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An Animal Model of Deep Brain Stimulation for Treating Tinnitus: A Proof of Concept Study

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**Objective:** This proof-of-concept study aimed to demonstrate therapeutic effects of deep brain stimulation (DBS) on noise-induced tinnitus.

**Study Design:** Experimental animal study.

**Methods:** After Institutional Animal Care and Use Committee approval, nine adult rats were implanted in the caudate nucleus with custom-made electrode array. The rats were exposed to noise to induce tinnitus. Auditory brainstem response was performed to evaluate hearing threshold changes. Noise-induced tinnitus and its suppression by DBS were evaluated using the gap-detection acoustic startle reflex behavioral paradigm and electrophysiological evaluation of modulatory effects on neural correlates of tinnitus. Various stimulation parameters were used to determine the most effective ones in affecting behavioral changes, along with corresponding neural activity in the caudate nucleus. The correlation between the caudate nucleus and auditory cortex also was determined. Analysis of variance with Bonferroni correction was performed to examine DBS-induced effects on behavioral evidence of tinnitus.

**Results:** Bursting activity, a neural marker of tinnitus, was noted to decrease compared to baseline in tinnitus (+) animals. After stimulation, spontaneous and bursting activity increased in the tinnitus (+) animals but decreased in the tinnitus (−) animals. Behavioral data suggested suppression of tinnitus after DBS. These effects lasted up to 5 days. To our knowledge, this is the first development of an animal model to test deep brain stimulation of the caudate region for the treatment of tinnitus.

**Conclusions:** Deep brain stimulation of the caudate nucleus can modulate tinnitus in a rat model of tinnitus.

**Key Words:** Rat, noise exposure, tinnitus, deep brain stimulation (DBS), caudate nucleus, behavioral testing.

**Level of Evidence:** NA

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**INTRODUCTION**

Noise-induced tinnitus is thought to result from central maladaptive changes after auditory pathway damage. It diminishes quality of life and has an economic toll on society.1–3 It is thought that noise-induced hearing loss leads to downregulation of inhibitory transmission to the central auditory system (CAS). This leads to abnormal hyperactivity in the CAS, such as increased spontaneous firing rate, and may lead to increased bursting and synchronous oscillations.4 Many investigations suggest that tinnitus manifests as increased spontaneous activity (SA), bursting activity (BA), neurosynchrony, and/or tonotopic reorganization in auditory brain structures.5–7 Bursting activity and neurosynchrony represent the emergence of temporal pattern of what are random discharges of SA. Similar effects are noted in the hippocampus and the amygdala, which may have a role in auditory fear conditioning and the acoustic startle reflex. In addition, the striatum receives auditory inputs and can modulate the startle reflex.8 Thus far, the underlying mechanism of tinnitus remains elusive.

The available treatments (sound therapy, medications, diet, cochlear stimulation, vagal nerve stimulation, somatosensory modulation) are inconsistently effective.9,10 Recently, electrical neuromodulation (transcranial direct current stimulation [tDCS], transcranial magnetic stimulation [TMS], and direct auditory cortex [AC] electrical stimulation) of the brain has gained interest. However, the effects on tinnitus have been short-lived and variable across individual subjects.10–12

A recent study demonstrated tinnitus suppression by using deep brain stimulation (DBS) of the dorsal cochlear nucleus (DCN) in a rat model of tinnitus.13 The effects might have been due to reduction of BA. Although there has been extensive work done on evaluating neural correlates of tinnitus in the classical auditory pathway, recently there has been increased interest in evaluating the nonclassical regions, such as the striatum, which may be involved in the perception of distress associated with tinnitus.8 Clinical studies have evaluated the effect of
DBS of nonauditory regions on tinnitus.\textsuperscript{14,15} Historically, DBS has been effective in many disorders, including Parkinson’s disease, essential tremor, chronic pain, epilepsy, and obsessive-compulsive disorder.\textsuperscript{16–19} Deep brain stimulation has the potential to stimulate deep brain regions of the classical and nonclassical auditory pathways. Recent human studies have targeted the ventral intermediate nucleus of the thalamus (VIM) and caudate nucleus to examine the suppressive effects on tinnitus.\textsuperscript{14,15}

To understand how nonauditory neural structures may interact with the classical auditory pathway, it is important to understand the functional connections between the regions. Anatomically, the caudate nucleus and putamen are termed the striatum. Their output is via gamma-aminobutyric acid (GABA)ergic inhibitory neurons to the globus pallidus (GP) and substantia nigra. The GP has inhibitory GABAergic output that is tonically active. It is involved in a direct and indirect pathway, and along with the basal ganglia are involved in motor control and reinforcement of behavior, controlling emotional tones and responsiveness to external stimuli through its connections with the limbic cortex.\textsuperscript{20–22} The limbic cortex has projections to the nuclei accumbens, where the head of the caudate and putamen meet. This region of the anterior caudate projects to the dorsomedial nucleus of the thalamus, which feeds back to the limbic cortex, maintaining behavioral tone and motivation.\textsuperscript{21,22} Animal and human studies show similarities in anatomical function connections that correspond to specific associative, sensorimotor, and limbic loops involving the dorsal, caudal, and ventral striatum, respectively.\textsuperscript{22} In addition, the striatum has extensive connections with the classical auditory pathway.\textsuperscript{8} These anatomical connections of the caudate nucleus would make it a promising target for modulating tinnitus and its related neural activity. Due to these similarities between animal and human functional connections, we may be able to apply findings in the animal model to human trials.

We hypothesize that DBS of the caudate nucleus suppresses tinnitus and downregulates its neural correlates. Presently, there is no animal model of DBS to evaluate the pathophysiology of tinnitus involving the caudate/basal ganglia region. By using a behavioral animal model, we can explore many electrical stimulation parameters that could be translated into clinical testing for better results. Additionally, recording from awake animals allows investigation of tinnitus behavior and its related activity over time and removes the effects of anesthesia on neural activity.

**MATERIALS AND METHODS**

**Animal Subjects and Surgical Implantation**

Adult male Sprague-Dawley rats (350–450 g) were used. All procedures were performed in accordance with guidelines by the Institutional Animal Care and Use Committee at Wayne State University (Detroit, Michigan, U.S.A.) and the National Institutes of Health. Before implantation and testing, animals were trained in a custom restrainer to acclimate animals to the gap-startle reflex behavioral procedure. The restrainer was later placed in a chamber (Kinder Scientific, Poway, California, U.S.A.) for testing gap-startle reflex. Nine animals with consistent and measurable behavioral startle responses were selected.

Surgical implantation of DBS electrode array was performed bilaterally in the anterior caudate nucleus under general anesthesia using a mixture of air (0.41/minute) and isoflurane (2%–3%, volume/volume). A stereotaxic apparatus was used (Kopf Model 1350, David Kopf Instruments, Tujunga, California, U.S.A.). The animal’s body temperature was maintained at 37°C. A craniotomy was performed, and bone screws inserted into the skull surrounding the surgical openings and the dura were removed over the anterior caudate region identified using coordinates in a rat brain atlas (Paxinos and Watson, 1982). A custom multichannel neural electrode was implanted using the Kopf stereotactical alignment system (David Kopf Instruments) and fixed in place with screws and dental cement (Fig. 1). A week was given to allow animals to recover from the surgical procedures before further experiments were conducted.

**Auditory Brainstem Response Recordings**

To determine hearing thresholds, auditory brainstem responses (ABRs) were measured before and after sound exposure and then weekly. After induction of anesthesia, the active electrode was placed on the top of the head; the reference electrode was inserted below the pinna and the ground electrode was inserted in the contralateral temporal muscle. Click and tone stimuli were generated by RX6 Multifunction Processor (Tucker-Davis Technologies [TDT], Alachua, Florida, U.S.A.) and SigGenRP software (TDT). Tone bursts of 10 ms duration were delivered at 4, 8, 10, 16, 20, 24, and 30 kHz (0.5 ms rise/fall). Each click or tone was presented separately from a 100 dB peak equivalent sound pressure level (SPL) down to 5 dB, decreasing by steps of 5 dB. ABR signals were amplified, band-filtered (300 Hz–3 kHz), and notch-filtered (60 Hz). Click and tone-evoked responses were averaged 300 and 400 times, respectively. Threshold was considered the lowest intensity at which a distinct biological waveform remained.

**Noise Exposure to Induce Tinnitus**

To induce tinnitus, six animals were noise-exposed in the left ear. The other three animals were used to determine the accuracy of our surgical targeting and for evaluating biocompatibility. Each animal was anesthetized as described above, and its right ear was plugged and sutured closed. Each animal was allowed to wake up prior to noise exposure. An 8 kHz to 16 kHz band noise was delivered at 115 dB SPL for 2 hours. After noise exposure, the sutures and earplug were removed. Using these parameters, we previously have achieved temporary threshold shifts (TTS) and chronic tinnitus. A TTS exposure noise was used to minimize confounding effects of hearing loss on gap-and prepulse-inhibition (PPI) data.

**Behavioral Testing for Tinnitus**

As previously described, gap-detection acoustic startle reflex behavioral assay was performed to evaluate tinnitus and DBS-induced suppression.\textsuperscript{23} In gap testing, 2 kHz narrow band noise of 6 to 8, 10 to 12, 14 to 16, 18 to 20, and 26 to 28 kHz and broadband noise (BBN) (2–30 kHz range) was presented at 60 dB SPL to animals as background noise in a pseudorandom order. For each band frequency, a total of 16 trials were performed, which consisted of eight startle-only and eight trials with a 40 ms silent gap prior to a 50 ms 115 dB white noise sound as a startle stimulus. Rats with tinnitus fail to hear the
silent gap when the background sound is similar to their tinnitus, preventing startle reflex suppression. Hearing was examined using a PPI startle-reflex behavioral procedure and measuring ABR thresholds before and after implantation and after noise exposure. The PPI procedure is similar to gap testing, except that no background noise is given. For PPI testing, the gap is replaced with a 40 to 50 ms prepulse at 60 to 65 dB SPL, starting 90 ms before the startle stimulus. Each prepulse consists of the same frequencies used for gap detection. Startle force is measured by piezoelectric transducers. When a rat hears a prepulse at a given frequency, its startle reflex will be diminished compared to the startle-only response. If a rat loses hearing at certain frequencies, its startle amplitude in trials with prepulses will be similar to startle-only trials.

**Deep Brain Stimulation Modulation of Behavioral Evidence of Tinnitus**

For modulation of behavioral evidence of tinnitus (gap-startle response), DBS was performed by delivering single charge-balanced unipolar pulses (duration = 1 ms) that were generated with TDT hardware. The electrical current, optically isolated with a multichannel stimulator (MS16, TDT), was delivered at 50 μA and 10 pulses per second (pps), 75 μA and 20 pps, and 150 μA and 40 pps, all at a pulse width of 100 μs and at different time points in two tinnitus (+) animals. The electrical pulses were delivered continuously, independent of the delivery of either gap or startle stimuli for 30 minutes. Finally, gap-detection test was repeated without electrical stimulation immediately after and at poststimulation days 1, 2, 3, 5, and 7. Bilateral and unilateral stimulation were performed to determine the optimal effect on tinnitus suppression.

**Electrophysiological Recording of Neural Correlates of Tinnitus in the Caudate Nucleus**

After implantation, baseline spontaneous and sound-driven multiunit and local field potentials were measured at the caudate nucleus. The implant was connected to a real-time signal processing system (RZ2, TDT) with a 25 kHz sampling rate and a 1,000 to 3,000 Hz band-pass filter. The threshold for spikes was set at two times the standard deviation. The response to different frequency-intensity combinations was used to determine the frequency tuning curves (FTCs) from the recording sites for 30 minutes. Spontaneous single and multiunit spikes were recorded twice, the first 5 minutes prior and the second 5 minutes after measurement of FTCs. Each spontaneous recording period lasted 5 minutes. Local neural response to BBN was measured for 5 minutes. Spontaneous activity data collected after the FTC measurements were used for analysis due to stability. In addition, bursts in spike trains were detected using the Poisson-surprise method with Neuroexplorer software (NexTechnologies, Herndon, Virginia, U.S.A.). This is based on the negative binary logarithm of the probability of the occurrence of a given number of spikes in a particular time interval. According to this method, spikes in a burst are added (from a minimum of three spikes) as long as the Poisson-surprise value increases. Only bursts with a surprise value of at least 4, which means that they were occurring 16 times as frequently as in a Poisson spike train with the same firing rate, were included in the analysis.

After noise exposure and hearing recovery, local neuronal activity with our implant in place was measured and compared between the animals with and without tinnitus. Frequency tuning curves were measured again and then response to BBN was measured for 5 minutes, which were followed by a 5-minute recordings of spontaneous single- and multiunit activity and local field potentials (LFPs) without stimulation. Testing was continued for 180 minutes.

Following determination of reliable tinnitus behavior, DBS was used to modulate neurophysiological correlates of tinnitus. Prior to DBS, the SA, FTCs, and BBN-driven responses were recorded. The right caudate nucleus was stimulated using single charge-balanced, bipolar, and biphasic pulses (duration = 1.0 ms) generated from TDT hardware (RX7 Microstimulator) and delivered at 50 μA and 10 pps through an optically isolated multichannel stimulator. The right anterior implant shaft (located...
in the anterior caudate nucleus) was chosen as the initial site of stimulation for 10 minutes, which was followed by 10 minutes of stimulation at the right posterior shaft. Spontaneous multi-unit activity and local field potentials then were again recorded.

**Electrophysiological Recording of Neural Correlates of Tinnitus in the Auditory Cortex**

Recording was made from the A1 region of the AC in the right hemispheres of each rat. After anesthesia, a craniotomy was performed to provide access to the A1. The skull and corresponding dura were removed on the right side to expose the temporal lobe using landmarks on the skull. Using the Kopf micromanipulator (David Kopf Instruments), a 16-channel micro wire array (Clunbury Scientific; Troy, Michigan, U.S.A.) was used. Each array consisted of 16 insulated platinum/iridium micro wires that were arranged in two rows with eight wires in each row. The array covered an area of about 0.4 × 3.2 mm and was inserted in the A1 region. The array was lowered 0.8 to 0.9 mm from the AC surface, corresponding to layers 4 to 5 of the brain. The output was connected to a signal processing system (RZ2, TDT) with 25 kHz sampling rate and 100 to 3,000 Hz band-pass filter from units in which the signal-
to-noise ratio was ≥ 1.5. The responses to different frequency-intensity combinations (2–42 kHz, 4.5 octave, 5–85 dB, 7 dB step, each played 5 times) were used to construct FTCs for the recording sites. Multichannel spontaneous single- and multiunit spikes were recorded before and after DBS for 3 hours; each recording block lasted 10 minutes, recorded at every half hour after stimulation.

**Histological Verification of Electrode Implantation**

Upon completion, all animals were euthanized and their brains processed histologically. Each brain was removed and postfixed for 4 to 6 hours and subsequently cryoprotected by immersion in 30% sucrose in 0.1 M PB (pH 7.4) at 4°C overnight. Coronal sections (50 μm thick) were examined for the accuracy of implant placement.

**Data Analyses**

To minimize variability in gap-startle responses across animals and tests, ratios were calculated and averaged. The ratio was calculated by dividing gap-detection responses by their corresponding mean startle-only responses. Significantly smaller responses within gap conditions compared to no-gap conditions reflect that the animal could clearly hear the silent gap. If tinnitus develops, gap detection would be compromised. To evaluate stimulation-induced suppressive effects, the gap-detection ratio values obtained during and after DBS were compared with those obtained before stimulation. Analysis of variance (ANOVA) with Bonferroni post hoc tests for multiple comparisons was performed to examine DBS-induced effects on behavioral evidence of tinnitus. Significance was set at $P < 0.05$.

Electrophysiologically, the characteristic frequency (CF) of each recording site was obtained by assessing the evoked neural activity, with the stimulus tone frequency presenting at the lowest intensity level. Each channel produced clear CFs. To avoid misrepresentation of spikes for particular CFs caused by variable penetrations in the brain across different rats, three frequency bands were established in the AC (2–4 kHz, 4–16 kHz, and 16–42 kHz) to represent low, intermediate, and high frequency bands. The matrix of pairwise peak correlation values was subjected to a hierarchical clustering procedure and analyzed by a custom-made program in MatLab (MathWorks, Natick, Massachusetts, U.S.A.) and NeuroExplorer (NexTechnologies). The peak cross-correlation coefficients ($C$) were obtained from the following equation: $C = C = \frac{s_{xy}}{\sqrt{s_x s_y}}$, where $s_x$ and $s_y$ represent the numbers of spikes in channel $x$ and $y$. 

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**Fig. 5.** Gap-detection results after DBS. Behavioral modulation of tinnitus using DBS. Gap-testing animal: CI2-12. No statistically significant decrease in gap ratio (one-way ANOVA with Bonferroni correction $df = 29$, $F = 3.724$). Gap testing animal DB-15: ANOVA Bonferroni ($df = 37$, $F = 4.160$): significant difference noted between pre-e-stim and during e-stim ($P = .034$) and between pre-e-stim and post-e-stim ($P = .039$). Dotted circle identifies the frequency range at which there was significant reduction in gap ratio, suggesting suppression of tinnitus at that frequency range. ANOVA = analysis of variance; BBN = broad band noise; e-stim = electrical stimulation; stl = startle only condition. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]
channel \( y \). For simultaneously recorded signals, the cross-correlation function, \( C(\tau) \), was calculated with one signal time shifted relative to the other signal by \( \tau \) time points (lags) for digital signals. \( C(\tau) \) was used to determine causality of network interactions between sites. When signal \( x \) causes \( y \) and occurs before signal \( y \) by \( \tau_{xy} \) time points, the peak of the \( C(\tau) \) function occurs at a time lag of \(-\tau_{xy}\). Bin size was 5 ms.

RESULTS

**Hearing Evaluation Before and After Implantation and Noise Exposure**

Figure 2 shows the apparatus used for implantation and the DBS implant in situ. After implantation, no hearing loss was noted (Fig. 3). After noise exposure, there was a temporary hearing threshold shift that recovered 1 month later (Fig. 3).

**Gap Detection**

Four of the six (67%) animals exposed to noise developed chronic tinnitus, tinnitus (+), as revealed by gap-startle reflex (Fig. 4); the other two were designated as tinnitus (-). The tinnitus (+) animals had significantly higher postnoise exposure gap ratios as compared to pre-exposure gap ratios, and not lower than the post-exposure startle-only ratios. There was a significant difference in gap ratio at 12 kHz, 20 kHz, and 28 kHz, and at BBN \((P < .05)\), suggesting presence of tinnitus at these frequencies.

**Deep Brain Stimulation Suppression of Behavioral Evidence of Tinnitus**

Only two animals with chronic tinnitus and consistent gap-startle responses were available for further study at 3 months after noise exposure to determine if DBS of the caudate can modulate the animals' tinnitus behavior, as measured by their gap-startle response. These two animals (CI2-12 and DB-15) had evidence of persistent tinnitus at 26 to 28 kHz and at BBN, with animal CI2-12 having slight but not significant increase in startle response at 10 to 12 kHz. Gap-startle response was measured during and after DBS for 180 minutes and then repeated at poststimulation days 1, 2, 3, 5, and 7.
Gap testing for animal CI2-12 showed decrease in gap-startle response immediately after DBS. However, this was not statistically significant (one-way ANOVA with Bonferroni correction df = 29, F = 3.724). Gap testing of animal DB-15 showed a significant reduction in tinnitus after DBS at 26 to 28 kHz, as noted by a decrease in gap ratio between pre e-stim and during e-stim (DBS) (P = .034) and between pre e-stim and post e-stim (P = .039) (ANOVA Bonferroni (df = 37, F = 4.160) (Fig. 5). The effect was persistent in animal CI2-12 up to 3 days after treatment, and in animal DB-15 the suppression of tinnitus was noted on day 5 after treatment (Fig. 6). In some cases, DBS may have elicited tinnitus; on day 5, animal DB-15 demonstrated a new onset of tinnitus at 10 to 12 kHz. No difference was noted in tinnitus suppression with different current levels (50, 75, and 150 μAmp).

Brain histology revealed accurate placement of the implants in the planned regions of the caudate nucleus.

**Effects of Deep Brain Stimulation on Neural Correlates of Tinnitus in the Caudate Nucleus**

After hearing recovery, animals in both groups were noted to have increased SA, a neural marker of tinnitus, with greatest activity noted in the region of the right caudate nucleus. However, BA, a neural marker of tinnitus, decreased in the right caudate region of the tinnitus (+) animals. After noise exposure and recovery of hearing, tinnitus (−) animals had an increase in BA in both the right and left caudate nuclei, which then returned to near baseline within 2 weeks (Fig. 7). Deep brain stimulation of the right ventral caudate nucleus, using a 10-minute bipolar electrical stimulation involving one distal electrode pair on the right anterior implant shaft, was performed first, followed by stimulation using a distal pair of electrodes in the right posterior shaft for a total of 20 minutes. Subsequently, SA and BA in the caudate nucleus were evaluated. In Figures 5 to 7, CH3 and CH4 were designated as the recording electrodes in the right anterior caudate region, with CH4 just posterior to CH3, whereas CH1 and CH2 were designated as the recording electrodes in the left anterior caudate, with CH1 just posterior to CH2. The site of DBS was in the region near CH3 and CH4, with the region around CH4 being the last region of stimulation before measuring neural activity. The tinnitus (+) animals had an increase in SA and BA after DBS, with a maximum noted at 120 minutes and 90 minutes, respectively. Interestingly, the tinnitus (−) animal had a decrease in SA and BA after DBS (Figs. 8 and 9).

![Post Noise Bursting Activity Tinnitus (+) Animals (n=4)](image1)

![Post Noise Bursting activity Tinnitus (-) Animals (n=2)](image2)

**Effects of Deep Brain Stimulation on Neurosynchrony Between the Caudate Nucleus and Auditory Cortex**

Evaluation of synchronous activity between the caudate nucleus and AC shows that, after DBS, there was a temporary decrease in the correlation between the two regions (Fig. 10). However, the effect only was noted in the lower frequencies. This suggests that DBS of the caudate nucleus leads to changes in the interaction between the AC and the caudate nucleus. This confirms our hypothesis that stimulation of the caudate can...
modulate activity in the AC, which in this case is the reduction of tinnitus activity.

DISCUSSION

Several regions of the auditory pathway play a role in the generation and/or modulation of tinnitus. Acoustic stimulation, repetitive TMS, tDCS, and cochlear stimulation are being studied to treat tinnitus but have shown inconsistent efficacy and poor reliability. Acoustic stimulation, cochlear implant stimulation, and direct stimulation of the AC take a top-down approach to suppress tinnitus, possibly utilizing corticofugal pathways. DCS, rTMS, and direct stimulation of the DCN use a bottom-up approach to modulate tinnitus. The mechanisms behind cochlear implant stimulation and the induced effects on tinnitus are not understood.

It is postulated that DBS works by silencing neurons, such as the effect of a “lesion” in the area. However, suppressive effects on tinnitus may be due to excitatory and inhibitory effects. Animal studies also have shown release of both GABA and glutamate. Meanwhile, human studies have suggested GABA and cyclic guanosine monophosphate (GMP) as the causative neurotransmitters.

I. Deep Brain Stimulation -Induced Tinnitus Suppression Involves Nonauditory Pathway

The data show that BA notably decreased in the caudate nucleus of tinnitus (+) animals and increased in the caudate nucleus of tinnitus (−) animals after noise exposure. Meanwhile the SA increased in both groups. This is somewhat similar to effects reported by Chen et al., who noted that after noise exposure in their rats, the spontaneous firing rates in the striatum only increased slightly. However, the tone-evoked activity decreased in the striatum while increasing in the AC. Because they did not evaluate for the behavioral presence of tinnitus in their animals, it is entirely possible that tinnitus (+) animals would have significantly increased SA. Further work needs to be done to better understand the differences noted in BA and SA in the
III. Electrical Stimulation of the Caudate Nucleus Modulates Neural Activity at the Auditory Cortex

Our findings suggest a mechanism by which the caudate nucleus may modulate tinnitus percept at the level of the AC. It is established that habit and attentional focus are controlled by the ventral striatum. Furthermore, limbic structures can add varying levels of distress. It is postulated that phantom awareness of sound is communicated to the AC and then modulated by external factors, ventral striatum, and the limbic cortex, with the dorsal striatum possibly acting as an additional gate or amplifier.

As described earlier, there are several anatomical and functional loops (direct and indirect) between various brain regions and the striatum. Our findings suggest that DBS of the caudate nucleus may be interacting with the AC via a similar indirect pathway. The data presented in Figure 10 suggest that correlational activity exists between the AC and caudate nucleus that can be modulated by DBS of the caudate nucleus, with resultant decrease in activity in the lower frequencies.

Figure 11 illustrates our proposed mechanism by which this modulation may occur. We suggest that stimulation of the caudate nucleus leads to increased neural activity (SA and BA) that amplifies inhibition of the globus pallidus externa via GABAergic neurons. The amplified inhibition may in turn reduce the baseline inhibition of the subthalamic nucleus, resulting in increased stimulatory effects on GP internus and enhancement of the inhibition of the thalamus, which results in decrease in thalamocortical input with subsequent decrease neural activity at the AC. This proposed mechanism utilizes the known connections between the various structures of the basal ganglia (striatum, globus pallidus, thalamus) and the AC, as described previously.

This work represents a preliminary proof of concept study. It is limited due to a small number of animals in the tinnitus (+) and tinnitus (−) groups and due to lack of a control group with implants but no noise exposure. In the future, we plan to include a larger number of animals to confirm our preliminary findings. In addition, we will further evaluate the correlational effects between the caudate nucleus and the AC to better understand the role that nonauditory structures may have in changing the neural activity in the AC.
CONCLUSION
Deep brain stimulation of the anterior caudate nucleus suppresses behavioral evidence of tinnitus in rats and suppresses the neural correlates of tinnitus. In addition, the findings suggest a neural loop that may be utilized to modulate tinnitus percepts in the auditory cortex. This loop is consistent with known neural connections/interactions.

BIBLIOGRAPHY