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TINNITUS MODULATION BY DEEP BRAIN STIMULATION IN LOCUS OF CAUDATE NEURONS (AREA LC)

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Abstract—Tinnitus is an auditory disorder characterized by perception of internally generated phantom auditory sensations without corresponding mechanical stimuli arising from the body or external environment. Current auditory based treatment approaches, sometimes in conjunction with non-auditory based strategies, such as Tinnitus Retraining Therapy and Cognitive Behavioral Therapy, have been helpful in mitigating symptoms for the majority of patients. Yet there are over 1 million tinnitus sufferers who still endure troublesome chronic, continuous head noises that are debilitating and interfere with activities of daily living. Here we show that application of deep brain stimulation (DBS) therapy to a locus of caudate neurons (area LC) in the body of the nucleus, a subsite of the striatum that is not part of the classical auditory pathway, can decrease or increase tinnitus loudness perception. The DBS lead traversed through or was adjacent to area LC in six Parkinson's disease and essential tremor subjects with concomitant tinnitus who underwent implantation of the subthalamic or ventral intermediate nucleus. In five subjects where the DBS lead tip traversed area LC, tinnitus loudness in both ears was suppressed to a nadir of level 2 or lower on a 0–10 rating scale. In one subject where the DBS lead was outside area LC, tinnitus was not modulated. In three subjects with preoperative and postoperative audiograms, hearing thresholds were unchanged by area LC stimulation. Neuromodulation of area LC may be interrupting perceptual integration of phantom sensations generated in the central auditory system. This new, basal ganglia based approach to tinnitus modulation warrants further investigation and may be ultimately refined to treat patients with refractory symptoms.

Key words: phantom perception, sensation, auditory, caudate nucleus, suppression, integration.

Tinnitus affects 10–15% of the general population and is growing in prevalence because injurious noise exposure in baby boomers and military personnel often precipitates symptoms. Whereas this common disorder affects a large number of people, over 80% with tinnitus are not behaviorally troubled by their phantom auditory sensations (Coles, 1984; Jastreboff, 2004). Nevertheless, 13 million with tinnitus in the US and Europe seek medical attention (Vio and Holme, 2005). Among putative neurophysiological correlates of tinnitus, central auditory system neuronal hyperactivity (Chen and Jastreboff, 1995; Kaltenbach and Afman, 2000; Norena and Eggermont, 2003; Kaltenbach, 2006), plastic change (Muhlnickel et al., 1998; Komiya and Eggermont, 2000; Syka, 2002), and thalamocortical dysrhythmia (Llinás et al., 1999; De Ridder et al., 2007) are leading considerations. Accordingly, current treatments typically target auditory pathway structures through the use of hearing aids (Melin et al., 1987; Surr et al., 1999; Folmer and Carroll, 2006), habituation and sound reclassification procedures, such as, Tinnitus Retraining Therapy and Cognitive Behavioral Therapy (Sweetow, 1985; Henry and Wilson, 2001; Zachriat and Kroner-Herwig, 2004; Jastreboff and Jastreboff, 2006; Jastreboff, 2007; Bessman et al., 2009), and transcranial magnetic (Kleinjung et al., 2005; Fregni et al., 2006; Marcondes et al., 2010) and direct electrical stimulation (De Ridder et al., 2006, 2010; Friedland et al., 2007) of auditory cortex. When intervention measures fail to mitigate tinnitus-related suffering, phantom auditory percepts can intrude on activities of daily living, trigger emotional distress, and compel obsessive behaviors.

Psychoacoustic measures of tinnitus loudness matching, pitch quality, and maskability cannot distinguish between those who merely experience tinnitus from those who suffer from tinnitus (Coles, 1984; Jastreboff, 2004). It follows that tinnitus sensation representations generated or expressed in auditory cortex (Komiya and Eggermont, 2000; Norena and Eggermont, 2003; Lanting et al., 2009) are necessary but not sufficient to account for suffering from tinnitus. The key distinction between the two groups may be the selection and attention to tinnitus neural correlates that engage autonomic and limbic systems (Jastreboff, 1990) in tinnitus sufferers. In this regard, the basal ganglia have been implicated in gating and selecting cortical representations (Humphries et al., 2006; Frank et al., 2007) for action or attention. Other basal ganglia functions that may play important roles in tinnitus suffering are procedural learning (Houk and Wise, 1995; Graybiel, 1998; Frank et al., 2001), categorization and classification of sensory information (Ashby et al., 2007; Seger, 2008), decision making (Frank and Claus, 2006; Johnson et al., 2007; Pennartz et al., 2009), reinforcement of obsessive-compulsive behaviors (O'Reilly and Frank, 2006; Huey et al., 2008), contribution to anxiety and affective disorders (LeDoux, 2000; Sturm et al., 2003; Hikosaka et al., 2008),

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Abbreviations: AC-PC, anterior commissure-posterior commissure; Area LC, locus of caudate neurons; CM, centrum medianum; DBS, deep brain stimulation; ET, essential tremor; OR, operating room; PD, Parkinson's disease; STN, subthalamic nucleus; Vim, ventral intermediate nucleus; 3D, 3 dimensional.

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and dysfunction of the autonomic system (Pazo and Belforte, 2002).

An alternative treatment strategy to current approaches is neuromodulation of basal ganglia function to presumably disrupt selection of or attention to auditory cortical representations of tinnitus. The candidate structures for direct neuromodulation by deep brain stimulation (DBS) to achieve tinnitus suppression are the caudate nucleus and putamen. Those striatal structures receive prominent input from auditory (Selemon and Goldman-Rakic, 1985; Yeterian and Pandya, 1998), visual (Faull et al., 1986; Yeterian and Pandya, 1995) and olfactory cortices (Cavada et al., 2000; Fudge et al., 2005). The clinical feasibility of striatal neuromodulation to suppress tinnitus was found in a case report of complete tinnitus cessation following a cerebrovascular accident that lesioned both the caudate and putamen (Lowry et al., 2004).

The caudate is routinely traversed during DBS implantation of the subthalamic nucleus (STN) and ventral intermediate nucleus (Vim) in awake patients for treatment of Parkinson's disease (PD) and essential tremor, respectively. Therefore, stimulation of the caudate can be performed without altering the normal surgical procedure. We report tinnitus modulation results from six movement disorder patients with comorbid tinnitus who underwent electrical stimulation of the caudate during DBS surgery to implant the STN or Vim.

EXPERIMENTAL PROCEDURES

Psychophysical tinnitus evaluation

Before and after surgery, all subjects reported on the following tinnitus attributes: (1) sound quality variation (constant or inconsistent), (2) temporal presence (continuous or intermittent), (3) sound quality description (tonal, noise-like, cricket-like, or musical), and (4) loudness rating for percept localized to each ear on a 0–10 scale. The interviews were conducted in the preoperative holding area and verified in the operating room (OR), which was maintained as quiet as possible. While desirable, use of a validated tinnitus severity rating instrument, such at the Tinnitus Handicap Inventory (THI) (Newman et al., 1998), was not performed due to considerable time constraints inherent in conducting the study entirely in the OR. During awake, interactive DBS surgery, subjects limited tinnitus perception reporting to sound quality description and loudness rating. Subjects were blinded to amplitude changes in electrical stimulation. The voltages at which tinnitus loudness ratings deviated from baseline values were repeated at least once. This report focuses on perioperative tinnitus loudness modulations.

Study cohort and caudate stimulation

All six male subjects had longstanding (range: 5–45 years) constant, continuous tinnitus, but with heterogeneous loudness levels and sound qualia (Table 1). Preoperative and postoperative hearing loss profiles for the cohort are shown in Table 2, which details audiometric air conduction thresholds (no air bone gaps>5 dB). There are full data on subjects 1, 3 and 4, postoperative data on subjects 2 and 5, and none for subject 6, who reported subjective hearing loss in both ears. Preoperative audiograms show the following high frequency hearing loss profiles (Clark, 1981): slight in subject 2, moderate to moderately severe in subjects 1, 3 and 5, and severe in subject 4.

Five of six subjects underwent electrical stimulation of the caudate (Table 1). Subjects 3, 4 and 5 had bilateral stimulation procedures. The time from conclusion of the first to start of the second DBS lead placement ranged from 20 to 40 min. Subject 1 was aphonic during surgery due to severe PD symptoms off medications. The caudate was not stimulated, but he was questioned about his tinnitus on the morning after surgery. The study was completed in accordance with an approved protocol by the UCSF Committee on Human Research.

Table 1. Subject demographics and tinnitus percept characteristics

Subject number (age/sex)	Deep brain stimulation					Tinnitus loudness rating (0–10)			Tinnitus quality
	Disorder (target)	Lead tip in AC-PC coordinates during stim		Approach angle sag/cor in degrees		Duration in years	Left Ear	Right Ear	constant and continuous
		Left	Right	Left	Right				
1 (63/m)	PD (STN)	n/a	n/a	72.0/17.4	67.5/26.2	10	5	1	Tonal
2 (51/m)	PD (STN)	n/a	x=10.4 y=11.5 z=17.5	n/a	32.5/7.6	13	5	5	Noise-like
3 (57/m)	ET (Vim)	x=−18.1 y=7.15 z=17.4	x=14.4 y=11.0 z=17.5	39.9/17.9	48.6/10.1	36	5	5	Cricket-like
4 (67/m)	PD (STN)	x=−19.4 y=13.7 z=16.8	x=12.3 y=9.0 z=13.5	40.3/18.3	37.6/8.8	45	4	4	Musical
5 (66/m)	PD (STN)	x=−15.6 y=16.2 z=8.3	x=13.4 y=17.7 z=11.2	51.3/12.7	51.8/2.2	5	3	7	Tonal
6 (59/m)	PD (STN)	n/a	x=18.5 y=8.1 z=17.2	n/a	30.0/16.7	10	8	8	Tonal

age, age in years; m, male; PD, Parkinson's disease; ET, essential tremor; STN, subthalamic nucleus; Vim, ventral intermediate nucleus; sag, sagittal; cor, coronal; AC-PC, anterior commissure-posterior commissure; stim, stimulation; n/a, not applicable.