2018

Cortical Stimulation Mapping of Heschl's Gyrus in the Auditory Cortex for Tinnitus Treatment

Austin Huang

Cortical Stimulation Mapping of Heschl's Gyrus in the Auditory Cortex for Tinnitus Treatment

A Thesis Presented

by

Austin Huang

To the Keck Science Department

Of Claremont McKenna, Pitzer, and Scripps Colleges

In partial fulfillment of

The degree of Bachelor of Arts

Senior Thesis in Molecular Biology

December 10th, 2018

Table of Contents

Abstract

Tinnitus is the perception of sound in the absence of an actual sound stimulus. Recent developments have shifted the focus to the central nervous system and the neural correlate of tinnitus. Broadly, tinnitus involves cortical map rearrangement, pathological neural synchrony, and increased spontaneous firing rates. Various cortical regions, such as Heschl's gyrus in the auditory cortex, have been found to be associated with different aspects of tinnitus, such as perception and loudness. I propose a cortical stimulation mapping study of Heschl's gyrus using a depth and subdural electrode montage to conduct electrocorticography. This study would provide high-resolution data on abnormal frequency band oscillations characteristic of tinnitus and pinpoint regions where they occur. The validity of the neural synchrony model would also be tested in this study.

Introduction

Tinnitus affects 10-15% of the adult population worldwide (Langguth et al., 2013). The main risk factor for tinnitus is hearing loss (Nondahl et al., 2011), and a diverse list of other factors includes various otological diseases, ototoxic drugs, depression, and temporomandibular joint disorder (Baguley et al., 2013). Tinnitus can result from lesions to various structures in the auditory pathway, from the cochlea to the auditory cortex. Tinnitus can affect the quality of life by causing irritability, depression, insomnia, and concentration difficulties, among others. In 1-2% of individuals with tinnitus, quality of life is affected to a severe degree (Langguth, 2011).

Objective tinnitus results from the perception of sound generated within the body. This can be related to a pathological symptom, such as the sound of increased blood flow as a result of anemia. It is a natural phenomenon in other cases, such as otoacoustic emissions, which is a type of sound that is naturally generated by cochlea outer hair cells when they process sound (Penner, 1990). When there is no actual sound source, the tinnitus is said to be of a subjective type.

The pathophysiology of tinnitus is still not completely understood. A steadily growing number of studies indicate a primary role of the central nervous system in most cases of tinnitus, rather than the peripheral nervous system which may be a common misconception among the public (Langguth et al., 2013). Additionally, the overall perception of tinnitus involves interactions between both auditory and non-auditory pathways (Lanting et al., 2009). For instance, a magnetoencephalography (MEG) study of different cortical hubs found evidence of long-range coupling between auditory and non-auditory structures in tinnitus patients at rest (Schlee et al., 2009). The degree of interaction between these different

structures was correlated to tinnitus distress. Modulation of non-auditory areas to affect

tinnitus is also possible. Deep brain stimulation (DBS) of a locus of neurons in the caudate

nucleus could increase or decrease tinnitus loudness perception (Cheung and Larson, 2010).

The failure of the limbic system in blocking tinnitus signals originating from the auditory

pathway may be an explanation for chronic cases of tinnitus (Rauschecker et al., 2010). The

interactions of diverse cortical regions in tinnitus may be explained by the need for

consciousness-supporting networks for auditory perception, such as the salience network

(Sadaghiani et al., 2009). The heterogeneity of tinnitus is one obstacle in the development of

an effective treatment for tinnitus.

Background

Cortical anatomy of the auditory system

The auditory system is organized according to tonotopy, the spatial arrangement of different sound frequencies within neural structures. Within the cochlea in the inner ear, the organ of Corti is responsible for encoding electrical impulses from the displacement of cochlear fluid caused by sound waves. Displacement of cochlear fluid along the length of the cochlea leads to the vibration of a basilar membrane and the stimulation of hair cells, the sensory cells of the auditory system. The wide spectrum of sound frequencies that we hear in our daily lives is partitioned out over the length of the cochlea by virtue of the physical characteristics of the basilar membrane. The basilar membrane is thinner and stiffer at the base where the sound waves first propagate through, and thicker and more flexible at the apex. These characteristics causes different sound frequencies to have different regions of the basilar membrane that they maximally vibrate. Hair cells at the base respond to high frequency sounds (20,000 Hz) while those at the apex respond to low frequencies (20 Hz). Tonotopy is present at all structures in the auditory pathway, up to the auditory cortex (Pickles, 2015).

The auditory cortex (Brodmann areas 41, 42, and part of 22) in the human brain consists of Heschl's gyrus (also known as the transverse temporal gyrus) and the superior temporal gyrus (Figure 1). It is bounded by the lateral sulcus and the superior temporal sulcus. Heschl's gyrus is oriented oblique to the sagittal and coronal planes (Reddy et al., 2010). The auditory cortex consists of a core, a belt region surrounding the core, and a parabelt region located lateral to the belt region. Immunocytochemical methods have revealed that the belt and parabelt regions are strongly connected to each other, but not to the

main core. The rostral sections of the belt and parabelt regions are strongly interconnected with each other, and the caudal sections with each other, but between rostral and caudal regions, only weak connections were observed. The core can further be divided into three regions, AI, R, and RT. AI is the largest and most caudal region, RT is the most rostral region, and R is located in between. These divisions have been classified on the basis of differences in immunocytochemical staining and on cortical and thalamocortical connections to these divisions (Hackett et al., 1998).

The auditory cortex receives signals from the medial geniculate body (MGB) within the thalamus via the acoustic radiations, the majority of which project to area 41. The MGB is tonotopically organized with higher frequencies represented in medial regions and lower frequencies represented in lateral regions. Signals reach the MGB from multiple structures, including the lateral tegmental area and the inferior colliculus. The MGB has laminated regions which project to the primary auditory cortex and unlaminated regions which project to the secondary auditory cortex. The auditory pathway contains a great number of contralateral connections, the majority of which are found within the trapezoid body of the pons. The combination of contralateral and ipsilateral connections means that lesions to the auditory cortex on one side will lead to only a partial deafness, but the deficits are experienced on both sides (Carpenter, 1991).
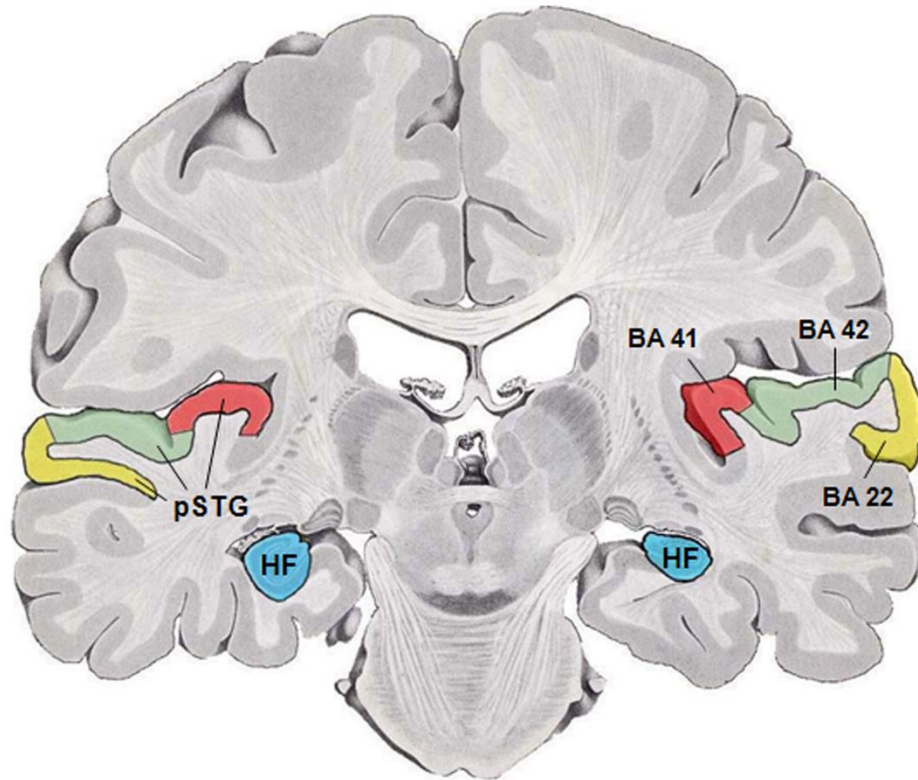
Figure 1. Human temporal lobe areas. Posterior superior temporal gyrus (pSTG) and intermediate rostrocaudal hippocampal formation (HF). Reproduced from "Synaptic Dysbindin-1 Reductions in Schizophrenia Occur in an Isoform-Specific Manner Indicating Their Subsynaptic Location" by Talbot K, Louneva N, Cohen JW, Kazi H, Blake DJ, et al. (2011) Reprinted courtesy of the Copyright Holder under a Creative Commons Attribution License CC BY 2.5 (https://creativecommons.org/licenses/by/2.5), via Wikimedia Commons

Within the auditory cortex are neuronal columns, and the neurons within each column all respond to a single best frequency of sound—the frequency at which a particular neuron's receptive field is centered around. Neighboring columns represent adjacent frequencies, so the result is a continuous spectrum of receptive fields in the auditory cortex that constitute a tonotopic map. Various electrophysiological studies have identified 4-8 different tonotopic maps in the auditory cortex. Spatially distinct areas in the auditory cortex have been observed to respond to a specific sound frequency, suggesting that there is some overlap within these tonotopic maps. These isofrequency columns have similar widths, but a larger proportion of

the auditory cortex is dedicated to higher frequencies, which may be explained by the higher

amount of innervation in the cochlea base versus the apex (Carpenter, 1991).

Neural synchrony

Neurons communicate with each other through action potentials that are propagated

by fluctuations in the electrochemical gradient, which can be measured as neural oscillations

(Hodgkin and Huxley, 1952). Neuronal networks in the brain can generate oscillatory activity

at various frequencies ranging from 0.05 Hz to 500 Hz. Neural oscillations are

conventionally divided into different frequency bands such as the delta (1-4 Hz), theta (4-8

Hz), alpha (8-13 Hz), beta (13-30 Hz), and gamma (30-80 Hz) bands (Buzsáki and Draguhn,

2004). Different frequency bands are related to different neural processes. For instance,

activity in the gamma frequency band has been correlated with awareness and consciousness,

and EEG readings during sleep show a transition from high frequency to low frequency

activity (Engel and Singer, 2001).

The cerebral cortex is responsible for many higher-order brain functions such as

perception, memory, and consciousness. The cortex has many distinct sub-areas that can be

defined on the basis of their function, but there is no one central area that collects all sensory

information and coordinates the activity of all of these sub-areas (Uhlhaas et al., 2009). The

segregated nature of different brain functions means that some neural mechanism is needed

for the organization of spatio-temporal activity patterns. For instance, a radio playing music

presents both visual and auditory stimuli that must be integrated together in the brain for a

faithful sensory representation of the object (Uhlhaas and Singer, 2006). It has been suggested that this neural organization is achieved through neural synchrony.

In neural synchrony, neurons release their action potentials in a concerted, rhythmic manner (Figure 2). This synchronization of spatially-distributed neurons serves different purposes. First, the synchronization of a certain output signal makes it more salient, which distinguishes it from other signals so that it can be processed further. Additionally, synchronization can modulate synaptic strength through long-term potentiation/depression, as these processes are temporally dependent on pre- and post-synaptic activation (Volgushev et al., 1998).

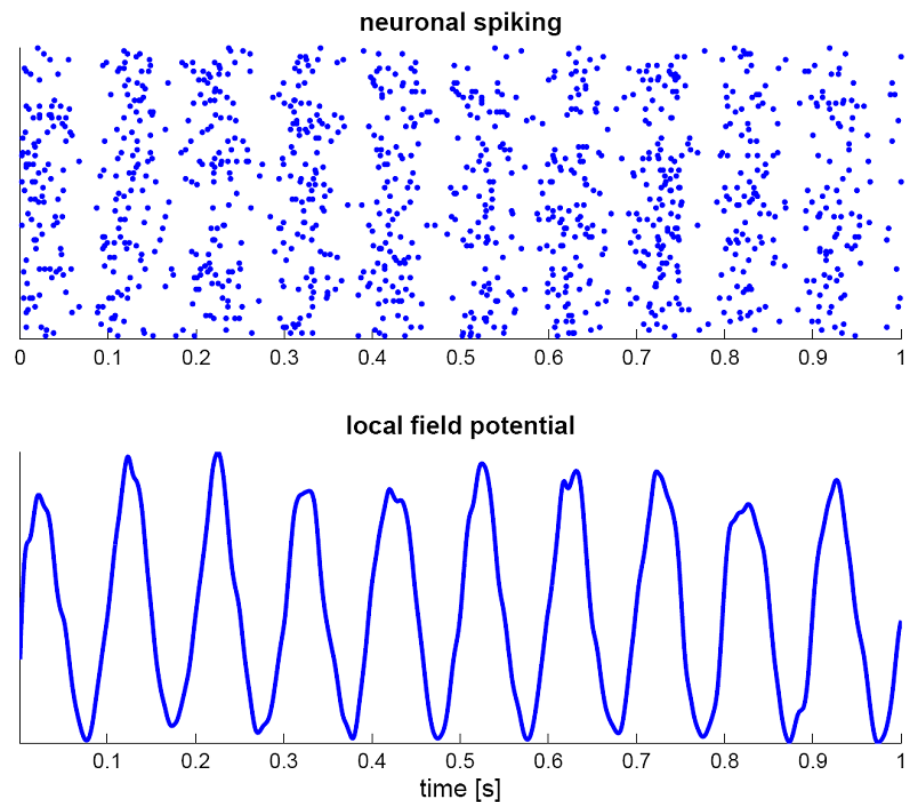**Figure 2.** Simulation of neural oscillations at 10 Hz. Upper panel: each individual dot represents the propagation of a single action potential of a neuron. Lower panel: the summed neural activity of the neuron population. The synchronized firing of individual neurons leads to a local field potential that oscillates over time on the mesoscopic or macroscopic scale. Reproduced from TjeerdB [Public domain], Wikimedia Commons.

Induction of neural synchrony

In the putative mechanism of neural synchrony induction, networks of fast-spiking interneurons rhythmically create inhibitory postsynaptic potentials that hyperpolarize other local neurons (Hasenstaub et al., 2005). Theoretically, gamma oscillations in these cells causes a rhythmic inhibition which attenuates inputs to the postsynaptic neuron that arrive at the peak of inhibition. Thus, narrow windows of time are generated during which target neurons can be excited. Evidence was shown in an *in vivo* study of the rodent barrel cortex which found that selective stimulation of inhibitory interneurons led to gamma oscillations and a temporal regulation of sensory processing (Cardin et al., 2009).

Organizational levels of neural synchrony

Neural synchrony can be divided into three levels of organization: microscopic, mesoscopic, and macroscopic synchrony. Microscopic synchrony involves the simultaneous firing of two neurons onto the same post-synaptic neuron. The effect is an increase in amplitude of the post-synaptic potential. Fundamentally, this increases the efficiency of neural activity, as the amplitude of the post-synaptic potential is proportional to the number of inputs from synchronized neurons, whereas in the case of asynchronous neurons it is proportional to the square root of the number of inputs (Eggermont and Tass, 2015). Consequently, a network of neurons oscillating in synchrony has the potential to create a larger post-synaptic potential than one that is asynchronous. Mesoscopic synchrony is observed on the scale of local neuronal networks, where synchronized oscillations in the membrane potential of multiple neurons lead to measurable local field potentials (LFP). On a larger scale, macroscopic synchrony is seen between different brain regions and can be

measured with electrophysiological monitoring methods such as electroencephalography (EEG).

Abnormal neural synchrony

Abnormal neural synchrony has been implicated in various neurological disorders including schizophrenia (Spencer et al., 2003), Parkinson's disease (Alberts et al., 1969), and tinnitus (Eggermont and Tass, 2015). In patients with Parkinson's disease, tremors in the limb were correlated with rhythmic activity at the tremor frequency in the motor and somatosensory cortexes, suggesting that synchronization of neural activity can be a pathological symptom (Alberts et al., 1969).

Synchronized gamma band activity has been proposed to bind sensory information into a conscious coherent percept. In the case of tinnitus, the perception of a phantom sound is expected to be correlated to gamma band activity. This was seen in a quantitative electroencephalography (QEEG) and magnetoencephalography (MEG) study where the presence of consistent gamma band activity in the auditory cortex of patients with tinnitus was confirmed (Van der Loo et al., 2009). In normal audition, the auditory cortex is activated in a sound level dependent manner. Tinnitus was found to also involve a sound level dependent activation of the contralateral auditory cortex, suggesting a fundamental similarity in pathways of perception. Taken together, these results suggest that synchrony in the gamma frequency band encodes tinnitus intensity, but not necessarily the perception of the tinnitus.

Measuring neural oscillations

Measuring neural oscillations is helpful from a diagnostic and imaging standpoint, as they are indicative of both normal and abnormal neural processes. Electrocorticography (ECoG) is a method of collecting electrophysiological data from cortical regions of the brain. In ECoG, a craniotomy is performed to expose the brain's surface and electrodes are placed directly on the cerebral cortex. These electrodes can measure local field potentials from neuronal regions of interest or provide targeted electrical stimulation (Schuh and Drury, 1997). This method of electrical stimulation is known as cortical stimulation mapping and allows researchers to determine the function, if any, of the brain region that has been implanted by an electrode (Lesser et al., 1998).

Acoustic coordinated reset (CR) neuromodulation®

Acoustic coordinated reset (CR) neuromodulation is a desynchronization technique developed by Tass and colleagues (Tass et al., 2012). In their clinical trial, subjects with chronic, tonal tinnitus received 4 to 6 hours of acoustic stimulation daily that consisted of a series of tones distributed around their self-reported tinnitus frequency. This trial, which lasted for 12 weeks, led to sustained, long-term reductions in tinnitus severity in 75% of patients. CR neuromodulation was previously studied in a computational model and then used in animal studies (Tass, 2003). The underlying basis of CR is that abnormal neural synchrony is the correlate of tinnitus and it can be reversed through desynchronization, leading to the reduction of tinnitus symptoms.

The putative mechanism behind desynchronization is that stimulation can be designed in a way (in this case, as a series of tones flanking the tinnitus frequency) that promotes unlearning of the pathological neural synchrony through a phase reset, or a soft phase reset. This unlearning occurs because of spike-timing-dependent plasticity, which suggests that the strength of synaptic connections between neurons is dependent on the timing between input spikes to postsynaptic neurons and the output spikes from them.

After 12 weeks of therapy, Tass and colleagues reported that there was a significant reduction in the patient self-reported tinnitus loudness and annoyance, even through a planned 4-week therapy pause. EEG analysis revealed a significant decrease in delta and gamma band power in the primary and secondary auditory cortices, and a significant increase in alpha band power in the auditory and prefrontal cortices. This was suggested to be indicative of neuroplastic changes.

Tass and colleagues provided two possible mechanisms of how CR neuromodulation works at the cortical level. By inducing a phase reset in delta band activity in spatially distinct populations at different times, desynchronization might occur. Another possibility is that this desynchronization could be propagated from an upstream nucleus. The results of this trial, while promising, require replication due to a small group size and the lack of direct comparison between different treatment groups (Wegger et al., 2017).

Proposed Study: Cortical Stimulation Mapping of Heschl's Gyrus

Overview

In this proposed study, Heschl's gyrus will be mapped out using cortical stimulation mapping to determine if there is a tinnitus onset originating from this region. Multiple cortical regions are involved in tinnitus and successful treatment will likely involve a holistic approach. The goal presently is to study the abnormal neural characteristics of these regions and determine their role in the overall pathophysiology of tinnitus.

Heschl's gyrus in the auditory cortex is one such region that is connected to tinnitus. MRI scans of the medial section of Heschl's gyrus in patients with tinnitus showed that gray matter volume was significantly reduced compared to control. Additionally, in the cases of patients with unilateral tinnitus the volume deficiency was observed in the Heschl's gyrus ipsilateral to the side with tinnitus, while bilateral tinnitus patients saw a deficiency in both gyri (Schneider et al., 2009).

One intracranial mapping study of a patient with bilateral tinnitus and hearing loss used ECoG to measure oscillatory power changes that occurred in response to residual inhibition (a transient decrease in tinnitus loudness following acoustic stimulation). Observed oscillatory power changes included widespread decreases in delta, theta, and alpha power in not only Heschl's gyrus but also certain regions within the parietal, temporal, and sensorimotor cortices. Widespread increases were also observed in similar regions for the gamma frequency band (Sedley et al., 2015). The results of this study, while supportive of previous literature on tinnitus, were obtained from a single patient with bilateral tinnitus and hearing loss using acoustic stimulation to induce residual inhibition. The patient's coexisting

hearing loss and the possibility of the stimulus being modulated by functional abnormalities as it ascends the auditory pathway suggests the need for a similar study that uses direct stimulation.

In a nonrandomized clinical trial, two patients with refractory tinnitus were treated using direct electrical stimulation. The first patient was stimulated within Heschl's gyrus and the second patient was stimulated on Heschl's gyrus. The first patient experienced a near complete tinnitus suppression while the second patient only experienced a moderate and transient suppression which could be attributed to differences in the sites stimulated and differences in tinnitus duration (Seidman et al., 2008). Tinnitus can also be temporarily induced in patients without it, as shown by tinnitus perception following electrical stimulation of cortical areas in the temporal lobe near Brodmann's areas 22 and 42 (Carpenter, 1991). More research is needed to elucidate the effects of direct stimulation of Heschl's gyrus.

There is also a general need for further ECoG studies to replicate past findings which hold promising results but suffer from small sample sizes. The high variability observed in human studies and the ethical obstacles in conducting extensive direct electrical stimulation studies on the human brain was addressed in part by the development of a rat model (Zhang et al., 2011). In this study, the efficacy of auditory cortex electrical stimulation (ACES) was measured by testing for the suppression of tinnitus-related behavior. The tinnitus rat model demonstrated that tinnitus suppression was due to auditory cortex activation and that frequency bands associated with tinnitus were restored to non-tinnitus amplitudes. Lastly, this study found that ACES caused tinnitus suppression in rats that had tinnitus and co-

existing noise-induced hearing loss. The results taken as a whole lend support to the further investigation of Heschl's gyrus as a target region for tinnitus suppression.

A study of the auditory representation of speech in the motor cortex used high-density multi-electrode cortical surface arrays to measure neural activity in the peri-Sylvian speech cortex (Cheung et al., 2016). Information obtained from the electrodes revealed the distribution of local field potentials in the high-gamma frequency range during listening and speaking tasks. The robust results obtained from this study along with the fact that Heschl's gyrus is adjacent to the peri-Sylvian speech cortex suggests the possibility of a study where implantation of stimulatory electrodes within Heschl's gyrus would produce a tinnitus percept in patients without tinnitus, and break up the tinnitus percept in patients with it.

Studying tinnitus requires high-resolution characterization of the neural activity in regions of the brain associated with tinnitus. While EEG and MEG studies of tinnitus are numerous, they cannot provide the same level of information that can be obtained from ECoG studies. Understanding how different regions contribute to the overall abnormal neural pattern will inform the development of future tinnitus therapies.

Methods

Patient selection

Procedures were approved by the institutional review board at the W.M. Keck Science Department of the Claremont Colleges in accordance with the currently applicable U.S. Public Health Service Guidelines. Written informed consent should be obtained from patients prior to experimentation.

ECoG is a highly invasive procedure, meaning that ECoG studies are best accomplished by doing them in patients who are already undergoing mapping for some other purpose. In other words, only one craniotomy would be required for the essential mapping procedure needed by the patient and the appended mapping study. These ECoG procedures provide research opportunities for neuroscientists to take neural recordings without having to subject physiologically normal individuals to an invasive procedure. Patients undergoing this evaluation typically have a waiting period between ictal recordings during which the electrodes remain implanted, and recordings for the purpose of this study could be conducted during this time. Cortical stimulation mapping is a routine component of the presurgical evaluation of patients undergoing resection of the left temporal lobe as a treatment for medically refractory complex partial seizures. These patients experience Type II ictal EEG patterns characteristic of a temporal neocortical onset (Ebersole and Milton, 2003; Ebersole and Pacia, 1996). In this proposed study, ECoG measurements will be taken from two patient populations. The first population should have left neocortical temporal lobe epilepsy (nTLE) and tinnitus, and the second population should have left nTLE but no reported tinnitus.

For patients with neocortical temporal lobe onset, the goal of the mapping is the distinction between the epileptic focus, Heschl's gyrus, and Wernicke's area, which is responsible for the comprehension of speech. Consequently, the mapping study for nTLE is done when the patient is awake so that concurrent speech tests can be done to define Wernicke's area. Patients are thus able to provide self-reported measures of their tinnitus percept during the proposed study.

Additionally, patient demographics and audiometric variables must be taken into account due to the heterogeneous nature of tinnitus. Patients with a tinnitus onset occurring

more than 5 years ago may not respond well to cortical stimulation, as cortical reorganization may have led to new and refractory cortical connections (Seidman et al., 2008). Studies using TMS (De Ridder et al., 2005) and microvascular decompression surgery (Møller et al., 1993) to treat tinnitus found that patients with longer tinnitus duration were more resistant to treatment. Amobarbital injection into the choroidal artery in patients with tinnitus had varying degrees of suppression that was dependent on tinnitus laterality and tinnitus duration (De Ridder et al., 2006). Patients with recent tinnitus onset are preferred, but any patient with tinnitus and nTLE will still provide useful data for a study. Multiple epilepsy centers should be contacted in the search for patients who fit the criteria.

Technical hurdles to cortical measurements

Several challenges to measuring neural activity in the auditory cortex have been noted. The superior temporal plane, which contains Heschl's gyrus, is one of the most folded regions in the human brain (Galaburda and Sanides, 1980) and core regions of Heschl's gyrus are also located deep within the Sylvian fissure. In a study conducted by Tass et al. (2012), oscillatory activity in the brain was measured using the standardized low-resolution brain electromagnetic tomography (sLORETA) technique which utilizes EEG and MEG data to form maps of oscillatory activity. sLORETA is the gold standard for noninvasive linear tomography, but its low spatial resolution which decreases even further with depth suggests that direct probing of Heschl's gyrus will give us more robust measures of changes in oscillatory activity (Jatoi et al., 2014). The complexity of the auditory cortex and the depth of Heschl's gyrus necessitates an electrophysiological method that has high spatial and temporal resolution, such as ECoG.

Core regions of Heschl's gyrus can be accessed with penetrating depth electrodes. The traditional method of placing depth electrodes in Heschl's gyrus requires a lateral insertion along with stereoscopic stereotactic angiography for successful implantation without injury. A more recent method that was proven to be safe and effective does not require angiography and allows for the simultaneous placement of subdural grid electrodes (Reddy et al., 2010).
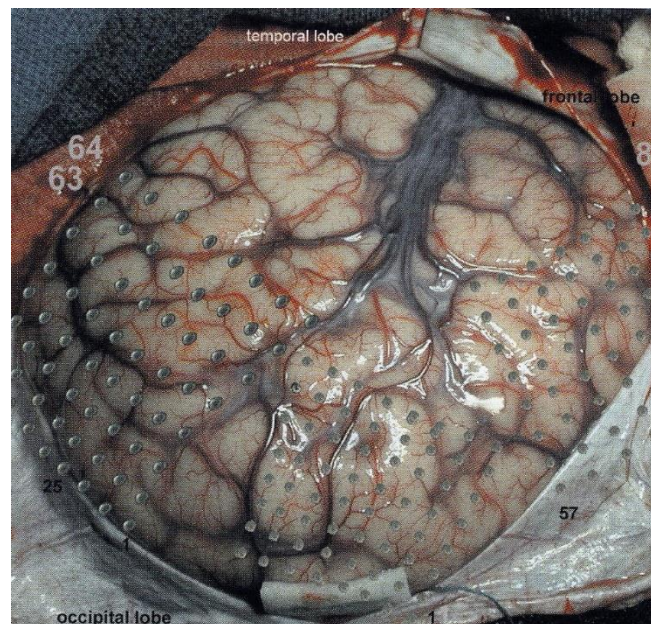

Figure 3. Placement of a subdural grid electrode array for electrocorticography. Reproduced from "Brain Connectivity and the Spread of Epileptic Seizures. In Handbook of Brain Connectivity" by Milton, J.G., Chkhenkeli, S.A., and Towle, V.L. (2007)., V.K. Jirsa, and A. McIntosh, eds. (Berlin, Heidelberg: Springer Berlin Heidelberg), pp. 477–503. Reprinted with permission.

Cortical studies are further complicated by the fact that anatomical landmarks do not perfectly predict underlying functional organization and individual differences in brain anatomy can make results difficult to compare between subjects (Nourski, 2017). Individual

differences in brain anatomy between subjects can be compensated for through co-registration of neural recordings to electrode locations. Depth electrode location can be obtained from MRI scans while subdural electrode location can be obtained from CT scans. The usage of both types of electrodes has been previously validated for use in probing Heschl's gyrus (Nourski et al., 2014). Brain maps from subjects can then be compared by spatial normalization to a reference brain such as the Talairach Atlas brain, which uses anatomical landmarks to affine transform a subject's brain (Lancaster et al., 2000). Statistical techniques such as a linear mixed effects model can be used to further account for anatomical differences between patients (Nourski et al., 2014).

Procedure

Electrode placements will depend on specific clinical indications. In a global ECoG mapping study, Heschl's gyrus was probed using four depth electrodes (Sedley et al., 2015). A high-resolution study might use additional depth electrodes as well as a subdural grid electrode over the auditory cortex surface near Heschl's gyrus.

Each individual electrode should be sequentially stimulated and the oscillatory power should be measured in each frequency band from 1 to 148 Hz. The electrical stimulation paradigm should be similar to the one used by Seidman et al. (2008). A good starting point is 1 volt intensity, 100 Hz, and 90 microsecond pulse width for a 60 second stimulation period followed by a 60 second rest period. Oscillatory activity should be measured after 2 minutes, and the patient should be asked to rate their tinnitus loudness and annoyance using the Visual Analog Scale (VAS) which is a subjective measure of reduction in tinnitus severity

(Adamchic et al., 2012). This questionnaire involves providing a rating on a numerical scale from 1 (no tinnitus distress) to 10 (indicating severe tinnitus distress).

Different stimulation parameters should be tested to see which elicits the best suppression of tinnitus. For the one patient that experienced long-term tinnitus relief in the study done by Seidman et al. (2008), the maximal suppression was achieved with a setting of 1-3 V, 25 Hz, and 460 microsecond pulse width. The most effective electrical stimulation paradigm is likely to be different for each patient, contingent on variables such as tinnitus severity and duration. Electrode manufacturer recommended stimulation parameters should be followed to ensure patient safety. Pre-stimulation ECoG measures should be taken for the normalization of post-stimulation measures. Additionally, care must be taken to distinguish inter-ictal spiking from the true measures of oscillatory activity in response to the electrical stimulation.

Results

If the neural synchrony model holds true and the electrical stimulation is effective in desynchronization, then this should be reflected in oscillatory band shifts and the disappearance of the tinnitus percept for patients with tinnitus. Similarly, a patient without tinnitus should experience a tinnitus percept when these same areas are stimulated.

The intracranial mapping study by Sedley et al. (2015) of a patient with bilateral tinnitus and hearing loss used ECoG to measure oscillatory power changes that occurred in response to auditory residual inhibition. Measured oscillatory power changes included widespread decreases in delta, theta, and alpha power in Heschl's gyrus. Widespread

increases were also observed for the gamma frequency band in Heschl's gyrus (HG, Figure

4). Similar results are expected for this study, but this is contingent on tinnitus similarity.
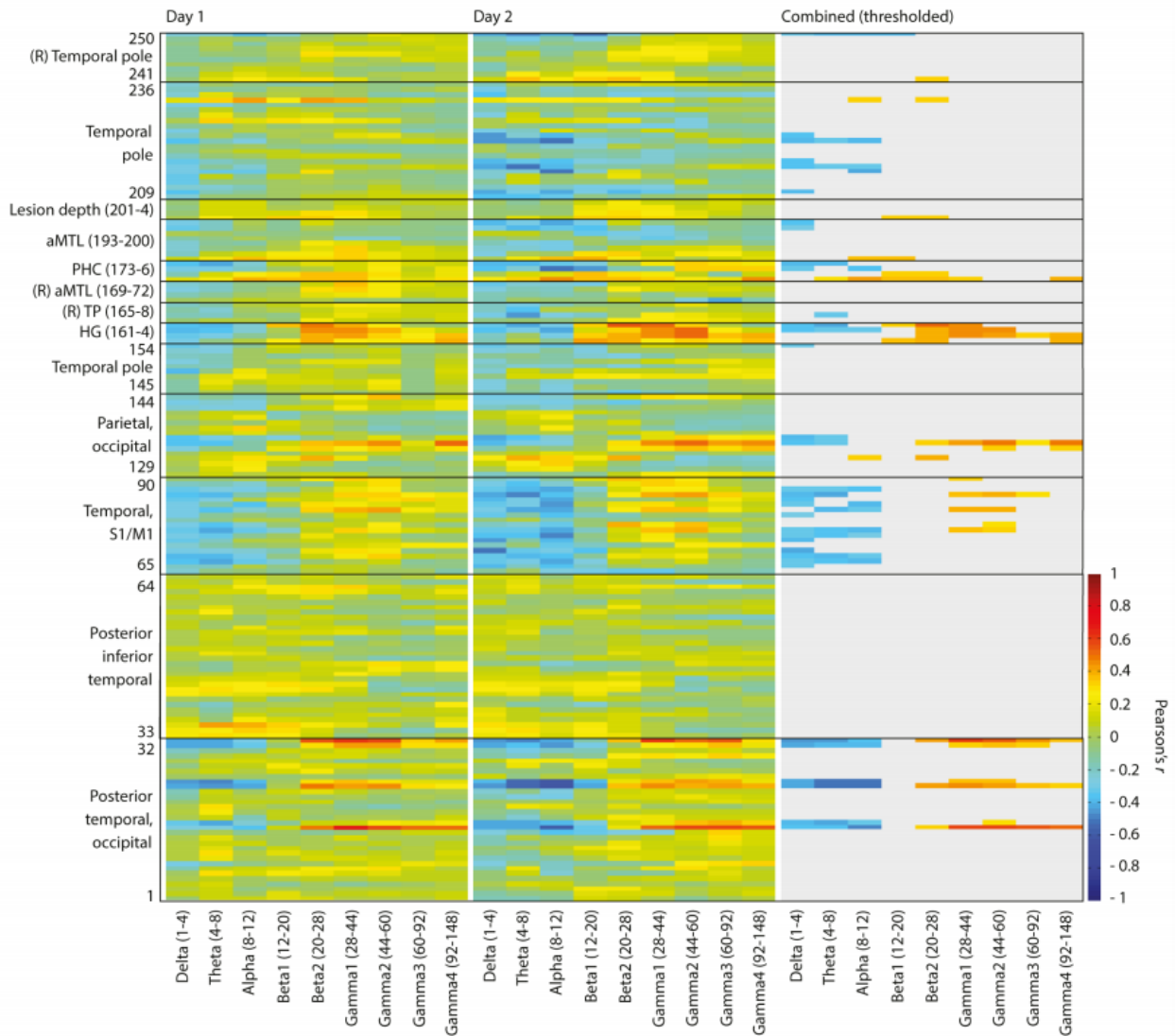

Figure 4. Oscillatory power changes in various cortical regions measured through ECoG. Rows represent individual electrodes and color denotes the correlation coefficients (Pearson's *r*). Hot colors indicate a power increase, cool colors indicate a power decrease, and gray indicates that no significant change was measured. Reproduced from "Intracranial Mapping of a Cortical Tinnitus System using Residual Inhibition," by Sedley, W., Gander, P.E., Kumar, S., Oya, H., Kovach, C.K., Nourski, K.V., Kawasaki, H., Howard, M.A., and Griffiths, T.D. (2015). Curr Biol 25, 1208–1214. Reprinted courtesy of the Copyright Holder under a Creative Commons Attribution License CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/)

Future Directions

Combination therapy of dorsolateral prefrontal cortex tDCS and acoustic CR

neuromodulation to counteract tinnitus.

CR neuromodulation, as described previously, is a technique that is promising, non-invasive, and safe, but lacking in validation. One region in the CR neuromodulation trial that saw frequency power band changes was the prefrontal cortex. Thus, stimulation of this region with tDCS prior could possibly lead to increased efficacy of CR neuromodulation. We would hope to see either a significant reduction of tinnitus in a shorter amount of time or a more intense reduction of tinnitus confirmed by EEG and improved patient self-reported measures of tinnitus.

The heterogeneous nature of tinnitus suggests that a combination therapy would be most effective in targeting the different neural subnetworks that underlie different clinical aspects of tinnitus such as distress, loudness, and duration. An approach that uses two different forms of stimulation could provide different advantages while compensating for any disadvantages that standalone methods have. Additionally, different variations are possible in the therapy paradigm, such as concurrent tDCS and CR neuromodulation.

One form of stimulation that has been applied to tinnitus is transcranial direct current stimulation (tDCS). tDCS is a noninvasive neuromodulation technique where two electrodes are placed on the scalp, acting as cathode and anode, causing neuromodulation of cortical tissue between them by affecting membrane resting potentials (De Ridder and Vanneste, 2012). Anodal tDCS (placement of the anode over the region of interest) uses a positive current flow from the anode, to elicit depolarization and excitation of targeted neurons.

Conversely, cathodal tDCS uses a negative current flow towards the cathode to elicit hyperpolarization and inhibition of targeted neurons. Thus, the placement of tDCS electrodes and their polarities allow for different neuromodulation strategies that can be used to alleviate abnormal hyper-activity or hypo-activity (Roche et al., 2015). There is evidence for the efficacy of tDCS in treating different neuropsychiatric disorders such as depression (Baeken et al., 2016; Lefaucheur et al., 2017; Yadollahpour et al., 2017). On a molecular level, tDCS is suggested to aid in synaptic plasticity. A study that applied tDCS to rat hippocampus brain slices observed a modulation of long-term potentiation (LTP) of synaptic activity (Ranieri et al., 2012).

A study of 567 tDCS sessions showed that tDCS was generally safe, with the most common adverse effects being a mild tingling sensation (70.6%) and moderate fatigue (35.3%) in both healthy participants and those with various neurological disorders, including tinnitus (Poreisz et al., 2007).

Other studies have used combination approaches towards tinnitus, such as tDCS followed by hearing aid sound therapy (Shekhawat et al., 2014). In this study, patients with chronic tinnitus (n = 40) underwent five sessions of anodal tDCS over the left temporoparietal area followed by six months of hearing aid sound therapy. The hypothesis was that neuromodulation techniques such as tDCS can prime the auditory system for the increased efficacy of hearing aid sound therapy. Benefits were observed after three months of hearing aid use, but this was attributed to the hearing aid sound therapy alone, independent of tDCS. tDCS applied to other areas, such as the dorsolateral prefrontal cortex (DLPFC) in conjunction with another form of tinnitus intervention, such as coordinated reset neuromodulation may lead to more promising results.

The dorsolateral prefrontal cortex (DLPFC) is a non-auditory region of the brain that has been implicated in tinnitus perception. In the monkey brain, DLPFC neurons showed an increase in firing levels during audio-visual short-term memory tasks (Bodner et al., 1996). A study of lesions in the DLPFC suggested that this region is also involved in inhibitory modulation of auditory input to the auditory cortex (Knight et al., 1989).

Most tDCS trials have examined the effects of short-term treatment on tinnitus symptoms only. In a meta-analysis done in accordance with PRISMA, it was found that the number of daily tDCS sessions in these trials ranged from three to ten sessions with each session lasting from 15 to 30 minutes. (Yuan et al., 2018). The findings of these trials were promising but varied, suggesting the need for further trials that control for differences in patient populations and technical aspects of tDCS. Long-term applications of tDCS towards tinnitus treatment should be studied as well.

Additionally, the heterogeneous nature of tinnitus mandates the need for the development of disease specific tDCS protocols. For instance, tDCS is not suitable for patients who have a history of seizures, such as those with epilepsy (Nitsche et al., 2008). This proposed study would further our understanding of the potential long-term benefits of tDCS on tinnitus symptoms as well as help guide the future use of long-term tDCS, especially in conjunction with CR. Different cortical areas are options for tDCS and combination therapies should be tailored to each patient's specific tinnitus case. The intent of a combination therapy approach is to provide a customizable and holistic approach to a heterogeneous tinnitus patient population.

Conclusion

        Tinnitus is a complex condition for which there is no strong consensus on the etiology. This proposed study will allow for the high-resolution characterization of neural activity in Heschl's gyrus and determine if there is a correlation between tinnitus and abnormal neural synchrony in this region. Further research should investigate other cortical areas implicated in tinnitus and the elucidation of the relationships between them. Such data will guide the development of future therapies that aim to reverse neural correlates of tinnitus.

Acknowledgements

First, I would like to thank my thesis advisors, Professor John Milton and Professor Dorsa Kay, for their invaluable guidance, feedback, and support in the completion of this thesis. I would also like to thank Dr. Hua Yu, who is not only a close family friend, but also an amazing scientist and role model. Your continuous support and guidance over the years has inspired me to pursue my own passions in science. Thank you to my friends, who kept me company throughout my college journey and throughout the countless hours spent in the computer lab. Thank you Claremont McKenna College for a wonderful educational opportunity.

Finally, I want to thank my parents for their unconditional love and support. I wouldn't be where I am today without your guidance and the sacrifices you've made for me. Even though I've almost completed four years of college, I still find myself learning much from you two.

References

Adamchic, I., Langguth, B., Hauptmann, C., and Tass, P.A. (2012). Psychometric Evaluation of Visual Analog Scale for the Assessment of Chronic Tinnitus. Am. J. Audiol. *21*, 215–225.

Alberts, W.W., Wright, E.W., and Feinstein, B. (1969). Cortical Potentials and Parkinsonian Tremor. Nature *221*, 670–672.

Baeken, C., Brunelin, J., Duprat, R., and Vanderhasselt, M.-A. (2016). The application of tDCS in psychiatric disorders: a brain imaging view. Socioaffective Neurosci. Psychol. *6*, 29588.

Baguley, D., McFerran, D., and Hall, D. (2013). Tinnitus. Lancet Lond. Engl. *382*, 1600–1607.

Bodner, M., Kroger, J., and Fuster, J.M. (1996). Auditory memory cells in dorsolateral prefrontal cortex. Neuroreport *7*, 1905–1908.

Buzsáki, G., and Draguhn, A. (2004). Neuronal oscillations in cortical networks. Science *304*, 1926–1929.

Cardin, J.A., Carlén, M., Meletis, K., Knoblich, U., Zhang, F., Deisseroth, K., Tsai, L.-H., and Moore, C.I. (2009). Driving fast-spiking cells induces gamma rhythm and controls sensory responses. Nature *459*, 663–667.

Carpenter, M.B. (1991). Core text of neuroanatomy (Baltimore: Williams & Wilkins).

Cheung, S.W., and Larson, P.S. (2010). Tinnitus modulation by deep brain stimulation in locus of caudate neurons (area LC). Neuroscience *169*, 1768–1778.

Cheung, C., Hamilton, L.S., Johnson, K., and Chang, E.F. (2016). The auditory representation of speech sounds in human motor cortex. ELife *5*, e12577.

De Ridder, D., and Vanneste, S. (2012). EEG Driven tDCS Versus Bifrontal tDCS for Tinnitus. Front. Psychiatry *3*, 84.

De Ridder, D., Verstraeten, E., Van der Kelen, K., De Mulder, G., Sunaert, S., Verlooy, J., Van de Heyning, P., and Moller, A. (2005). Transcranial magnetic stimulation for tinnitus: influence of tinnitus duration on stimulation parameter choice and maximal tinnitus suppression. Otol. Neurotol. Off. Publ. Am. Otol. Soc. Am. Neurotol. Soc. Eur. Acad. Otol. Neurotol. *26*, 616–619.

Ebersole, J.S., and Milton, J. (2003). The Electroencephalogram (EEG): A Measure of Neural Synchrony. In Epilepsy as a Dynamic Disease, J. Milton, and P. Jung, eds. (Berlin, Heidelberg: Springer Berlin Heidelberg), pp. 51–68.

Ebersole, J.S., and Pacia, S.V. (1996). Localization of temporal lobe foci by ictal EEG patterns. Epilepsia *37*, 386–399.

Eggermont, J.J., and Tass, P.A. (2015). Maladaptive Neural Synchrony in Tinnitus: Origin and Restoration. Front. Neurol. *6*.

Engel, A.K., and Singer, W. (2001). Temporal binding and the neural correlates of sensory awareness. Trends Cogn. Sci. *5*, 16–25.

Galaburda, A., and Sanides, F. (1980). Cytoarchitectonic organization of the human auditory cortex. J. Comp. Neurol. *190*, 597–610.

Hackett, T.A., Stepniewska, I., and Kaas, J.H. (1998). Subdivisions of auditory cortex and ipsilateral cortical connections of the parabelt auditory cortex in macaque monkeys. J. Comp. Neurol. *394*, 475–495.

Hasenstaub, A., Shu, Y., Haider, B., Kraushaar, U., Duque, A., and McCormick, D.A. (2005). Inhibitory postsynaptic potentials carry synchronized frequency information in active cortical networks. Neuron *47*, 423–435.

Hodgkin, A.L., and Huxley, A.F. (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve. J. Physiol. *117*, 500–544.

Jatoi, M.A., Kamel, N., Malik, A.S., and Faye, I. (2014). EEG based brain source localization comparison of sLORETA and eLORETA. Australas. Phys. Eng. Sci. Med. *37*, 713–721.

Knight, R.T., Scabini, D., and Woods, D.L. (1989). Prefrontal cortex gating of auditory transmission in humans. Brain Res. *504*, 338–342.

Lancaster, J.L., Woldorff, M.G., Parsons, L.M., Liotti, M., Freitas, C.S., Rainey, L., Kochunov, P.V., Nickerson, D., Mikiten, S.A., and Fox, P.T. (2000). Automated Talairach atlas labels for functional brain mapping. Hum. Brain Mapp. *10*, 120–131.

Langguth, B. (2011). A review of tinnitus symptoms beyond 'ringing in the ears': a call to action. Curr. Med. Res. Opin. *27*, 1635–1643.

Langguth, B., Kreuzer, P.M., Kleinjung, T., and De Ridder, D. (2013). Tinnitus: causes and clinical management. Lancet Neurol. *12*, 920–930.

Lanting, C.P., de Kleine, E., and van Dijk, P. (2009). Neural activity underlying tinnitus generation: Results from PET and fMRI. Hear. Res. *255*, 1–13.

Lefaucheur, J.-P., Antal, A., Ayache, S.S., Benninger, D.H., Brunelin, J., Cogiamanian, F., Cotelli, M., De Ridder, D., Ferrucci, R., Langguth, B., et al. (2017). Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clin. Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol. *128*, 56–92.

Lesser, R.P., Arroyo, S., Crone, N., and Gordon, B. (1998). Motor and sensory mapping of the frontal and occipital lobes. Epilepsia *39 Suppl 4*, S69-80.

Møller, M.B., Møller, A.R., Jannetta, P.J., and Jho, H.D. (1993). Vascular decompression surgery for severe tinnitus: selection criteria and results. The Laryngoscope *103*, 421–427.

Nitsche, M.A., Cohen, L.G., Wassermann, E.M., Priori, A., Lang, N., Antal, A., Paulus, W., Hummel, F., Boggio, P.S., Fregni, F., et al. (2008). Transcranial direct current stimulation: State of the art 2008. Brain Stimulat. *1*, 206–223.

Nondahl, D.M., Cruickshanks, K.J., Huang, G.-H., Klein, B.E.K., Klein, R., Nieto, F.J., and Tweed, T.S. (2011). Tinnitus and its risk factors in the Beaver Dam Offspring Study. Int. J. Audiol. *50*, 313–320.

Nourski, K.V. (2017). Auditory processing in the human cortex: An intracranial electrophysiology perspective. Laryngoscope Investig. Otolaryngol. *2*, 147–156.

Nourski, K.V., Steinschneider, M., McMurray, B., Kovach, C.K., Oya, H., Kawasaki, H., and Howard, M.A. (2014). Functional organization of human auditory cortex: Investigation of response latencies through direct recordings. NeuroImage *101*, 598–609.

Penner, M.J. (1990). An estimate of the prevalence of tinnitus caused by spontaneous otoacoustic emissions. Arch. Otolaryngol. Head Neck Surg. *116*, 418–423.

Pickles, J.O. (2015). Chapter 1 - Auditory pathways: anatomy and physiology. In Handbook of Clinical Neurology, M.J. Aminoff, F. Boller, and D.F. Swaab, eds. (Elsevier), pp. 3–25.

Poreisz, C., Boros, K., Antal, A., and Paulus, W. (2007). Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. Brain Res. Bull. *72*, 208–214.

Ranieri, F., Podda, M.V., Riccardi, E., Frisullo, G., Dileone, M., Profice, P., Pilato, F., Di Lazzaro, V., and Grassi, C. (2012). Modulation of LTP at rat hippocampal CA3-CA1 synapses by direct current stimulation. J. Neurophysiol. *107*, 1868–1880.

Rauschecker, J.P., Leaver, A.M., and Mühlau, M. (2010). Tuning out the noise: limbic-auditory interactions in tinnitus. Neuron *66*, 819–826.

Reddy, C.G., Dahdaleh, N.S., Albert, G., Chen, F., Hansen, D., Nourski, K., Kawasaki, H., Oya, H., and Howard, M.A. (2010). A method for placing Heschl gyrus depth electrodes. J. Neurosurg. *112*.

Roche, N., Geiger, M., and Bussel, B. (2015). Mechanisms underlying transcranial direct current stimulation in rehabilitation. Ann. Phys. Rehabil. Med. *58*, 214–219.

Sadaghiani, S., Hesselmann, G., and Kleinschmidt, A. (2009). Distributed and Antagonistic Contributions of Ongoing Activity Fluctuations to Auditory Stimulus Detection. J. Neurosci. *29*, 13410–13417.

Schlee, W., Mueller, N., Hartmann, T., Keil, J., Lorenz, I., and Weisz, N. (2009). Mapping cortical hubs in tinnitus. BMC Biol. *7*, 80.

Schneider, P., Andermann, M., Wengenroth, M., Goebel, R., Flor, H., Rupp, A., and Diesch, E. (2009). Reduced volume of Heschl's gyrus in tinnitus. NeuroImage *45*, 927–939.

Schuh, L., and Drury, I. (1997). Intraoperative electrocorticography and direct cortical electrical stimulation. Semin. Anesth. Perioper. Med. Pain *16*, 46–55.

Sedley, W., Gander, P.E., Kumar, S., Oya, H., Kovach, C.K., Nourski, K.V., Kawasaki, H., Howard, M.A., and Griffiths, T.D. (2015). Intracranial Mapping of a Cortical Tinnitus System using Residual Inhibition. Curr. Biol. *25*, 1208–1214.

Seidman, M.D., Ridder, D.D., Elisevich, K., Bowyer, S.M., Darrat, I., Dria, J., Stach, B., Jiang, Q., Tepley, N., Ewing, J., et al. (2008). Direct electrical stimulation of Heschl's gyrus for tinnitus treatment. The Laryngoscope *118*, 491–500.

Shekhawat, G.S., Searchfield, G.D., and Stinear, C.M. (2014). Randomized Trial of Transcranial Direct Current Stimulation and Hearing Aids for Tinnitus Management. Neurorehabil. Neural Repair *28*, 410–419.

Spencer, K.M., Nestor, P.G., Niznikiewicz, M.A., Salisbury, D.F., Shenton, M.E., and McCarley, R.W. (2003). Abnormal neural synchrony in schizophrenia. J. Neurosci. Off. J. Soc. Neurosci. *23*, 7407–7411.

Talbot, K., Louneva, N., Cohen, J.W., Kazi, H., Blake, D.J., and Arnold, S.E. (2011). Synaptic Dysbindin-1 Reductions in Schizophrenia Occur in an Isoform-Specific Manner Indicating Their Subsynaptic Location. PLOS ONE *6*, e16886.

Tass, P.A. (2003). A model of desynchronizing deep brain stimulation with a demand-controlled coordinated reset of neural subpopulations. Biol. Cybern. *89*, 81–88.

Tass, P.A., Freund, H.-J., von Stackelberg, T., Hauptmann, C., and Adamchic, I. (2012). Counteracting tinnitus by acoustic coordinated reset neuromodulation. Restor. Neurol. Neurosci. 137–159.

Uhlhaas, P., and Singer, W. (2006). Neural Synchrony in Brain Disorders: Relevance for Cognitive Dysfunctions and Pathophysiology. Neuron *52*, 155–168.

Uhlhaas, P., Pipa, G., Lima, B., Melloni, L., Neuenschwander, S., Nikolić, D., and Singer, W. (2009). Neural synchrony in cortical networks: history, concept and current status. Front. Integr. Neurosci. *3*.

Van der Loo, E., Gais, S., Congedo, M., Vanneste, S., Plazier, M., Menovsky, T., Van de Heyning, P., and De Ridder, D. (2009). Tinnitus Intensity Dependent Gamma Oscillations of the Contralateral Auditory Cortex. PLOS ONE *4*, e7396.

Volgushev, M., Chistiakova, M., and Singer, W. (1998). Modification of discharge patterns of neocortical neurons by induced oscillations of the membrane potential. Neuroscience *83*, 15–25.

Wegger, M., Ovesen, T., and Larsen, D.G. (2017). Acoustic Coordinated Reset Neuromodulation: A Systematic Review of a Novel Therapy for Tinnitus. Front. Neurol. *8*.

Yadollahpour, A., Jalilifar, M., and Rashidi, S. (2017). Transcranial Direct Current Stimulation for the Treatment of Depression: a Comprehensive Review of the Recent Advances. Int. J. Ment. Health Addict. *15*, 434–443.

Yuan, T., Yadollahpour, A., Salgado-Ramírez, J., Robles-Camarillo, D., and Ortega-Palacios, R. (2018). Transcranial direct current stimulation for the treatment of tinnitus: a review of clinical trials and mechanisms of action. BMC Neurosci. *19*.

Zhang, J., Zhang, Y., and Zhang, X. (2011). Auditory cortex electrical stimulation suppresses tinnitus in rats. J. Assoc. Res. Otolaryngol. JARO *12*, 185–201.