

PROTOCOL

Investigating the Impact of Cognitive Training For Firefighters with Tinnitus

HRPO: 201110046

CCIR: 0492

Clinical Trials Registration Number: NCT01458821

Federalwide Assurance number: FWA00002284 Washington University

Principal Investigator

Jay F. Piccirillo, M.D., FACS, CPI
Department of Otolaryngology - Head and Neck Surgery
Washington University School of Medicine
660 South Euclid Avenue
Campus Box 8115
St. Louis, Missouri 63110
Phone: 314-362-8641 (office)
Piccirilloj@ent.wustl.edu

Andre Wineland, MD, Sub-Investigator, Resident Physician Department of Otolaryngology-Head and Neck Surgery

Joyce Nicklaus, RN, BSN, CCRC, Clinical Research Nurse Coordinator, Department of Otolaryngology-Head and Neck Surgery

Dorina Kallogjeri, MD, MPH, Biostatistician, Department of Otolaryngology-Head and Neck Surgery

Joshua Shimony MD, PhD, Mallinckrodt Institute of Radiology, Assistant Professor

PROTOCOL

BACKGROUND

Subjective, idiopathic, non-pulsatile tinnitus (“tinnitus”) is an auditory sensation without the presence of an acoustic stimulus.(Lockwood, Salvi, and Burkard 2002) Approximately 60 million Americans experience chronic tinnitus and 15 million of these people have bothersome tinnitus.(Hoffman and Reed 2004) Bothersome tinnitus is associated with deficits in attention, memory, anxiety, depression, and sleep disturbances, all of which interfere with firefighter readiness and performance. Tinnitus is estimated to affect more than 1 million firefighters. Tubbs identified 14% of firefighters reporting tinnitus.(Tubbs and Flesch 1982) Based on the US National Health Interview Survey Disability Supplement (1994-1995), firefighters and policemen have ~10% increased risk for developing tinnitus when compared to physicians or other health care professionals.(Hoffman and Reed 2004) The prevalence of tinnitus amongst firefighters is uncertain partly because of their reluctance to self-report, out of fear of dismissal or restriction in job duties. It is believed that more than 1 million firefighters are at risk for noise-induced hearing loss and tinnitus due to exposure to hazardous levels of intermittent noise.(Hong and Samo 2007) Neural rehabilitation programs, like the *Brain Fitness Program-Tinnitus (BFP-T)*, may mitigate the cognitive impairments associated with tinnitus and should be assessed as a cost-effective treatment for firefighters with tinnitus.

Tinnitus Can Impact Attention, Reaction Time, and Other Cognitive Functions

According to Robert M. Winston, Boston Fire Department District Fire Chief (ret) and former Fire Chief Pickens County Georgia 2010, and as reported in *Fire Chief*, “Tinnitus interferes with most facets of daily living including sleep and activities dependent on seeing and hearing.”(Winston 2010) Tinnitus sufferers have poorer working memory, slower processing speeds and reaction times, and deficiencies in selective attention.(Hallam, McKenna, and Shurlock 2004; Rossiter, Stevens, and Walker 2006)

Research at Washington University (WU), directed by Dr. Katherine Pierce, showed that tinnitus patients had deficits in verbal learning, auditory attention, and phonemic verbal fluency that depend on attention resources. These findings indicate that tinnitus interferes with attention. An impaired ability to maintain attention in firefighters with tinnitus can have dire consequences for the affected individual, fellow firefighters, and the public.

OBJECTIVES

The objective of this pilot research project is to advance knowledge about the roles of attention, control, and other cortical networks in the development and maintenance of bothersome tinnitus.

We have three specific aims.

- 1) to determine whether the *Brain Fitness Program-Tinnitus* affects the tinnitus percept.
- 2)to determine whether an inexpensive computer program, *Brain Fitness Program-Tinnitus*, aids the recovery of cognitive functions (attention, cognition, memory) apparently “hijacked” by the tinnitus. *Brain Fitness Program-Tinnitus* was developed to improve cognitive function by engaging the brain’s neuroplasticity; the program is novel, non-invasive, and inexpensive.
- 3)to establish specific default mode, attention system, and cognitive control network deficits in patients with bothersome tinnitus through the use of advanced neuroimaging techniques, and assess whether exposure to the *Brain Fitness Program-Tinnitus* impacts changes in the default mode, attention system, and cognitive control network deficits.

PRELIMINARY WORK

Neuroimaging at Washington University

Professor Harold Burton directed research examining resting-state brain activity in 14 individuals (mean age 52 yrs, range 42 to 59) with bothersome tinnitus (*Tinnitus Handicap Inventory* median

score of 51; 95% CI 40 to 70) compared to age-matched controls. The study discovered significant alterations in several critical functional networks in the tinnitus group. (Burton et al. 2012)

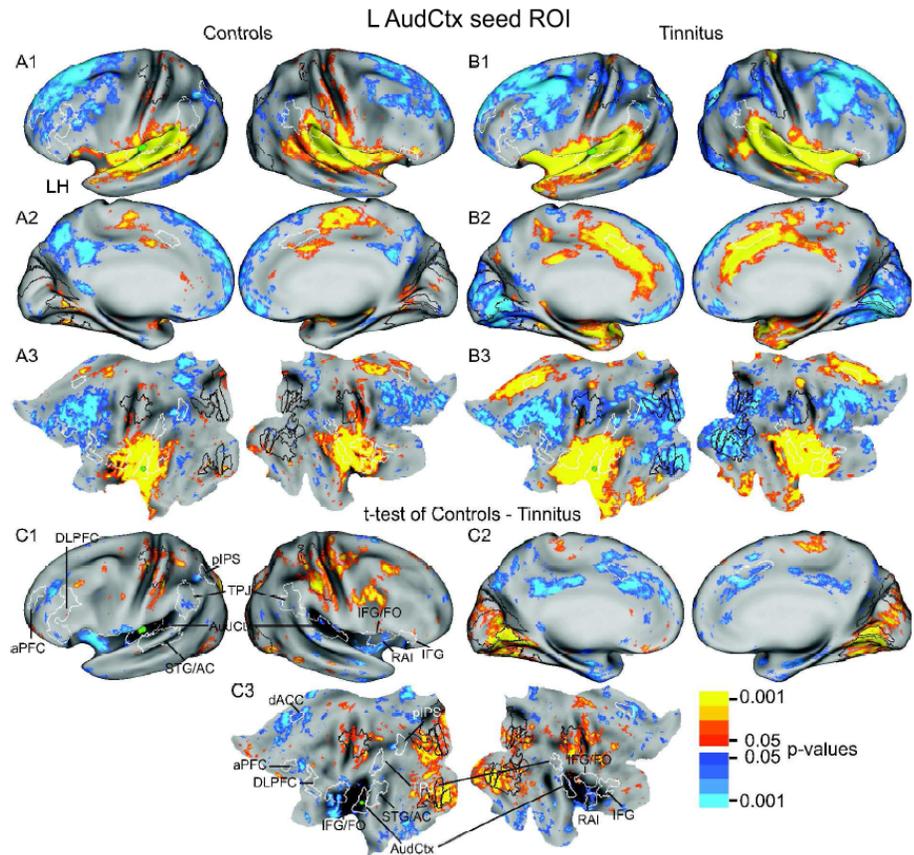
A seed (green marker) placed in the left primary auditory cortex showed group differences in connectivity patterns in several cortical regions. As shown in the Figure, the control group (left 2 columns) had few significant positive correlations

(area colored yellow-orange) in somatomotor and visual cortex (locations with black borders) whereas the tinnitus group (right 2 columns) had connectivity with substantial negative correlations (area colored blue) in occipital and somatomotor cortex (B). These findings indicate that when activity increased in auditory cortex, they decreased in the regions showing negative correlations. Positive correlations in the auditory cortex and nearby frontal/parietal cortex were similar between the groups.

In tinnitus subjects, the findings indicated that as activity increased in auditory cortex they decreased in the visual, somatosensory, and parts of the involuntary re-orienting attention networks. The consequence of this altered, reciprocated suppression of activity is that the tinnitus percept robs or

“hi-jacks” other sensory systems. For example, when the visual system is called upon to do something, it attempts to shut down the auditory system. The auditory system, on the other hand, attempts to shut off the visual system, which prevents patients from attending to what they are doing.

The implications of these findings are profound: they suggest that when tinnitus patients attend to a visual event, the auditory network and cognitive control elements utilized during involuntary shifts in attention are shut down. Therefore, we hypothesize that tinnitus compromises patients’ normal ability to shift attention resources.



EXPERIMENTAL DESIGN AND METHODS

Specific Aims

There are three Specific Aims to this project

Specific Aim 1.- To evaluate the effect of *Brain Fitness Program-Tinnitus (BFP-T)* on the perception of tinnitus as measured by the *Tinnitus Handicap Inventory*.

Specific Aim 2 — To evaluate the effect of *Brain Fitness Program-Tinnitus* on the attention, cognition, and memory deficits in patients with bothersome tinnitus, as measured by a battery of validated neurocognitive tests.

Specific Aim 3 — To use functional connectivity magnetic resonance imaging (fcMRI) to explore the default, dorsal attention, ventral attention, auditory, vision, somatosensory, and cognitive/control cortical networks in firefighters. and assess the impact of the *Brain Fitness Program-Tinnitus* on these networks. We will explore both subjects with tinnitus, using BFP-T; those with tinnitus who are controls, and healthy age and gender matched controls without tinnitus.

Study Design

This will be a randomized controlled trial of *BFP-T* in 40 subjects with bothersome tinnitus. In addition, a resting-state functional connectivity MRI (rs fcMRI) paradigm will be used to study brain activity in regions associated with voluntary, involuntary, and executive control of attention.

This research project will employ a longitudinal study design with a nested open-label randomized intervention/controlled clinical trial. Subjects with bothersome tinnitus will be randomized to either *Brain Fitness Program-Tinnitus* or no intervention. A planned enrollment of 40 subjects with tinnitus in the clinical trial will have sufficient statistical power to detect a 17-point change in *Tinnitus Handicap Inventory* scores. Twenty subjects without tinnitus will be enrolled as healthy controls. They will not undergo *BFP-T* training, but will complete all standard questionnaires and imaging tests at Visits 1 and 2.

Study Population

Men and women between the ages of 20 and 65 of either sex, all races and ethnicity, will be recruited from the Greater St. Louis Fire Departments and the public at large. All attempts possible will be made to recruit firefighters and First Responders. Access to the first fire-personnel will be coordinated through the office of St. Louis Fire Chief Dennis Jenkerson (see Letter of Support), and other municipality Fire Chiefs in the area. The neurocognitive tests and rs-fcMRI protocol were selected for the study of brain activity in regions associated with voluntary, involuntary, and executive control of attention in 60 firefighters and first responders (40 firefighters with tinnitus and 20 firefighters without tinnitus in total).

Participation will include two separate days of testing. The second visit will occur eight to ten weeks after the first, or within two weeks of the subject's completion of BFP-T, whichever is later. Each day of testing will involve a series of patient-based questionnaires, assortment of psychological and neurocognitive tests, computer-based attention tests, and a resting-state functional connectivity MRI.

Inclusion Criteria

Inclusion Criteria —All

- Active-duty or retired firefighters from study-selected firehouses or if recruitment numbers do not meet goal with firefighters and EMS personnel we will recruit from the population at large to meet study completion deadline
- Able to give informed consent
- Men and women between the ages of 20 and 65 years
- Must be able to read, write, and understand English

Inclusion Criteria-Tinnitus subjects:

- Subjective, unilateral or bilateral, non-pulsatile tinnitus of 6 month's duration or greater (Newman, Jacobson, and Spitzer 1996)
- Either "Bothered more than a little but not a lot", "Bothered a lot", or "Extremely bothered" on the Global Bothersome scale
- Have access to uninterrupted use of computer in quiet setting for minimum of 1 hour per day/5 days per week for 2 months
- Be willing to be randomized to either arm of the study

Exclusion Criteria All

- Currently taking medication for depression, anxiety, or other DSM IV Axis 1 disorder
- History of head trauma sufficient to cause loss of consciousness for ≥ 30 minutes
- History of surgery to the brain
- History of claustrophobia, which will prevent subject from completing MRI
- Presence of metallic implants in the head and upper cervical region that are non-MRI compatible and would prohibit use of MRI
- Patients with cardiac pacemakers, intracardiac lines, implanted medication pumps, implanted electrodes in the brain, or any other contraindication for MRI scan
- Patients who are currently pregnant
- Patients with an acute or chronic unstable medical condition, which, in the opinion of the investigator, would prevent them from successfully participating in the study
- Patients with any active ear disease, which, in the opinion of the PI, needs to be further evaluated
- Patients with symptoms of depression as evidenced by a score of 10 or greater on the *PHQ-9*
- Any psychiatric co-morbidity that may complicate the interpretation of study results
- History of seizure disorder or any other neurological condition
- Weight greater than 350 pounds
- Inability to lay flat for 2 hours
- Active alcohol and/or drug dependence, or history of alcohol and/or drug dependence within the last year
- Any medical condition, which, in the opinion of the PI, confounds study results or places the subject at greater risk
- Prior use of Posit Science *Brain Fitness Program*, or any other cognitive training program (regular or tinnitus) in the past year
- Patients with hyperacusis (hyper-sensitivity to noises) or misophonia (abnormally strong reactions of the autonomic and limbic systems to sound)

For subjects with tinnitus, additional Exclusion Criteria include:

- Tinnitus related to cochlear implantation, retrocochlear lesion, Meniere's Disease, or other known anatomic lesions of the ear or temporal bone
- Tinnitus related to a Workman's Compensation claim or litigation-related event that is still pending.

For subjects without tinnitus, additional exclusion criteria include:

- History of irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, or other illnesses or disorders that fall into the category of functional somatic syndromes. (Barsky and Borus 1999)

Recruitment Process

We will utilize flyers and posters to describe the study and inclusion criteria to firefighters in study-selected firehouses. In addition we will open the study to non firefighters if recruitment of firefighters is not able to produce enough subjects. We will notify our FEMA representative prior to enrolling non firefighters. Non firefighters will be recruited from WU Otolaryngology and Audiology clinics and from the population at large by using flyers and posters, as well as recruiting from Otolaryngology Research Participant Registry, HRPO 201108146 via email. Potential subjects may complete a pre-screening survey via telephone or on-line, using REDCap software, which will feature the same questions as the phone screening script. Either method will be utilized for interested firefighters to determine their eligibility for the study.

In order to be considered for the study, the potential subject must have an audiogram. Each subject will be given the option to provide a copy of a comprehensive audiogram performed within the past 18 months, or receive an audiogram at visit one. If the subject wishes to use his/her own audiogram, a copy of the audiogram must be sent to Dr. Piccirillo prior to participation. Individuals with bothersome tinnitus will be identified from pre-screening.

Subjects with tinninitus who remain eligible at the end of the screening period will be randomized according to a computer-generated random code, to either complete Brain Fitness Program Tinnitus (BFP-T) (Condition A) or to serve as a control and not receive the program (Condition B). *The subjects without tinnitus will be matched by age (+/-5 years) and gender to a subject with tinnitus.*

The study statistician will provide the clinical nurse coordinator with the randomization schedule. The schedule will list whether the subject is to receive Condition A or B. Each subject will be sequentially randomized according to the randomization schedule, which will be kept in the clinical nurse coordinator's office.

If any subject withdraws between the completion of visit one and his/her return for the second visit, or if the subject is found to be less than 85 % compliant on BFP-T performance, a consecutive subject will be enrolled and randomized until we achieve our recruitment goal. The goal of this study is to obtain full data, for complete analysis, on 60 participants — 40 with bothersome tinnitus, and 20 healthy controls. Based on the study history to date, as well as anticipating an on-going maximum drop out of 10% and screen fail rate of 15 % we seek permission to enroll a total of 90 subjects, but will stop enrollment once we have our 60 evaluable subjects. If a subject completing BFP-T is less than 85% compliant, then that subject will be dropped from the study and his/her performance will be removed from analysis.

Informed Consent

The PI, or his designee, will obtain written informed consent during the participants' visit to Washington University Medical Center (WUMC) prior to any study-related tests. Before their arrivals to WUMC, all potential participants will have had the opportunity to review the consent form, discuss it with anyone they wish, and have all questions answered by the study team. Participants must meet all of the inclusion and none of the exclusion criteria before undergoing study tests. Written informed consent will be obtained in a private room on the 8th floor of the McMillan Building or in the Center for Clinical Imaging Research.

Study Measures And Procedures

Descriptive and Clinical Variables

Age, gender, and race, will be captured through questionnaires. Audiometry results will be obtained from the subject's annual employee physical examination results.

Subjects will complete the following forms from the Oregon Hearing Research Center [<http://www.tinnitusarchive.org/forms>]: *Medical and Health Information, Hearing History, and Occupation Exposure* forms. These forms have been slightly modified to allow collection of information from both tinnitus and non-tinnitus subjects. Subjects with tinnitus will also complete the Oregon Hearing Research Center's *Tinnitus Description and History* and complete a global rating of tinnitus severity question.

Demographic Form — Captures information such as age, gender, handedness, education level , etc. **(5 minutes; Visit 1)**

Medical and Health Information — This questionnaire asks about the subject's other medical conditions and general health. **(5 minutes; Visit 1 and review at Visit 2)**

Hearing History and Occupational Exposure — This form explores difficulties with speech, hearing sounds, and exposure to loud noise. **(5 minutes; Visit 1 and review at Visit 2)**

Tinnitus Description and History — This questionnaire seeks information about the type, frequency, and duration of tinnitus, as well as mitigating factors related to the subject's perception of tinnitus. Completed by tinnitus subjects only **(5 minutes; Visit 1 and review at Visit 2, tinnitus subjects only)**

Tinnitus Handicap Inventory (THI)(Newman, Jacobson, and Spitzer 1996; Newman, Sandridge, and Jacobson 1998) — The *THI* will be used to describe the subject's severity of tinnitus. The *THI* is a validated self-report measure that lists 25 different problems people with tinnitus may experience. The overall score on the instrument can range from 0 – 100, with higher scores reflecting a greater handicap. A score of 38 or greater is roughly in the 75th percentile of scores of patients seeking medical attention at an academic medical center. Our primary outcome measure will be a change of 20 points or greater on the *THI* to represent a clinically significant difference, based on personal communication between Drs. Piccirillo and Jacobson (1996). The difference of 17 points in the *THI* is very close to the difference of 20, or effect size (ES) of 2.0, identified by Bartels et al(Bartels et al. 2008) as the minimally clinically significant difference in the *THI*. Recently, Zeman et al.(Zeman et al. 2011) compared the absolute change of the *THI* with the Clinical Global Impression-Improvement (CGI-I) score to determine the minimum change of the Tinnitus Handicap Inventory (*THI*) score that could be considered clinically relevant. The authors found that a CGI-I value of 3 (minimally better) corresponded to a *THI* score reduction of 6, whereas the CGI-I value of 4 (no change) corresponded to the range between improvement by 5 points and worsening by 4 points. For separating the no-change and minimally better groups, an effect size $d = 0.5$ was determined, resulting in a minimal clinically relevant difference of $\Delta TH I = 7$. The authors concluded that a reduction in the *THI* score of between 6 and 7 points was the minimal clinically relevant change. Therefore, in addition, we will evaluate subjects with a 10 point or greater drop. The *THI* will be completed by tinnitus subjects only. **(5 minutes; Visit 1 and Visit 2- tinnitus subjects only)**

Tinnitus Functional Index (TFI). — The *TFI* is a newer self-report measure of tinnitus severity that records answers using a Likert scale instead of the Yes/No/Sometimes format of the *THI*. Thus, it may serve as a more sensitive measure of small changes in tinnitus severity. The *TFI* will be completed by tinnitus subjects only. Meikle et al. suggest a reduction in *TFI* of 13 points as a preliminary criteria for meaningful reduction in *TFI* outcome measures {Meikle, 2011 21730 /id}. **(5 minutes, Visit 1 and Visit 2 -tinnitus subjects only)**

Other Questionnaires

Brief Symptom Inventory-18 (BSI-18)(Derogatis 2000) — *BSI-18* contains subscales measuring somatization, depression, and anxiety. **(5 minutes; Visit 1 and Visit 2)**

PHQ-9(Kroenke, Spitzer, and Williams 2001) — *PHQ-9* is a 9-item questionnaire designed to assess and aid in diagnosing patients with depression in clinical and community settings. A score of 15 or greater is indicative of moderate depression. **(5 minutes; Visit 1 and Visit 2)**

Short Blessed Test(Katzman et al. 1983) — The Short Blessed Test is a weighted six-item diagnostic tool used to evaluate a subject's cognitive ability. A score of 9 or greater is indicative of cognitive impairment. The SBT has demonstrated a sensitivity and specificity for identifying dementia of 82% and 88% respectively. Its specificity is influenced by race and education, and it's simpler to administer than MMSE. **(5 minutes; Visit 1)**

Whiteley-7 Scale (Fink et al. 1999) — This 7-item validated scale measures hypochondriacal traits. **(5 minutes; Visit 1)**

Cognitive Failures Questionnaire (Broadbent et al. 1982) — This validated self-report questionnaire measures failures in perception, memory, and motor function. **(5 minutes; Visit 1 and Visit 2)**

Adult Attention Deficit Hyperactivity Disorder Self-Report Scale (ASRS-v1.1) Symptom Checklist (Kessler et al. 2005) — Research suggests that the symptoms of ADHD can persist into adulthood, having a significant impact on the relationships, careers, and even the personal safety of the affected.(Barkley 1998; Biederman et al. 1993; Schweitzer, Cummins, and Kant 2001) The World Health Organization (WHO) *Adult ADHD Self-Report Scale (ASRS)* is a self-report screening scale of adult attention-deficit/hyperactivity disorder (ADHD). The ASRS includes 18 questions about the frequency of recent DSM-IV Criterion A symptoms of adult ADHD. The ASRS Screener consists of six out of these 18 questions that were selected based on a stepwise logistic regression to optimize concordance with the clinical classification. The ASRS screener outperformed the unweighted 18-question ASRS in sensitivity, specificity, total classification accuracy, and κ value.(Kessler et al. 2007) **(5 minutes; Visit 1 and Visit 2)**

MRI Screening Form — Assesses for conditions, which, if present, may put a subject at increased risk during MRI scan. **(5 minutes; Visit 1 and Visit 2)**

Medication Log — Self-report of current medication usage. **(5 minutes; Visit 1 and review at Visit 2)**

Reimbursement Form — Captures personal information, includes social security number, for reimbursement and billing matrix. **(5 minutes; Visit 1 and Visit 2)**

Audiogram: A comprehensive audiogram will be performed if the subject is unable or unwilling to provide a copy of a comprehensive audiogram done within the past 18 months. **(30 Minutes)**

Physician Exam

Drs. Piccirillo, Okuyemi, or Wineland will perform directed ear, nose, and throat medical evaluations and review the audiograms of all participants. Upon completion of the directed ear, nose, and throat examination, the physician will complete the MD screening form. **(15 minutes; Visit 1. If subject has any reported study-related Adverse Events, then an additional form will be completed)**

Cognitive Performance

Subjects will undergo state-of-the-art neurocognitive testing to properly measure cognitive performance in a variety of areas, including working (verbal and spatial) and episodic (verbal and spatial) memory, sustained and selective attention, auditory information processing, and cognitive and motor processing speed. Multiple aspects of executive control, such as set-shifting, resistance to auditory and visual distraction, inhibitory control, and goal maintenance are evaluated as well. The neurocognitive functioning tests will be performed by a member of the *Research Team*.

Memory

The California Verbal Learning Test (CVLT-II)(Delis et al. 1987) — The *CVLT-II* is a neuropsychological test that assesses an individual's verbal learning and memory abilities. **(30 minutes; Visit 1 and Visit 2)**

Wechsler Memory Scale — Fourth Edition Flexible Approach (WMS-IV Flexible Approach)(Wechsler 2003) — The *Wechsler Memory Scale- Fourth Edition- Flexible Approach* is a reliable survey of auditory and visual memory abilities. The *WMS[®]-IV Flexible Approach* uses core and supplemental memory measures to expand the usability and utility of the *Wechsler Memory Scale[®]*, Fourth Edition. The *WMS-IV* enables clinicians to identify memory difficulties by using alternate indexes derived from new subtest configurations. These alternate indexes and supplemental subtests were designed to create shorter or alternate memory assessments for use with the standard *WMS-IV* kit. The *WMS-IV Flexible Approach* allows the examiner to complete a survey of memory functions when a comprehensive evaluation of memory functioning is not required or cannot be completed. The *WMS-IV* offers a number of subtest configurations that yield Immediate, Delayed, Visual, and Auditory Memory Index scores. The combinations of subtests reflect the desire to reduce administration time and address specific clinical situations (e.g., limited motor ability). Two shorter alternative batteries were developed: *LMVR*, consisting of Logical Memory (LM) and Visual Reproduction (VR), and *LMDE*, consisting of Logical Memory and Designs (DE). LM and VR are the most frequently used subtests in the previous editions of the *WMS* and provide coverage for all of the memory indexes. **(20 minutes; Visit 1 and Visit 2)**

Sustained and Selective Attention

Conners Continuous Performance Test (CCPT-II)(Conners 2000) — The *CCPT-II* is a test that requires focused attention to a visual-motor task, which is used to assess sustained attention and freedom from distractibility. **(15 minutes; Visit 1 and Visit 2)**

Neuroimaging

Subjects will undergo resting-state fMRI brain scans at the Mallinckrodt Institute of Radiology's Center for Clinical Imaging Research (CCIR). MRI must occur within 4 weeks of pre-screening or the prescreening responses will be reviewed with the subject prior to imaging. **(40 Minutes; Visit 1 and Visit 2)**

Functional Connectivity MRI

Resting-state functional connectivity MRI (rs-fMRI) is based on measures of resting-state spontaneous brain activity. Through correlation analyses of the time course of activity in selected brain regions and the rest of the brain, functional connectivity can be identified for selected networks. For example, the functional connectivity between vision and attention networks is evaluated through examination of correlated activity between a selected visual cortex region (e.g., primary visual area in calcarine sulcal cortex) and areas of the brain previously identified as being associated with attention. Cortical neural network connectivity reflects structural connections or indirect synaptic linkages between different regions of the brain. The strength of these connections can reflect the structural integrity and/or usage-dependent strength synapses between network components. Past(Fox et al. 2005; Fox and Raichle 2007)and present work in neuroimaging at Washington University (WU) and the affiliated Mallinckrodt Institute of Radiology (MIR) has shown that at-rest spontaneous activity in the human brain is organized into identifiable discrete functional networks, and each of these networks resemble those recruited during active behavior.(Cordes et al. 2000; Fox et al. 2006) The strength of activity correlation at rest between nodes of different networks specifically correlates across subjects with behavioral measures. An advantage of fMRI techniques over task-based functional MRI is that fMRI is not affected by participant heterogeneity in task-performance ability, which could result from genomic,

environmental, or behavioral differences. Therefore, fcMRI provides a picture of functionally related regions of the brain at rest without the confounding effect of performance variability. Examples of functional neural networks include the visual, motor, somatosensory, language, attention, cognitive control, and default mode networks. WU and MIR researchers demonstrated that there are changes in the attention networks of patients with neglect syndrome after stroke.(Corbetta et al. 2005) Changes in the default mode network are associated with depression(Sheline et al. 2009), pain perception(Ploner et al. 2010), and Alzheimer's disease.(Greicius et al. 2004)

MRI Methods

Participants will undergo magnetic resonance imaging in a dedicated research facility, the Clinical Center for Imaging Research (CCIR) at the Mallinckrodt Institute of Radiology. Images are acquired using a Siemens 3 Tesla TRIO scanner (Erlangen, Germany). Images of blood oxygenation level-dependent (BOLD) contrast responses are obtained using a gradient recalled echo-planar sequence (EPI: repetition time [TR]=2000ms, echo time [TE]=27ms, flip angle=90°, 4x4x4 mm voxels).(Kwong et al. 1992; Ogawa et al. 1990) During each TR frame, whole brain coverage is obtained across 33 contiguous, interleaved, bicommissurally aligned axial slices, and 4 mm³ isotropic voxels. Additionally, a T1-weighted structural magnetization prepared rapid gradient echo (MP-RAGE) image is acquired across 176 sagittal slices (TR=2100ms; TE=3.93ms; flip angle=7°; inversion time [TI]=1000ms; 1 x 1 x 1.25 mm voxels). An additional T2-weighted structural image is obtained across 33 axial slices (TR=8430ms, TE=98ms, 1.33 x 1.33 x 3 mm voxels). The T2 images are aligned with the axial EPI and aid registration of the EPI to the sagittal MP-RAGE.(Ojemann et al. 1997)

EPI images from each participant are corrected for systematic slice-dependent differences due to interleaved odd-even slice acquisition, realigned to atlas space, and filtered to remove nuisance variables. Processing begins by aligning the time for each slice to the beginning of each TR using sinc interpolation. Next, intensity differences between slices are corrected using a whole brain mean signal intensity that is normalized to mode 1000 across EPI runs. These time- and intensity-adjusted slices are realigned within and across runs using rigid body correction for inter-frame head motion. The across-run-realigned slices are resampled to 2mm cubic voxels, spatially smoothed using a 2-voxel Gaussian kernel (4mm FWHM), and registered to an atlas template by computing 12 parameter affine transforms between an average from the first frames of each EPI run and an atlas template.(Ojemann, Akbudak, Snyder, McKinstry, Raichle, and Conturo 1997) The representative atlas template is created using MP-RAGE structural images combined from middle-aged participants(Talairach and Tournoux 1988); the template conforms to Talairach atlas space based on spatial normalization methods.(Buckner et al. 2004; Lancaster et al. 1995) The same imaging protocol was used in Dr. Piccirillo's research study, *Collaborative Tinnitus Research at Washington University*, HRPO # 07-0689.

All participants' baseline anatomic MRI scans will be reviewed by a neuro-radiologist to screen for any brain lesions or any abnormal findings. The neuro-radiologist will report any abnormal findings to the PI. Any incidental findings on MRI that may affect the participant's health will be shared with the participant, and, with the participant's consent, shared with the primary care physician. If the participant does not have a primary care physician, a referral will be offered. The PI will decide if the abnormal finding excludes the participant from the study.

Rs fcMRI Data Processing Steps

Preprocessing steps will include intensity and motion correction and atlas registration.(Sheline et al. 2001) Correlation maps will be produced by extracting the BOLD time course from a seed region, then computing the correlation coefficient between that time course and the time course from all other brain voxels. The principal techniques are: 1) measurement of regional BOLD fluctuation power, 2) measurement of inter-regional (ROI-ROI) covariance and correlation, and 3) computation of whole brain, voxel-wise intrinsic functional connectivity maps. Each rs fcMRI run thus provides a series of BOLD signal measurements at each

voxel within the field of view. BOLD signal fluctuations will be analyzed on voxel wise and regional bases after preprocessing and atlas transformation.

Neuroimaging Data Management

A validated Central Neuroimaging Data Archive (CNDA) pipeline at WU integrates image processing. The CNDA provides a framework to upload acquired MRI data at WU, a web application to access and explore the image data and to enter related non-imaging measures (e.g. clinical assessments, such as neurocognitive tests), a pipeline service to automate processing and analysis of data, and a software library for accessing data from command line and client applications. It has been in operation for more than 6 years and houses over 4,000 imaging sessions (30,000 individual scans). Stored data is replicated every 3 hours to a physically disparate disaster recovery site. Analysis of all data by our laboratory will be performed using a computing cluster embedded within the CNDA.

Cognitive Brain Training Intervention — *Brain Fitness Program-Tinnitus* (Fisher et al. 2009; Mahncke, Bronstone, and Merzenich 2006; Smith et al. 2009; Wolinsky et al. 2006; Wolinsky et al. 2010)

The Posit Science® *Brain Fitness Program (BFP)* is a cognitive training program containing ten interactive training exercises in which participants listen to recorded sounds, including simple acoustic stimuli and continuous speech, for approximately one hour per day, 5 days per week. Program usage extends for 8 weeks (i.e., approximately 40 hours of training). Exercise parameters calibrate to individual performance at the onset of training and adapt in difficulty with performance progression, giving constant progress feedback. Each exercise focuses on one of the following cognitive processes: (1) auditory processing speed, (2) discriminating sounds, (3) sound precision, (4) sound sequencing, (5) working memory, and (6) narrative memory.

The BFP has been modified in an attempt to address the attentional impact of tinnitus. This modification has three purposes: 1) To define the domain of 'distractor' stimuli applied in working memory-based listening tasks now incorporated into the BFP. This task has been shown to effectively reduce the neurological responses evoked by a specific domain of distracting stimuli -- in this case, the tinnitus itself. 2) To define the target stimuli applied in a reverse-conditioning task now incorporated in the BFP. In reverse conditioning, a target stimulus FOLLOWS rewards. Reverse conditioning has been shown to result in a systematic reduction in neurological responses to that stimulus.

We believe these strategies should increase the positive impacts of the *BFP-T* on tinnitus by further attenuating the attentional power of the tinnitus, which should help the user further suppress the frequency and magnitude of tinnitus itself.

The subjects with tinnitus, randomized to intervention, will receive access to the *BFP-T* program. Those subjects randomized to complete the *BFP-T* will be loaned a set of monitor-type headphones to be used with *BFP-T*. This provision of headphones provides assurance that all subjects will have access to high-quality headphones for their *BFP-T* experience. For maximal standardization of the study, all subjects will receive the same type of headphones and are asked to use only the study-provided headphones. Posit Science® will monitor individual subject's *BFP-T* compliance and progress data. This compliance and performance information will be provided to the PI. Posit Science® will only have access to subjects' unique study identifiers.

Timeline and Compensation for Each Subject

All testing will be completed over one to two days for both Visits 1 and 2. The informed consent process, history and physical, completion of questionnaires, neurocognitive testing, and MRI scan will take approximately four to five hours. Depending upon MRI scheduling or the participant's availability, the MRI may be done on a separate, second day for both Visits 1 and 2.

Participants will be compensated \$100 for completing Visit 1, including the screening procedures, data collection forms, and MRI scan. Subjects will be paid \$200 for completion of Visit 2, including MRI. If a

subject fails screening or stops participation prior to the MRI at either Visit 1 or 2 there will be no compensation for that portion of the study. Parking in WU and BJC garages for required visits will be paid for by the study.

Data Collection Methods

All participant forms and questionnaires will be labeled using unique study ID numbers, and are void of personal identifiers. Source Documents will be used as the Case Report Forms (CRF's) in this study. When possible we will use REDCap as data entry, CRF, and source documentation. Paper forms will be used only on those items that are needed in paper form.

Research Subject Identification

A unique study ID number will be generated for each participant after written informed consent has been obtained. The participants' names and unique ID numbers will be recorded in an electronic file stored in a restricted-access drive in a secure server maintained by Washington University Pediatric Computing Facility. Only Dr. Piccirillo and the research team will have access to this secure drive.

Confidentiality

All data will be safeguarded in accordance with HIPAA regulations and the principles and practices of strict confidentiality. The investigators will use their best efforts to keep all information secure and estimate the risk of accidental disclosure to be very small. All participants will be assigned a unique study ID. Research records will be stored in a confidential manner so as to protect the privacy of participant information.

Disposition of Data

Hard-copy research records will be stored in a double-locked manner in the Clinical Outcomes Research facility; electronic data will be stored in a restricted-access drive in a secured server maintained by Washington University Pediatric Computing Facility. Only Dr. Piccirillo and the research team have access to this secure drive. Hard-copy and electronic research records will be kept for 7 years, in compliance with HIPAA, or one year after publication, whichever happens at a later date. All identifiers will be removed from the records and it will not be possible to link the data to individuals after that time.

Scientific Community

We will consider sharing the data with researchers from other scientific institutions, upon review of their requests. The neuroimaging data will be available to Washington University researchers through the Central Neuroimaging Data Archive (CNDA). CNDA is the major imaging informatics platform utilized by the Neuroimaging Informatics and Analysis Center at Washington University in St. Louis (NIAC). NIAC provides neuroimaging support through integrated storage of neuroimaging data and associated clinical and neurocognitive-assessment data in a web-accessible secure database. The CNDA features embedded, automated processing and analytic methods as web-accessible pipelines that are executed on a computer cluster hosted by the NIAC. Over 5000 pipelines have been executed through the CNDA to date. The availability of NIAC and CNDA at the WU Medical Center will ensure successful completion of fMRI data management, processing, analysis, and data sharing.

Dissemination and Implementation

The results generated in this study are investigational in nature; however, the results and subsequent publications will be shared with the St. Louis area Fire Departments and firefighters from other regions. Modes of information distribution may include the electronic magazine, *Fire Chief*, which is an excellent option to disseminate the results among Fire Chiefs across the country. The Fire Chief for the St. Louis Fire Department, Dennis Jenkerson, has agreed to assist with the dissemination of research results through the firefighter community in St. Louis, Missouri, and across the country. In addition, he will propose the PI as an invited guest

speaker to the Safety, Health, and Survival Section of the annual Fire Rescue International meeting of the International Association of Fire Chiefs. Dr. Piccirillo will present the results of his research at national and international scientific meetings. He regularly attends the yearly Tinnitus Research Initiative conference, the American Academy of Otolaryngology-Head and Neck Surgery Annual meeting, and the Combined Otolaryngological Spring meetings where he presents results of his research.

All research resources in this application will be shared with individuals within the scientific community. The neuroimaging data will be available to Washington University researchers through the Central Neuroimaging Data Archive (CNDA).

Clinicaltrials.gov

The trial will be registered on clinicaltrials.gov. We will post our study design and all pertinent results on Clinicaltrials.gov.

Neuroimaging

All neuroimaging images will be kept in Washington University's Central Neuroimaging Data Archive (CNDA) in a de-identified manner using subject study IDs. The list linking subjects back to their study ID values will be kept by Dr. Piccirillo or the study nurse coordinator in a Washington University research server and access will be limited to himself and his research staff. All folders with identifiable information will be password protected. The list of identifiers will be kept for 7 years after the completion of research. At the end of 7 years, the list will be destroyed and study-acquired information will no longer be linked to individual participants.

Statistical Analysis

We will use standard descriptive statistics to describe the study population, responses to questionnaires, severity of tinnitus and other health conditions, and the scale scores and z distributions for the neurocognitive assessments and performance on the *Brain Fitness Program-Tinnitus*. To improve the symmetry of the rs-fcMRI and other data distributions, we may elect to change the values by using a square root or logarithmic transformation. Data will be analyzed using SAS version 9.2 statistical software (SAS Institute, Inc. Cary, NC).

Description of Compliance and Performance on *Brain Fitness Program-Tinnitus*

Posit Science will create a 'research portal' through which the study team will monitor the compliance, effort, and progress of each firefighter assigned to the *BFP-T* arm of the trial. Documentation of weekly compliance, effort, and progress will be maintained by the Washington University research team. The research study ID alone will be used and Posit Science technicians will not have access to participant identifiers.

Resting State Functional Connectivity MRI - Cortical Neural Networks and Regions of Interest

In the Table below, the standard set of brain coordinates for each region of interest (ROI) within different networks — Default, Dorsal Attention, Ventral Attention, Auditory, Vision, Somatosensory, and Cognitive/Control are shown. Correlation values based on the time-course of BOLD signals will be determined amongst brain regions. Functional correlation maps will be produced by extracting the BOLD time course from a seed region (a ROI within a network of interest), then computing the correlation coefficient between that time course and the time course from all other brain voxels. Correlation values will be converted to a normal distribution using Fischer's r-to-z transformation and a random effects analysis corrected for multiple comparisons will be performed. A composite fcMRI map for each of the distinct networks will be determined for each subject by averaging the z scores from each of the ROIs of the respective network. Group averages will be overlaid on structural brain images and compared using a free, open-source, software package for structural and functional analyses of the cerebral and cerebellar cortex developed at WU (brainvis.wustl.edu/wiki/index.php/Main_Page).

Regions of Interest Within Different Cortical Neural Networks

NETWORK	SEED REGION NAME	TALAIRACH COORDINATES		
		X	Y	Z
DEFAULT	Posterior Cingulate Cortex (PCC)	1	-55	17
	Ventromedial Prefrontal Cortex (vmPFC)	0	51	-7
	Right Medial Prefrontal (RMPFC)	1	54	21
	Left Superior Frontal (LSF)	-14	38	52
	Right Superior Frontal (RSF)	17	37	52
	Left Posterior Inferior Parietal (lpIPL)	-47	-71	29
	Right Posterior Inferior Parietal (lpIPL)	47	-64	27
	Left Inferior Temporal (LIT)	-61	-33	-15
	Right Inferior Temporal (RIT)	65	-17	-15
	Left Hippocampal Formation (IHF)	-21	-25	-14
Right Hippocampal Formation (RHF)	24	-19	-21	
Dorsal Attention Network	Left Posterior Intraparietal Sulcus (LpIPS)	-23	-66	46
	Right Posterior Intraparietal Sulcus (RpIPS)	26	-58	52
	Left Frontal Eye Fields (LFEF)	-25	-8	50
	Right Frontal Eye Fields (RFEF)	27	-8	50
	Left Ventral Intraparietal Sulcus (LvIPS)	-24	-69	30
	Right Ventral Intraparietal Sulcus (RvIPS)	30	-80	16
Ventral Attention Network	Right Temporoparietal Junction (rTPJ)	49	-50	28
	Right Middle Frontal Gyrus (rMFG)	39	12	34
	Right Superior Temporal Sulcus (rSTS)	55	-50	11
	LTPJ	-54	-48	37
	Right Precentral Gyrus (rPrCe)	38	-3	50
AUDITORY	Left auditory (LAud)	-51	-19	6
	Right auditory (RAud)	51	-21	9
	Left Auditory Cortex (LAud_Ctx)	-41	-26	7
	Left Superior Temporal Gyrus (LSTG_AC)	-57	-34	7
VISION	Left Primary Visual (LV1)	-8	-81	5
	Right Primary Visual (RV1)	11	-81	5

	RV1d	4	-79	17
	LV2d	-4	-85	19
	LV3A	-22	-85	16
	RV3A	18	-88	18
	Left Visual 4 and Ventral Posterior (LV4_VP)	-18	-70	-10
	Right Visual 4 and Ventral Posterior (RV4_VP)	23	-80	-10
	RV7	25	-79	31
	Left Lateral Occipital Cortex (LLOC)	-36	-83	3
	Right Lateral Occipital Cortex (RLOC) 7	38	-80	3
	Left Middle Temporal Area (LMT) 6	-45	-69	-2
	Right Middle Temporal (RMT) 6	50	-70	-3
	Left Visual 8 (LV8_rev)	-34	-85	19
	Right Visual 8 (RV8) 7	32	-61	-15
	Right Parietal-Occipital Sulcal Cortex (RPOSC)	17	-57	10
	LPOSC	-21	-68	15
SOMATOSENSORY	Left Primary Somatosensory (LS1)	-56	-18	37
	Right Primary Somatosensory (RS1)	51	-18	44
	Left Second Somatosensory (LS2)	-35	-27	17
	Right Second Somatosensory (RS2)	48	-14	16
	Posterior Potcentral Gyral Cortex (rBA2)	43	-27	44
COGNITIVE/CONTROL	Dorsal Anterior Cingulate (dACC)	-9	8	40
	Anterior Cingulate Cortex (aCC)	3	31	27
	Left Dorsolateral Prefrontal Cortex (ldlPFC)	-39	37	15
	Right Dorsolateral Prefrontal Cortex (rdlPFC)	26	35	36
	Left Anterior Insula (LAI)	-30	11	2
	Right Anterior Insula (RAI)	36	3	6
	Left Anterior Prefrontal Cortex (aPFC)	-36	57	9
	Right aPFC	34	52	10
	Left Anterior Intraparietal Sulcal Cortex (aIPL)	-52	-49	47
	Right aIPL	56	-41	40
	Left Inferior Frontal Gyrus/ Frontal Operculum (IFG/FO)	-41	6	9
	RIFG/FO	45	-3	12

fcMRI Calculation

The relationships between seed regions will be evaluated using a simple metric to compute the temporal correlation coefficient between the extracted time courses of each region with the other regions. Correlation values will be determined amongst brain regions, using a standard set of brain coordinates for each of the nodes within each of the various networks of interest. Independent t-test or a non-parametric equivalent, Wilcoxon Mann Whitney U test, will be used to compare MRI z-scores between the subjects with tinnitus and those with no tinnitus.

Specific Aim 1 — To Evaluate The Effect Of Brain Fitness Program-Tinnitus On The Perception Of Tinnitus As Measured By The Tinnitus Handicap Inventory and Overall Bother Score (OBS)

The effect of the *BFP-T* will be assessed through our randomized trial. The primary outcome of the study, labeled as “The primary efficacy parameter,” will be the change in average Tinnitus Handicap Inventory score between the *BFP-T* arm (Condition A) and Control (Condition B) arm and will be defined as follows:

Change in Tinnitus Handicap Inventory score after *BFP-T*

$$\Delta THI_{BFP-T} = THI_{BFP-T \text{ before}} - THI_{BFP-T \text{ after}}$$

Change in Tinnitus Handicap Inventory score after Control

$$\Delta THI_{\text{control}} = THI_{\text{control before}} - THI_{\text{control after}}$$

Primary Efficacy Parameter

$$\Delta(\Delta THI) = \Delta THI_{BFP-T} - \Delta THI_{\text{control}}$$

To assess the effect of *BFP-T* we will test the null hypothesis that the value $\Delta(\Delta THI)$ will not be statistically different from zero. The alternative hypothesis is that ΔTHI_{BFP-T} will be significantly different from the $\Delta THI_{\text{control}}$.

The authors of the *THI* define a clinically significant difference in the *THI* as a difference of 20 points or greater. To assess whether the impact of *BFP-T* in tinnitus is clinically significant we will test the one-sided null hypothesis that the value $\Delta(\Delta THI)$ will significantly different from twenty. The alternative hypothesis is that ΔTHI_{BFP-T} will be less than 20 points different from the $\Delta THI_{\text{control}}$. In addition, we will investigate the number and characteristics of patients with a drop of at least 10 points in *THI*.

The effect of *BFP-T* will also be tested through the change in *OBS*. The null hypothesis that will be tested is that the change in *OBS* ($OBS_{BFP-T \text{ before}}$ minus $OBS_{BFP-T \text{ after}}$) for the *BFP* group will be equal to the change in *OBS* for the control group ($OBS_{\text{control after}}$ minus $OBS_{\text{control before}}$). The authors pre-define that a change in *OBS* by 2 or more points will be considered clinically important. To assess whether the *BFP-T* has a clinically important effect on tinnitus we will assess the percentage of subjects that experience and report a reduction of 2 or more points in the *OBS*.

We will use unadjusted bivariate analysis, paired t-test or its non-parametric equivalent (Wilcoxon signed rank test) to compare *THI* scores at start of the study with *THI* scores after completion of *BFP-T* for each of the groups of the 20 subjects randomized to either arm 1 or arm 2 of the study. An independent samples t-test or its non-parametric equivalent Mann Whitney U test (if parametric assumptions are not met) will be used to test if ΔTHI_{BFP-T} is significantly different from the $\Delta THI_{\text{control}}$.

Cochran’s Q test will be used to compare the *OBS* pre- and post-*BFP-T* per each group. Difference in *OBS* scores post-*BFP-T* and *OBS* pre-*BFP-T* will be calculated. The number and percentage of subjects with a reduction in score by 2 or more points will be calculated and reported. A chi-square test of independence will be used to test the null hypothesis that the proportion of subjects with 2 or more points change in *OBS* in *BFP-T* group is equal to the proportion of subjects with a 2 or more points change in *OBS* in the Control group. A mixed-model analysis using the SAS MIXED procedure will be used to assess for changes (ie., baseline *THI* score minus 2-month *THI* score) in *THI*. The mixed procedure through the testing of different within-between subjects interaction terms, allows for the identification of pre-post changes in each subject’s assessment of *THI* after controlling for treatment arm (intervention versus no intervention) and other between-subject characteristics or covariates, such as age and education level.

Partial Spearman correlation tests will be performed to assess the relationships of *Brain Speed Test* scores with *THI* at each time point. The relationship between the magnitude of change in *Brain Speed Test* scores with

magnitude of change in *THI* score, with adjustment for other significant variables, will be evaluated as well. A logistic regression analysis will be used to identify important predictors of a change of 2 or more points in *OBS*, in addition to *BFP-T*.

Specific Aim 2 — To Evaluate The Effect Of *Brain Fitness Program-Tinnitus* On The Attention, Cognition, And Memory Deficits In Patients With Bothersome Tinnitus, As Measured By A Battery Of Validated Neurocognitive Tests.

Independent samples t-tests will test for differences in neurocognitive test scores at baseline between the firefighters with bothersome tinnitus and firefighters with no tinnitus.

The effect of the *BFP-T* on neurocognitive test scores will be assessed through our randomized trial. We will use unadjusted bivariate analysis, paired t-test or its non-parametric equivalent (Wilcoxon signed rank test) to assess for within subjects differences in neurocognitive scores by comparing scores of each of the neurocognitive tests at start of the study with neurocognitive test scores after completion of *BFP-T* for the 20 subjects randomized in each of the intervention study arms (arm 1 and arm 2). Furthermore, a mixed-model analysis using the SAS MIXED procedure will be used to assess for changes in neurocognitive scores pre-and post-*BFP-T* intervention in the intervention and control arm. Through the mixed analysis, the real impact of *BFP-T* in neurocognitive performance—after controlling for treatment arm and other between subject characteristics or covariates, like age and education level—will be described. Compliance and progress data will be incorporated in all analyses of *BFP-T* data.

Specific Aim 3 — To Use Functional Connectivity (fcMRI) To Explore The Default, Dorsal Attention, Ventral Attention, Auditory, Vision, Somatosensory, And Cognitive/Control Cortical Networks In Subjects With Bothersome Tinnitus And Non-Tinnitus Controls And Assess The Impact Of The *Brain Fitness Program-Tinnitus* On These Networks.

We will use a resting-state fcMRI protocol that shows independent levels of activity in different cortical neural networks, especially the attention system. Specific Aim 3 has the following sub-aims:

1. Compare activation values amongst the various brain regions within the default, dorsal attention, ventral attention, cognitive control, and auditory cortical networks at baseline in subjects with bothersome tinnitus and non-tinnitus controls. The contrast between the two groups assess default mode, attention, cognitive control, and auditory component differences in age-matched subjects with and without tinnitus. Independent samples t-tests will be employed to compare the z-transformed correlation values at baseline for each of the networks of interest: Default, Dorsal Attention, Ventral Attention, Auditory, Vision, Somatosensory, and Cognitive/Control Cortical, between the firefighters with bothersome tinnitus and firefighters with no tinnitus.

2. Utilize *BFP-T*, which modulates attention (Mahncke, Bronstone, and Merzenich 2006), in tinnitus patients to evaluate if usage of this program alters defective functioning of different attention network components. We will use rs-fcMRI to assess the impact of the *BFP-T* by comparing:

- a. Baseline and post-intervention activation values amongst the various brain regions within the ventral, dorsal, and cognitive control cortical attention networks of the subjects with bothersome tinnitus randomized to the *BFP-T*.

A paired t-test will be used to compare the z-transformed correlation values at baseline for each of the networks of interest: Default, Dorsal Attention, Ventral Attention, Auditory, Vision, Somatosensory, and Cognitive/Control Cortical, between the subjects with bothersome tinnitus pre- and post-intervention.

- b. Post-intervention activation values amongst the various brain regions within the ventral, dorsal, and cognitive control cortical attention networks of the firefighters with bothersome tinnitus randomized to the *BFP-T* compared to the:
 - i. Subjects with tinnitus randomized to different intervention arms (BFP versus active controls).
 - ii. Subjects without tinnitus (controls).

One way ANOVA will be employed to investigate whether the z-transformed correlation values for each network are significantly different among participants in each intervention arm (BFP versus Active Controls) and the normal controls imaged 2 month post-baseline assessment. If ANOVA results are significant, a post hoc analysis using Tukey's test will be used to investigate pair-wise differences. Proc GLM procedure will be employed to investigate the differences z-transformed correlation values for each network after controlling for other important characteristics.

As a control, to ensure that the changes we detect in the fcMRI are due to a learning effect, we will compare baseline and 2-month follow-up activation values at various brain regions within the default, dorsal attention, ventral attention, cognitive control, and auditory cortical networks of:

- a. Subjects with tinnitus not randomized to *BFP-T*.
- b. Subjects without tinnitus (controls).

The vision and somatosensory regions will serve as controls for the default, dorsal attention, ventral attention, cognitive control, and auditory systems.

Mixed design (Proc Mixed procedure in SAS) will be used to investigate the change in pre- and post-intervention after controlling for intervention arm or other important between subjects characteristics. Change in the z-transformed correlation values (ΔZ) between post-intervention and baseline will be calculated for each of the networks of interest: Default, Dorsal Attention, Ventral Attention, Auditory, Vision, Somatosensory, and Cognitive/Control Cortical. One-way ANOVA will be employed to investigate whether the change in z-transformed correlation values (ΔZ) for each network is significantly different among participants in each intervention arm (BFP versus Active Controls) and the normal controls. The change (ΔZ) in normal controls, if present, will be due to time effect only. If ANOVA results are significant, a post hoc analysis using Tukey's test will be used to investigate pair-wise differences. Proc GLM procedure will be employed to investigate the differences in ΔZ s after controlling for other important characteristics.

Sample Size Justification

The power computation and sample size justification is based on the 2-sided independent samples t-test with data from the NIH-sponsored randomized controlled trial "*Gabapentin for the Treatment of Tinnitus*" (NCT00317850). (Piccirillo et al. 2007) With the assumptions of the t-test and based on the observations from the 135 tinnitus patients in the gabapentin trial, a sample size of 17 subjects with tinnitus and 17 =subjects without tinnitus (i.e., 34 subjects in total) will provide 85% power to detect a change in the *THI* of 17 points or greater between those who receive *BFP-T* and those who do not (std dev of the difference=16) at the 0.05 alpha level. The difference of 17 points in the *THI* is very close to the difference of 20, or effect size (ES) of 2.0, identified by Bartels et al (Bartels et al. 2008) as the minimally clinically significant difference in the *THI*. An enrollment of 20 subjects per group ensures a requisite sample size of 17 per group with minimal withdrawals.

Power analyses of fcMRI data performed by Professor Burton and WU colleagues indicates adequacy with a sample size as small as 15. (McAvoy et al. 2004)

INFORMATION ON STUDY POPULATION

Human Subjects

Human subjects investigation will not proceed until our protocol is approved by the Washington University Human Research Protection Office (WUHRPO).

Risks and Benefits

Risks

The participant may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that are not anticipated, associated with being in this study.

Interviews and Questionnaires

Likely: None

Less Likely: Participants may experience frustration and/or boredom completing the questionnaires. The participants may refuse to answer any questions for any reason, including questions that may be asked by the study physicians.

Rare: None

MRI

Likely: Lying still in the scanner may produce some stiffness. Study staff will be nearby to stop the study in case participants become uncomfortable.

Less Likely: Being in a closed tight area may produce some anxiety and discomfort. If a participant experiences these symptoms and does not wish to continue, the study will be stopped immediately. The MRI scanner produces a loud repetitive knocking noise during the study that some people find bothersome. Study staff will be nearby to stop the study in case participants become uncomfortable.

Rare: A small number of people experience claustrophobia or panic (severe anxiety due to being restrained or in a confined area), while some experience dizziness or feel faint. The study requires the participants to lie flat for approximately 40 minutes to complete the fcMRI. If unable to complete the entire fcMRI, the study will be stopped and the obtained results will be analyzed.

Brain Fitness Program

Likely: None

Less Likely: Subjects with tinnitus may experience frustration completing the testing if their tinnitus makes it difficult to hear the sounds on the computer or if they have hearing loss and therefore find it difficult to hear the program.

Rare: None

Breach of Confidentiality

Likely: None.

Less Likely: None.

Rare: One potential risk of participating in this study is that a subject's confidential information may be accidentally disclosed. All data will be safeguarded in accordance with HIPAA and the principles and practices of strict confidentiality. The investigators will use their best efforts to keep subject information secure, and estimate the risk of accidental disclosure to be very small. If, for any reason, subjects screened for this study are not allowed to enter, their personal information will be destroyed upon screening completion.

Benefits

Individual

This study provides no promise of direct benefit to participants. The participant may or may not experience improvement of tinnitus or attention with the *Brain Fitness Program-Tinnitus*.

All tests are purely for research purposes and have no benefit to the subject. No copies of the testing will be made available to the subject, to any insurance companies, or placed in any medical records; they will be maintained in the research record only.

Society

The participant may help society by participating in a study that better characterizes the effect of tinnitus on attention networks, and thus contribute to the identification of methods to prevent and treat tinnitus in the future. Tinnitus is a very common yet poorly understood disease that affects people differently. At this time medical professionals lack a clear understanding of why certain people seem to be more affected than others. Preliminary data obtained at this institution provides some insight that certain pathways within the brain may explain this effect. Using fMRI, we intend to analyze specific areas of the brain that we feel are important in tinnitus.

The risks of participation are reasonable given the importance of the knowledge to be gained and the possibility of reduction in future suffering.

Risk Management and Emergency Response

Protections Against Risk

Questionnaires

Subjects may decline to answer any questions that may make them uncomfortable, including questions that may be asked by the study physicians.

Other Safeguards

This protocol is performed at the Washington University Medical Center during normal business hours when the Principal Investigator and/or his colleagues are available. The P.I. is available by phone or pager 24 hours a day and 7 days a week for reporting of any serious adverse events experienced by subjects in this study.

Handling of Depressed or Suicidal Subjects

Subjects who score ≥ 15 on their *PHQ-9* will be excluded from the study and will be referred to their primary care physician (PCP) for follow-up. Any subject who marks on the *PHQ-9* that he/she has had “thoughts of being better off dead, or thoughts of hurting himself in some way” will be a screen fail and withdrawn from the study.

Drs. Piccirillo, Okuyemi, or Wineland will be notified and will examine the subject if necessary. If clinically indicated, or if the subject is deemed to be an immediate risk to him/herself or others due to depression or other psychiatric conditions, Washington University Security will be notified and the subject will be escorted to the Barnes-Jewish Hospital Emergency Department. The purpose of transfer to the ED is to allow for close monitoring of the patient and, if deemed appropriate by the ED physician, a psychiatric evaluation to be performed. This event will be reported as a serious adverse event and the participant will be withdrawn from the study.

If a subject endorses suicidal thoughts but Drs. Piccirillo, Okuyemi, or Wineland do not determine the subject to be an immediate risk to him/herself, the subject will be offered a referral to our Psychiatric clinic or referred to their primary care physician for treatment. The subject will be determined to be a screen fail and withdrawn from the study.

Pregnancy

All females of childbearing potential must undergo a urine pregnancy test after consent and prior to any imaging studies performed at either visit. If a pregnancy test is positive, the subject will be withdrawn from the study..

Key Personnel Contact List

Ms. Nicklaus will maintain a database of phone numbers and e-mail addresses of all participating investigators and staff.

Withdrawal From The Protocol

Participants may withdraw from this study at any time and not suffer any consequences, such as withholding of medical care or loss of benefits. Participants who are unable to complete the tasks required of this study (i.e. completion of forms, completion of fcMRI) will be withdrawn.

Reporting of Adverse Events and Serious Adverse Events

Adverse Events will be tracked at each visit for each firefighter and a compilation documented for the yearly Washington University Human Research Protection Office (WUHRPO) and Department of Homeland Security/Federal Emergency Management Agency (DHS/FEMA) renewal review.

The PI Will Notify WUHRPO and DHS/FEMA Promptly Of The Following Events

- a. Any unanticipated study-related problems involving risks to participants or others which occur at WU, any BJH or SLCH institutions or that impacts participants or conduct of the study.
- b. Noncompliance with federal regulations or the requirements or determinations of the IRB.
- c. Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

Timeframe For Reporting

- a. The events described above will be reported within 10 working days of the occurrence of the event or notification to the PI/PD of the event.
- b. The death of a research participant enrolled at WU/BJH/SLCH that qualifies as a reportable event under the policy as described above will be reported within one working day of the occurrence of the event or notification to the PI/PD of the event.

Additional Reporting Requirements — Audits/Inspections/Inquiry

- a. The PI/PDs will immediately contact the WUHRPO and DHS/FEMA upon notice of any "for cause" audit. This notification should occur via email to the manager of the Washington University Education and Compliance Team.
- b. Follow-up information should be provided and include any reports or determinations from the audit.
- c. If audited by the Food and Drug Administration (FDA), the PI/PD will provide follow-up information that will include any 483 reports, responses by the PI/PD to the FDA, warning letters or any other correspondence from the FDA.
- d. Routine audits/inspections/inquiries that result in findings of noncompliance will be reported in accordance with WUHRPO policy. The study will be stopped promptly if a serious adverse event is related to the study. A complete investigation of the event and its relation to the study will be performed by the PI and results shared with WUHRPO and DHS/FEMA. No further study sessions will be performed until the Investigators, WUHRPO, and DHS/FEMA are satisfied that subjects are not at an increased risk. Adverse events that are unexpected, serious, or might impact the conduct of the study and increase risk to participants will be reported to WUHRPO and DHS/FEMA, as well as expected adverse events that occur in a greater

frequency than expected. Modifications to the informed consent and protocol may be made with the approval of WUHRPO.

We will keep a cumulative record of all protocol deviations and report them to WUHRPO and to DHS/FEMA with our yearly continuing renewal. The safety plan includes monitoring this single site, minimal risk study for any complaints about study participation, expected and unexpected adverse events, and serious adverse events for subjects enrolled in this protocol.

Continuing Review and Final Report

A copy of the approved WUHRPO continuing review report will be submitted to the DHS/FEMA as soon as these documents become available. A copy of the approved final study report and WUHRPO approval notification will be submitted to the DHS/FEMA as soon as these documents become available.

DATA STUDY MONITORING PLAN

The PI (Dr. Piccirillo) and the Clinical Research Coordinator (Ms. Joyce Nicklaus, or designee) will meet weekly for research meetings to focus on screening forms, inclusion/exclusion criteria; case report form review, adverse events, and other WUHRPO-required monitoring and reporting activities. The CRC will record each subject screened for study inclusion and maintain records of reasons for subject exclusions. This information will be included in a de-identified manner in yearly renewals with the WUHRPO.

The entire investigative team will meet once every 6 months. The main points of these meetings will be to address participant safety, participant accrual, overall study progress, administrative issues, study coordination, protocol adherence, ethical concerns, adverse events, and any proposals for protocol revisions. The meetings will be scheduled at a time when Dr. Piccirillo, Dr. Kallogjeri, Ms. Nicklaus are available. Ad-hoc meetings will be convened for discussion and review of SAEs or proposed protocol changes. Minutes of each research team meeting will be kept to document oversight and the minutes will be maintained in a study folder on a Washington University secure server. Dr. Piccirillo will review and sign off on the contents of all meeting minutes.

REFERENCES

- Barkley,R.A. 1998. Attention-deficit hyperactivity disorder. *Scientific American* 279(3):66-71.
- Barsky,A.J. and J.F.Borus. 1999. Functional somatic syndromes. *Annals of Internal Medicine*. 130(11):910-21.
- Bartels,H., B.L.Middel, d.van, M.J.Staal, and F.W.Albers. 2008. The additive effect of co-occurring anxiety and depression on health status, quality of life and coping strategies in help-seeking tinnitus sufferers. *Ear & Hearing*. 29(6):947-56.
- Biederman,J., S.V.Faraone, T.Spencer, T.Wilens, D.Norman, K.A.Lapey, E.Mick, B.K.Lehman, and A.Doyle. 1993. Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with attention deficit hyperactivity disorder. *Am.J.Psychiatry* 150(12):1792-8.
- Broadbent,D.E., P.F.Cooper, P.Fitzgerald, and K.R.Parkes. 1982. The Cognitive Failures Questionnaire (CFQ) and its correlates. *Br.J.Clin.Psychol*. 21 (Pt 1):1-16.
- Buckner,R.L., D.Head, J.Parker, A.F.Fotenos, D.Marcus, J.C.Morris, and A.Z.Snyder. 2004. A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume. *Neuroimage* 23(2):724-38.
- Burton,H., A.Wineland, M.Bhattacharya, J.Nicklaus, K.S.Garcia, and J.F.Piccirillo. 2012. Altered networks in bothersome tinnitus: a functional connectivity study. *BMC.Neurosci*. 13(1):3.
- Conners,C. 2000. *Conners CPT II for Windows*. North Tonawanda, NY: Multi-Health Systems.

Corbetta, M., M.J. Kincade, C. Lewis, A.Z. Snyder, and A. Sapiro. 2005. Neural basis and recovery of spatial attention deficits in spatial neglect. *Nat. Neurosci.* 8(11):1603-10.

Cordes, D., V.M. Haughton, K. Arfanakis, G.J. Wendt, P.A. Turski, C.H. Moritz, M.A. Quigley, and M.E. Meyerand. 2000. Mapping functionally related regions of brain with functional connectivity MR imaging. *AJNR Am J Neuroradiol* 21(9):1636-44.

Delis, D.C., J.H. Kramer, E. Kaplan, and B.A. Ober. 1987. *California Verbal Learning Test (CVLT) Adult version (Research ed.)*. San Antonio, TX: Psychological Corporation.

Derogatis, L.R. 2000. *BSI-18 administration, scoring and procedures manual*. Minneapolis: NCS Pearson, Inc.

Feinstein, A.R. 1987. *Clinimetrics*. New Haven, CT: Yale University Press.

Fink, P., H. Ewald, J. Jensen, L. Sorensen, M. Engberg, M. Holm, and P. Munk-Jorgensen. 1999. Screening for somatization and hypochondriasis in primary care and neurological in-patients: a seven-item scale for hypochondriasis and somatization. *J Psychosom. Res.* 46(3):261-73.

Fisher, M., C. Holland, M.M. Merzenich, and S. Vinogradov. 2009. Using neuroplasticity-based auditory training to improve verbal memory in schizophrenia. *Am. J. Psychiatry* 166(7):805-11.

Fox, M.D., M. Corbetta, A.Z. Snyder, J.L. Vincent, and M.E. Raichle. 2006. Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. *Proc Natl Acad Sci U S A* 103(26):10046-51.

Fox, M.D. and M.E. Raichle. 2007. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat Rev Neurosci* 8(9):700-11.

Fox, M.D., A.Z. Snyder, J.L. Vincent, M. Corbetta, E. Van, and M.E. Raichle. 2005. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci U S A* 102(27):9673-8.

Greicius, M.D., G. Srivastava, A.L. Reiss, and V. Menon. 2004. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proc Natl. Acad. Sci. U.S.A* 101(13):4637-42.

Hallam, R.S., L. McKenna, and L. Shurlock. 2004. Tinnitus impairs cognitive efficiency. *International Journal of Audiology*. 43(4):218-26.

Hoffman, H.J. and G.W. Reed. 2004. Epidemiology of tinnitus. In *Tinnitus. Theory and Management.*, edited by J.B. Snow, Jr., 16-41. Hamilton, Ont.: B.C. Decker, Inc.

Hong, O. and D.G. Samo. 2007. Hazardous decibels: hearing health of firefighters. *AAOHN.J.* 55(8):313-9.

Katzman, R., T. Brown, P. Fuld, A. Peck, R. Schechter, and H. Schimmel. 1983. Validation of a short Orientation-Memory-Concentration Test of cognitive impairment. *American Journal of Psychiatry*. 140(6):734-9.

Kessler, R.C., L. Adler, M. Ames, O. Demler, S. Faraone, E. Hiripi, M.J. Howes, R. Jin, K. Secnik, T. Spencer, T.B. Ustun, and E.E. Walters. 2005. The World Health Organization Adult ADHD Self-Report Scale (ASRS): a short screening scale for use in the general population. *Psychol. Med.* 35(2):245-56.

Kessler,R.C., L.A.Adler, M.J.Gruber, C.A.Sarawate, T.Spencer, and D.L.Van Brunt. 2007. Validity of the World Health Organization Adult ADHD Self-Report Scale (ASRS) Screener in a representative sample of health plan members. *Int.J.Methods Psychiatr.Res.* 16(2):52-65.

Kroenke,K., R.L.Spitzer, and J.B.Williams. 2001. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern.Med* 16(9):606-13.

Kwong,K.K., J.W.Belliveau, D.A.Chesler, I.E.Goldberg, R.M.Weisskoff, B.P.Poncelet, D.N.Kennedy, B.E.Hoppel, M.S.Cohen, R.Turner, and . 1992. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proc Natl.Acad.Sci.U.S.A* 89(12):5675-9.

Lancaster,J.L., T.G.Glass, B.R.Lankipalli, H.Downs, H.Mayberg, and P.T.Fox. 1995. A modality-independent approach to spatial normalization of tomographic images of the human brain. *Human Brain Mapping* 3(3):209-23.

Lockwood,A.H., R.J.Salvi, and R.F.Burkard. 2002. Tinnitus. *The New England Journal of Medicine* 347(12):904-10.

Mahncke,H.W., A.Bronstone, and M.M.Merzenich. 2006. Brain plasticity and functional losses in the aged: scientific bases for a novel intervention. *Prog.Brain Res.* 157:81-109.

McAvoy, M., Brown, T., Burton, H., Schlaggar, B. L., and Petersen, S. Voxel power for repeated measures ANOVA with nonsphericity. *Proceedings International Soc.For Magnetic Resonance in Medicine* . 2004.

Ref Type: Abstract

Newman,C.W., G.P.Jacobson, and J.B.Spitzer. 1996. Development of the Tinnitus Handicap Inventory.

Archives of Otolaryngology -- Head & Neck Surgery 122(2):143-8.

Newman,C.W., S.A.Sandridge, and G.P.Jacobson. 1998. Psychometric adequacy of the Tinnitus Handicap Inventory (THI) for evaluating treatment outcome. *Journal of the American Academy of Audiology*. 9(2):153-60.

Ogawa,S., T.M.Lee, A.R.Kay, and D.W.Tank. 1990. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci U S A* 87(24):9868-72.

Ojemann,J.G., E.Akbudak, A.Z.Snyder, R.C.McKinstry, M.E.Raichle, and T.E.Conturo. 1997. Anatomic localization and quantitative analysis of gradient refocused echo-planar fMRI susceptibility artifacts. *Neuroimage* 6(3):156-67.

Piccirillo,J.F., J.Finnell, A.Vlahiotis, R.A.Chole, and Spitznagel E Jr. 2007. Relief of idiopathic subjective tinnitus: is gabapentin effective? *Archives of Otolaryngology -- Head & Neck Surgery* 133(4):390-7.

Ploner,M., M.C.Lee, K.Wiech, U.Bingel, and I.Tracey. 2010. Prestimulus functional connectivity determines pain perception in humans. *PNAS* 107(1):355-60.

Rossiter,S., C.Stevens, and G.Walker. 2006. Tinnitus and its effect on working memory and attention. *Journal of Speech Language & Hearing Research*. 49(1):150-60.

Schweitzer,J.B., T.K.Cummins, and C.A.Kant. 2001. Attention-deficit/hyperactivity disorder. *Med.Clin.North Am.* 85(3):757-77.

Investigating the Impact of Cognitive Training for Firefighters with Tinnitus

PI: Piccirillo, Jay F.

Sheline, Y.I., D.M.Barch, J.M.Donnely, J.M.Ollinger, A.Z.Snyder, and M.A.Mintun. 2001. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. *Biol.Psychiatry* 50(9):651-8.

Sheline, Y.I., D.M.Barch, J.L.Price, M.M.Rundle, S.N.Vaishnavi, A.Z.Snyder, M.A.Mintun, S.Wang, R.S.Coalson, and M.E.Raichle. 2009. The default mode network and self-referential processes in depression. *Proc Natl.Acad.Sci.U.S.A* 106(6):1942-7.

Smith, G.E., P.Housen, K.Yaffe, R.Ruff, R.F.Kennison, H.W.Mahncke, and E.M.Zelinski. 2009. A cognitive training program based on principles of brain plasticity: results from the Improvement in Memory with Plasticity-based Adaptive Cognitive Training (IMPACT) study. *J Am.Geriatr.Soc.* 57(4):594-603.

Talairach, J. and P.Tousignant. 1988. *Co-planar Stereotaxic Atlas of the Human Brain*. New York: Thieme Medical.

Tubbs, R. and Flesch, J. Health Hazard Evaluation Report. HETA 81-059-1045. 1982. National Institute of Occupational Safety and Health.

Ref Type: Report

Wechsler, D. 2003. *WISC-IV Technical and Interpretative Manual*. San Antonio, TX: Psychological Corporation.

Winston, R. March 1. Stop the Ringing. *Fire Chief* (March 1),

Available at <http://firechief.com/health-safety/ar/tinnitus-risk-201003/> .

Investigating the Impact of Cognitive Training for Firefighters with Tinnitus

PI: Piccirillo, Jay F.

Wolinsky, F.D., H. Mahncke, M.W. Vander Weg, R. Martin, F.W. Unverzagt, K.K. Ball, R.N. Jones, and

S.L. Tennstedt. 2010. Speed of processing training protects self-rated health in older adults: enduring effects observed in the multi-site ACTIVE randomized controlled trial. *Int. Psychogeriatr.* 22(3):470-8.

Wolinsky, F.D., F.W. Unverzagt, D.M. Smith, R. Jones, A. Stoddard, and S.L. Tennstedt. 2006. The ACTIVE cognitive training trial and health-related quality of life: protection that lasts for 5 years. *J. Gerontol. A Biol. Sci. Med. Sci.* 61(12):1324-9.

Zeman, F., M. Koller, R. Figueiredo, A. Azevedo, M. Rates, C. Coelho, T. Kleinjung, R.D. De, B. Langguth, and M. Landgrebe. 2011. Tinnitus handicap inventory for evaluating treatment effects: which changes are clinically relevant? *Otolaryngol Head Neck Surg* 145(2):282-7.