Blast-exposed Veterans with Auditory Complaints, NCT02122458

Funding Agency: VA ORD, RR&D

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Version 06/11/2017

Abstract

Clinical audiologists at the VA Pittsburgh Healthcare System (VAPHS) have observed a substantive increase in the number of veteran's presenting with self-reported hearing problems but who demonstrate normal or near normal hearing sensitivity when tested with a standard audiometric test battery. The primary complaint of these veterans is difficulty hearing speech in background noise, and preliminary clinical data have suggested poor performance on some tests of central auditory processing. Moreover, when fitted with mild-gain open-fit hearing aids, which amplify the high-frequency part of the speech spectrum, these patients have reported a reduction in their hearing-related problems. Nearly all of these veterans have reported histories of blast exposure and concussion while Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) deployed and described symptoms consistent with post-concussive syndrome. Similar auditory patterns for veterans with mTBI have been reported by clinical audiologists from other VA medical centers and military facilities although the auditory problems of this group of veterans have not been well described or studied (Fausti et al., 2009; Lew et al., 2007).

This study was developed in response to the clinical complaints offered by these veterans, with the goal being to better understand their problems by extensively assessing their auditory and auditory-related characteristics. A group of veterans with histories of blast exposure, histories consistent with mTBI, and normal audiometric results, but notable auditory complaints will be evaluated with a standard audiometric test battery, health status and quality of life questionnaires, auditory physiological test procedures, and behavioral central auditory processing tests. We also will administer speech perception and psychoacoustic tasks, and verbal working memory and language processing tests to better understand various aspects of their ability to hear, remember, and process speech and language through audition. A reading test that parallels an auditory language-processing task also will be administered to determine if any identified language processing problems are limited to the auditory system. Comparisons will be made to a control group of veterans who are negative for auditory and brain impairments, as well as to a group of veterans with Post Traumatic Stress Disorder (PTSD) but without histories of blast exposure or brain injury. In addition, the influences of coexisting PTSD will be examined. Secondarily, the benefit of fitting this population of veterans with mild-gain hearing aids that amplify the high-frequency part of the speech spectrum will be tested.

The information obtained from this study will be a first step in elucidating the problems of these veterans and will lay the groundwork for future studies that will focus on specific deficit mechanisms. This study also should contribute to the development of an effective assessment battery and interventions for this population.

List of Abbreviations

ABR – Auditory Brainstem Response
ANOVA – Analysis of Variance
ANCOVA – Analysis of Covariance
APHAB – *Abbreviated Profile of Hearing Aid Benefit*
BSI-18 – Brief Symptom Inventory – 18 Item
BTBIS – *The Brief Traumatic Brain Injury Screen*
CCT – *California Consonant Test*
CRTT – *Computerized Revised Token Test*
CRTT-R – *Computerized Revised Token Test – Reading*
CRTT-R-Stroop – *Computerized Revised Token Test – Stroop*
CT – Computed Tomography
CPRS – Computerized Patient Record System
DDT – *Dichotic Digits Test*
DoD – Department of Defense
dB – Decibel
DPOAE – Distortion Product Otoacoustic Emissions
FPTC – Fast Psychophysical Tuning Curves
GIN – *Gaps in Noise*
HHIA – *Hearing Handicap Inventory for Adults*
HHIE- SO – *Hearing Handicap Inventory for Adults – Significant Others*
HL – Hearing Level
Hz – Hertz
IOI-HA – International Outcome Inventory – Hearing Aids
IRB – Internal Review Board
LDL – Loudness Discomfort Level
LLR – Long Latency Response
LiSN-S - *Listening in Spatialized Noise – Sentence Test*
M – Mean
MVPT-4 – *Motor-Free Visual Perception Test, version 4*
MLD – Masking Level Difference
MLR – Middle Latency Response
MRI – Magnetic Resonance Imaging
mTBI – Mild Traumatic Head Injury
NCRAR – National Center for Rehabilitative Auditory Research
NU-6 – *Northwestern University # 6*
OEF/OIF – Operation Enduring Freedom/Operation Iraqi Freedom
OIO-HA – *International Outcome Inventory-Hearing Aids*
PCL-M – *PTSD Checklist-Military*
PTSD – Post Traumatic Stress Disorder
PVAMC – Portland VA Medical Center
SCAN-3A – *SCAN-3: A Test for Auditory Processing Disorders in Adolescents and Adults*
SD – Standard Deviation
SPL – Sound Pressure Level
SSQ - *The Speech Spatial Qualities of Hearing Scale*

SSW – *Staggered Spondaic Word Test*
SWLS – *Satisfaction with Life Scale*
TBI – Traumatic Head Injury
TFI – *Tinnitus Functional Index*
TFS1 – *Temporal Fine Structure 1 Test*
USD – University of South Dakota
VA – Veterans Administration
VAPHS – VA Pittsburgh Healthcare System
VASFHS – VA Sioux Falls Healthcare System
VINCI – VA Informatics and Computing Infrastructure
WAIS-IV – Wechsler Adult Intelligence Scale – Fourth Edition
WHODAS II – *World Health Organization Disability Assessment Schedule II*
WIN – *Words-in-Noise*

Contents

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- Study personnel are listed below:

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2.0 Introduction

BACKGROUND AND SIGNIFICANCE

Between October 1, 2001 and December 31, 2012 a total of 1,599,575 unique OEF/OIF and Operation New Dawn (OND) military personnel separated from active duty and became eligible for benefits through the Veterans Health Administration (Department of Defense, Defense Manpower Data Center, 2013). Utilization data suggested that approximately 56% of these veterans have accessed some level of VA healthcare services, which is in contrast to the 28-24% utilization rate by the overall veteran population (National Center for Veterans Analysis and Statistics, 2013). Among this population of veterans, traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) are evident at high rates and frequently are comorbid conditions. Moreover, these two conditions are associated with substantially elevated healthcare costs. Auditory problems are a common complaint among veterans with TBI and PTSD even when hearing is normal upon standard audiometric testing; yet optimal methods for diagnosis and treatment of their auditory problems have not been well established or studied. Understanding and improving their auditory function could advance their interactions within the VA healthcare system, positively impact the services that they receive, affect their abilities to work and learn, and improve their quality of life.

Mild Traumatic Brain Injury

Traumatic brain injury is considered a signature injury of current and recent U.S. military engagements largely due to blast injuries (Wilk et al., 2010). An estimated 20% of soldiers with blast injuries suffer from acute TBI with most cases being mild (Armed Forces Health Surveillance Center, 2010). It is a significant healthcare issue among veterans with 10 to 15% of all OIF/OEF veterans having mTBI; a prevalence rate substantively higher than in the civilian population (Hoge et al., 2008). Sensory problems, such as hearing and vision loss are common in persons with mTBI especially

in persons with injuries due to blast exposure. In the acute phase, individuals with mTBI complain of difficulties with headache, tinnitus, dizziness, nausea, fatigue, hypersensitivity, irritability, memory deficits, and depression (Sheedy et al., 2006). Cognitive deficits can be of the magnitude to interfere with daily activities (Alexander, 1995) and typically include problems of attention and working memory (McAllister et al., 2006), processing speed, verbal fluency (Ruff et al., 2010), comprehension and production of complex connected language (LeBlanc et al., 2006) and areas of executive function (Belanger et al., 2005). Most adults with mTBI make a favorable recovery within days to weeks of injury but those with more severe injuries are inclined to exhibit persistent neuropsychological deficits (Bilger, 2008; Iverson et al., 2007). The expression of symptoms is variable and a substantial number of individuals diagnosed with mTBI do not exhibit frank impairments upon neuropsychological testing (Tombaugh et al., 2007), although others will be symptomatic on both behavioral and neurophysiologic tests (Ruff et al., 2010). An added complexity is that post-concussive symptoms associated with mTBI can manifest months or even years after the insult (Bales et al., 2009; Terrio et al., 2009). These persistent and later emerging symptoms can result in long-term impairments of daily function with as many as 43% of individuals hospitalized for TBI reporting at least one unmet rehabilitative need at 1-year post-injury (Corrigan et al., 2010). The delayed onset of symptoms might represent a gradually-emerging consequence of the brain injury or a failure to detect persistent subclinical neurobehavioral signs of the injury (Ivins et al., 2009). Regardless of whether these potentially handicapping symptoms are unidentified or late emerging, they represent a significant concern among returning OIF/OEF warriors and veterans. Similar findings are expected for veterans who only served in OND but their overall numbers are expected to be considerably smaller.

Blast Injury

Blasts have been responsible for about two-thirds of all combat injuries in the OIF/OEF conflicts (Murray et al., 2005), and although blast injuries have long been associated with modern warfare, the expansion of insurgent and terrorist tactics in these recent conflicts has been linked to increasing numbers of injuries and deaths due to the use of improvised explosive devices. The blasts from these and other types of explosive devices are complex, as are the resulting injuries (Kocsis & Tessler, 2009; Wightman & Gladish, 2001). Upon detonation there is rapid conversion of the explosive (solid or liquid) into gases that expand rapidly and in turn compress the surrounding air. This initial pressure pulse is referred to as the blast overpressure. As the gases continue to expand the air pressure drops behind the pressure pulse creating a relative vacuum or blast underpressure, which reverses the direction of the blast forces. With high explosives the blast occurs instantaneous and the pressure waves propagate faster than the speed of sound. Acoustic energy is compressed in front of the pressure pulse and eventually the blast waves deteriorate into acoustic waves (Wightman & Gladish, 2001). These extreme pressure changes can produce a shattering effect and barotrauma, which are considered the primary blast injuries. Barotrauma results from excessive stretching and shearing due to differential acceleration and deceleration across the body relative to density. The gas and fluid-filled structures of the body, such

as the lungs, bowel, and the middle ear are believed to be most vulnerable (Kocsis & Tessler, 2009).

In warfare the injuries from blasts are heterogeneous and confounded by the secondary (projectiles), tertiary (effects of wind), and quaternary (burns, asphyxia, toxins) effects of blasts (DePalma et al., 2005; Wightman & Gladish, 2001). Objects propelled by the energy of the explosions strike victims and cause blunt or penetrating ballistic trauma. Bodies can be propelled by the force of the blast and strike objects, and victims can be injured by structures collapsing onto them. Additional injury can occur due to inhalation of toxic gases and exposure to chemicals resulting from the explosives, as well as resulting heat, fire and smoke. Severe head injury is the leading cause of death due to blast with subarachnoid and subdural hemorrhage being the most common finding. The brain is somewhat protected from the blast pressure waves because its water density is homogeneous but stress waves are capable of penetrating the skull (Chavko et al., 2007) and in extreme cases can shatter the cranium from within (Wightman & Gladish, 2001). Brain injury also can occur as a consequence of injuries to other vulnerable organs, such as the lung, gastrointestinal track, heart, and long bones, producing air emboli, fat emboli, increased venous pressure, and hypoxia/ischemia that can result in more brain damage than the blast itself (Mayorga, 1997). Because the brain is protected from the forces of the blast wave, most blast-related head injuries are believed to be secondary, tertiary and quaternary injuries (DePalma et al., 2005; Wightman & Gladish, 2001). Yet evidence is mounting that the brain and spinal cord incur primary blast injuries from the pressure wave itself, although the injury mechanisms are unclear. Furthermore, because of the advanced body armor worn by soldiers, damage to the central nervous system from combat-related blasts is increasingly attributed to the primary effects of the blast (DePalma et al., 2005; Haberstroh, 2004).

Experimental animal models using shock and blast tubes have shown alterations of the central nervous system that are consistent with primary blast injuries. Connell et al. (2011) used a guinea pig model and demonstrated that blast waves compress neural tissue and produce axonal membrane damage. Similar studies with rats and rabbits have produced myelin disruption, defuse axonal damage, neuronal degeneration and increased oxidative stress (Cernak et al., 2001). Blast injuries in animals also have been associated with behavioral changes and long-term learning deficits.

Of the veterans exposed to blasts and associated acoustic trauma, neuropathologic changes have been reported and include small hemorrhages within white matter, chromatolytic changes in neurons, diffuse brain injury and subdural hemorrhage at the frontal and parietal convexities (Taber et al., 2006). Diffuse axonal injuries also occur often in the frontotemporal areas, the internal capsule, deep grey matter (such as the basal ganglia), upper brainstem and the corpus collosum. Computer simulations have suggested that high stresses caused by primary pressure waves are associated with coup and contrecoup damage (Chafi et al., 2010) with orbitofrontal regions and the posterior fossa (cerebellum and brainstem) particularly susceptible. Injuries also can be due to system reaction to the initial brain insult, such as swelling and oxidative stress.

In cases of mTBI many of the lesions and changes in brain matter remain undetected on MRI or CT scans (Niogi & Mukherjee, 2010), although improved imaging techniques are proving sensitive to the unique neurological abnormalities of this population. MacDonald et al. (2011) used diffusion tensor imaging and showed marked abnormalities in the middle cerebellar peduncles, cingulum bundles, and the orbitofrontal white matter when testing military personnel with blast-related mTBI, although their participants were mixed relative to the type of injury. Davenport et al. (2012) studied two groups of OIF/OEF veterans with mTBI. One group had mTBI due to blast exposure whereas the other group had non-blast related brain injuries. They also used diffusion tensor imaging and found white matter disruptions with both groups but the disruptions were more diffuse with the blast-exposed veterans. Moreover, the disruptions were more pervasive with increased number of blast exposures. Multiple blast exposures is an issue with the OIF/OEF veteran population because military personnel with mild concussions often return to full duty status shortly after injury with about 85% being re-injured within 3 months of returning to duty (MacGregor et al., 2011).

Auditory Impairment and mTBI

Hearing and visual impairments are common in persons with TBI and likely contribute to their communication, social and employment handicaps. Furthermore, the more severe the TBI the more marked hearing loss tends to be, especially for high-frequency test signals. Peripheral hearing loss is commonly associated with TBI particularly in blast injury cases with concurrent abnormalities of the central auditory system noted in some individuals (Fausti et al., 2009; Lew et al., 2007). As indicated above, blast pressure waves can affect both fluid and gas filled structures, such as the ear, with the proximity and intensity of the blast influencing the magnitude of the injury (Lew et al., 2007; Patterson & Hamernik, 1997). In the OIF/OEF conflicts, tinnitus and hearing loss have been responsible for the largest number of primary disabilities, with auditory problems being the fourth leading cause of medical referral for combatants returning from deployment (McIlwain et al., 2008). Moreover, veterans with blast-related mTBI are more likely to have auditory complaints than non-blast related mTBI (Belanger et al., 2011). Auditory system injuries also are the most common single type of injury consequent to blast exposure, resulting in tympanic membrane perforation and middle ear and cochlear damage (Gondusky & Reiter, 2005; Patterson & Hamernik, 1997). In a review of veterans' post-deployment hearing status, Helfer et al. (2005) found that post-combat veterans were 50 times more likely to have ear-related problems than those who did not have combat experiences. However, most of the reported auditory problems were peripheral in nature, usually middle ear and cochlear, and not necessarily associated with documented TBI (Gondusky & Reiter, 2005).

Complaints of auditory problems with no peripheral hearing loss have been reported in individuals with known mTBI but their auditory complaints have not been studied widely or systematically, nor have effective treatments been established (Fausti et al., 2009; Lew et al., 2007). Nonetheless, a recent publication by Gallun et al. (2012) reported on

standard audiometric and central auditory assessment results from 36 hospitalized OIF/OEF warriors with histories of blast exposure and a similar group of non-hospitalized veterans with no blast exposures. All of the blast-exposed warriors had been evaluated for TBI with 19 of 36 having a diagnosis of TBI, and upon interview, 13 also indicated that they had symptoms of PTSD. Although hearing handicap was not measured, 39% reported increased difficulty hearing in quiet and 78% reported more difficulty hearing in noisy environments since their blast exposures. As expected, the two groups were similar and within normal limits on the standard audiometric measures, but differences emerged on some, but not all of the central auditory measures. The blast-exposed patients were most notably different on several behavioral measures of central auditory processing and speech perception in noise (i.e., Gaps-in-Noise, Masking Level Difference, Staggered Spondaic Words, QuickSIN) and a long latency event-related potential test. It should be noted, however, that on none of these tasks did a majority of the blast-exposed warriors demonstrate abnormal results. Furthermore, no soldier produced abnormal results on all of the central auditory tests, suggesting substantial group heterogeneity. The composition of the blast-exposed group likely contributed (e.g., not all reported auditory complaints), but possible differences in the extent and location of the blast-related damage were considerations and highlight the complexity of this group of patients.

Auditory problems experienced by blast-exposed warriors and veterans could relate to subclinical cochlear damage or indirect responses to damaged central auditory structures or compromised neural structures that subtend the auditory system. Poor processing of auditory signals also might reflect difficulties in cognitive functions secondary to or supported by the auditory system. For example, the reported difficulties might be due to reduced attention modulation of the auditory system or poor auditory working memory secondary to the brain injury. However, for some individuals their problems likely reflect global cognitive deficits that are most noticeable within the auditory domain. Common cognitive sequelae of TBI that might be related to or exacerbated by auditory dysfunction include difficulty comprehending complex language at pragmatic (Angeleri et al., 2008; Henchliffe et al., 1998) discourse (Coelho et al., 2002) and sentence levels (Henchliffe et al., 1998; Le Blanc et al., 2006). Sentence level processing has been identified as particularly vulnerable and sensitive to TBI. For example, Hinchliffe et al. (1998) found the Revised Token Test (McNeil & Prescott, 1978), a sentence level auditory processing test, to be the first factor selected in the identification of TBI, among 18 language factors investigated, and it predicted highly the other language and memory factors.

As suggested above, individuals with mTBI are at high risk for poor post-discharge outcomes. They often show decreased social and family integration and difficulty returning to work and school (Cattelani et al., 2002; Drake et al., 2000). Difficulty dealing with auditory information and background noise likely contributes to their poor outcomes, although no published studies have examined this relationship to date. Veterans targeted by the current study are unlikely to receive appropriate referral because even soldiers who have both peripheral hearing loss and mTBI have low referral rates to audiology clinical services (Helfer et al., 2011). Moreover, even if

referred, they have a reduced likelihood of receiving adequate auditory rehabilitative services due to their normal performance on standard audiometric test measures. Yet, given the elevated incidence of mTBI in military and veteran populations, the scope of this problem is certain to grow as the remaining OIF/OEF warriors convert to veteran status and age-related hearing loss confounds their auditory processing difficulties. A reflection of this increase is the formation of an online Auditory Processing Disorder group consisting of 36 VA audiologists who correspond regularly by email about how to best assess and treat these veterans. Consistent concerns expressed by this group have related to test battery composition and management of patients once they have been identified and diagnosed.

Post-Traumatic Stress Disorder and mTBI

The coexistence of PTSD with mTBI is a confounding factor in OIF/OEF veterans with blast-related mTBI. Hoge et al. (2008) found that approximately 44% of the returning OIF/OEF soldiers who reported loss of consciousness following blast injury met the criteria for PTSD. In a similar study, Pietrzak et al., (2009) observed that approximately 65% of their sample of OIF/OEF veterans with mTBI screened positive for PTSD, although loss of consciousness was not a strong predictor of comorbid PTSD, as was observed in the Hoge et al. (2008) study. A range of psychosocial, somatic and cognitive problems are characteristic of PTSD such as flashbacks, nightmares, hyperarousal, and avoidance of stimuli related to traumatizing events, but a number of symptom overlap with mTBI including impaired concentration, headaches, irritability, anger and sleep disturbances (Ruff et al., 2010). Persons with PTSD and mTBI also tend to experience problems with memory and appropriate modulation of attention. Veterans with both mTBI and PTSD also fair worse than veterans with isolated impairments in that they have greater health and psychosocial difficulties, poorer quality of life, and perceive themselves as having greater barriers to mental healthcare. They also are more likely to experience employment and marital problems and unmet psychosocial needs. Pietrzak et al. (2009) found that PTSD and related psychiatric conditions such as depression mediate the physical and post-concussive symptoms observed in mTBI veterans, suggesting that appropriate treatment of depression and PTSD symptoms might improve functional recovery of veterans with mTBI. It also is possible that problems with hearing, which tend to increase the likelihood and severity of depression, can interfere with the treatment of mTBI and PTSD.

Background Noise

Difficulty listening in noise is a commonly reported complaint of persons with a history of TBI although the ability of this population to cope with and listen in background noise has not been well studied (Fausti et al., 2009; Landon et al., 2012). It is not known whether they are hypersensitive to background noise as is common in cases of PTSD, are unable to focus attention on target sounds when background noise is present (e.g., listening in the dips), are unable to suppress background noise, or whether their auditory systems cannot process and separate or stream target signals from the background noise. However, difficulty listening in background noise is not unique to

TBI. It is nearly ubiquitous in person with sensorineural hearing loss due to damage to the cochlea and subsequent deterioration of the eighth nerve and central nervous system (Summers & Leek, 1998). Background noise also is problematic for young children because of central auditory immaturity (Johnson, 2000) and elderly adults due to auditory aging and cognitive decline (Humes & Floyd, 2005). For example, older adults with normal peripheral hearing usually perform similarly to younger adults on auditory language processing tasks in quiet but are more adversely affected in noise. Even after accounting for peripheral hearing loss, older adults hear speech less well in background noise, and have difficulties in attention-demanding situations such as when speech rate is increased, when processing or response rates are high, when speakers use a non-native dialect, or when linguistic, cognitive and memorial demand are increased (Burda, Scherz, Hageman & Edwards, 2003; Gordon-Salant & Fitzgibbons, 2004; Humes & Floyd, 2005; Schneider, Daneman, Murphy & Kwong, 2000). Older adults also have difficulty performing cognitive tasks (e.g., working memory tasks) in noise (Heinrich & Schneider, 2010). Older adults appear to have more difficulties with voice segregation than do young adults, which have been attributed to problems with synchrony of coding (Schneider, Daneman & Pichora-Fuller, 2002). Synchrony of coding allows access to the fine structure of speech signals, such as vocal F_0 and harmonics, and facilitates the separation of speech from background noise and co-occurring speech signals (Summers & Leek, 1998).

Although not well studied, the auditory complaints of mTBI patients with normal audiometric test results appear to be similar in nature to those ascribed to older adults with normal hearing thresholds. The parallels are of interest in accounting for and differentiating between the influences of peripheral and central auditory damage, as well as understanding mechanisms that impede efficient processing, but such an approach should be considered with caution as auditory decline in the aging model might not match with deficits associated with brain deficits due to traumatic insult.

A common model of auditory perception, the Auditory Image Model (AIM; Patterson, 2000) provides a general perspective on the possible auditory problems of blast-exposed veterans. The model argues that the auditory system forms images that are coded early at the level of the cochlea and eighth nerve, and then are integrated and processed as the auditory signals proceed through the central nervous system. Recent work looking at the response to vowels and consonant-vowel syllables at the level of the eighth nerve and subcortical regions is consistent with this notion of early coding (e.g., Aikin & Picton, 2008; Krizman, Skoe & Kraus, 2010). As such, breakdown and sensitivity to noise can occur very early in the system, and also becomes evident at higher cortical levels and possibly impacts cognitive and linguistic functions. Conversely, cognition and linguistic status can influence the manner in which primary signals and noise are processed by the auditory system. Such an approach also supports the argument that auditory perceptual learning through exposure to modified input (e.g., cochlear implants, frequency and intensity shifted feedback, spectrally shifted vowels) and targeted perceptual training can influence performance across various levels of the auditory system. However, the plasticity of the auditory system in blast-exposed patients likely is dependent on the nature and extent of their impairments.

Treatment Options

There is a range of treatments for veterans with mTBI depending on the magnitude and type of injury, the presence of comorbid injuries, time post-injury and the presenting impairments. After a patient is physically stable a number of rehabilitation approaches can be implemented (e.g., psychiatry, neuropsychology, speech-language pathology, rehabilitation and vocational counseling, physical therapy, occupational therapy), but unless a veteran has a hearing loss that is evidenced with standard audiometric test procedures the auditory intervention offerings are very limited. Blast-exposed veterans with marked auditory complaints but normal audiometric test results appear to benefit from the use of assistive listening devices such as frequency modulated (FM) systems and hearing aids with remote microphones that can be configured to reduce the impact of background noise and reverberation (See preliminary studies). There also is some evidence that these patients can benefit from auditory perceptual training procedures (Murphy et al., 2011; See preliminary studies), but acceptance and compliance with these device and behavioral treatment approaches are low.

An untested treatment option is to amplify acoustic signals with mild-gain hearing aids in order to enhance the high-frequency portion of the speech spectrum. Providing high-frequency gain can increase contrast for the high-frequency speech cues that tend to be of lower intensity and more easily masked than mid- and low-frequency cues. For example, Hornsby and Ricketts (2006) reported that by increasing high-frequency information, people with normal hearing demonstrated improved speech perception. Furthermore, even participants with flat hearing losses demonstrated substantive improvement with high-frequency emphasis. They also benefited from extended high-frequency bandwidths (Hornsby et al., 2011). Woodall and Liu (2013) similarly found that enhancing vowel second formants improved vowel discrimination in persons with high-frequency hearing loss, although the investigators did not also enhance the third formant. In addition to adding contrast, increased high-frequency gain might increase the acoustic drive to the central auditory system and reduce demands on the cognitive system. For example, Heinrich and Schneider (2011) found that older adults benefited from added gain when performing an auditory memory word-association task with distorted words, in contrast to younger adults who failed to show the benefit. They argued from a resource-allocation perspective that the added gain reduced the demands on cognitive resources that were used by the older adults to process and remember the distorted signals. Pratt et al. (2007) observed a similar pattern with persons with aphasia secondary to left hemisphere stroke, where they required about +10 dB gain above that needed by non-brain-injured participants to perform an auditory language-processing task.

Another potential benefit of fitting mild-gain hearing aids on individuals with mTBI and auditory complaints is that it is a relatively passive process and more likely to be adopted than auditory training and other behavioral treatment measures because it takes less effort, and is less obtrusive and visible than personal FM systems. Furthermore, mild-gain hearing aids have the potential of stimulating auditory plasticity

and perceptual learning because they are more consistent with the natural perceptual learning process, which does not require feedback and reinforcement (Seitz & Dinse, 2007). Most perceptual learning occurs with simple exposure and without conscious effort, which is quite different from the learning processes used in most auditory training programs. So, although the use of mild-gain hearing aids will not result in substantive improvements in signal-to-noise ratio, as measured in the ear canal, the hearing aids might stimulate reorganization of the central auditory system such that there is improved filtering and segregation of signals from noise.

Although anecdotal, audiologists at the VHAPHS have been offering mild-gain open-fit hearing aids to blast-exposed veterans with normal audiometric results for the last 4 years out of frustration with the lack of practical treatment options. Patient feedback has been positive with only one patient returning his hearing aids due to tolerance problems.

3.0 Objectives

The purpose of the current proposal is to examine the characteristics and nature of this population's auditory and auditory-related skills, and assess whether coexisting PTSD contributes to their deficits. A group of these veterans will be grouped by whether they are symptomatic for PTSD, and will be compared to a control group of veterans without auditory complaints, and no PTSD or history of blast exposure. Comparisons also will be made to a group of veterans with no significant blast histories and with disabilities limited to PTSD.

After completing a clinical audiometric test battery, and PTSD, TBI, hearing handicap, and vision screens the veterans will complete measures of quality-of-life, central auditory processing, speech perception in noise, language processing and executive function to better understand various aspects of their ability to hear, remember, attend to and process speech and language through audition. The procedures will provide information about the loci of their auditory deficits and determine the extent to which language processing load and PTSD play a role. Secondarily, we will assess whether this population of veterans benefits from mild-gain open-fit hearing aids and if PTSD influences outcomes.

The information obtained from this study will help us understand the auditory problems experienced by these veterans, and eventually contribute to the development of an efficient and effective assessment battery and intervention approaches. This study is framed from both a behavioral and physiological perspective in order to document the problems experienced by this group of veterans. The tasks in the current proposal will provide insight into this population of veterans and lay the groundwork for future research looking at auditory-specific disorders secondary to blast-exposure and mTBI. The current study also will provide background support for a more extensive intervention study with this population.

Specific Questions to be Addressed

a. Across a range of central auditory processing, speech perception, psychoacoustic, verbal working memory, and language processing tasks, does this population of veterans differ from veterans who have normal hearing and no auditory complaints? Moreover, does the coexistence of PTSD influence performance?
b. Are certain test procedures and stimuli particularly sensitive to the deficits found with this population of veterans and are deficit patterns influenced by the coexistence of PTSD?
c. Does the addition of background noise produce over-additive effects in this population of veterans and does PTSD increase the effect?
d. Does this population of veterans perceive and demonstrate benefit when fitted with hearing aids that provide mild high-frequency gain and does PTSD influence benefit?
e. Is hearing aid benefit predictable by measures of auditory processing, speech perception, psychoacoustic, verbal working memory, and language processing? Furthermore, does the coexistence of PTSD influence the relationship between these measures and hearing aid benefit?

Expected Outcomes

a. This population of veterans will differ from veterans with no history of blast exposure, and the presence of PTSD will increase severity and alter the deficit pattern.
b. This population of veterans will experience significant problems with the addition of background noise and the effect will be influenced by linguistic load, verbal working memory and attention.
c. This population of veterans will demonstrate and perceive benefit from being fitted with mild-gain high-frequency hearing aids, although the coexistence of PTSD will restrict perceived benefit.
d. Mild-gain high-frequency amplification will improve speech perception skills in quiet and noise, and improve linguistic processing and executive function.
e. Benefit from amplification will relate to the deficits that the veterans present.

4.0 Resources and Personnel

This study will be conducted at the VA Pittsburgh Healthcare System (VAPHS), the Portland VA Medical Center (PVAMC), and through the VA Sioux Falls Healthcare System with data collected at the University of South Dakota. The personnel are listed below.

Sheila Pratt, Ph.D. (VAPHS) will assume overall responsibility for the conduct of the proposed investigation and will be involved in all aspects of the proposed studies including project oversight, human subject IRB compliance, personnel training and supervision, task and stimuli refinement, subject recruitment and retention, protocol administration, data analysis and data dissemination. In addition, she will meet regularly with the research staff and Co-Investigators to establish short-term goals, monitor

progress, and resolve any problems that arise with respect to project implementation, data collection or data management.

Malcolm McNeil, Ph.D. (VAPHS) will review unusual behavioral constellations, which is likely given the target populations. He also will play an important role during data interpretation and manuscript preparation.

Laurie Smith-Seemiller, Ph.D. (VAPHS) will provide clinical and technical expertise in the areas of TBI and PTSD. She also will facilitate the recruitment of participants.

David Jedlicka, Au.D. (VAPHS) is a fulltime Clinical Audiologist in the VAPHS Audiology Clinic and will assist with participant recruitment and testing, and clinical data analysis and interpretation.

Maureen Wargo, M.A. (VAPHS) is the Director of the VAPHS Audiology Clinic and will assist with participant recruitment and testing, and clinical data analysis and interpretation.

Gretchen Haas, Ph.D. (VAPHS) will serve as a consultant and provide content support in her areas of expertise and will assist with data interpretation.

Lindsey Jorgensen, Ph.D. (VASFHS and the University of North Dakota) will act as the lead investigator and co-ordinator for this project at the VASFHS and will be responsible for personnel training, protocol supervision, participant recruitment, protocol implementation, and IRB submission and compliance at the South Dakota site. She will help coordinate activities between the project and the South Dakota and Nebraska Audiology clinical services. She also will be responsible for coordination of data entry and data monitoring at the VASFHS/University of South Dakota site, and will be actively involved in the dissemination of the results and manuscript preparation.

Frederick Gallun, Ph.D. (PVAMC) will oversee the research and regulatory activities of the project at the PVAMC site, and work with Drs. Pratt and Jorgensen to maintain consistency across test sites. Dr. Gallun and collegues recently completed a treatment study with the target populations and his technical support and research background will be vital throughout the project, especially during data interpretation and manuscript preparation.

Bedda Rosario, Ph.D. (VAPHS, University of Pittsburgh) is a statistician at the University of Pittsburgh Epidemiology Data Center. She will be responsible for the statistical analysis of the data. She has a WOC appointment at the VAPHS.

Elizabeth Haley, Au.D., (VAPHS, University of Pittsburgh) will act as the study coordinator and work with the study PI to oversee subject recruitment, experiment fidelity, data collection, regulatory compliance. Elizabth has worked in Dr. Pratt's lab previously and has a contract appointment through the University of Pittsburgh.

The study personnel who will obtain informed consent include: Sheila Pratt, David Jedlicka, Lindsey Jorgensen, Frederick Gallun, Elizabeth Haley and the study staff designated at each local site.

The study personnel who will have access to identifiable data include: Sheila Pratt, Malcolm McNeil, David Jedlicka, Maureen Wargo, Laura Smith-Seemiller; Lindsey Jorgensen, Frederick Gallun, Elizabeth Haley and the study staff designated at each local site.

A Data Use Agreements was approved for this project for the data collected through the VASFHS because data collection will occur at the University of South Dakota due to limited facilities and equipment at the VASFHS facility.

5.0 Study Procedures

5.1 Study Design

This study will consist of two parts. Part 1 is diagnostic in nature, whereas Part 2 is a preliminary treatment study that will include a portion of the participants from Part 1.

Part 1 Procedures

The participants completing this study will be veterans between the ages of 20 and 50 years and divided into 4 groups: 2 groups of 117 veterans who report histories of blast exposure and blast-related clinical signs consistent with the VA/DoD definition of mTBI (VA/DoD, 2009) and present with normal or near normal results on standard audiometric testing but who report substantive problems with audition; a group of 117 normal hearing controls who report no auditory problems and no histories of blast exposure, brain injury, or psychiatric disorder (Normal Controls); and a group of 117 normal hearing veterans with PTSD and no blast exposure or blast-related clinical signs (PTSD-only). Of the two groups of veterans with auditory complaints one group will present with little or no PTSD (mTBI-only), whereas the other group will be symptomatic for PTSD (mTBI+PTSD). A total of 468 participants will complete the study and 50 additional participants will be allowed for experimental attrition.

In addition to the 468 veteran participants, 468 family members or friends (significant others) will complete a questionnaire about the veterans' hearing handicap.

After a telephone screen and preliminary testing, a battery of behavioral and physiological measures will be administered to all 4 groups of veterans to characterize the level and nature of their auditory impairments. Included are tests and procedures that likely will capture underlying or related problems and are commonly used in clinical and experimental studies of the peripheral auditory system, central auditory processing disorders, speech and language perception in noise, and executive function in persons with brain injury.

Interested veterans will first be screened by telephone. For those veterans who pass the screen, the testing (preliminary and experimental) will be conducted across multiple sessions at one of the study sites. The first session will include the preliminary measures such as standard audiometric tests, questionnaires, and a vision screen to ensure appropriate inclusion and exclusion of participants. The subsequent experimental sessions will include additional questionnaires and assessment procedures. It is estimated that the preliminary and experimental testing will require about 8 to 12 hours, with the total time dependent on patient characteristics (e.g., fatigue, response speed, need for breaks, task tolerance). It is anticipated that most participants will be able to complete all of the procedures in Part 1 within 4 to 5 sessions, but 4 additional sessions will be allowed if more time, shorter sessions, or frequent breaks are needed. Our clinical experience with the targeted populations is that 2 to 3 hour sessions are tolerated well and not burdensome. Gallun et al. (2011) used a similar battery and test burden was not mentioned as a factor in their publication.

Telephone Screen – After describing the study to prospective veteran participants, those who remain interested in participating will be asked a series of screening questions to ensure that they are within the targeted age range, can read and write well enough to complete the tasks, have no prior history of hearing aid use, have brain injury or disorder within the severity range targeted by the study, and whether they can be paid by direct deposit. Veterans passing the telephone screen and who wear corrective lenses will be asked to bring their glasses or contacts to the subsequent sessions so they will be able to complete forms, the Snellen screen, questionnaires, and other tasks involving visual processing.

Preliminary Tests – Preliminary assessment procedures will be administered to determine group placement and exclude participants who might have difficulty completing the study. The procedures include the following:

a. A case history that includes questions targeting hearing, tinnitus, blast exposure, concussion, brain injury, PTSD, headache, pain, communication problems, academic histories, employment status and other demographic data (Attached).
b. Brief Traumatic Brain Injury Screen (BTBIS; Schwab et al., 2006) to determine probable mTBI
c. PTSD Checklist-Military Version (PCL-M: National Center for PTSD-Behavioral Division; Weathers et al., 1994) to screen for PTSD
d. Hearing Handicap Inventory in Adults (HHIA, Newman et al., 1993) to document self-perceived hearing handicap. It will be administered at the beginning and end of Part 1 to document baseline handicap status prior implementing Part 2 of the study.
e. A standard audiometric hearing test battery that includes otoscopy, tympanometry, and an acoustic reflex screen at 1000 Hz, air- and bone-conduction pure-tone threshold testing (ASHA, 2005), and the Northwestern University Test # 6 (NU-6; Tillman & Carhart, 1966)
f. Loudness discomfort levels (LDLs) for tones at 500, 1000, 2000 and 4000 Hz according to procedures recommended by Sherlock and Formby (2005) to document hyperacousis
g. Snellen chart to screen vision

h. Motor-Free Visual Perception Test, version 4 (MVPT-4) to document that the subjects have the basic visual processing skills to perform tasks that include visual stimuli

Table 1. Group inclusion criteria based on preliminary test measures.

PRELIMINARY ASSESSMENT	**GROUPS**			
	mTBI-only	**mTBI+PTSD**	**PTSD-only**	**Normal Controls**
Blast Exposure History	Yes	Yes	No	No
Normal or Near Normal Standard Audiometric Test Results	Yes	Yes	Yes	Yes
History of Wearing Hearing Aids Consistently	No	No	No	No
BTSI	Evidence of Brain Injury	Evidence of Brain Injury	No Evidence of Brain Injury	No Evidence of Brain Injury
PCL-M	$\leq$20	>20	>20	$\leq$20
HHIE	>16	>16	Not considered	$\leq$ 16
LDLs	No Hyperacousis	No Hyperacousis	No Hyperacousis	No Hyperacousis
Snellen (corrected or uncorrected)	20/30	20/30	20/30	20/30
MVPT-4	>5th percentile	>5th percentile	>5th percentile	>5th percentile

Experiment Procedures

Part 1 Procedures

The experimental procedures are listed below according to type of assessment. Most are commonly used clinical procedures and will be completed in the standard manner.

Health and Quality of Life Questionnaires –

a. World Health Organization Disability Assessment Schedule II (WHODAS II) as a measure of general health status and quality of life (McArdle et al., 2005)
b. Satisfaction with Life Scale (SWLS) to document health-related quality of life
c. Brief Symptom Inventory-18 Item (BSI-18) to document self-perceived psychiatric and psychological status
d. The Speech, Spatial and Qualities of Hearing Scale (SSQ; Gatehouse & Noble, 2004) to assess self-perceived functional and situational auditory skills not covered by the other questionnaires. Like the HHIA, the SSQ will be presented at the beginning and end of Part 1 to establish the pretreatment baseline for Part 2.
e. The Tinnitus Functional Index (TFI; Meikle et al., 2012) will be administered because many patients with mTBI and PTSD complain of tinnitus and it can impact perceived handicap and quality of life (Fagelson, 2007), although it should be noted that in our chart review of the target population tinnitus was not a primary complaint with only 21.7% reporting any tinnitus.
f. The Hearing Handicap Inventory for Adults-Significant Other (HHIA-SO; Newman & Weinstein, 1988) will be completed by a significant family member or friend (if available) to capture auditory-related problems noticed by others but not by the participants. The veteran will give the questionnaire to a family member or friend to complete and mail to the study site. These data will be kept confidential from the veteran, and the family members or friends can refuse to participate by not completing or mailing the questionnaire.
g. HHIA will be repeated to document stability of handicap.
h. Information about general medical history, blast and head injury, neurological history; audiology assessment history and behavioral health diagnosis and treatment history also will be collected from the VA Computerized Patient Record System (CPRS) to confirm status.

Peripheral Auditory System –

a. Distortion product otoacoustic emission (DPOAE) to assess cochlear integrity
b. Fast Psychophysical Tuning Curves (FPTC) to determine filtering and spectral tuning properties of each ear. The fast tuning curves will be obtained for 2000 and 4000 Hz signals using the procedures and software developed by Sęk and Moore (2011).
c. Temporal Fine Structure 1 test (TFS1; Moore & Sęk, 2009) to assess the ability of the cochlea to process fine acoustic structures.

Central Auditory System –

a. Tonal and speech Masking Level Difference (MLD) tests according to procedures described by (Wilson et al, 2003; Wilson et al., 1994).
b. Competing Sentences subtest from the SCAN-3A to measure the ability to focus on a primary speech signal and ignore background speech
c. Two-digits section of the Dichotic Digits Test (DDT; Musiek, 1983) to assess dichotic auditory function

d. Staggered Spondaic Word Test (SSW) to measure timing and inter-hemispheric processing of words
e. Gaps in Noise Test (GIN) to assess temporal processing in noise
f. Auditory brainstem response (ABR), middle latency response (MLR), long-latency response (LLR) and active event-related P300 to assess the electrophysiological status of the central auditory system.

Speech and Language Processing in Noise –

a. The Words-in-Noise test (WIN; VA Compact Disk 4.0; Wilson & Burk, 2005) to target listening at the single word level
b. The Listening in Spatialized Noise - Sentences Test (LiSN-S; Cameron & Dillion, 2012) to assess sentence perception in noise within a simulated 3-dimensional acoustic space
c. Auditory and reading versions of subtests 1 through 10 from the Computerized Revised Token Test (CRTT and CRTT-R respectively; McNeil et al., 2009) will be administered in quiet and in +3 dB signal-to-babble to assess sentence level processing in both auditory and reading domains. The preliminary CRTT pretests will be administered prior to these tests to assure that the participants have the basic skills to complete the tasks and to measure baseline reaction time.

Executive Function –

a. Digit span forwards and backwards both acoustically and visually according to Kemtes and Allen (2008) to assess verbal short term and computational memory skills
b. The CRTT Stroop task (CRTT-R-Stroop; McNeil et al., 2010) to assess the interaction between language and executive function
c. Rey Auditory Verbal Learning Test (Schmidt, 1996) to assess immediate and delayed verbal memory, efficiency of learning and the effects of interference
d. Trail Making Test (Reitan, 1992) to measure attention and processing speed

PART 2 Procedures

Hearing Aid Fittings (treatment groups) – In Part 2 a subset of the participants from the mTBI-only and mTBI+PTSD groups from Part 1 will be fitted binaurally with open-fit hearing aids with mild high-frequency gain. Each group will consist of 25 participants. They will be randomly selected and randomly replaced if they decline to participate at any point during the treatment protocol.

Standardized fitting and verification procedures consistent with the American Academy of Audiology guidelines for audiologic management of adult patients will be used. The hearing aids will be obtained through the VA hearing aid procurement procedures because the participants qualify for hearing aids due to their auditory impairment. High-end behind-the-ear hearing aids (Phonak Bolero Q90) will be fitted binaurally. The hearing aids will provide mild gain with high-frequency emphasis, which will be verified acoustically with real ear measures. The noise suppression circuitry of the hearing aids will be activated but the frequency compression or shifting will be deactivated.

Additionally, to reduce the risk of sounds being too loud for the participants, Maximum Power Output will be set below the loudness discomfort levels of the participants.

Prior to their hearing aid fitting the participants in the two treatment groups will complete the unaided portion of the Abbreviated Profile of Hearing Aid Benefit (APHAB, Cox & Alexander, 1995), along with the HHIA, and SSQ as pretreatment measures of self-perceived hearing handicap, and situational hearing skills. To assess pre-fitting speech perception and language processing the California Consonant Test (CCT; Owens & Schubert, 1997) will be administered in the sound field at 65 dB HL in quiet and with multi-talker babble.

Recovery of co-articulation (phonetic context effect) will be measured with a vowel identification task. The vowels will be presented in the context of /d/ and /b/ sounds (Holte & Lotto, 2006). The extent to which the consonant context changes the perception of vowel categories will be measured.

As in Part 1 of the study, sentence level processing will be measured with the auditory and reading versions of subtests 1 through 10 from the Computerized Revised Token Test (CRTT and CRTT-R respectively) and will be administered in quiet and in babble to assess sentence level processing in both auditory and reading domains in optimal and adverse acoustic conditions.

Follow-up Testing – The participants will be followed over a 6-month period. One week (+/- 3 days) after the fitting the participants will be seen in the lab to re-verify the fit of their hearing aids and to determine any problems. The hearing aid use-time will be recorded from the data-logging system of the hearing aids as a reflection of hearing aid benefit and to document the extent to which the participants are wearing their hearing aids. During this session, both the aided and unaided portions of the APHAB will be administered along with the International Outcomes Inventory for Hearing Aids (IOI-HA; Cox & Alexander, 2002). In addition, the participants will answer a single question about their likelihood to continue hearing aid use. Intent to continue use tends to be related to user satisfaction with commercial products and service provision in other areas of healthcare. The participants also will complete the HHIA, and SSQ. The CCT, CRTT, CRTT-R and the phonetic context effect tasks will be re-administered with and without hearing aids.

Home Visits – The participants will be visited in their homes by study staff at three different times: 1-, 2- and 4-months post-fitting (+/- 1 week). The home visits will occur to reduce participant burden and encourage retention. However, some participants might prefer to be seen in the lab or clinic than their homes, and if that is the case those participants will be accommodated. Hearing aid use-time will be recorded from the data-logging system of the hearing aids and the hearing aids will be checked to determine appropriate function. During these visits the HHIA, SSQ, APHAB, IOI-HA, and the intent to continue use question will be re-administered. New hearing aid batteries will be provided and participants will be encouraged to wear their hearing aids for longer periods of time if their use-time is below 8 hours a day. At 6-months post-fitting (+/- 1 week) the laboratory follow-up testing will be repeated.

Delayed-Treatment Control Group – The participants in the delayed-treatment control group will be selected from the mTBI-only group and followed over a 12-month period (+/- 2 weeks). At the onset of Part 2 they will complete the HHIA, SSQ, and the unaided portion of the APHAB. They will complete the speech perception and language tasks administered to the treatment group (CCT, phonetic context effect, and CRTT tasks) but unaided only. The delayed-treatment groups will receive home visits at 1, 2, 4 months (+/- 1 week) post-entry, at which times they will complete the HHIA, SSQ, and the unaided portion of the APHAB. At 6 months post-entry their pure tone hearing thresholds will be measured to determine possible changes in hearing sensitivity, and the procedures used with the treatment groups will be applied with the same sequence of follow-up sessions.

5.2 Recruitment Methods

Part 1 Recruitment

The participants (other than significant others) completing this study will be veterans aged 20 to 50 years and divided into 4 groups: 2 groups of 117 veterans who report histories of blast exposure and blast-related clinical signs consistent with the VA/DoD definition of mTBI (VA/DoD, 2009) and present with normal or near normal results on standard audiometric testing but who report substantive problems with audition; a group of 117 normal hearing controls who report no auditory problems and no histories of blast exposure, brain injury or psychiatric disorder (Normal Controls); and a group of 117 normal hearing veterans with PTSD and no blast exposure or blast-related clinical signs (PTSD-only). Of the two groups of veterans with auditory complaints one group will present with little or no PTSD (mTBI-only), whereas the other group will be symptomatic for PTSD (mTBI+PTSD). A total of 468 participants will complete the study and 50 additional participants will be allowed for experimental attrition. It should be noted that the participants do not need to have a previous diagnosis of mTBI or PTSD, or even believe that they have mTBI or PTSD to participate in this study.

All these participants (including normal controls) will be recruited using the following procedures. They will be recruited through flyers distributed in various clinics (e.g., audiology, behavioral health, neuropsychology) at the three participating VA sites. In addition, participants will be recruited through research registries at the study sites and national VA and military research registries, such as the Corporate Data Warehouse through Data Access Request Tracker (DART) via the VA Data Portal/VINCI and the VA database for individuals who have initial positive TBI screens (https://vssc.med.va.gov/tbireports/TBI.aspx). The study will adhere to contact methods approved by the individual registries Flyers and list serve announcements will be provided to veteran organizations/offices at the university affiliates of the participating sites for distribution (flyer and announcement attached). Flyers and list serve announcements also will be provided to local veteran organizations for distribution. Clinical audiologists at the three sites will be informed of the study and if they so choose, can provide potential participants with flyers so that the potential participants can contact study personnel to learn more about the study. Research staff members

and investigators, when possible, will participate in public events for veterans (e.g., Research Week, VA athletic events and fairs, Veteran's information tables at local university information and health fairs) where flyers and information will be offered about the study. Potential veterans can provide contact information at the time of the events if interested in participating in the study, or they can contact the study personnel at a later time. At the onset of the study and during Years 3 and 4, a review of audiology records in CPRS may be conducted for each site to identify possible participants based on target age range and normal or near normal pure tone audiometric test results. These individuals will be sent a letter describing the study and inviting them to contact local study personnel if they are interested in participating in the study. Also included in the mailing will be a stamped return envelope and a form that the veterans can return indicating that they would like to be contacted via telephone to discuss the study or opt-out and not be contacted about the study. Veterans who fail to return the form within 2 weeks will be contacted by telephone by study staff members to determine if they received the mailing. After the letters have been mailed, all information obtained from CPRS will be maintained in accordance with the VHA Records Control Schedule. Social Security Numbers will be used for CPRS access for recruitment, and then later for study data collection and subject payment purposed.

The significant others completing the HHIA-SO will be a family member or friend selected by the veteran participating in the study. The significant other is not required to complete or mail the questionnaire, and the veteran will not be penalized or withdrawn from the study if the questionnaire is no returned or if they do not have a person available or willing to complete the questionnaire.

Part 2

A subset of the participants from the mTBI-only and mTBI+PTSD groups from Part 1 will be selected to participate in Part 2. They will be placed into four groups of 25. The groups will consist of an mTBI-only treatment group and an mTBI+PTSD treatment group, along with an mTBI-only delayed-treatment control group and an mTBI+PTSD delayed-treatment control group.

Using the order in which participants complete Part 2 as an identifier, the participants from the mTBI-only and mTBI+PTSD groups will be randomly assigned to receive either treatment or delayed treatment, and then ranked in random order for participation in Part 2. Each of the groups will be populated using this selection procedure. The assignments will be determined at the onset of the study by the PI with subsequent replacement as needed. Because Part 2 is preliminary in nature (not a randomized control trial) and includes low numbers of participants, any participants opting out of Part 2 will be replaced using the rank ordered list. Participants will be informed at the conclusion of Part 1 whether they can enroll in Part 2. If participants do not qualify, they will be informed that they could be contacted at a later date to act as a replacement. The study staff will be responsible for discussing enrollment in Part 2 with participants.

Payment

The veteran participants will be paid $50 per session (laboratory and home visits) for their participation, and a $25 travel allowance for each session requiring travel to one of the testing sites. They will be paid through the preferred method at each site (e.g., Financial Management System, vouchers, payment cards). When the Financial Management System is used the payment will not be immediate. The significant others who complete the HHIA-SO will not receive any payment.

5.3 Informed Consent Procedures

The veteran participants will complete a telephone screen to ensure that they meet basic criteria and to reduce burden for those veterans who would not qualify from the onset. The study will be described to them and if they remain interested in participation verbal permission will be requested to ask the screening questions (See script and flow chart for telephone screen.)

Written and verbal informed consent will be obtained from the veteran participants before implementation of the remaining study procedures. Two consent forms; one for each part of the study and will be completed. The consent form for Part 1 will be completed by all participants and the consent form for Part 2 will only be signed by participants who complete Part 1 and are selected to complete Part 2. Informed consent will be obtained from the participants in person in a private room by the investigators or study staff approved to obtain informed consent. Human subjects protection requirements and how to obtain and document informed consent will be reviewed during the initial training of study personnel to insure procedural uniformity across sites. The training will occur at the beginning of the study and as new personnel are added to the study by the lead investigators at each site.

Written and verbal informed consent will not be obtained from the significant others who complete the HHIA-SO. The instructions will indicate that completion and mailing of the questionnaire will be voluntary and that all information on the questionnaire will be kept confidential and not accessible to the veteran. No identifying information will be requested or included on the questionnaire except for the subject ID number assigned to the veteran participant.

5.4 Inclusion/Exclusion Criteria

The inclusion and exclusion criteria for the veteran participants will be based on the telephone screen and preliminary assessment procedures specified previously. These procedures will be used to form the 4 participant groups and to insure that the participants can complete the tasks (See Table 1 above). All of the participants will be aged 20 to 50 years, have normal or near normal audiometric test results, corrected or uncorrected vision of 20/30 or better, and no evidence of hyperacousis. The mTBI-only group will have a history of blast exposure, evidence of possible brain injury, no significant symptoms consistent with PTSD, but elevated hearing handicap scores on

the Hearing Handicap Inventory for Adults (HHIA). The mTBI+PTSD group will have a history of blast exposure, evidence of possible brain injury, significant symptoms consistent with PTSD, and elevated hearing handicap scores on the HHIA. The PTSD-only group will have no history of blast exposure or brain injury but they will have significant symptoms consistent with PTSD. The Normal control group will have no history of blast exposure or brain injury, and little or no symptoms of PTSD (or other psychiatric disorder) or hearing handicap. All of the veteran participant must not have a history of hearing aid use, or brain injury or disease more severe than that targeted by the study. In addition, the veteran participants must be able to be paid for their participation.

5.5 Study Evaluations

All of the evaluations to be conducted are listed above under study procedures (5.1). The data will be collected by the investigators and study staff. The types of assessment methods vary and include questionnaires, review of records, behavioral tests, and physiological procedures. Some data will be acquired via computer, while others will be administered face to face and via paper-and-pencil.

5.6 Data Analysis

Part 1 Analysis

Preliminary Analyses - The analysis will begin with basic descriptive statistics including means and standard deviations for continuous data and examination of distributional assumptions for all study measurements including the questionnaire data (e.g., HHIA, WHODAS-II, SSQ and HHIA-SO) for each group of interest. These analyses will be used to evaluate the extent of missing data and to identify outliers.

Primary Analyses - Random Forests (RF, Breiman, 2001) will be applied to determine which auditory, language processing, and executive function variables best discriminate the three groups. This technique performs variable selection and the variables are ranked by Gini score, a measurement of average accuracy of all trees containing a particular variable. One-way ANOVA will be used to determine differences between groups for normally distributed continuous data. Analysis of covariance (ANCOVA) will be used to adjust for differences between groups. If assumptions for the parametric test are not met, a non-parametric alternative will be used (e.g., Kruskal-Wallis, non-parametric ANCOVA). The p-values will be adjusted for multiple testing by using a false discovery rate method whenever more than one variable is being tested. Statistical assumptions (e.g., linearity, normality) will be verified prior to hypothesis testing. All statistical analyses will be two sided and the significance level will be 0.05.

Sample Size and Power - A sample size of 117 per veteran group will achieve 80% power at a 0.05 significant level to detect an effect size (i.e., odds ratio) of 2.50. This sample size was computed based on an adjustment that was made assuming that a multiple regression of the independent variable of interest on the other independent

variables in the model will result in an R-squared of 0.20. For one-way ANOVA, the total sample of 468 subjects achieves 80% power to detect an effect size of 0.18 or larger with a two-sided significance of 0.01 to account for multiple hypotheses testing. For analysis of covariance, the study is powered (0.80) to detect an effect size of 0.16 assuming the strength of the relationship between the response of interest and the covariates, measured as R-squared, is 0.20.

Part 2 Analysis

Primary Analyses – Basic descriptive statistics will be computed and examination of statistical assumptions will be performed for all study measurements. For questionnaire data, analysis of variance (ANOVA) or Kruskal Wallis test will be used to determine differences in the overall and subset scores between the mTBI groups. The analysis will also include basic descriptive statistics for behavioral data test measures at baseline and at 6 months for the mTBI-only and mTBI+PTSD groups, and at baseline and 12 months for the delayed-treatment groups. We will focus on the changes in the behavioral test measures from baseline to 6 months (mTBI-only and mTBI+PTSD treatment groups) and from baseline to 12 months (delayed-treatment groups). Specifically, paired t-test or Wilcoxon signed rank test will be used to determine change at 6 or 12 months and this test will be applied to each behavioral test measure separately. False discovery rate will be used to adjust the p-values for multiple hypotheses testing. All statistical analyses will be two sided and the significance level will be 0.05.

Secondary Analyses – For longitudinal analysis, the data will be modeled using linear-mixed models for which the outcome is the behavioral test measure across time. The predictors will include time, group and interaction between group and time. Covariates will be added to the model as needed. In addition, variables with a high Gini score from Part 1 will be correlated with final hearing aid results as a preliminary investigation of whether hearing aid benefit can be associated by any of the variables obtained above. We will measure correlations using either Pearson's or Spearman's correlation coefficient. We will adjust the p-values for multiple testing by using a false discovery rate method whenever more than one variable is being tested. Single-subject design metric also will be used to investigate individual responses to the hearing aid treatment.

Sample Size and Power – This analysis will include data from 100 participants (25 for each group). For any comparisons of the four groups based on ANOVA with a significance level of 0.01 to account for multiple comparisons and a power of 0.80, an effect size of 0.38 or greater will be detectable. For the paired analyses described above, there is sufficient power (0.80) to detect an effect size of 0.50 (baseline versus 6 months) or 0.50 (baseline versus 12 months), or greater assuming a two-sided significance level of 0.01 to account for multiple comparisons. For the longitudinal modeling, there will be sufficient sample size to support the proposed modeling that will allow approximately 10 observations to be estimated for each parameter. The number of covariates in each model will depend on the sample size to insure that there are approximately 10 observations available for each parameter estimated. For correlation

based analyses, the study is powered (0.80) to detect correlations of 0.26 or greater in absolute value for a total sample size of 100.

Once the data are formatted and cleaned by a staff member at the VA Pittsburgh site under the supervision of the statistician, the data will be analyzed by the statistician.

5.7 Withdrawal of Subjects

Participants can be withdrawn from the study by the investigators and study staff if they do not meet all of the inclusion criteria, have more than 4 no-show appointments without excuse, demonstrate non-compliance on study tasks, exhibit excessive frustration and emotional reactions to study procedures that do not subside with re-instruction, discussions about the purpose of the tasks, breaks or rescheduling.

Participants can withdraw at any time without penalty. They can inform an investigator or study staff in person, by telephone or in writing. Participants withdrawn from the study will be informed in person or by telephone by an investigator or study staff. All participants who withdraw or are withdrawn from the study will be supplied with form 10-1016 - Revocations for use and release of IIHI for VHA Research.

All of the participants with hearing impairment will be referred to their local VA for audiological services and follow-up. Participants with PTSD will be referred to their local VA for behavioral health services if they are not receiving services currently.

6.0 Reporting

The occurrence of Serious Adverse Events, Unanticipated Problems and Protocol Deviations will be reported to the local lead investigator via telephone, encrypted VA email, or in person with documentation submitted to the project PI though encrypted VA email or in person. A report will be developed by the local lead investigator and submitted to the VA Central IRB through its secure SharePoint site, and as required to the local site R&D Committee.

7.0 Privacy and Confidentiality

Protected Health Information will be collected during the course of this study but not disclosed outside of approved study investigators and staff. The following include the steps that will be taken to ensure participant privacy and confidentiality.

- All paper records with identifiable information will be retained at each site in a locked cabinet within a secure laboratory space.
- All coded paper records with will be retained at each site in a locked cabinet in a secure laboratory space and kept separate from all identifiable information.
- The study PI and each site will retain linkage code documentation that is kept secure and separate from data and other identifiable information.
- Only information related to the study will be requested and obtained.

- Only investigators and study staff will have access to identifiable participant information and data.
- The laboratory desktop computers with custom and non-VA software used for data acquisition will be password protected and disconnected from the internet and VA intranet. Laboratory desktop computers connected to the VA intranet will be used for administration of questionnaires and data entry into REDCap. We will use the VA-approved version of REDCap within the VA Informatics and Computing Infrastructure system (VINCI). The VINCI system also will be used for data storage and analysis. Laboratory laptops will be encrypted per VA guidelines, password protested and blocked from internet use.
- Coded raw data residing on the laboratory computers will be copied onto storage drives for backup at each site. These drives will be in physically locked and secured laboratory spaces. They will be encrypted to FIPS 140-2 standards and approved by the site ISOs prior to purchase and use. It should be noted that the PI currently uses this type of backup system in her laboratory.
- Some data will be transferred to the drive allocated to the study PI on the VAPHS research server (currently is the "L:\Hearing_Lab). . However, most of the raw data acquired from this study will be acquired and stored in the VA-approved version of REDCap with the VINCI system or directly inputted into VINCI for storage. These data will be coded with access limited to study investigators and staff.
- No identifiable data will be included in presentations and publications.
- Interviews and private study related conversations will be conducted in private rooms.
- After participants have provided informed consent to participate in the study, contact relating to scheduling, session reminders, and participant questions about non-sensitive information will be allowed by e-mail and telephone text if preferred by the individual participants. No sensitive information will be transmitted my e-mail or text.

8.0 Communication Plan

The PI and lead investigators will have conference calls at least twice per month to maintain coordination of the study activities and to address any issues. Once a year, the PI will meet face-to-face with Drs. Jorgensen and Gallun and their respective study teams to check procedural fidelity and data integrity. Additional meetings will be scheduled as needed.

Data monitoring will occur monthly by the lead investigator at each sites with monthly reports submitted to the PI for review and signature. The participant safety and data accrual, security, and fidelity will be reviewed by site and in aggregate. In addition, all three teams will complete yearly internal audits to confirm the fidelity of their procedures and documentation, and to insure appropriate data quality and security. The results of these audits also will be reviewed by the PI with corrective actions taken and reported as needed. The data accrual is expected to be 50% at the Pittsburgh site, 25% at the PVAMC site and 25% at the VASFHS/University of South Dakota site. If more than 5%

of participants per year per site have protocol deviations, the study personnel at that site will receive re-training. The lead investigators at each site will receive copies of the documents approved by the Central IRB for the study, and the documents required for submission at the local site.

To ensure that all regulatory and IRB requirements have been met at each site prior to implementing the study procedures, the lead investigators at each site will submit a copy of the local IRB application, consent forms, HIPAA documents and approval letters to the PI.

Copies of all Central and local IRB documents will be retained in regulatory binders by the PI and the lead investigators at each site will retain copies of the Central IRB documents transmitted to them, as well as their local IRB documents.

Serious Adverse Events and Unanticipated Problems will be reported to the lead investigator at each site who will contact the PI. Documentation will be submitted to the Central IRB by the lead investigator with copies submitted to the PI. Copies of the reports will be retained by the PI and the lead investigator at their site. The PI also will submit interim results that may impact conduct of the study.

All sites will continue to collect data until the full complement of participants has completed the study or until the study has been concluded.

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