

6-2011

# Repetitive Transcranial Magnetic Stimulation Used for Tinnitus Suppression: A Voxel-Based Morphometry Study

Lauren E. Laitman

*Union College - Schenectady, NY*

Follow this and additional works at: <https://digitalworks.union.edu/theses>



Part of the [Otorhinolaryngologic Diseases Commons](#)

---

## Recommended Citation

Laitman, Lauren E., "Repetitive Transcranial Magnetic Stimulation Used for Tinnitus Suppression: A Voxel-Based Morphometry Study" (2011). *Honors Theses*. 1014.

<https://digitalworks.union.edu/theses/1014>

This Open Access is brought to you for free and open access by the Student Work at Union | Digital Works. It has been accepted for inclusion in Honors Theses by an authorized administrator of Union | Digital Works. For more information, please contact [digitalworks@union.edu](mailto:digitalworks@union.edu).

Running title: EFFECTS OF RTMS ON TINNITUS SUPPRESSION

Repetitive Transcranial Magnetic Stimulation Used for  
Tinnitus Suppression: A Voxel-Based Morphometry Study

By

Lauren Elisabeth Laitman

\* \* \* \* \*

Submitted in partial fulfillment  
of the requirements for  
Honors in the Department of Neuroscience

UNION COLLEGE

June, 2011

## ABSTRACT

LAITMAN, LAUREN      Repetitive Transcranial Magnetic Stimulation Used  
for Chronic Tinnitus Suppression: A Voxel-Based Morphometry Study

ADVISOR: Professor Stephen Romero

Tinnitus is a debilitating disorder with unknown underlying mechanisms, often induced by loud noises. Tinnitus symptoms include the conscious perception of constant sound absent an external source. This study sought to determine effectiveness of treatment with repetitive transcranial magnetic stimulation (rTMS), and to use voxel-based morphometry (VBM) to identify treatment related neuronal reorganization. One hertz rTMS was delivered for 20 minutes on each of 5 consecutive days. Tinnitus suppression was measured with the Tinnitus Handicap Questionnaire (THQ), and VBM was carried out on structural Magnetic Resonance images collected before and after sham-treatment and rTMS. Findings indicate the effectiveness of rTMS for tinnitus suppression, and changes in grey and white matter volume due to both rTMS and sham treatment.

## Repetitive Transcranial Magnetic Stimulation Used for Chronic Tinnitus Suppression: A Voxel-Based Morphometry Study

Tinnitus is an auditory condition manifested as noise or ringing in the ears in the absence of an external source. The ringing commonly results from hearing loss following exposure to loud noise. Tinnitus is a heterogeneous disorder and individuals can hear continuous, or intermittent sounds that range from a hissing sound to a roaring sound that may differ across the frequency range (Landgrebe et al., 2008). Classification of tinnitus is either objective or subjective. Objective tinnitus is very rare and originates from an internal source within the body, such as the sound of turbulent blood flow. Subjective tinnitus represents the more common form of the disorder and refers to the perception of phantom sound in the absence of an external stimulus (Moller, Langguth et al., 2006). Among other conditions of altered perceptions of sound, tinnitus is often associated with hyperacusis, which is the louder perception of normal amplitude sounds, and with phonophobia, which is the painful or unpleasant perception of sounds. These auditory hallucinations and phantom perceptions of sound greatly impact quality of life by disrupting normal sleeping patterns, interrupting concentration and altering one's emotional and psychological well-being.

The underlying mechanisms and pathophysiology of tinnitus are generally unknown. It has been suggested that tinnitus is a representation of auditory pathologic process in the brain resulting from a dysfunction in the ear (Langguth et al., 2006). Certain occupations and recreational activities pose a greater likelihood of exposure to very loud noises and thus a greater probability for developing tinnitus. For example individuals that have served in the armed forces and have been exposed to high intensity

or long durations of loud noise are at risk for developing the condition. Eggermont and Roberts (2004) have speculated that tinnitus arises from hearing loss caused by continuous exposure to loud noise that damages sensory cells in the central nervous system and prevents the activity of the inhibitory cells in the cochlea, which is the auditory sensory organ of the inner ear. The auditory cortex is located in the superior part of the temporal lobe and the cochlea projects to subcortical relay areas in the medial geniculate nucleus of the thalamus (Gazzaniga, Ivry & Mangun, 2009). It is theorized that dysfunction of the sensory cells results in the hyperexcitability of nerve fibers in the central auditory cortex leading to increased spontaneous discharge and structural reorganization (Langguth et al., 2007). Following from the hyperexcitability theory spontaneous neuronal firing and neuralplastic changes of the auditory system are responsible for the debilitating ringing and phantom perceptions of sound.

Electrophysiological and neuroimaging studies of tinnintus have found abnormal functioning in the central auditory system supporting the hyperexcitability theory. Nevertheless the same studies have also found abnormal function in non-auditory brain regions in tinnitus patients, which suggests that tinnitus not only influences the auditory system, but also peripheral structures outside of the central auditory cortex (Landgrebe et al., 2009; Eichhammer et al., 2003; Cacace et al., 1999; Langguth et al., 2006). For example using Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI), increased neuronal excitability was found in the temporal cortex of patients suffering from chronic tinnitus (Langguth et al., 2006; Langguth et al., 2007). Yet other dysfunction has been detected within the central auditory pathway, specifically in the inferior colliculus, the thalamus and the central auditory cortex

(Eichhammer et al., 2003; Cacace et al., 1999; Langguth et al., 2006). Thus increased neural firing in the auditory pathway may be responsible for the primary effects of tinnitus, manifested as the debilitating ringing in the ears, but is not the entire story.

Abnormal neural functioning in both auditory and non-auditory regions suggests that the phantom perception of sound cannot exclusively be localized to the central auditory system. Peripheral structures may be involved in perception of the auditory hallucinations or conversely, be involved in other cognitive processes that compensate for the debilitating noise (i.e., secondary symptoms). The secondary symptoms of tinnitus include the psychological, social, emotional, and behavioral consequences of tinnitus that are indirectly related to the primary effects (i.e., hearing loss and debilitating ringing). Using electrical stimulation to modify cortical excitability, alterations of cortical excitability were observed in the motor cortex following stimulation treatment, and subsequent reduction in overall tinnitus severity as measured by Goebel and Hiller's Tinnitus Questionnaire indicate the connection between activation of non-auditory brain regions and alleviation of both the primary and secondary effects of tinnitus (Langguth et al., 2007) Alterations in neural activity outside of the auditory cortex, specifically in the limbic structures have also been found (Lockwood et al., 1998).

Given that there are primary and secondary symptoms associated with the disorder it is important to measure both types of symptoms during treatment. The Tinnitus Handicap Questionnaire (THQ) created by Kuk, Tyler, Russell and Jordan (1990) measures both the primary effects and the secondary effects of tinnitus. Comprised of 27 questions the THQ is designed to monitor primary and secondary effects of a patient's tinnitus and their progress with treatment. The primary effects of

tinnitus include tinnitus severity measured by the magnitude of tinnitus loudness. The secondary effects of tinnitus are composed of the emotional, behavioral and psychological factors due to this debilitating ringing in the ears. The THQ is designed to encompass the analysis of the following three factors; hearing ability, the patient's view of tinnitus, and the physical social and emotional consequences of tinnitus. The consequences assessed are perceived loudness of tinnitus, life satisfaction, depression, health, general health, illness checklist, and social desirability. Some examples from the questionnaire are "I do not enjoy life because of tinnitus" and "tinnitus causes me to feel depressed" (Kuk et al., 1990). The perceived loudness of tinnitus represents the psychophysical measure of primary effects of tinnitus and is measured by subjectively asking the patients to judge the loudness of their tinnitus in their everyday lives. All of the other psychometric properties of the THQ measure the secondary effects associated with tinnitus.

Although a widely accepted treatment for the tinnitus has yet to be fully developed repetitive Transcranial Magnetic Stimulation (rTMS) has been used as an effective method for chronic tinnitus suppression (Langguth et al., 2006; Langguth et al., 2007; Pridemore et al., 2006; Landgrebe et al., 2008). Using the principles of electromagnetism, a magnetic field is delivered to areas on the cerebral cortex which can induce or suppress neuronal firing. By modifying cortical excitability, rTMS presents a noninvasive method for altering neuronal firing and has been used for examining hyperactivity of cortical regions responsible for phantom sensations. In the past, rTMS has been used as a successful treatment for other diseases caused by hyperexcitability of neurons in the brain that produce phantom sensations such as focal epilepsy and

schizophrenia (Hoffman and Cavus, 2002; Eichhammer, Langguth, Marienhagen, Kleinjung, & Hajak, 2003).

Repetitive transcranial magnetic stimulation specifically involves the placement of an encapsulated coil of wire on the surface of the skull over a specific region of interest. An electric current is passed through the coil which induces a magnetic field perpendicular to the surface of the brain. This magnetic field attenuates through the skull, but still alters excitability of cortical regions directly below the coil. Along with the actual stimulation, individuals experiencing rTMS feel physical vibrations and hear an auditory discharge. Low frequency rTMS ( $\leq 1$  Hz) has been used to reduce cortical excitability and treat hyperexcitability disorders such as tinnitus (Hoffmann & Cavus, 2002). In contrast, high frequency rTMS (5 – 20 Hz) induces cortical excitability and has been used to treat major depression (Marcondes, Fregni, & Pascual-Leone, 2006).

Given that TMS can alter cortical excitability it is important to understand any neuralplastic changes that maybe induced by treatment with TMS. Following from Ashburner and Friston (2000) and Good et al. (2001), Voxel-Based Morphometry (VBM) is a technique used to compare cerebral volume and tissue concentrations of grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) in structural magnetic resonance images (MRIs). Thus, VBM can be an effective tool for assessing neuralplasticity of the brain by examining differences in brain matter volume following stimulation treatments and has been useful in determining pathologic plasticity in the brain. For example, Gaser and Schlaug (2003) investigated differences in brain structures between musicians and non-musicians. Using VBM they found differences in grey matter volume in the motor, auditory, and visual-spatial brain regions between musicians and

non-musicians. This finding suggests that differences in grey matter volume of particular regions in the brain may be associated with specific tasks that are common to a specific lifestyle. More specifically, Gaser and Schlaug (2003) hypothesized that structural adaptation can be attributed to long-term skill acquisition and rehearsal of these specific skills. The general implications of these findings can be applied to this present study. Neuralplastic changes arise due to particular patterns of activation as seen in the voluntary use of specific regions, such as the auditory cortex in musicians, or involuntary activation as experienced by tinnitus sufferers. The utilization of specific sensory and perception processes corresponds to specific demands on cortical regions, which may be represented as differences in brain volumes in specific areas. Therefore, dynamic structural changes may be the result of alterations in functional processing and specific cognitive demands (May et al., 2007).

The present study focused on only those individuals suffering from subjective, chronic, noise-induced tinnitus, and investigated the efficacy of low frequency rTMS over the auditory cortex of the left and right hemisphere for suppression this type of tinnitus. The VBM analysis was then used to examine the changes in structural brain structures modulated by rTMS treatment.

## Method

### *Participants*

Twenty-five individuals ranging from 21-90 years of age with a 1 year history of chronic unilateral or bilateral tinnitus were enrolled in this study at Wayne State University. A history of chronic tinnitus was defined as noise-induced tinnitus or tinnitus characterized by sensorineural hearing loss from a range of 1.0 kHz to 8.0 kHz. To ensure

that participants' tinnitus was caused by only noise exposure, all participants were subject to a detailed medical examination to rule out possible causes of tinnitus such as medical, pharmacologic, and psychiatric causes.

Individuals with metal objects or other medical hardware were not permitted to participate in the study because they posed a severe safety risk for MRI scanning. Additionally, pregnant women were excluded from this study for fear of harm to the fetus as a result of the imaging procedures. All participants were paid for their participation.

### *Design*

Each participant was tested twice, under an identical protocol, for both the active and the sham conditions. Sham or active rTMS treatment was applied for 20 minutes at 1 Hz on each of 5 consecutive days. The Tinnitus Handicap Questionnaire scores were used to measure changes in tinnitus symptoms and structural alterations in grey and white matter volumes associated with the different treatments was measured through VBM. Each individual was tested twice, once under the active condition and once under the sham controlled condition, with MRIs obtained both before and after each condition. The participants were randomly assigned to receive either the sham condition first or rTMS condition first.

### *Procedure*

#### *Repetitive transcranial magnetic stimulation*

Repetitive transcranial magnetic stimulation treatment was applied at 1 Hz separately on the lateral surface of both the left and right auditory cortex. The treatment was presented over a 5-consecutive day period for 20 minutes over each hemisphere,

separately each day (1,200 stimuli a day per hemisphere, 12,000 stimuli total). The total session time each day lasted slightly under one hour. The stimulation was presented at 110% above the motor threshold (MT), which was determined from electrophysiological recordings from the abductor pollicis brevis muscle.

A figure 8 coil was used for rTMS treatment and coil placement was determined using the 10 – 20 System of the International Federation according to Cacace, Dowman, and Wolpaw, (1988) who determined the auditory association cortex to be halfway between the T3 and T5 locations for the left hemisphere and halfway between the T4 and T6 on the right hemisphere as viable locations for the placement of stimulation devices used for tinnitus suppression.

#### *Structural MRI Scanning Protocol*

After obtaining consent, each subject was placed in a high field 3 Tesla (T) MR system using a standard, quadrature head coil. T1-weighted MRIs were taken prior to the first rTMS treatment to provide a prestimulus baseline and once again obtained after the completion of the 5-day rTMS treatment series. A 3-D, spoiled gradient recalled acquisition (SPGR) T1 weighted pulse sequence (field-of-view, FOV 22cm; slice thickness, 2mm; matrix 256 x 125, NEX = 1; flip angle 15°, echo time TE = 5.2 ms; inversion time TI = 300 ms, repetition time TR 12 ms) was used for anatomical imaging. Data acquisition for the pulse sequence lasted approximately 5 minutes.

#### *Data Processing and Statistical Analysis*

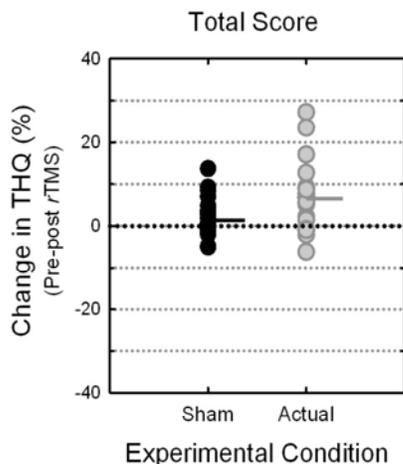
Data preprocessing and analysis were performed using the Voxel-Based Morphometry 5 (VBM5) toolbox within Statistical Parametric Mapping 5 (SPM5) as outlined by Ashburner and Friston, 2000 and Good et al., 2001 (Wellcome Department of

Cognitive Neurology, London, UK). Before beginning the preprocessing, the origin of all the images was set at the anterior commissure. Preprocessing of the images involved spatial normalization, which put all images into the same stereotaxic space in order to accurately compare across different brains. The spatially normalized images were then segmented into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF). Following segmentation, each set of images was modulated using a mathematical process that corrects for overcorrection from the normalization process due to differences in skull size, and thus allowing for the analysis of differences between conditions while controlling for skull size. Finally, the modulated, segmented, normalized images are spatially smoothed with an isotropic Gaussian kernel Full Width at Half Maximum (FWHM) of 12 mm. Smoothing makes the intensity of each voxel to be the average of each voxel and the surrounding (12mm in three dimensions) voxels, which helps to satisfy the assumptions of parametric statistical analysis. (Mechelli, Price, Friston & Ashburner, 2005).

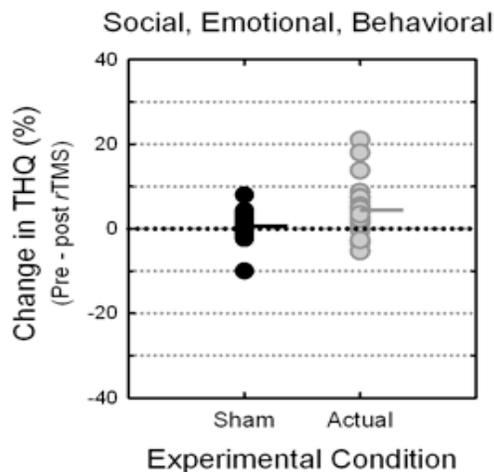
## Results

*THQ Results.* It was necessary to first examine the results from the THQ because if no effect of rTMS on tinnitus existed, volume changes would not matter. Data from the Tinnitus Handicap Questionnaire yielded significant results, such that there was a significant decrease in tinnitus symptoms following rTMS treatment but not after the sham condition. In the overall score of the questionnaire, there was a significant percent change from pre to post TMS but not from pre to post sham, indicating that TMS treatment resulted in decreases tinnitus symptoms (Figure. 1). Similarly, a significant percent change was found in the social, emotional, and behavioral subscales of the THQ

in the active, rTMS condition but not in the sham condition (Figure. 2). This result shows the alleviation of symptoms associated with tinnitus following rTMS but not following the sham condition.



**Fig. 1.** Boxplot displaying percentage change in total score of THQ between sham condition and actual condition.



**Fig. 2.** Boxplot displaying the percentage change in THQ scores on social, emotional, and behavioral subscales between sham condition and TMS condition.

A 2 X 2 Analysis of Variance (ANOVA) was conducted with scan time (pre vs. post) and stimulation condition (rTMS vs sham) representing the two independent variables, producing four conditions: presham postsham, preTMS and postTMS was performed on the VBM data. There was no significant interaction between scan time (ie. pre/post) and stimulation condition (ie. tms/sham).

*Grey Matter.* Analyses of the GM images produced two significant findings. GM volume increased from the pre sham to post sham condition in the left middle frontal gyrus (Brodmann's Area 11), such that there was greater GM volume following sham stimulation than before sham condition, (corrected  $p = .016$ , Figure. 3). Additionally,

greater volume was found in the pre TMS condition than in the post TMS condition in the right inferior parietal lobe (Brodmann's Area 40), such that GM volume decreased from the pre TMS condition to the post TMS condition ( $p = .017$ ; Figure. 4).

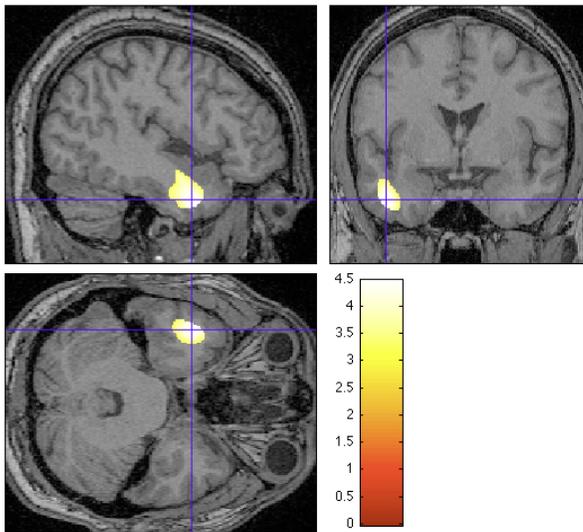
QuickTime™ and a  
TIFF (LZW) decompressor  
are needed to see this picture.

QuickTime™ and a  
TIFF (LZW) decompressor  
are needed to see this picture.

**Fig. 3.** Grey matter volume increase from pre to post sham condition in the left middle frontal gyrus overlaid onto a T1 weighted image.

**Fig. 4.** Grey matter volume decrease from pre tms to post tms condition in the right inferior parietal lobe.

*White Matter.* Six significant findings were observed from the analyses of WM. Volume increased from pre-sham to post-sham in the left middle temporal gyrus (Brodmann's Area 21), ( $p = .015$ ; Figure. 5). The remaining five significant findings resulted from the TMS stimulation. White matter volume increases and decreases were found following rTMS (Figure. 6). WM volume increased from pre to post rTMS in the right putamen, right medial geniculate nucleus of the thalamus, and the right inferior parietal lobe (Figure 6 in red). Decreases in WM volume from pre to post rTMS were found in the right superior frontal gyrus and the left caudate (Figure 6 in blue).



**Fig. 5.** White matter volume increase following sham condition in the left middle temporal gyrus, Brodmann's Area 21).

QuickTime™ and a  
TIFF (LZW) decompressor  
are needed to see this picture.

**Fig. 6.** Rendering of white matter volume changes following TMS. WM increases are shown in red in the right putamen, right medial geniculate nucleus of the thalamus, and the right inferior parietal lobe (Brodmann's Area 40). Blue regions indicate WM volume decreases from pre to post TMS in the right superior frontal gyrus and the left caudate.

## Discussion

The aim of this study was to examine the effectiveness of rTMS on chronic, noise-induced tinnitus as measured by the Tinnitus Handicap Questionnaire before and after sham and active treatment, and using VBM to ascertain if specific, underlying brain regions were altered as a result of tinnitus suppression. Low frequency rTMS for tinnitus suppression has been used in the past as a diagnostic tool and treatment method and the results of the present study are consistent with previous research (Langguth et al., 2006; Langguth et al., 2007; Landgrebe et al., 2008; Eichhammer et al., 2003).

Data from the Tinnitus Handicap Questionnaire support one of the aims of this study. The decrease in total THQ score observed following rTMS treatment indicates that this method was effective for reducing the primary symptoms of tinnitus, mainly the debilitating ringing. This finding is consistent with Langguth et al. (2006) who found significant changes in THQ following rTMS. Data from the social, emotional and behavioral subscales follow a similar trend and suggest that rTMS not only decreased the primary effects, but also alleviated some of the secondary effects associated with this disorder. The changes in the social, behavioral, and psychological subscales of the THQ score indicate the rTMS was an effective treatment for secondary aspects of tinnitus. Figure. 1 illustrates that there was a difference from pre to post tms in the total THQ score, but not from pre to post sham. Similarly, there was a difference in the social, emotional and behavioral subscales of the THQ following rTMS but not after the sham condition (Figure. 2). Changes in both THQ score and within GM and WM volume were found from pre to post rTMS relating to the primary effects of tinnitus (i.e., the ringing in the ears). Decreases in GM volume were observed following rTMS treatment in the right

inferior parietal lobe (Figure 4). WM volume increased in the right medial geniculate nucleus of the thalamus (Figure. 6), which as part of the auditory pathway receives information from the inferior colliculus and delivers signals to the primary auditory cortex (Gazzaniga et al., 2009). Landgrebe et al (2009) found significant differences between tinnitus patients and healthy controls in GM volume in the auditory pathway in the inferior colliculus, but not in the medial geniculate nucleus of the thalamus, which was attributed to alterations in the hyperexcitability of the neurons responsible for tinnitus. As mentioned before the underlying mechanism for the primary effects, may be localized in the auditory pathway (Eichhammer et al., 2003; Cacace et al., 1999; Langguth et al., 2006), and the present data support this assertion in the form of changes in the auditory pathway due to TMS. It is possible that subcortical areas that are connected to areas in the primary auditory cortex may be responsible for the secondary effects of tinnitus (i.e., the social, emotional, and behavioral consequences). Imaging studies identified increased subcortical activity in the secondary auditory cortex and limbic structures and changes in these areas following rTMS, which suggests that neuralplasticity occurs not only in the primary auditory cortex, but also in the subcortical areas (Muhlau, et al., 2006). The close association of tinnitus with emotional symptoms indicates that there may a neural pathway connecting areas that mediates the primary effects of tinnitus with the emotional control centers within the limbic system.

With regard to the secondary effects of tinnitus, information from the social, emotional, and behavioral subscales of the THQ in the present study demonstrate the effectiveness of rTMS in the reduction of the severity of the secondary symptoms. Together with the changes on the secondary THQ scales, structural brain volume changes

outside of the auditory pathway may indicate brain areas associated with the secondary effects of tinnitus. Changes in the right inferior parietal lobe and the right superior frontal gyrus (Figure. 4 and Figure. 6) in the present study suggest that changes in these areas maybe associated with the alleviation of secondary symptoms. More specifically, the GM volume decrease in the right inferior parietal lobe (Brodmann's Area 40) following rTMS is supported by previous research, demonstrating that structural reorganization results from rTMS (May et al., 2007). The inferior parietal lobe and the superior frontal gyrus represent areas involved in the neural mechanisms of attention and selective perception. A possible explanation for the reduction of tinnitus symptoms and altered brain volumes outside of the auditory cortex following electrical stimulation may be that activation changes occur in brain regions involved in the noise-cancellation of the debilitating ringing. Once the ringing in the ears subsided, it is possible that compensatory mechanisms involving noise-cancellation, ignoring the perception of the sound, and overusing other cognitive functions to displace the handicap due to the primary effects of tinnitus.

Additional GM and WM volume changes were found in regions peripheral to the auditory pathway, whose functions may be related to the some of the secondary effects. Grey matter volume increased in the right putamen and the right inferior parietal lobe but decreased in the right superior frontal gyrus and the left caudate (Figure. 6). The caudate and the putamen, collectively referred to as the neostriatum, are part of the basal ganglia and have a role in the control of movement (Gazzaniga et al., 2009). More information regarding the differences in movement control as related to tinnitus needs to be obtained, but this change may be associated with changes in some cognitive functions due to the

alleviation of the primary effects. It is unclear if these areas are directly or indirectly connected to the neural circuitry of the auditory pathway but, further research should concentrate on specific neurobehavioral connections between the primary and secondary effects of tinnitus and the modulation of these effects from rTMS using both changes of brain volume using VBM and the subscales of THQ.

Grey matter and WM volume changes found from pre to post sham suggest that the actual stimulation may not be the only factor responsible for changes in brain volume. Even though the observed structural brain changes do not serve as an indication that the sham treatment resulted in the reduction of tinnitus severity as (demonstrated by no significant changes in THQ from pre to post sham), both conditions present the patient with the same auditory discharge and a similar physical vibrations and the only difference between the control and the actual condition is the induction of a magnetic field perpendicular to the skull that modifies cortical excitability. The findings from the VBM data indicate alterations in brain structure in both the grey matter and white matter volume following the sham condition. Grey matter volume increased following sham treatment in the left middle frontal gyrus (Figure. 3). WM volume also increased from pre to post sham treatment in the left middle temporal gyrus (Figure. 5). These findings differ from May et al., (2007), in which no significant increases or decreases were observed in GM and WM as a result of the sham condition. The differences observed from pre to post sham condition suggest that the control has some influence brain volume as well, but the direct effects of the sham treatment on any behavioral or cognitive processing are still unknown. Future research on sham treatment should focus on the location of structural volumes changes in relation to placement of the coil. Additionally, it would be beneficial

to examine the differences in THQ and other measures of behavioral and cognitive processing between sham conditions when placed on the auditory cortex and at a location outside of the primary auditory cortex.

In conclusion, the changes observed in GM and WM volume following rTMS represent a more pertinent contribution to the overall objectives of this study than the results of the sham, control condition. The connections between the structural neuralplastic changes from VBM analyses and the behavioral alterations as measured by the THQ represent the effectiveness of rTMS treatment for chronic tinnitus suppression. Chronic, noise-induced tinnitus is a disorder manifested by both primary effects (ie. ringing in the ears) and associated secondary effects including depression, insomnia, and general life dissatisfaction. As shown from the VBM data, alterations in structural brain regions occurred both in the auditory pathway (medial geniculate nucleus of the thalamus) and in non-auditory areas (superior frontal gyrus and the inferior parietal lobe). These neuralplastic changes resulting from stimulation may be suggestive of the influence of these brain regions on alleviation of the primary and secondary effects of tinnitus. Further research correlating the brain regions that undergo changes in neuronal excitability with the alleviation of symptoms following treatment may provide a framework for categorizing the subgroups within chronic tinnitus sufferers. Once this is accomplished, a more individualized treatment protocol can be used to best suppress one's tinnitus and alleviate many of the symptoms. By classifying chronic tinnitus sufferers by their clinical characteristics and pathophysiology, more extensive research can be conducted and VBM can be used to analyze specific regions of the brain beyond auditory areas to gain insight into the secondary effects of tinnitus.

## References

- Ashburner, J., & Friston, K. (2000). Voxel-Based Morphometry – The Methods. *NeuroImage, 11*, 805 – 821.
- Cacace, A., Dowman, R., & Wolpaw, J. (1988). T-complex hemispheric asymmetries: Effects of stimulus intensity. *Hearing Research, 34*, 3.
- Cacace, A., Cousins, J., Parnes, S., McFarland, D., Semenoff, D., Holmes, T., Davenport, C., Stegbauer, K., & Lovely, T. (1999). Cutaneous-Evoked Tinnitus. *Audiology & Neuro-Otology, 4*, 258 – 268.
- Eggermont, J. & Roberts, L. (2004). The neuroscience of tinnitus. *TRENDS in Neuroscience, 27*, 11.
- Eichhammer, P., Langguth, B., Marienhagen, J., Kleinjung, T., & Hajak, G. (2003). Neuronavigated Repetitive Transcranial Magnetic Stimulation in Patients with Tinnitus: A Short Case Series. *Biological Psychiatry, 54*, 862 – 865.
- Gaser, C., & Schlaug, G. (2003). Brain Structures Differ between Musicians and Non-Musicians. *The Journal of Neuroscience, 23*, 27.
- Gazzaniga, M., Ivry, R., & Mangun, G. (2009). *Cognitive Neuroscience: The Biology of the Mind*. New York, NY: W. W. Norton & Company, Inc.
- Good, C., Johnsrude, I., Ashburner, J., Henson, R., Friston, K., & Frackowiak, S. (2001). A Voxel-Based Morphometric Study of Ageing in 465 Normal Adult Human Brains. *NeuroImage, 14*, 21 – 36.
- Hoffman, R. & Cavus, I. (2002) Slow transcranial magnetic stimulation, long-term potentiation, and brain hyperexcitability disorders. *American Journal of Psychiatry, 159*, 1093 – 1102.

- Kuk, F., Tyler, R., Russel, D., & Jordan, H. (1990). The Psychometric Properties of a Tinnitus Handicap Questionnaire. *Ear and Hearing, 11*, 6.
- Kolbinger, H., Hoflich, G., Hufnagel, A., Moller, H. & Kasper, S. (1995). Transcranial Magnetic Stimulation(TMS) in the Treatment of Major Depression – A Pilot Study. *Human Psychopharmacology, 10*, 305 – 310.
- Landgrebe, M., Binder, H., Koller, M., Eberl, Y., Kleinjung, T., Eichhammer, P., Graf, E., Hajak, G., & Langguth, B. (2008). Design of a placebo-controlled, randomized study of the efficacy of repetitive transcranial magnetic stimulation for the treatment of chronic tinnitus. *BMC Psychiatry, 8*, 23.
- Landgrebe, M., Langguth, B., Rosengarth, K., Braun, S., Koch, A., Kleinjung, T., May, A., de Ridder, D., & Hajak, G. (2009). Structural brain changes in tinnitus: Grey matter decrease in auditory and non-auditory brain areas. *NeuroImage, 46*, 1.
- Langguth, B., Kleinjung, T., Marienhagen, J., Binder, H., Sand, P., Hajak, G., & Eichhammer, P. (2007). Transcranial Magnetic Stimulation for the treatment of tinnitus: Effects on cortical excitability. *BMC Neuroscience, 8*, 45.
- Langguth, B., Hajak, G., Kleinjung, T., Pridemore, S., Sand, P. & Eichhammer, P. (2006). Repetitive transcranial magnetic stimulation and chronic tinnitus. *Acta Oto-Laryngological, 126*, 102 – 105.
- Langguth, B., Eichhammer, P., Kreutzer, A., Maenner, P., Marienhagen, J., Kleinjung, T., Sand, P., & Hajak, G. (2006). The impact of auditory cortex activity on characterizing and treating patients with chronic tinnitus – first results from a PET study. *Acta Oto-Laryngological, 126*, 84 – 88.

- Lockwood, A., Salvi, R., Coad, M., Towsley, M., Wack., D. & Murphey, B. (1998). The functional neuroanatomy of tinnitus: Evidence for limbic system links and neural plasticity. *Neurology*, *50*, 114 – 120.
- Marcondes, R., Fregni, F., & Pascual-Leone, A. (2006). Tinnitus and brain activation: Insights from transcranial magnetic stimulation. *ENT – Ear, Nose & Throat Journal*, *85*, 4.
- Mechelli, A., Price, C., Friston, K., & Ashburner, J. (2005). Voxel-Based Morphometry of the Human Brain: Methods and Applications. *Current Medical Imaging Reviews*, *1*, 00 - 00.
- Møller, A. R. (2000). Tinnitus, Hypercausis, and Phonophobia. Academic Press, *Hearing: Its Physiology and Pathophysiology* (pp. 461 – 483)
- Mühlau, M., Rauschecker, J., Oestreicher, E., Gaser, C., Röttinger, M., Wohlschläger, A., Simon, F., Etgen, T., Conrad, B., & Sander, D. (2006). Structural Brain Changes in Tinnitus. *Cerebral Cortex*, *16*, 1.
- Mühlnickel, W., Elbert, T., Taub, E., & Flor, H. (1998). Reorganization of auditory cortex in tinnitus. *Proceedings of the National Academy of Sciences*, *95*, 10340 – 10343.
- Pridemore, S., Kleinjung, T., Langguth, B., & Eichhammer, P. (2006). Transcranial magnetic stimulation: Potential treatment for tinnitus? *Psychiatry and Clinical Neurosciences*, *60*, 133 – 138.

### Acknowledgements

Data was obtained from a Tinnitus Research Initiative (TRI) grant entitled “Mechanisms of tinnitus suppression using repetitive transcranial magnetic stimulation (rTMS): A prospective randomized sham-controlled proton magnetic resonance spectroscopy ( $^1\text{H}$  MRS) study.”