in attention. It is an open question whether striatal gating dysfunction plays an underappreciated role in Parkinson disease–related sensory phantom percepts.

Study Limitations

A limitation of this study is that triggered auditory percepts in subjects without baseline tinnitus may represent activation of fragments of complex auditory representations laid down by previous auditory experience and not strictly auditory phantoms per se. Use of the term auditory phantoms is based on the simple hypothesis that electrical stimulation in area LC acts to modulate auditory phantom percepts. The triggering of auditory phantoms in subjects without tinnitus may be viewed as modulating potential tinnitus percepts normally at loudness level 0 to a level higher for consciousness awareness. A more complex hypothesis is to consider differential effects of electrical stimulation in area LC for those with and without tinnitus. For those with tinnitus, auditory phantoms are being triggered. For those without tinnitus, sounds embedded in auditory memory are being accessed. Both hypotheses are plausible. At this time, there are no data to suggest that either hypothesis is incorrect. Another limitation of this study is that the investigated patients had movement disorders, which are related to abnormalities of basal ganglia function. The generalizability of the study results to populations without movement disorders will need to be demonstrated.

CONCLUSION

Results of this study suggest long-term DBS neuromodulation of dorsal striatal area LC may be deployed to control gating of problematic auditory phantoms embedded in central auditory activity. For translation to clinical therapy, efficacy assessment of striatal neuromodulation on tinnitus severity will be required in a pivotal clinical trial.

Disclosure

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COMMENTS

The authors refer to the new sounds that were described by their patients without tinnitus as auditory phantoms. That is a provocative claim. There is a stimulus here (DBS) that might conceivably activate through neural pathways fragments of complex auditory representations laid down by previous auditory experience. Tinnitus, on the other hand, is truly a phantom sound that is perceived under conditions in which no percept would be expected. The interpretation of the new sounds as phantoms may confuse a potentially important distinction.

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This article is an impressive example of how brain stimulation complements imaging studies in the investigation of brain function. The authors describe that electrical stimulation in area LC, a locus of the caudate nucleus positioned at its anterior body, can trigger phantom tones, can modulate sounds, and can alter sound quality of an existing tinnitus. Based on these results, the authors propose a striatum-centered gating model of auditory phantoms. They further assume that gate control is modulated by the ventral striatum and related circuits.

It has been clearly demonstrated that alterations in primary sensory areas are not sufficient for the conscious perception of phantom perceptions such as tinnitus or phantom pain.[1] Imaging studies suggest that phantom percepts rather emerge as a consequence of altered network activity in several overlapping networks involving auditory and non-auditory brain areas.[2-4] However, an inherent limitation of these functional imaging studies is that they provide only correlations and cannot prove whether identified brain networks play a causal role or represent rather pure epiphenomena. Deep brain stimulation of specific brain regions provides a unique opportunity to verify and specify the relevance of these areas. Exactly this has been done in the study of Larson and Cheung. Different aspects of auditory perception have been investigated in patients who received deep brain stimulation in area LC for the treatment of movement disorders. Even if the interpretation of the findings is to some extent limited by the abnormalities of basal ganglia function from which the investigated patients suffered, the results provide important new insights in the functional relevance of area LC. Under specific stimulation conditions, area LC stimulation contributes to the emergence of phantom auditory percepts and modulates the perception of real and phantom sounds. Based on this finding, the authors propose a unique gating role for the dorsal striatum and develop a striatum-centered model of phantom perceptions. This may be

a somewhat speculative interpretation because it is not known whether the observed effects occur only in area LC and whether this area is really the critical gate in the circuits involved in auditory perception. Moreover, animal studies challenge the proposed model by demonstrating that perception gradually builds up across various cortical areas and that phantom perceptions can be generated in any part of the distributed system.[5,6] However, even if the proposed striatum-centered model based on an unique role for area LC remains speculative, the presented study clearly indicates a critical role for this area in the modulation of auditory perception. From a practical perspective, this is an extremely important finding because it provides a first hint for a potential new therapeutic target. Given the fact that many new therapeutic approaches in the treatment of central nervous system disorders evolved from careful clinical observation of unexpected findings, the authors are to be congratulated for systematically exploring the effect of area LC stimulation on auditory perception in the time-constrained operating room setting.

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The authors' results further strengthen the neurophysiological model of tinnitus, which includes the crucial involvement of other than auditory systems in the brain in clinically significant tinnitus, with stress on the limbic and autonomic nervous systems, further pointing out the role of a gaiting system.[1-4] Although it is possible to argue with the hypothesis proposed by the authors, its correctness is of secondary importance at this stage of investigation. Praiseworthily, the authors' results point out a new dimension in research on the mechanisms of tinnitus.

It is still not clear whether these findings may have direct implication on tinnitus treatment; nevertheless, they are helpful in understanding the mechanisms of tinnitus distress as well as indicating potential new clinical approaches. For example, potentially the stimulation of the caudate nucleus could be achieved by transcranial magnetic stimulation (rather than direct electrical simulation described in the article), and this approach would facilitate clinical trials as well as further basic research.

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