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Research Paper

Glutamate is down-regulated and tinnitus loudness-levels decreased following *rTMS* over auditory cortex of the left hemisphere: A prospective randomized single-blinded sham-controlled cross-over study

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ABSTRACT

Using a prospective randomized single-blinded sham-controlled cross-over design, we studied the efficacy of low frequency (1-Hz) repetitive transcranial magnetic stimulation (*rTMS*) over auditory cortex of the left temporal lobe as an experimental treatment modality for noise-induced tinnitus. Pre/post outcome measures for sham vs. active *rTMS* conditions included differential changes in tinnitus loudness, self-perceived changes in the Tinnitus Handicap Questionnaire (THQ), and neurochemical changes of brain metabolite concentrations using single voxel proton magnetic resonance spectroscopy (¹H-MRS) obtained from left and right auditory cortical areas. While no subject in our sample had complete abatement of their tinnitus percept, active but not sham *rTMS* significantly reduced the loudness level of the tinnitus perception on the order of 4.5 dB; improved subscales in several content areas on the THQ, and down regulated (reduced) glutamate concentrations specific to the auditory cortex of the left temporal lobe that was stimulated.

In addition, significant pair-wise correlations were observed among questionnaire variables, metabolite variables, questionnaire-metabolite variables, and metabolite-loudness variables. As part of this correlation analysis, we demonstrate for the first time that active *rTMS* produced a down regulation in the excitatory neurotransmitter glutamate that was highly correlated ($r = 0.77$, $p < 0.05$) with a reduction in tinnitus loudness levels measured psychoacoustically with a magnitude estimation procedure. Overall, this study provides unique information on neurochemical, psychoacoustic, and questionnaire-related profiles which emphasizes the emerging fields of perceptual and cognitive MRS and provides a perspective on a new frontier in auditory and tinnitus-related research.

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1. Introduction

Repetitive transcranial magnetic stimulation (*rTMS*) is one of several experimental procedures thought to be of value in

suppressing chronic tinnitus by modulating neural activity underlying the stimulating magnetic coil. Based on theoretical considerations and relevant animal studies, low frequency *rTMS* (≤ 1 Hz) is thought to modulate cortical excitability via *inhibitory* mechanisms (e.g., Chen et al., 1997) whereas higher frequency *rTMS* stimulation (≥ 5 Hz), is thought to modulate *excitatory* mechanisms and reactive plasticity (Pascual-Leone et al., 1994; Wang et al., 1996). As a consequence, *rTMS*-based neuromodulation can influence underlying brain physiology and cognitive functions (Walsh

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and Cowey, 2000). Other non-invasive and/or invasive neuromodulation techniques utilized for tinnitus suppression and/or attempts to treat an individual's reaction to the tinnitus percept include: transcranial direct current stimulation, transcutaneous electrical nerve stimulation, cortical neurofeedback, electrical stimulation of auditory cortex, dorsolateral prefrontal cortex stimulation, deep-brain stimulation, and vagus-nerve stimulation paired with tones (e.g., Cheung and Larson, 2010; Vanneste and De Ridder, 2012; De Ridder et al., 2014, 2017; Tyler et al., 2017). However, based on systematic reviews of the available scientific literature, the data is mixed concerning the utility low-frequency rTMS as a means for tinnitus suppression (e.g., Meng et al., 2011; Peng et al., 2013; Lefaucheur et al., 2014). Furthermore, while rTMS as a treatment modality for tinnitus appears safe in the short term, long term treatment effects are not known (e.g., Muller et al., 2012; Peng et al., 2013).

Herein, the main thrust behind this work was to determine: if changes in tinnitus loudness measured psychoacoustically, if self-perceived changes associated with responses on the Tinnitus Handicap Questionnaire (THQ), and if changes in neurochemical concentrations of metabolites localized to auditory cortical areas in the left and right hemispheres using proton magnetic resonance spectroscopy ($^1\text{H-MRS}$) could be modulated with rTMS within the context of this experimental design. The design features of this experiment were in response to 5 sequential days of either active or sham rTMS over the left auditory cortex (20 min per day; 1200 pulses per session) using a prospective randomized single-blinded sham-controlled cross-over design.

2. Methods

2.1. Participants

Participants in this study were 30 males, ranging in age from 24 to 80 years (mean age: 54.2 years, SD: 14.2 years). These individuals were recruited from advertisements placed in area newspapers, by word-of-mouth, and/or referred from area professionals (physicians and audiologists). No restrictions were placed on gender, ethnicity, or socioeconomic status but participants were required to have a history of noise exposure as the probable inducer for their tinnitus and be ≥ 18 years and < 90 years of age. This study was approved by the Institutional Review Board (IRB) of Wayne State University. All participants signed informed consent prior to entering the study and were paid for their participation.

A total of five individuals did not complete the entire study and therefore, were not used in this data analysis. In three people, work-related issues (unemployment and re-employment during the study period) were the underlying cause for not completing the study. In two others, MRI data files were corrupted due to equipment (computer) malfunction and these participants would not return to the MRI Research Facility for re-scanning.

2.2. Tinnitus perceptions

Of the remaining individuals that participated ($n = 25$), tinnitus descriptions ranged from a constant high-pitched tone, ringing, buzzing, humming, or hissing sounds, while others reported an alarm clock like sound, or cricket-like perceptions. Because of these complex individual perceptions, no attempt was made to match the frequency of the tinnitus by psychoacoustic methodology.

2.3. Inclusion criteria

All participants were required to have chronic tinnitus, defined operationally as being persistently present over the preceding 6-

month period and scoring in the moderate or higher range on the Tinnitus Handicap Inventory (THI; score ≥ 38). Additionally, all participants were required to have a history of occupational, recreational, and/or military noise exposure; typically, but not always documented by pure-tone audiometry (i.e., a notch in the audiogram at or near 4 kHz) in one or both ears.

2.4. Exclusion criteria

Documented history of retro-cochlear or neurologic disease (acoustic tumors, brain tumors, strokes, demyelinating disease, etc.), history of epilepsy or seizures, metal in the head, neck, or chest regions, implanted devices that might be damaged in a high field magnetic environment (i.e., implanted ferrous electrodes, implants of various sorts, including: a cochlear implant, vagus-nerve stimulator module, cardiac pace maker, stents, certain heart valves, etc.), use of GABAergic agonist medications, and/or other types of pharmaceuticals used to treat depressive illness. Individuals with a history of "blast" exposures were also excluded.

We also note that other medications were being taken by individuals that were not deemed exclusionary by the criteria described above. We report this information to be as transparent as possible with respect to considering any pharmaceuticals that could potentially have impact on this experiment.

Overall, 13/25 (52%) of the participants were not taking any additional medications; however, 12/25 (48%) were taking one or more of the following pharmaceuticals, which included: 1 baby aspirin (81 mg) per day to reduce/prevent the possibility of myocardial infarction and/or stroke; and use of: Atorvastatin to treat high cholesterol levels; Ramapril or Linsinopril to treat high blood pressure; Metformin and Glipizide to treat Type II diabetes; Finasteride to treat benign prostrate hyperplasia; folic acid to treat a vitamin B3 deficiency; and multivitamins for general health-related maintenance.

2.5. Research design

A prospective randomized single-blinded sham-controlled cross-over design was used (see Fig. 1) for a graphic representation

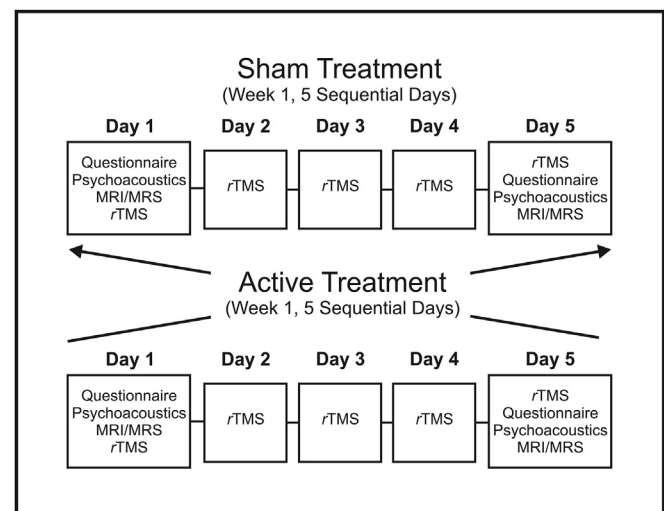


Fig. 1. Block diagram of the single-blinded sham-controlled cross-over design. Participants were randomly assigned to either the sham or active arm of the study in the initial phase. Then individuals underwent 5 sequential days of rTMS. During the first and fifth day, participants also completed the THQ, made psychoacoustical loudness judgments of their tinnitus, and had MRI/MRS testing performed.

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