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Vestibular, balance, microvascular and white matter neuroimaging characteristics of blast injuries and mild traumatic brain injury: Four case reports

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Abstract

Background: Case reports are presented on four Veterans, aged 29–46 years, who complained of chronic dizziness and/or postural instability following blast exposures. Two of the four individuals were diagnosed with mild traumatic brain injury and three of the four were exposed to multiple blasts. Comprehensive vestibular, balance, gait, audiometry and neuroimaging procedures were used to characterize their injuries.

Case report: Vestibular assessment included videonystagmography, rotary chair and cervical and ocular vestibular evoked myogenic potentials. Balance and gait testing included the sensory organization test, preferred gait speed and the dynamic gait index. Audiometric studies included pure tone audiometry and middle-ear measurements. Neuroimaging procedures included high resolution structural magnetic resonance imaging, susceptibility-weighted imaging and diffusion-tensor imaging.

Findings: Based on the neuroimaging and vestibular and balance test results, it was found that all individuals had diffuse axonal injuries and had one or more micro-hemorrhages or vascular anomalies. Three of the four individuals had abnormal vestibular function, all had abnormally slow walking speeds and two had abnormal gait and balance dysfunction.

Conclusion: The use of contemporary neuroimaging studies in conjunction with comprehensive vestibular and balance assessment provided a better understanding of the pathophysiology and pathoanatomy of dizziness following blast exposures than standard vestibular and balance testing alone.

Introduction

In the recent wars in Iraq and Afghanistan, many soldiers have been exposed to blasts from improvised explosive devices (IEDs), roadside bombs, rocket-propelled grenades or other explosives that have resulted in mild traumatic brain injury (mTBI). The negative effects of these blast exposures have been called the ‘signature injury’ of combat Veterans in these wars. Dizziness and postural instability are often associated with mTBI [1-3] and the associated symptoms may last for 6 months or even longer [4,5]. The causes of dizziness or imbalance following mTBI have been linked to white matter (WM) abnormalities, diffuse axonal injury (DAI) in the brain [6,7] or peripheral vestibular system damage [8].

In many individuals with blast-related mTBI, the cause(s) of their dizziness is unclear as studies have limited their evaluation to symptom-based questionnaires or restricted the actual assessment to only a limited portion of the vestibular and balance systems [2,9]. Until recently, the inner ear vestibular and balance assessment was restricted to measuring horizontal semicircular canal function and its connections to the eyes (known as the vestibulo-ocular reflex; VOR). Contemporary studies have shown that the otolith organs, rather than the horizontal semicircular canals, may be more vulnerable to damage from blast exposure or head injury [10]. Conventional vestibular and balance assessment often excludes tests of otoloth organ function (e.g. vestibular evoked myogenic potentials; VEMPs) [11].

Furthermore, the physics of blast over- and under-pressures, blunt trauma and forces associated with these events are complex and multi-dimensional [12]. Therefore, advanced magnetic resonance imaging (MRI) procedures like high resolution structural MRI, diffusion-tensor imaging (DTI) and susceptibility-weighted imaging (SWI) are capable of generating biomarkers.
of regional brain injury to correlate with clinical signs and symptoms [6,13,14] and to help elucidate the underlying basis of blast and mTBI injuries. This includes small vessel vascular manifestations of dysfunction (micro-hemorrhages/micro-bleeds) and their effects on grey and WM microstructure.

This article describes four case reports on blast and concussion-exposed individuals using a comprehensive assessment approach which examines the cause(s) of dizziness and imbalance.

**Methods**

This study was approved by the Institutional Review Board (IRB) of the James A. Quillen VA Medical Center. All participants completed a written informed consent form prior to participation in the study and were given nominal payment for their time. Each individual underwent comprehensive vestibular/balance assessment and contemporary neuroimaging studies at the Vestibular and Balance Research Lab and the MRI facility at the James A. Quillen VA Medical Center. Comprehensive vestibular/balance assessment included vestibular site-of-lesion tests, balance and gait assessment and audiological assessment. Neuroimaging studies included high-resolution MRI, DTI and SWI.

**Vestibular/balance assessment**

Vestibular site-of-lesion tests included videonystagmography (VNG), rotary chair and cervical and ocular vestibular evoked myogenic potentials (cVEMPs and oVEMPs). VNG and rotary chair were used to assess the horizontal semicircular canals/superior vestibular nerve (hSCC/SVN) via vestibulo-ocular reflex (VOR) and ocular-motor function. cVEMPs and oVEMPs were used to assess otolith organ function (i.e. gravitational receptor organs within the inner ear). The Dix-Hallpike and roll tests were used to identify the presence of benign paroxysmal positional vertigo (BPPV). Balance and gait assessment included computerized dynamic posturography and the dynamic gait index (DGI). The Dizziness Handicap Inventory (DHI) was used as a measure of self-perceived balance handicap. Audiological assessment was performed to determine pure tone hearing sensitivity, middle-ear function and assessment of ipsilateral and contralateral acoustic reflex pathways. Pre-test instructions for individuals undergoing assessment included refraining from the use of alcohol, recreational drugs, over-the-counter antihistamines, ‘anti-dizziness’ medications and sleeping pills.

**Vestibular site-of-lesion tests**

Videonystagmography was performed using a computer-based system (ICS Chartr) to record, digitize and analyse eye movement data; and a water irrigator (ICS NCI-440) to deliver the caloric stimulus. Caloric irrigations consisted of 250 ml of water for 30 seconds at temperatures of 44°C and/or 30°C, with the participant in a supine position and the head elevated 30°. Following cessation of the caloric irrigations, each participant engaged in mental alerting tasks to avoid response suppression of the induced nystagmus. The peak of the response was calculated as the average slow component eye velocity (SCEV) of the three strongest beats of nystagmus. Normal responses were defined as either an inter-ear difference of ≤ 10% for the monothermal warm caloric test [15] or a unilateral weakness of ≤ 25% for the alternating binaural bithermal caloric test [16]. A unilateral weakness > 25% or a bilateral caloric weakness (total warm SCEV < 11° s⁻¹ and total cool SCEV 6° s⁻¹) was interpreted as hSCC/SVN dysfunction.

The rotary chair test (System 2000; Micromedical Technologies, Chatham, IL) was used to stimulate the hSCCs/SVN using slow harmonic acceleration over a frequency range that included 0.01, 0.04, 0.16 and 0.64 Hz. Participants were seated in a chair mounted in a light-proof booth with the head upright so that rotation occurred in the plane of both hSCCs and mentally alerted to prevent suppression of the VOR response. Phase, gain and asymmetry were calculated for the SCEV response at each frequency. SCEV responses were defined as normal if values were within ±2 standard deviations (SDs) of the laboratory normative values for phase, gain and asymmetry. Rotary chair results were considered abnormal when phase, gain or asymmetry was abnormal at two or more adjacent frequencies [17].

Ocular motor and vestibular suppression tests were performed as part of the VNG and rotary chair test battery to identify central nervous system (CNS) involvement. Ocular motor tests included: (1) testing for pathologic nystagmus with changes in fixation and gaze position, (2) random saccades, (3) smooth pursuit of a visual target moving sinusoidally at several frequencies and (4) optokinetic nystagmus performed in full-field.

cVEMPs were performed as a measure of saccular/inferior vestibular nerve (IVN) function [18]. Participants were seated upright and instructed to turn their head laterally to maximally contract the sternocleidomastoid (SCM) muscle. A two-channel recording of the cVEMP was obtained using the ICS Chartr® EP200 (version 6.2.1). Non-inverting electrodes were placed at the midpoints of the SCM muscles, inverting electrode at the sternoclavicular junctions and the ground electrode was placed on the forehead. Air conduction cVEMPs were obtained using 500-Hz tone-burst stimuli presented monaurally via insert earphones (Etymotic ER3A) at 90 dB nHL. The magnitude of the tonic EMG level was recorded from the non-inverting electrode and obtained simultaneously in a third channel during the cVEMP recording. The cVEMP amplitude was normalized for EMG level. Bone conduction cVEMPs were obtained in participants with absent AC cVEMPs and with evidence of middle-ear pathology. The criterion for abnormal cVEMP was defined as an absent cVEMP and/or a corrected cVEMP amplitude asymmetry ratio ≥ 40%; this finding suggests a unilateral vestibular (saccular/IVN) loss [19]. A bilateral vestibular loss was indicated by absent cVEMPs bilaterally.

oVEMPs were used as a measure of utricular and superior vestibular nerve (SVN) function [20]. Participants were seated in a reclining chair with their gaze fixed on a stationary target located straight ahead at a vertical gaze angle of 30° and at a distance of 1 metre. The stimulus was a 500-Hz Blackman windowed tone-burst presented at a repetition rate of 5 Hz and at a level of 155 dB peak Force Level (re: 1 µNewton). The stimulus level was measured using an artificial mastoid (Bruel & Kjær, model 4930; Atlanta, GA) and a sound-level meter (Bruel & Kjær, model 2250). Stimuli were
generated by a commercial evoked potential instrument (ICS Chartr® EP200; version 6.2.1), amplified (Bruel & Kjaer power amplifier, model 2810; drive voltage of 5 V peak-to-peak), and delivered by a hand-held vibrator (Bruel & Kjaer Mini-Shaker, model 4810) fitted with a custom acrylic rod that measured 9.2 cm in length and 2.5 cm in diameter. The Mini-Shaker was hand-held by the examiner such that the axis of the acrylic rod was approximately perpendicular to the subject’s skull at a standard EEG electrode location (Fz). Prior to stimulation, the Fz location was marked on each subject’s head according to the 10–20 electrode system of the International Federation [21]. The weight of the Mini-Shaker (1 kg) was used in an attempt to standardize the force of the shaker against the skull as no additional force was applied to Fz by the examiner. The criterion for abnormal function was defined as an absent oVEMP and/or an oVEMP amplitude asymmetry ratio ≥ 40%; this finding suggests a unilateral vestibular (utriclear/SVN) loss [22]. A bilateral vestibular loss was indicated by absent oVEMPs, bilaterally.

Balance and gait assessment

The Sensory Organization Test (SOT), as part of computerized dynamic posturography testing, was used to assess the integration of sensory information for balance by measuring postural sway under conditions in which visual and somatosensory feedback is altered [23]. The SOT is organized into a series of six conditions of increasing difficulty/complexity. The first three conditions were performed on a firm surface with eyes open (Condition 1), eyes closed (Condition 2) and finally with vision sway-referenced (Condition 3). The final three conditions were performed with the support surface sway-referenced with eyes open (Condition 4), eyes closed (Condition 5) and with vision sway-referenced (Condition 6). Sway-referencing refers to either the visual surround or the support surface moving in the same direction and amplitude as the person’s sway. Sway-referencing provided inaccurate visual or somatosensory input. Results of the SOT were calculated based on maximum peak-to-peak anterior-posterior sway and expressed as an equilibrium score ranging from 0–100, with 0 indicating loss of balance (i.e. required support of harness, took a step, touched walls for support or opened eyes in eyes closed conditions) and 100 indicating perfect stability. The outcome measure was the equilibrium composite score and was calculated by the software as the weighted average of the equilibrium scores for the six conditions. For ages 18–59 years, the cutoff for the composite score is 70 based on the manufacturer’s normative data (NeuroCom®, a Division of Natus®, Pleasanton, CA)

Gait speed was assessed by having participants walk at their preferred gait speed over a level indoor surface without an assistive device. The time to walk 6 metres (m) was recorded using a stopwatch [24]. The participant began the trial 1.5 m behind the start point for the 6-m distance and continued walking for 1.5 m past the end of the 6-m distance. Timing began when the first foot crossed the start point and ended when both feet crossed the end point. Participants were instructed first to walk at their ‘normal preferred pace’. Participants wore a safety belt and were accompanied by either a physical therapist or trained research assistant to ensure safety. Three trials were performed and average speed was calculated. Normal walking speed (95% Confidence Interval) is 1.22–1.47 m s⁻¹ for 20-year old males and 1.27–1.47 m s⁻¹ for 40-year old males [24].

The ability to adapt gait in the presence of external demands was assessed using the Dynamic Gait Index (DGI). The eight items of the DGI include walking while changing speed and turning the head, walking over and around obstacles and stair climbing [25]. Scoring of the DGI items was based on a 4-point scale from 0–3; with 0 indicating severe impairment and three indicating normal ability. The maximum total score was 24, and < 20 was considered abnormal indicating high risk for falling [25,26].

The Dizziness Handicap Inventory (DHI) is a 25-item self-report questionnaire that quantifies the emotional, functional and physical impact of dizziness on daily life by measuring perceived handicap [27]. The DHI score ranges from 0–100, with 0–30 indicating mild handicap, 31–60 indicating moderate handicap and 61–100 indicating severe handicap [28].

Audiological assessment

The audiological assessment included pure tone air and bone conduction audiometry. Audiometric testing was conducted in a commercial test booth (Model A-3712; Industrial Acoustics Company, Bronx, NY) using a clinical audiometer (Model 61; Grason-Stadler, Eden Prairie, MN) and insert earphones (ER3A, Etymotic Research, Inc.; Elk Grove Village, IL). Pure-tone air-conduction audiometry was performed at octave frequencies from 0.25–8 kHz bilaterally. Bone conduction testing used a standard oscillator (B-71; RadioEar Corporation, New Eagle, PA) and headband with the oscillator placed on the mastoid; bone-conduction thresholds were assessed at octave frequencies from 0.25–4 kHz. Normal hearing was defined as pure-tone thresholds ≤ 20 dB HL [29] at octave frequencies from 0.25–8 kHz. Tympanometry was performed using a 226-Hz probe tone signal at 85 dB SPL (GSI-33 Middle Ear Analyzer; Grason-Stadler, Eden Prairie, MN). Acoustic reflex thresholds were obtained using ipsilateral and contralateral stimulation of each ear at 0.5, 1, and 2 kHz at levels ranging from 70–105 dB HL.

Neuroimaging studies

Magnetic resonance imaging data were collected on a Philips 1.5 Tesla (T) scanner. Data were stored digitally and subsequently sent to researchers at Wayne State University for quantification and detailed analysis. Conventional MRI consisting of T2- and T1-weighted images were collected in the axial, coronal and sagittal planes to identify any structural damage to the CNS. Diffusion tensor imaging and SWI were obtained in addition to conventional MRI tests.

The DTI acquisition included a spin echo-planar diffusion weighted sequence in 30 non-collinear directions with a TR of 8500 milliseconds (ms), TE of 85 ms, field-of-view of 256 × 256, image matrix size of 128 × 128 yielding an in-plane resolution of 2 millimetres (mm) × 2 mm and slice thickness of 3 mm with 45 contiguous slices and two b-values of 0 and 1000 s mm⁻².
The SWI acquisition included a 3-dimensional, T$_2^*$-based velocity compensated gradient-echo sequence with a field of view of 256 × 256, image matrix size of 512 × 512 yielding an in-plane resolution of 0.5 mm × 0.5 mm and slice thickness of 4 mm of contiguous 72 slices with TR of 80 ms and TE of 40 ms.

**DTI processing**

Pre-processing of the DTI scans was carried out by using DTI studio software developed at the John's Hopkins University School of Medicine [30]. The pre-processing steps included motion correction and eddy current correction using automatic image registration (AIR) of all the diffusion weighted images using the B0 image (no diffusion weighting) as the reference image followed by the creation of Eigenvalue maps including axial diffusivity maps (AD), radial diffusivity maps (RD), fractional anisotropy (FA) maps and apparent diffusion coefficient (ADC) maps. Background noise in the FA map was masked out using a noise threshold of 30 units on the B0 image. Skull stripping of the B0 image is done using the brain extraction tool (BET) routine in Micro [31] using a fractional intensity value of 0.1. A binary mask of the skull stripped B0 image is used on all of the generated DTI maps to eliminate non-brain matter such as bone and sinuses.

**Global white matter FA analysis**

Skull stripped FA images are spatially normalized in Statistical Parametric Mapping, (SPM, version 8) to an in-house built FA template creating linearly normalized FA maps [32]. Segmentation of these normalized FA images resulted in individual WM probability maps for each participant. For creating individual binary masks, a threshold of 0.55 is applied to these WM segmented probabilistic maps. As a result, all of the voxels that are below the applied threshold of 0.55 on these probabilistic maps are considered non-white matter and are set to zero. These binary masks are used on the normalized FA maps to extract global WM FA values and to create global WM histograms for all the participants.

**Regional FA analysis**

Regional WM FA analysis was performed on the spatially normalized FA maps in a semi-automated fashion using probabilistic maps derived from the International Consortium of Brain Mapping (ICBM-DTI-81). The skull stripped FA image is non-linearly normalized to the standard (Oxford Center Functional MRI of the Brain, FMRI B) FA template for all controls and normal subjects (10 controls, two blast-exposed and two mTBI and blast-exposed subjects) in SPM8. White matter regions-of-interest (ROI) consisted of six commissural regions and 21 regions that are divided bilaterally into right and left hemispheres. Commisural regions included middle-cerebellar peduncle, pontine-crossing tract, genu, body and splenium of the corpus callosum and fornix. Bilateral regions are listed starting from the cortical spinal tract in Table 1. Mean FA values are extracted for each of these ROIs for all the controls and blast subjects. The mean FA values of the individual regions of the mTBI/blast subjects were converted to z-scores using mean FA and standard deviation values of FA of individual regions in normal subjects. Negative z-scores indicate decreased FA and positive z-scores indicate increased FA value compared to the control group for that region.

**Tract-based spatial statistics (TBSS)**

Tract-based spatial statistics were used to compare the control group and individual blast subjects in order to evaluate the WM changes caused by either TBI or blast-induced TBI. All the processing steps were performed as explained in the TBSS manual [33]. Each participant’s FA image was spatially normalized using the functional magnetic imaging of the brain (FMRI B) non-linear image registration tool (FNIRT); a non-linear registration algorithm to a standard FA FMRIB template and transformed into a standard space using a functional software library (FSL) of the software package [34]. Subsequently, a mean FA image is created from these sets of non-linearly transformed images. A search algorithm then creates a mean skeleton, looking for the local maxima perpendicular to the WM track across the whole brain volume in all the transformed images and then projects this skeleton across all the participants in the group; thus, extracting individual skeletons. Then, a voxel-wise permutation-inference analysis is carried out between the skeletons of two groups. A two tailed t-test was performed to extract the voxels that fall above or below a certain threshold. These voxels are converted to a p-value based on the threshold set by the t-statistic and the cluster size. A skeleton threshold of 0.2 was used to eliminate grey matter (GM) voxels or partial volume effects and a voxel-wise permutation-inference analysis was carried out between the skeletons of control subjects and individual cases. During this analysis, the voxels in an individual

| Table I. List showing the white matter regions used for the regional analysis. |
|---------------------|---------------------|
| MCP | Middle cerebellar peduncle |
| PCT | Pontine crossing tract (a part of MCP) |
| GCC | Genu of corpus callosum |
| BCC | Body of corpus callosum |
| SCC | Splenium of corpus callosum |
| FX | Fornix (column and body of fornix) |
| CST | Corticospinal tract |
| ML | Medial lemniscus |
| ICP | Inferior cerebellar peduncle |
| SCP | Superior cerebellar peduncle |
| CP | Cerebral peduncle |
| ALIC | Anterior limb of internal capsule |
| PLIC | Posterior limb of internal capsule |
| RLIC | Retrolenticular part of internal capsule |
| ACR | Anterior corona radiata |
| SCR | Superior corona radiata |
| PCR | Posterior corona radiata |
| PTR | Posterior thalamic radiation |
| SS | Sagittal stratum |
| EC | External capsule |
| CGC | Cingulum (cingulate gyrus) |
| CGH | Cingulum (hippocampus) |
| FX/ST | Fornix (cres)/Stria terminalis |
| SLF | Superior longitudinal fasciculus |
| SFO | Superior fronto-occipital fasciculus |
| IFO | Inferior fronto-occipital fasciculus |
| UNC | Uncinate fasciculus |
subject’s FA image is considered significantly different based on a two-tailed t-test with a threshold of \( t = 2 \) and a cluster forming threshold of 20 voxels or more.

**Z-score analysis**

A voxel-based analysis (VBA) using a z-score map is created for each individual blast subject by taking the difference between the individual FA map and mean FA map created from the control group weighted by the standard deviation map created from the control group.

**Masking out non-WM voxels in regional and TBSS/VBA analysis**

These voxels are further filtered to eliminate the GM voxels and the non-WM voxels accounting for the partial-volume effects arising from CSF and GM voxels. This filtering is done by segmenting each non-linearly normalized FA map and the mean FA map from the controls into WM, GM and cerebrospinal fluid (CSF) in SPM8. A threshold mask is created between each subject’s WM image and control group mean WM FA image; thus, creating a compound mask by applying a threshold \( (p > 0.78) \) on these two segmented WM FA probabilistic images. In this way, this study able to remove false positives arising at the edges because of the mis-registration. Spurious voxels that do not form a cluster size less than 20 are discarded as random noise in TBSS and z-score analysis. To strengthen the results from the analysis, t-stat maps from the TBSS analysis showing decreased FA and z-score maps of individual blast subjects are averaged together so that the common findings between the two analyses will be preserved and all other voxels highlighted in these two methods will be discarded when they fall below the threshold of 2 SDs.

**Susceptibility-weighted imaging**

All SWI were processed by using software developed by Magnetic Resonance Innovations, Inc. (Detroit, MI), also known as Signal Processing for NMRI (SPIN). Susceptibility-weighted image processing steps included: (a) high-pass filtering of the phase data by a 64 x 64 low-pass filter to remove the low frequency spatial components of the background field which enhances the ability to differentiate one tissue from another depending on their susceptibilities; (b) application of a phase mask to create the SWI magnitude images; and (c) creating a minimum intensity projection of the SWI images over four slices to visualize the connectivity of the veins. The latter step makes it possible to track the path of the veins from slice-to-slice and ensure that veins are not misinterpreted as microbleeds.

**Results**

**Case report 1**

**History**

This 43-year-old male complained of chronic vertigo and imbalance (6 years in duration) following multiple blast exposures from mortars and IEDs. A DHI score of 48 suggested moderate self-perceived handicap. Pure tone air and bone conduction audiometry showed bilateral borderline-normal hearing sensitivity (Figure 1, Case 1). Middle-ear measurements (tymanometry and acoustic reflexes) indicated normal middle ear function.

**Vestibular/balance assessment**

**Vestibular site-of-lesion function.** The Dix-Hallpike and roll tests were negative for BPPV. Bithermal caloric irrigations revealed normal and symmetrical responses (UW = 9%). The rotary chair test revealed normal phase, gain and asymmetry across frequencies. cVEMPs and oVEMPS were present bilaterally and showed symmetrical responses (AR = 32% and 35%, respectively). Ocular motor tests revealed slow saccadic velocity and normal smooth pursuit. These results were consistent with normal peripheral vestibular function (Figure 2). The ocular motor tests suggest the possibility of central pathology.

![Figure 1](image_url)

**Figure 1.** Pure tone audiograms showing hearing sensitivity for each case study. The air conduction (AC) pure-tone thresholds for the left ears are indicated by an X and shown across frequencies in the left column of panels; AC pure-tone thresholds for the right ears are indicated by an O and shown across frequencies in the right column of panels. Pure tone thresholds \( \geq 25 \) dB HL suggest a loss in hearing sensitivity. Bone conduction (BC) pure-tone thresholds are shown for Case 2 and suggest a bilateral mixed (both sensorineural and conductive components) hearing loss for this individual. AC pure-tone thresholds approximated BC pure-tone thresholds for Cases 1, 3 and 4 (sensorineural hearing losses); therefore, only AC pure-tone thresholds are shown for these individuals.
Balance and gait function. The SOT composite score was 67, indicating poor use of sensory input for balance (Figure 2). The total score on the DGI was 22/24, indicating low risk for falls and the preferred gait speed (1.13 m s\(^{-1}\)) was abnormally slow for age and gender.

Neuroimaging studies

DTI. Global WM measures were within normal limits. However, regional analysis showed that the fornix/stria terminalis on right side has decreased FA. Track-based spatial statistics and z-score analysis revealed lower FA values in the superior cerebellar peduncle, fornix (right side), splenium of the corpus callosum and posterior limb of internal capsule (right side). These data are shown in Figure 3 (top row (a–c)) and Figure 4 (vertical bar graphs in (a)) depicts z-scores (y-axis) vs anatomical region (x-axis).

SWI. Two microbleeds were observed above the ventricle in the anterior corona radiata of the frontal WM region (anterior portion of the brain) (Figure 5(a)). In summary, regional and voxel-based analyses indicate diffuse axonal injury (DAI).

Case report 2

History

This 44-year-old male complained of ‘jumping’ vision, imbalance, lateropulsion and lightheadedness following a blast exposure within ~5 feet from his right side 24 years earlier. He has a history of tympanic membrane perforations following the blast and underwent tympanoplasty on both sides. Pure-tone audiometry revealed a mild-to-moderate mixed hearing loss in the left ear and a profound mixed hearing loss in the right ear (Figure 1, Case 2). Middle-ear measurements indicated normal static admittance at normal peak pressure and absent acoustic reflexes bilaterally. However, normal static admittance in lieu of previous tympanic membrane perforations and related surgery may not be clinically useful. The DHI score of 12 suggested mild self-perceived handicap.

Vestibular/balance assessment

Vestibular site-of-lesion function. The Dix-Hallpike and roll tests were negative for BPPV. Bithermal caloric irrigations revealed a right unilateral weakness (90%) and rotary chair testing revealed low VOR gain at 0.01–0.64 Hz. Air conduction cVEMPs and oVEMPs were absent bilaterally due to the middle-ear pathology. In contrast, bone conduction cVEMPs and oVEMPs were present and symmetrical bilaterally (AR = 4% and 11%, respectively). Smooth pursuit and saccades were within normal limits, suggesting normal ocular motor function. These results are consistent with right horizontal semicircular canal dysfunction (Figure 6).
The DGI total score was 24/24, indicating low risk for falls, and the preferred gait speed (0.94 m s\(^{-1}\)) was abnormally slow.

Neuroimaging studies

**DTI.** Global WM assessment was normal. Regional WM analysis showed reduced FA in the fornix (right side). Track-based spatial statistics and z-score analysis showed reduced FA bilaterally in regions of the cingulum and superior corona radiata (Figures 3(d–f) and 4(b)).

**SWI.** One microbleed was observed in the left posterior-superior cerebellar hemisphere (Figure 5(b)).

Figure 3. Tract-based spatial statistics (TBSS) and z-score analysis revealed lower fractional anisotropy (FA) compared to the normal control group. These abnormal areas are highlighted in red rectangles or ovals for each individual from top to bottom. Case 1: (a) and (b) right axial and sagittal slices highlighting fornix/stria terminalis; (c) splenium of the corpus callosum and posterior limb of the internal capsule. Case 2: (d) cingulum (hippocampus) bilaterally, (e) and (f) superior corona radiata. Case 3: (g) right retrolenticular area of the internal capsule and left posterior corona radiata, (h) superior corona radiata bilaterally and (i) superior longitudinal fasciculus, bilaterally. Case 4: (j) right external capsule, (k) cingulum, bilaterally and (l) superior longitudinal fasciculus, bilaterally.

Figure 4. Vertical bar graphs (y-axis, z-score; x-axis, anatomical region) quantifying regions in the previous slide having lower FA compared to normal controls: (a) Case 1 having bilateral Fornix/stria terminalis, (b) Case 2 having right Fornix/stria terminalis, (c) Case 3 having bilateral superior longitudinal fasciculus and (d) Case 4 having right Fornix/stria terminalis and bilateral external capsule. See Table I for a key to anatomical region abbreviations.

Case report 3

**History**

This 29-year-old male complained of imbalance and lateropulsion following multiple blast exposures (\(n = 22\)). He also reported feeling ‘wobbly’, with difficulty walking a straight line or on stairs; this sensation was also prominent in elevators and on swings. The worst blast exposure occurred 4 months prior to the assessment for this study and resulted in
a diagnosis of mTBI. Pure-tone audiometry revealed normal hearing sensitivity, bilaterally (Figure 1, Case 3). The DHI score was 14, suggesting a mild self-perceived handicap.

Vestibular/balance assessment

Vestibular site-of-lesion function. The Dix-Hallpike and roll tests were negative for BPPV. Monothermal warm caloric irrigations revealed normal and symmetrical responses (inter-ear difference = 2%). Cool caloric irrigation was not performed because the warm caloric inter-ear difference was ≤ 10%. The rotary chair revealed normal phase, gain and asymmetry across frequencies. cVEMPs were present and symmetrical (AR = 5%). Air and bone conduction oVEMP were present bilaterally, but the response recorded from the right eye was reduced in amplitude (AR = 72%). As the oVEMP is a contralateral response, these results are consistent with left utricular (otolith organ) dysfunction (Figure 7). Saccades and smooth pursuit were within normal limits, suggesting normal ocular motor function.

Balance and gait function. The SOT composite score was 78, indicating normal use of sensory input for balance (Figure 7). The DGI total score was 24/24, indicating low risk for falls, and the preferred gait speed (1.06 m s⁻¹) was abnormally slow.

Neuroimaging studies

DTI. Global WM analysis was normal; however, regional WM analysis shows decreased FA in superior longitudinal fasciculus (Figures 3(g–i)). Track-based spatial statistics and z-score analysis (Figure 4(c)) showed reduced FA in the retrolenticular part of internal capsule (left side), posterior corona radiata, bilateral superior corona radiata and bilateral superior longitudinal fasciculus. Regional analysis and voxel-based analysis indicate DAI.

SWI. An abnormally dark signal in the draining septal vein was observed on the left side (Figure 5(c)).

Case report 4 (TB30)

History

This 46-year-old male reported imbalance and lateropulsion following multiple blast exposures from mortars and IEDs (>5), with the most recent blast occurring 5 years prior to this assessment; he was diagnosed with mTBI. He also reported that, when lying down, he experiences a feeling ‘like the bed is moving’. Pure-tone audiometry revealed a mild-to-moderate high frequency sensorineural hearing loss.
on the left side associated with a noise notch and mild high frequency sensorineural hearing loss on the right side (Figure 1, Case 4). The DHI score was 42, suggesting moderate self-perceived handicap.

Vestibular/balance assessment

Vestibular site-of-lesion function. The Dix-Hallpike and roll tests were negative for BPPV. Monothermal warm caloric irrigation revealed normal and symmetrical caloric responses (inter-ear difference = 1%). Cool caloric irrigation was not performed because the warm caloric inter-ear difference was ≤ 10%. The rotary chair revealed normal phase, gain and asymmetry across all frequencies. cVEMPs were present on the right side and absent on the left side (AR = 100%). oVEMPs were present bilaterally and symmetrical (AR = 28%). Ocular motor tests revealed normal smooth pursuit, but with prolonged latency for rightward saccades. These results are consistent with left-sided saccular (otolith organ) and/or inferior vestibular nerve dysfunction (Figure 8). The ocular motor tests suggest the possibility of central pathology.

Balance and gait function. The SOT composite score was 41, indicating poor use of sensory input for balance (Figure 8). The total DGI score was 18/24, indicating high risk for falls and the preferred gait speed (1.01 m s⁻¹) was abnormally slow.

Neuroimaging studies

DTI. Lower global WM FA and higher global WM RA were observed for this particular individual compared to the normal; regional WM analysis showed reduced FA in the area of the fornix/stria terminalis and external capsule on the right side (Figure 9). Track-based spatial statistics and z-score analysis showed reduced FA in the cerebral peduncle and external capsule on the right side and reduced FA in the cingulum (hippocampus) and superior longitudinal fasciculus bilaterally (Figures 3(i–l)). Regional analysis and voxel-based analysis indicate DAI (Figure 4(d)).

SWI. A single microbleed was observed in the superior frontal region of the corona radiata on the left side (Figure 5(d)).

Discussion

Although it is well known that symptoms of dizziness and imbalance may follow blast exposure or mTBI, the site(s)-of-lesion are often less clear. Specifically, traumatic dizziness and imbalance can be related to damage in the peripheral and/or central vestibular system including associated pathways and brain areas. A comprehensive vestibular, balance and neuroimaging test battery was performed in four individuals with blast-related dizziness or imbalance and summarized in Table II. Patterns of vestibular and balance test results varied across the four individuals, with three
of the cases presenting with clinical signs of vestibular dysfunction, all four cases presenting with abnormally slow gait speed and two cases presenting with clinical signs of balance dysfunction.

**Vestibular and balance assessment**

Case 1 had normal vestibular function, yet abnormal static balance function and gait speed. These findings suggest that balance dysfunction is unrelated to the vestibular system and the neuroimaging findings provided objective evidence to support the balance-related dysfunctions. The complaint of vertigo is often associated with vestibular dysfunction; however, the comprehensive assessment of vestibular function yielded normal findings. This case demonstrates the limitations of symptoms (or questionnaires) in the diagnosis of vestibular dysfunction and underscores the need for vestibular function assessment in the differential diagnosis of patients who experience vertigo.

Three of the four cases had evidence of vestibular dysfunction; however, the vestibular site-of-lesion was isolated to one vestibular organ/pathway and the site differed for all three cases. Case 2 demonstrated abnormal horizontal SCC function, but normal otolith organ function and balance and gait tests were within normal limits, with the exception of abnormally slow gait speed. Dizziness and imbalance are common symptoms of damage to the horizontal SCC and the vestibulo-ocular reflex; however, the symptoms are often resolved following vestibular compensation. The presence of normal balance function in Case Report 2 may be related to recovery driven by vestibular compensation.

Two cases demonstrated isolated otolith organ dysfunction. Specifically, Case 3 revealed abnormal utricular function; whereas Case 4 had abnormal saccular function. The utricle and saccule are otolith organs that sense gravity and contribute to maintaining upright posture or balance. These cases highlight the need for inclusion of otolith organ tests in the differential diagnosis of trauma-related dizziness, as the tests of horizontal SCC function were within normal limits. Thus, vestibular-system dysfunction would have been missed if assessment was limited to routine clinical vestibular assessment (e.g. standard caloric testing), which often excludes tests of otolith organ function (e.g. cVEMPs and oVEMPs). Furthermore, there is increasing evidence that the saccule may be particularly susceptible to noise or blast-related damage [35–39]. Recent studies have demonstrated that absent cVEMPs are prevalent in individuals who experience dizziness or balance problems following a head injury and occur more often than horizontal SCC dysfunction [10,40]. Both cases with isolated otolith organ dysfunction had abnormally slow gait speed. Case 4 had abnormal saccular pathway function (abnormal cVEMP) and was the only individual with an abnormal DGI. This was an interesting finding because of the ceiling effect that is often observed with the DGI [41].

In accordance with recommendations for assessment following mTBI, multiple measures of balance and gait were used to characterize postural stability in this case...
All four cases presented with abnormally slow gait speed and varying vestibular deficits; thus, gait speed may not be a sensitive indicator of specific peripheral vestibular deficits. Rather, gait speed may reflect the overall status of the central nervous system. Two of the four cases demonstrated abnormal use of sensory input for balance, even though one of the two had normal vestibular function. This finding may highlight the need for comprehensive balance testing in addition to vestibular testing. A single case presented with an abnormal DGI score indicating fall risk. The use of the DGI to assess gait in this younger Veteran population is a limitation of the case report given the ceiling effect in younger individuals. Standardized measures of gait that incorporate high-level mobility items are recommended for this population.

**Neuroimaging**

The neuroimaging data presented herein were, in part, driven by the work of Benson et al. [43] which speak to the urgency by which advanced MRI methods, like DTI and SWI, are needed to detect and diagnose milder forms of brain injuries effecting WM microstructure and connectivity, including microvascular insults. Evidence is accumulating to help ensure that these capabilities will enable the pathoanatomical and pathophysiological consequences of brain trauma to be explicated in a more judicious manner than has been possible in the past.

It is known in animal models that blast over and under pressures can have local, systemic, and CNS effects [44]. While vestibular and balance related issues were not specifically addressed in the review by Cernak and Noble-Haeusslein [44], effects of blasts can have simultaneous and deleterious effects on the auditory and vestibular receptor organs in periphery and in grey and WM interfaces in the CNS. In Sprague-Dawley rats, for example, blast over-pressure vis-à-vis shock tube insults can produce axonal injury in brainstem and cervical WM tracks characterized by neuronal swellings, retraction bulbs and membrane disruptions [45]. Furthermore, one should not lose sight of the fact that, in the CNS, shock waves are translated to compression waves in the brain that can also be responsible for stress and strain injuries and in modulating intracranial pressure [46].

In humans, Taber et al. [47] also reported that WM compromise was consistent with mTBI criteria based on self-reported symptoms in individuals with or without primary blast exposure. These authors indicate that DTI abnormalities, including reductions in FA, were broadly distributed and heterogeneous within the brain; indeed, such effects may reflect individual differences in vulnerability. Moreover, Taber et al. [47] also observed relationships between WM compromise and several neuropsychological/neurocognitive tests including simple reaction time and set shifting. These
Specific tasks can be attributed to an executive function served by widely distributed neural systems in the dorsolateral prefrontal, parietal, orbitofrontal and anterior cingulate cortices. Interestingly, other tests of executive function, such as decision-making, planning and organization, were not related to the abnormal DTI metrics they studied. The DTI data reported herein showed that global WM was not impaired in any individual, but that regional WM anomalies, examined by TBSS and z-score analyses (Figure 3), were always abnormal and were consistent with DAI within the brain.

In addition to DTI-related abnormalities, this study also detected micro-hemorrhages in various brain areas based on SWI. In combination, DAI and microvascular anomalies are consistent with pathological expectations previously observed in blast over-pressures [38]. Indeed, complex stress and strain effects at grey and white matter interfaces and other anomalies such as tearing of bridging veins can account for some of these effects. In considering the data in relation to the tests performed, all individuals had abnormal vestibular (3/4) or balance function tests (2/4). Susceptibility-weighted imaging studies were abnormal in all, characterized by either one or more micro-haemorrhagic lesions or unilateral markedly darkened sections of draining veins. Diffusion-tensor imaging data were also consistent with DAI, as the regional WM analysis showed reduced FA in all four cases.

The impact of determining the site-of-injury in the management of individuals with dizziness or postural stability following a blast or head injury is unclear and requires further investigation. Presently, there is little research evidence to guide physical therapy treatment of Veterans with mTBI. Recent recommendations for best practice based on the available evidence were developed by a team of multidisciplinary experts in 2007 and then revised in 2009 [42]. The recommendations for dizziness and imbalance involve focused assessment to determine the presence of BPPV, unilateral vestibular hypofunction or high-level mobility limitations. The recommendations for intervention are a customized rehabilitation programme based on the identified impairments and include: canalith repositioning manoeuvre, gaze-stability exercises, habituation and balance and gait activities as needed. Balance activities should be made progressively more challenging, while monitoring perception of exertion and adjusting intensity accordingly. These recommendations were based on the assumption that vestibular damage as a result of blast injury is similar to damage sustained by civilians. However, this may or may not be the case. Currently, imaging findings are not utilized to guide treatment, but the use of imaging may be beneficial in the future if relationships are found between advanced imaging results and functional outcomes.

In summary, the four cases demonstrate the complex nature of dizziness and imbalance following traumatic blast injury. Although the symptoms were somewhat similar across the four individuals, the patterns of vestibular and balance test results varied across the four individuals; this observation is noteworthy and one that requires further attention and scrutiny. A comprehensive battery of vestibular, balance and neuroimaging tests provides information that is unavailable using current standard clinical protocols. As research moves forward in this area, the clinical utility of the vestibular and

Table II. Summary of vestibular, balance, ocular motor and neuroimaging findings in four individuals with dizziness following blast exposure.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>mTBI</th>
<th>Calorics</th>
<th>RC</th>
<th>cVEMP</th>
<th>oVEMP</th>
<th>SOT</th>
<th>DGI</th>
<th>GS</th>
<th>SP</th>
<th>Saccades</th>
<th>DTI</th>
<th>SWI</th>
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<tbody>
<tr>
<td>43</td>
<td>Neg</td>
<td>Ni</td>
<td>Ni</td>
<td>Ni</td>
<td>Ni</td>
<td>Abn</td>
<td>Ni</td>
<td>Abn</td>
<td>Ni</td>
<td>Abn</td>
<td>Abn</td>
<td>Abn</td>
</tr>
<tr>
<td>44</td>
<td>Neg</td>
<td>Abn</td>
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<td>Ni</td>
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<td>Abn</td>
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<tr>
<td>29</td>
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<td>Ni</td>
<td>Ni</td>
<td>Ni</td>
<td>Abn</td>
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<tr>
<td>46</td>
<td>Pos</td>
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</tr>
</tbody>
</table>

H_SCC, horizontal semicircular canal; yrs, years; mTBI, mild traumatic brain injury; RC, rotary chair; cVEMP, cervical vestibular evoked myogenic potential; oVEMP, ocular vestibular evoked myogenic potential; SOT, sensory organization test; DGI, dynamic gait index; GS, preferred gait speed; SP, smooth pursuit; DTI, diffusion tensor imaging; SWI, susceptibility weighted imaging; Neg, negative; Pos, positive; Ni, normal; Abn, abnormal.
neuroimaging site-of-lesion framework described herein may set the stage for improved management of dizziness or balance disorders related to blast or mTBI.

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Declaration of interest

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