Vestibular Related Traumatic-Brain Injury: Imaging Overview

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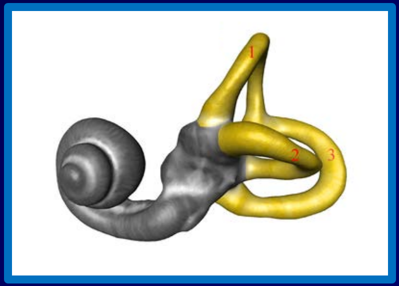

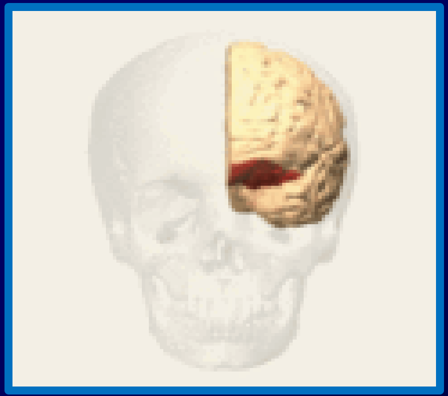

Audience Demographics

- Students
- Audiologists
- Physical therapists
- Psychologists
- Physicians
- Other allied health care providers
- Basic scientists

Acknowledgments

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Acknowledgments

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Disclaimer

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United States Government

Veterans Health Administration
Research & Development

DISCOVERY ★ INNOVATION ★ ADVANCEMENT

Evaluating the Vestibular Consequences of Blast Injuries and *m*TBI

- VA merit based research project performed at the Vestibular/Balance Laboratory, VA Medical Center, Mountain Home, Tennessee
- Principal Investigator: Faith Akin, Ph.D.
  - Co-Is: Drs. Murnane, Hall, Cacace, Haacke
- Includes:
  - Comprehensive vestibular studies
  - Interviews and questionnaires
  - Neuroimaging
    - Collaboration with Wayne State University investigators

Blast-Induced Injuries

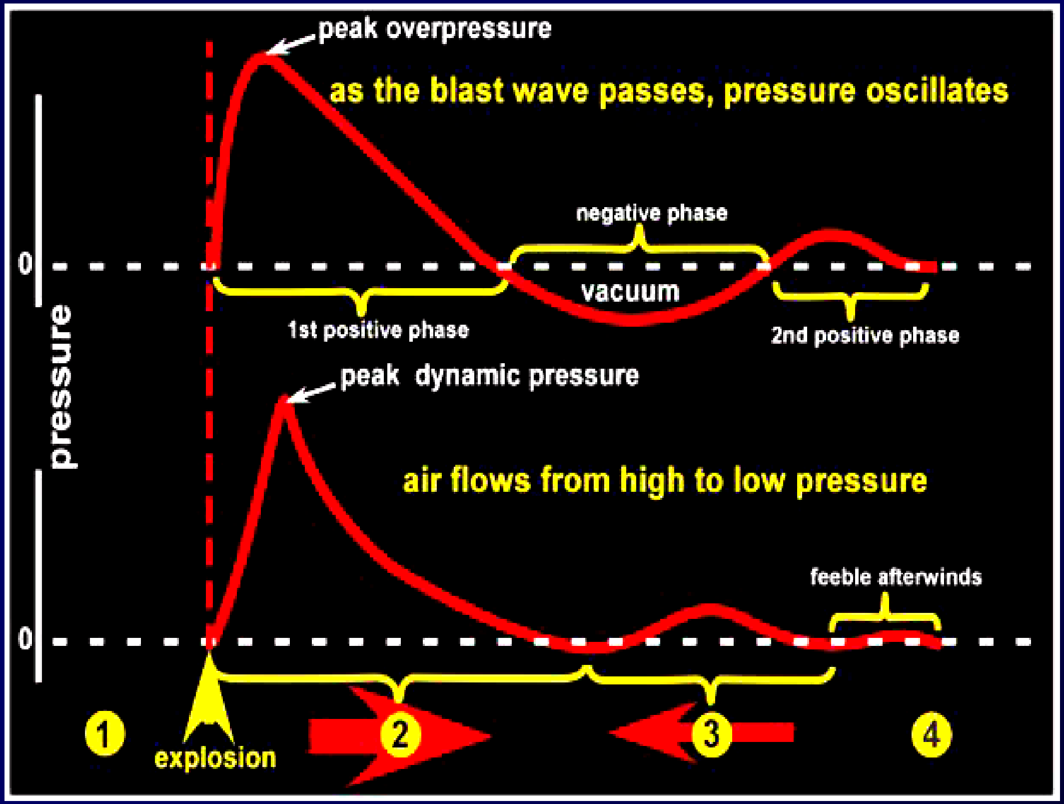
- Becoming increasingly problematic for health related agencies like the VA, because
  - Injuries are not well defined
  - Long-term effects are unknown
  - Wide gaps in knowledge exist concerning:
    - Underlying processes
    - Site(s)-of-lesion, and
    - Mechanisms involved in the auditory/vestibular apparatus and brain

Conceptualization of the Problem

- Blasts can simultaneously affect the periphery and central nervous system
- Blast over pressures are represented as a compression wave in the brain
  - Gelatin like structure of the brain shifts violently inside the skull
  - Contusions and micro-hemorrhages can occur at gray/white matter junctions
  - Disruption or shearing effects can occur within white matter tracts that interconnect various brain areas that subserve various sensory, motor, and cognitive functions
  - Alterations in the neurobiochemical environment in numerous regions-of-interest

Physical Acoustics of Blast Waves

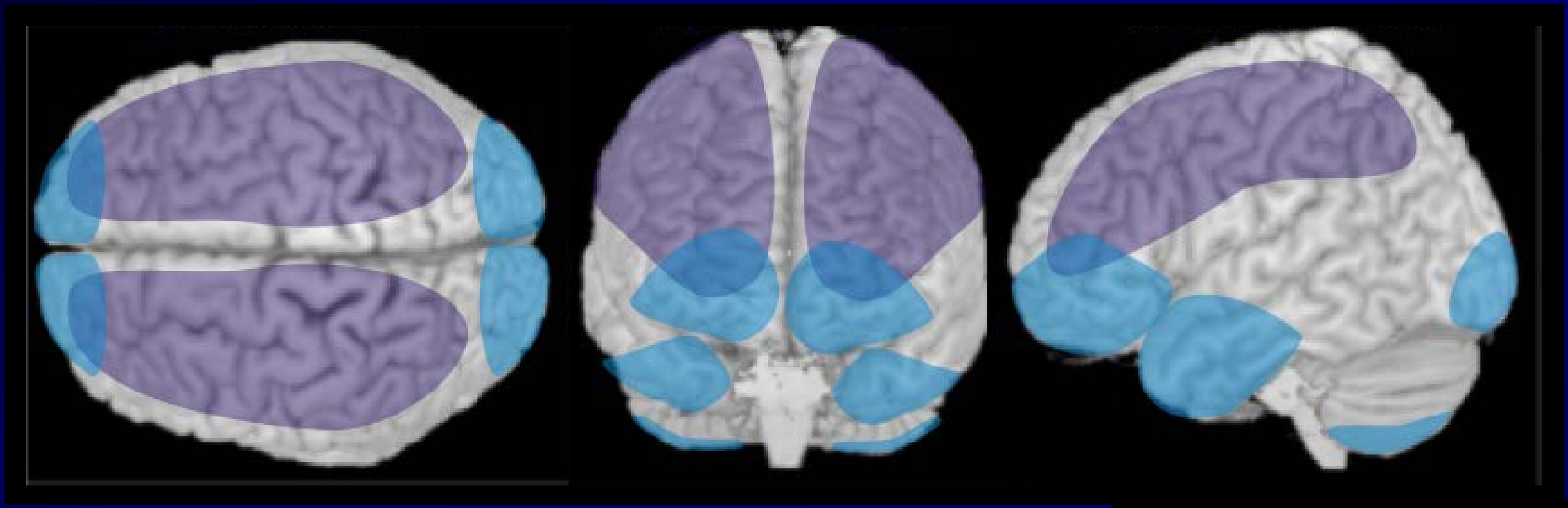
1) Normal pressure
2) Blast forces max; wind flows away from explosion
3) Followed by reverse blast wind & drop in atmospheric pressure
4) Atmospheric pressure returns to normal after blast wave subsides



(From: Taber et al (2006). Blast-related traumatic brain injury: What is known. J Neuropsychiat Clin Neurosci 18, 141-145).

Blast-Related Non-penetrating TBI

From above From in front From the side



Diffuse axonal

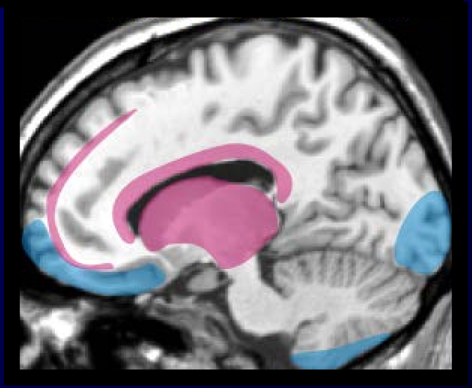
-cortical/medullary
-internal capsule
-deep gray matter
-upper brainstem
Corpus callosum

Contusion

-Superficial gray matter
-infer, lat, ant frontal lobe
-temp. lobes

Subdural hemorrhage

-frontal and parietal convexities



From the midline

Neuroimaging Biomarkers
(Anatomical-Based Measures)

- Standard T_1-weighted high resolution anatomical MRI (1.5 Tesla)
- Voxel-based morphometry (VBM)
  - Group comparison study
  - Useful for developing hypotheses
- Diffusion-Tensor Imaging (DTI)
  - Useful for evaluating white matter tracks, microstructure, and connectivity that cannot be seen with standard MRI
- Susceptibility-Weighted Imaging (SWI)
  - Efficacious for detecting small vascular lesions (i.e., microhemorrhages) that cannot be seen by standard MRI or DTI

Some Relevant References

- Ashburner, J., Friston, K. J. (2000). Voxel-based morphometry – the methods. NeuroImage, 11, 805-821.
- Benson, R., Gattu, R., Cacace, A. T. (2014). Left hemisphere fractional anisotropy increase in noise-induced tinnitus: A diffusion tensor imaging (DTI) study of white matter tracts in the brain. Hear Res. 309, 8-16.
- Gattu, R., Akin, F. W., Cacace, A. T., Hall, C. D., Murnane, O., Haacke, E. M. (2016). Vestibular, balance, microvascular, and white matter neuroimaging characteristics of blast injuries and mild traumatic brain injury: Four case reports. Brain Trauma, 30, 1501-1514.
- Haacke, E.M., et al. (2009). Susceptibility-weighted imaging: Technical aspects and clinical applications, Part 1. Am. J. Neuroradiol., 30, 19-30.

Patient Characteristics

- Diagnoses:
  - Mild traumatic brain injury (*m*TBI)
  - Post traumatic stress disorder (PTSD)
- History:
  - Exposure to single or multiple blasts (IED's, roadside bombs, rocket-propelled grenades, mortars, etc.)
  - Blast + concussion
  - Concussion alone (i.e., MVAs)
- Vestibular-related symptoms/complaints:
  - Imbalance
  - Lateropulsion
  - Light headedness
  - Vertigo

Vestibular-Related Symptoms and/or Complaints

- Imbalance (*IMB*): Experience difficulty walking in a straight line, clumsiness and coordination problems, difficulty maintaining an upright posture
- Lateropulsion (*LP*): the tendency to fall toward one side or the other
- Light Headedness (*LH*): feeling faint or about to pass out; often subsides when you lie down
- Vertigo (*VERT*): the sensation of motion (i.e., either that you or your environment are spinning, whirling, falling, tilting, etc.)

Aims and Hypotheses for Imaging-Related Studies

- Do the vestibular and *m*TBI-related symptoms experienced by individuals have an anatomical basis?
- What methodology can/should be used to test this hypothesis?

Voxel-Based Morphometry (VBM)

- Unbiased technique to characterize anatomical differences between brains of well-defined *groups* using high resolution T_1-weighted MRI
  - Useful for developing hypotheses
- Accomplished by:
  - Normalizing individual MRIs into a standardized anatomical space
  - Segment images into gray matter, white matter, and cerebrospinal fluid (CSF)
  - Performing a statistical analysis on a voxel-by-voxel basis between groups (*a priori*, $p<0.01$)
    - Accounting for multiple comparisons in the statistical analysis
  - Co-register statistically significant differences in anatomy on a standard anatomical template

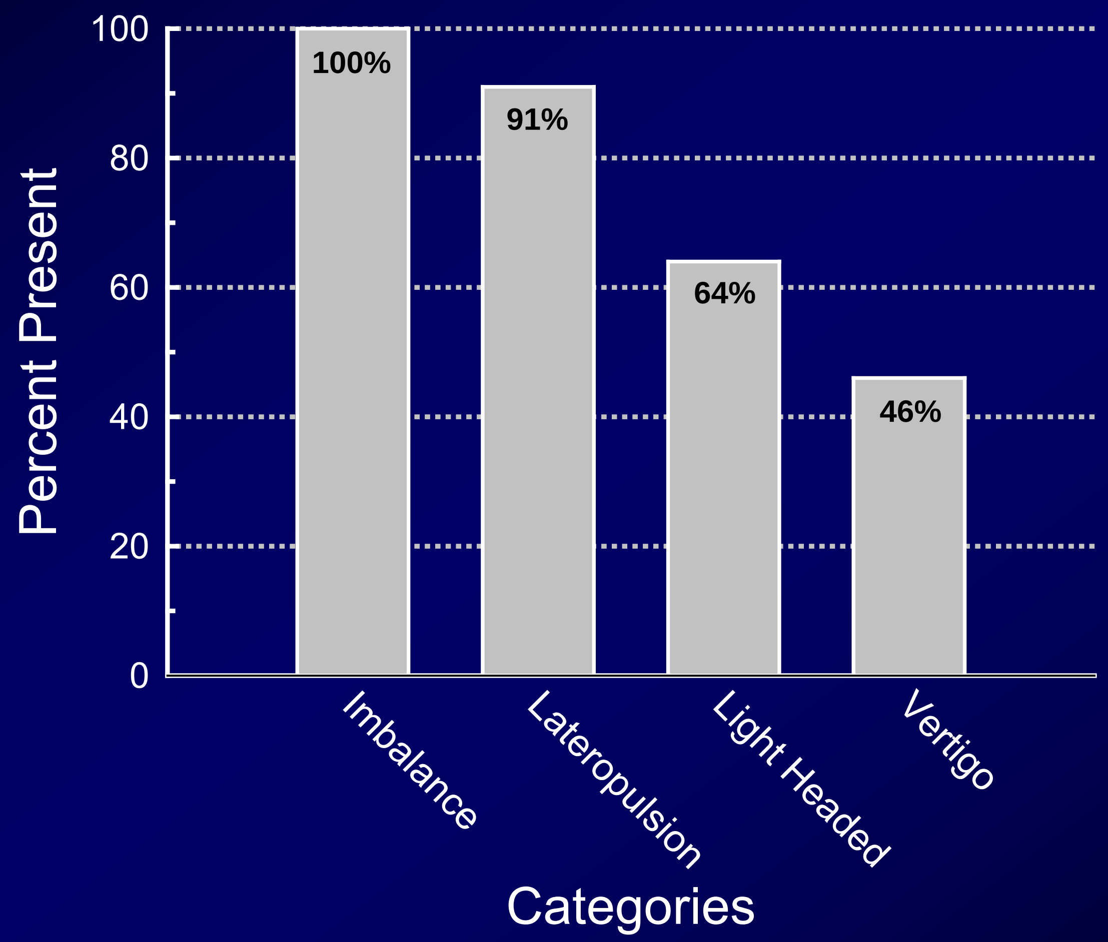
Participants

- 10 healthy normal controls
- 11 individuals diagnosed with TBI and/or PTSD
  - With primary vestibular-related complaints
- Matched for age and gender
  - Controls (n = 10 males; mean age: 25.7 yrs; SD: 4.2 yrs)
  - TBI/PTSD (n = 11 males; mean age: 36.1 yrs; SD: 11.6 yrs)
- Groups differed with respect to vestibular-related symptoms, complaints, and diagnoses

Demographics
(Experimental Group)

Subjects	Age (yrs)	Gender	Diagnosis	History	Vestibular Symptoms/Complaints
1	24	M	mTBI, PTSD	BL	*IMB, LP*
2	28	M	mTBI, PTSD	BL	*IMB, LP, LH, VERT*
3	28	M	PTSD	BL	*IMB, LP, LH, VERT*
4	28	M	mTBI, PTSD	BL	*IMB, LP, LH, VERT*
5	29	M	mTBI, PTSD	BL + C	*IMB, LP*
6	30	M	mTBI, PTSD	BL	*IMB*
7	35	M	mTBI, PTSD	BL	*IMB, LP, LH*
8	41	M	mTBI, PTSD	C	*IMB, LP, LH, VERT*
9	45	M	mTBI, PTSD	BL + C	*IMB, LP, LH, VERT*
10	46	M	mTBI, PTSD	BL	*IMB, LP*
11	63	M	mTBI, PTSD	BL	*IMB, LP, LH*

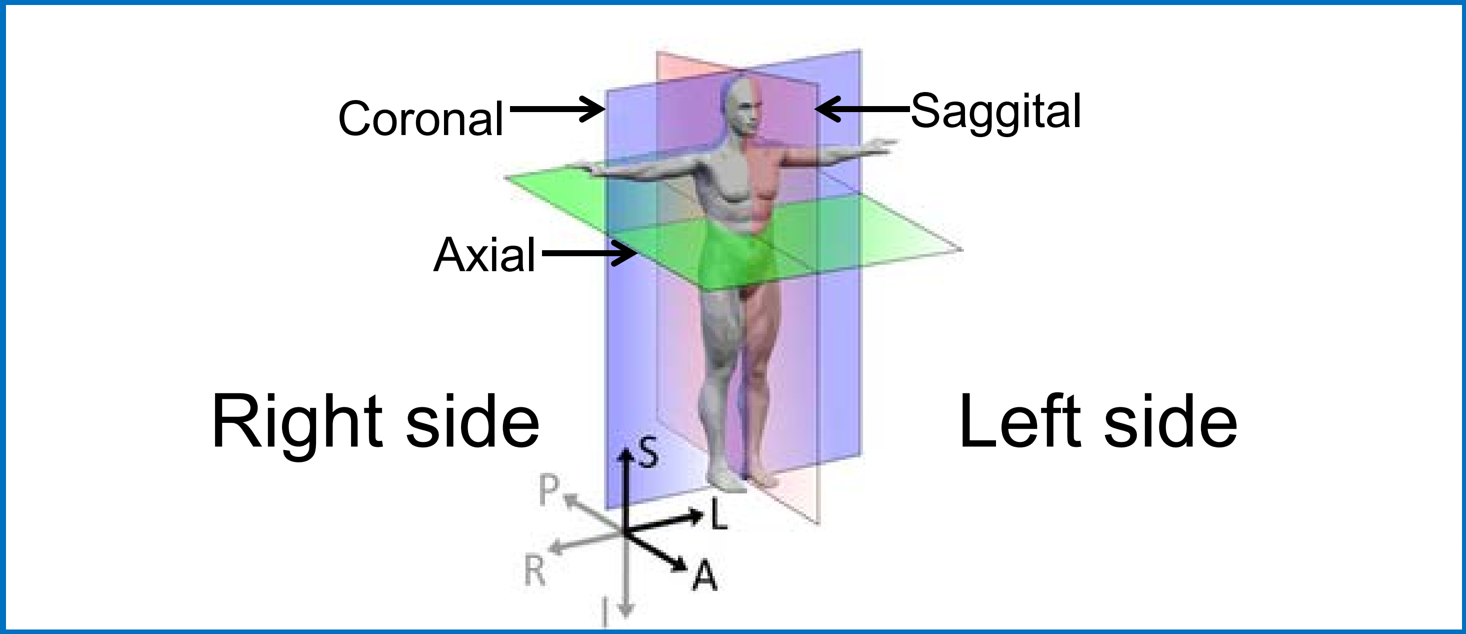
Vestibular Related Symptoms/Complaints



Demographics
(Control Group)

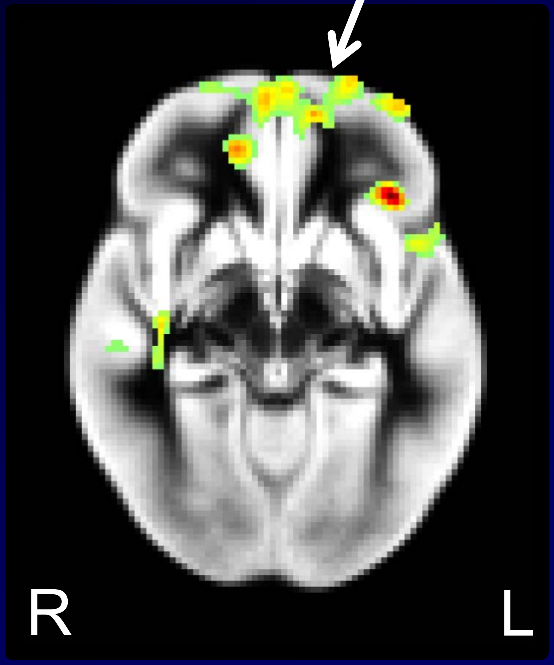
Subjects	Age (yrs)	Gender	Diagnosis	History	Vestibular Symptoms/Complaints
1	20	M	Normal	N/A	None
2	20	M	Normal	N/A	None
3	22	M	Normal	N/A	None
4	24	M	Normal	N/A	None
5	25	M	Normal	N/A	None
6	27	M	Normal	N/A	None
7	28	M	Normal	N/A	None
8	28	M	Normal	N/A	None
9	31	M	Normal	N/A	None
10	32	M	Normal	N/A	None

Anatomical Coordinates and Planes-of-Reference

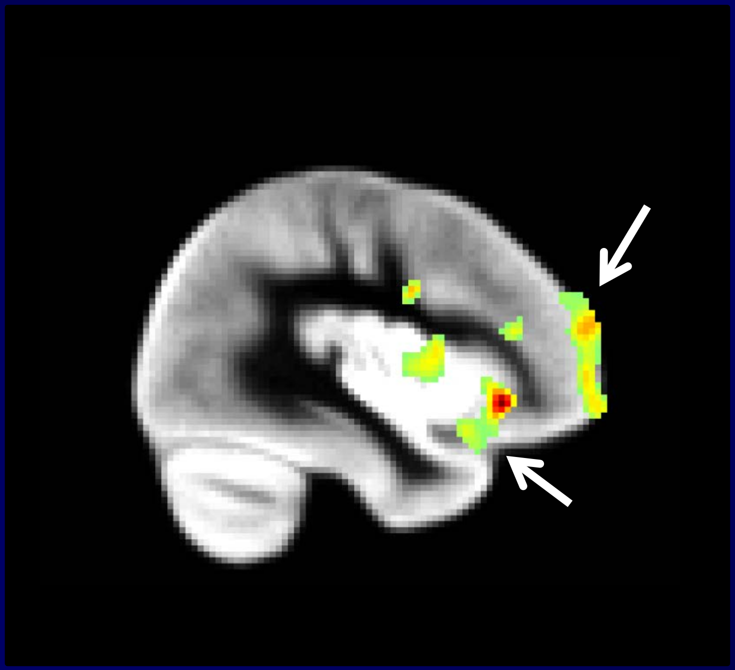


Results of
Voxel-Based Morphometry

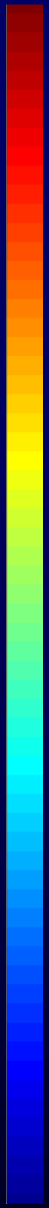
Axial



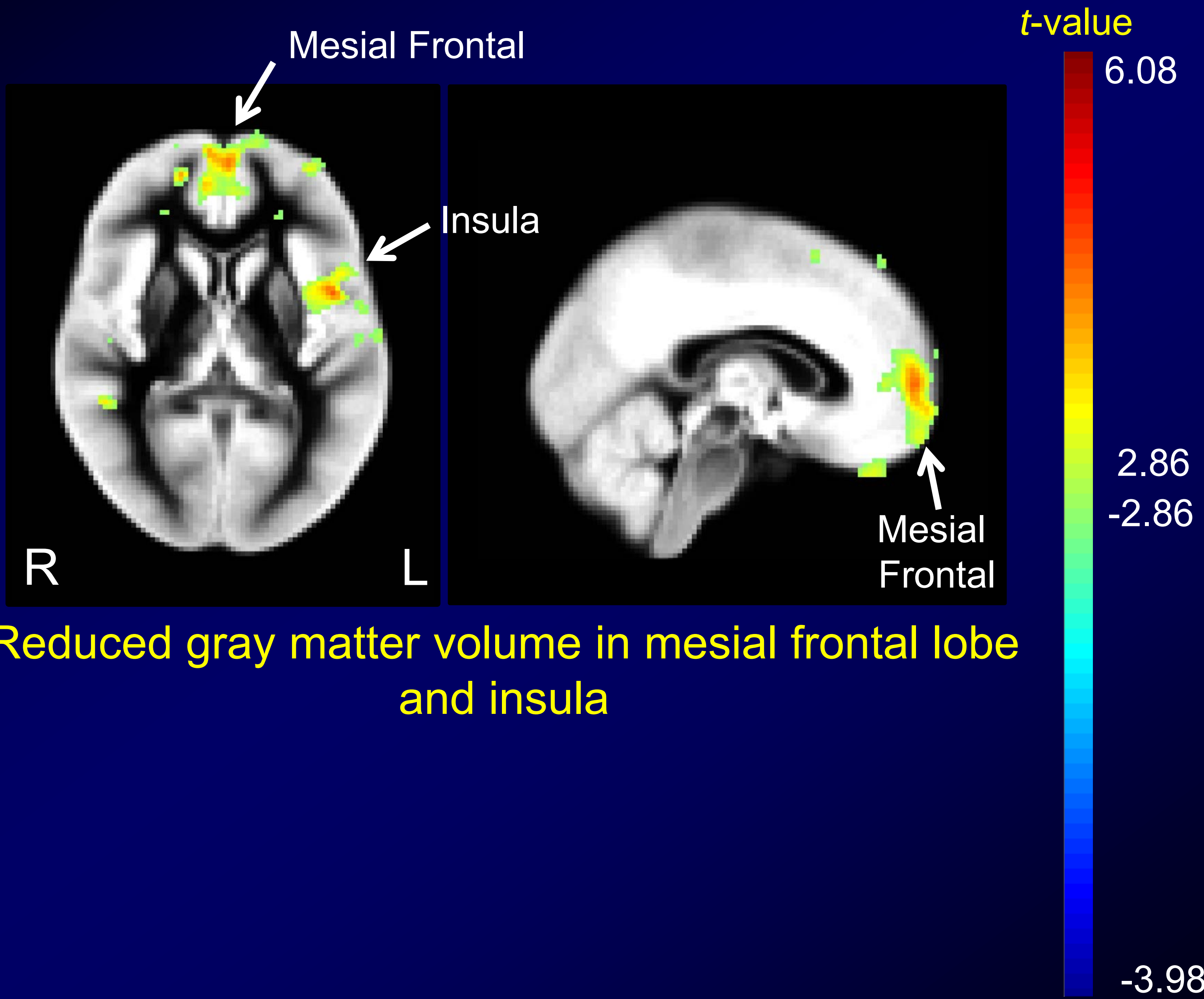
Saggital



t-value

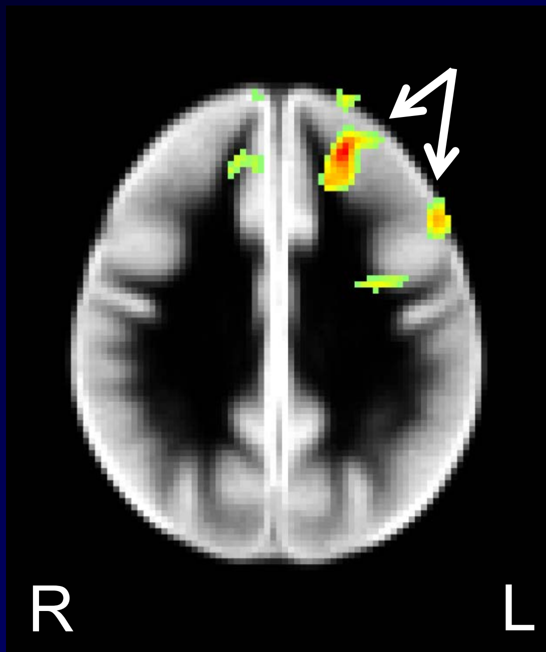


Reduced gray matter volume in anterior frontal and orbitofrontal regions

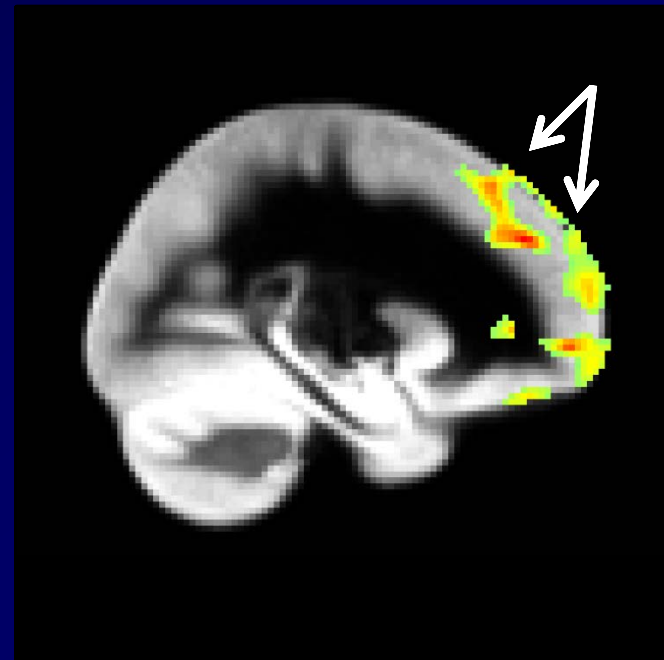


Reduced gray matter volume in mesial frontal lobe and insula

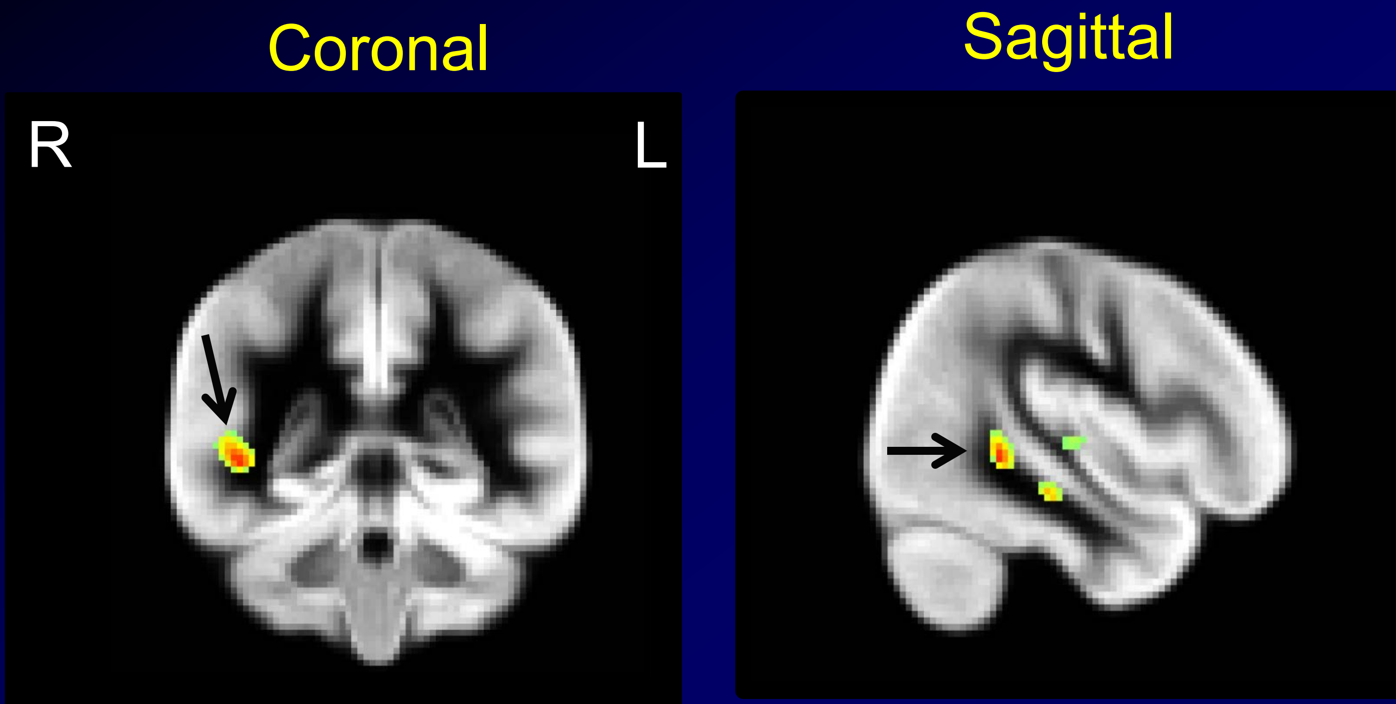
Axial

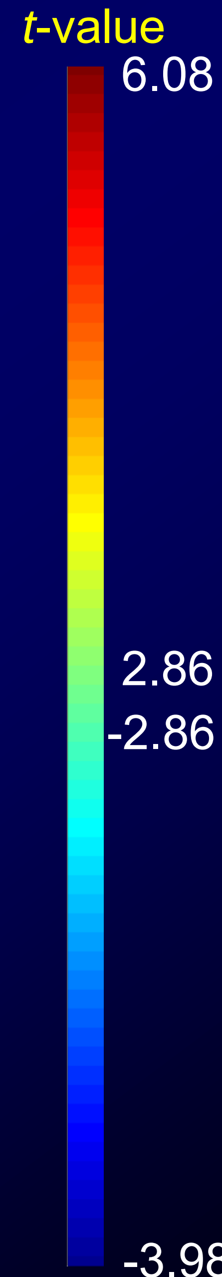


Saggital

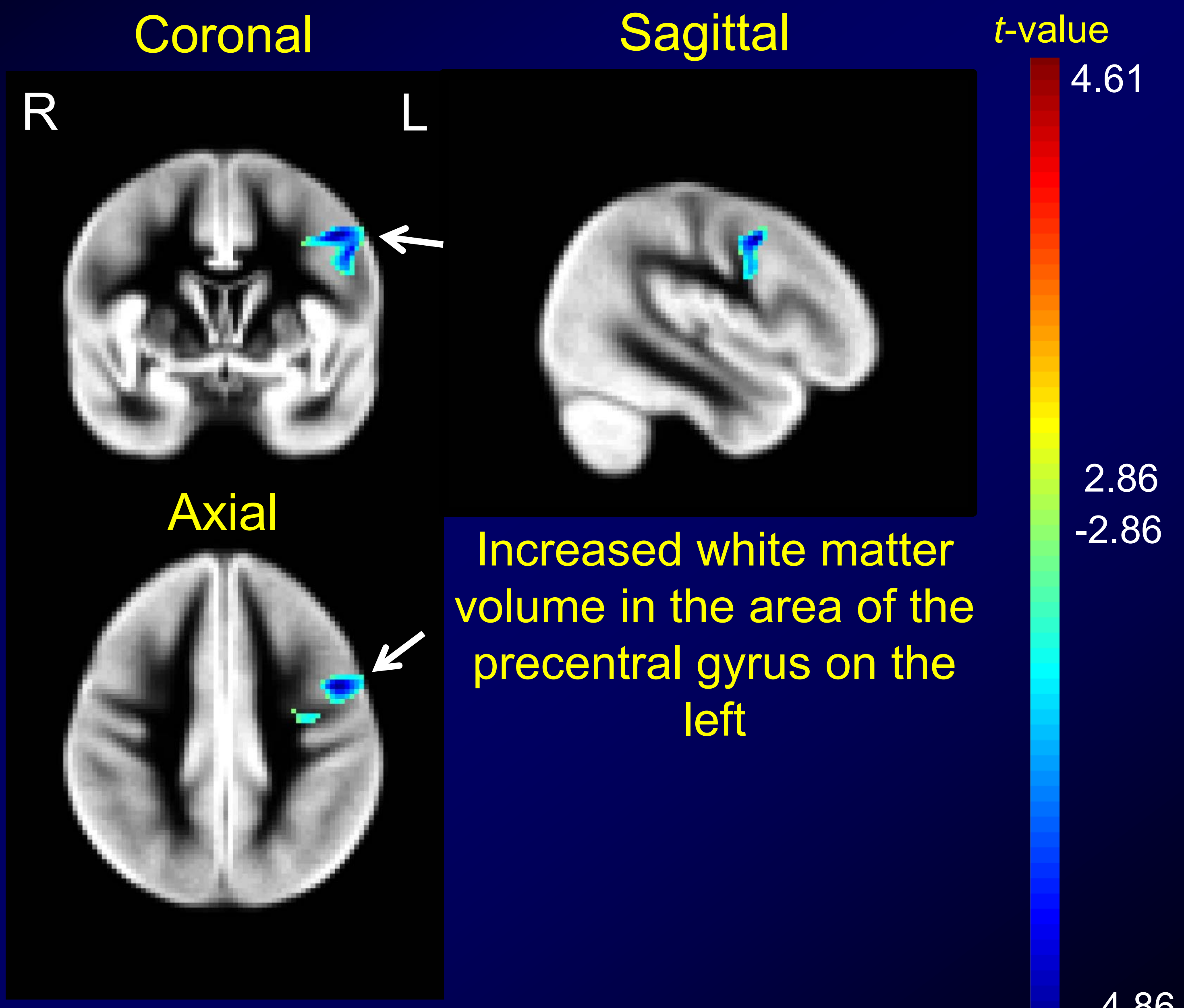


Reduced gray matter volume in frontal and fronto-midline structures on the left side





Decreased gray matter volume in the temporal lobe

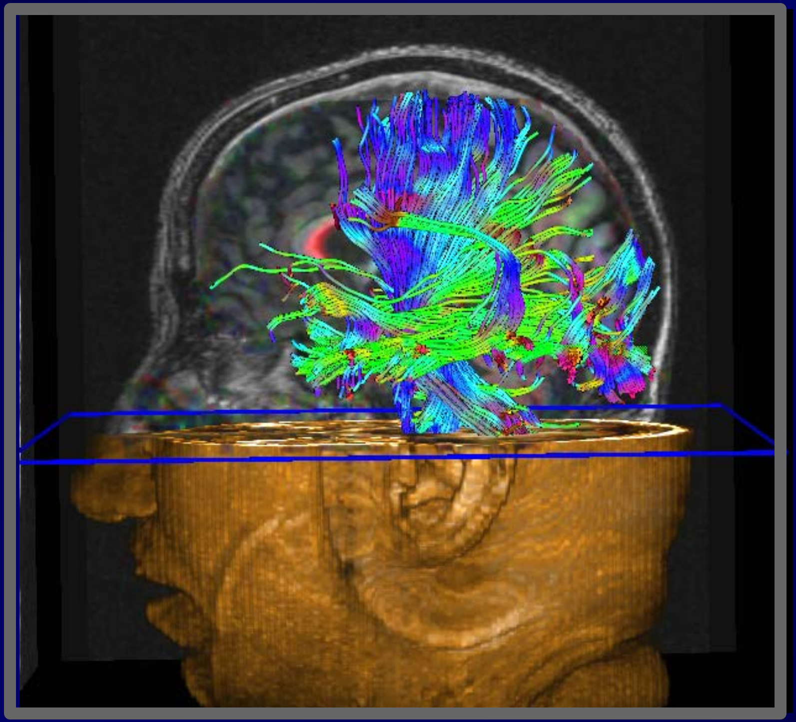


Increased white matter volume in the area of the precentral gyrus on the left

Summary

- Reductions in gray matter volume found in:
  - Orbitofrontal and middle frontal gyrus
  - mesial frontal lobe, and
  - insular area in the left mesial temporal lobe
- Increased white matter volume found in:
  - precentral gyrus on the left side

Diffusion Tensor Imaging



Conclusions

- These preliminary VBM analyses show:
  - Distributed gray matter changes in key frontal and temporal areas of the brain associated with *m*TBI, PTSD, and vestibular-related dysfunction
  - A single area of increased white matter volume was noted in the precentral gyrus localized to the left side of the brain

Conclusions

- These VBM data starting to show a pattern of results including changes in:
  - Frontal lobe structures (e.g., orbitofrontal and DLPF cortices) represent integration hubs for distributed and highly processed sensory, polysensory, and emotion-related (psychological and psychiatric) information
  - These new data represent areas-of-interest to explore in future studies

Diffusion Tensor Imaging (DTI)

- A contemporary imaging modality used to study connectivity patterns and microstructure of white matter tracts in the brain
- Relatively unexplored imaging modality in the study of vestibular and balance related dysfunctions

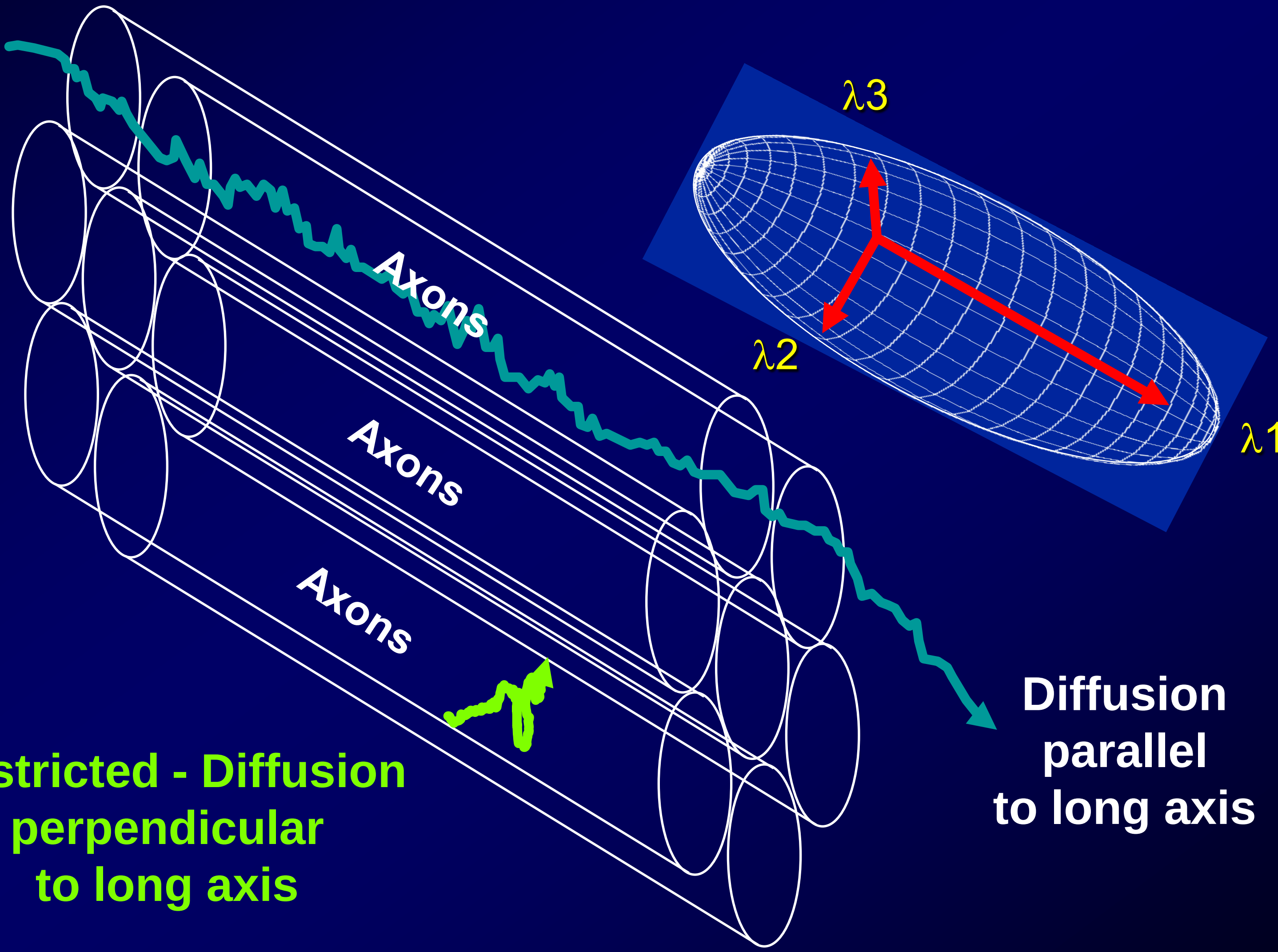
Diffusion Tensor Imaging

- Measures the magnitude and orientation of water in brain tissue
- For each voxel, DTI estimates diffusion in terms of the axes of the eigenvectors of an ellipsoid
- Fractional anisotropy (FA), is a normalized metric (or scalar) that represents the fraction of the tensor that can be assigned to the anisotropic diffusion

DTI

- Terms to know: isotropic and anisotropic
- The FA metric ranges between 0 and 1, where:
  - "0" (zero) represents perfectly "isotropic" diffusion, such as is found in the cerebrospinal fluid where diffusion is equivalent in all direction
  - "1" is the *extrema* for "anisotropic" diffusion, indicating maximum difference between directional components, such is found in coherent white matter tracts which consist of long tubes

Diffusion Tensor Imaging

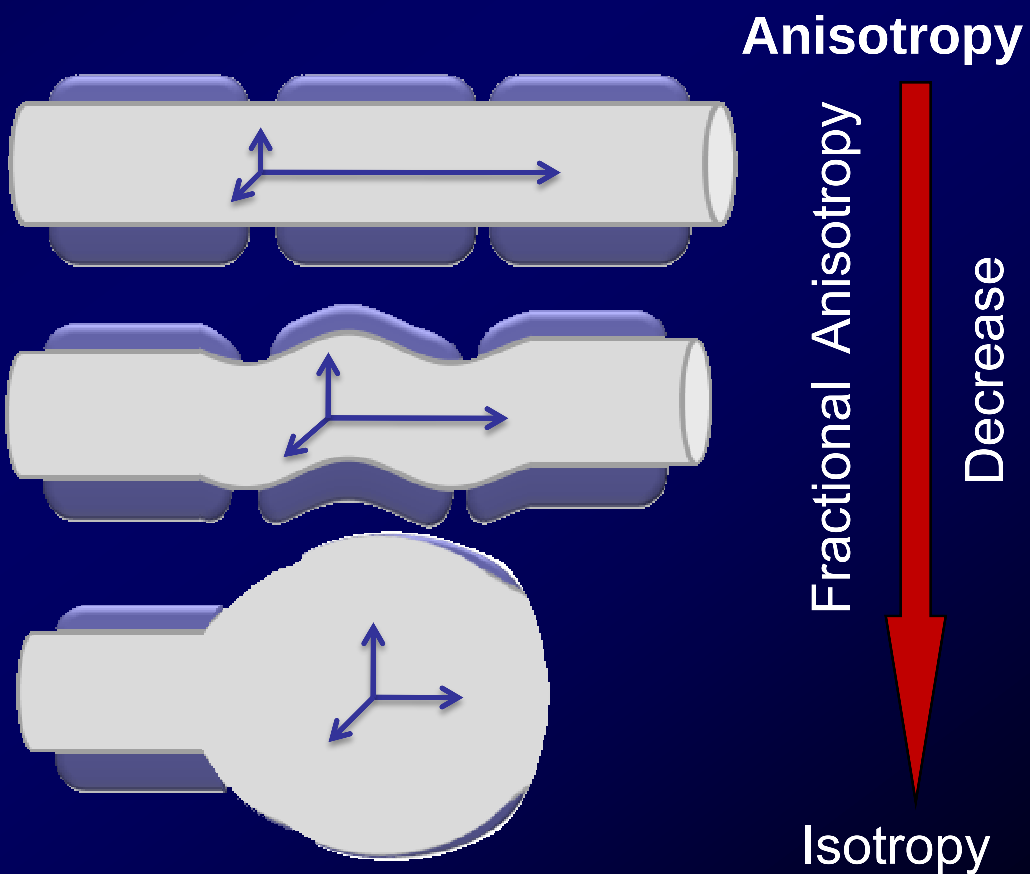


Diffusion parallel to long axis

Restricted - Diffusion perpendicular to long axis

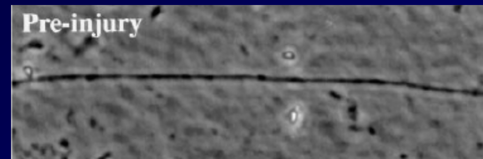
Effect of Diffuse Axonal Injury on Fractional Anisotropy

- TBI causes DAI
- Axonal injury creates barriers for diffusion along the axon
- TBI can also result in membrane permeability changes



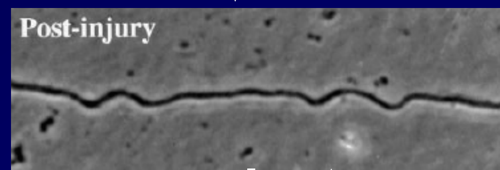
Secondary Axotomy Stages

Pre-injury



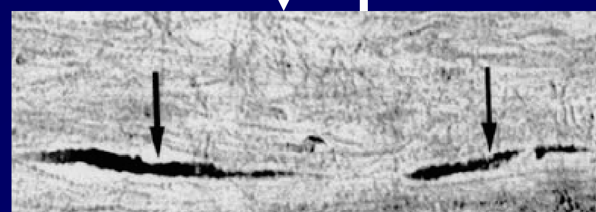
Stretch and Shear

Seconds post



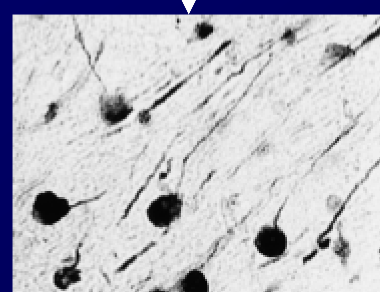
(Reversible disruption of cytoskeletal elements)

Minutes-to-hours post



Poration and depolarization with NMDA initiated Ca^{2+} influx, increased Na^{+} influx-induced swelling

Days-to-weeks



Ca^{2+} influx → activation of cysteine proteases → degradation of cytoskeletal elements → interruption of axonal transport → detachment from distal stump → bulb formation

Fractional Anisotropy (FA)

Fractional Anisotropy is calculated from the eigenvalues λ_1, λ_2, λ_3 of the diffusion tensor:

λ_1 is the principle eigenvector
λ_2 is the intermediate eigenvector
λ_3 is the minor eigenvector

$$FA = \frac{\sqrt{3}}{\sqrt{2}} \frac{\sqrt{(\lambda_1 - \lambda)^2 + (\lambda_2 - \lambda)^2 + (\lambda_3 - \lambda)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

FA values scale from 0-1

Susceptibility-Weighted Imaging (SWI)

- SWI exploits the *susceptibility* differences between tissues and uses the phase image to detect these differences.
- Magnitude and phase data are combined to produce an enhanced contrast magnitude image which is exquisitely sensitive to venous blood, hemorrhage and iron storage.
- The imaging of venous blood with SWI is a *blood-oxygenation-level dependent* (BOLD) technique which is why it was (and is sometimes still) referred to as BOLD venography.
- Due to its sensitivity to venous blood SWI is commonly used in TBI and for high resolution brain venographies but has many other clinical applications.

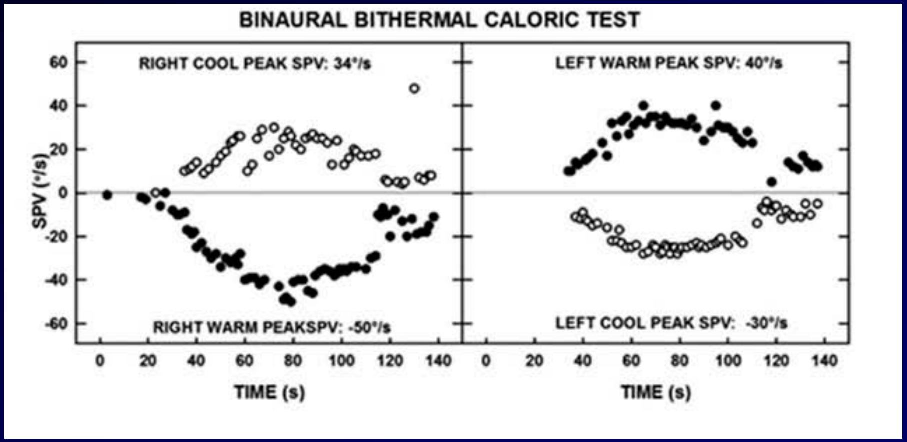
Temporal Lobe Vasculature

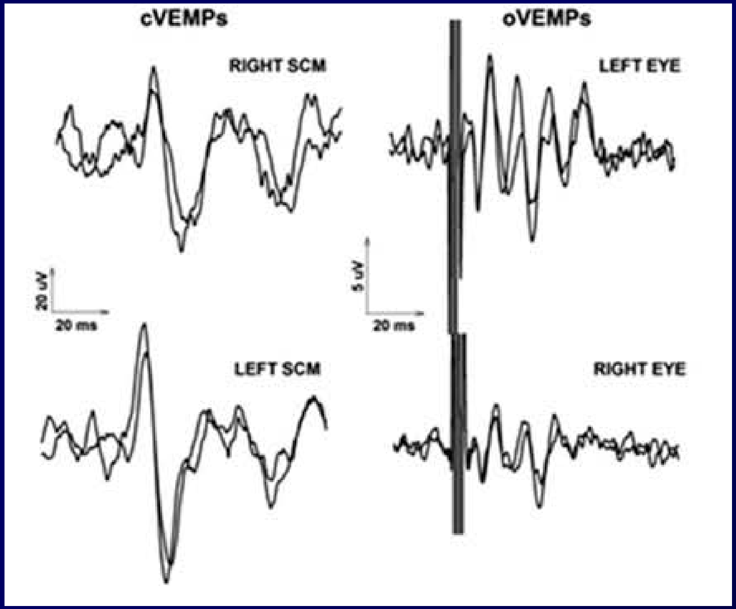
(From: Harrison, R.V. et al (2002). Blood capillary distribution correlates with hemodynamic-based functional imaging in cerebral cortex. *Cerebral Cortex, 12*, 225-233).

Case Reports

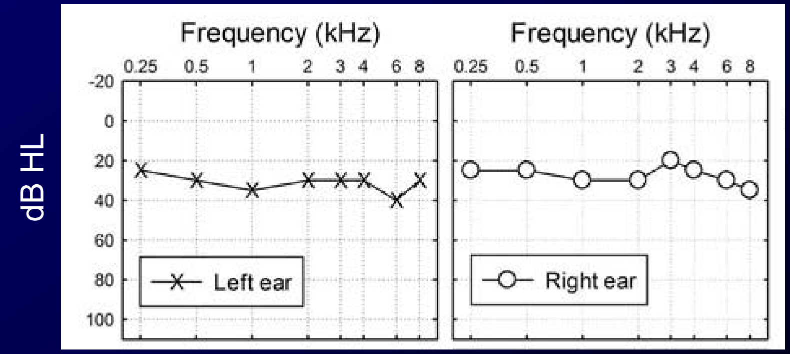
- Four Veterans, aged 29–46 years, complaints of chronic dizziness and/or postural instability following blast exposures.
- Comprehensive vestibular, balance, gait, audiometry and neuroimaging procedures were performed.
- Based on the neuroimaging and vestibular and balance test results, it was found that all individuals had DAI and all had one or more micro-hemorrhages or vascular anomalies.
- alone.

Case 1

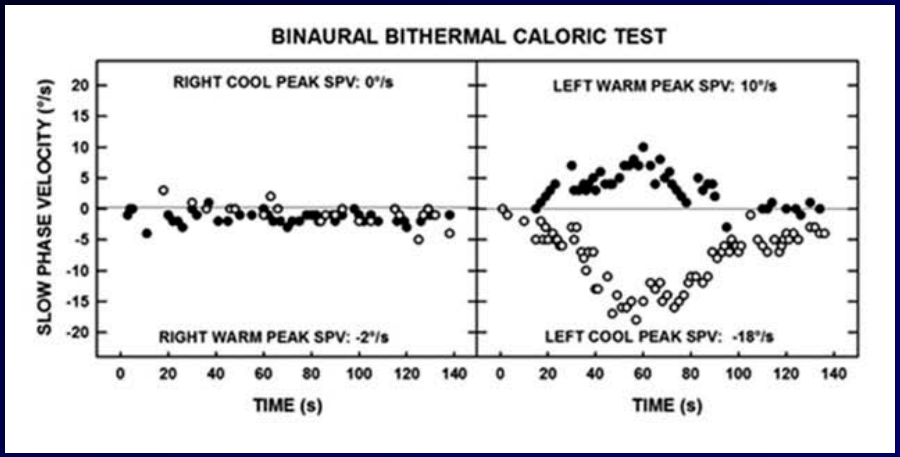


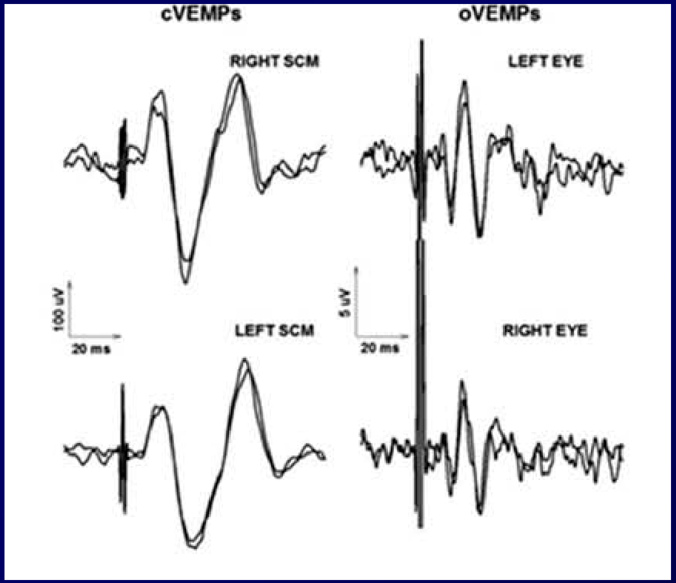


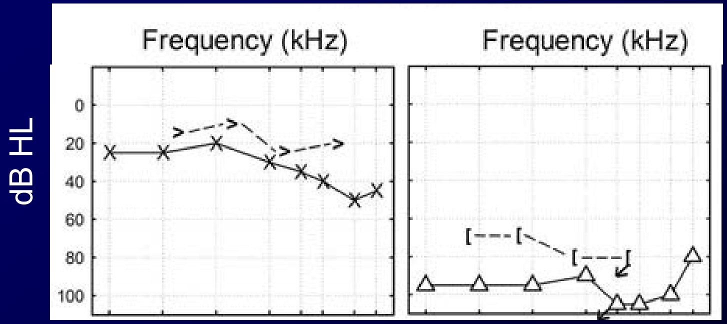
1. Calorics, rotary chair, cervical and ocular vestibular evoked myogenic potentials (cVEMPs and oVEMPs) were WNL; normal peripheral function
2. Low Sensory Organization Test (SOT) score suggests abnormal balance function.



Case 2

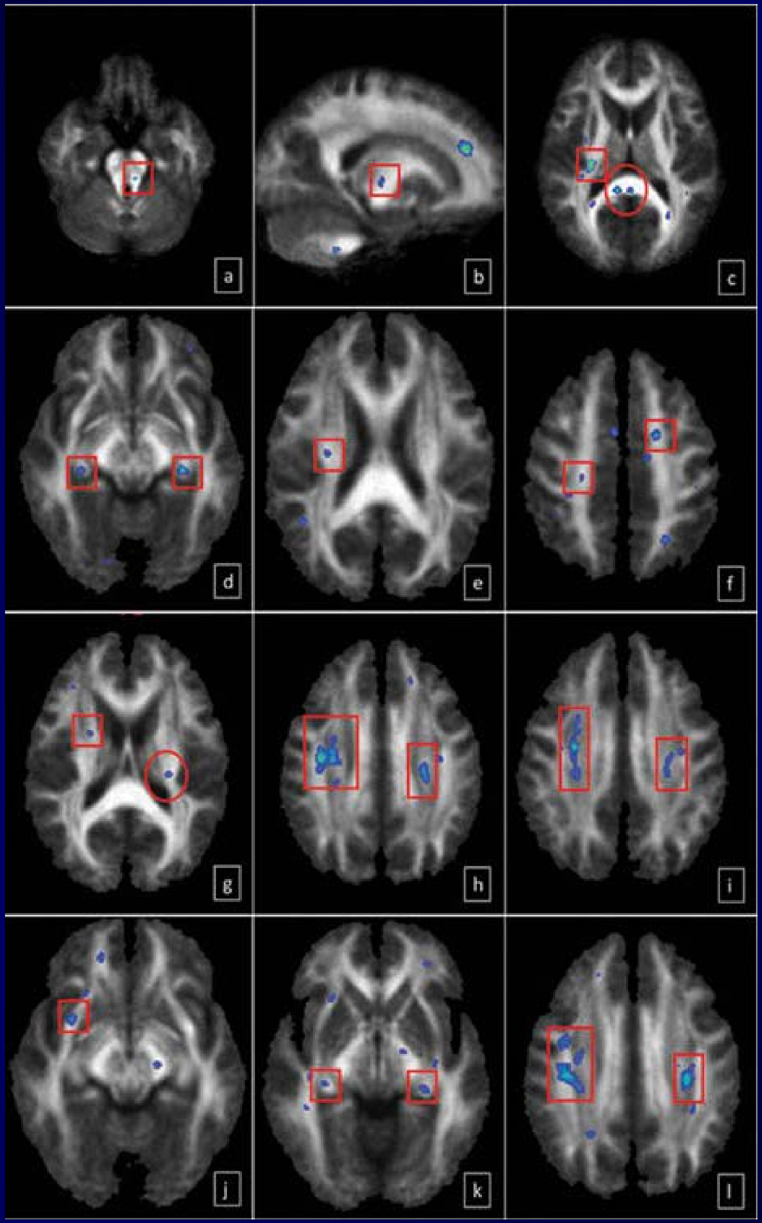






1. Vestibular and balance function tests revealed a right unilateral weakness on the caloric test and low gain on rotary chair, suggesting right horizontal semicircular canal dysfunction.
2. Bone conduction cVEMPs and oVEMPs revealed normal otolith organ function and the SOT revealed normal balance function.

Regional Areas of Lower FA Values



Case 1.

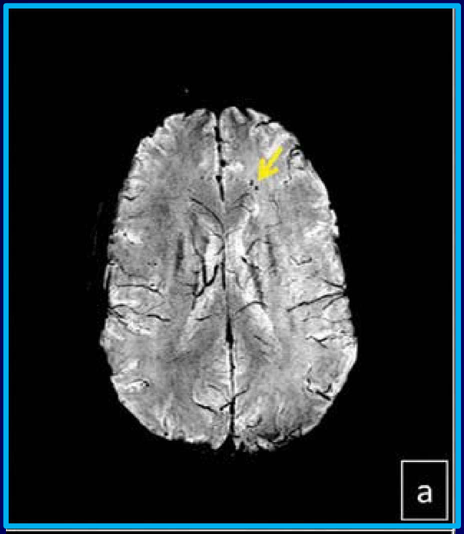
Case 2.

Case 3.

Case 4.

Examples from Gattu et al., (2016)

Case 1: Micro-hemorrhages above the ventricle in the ACR of frontal white matter region



Case 2: Micro-hemorrhage in the left posterosuperior cerebellar hemisphere

Case 3: an abnormally dark signal in the veins draining into the left septal vein

Case 4: Micro-hemorrage in the superior frontal region of the CR

Magnetic Resonance Imaging (MRI)

- Often stated that MRI is "*insensitive*" to TBI
  - Broad generalized statements need to be qualified and updated
- This statement depends on type of imaging paradigm being employed (pulse sequence)
- Methodologies described herein have many advantages and few disadvantages
- Ideal for:
  - biomarker development
  - drug discovery and development
  - longitudinal experimental designs requiring repeated measures over time

- The use of contemporary neuroimaging studies in conjunction with comprehensive vestibular and balance assessment is starting to provide a better understanding of the pathophysiology and pathoanatomy of dizziness following blast exposures than standard vestibular and balance testing alone.


THANK YOU

Neuroimaging & Rehabilitative Options in Vestibular & Balance-Related Dysfunction Following Noise & Blast

Courtney D. Hall, PT, PhD
Research Health Scientist
Auditory and Vestibular Research Enhancement Award Program
James H Quillen VAMC

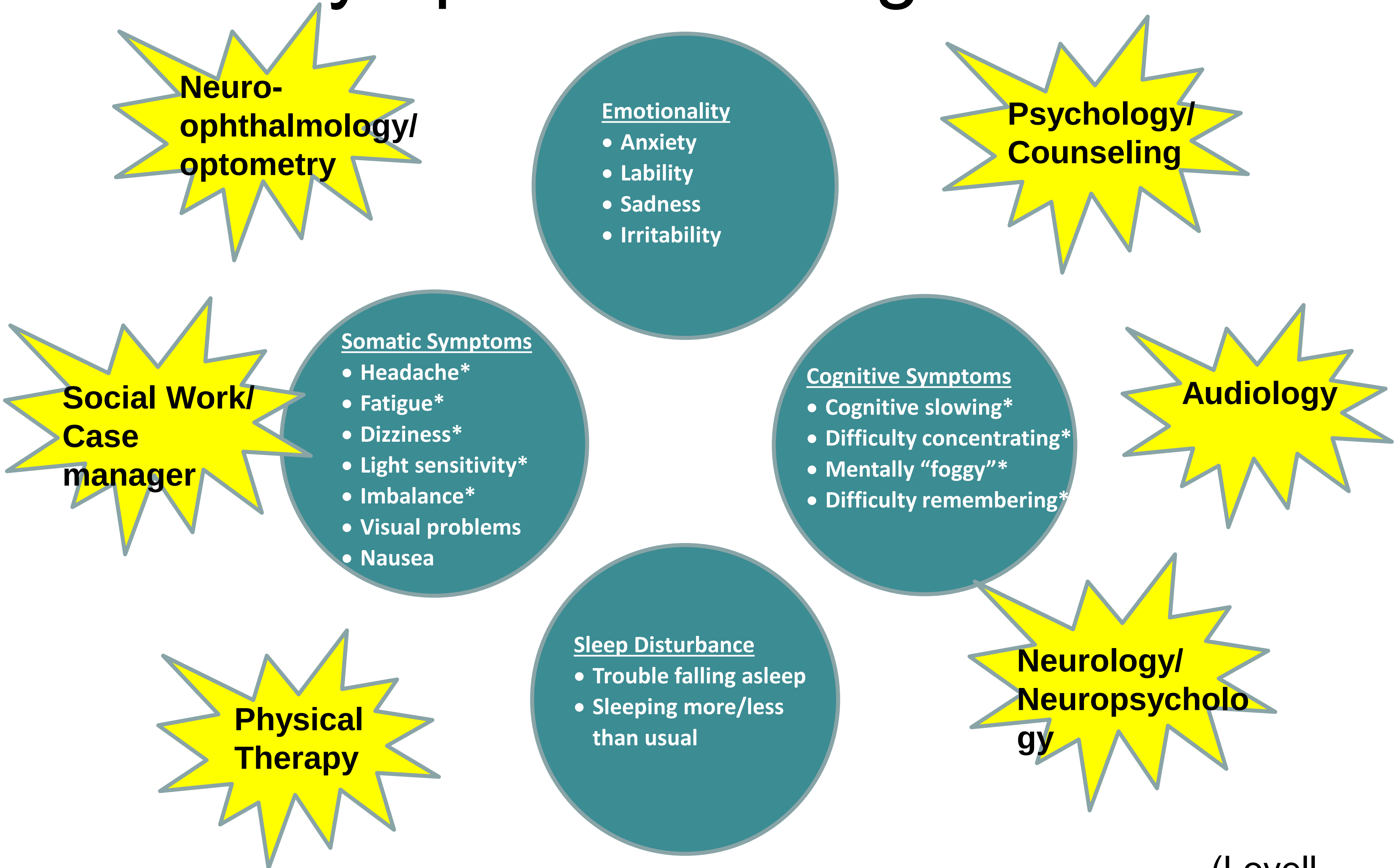
Associate Professor
Department of Physical Therapy
East Tennessee State University

Consequences of blast/mTBI

- Complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces
  - Concussion/mTBI often used interchangeably
- Resolution of post-concussion symptoms generally quick, but prolonged in some individuals
  - 80-90% resolve in 7-10 days
  - Poor prognosis for dizziness/imbalance that lasts for six months or longer

(Hoffer, 2004; McCrory, 2013)

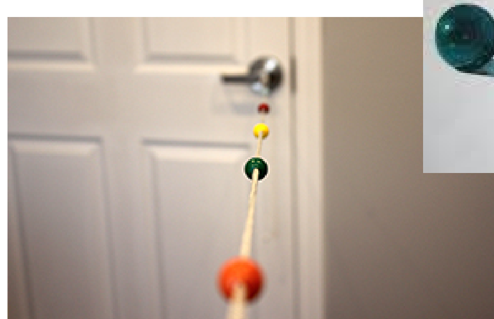
Post-Concussion Symptoms/Management



(Lovell, 2006)

Oculomotor abnormalities

- Convergence impairments – decreased positive fusional vergence with near target
  - ~50% of combat-injured personnel (blast and non-blast)
  - May contribute to dizziness because of diplopia, impact on vestibulo-ocular reflex
  - Vision therapy can improve convergence insufficiency



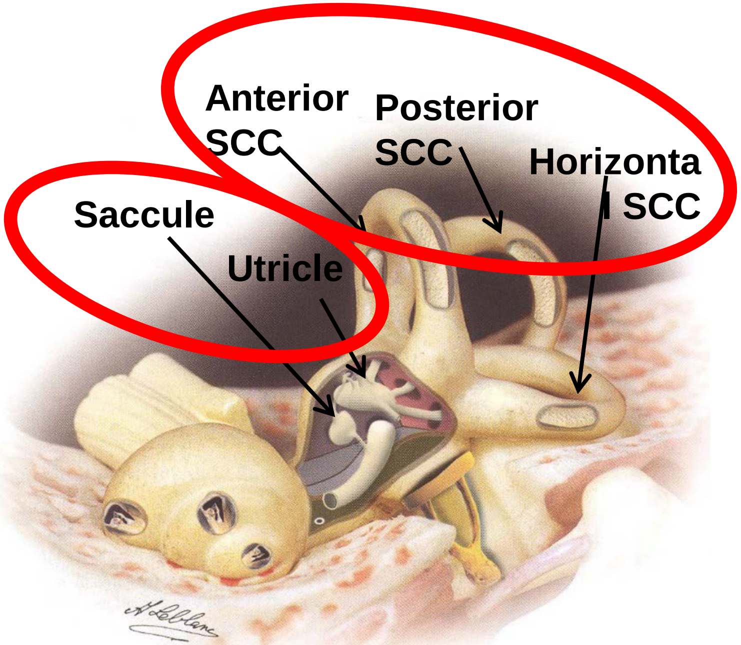
(Barnett, 2015; Brahms, 2009)

Prevalence of dizziness

- Up to 77% of cases immediately after sports-related injury (Marshall, 2015)
- Most common symptom in blast-related mTBI (Hoffer, 2010)
  - 98% acute; 84% chronic
- In non-sports, non-military adults 51% at injury and persistent in 28.5% up to one year (Theodom, 2016)

Vestibular consequences of blast/mTBI

- Cause(s) of dizziness unclear: brain injury vs. peripheral vestibular dysfunction
  - symptom-based questionnaires
  - limited assessment of vestibular system (horizontal semicircular canals, SCC)
- Post-traumatic BPPV common (5-28%) (Alsalaheen, 2010; Hoffer, 2004)
- Otolith organs may be more vulnerable to blast exposure or head injury (Kerr & Byrne, 1975; Akin & Murnane, 2011)
- Conventional vestibular assessment excludes tests of otolith organ
  - vestibular evoked myogenic potentials (VEMPs)



Functional consequences of blast/mTBI

- Abnormal visual acuity with head turns
- Impaired integration of sensory input for balance
- Gait impairments
  - Conservative gait strategy: increased medial-lateral sway and slower speed
  - Difficulty dividing attention

(Akin, 2015; Zhou & Brodsky, 2015; Parker, 2005, 2006)

Prevalence of vestibular dysfunction

- 90% of adolescents with sports-related concussion and dizziness (n=42) had vestibular/balance abnormalities
  - Spontaneous nystagmus (24%)
  - Caloric tests (21%)
  - Subjective visual vertical (13%)
  - Dynamic visual acuity (57%)
  - Computerized dynamic posturography (56%)

(Zhou, 2015)

Prospective case-controlled study of Veterans with blast exposure/mTBI

Research funded by VA Rehabilitation R&D Merit Review Grant (Akin, PI)

Summary of Descriptive Statistics for Group Demographics

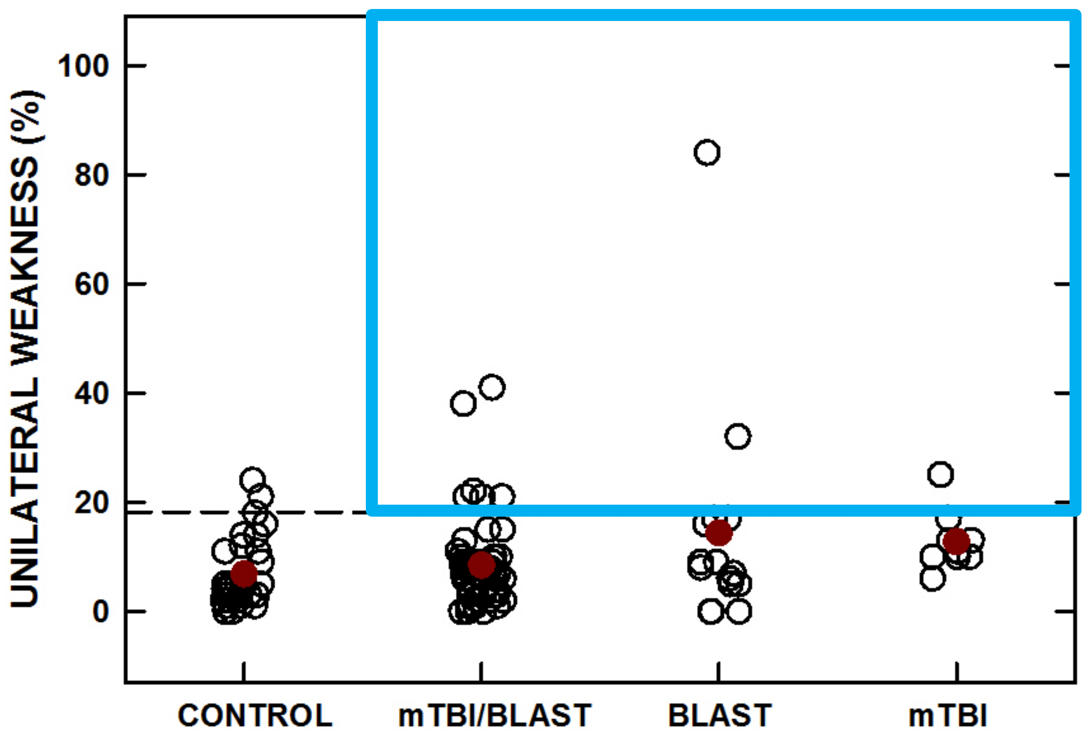
Group	N	Age (years) X ± SD	Age (years) Range	MMSE X ± SD	DHI X ± SD	Time since onset (mos) X ± SD	PTSD N (%)
Control	31	31 ± 10	20 - 59	30 ± 0.5	0	N/A	N/A
mTBI/Blast	56	37 ± 10	22 - 67	29 ± 2	50 ± 23	88 ± 44	53 (95)
Blast	17	40 ± 11	26 - 63	29 ± 2	49 ± 25	119 ± 87	10 (59)
mTBI	8	40 ± 12	22 - 57	29 ± 0.5	41 ± 17	91 ± 96	3 (38)

(Akin, 2015)

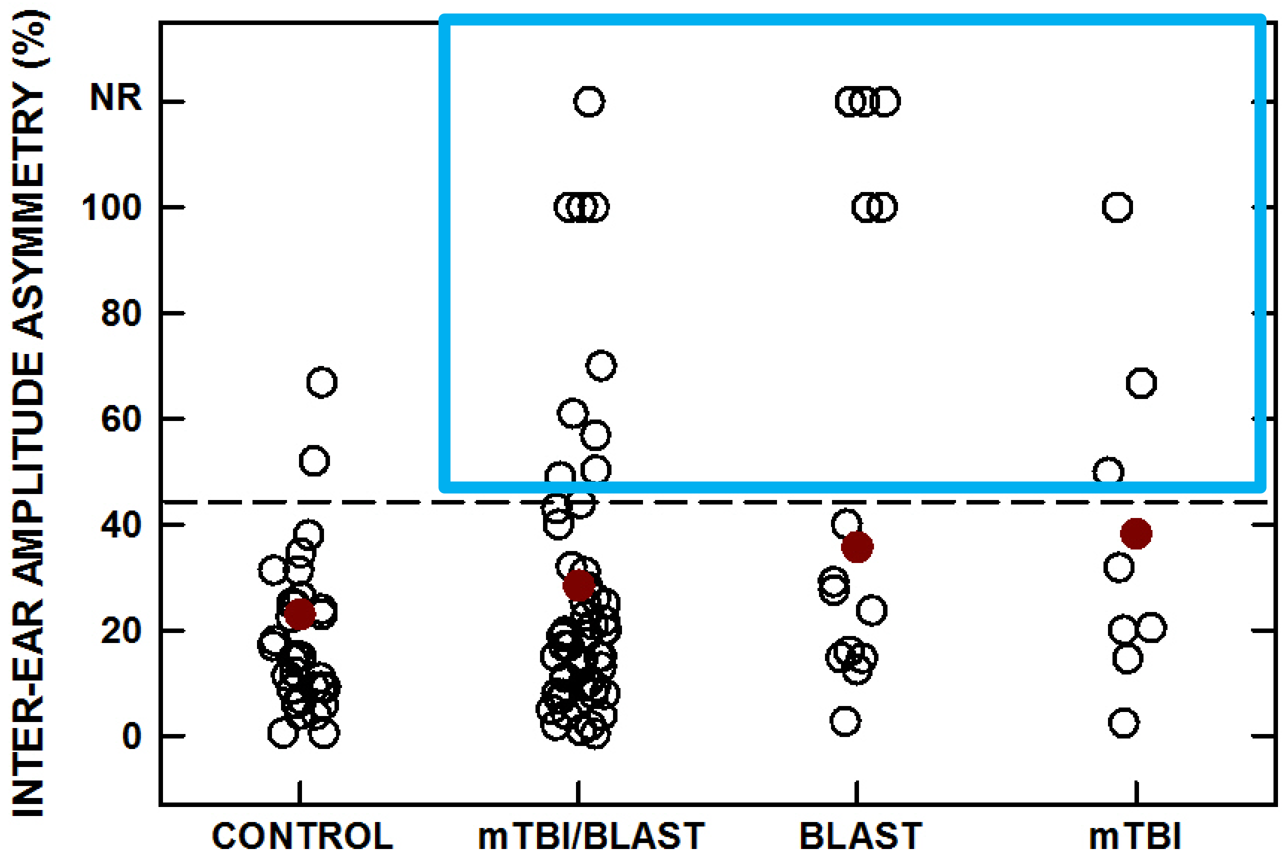
Symptom Frequency (%) Reported for Each Group

Group	Vertigo	Imbalance	Lateropulsion	Lightheadedness	Oscillopsia
Control	0	0	0	0	0
mTBI/Blast	29 (52)	52 (93)	31 (55)	43 (77)	10 (18)
Blast	12 (71)	12 (71)	10 (59)	14 (82)	8 (47)
mTBI	3 (38)	8 (100)	3 (38)	7 (88)	4 (50)

Caloric Test

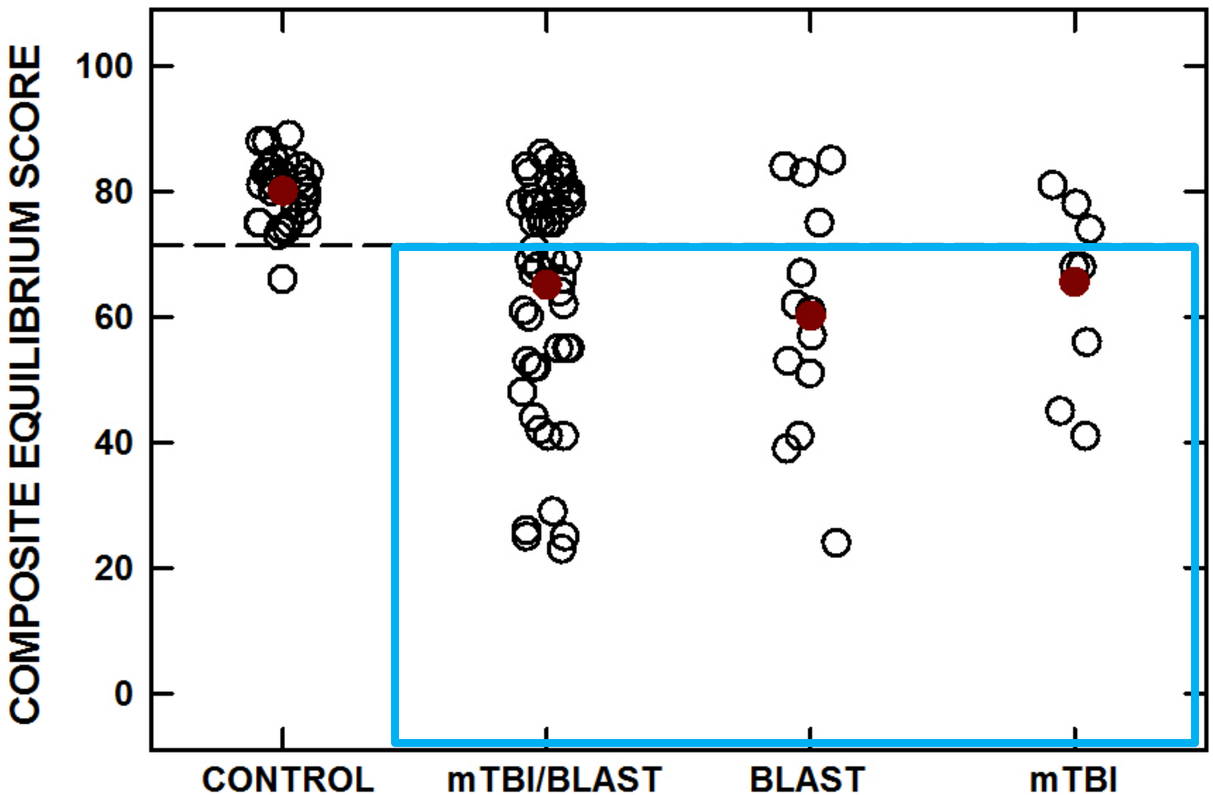


Cervical Vestibular Evoked Myogenic Potentials



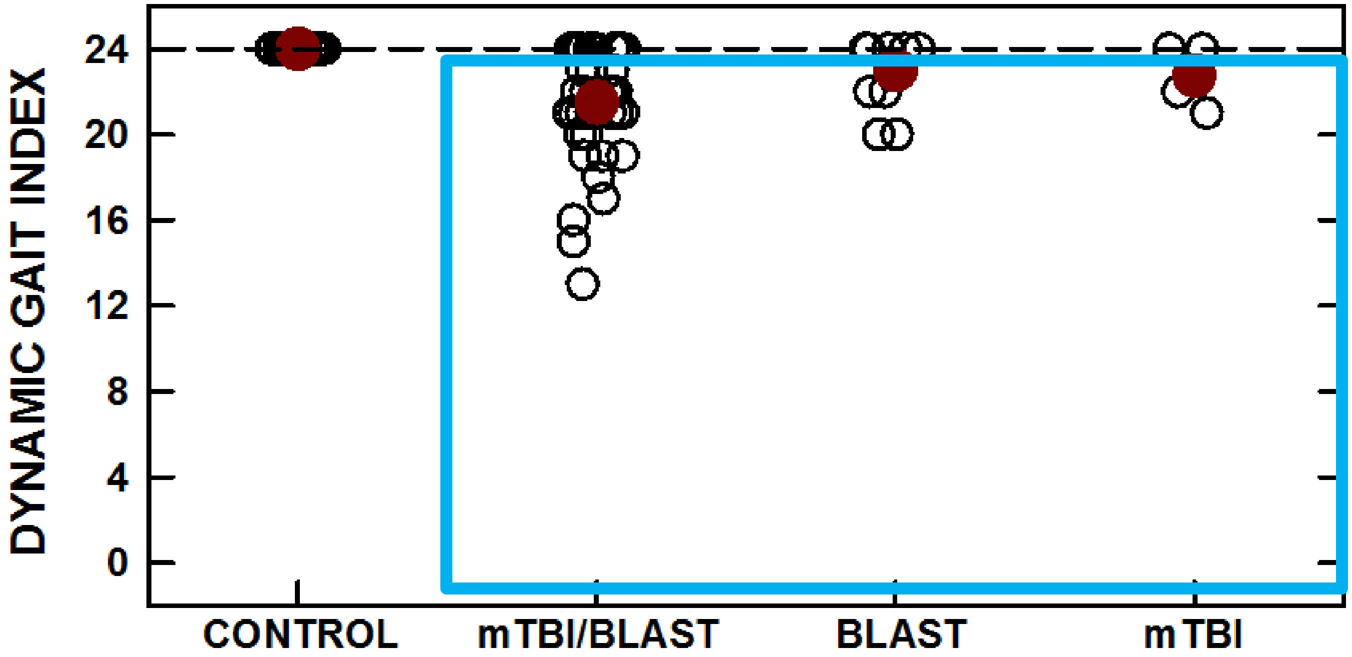
(Akin, 2016)

Sensory Organization Test

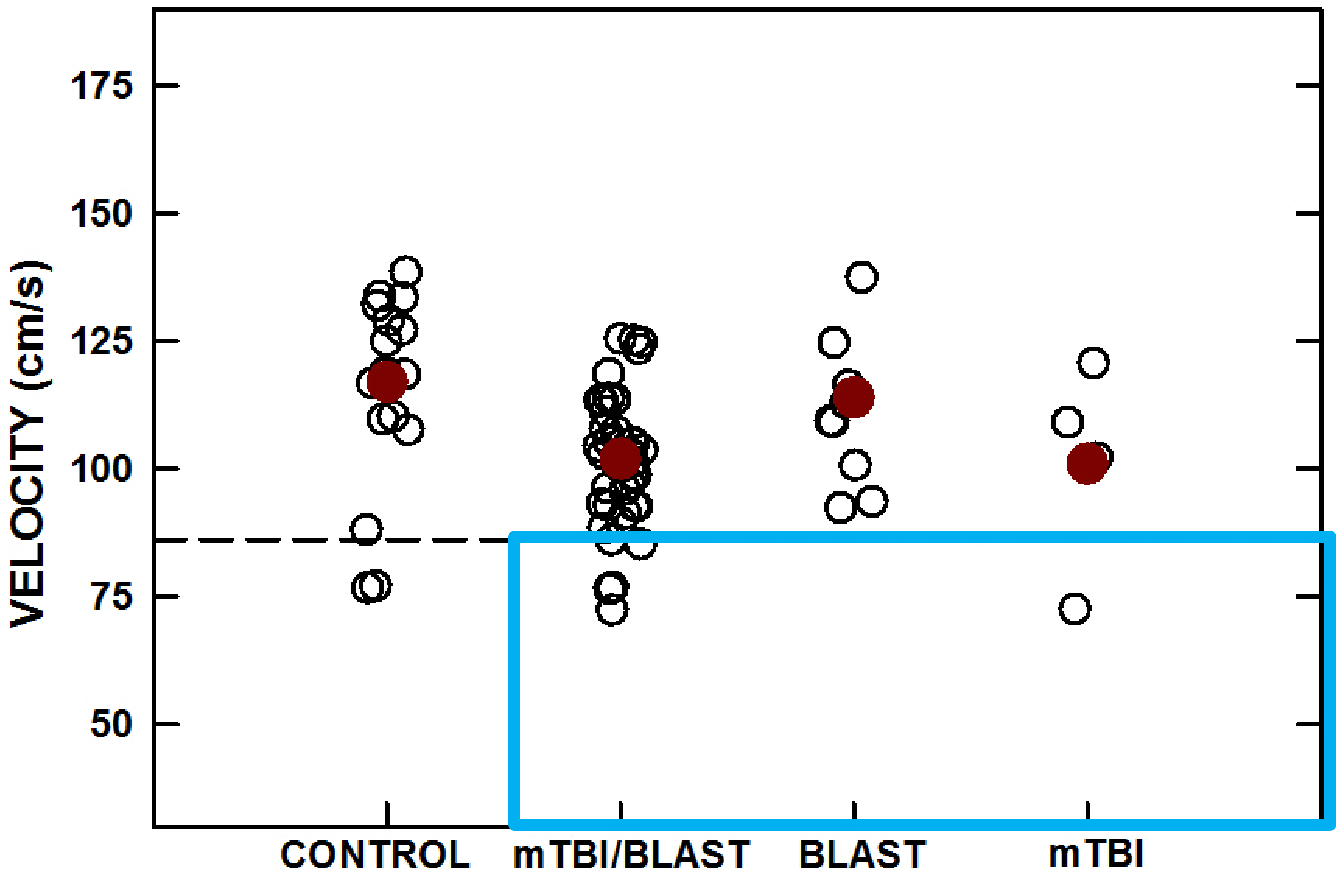


(Akin, 2016)

Dynamic Gait Index

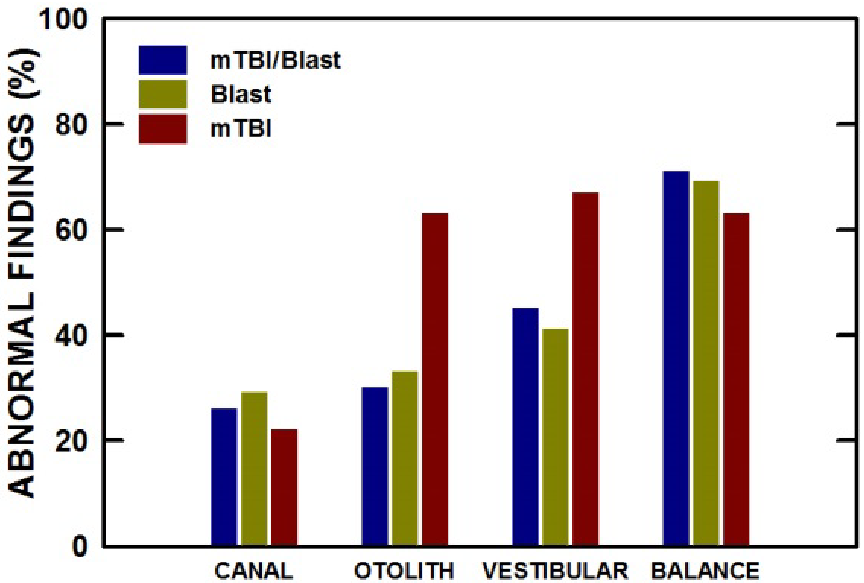


Gait Speed



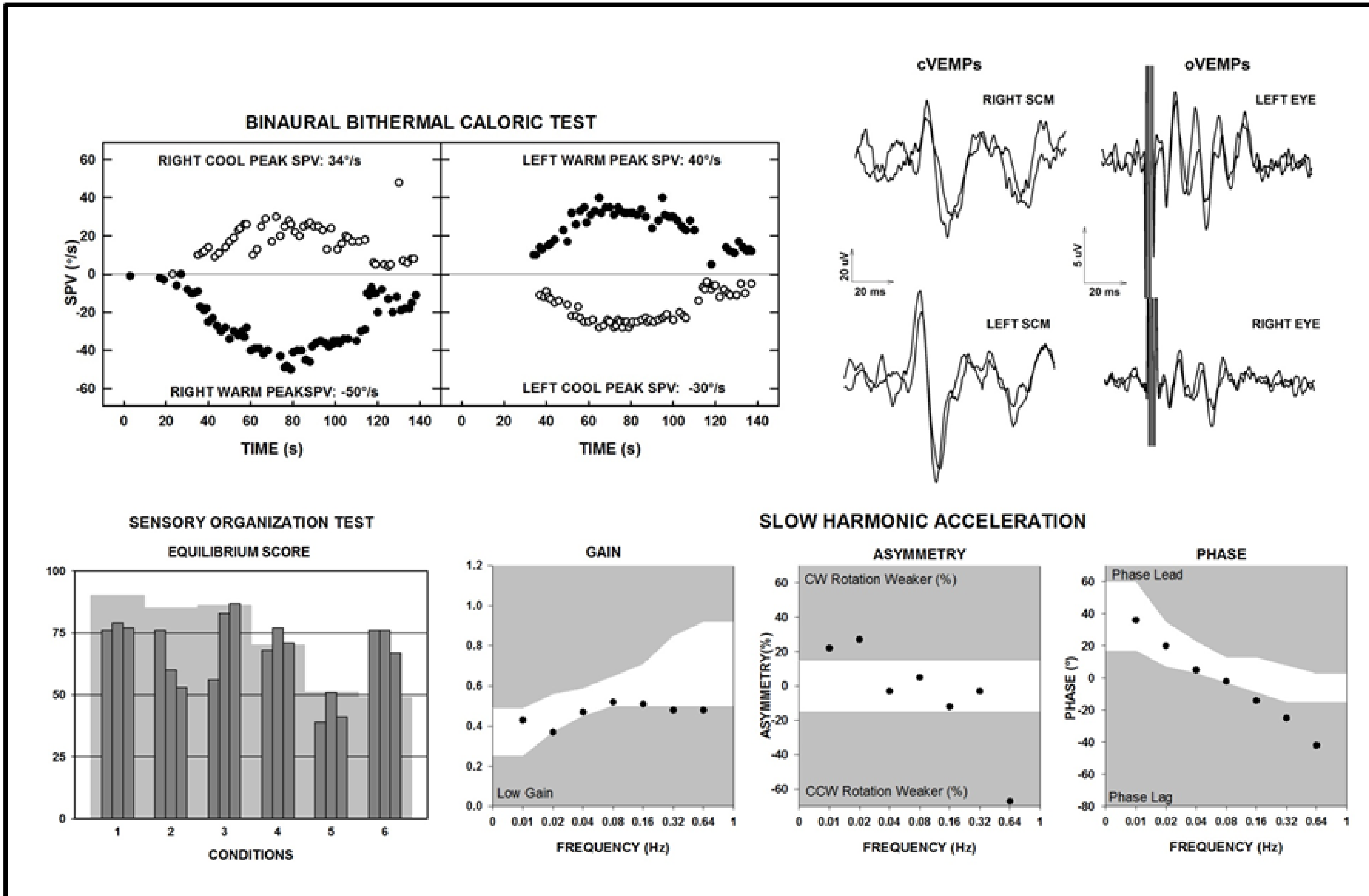
VELOCITY (cm/s)
175
150
125
100
75
50
CONTROL
mTBI/BLAST
BLAST
mTBI

Summary of Vestibular/Balance Findings



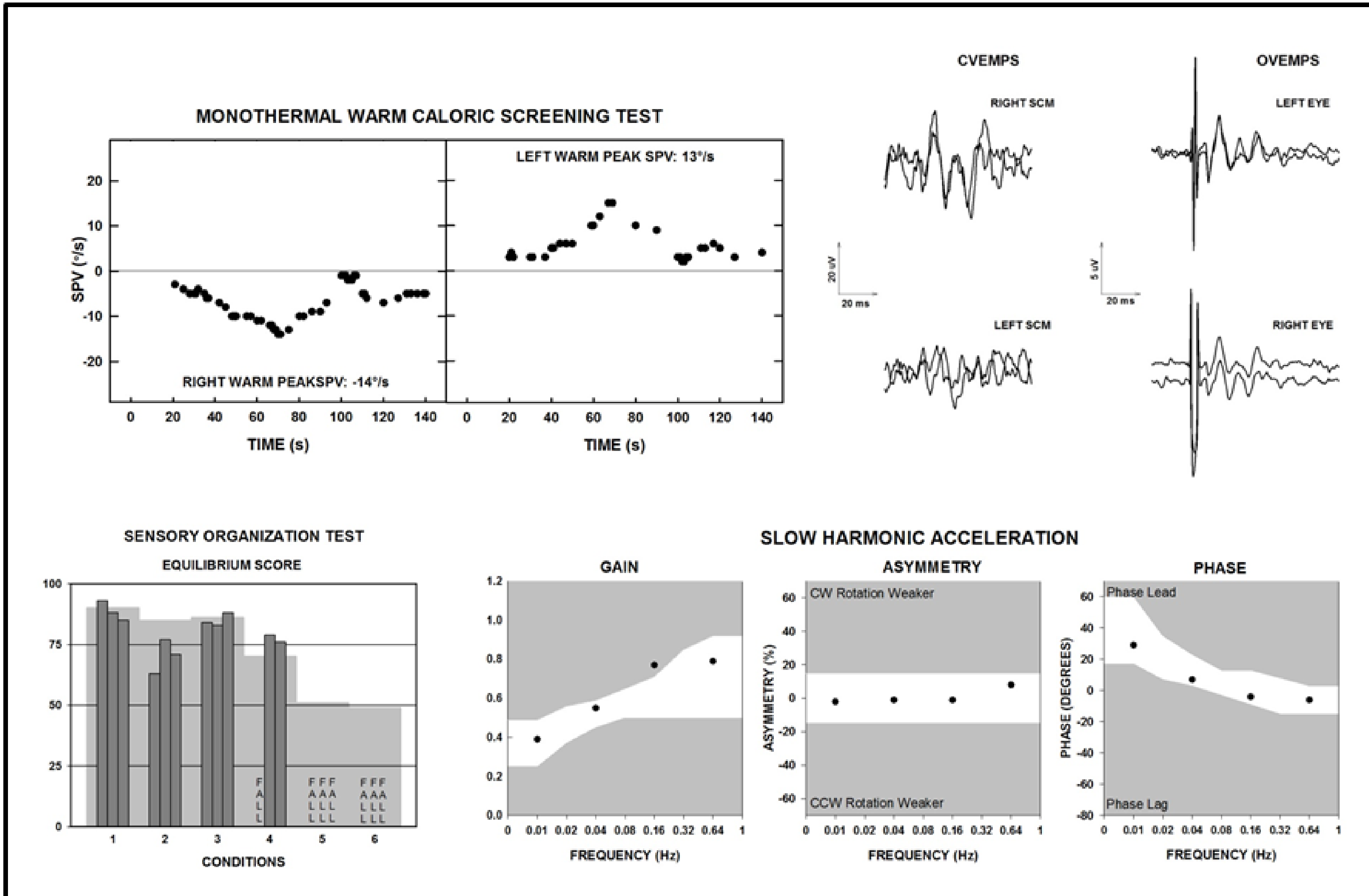
- Significant differences between CON (n=31) and EXP (n=81) for otolith function, balance and gait
- 48% with mTBI and/or blast had abnormal vestibular function
  - Frequency of abnormalities of otolith organ > semicircular canal
- 22-71% with mTBI and/or blast had abnormal balance and/or gait function

Case 1



(Gattu, 2016)

Case 4



(Gattu, 2016)

Efficacy of Vestibular Rehabilitation Therapy (VRT)

- Consensus statement on concussion in sport:
  - Persistent symptoms should be managed by multidisciplinary team of healthcare providers
  - Therapies including cognitive, physical, psychological and vestibular should be considered
- A systematic review suggests that VRT is beneficial in mTBI/concussion with evidence of earlier return to sport
  - Weak evidence (level 3): high risk of bias in 7 of 10 studies
  - Need for high quality randomized controlled trials!

(McCrory, 2013; Murray, 2017)

Primary outcomes for VRT

- Dizziness
  - Dizziness handicap inventory, vertigo symptom scale, motion sensitivity quotient, dizziness analog scale
- Gaze stabilization
  - Dynamic visual acuity or gaze stabilization
- Balance and gait
  - Activities-specific balance confidence scale, functional gait assessment, timed up and go, dynamic gait index, high-level mobility assessment tool
- Return to work/sport

Components of VRT

- Habituation exercises
  - Gradual increase in exposure to provoking stimuli (8 of 10 studies)
  - Optokinetic stimulation and gaze stabilization challenges
- Gaze stability exercises
  - Vestibulo-ocular exercises (8 of 10 studies)
- Balance exercises
  - Challenging exercises for balance and function (9 of 10 studies)
- Aerobic exercises
  - Muscle conditioning (3 of 10 studies)

(Alsalaheen, 2010; Gottshall, 2010; Hoffer, 2004; Moore, 2016; Schneider, 2014)

Prescription of VRT

- Frequency
  - 1-2x/week supervised PT sessions
  - Daily home exercise program
- Intensity
  - Increased as tolerated (Hoffer, 2004)
  - Encouraged to work at maximum tolerance (Gottshall, 2010)
- Time
  - 2 weeks to 16 weeks

Progression of VRT

Progression

- Rest followed by graded exertion, cervical spine PT and VRT (Schneider, 2014)
  - Use symptoms to guide progression
- Modifiers manipulated to increase challenge: (1) posture, (2) surface, (3) base of support (BOS), (4) trunk position, (5) arm position, (6) head movement, (7) whole body movement, (8) visual input, (9) cognitive dual task (Alsalaheen, 2010)

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