Repercussions of Blast-Related Traumatic Injury on Peripheral and Central Auditory Function

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Overview

- Describe initial work on the development of parallel human and animal models to better understand blast-induced TBI focusing on the auditory modality.
- Appeal for the development of more objective biomarkers (imaging paradigms) that can be correlated with behavioral, electroacoustic, electrophysiological data.
- Consider a paradigm shift in the assessment of (C)APD, focusing on the specificity of the deficit.
Interdisciplinary Effort AT Wayne State University

- Communication Sciences & Disorders
  - Dr. Anthony T. Cacace
- Otolaryngology/Communication Sciences & Disorders
  - Dr. Jinsheng Zhang
- Neurology
  - Dr. Randall Benson
- Biomedical Engineering
  - Dr. Pamela VandeVord
- Physics/Radiology
  - Drs. E. Mark Haacke, Jiani Hu
- Anatomy and cell biology
  - Drs. Averil Genene Holt, Bruce Berkowitz
- Psychology
  - Drs. Scott Bowen, George Borszcz
Collaborator for CAPD

- **Dennis J. McFarland, Ph.D.**, staff scientist, Laboratory of Nervous System Disorders, Wadsworth Laboratories, NYS Health Department, Albany, NY; recognized for many original and important ideas and contributions in addressing this topic.
Consider Injuries from the War-on-Terror

- Overtly visible vs.
- Invisible to the naked eye
Visible Injuries of the War-on-Terror

• Loss of
  – Arm
  – Leg
  – Hand
  – Brain lesions (bullet wounds, projectiles, explosions, etc.)
Invisible Injuries from the War-on-Terror

• Blast induced
  – Loss of hearing and chronic tinnitus
  – The most common co-morbidities associated with primary blast exposures and related problems, also include:
    • Inability to tolerate normal sound levels in the environment (hyperacusis)
    • Difficulty hearing in noise
Invisible Injuries from the War-on-Terror (Cont.)

- Vestibular-related problems
- Disturbances in processing various types of sensory information
- Cognitive problems associated with memory and attention
- Psychiatric disturbances associated with post-traumatic stress, emotion (anger management), depression, sleep, and suicide

• Invisible injuries can be just as debilitating as the more overt injuries
Blast-Induced Injuries

• Becoming increasingly problematic for health related agencies like the VA, because:
  – Injuries are not well defined
  – Long-term effects are unknown
  – Appropriate paradigms are not in place to either evaluate or effectively treat individuals

• With respect to blast-induced trauma to the ear and brain, fair to say:
  – wide gaps in our knowledge exist concerning underlying processes and mechanisms
Conceptualization of the Problem

• Blasts exposure simultaneously affect the periphery (ear) and central nervous system
• Manifestations of blast overpressures 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 of white matter tracts that interconnect various brain areas
     • subserving neural networks vital to sensory and cognitive functions
  – Alterations in the neurobiochemical environment also occur in specific regions-of-interest
Primary and Secondary Effects of Blast Injuries

External, Middle, and Inner ear

Cochlea

Organ Of Corti

Scala vestibuli
Scala tympani
Vasculareri
Organ of Corti

Mesencephalon

Brainstem

Cortex

Cortical

Heschl's Gyrus

Non specific Thalamus

Medial geniculate body

Inferior Colliculus

Dorsal and Ventral Coclear nuclei

Lateral Olivary Complex

Medical Olivary Complex

Auditory Nerve

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Auditory Nerve
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

**Blast-Related Non-penetrating TBI**

- **From above**
  - Contusion
    - Superficial gray matter
    - Infer, lat, ant frontal lobe
    - Temp. lobes
  - Subdural hemorrhage
    - Frontal and parietal convexities
  - Diffuse axonal
    - Cortical/medullary
    - Internal capsule
    - Deep gray matter
    - Upper brainstem
    - Corpus callosum

- **From in front**

- **From the side**

- **From the midline**
Imaging Modalities

(Adopted from Spore Programs: JHU)
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 MRI paradigm being employed and pulse sequence utilized
- Methodology has many advantages and few real disadvantages
- Ideal for:
  - biomarker development
  - drug discovery and development
  - those experimental designs requiring repeated measures over time
Biomarker Development for mTBI
(Appatomical-based MRI measures)

- Voxel-based morphometry (VBM)
  - Unbiased assessment of anatomical differences
  - Group comparison study
  - Useful for developing hypotheses

- Individual morphological segmentation
  - Focused on specific regions-of-interest
  - Medial partition of Heschl’s gyrus

- Diffusion-tensor imaging (DTI)
  - Assessment of white matter tracts exposed to shearing injuries

- Susceptibility-weighted imaging (SWI)
  - Detection of micro-hemorrhagic lesions
Biomarker Development for mTBI
(Functional measures)

• **Functional (fMRI)**
  – using BOLD response
  – manganese enhanced MRI (MEMRI)

• **Magnetic resonance spectroscopy (MRS)**
  – Assessment of neurobiochemical information, including:
    • Metabolites
    • Neurotransmitters
Audiometric Profile of Blast-Induced Acoustic Injury

Reflectance

Audiogram

DP-Gram

(Distortion product Otoacoustic emissions)

(note: filled yellow circles denotes the standard discrete frequencies often used during acoustic admittance testing vs. the broadband response of middle ear power reflectance.)
Imaging Techniques for Studying Tinnitus: Overview

• **Structural**
  – Magnetic Resonance Imaging (MRI)
  – Voxel-based morphometry (VBM)
  – Individual morphological segmentation

• **Functional**
  – fMRI
  – Manganese enhanced (MEMRI)

• **Neurobiochemical**
  – Magnetic resonance spectroscopy (MRS)

“*The Scream*”
Edvard Munch
1893
Voxel-Based Morphometry (VBM)

• Unbiased technique to characterize differences between brains of well-defined groups using high resolution structural/anatomical MRI

• Accomplished by:
  – Normalize in individual MRIs into a standardized template
  – Segment images into gray matter, white matter, and CSF
  – Perform a statistical assessment of voxel-wise comparisons in different groups of subjects
  – Co-register statistics on MRI scans
VBM Experiment

- 28 healthy controls without tinnitus
- 28 individuals with tinnitus
- Matched for age and gender
  - mean controls 40 yrs; tinnitus 39 yrs
  - 15 females, 13 males

VBM and Tinnitus
(Whole Brain Analysis)

Reduced gray matter in subcollasal area (SCA): including nucleus accumbens
VBM and Tinnitus
(Region-of-Interest Analysis)

(Increase in gray matter concentration; right MGB; thalamus)
Preliminary Model
(Author’s Interpretation)

- Tinnitus related neural activity is perpetuated in thalamus (MGN) resulting in reorganization after hearing loss.
- Gray matter decrease in SCA results in reduced inhibitory feedback and puts people at risk for developing tinnitus.
- Inhibitory feedback from SCA may normally help suppress tinnitus related neural activity.
Repetitive Transcranial Magnetic Stimulation (rTMS)

- Presently, approved to treat depression
- Has been applied as a method for tinnitus suppression
Transcranial Magnetic Stimulation

- Possible to depolarize neurons in the brain using external magnetic stimulation (Barker et al., 1985)
- Involves applying strong impulses of a magnetic fields
  - Duration: 100-300 us
  - Strength: 1.5-2.0 Tesla
- Takes advantage of fact that magnetic fields pass largely undistorted through scalp and skull
- Repetitive (rTMS) induces an electric current in the brain that can cause neuronal depolarization in the cortex of humans

Historical Perspective (cont.)

- Barker and colleagues (1985) first to stimulate central nervous system and different cortical regions
- Single pulse devices adopted by neurologists to measure nerve conduction times
- Therapeutic potential not realized until the availability of higher stimulation rate devices (1990’s)

TMS (cont.)

• Lines of magnetic flux are oriented perpendicular to the plane of the coil
Safety and Risks

- Similar restriction/precautions to MRI; metal may heat up or move (aneurism clips); electronic implants could be damaged, etc.
- Because it induces a current in the brain can induce a seizure
- Seizure risk is low, except for people with history of seizures (important exclusion criteria)
- Can produce discomfort in nerves or muscles of overlying scalp
- Individual pulses result in loud click sounds
  - need hearing protection (insert ear plugs)
  - also guards against acoustic effects of “residual inhibition”
rTMS

• rTMS has been used as a method of tinnitus suppression
• Low frequency pulses (1s; inhibitory)
• High frequency stimulation (>10 s; excitatory)
• Treatment
  – 20 minutes per day; 5 sequential days
rTMS and VBM
Increased gray matter near Brodmann’s area 22

(From: May et al. (2007). Structural brain alterations following 5 days of intervention: Dynamic aspects of neuroplasticity. Cerebral Cortex, 17, 205-210).
Individual Morphological Segmentation
Individual Morphological Segmentation (IMS)

• In contrast to VBM, IMS is used on an individual basis
• Auditory cortices are reconstructed from T1-weighted MRI data
• Saggital MRI segmented along the Sylvian fissure, including planum temporale, Heschl’s gyrus, and anterior supratemporal sulcus
Auditory Cortex
(Axial Plane)

(From: Schneider, P. et al. (2009). Reduced volume of Heschl’s gyrus in tinnitus. NeuroImage (In-press).)
Some Individual Segmentations

Musicians with tinnitus (MT)

<table>
<thead>
<tr>
<th>Tinnitus</th>
<th>Left ear</th>
<th>Both ears</th>
<th>Right ear</th>
<th>Without tinnitus (MN)</th>
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Nonmusicians with tinnitus (NT)

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<th>Tinnitus</th>
<th>Left ear</th>
<th>Both ears</th>
<th>Right ear</th>
<th>Without tinnitus (NN)</th>
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Results

• Tinnitus vs. non-tinnitus
  – Reduced gray matter volumes found in mesial Heschl’s gyrus (mHG) in musicians and non-musicians

• Unilateral tinnitus
  – Reduced gray matter volumes of mHG localized to hemisphere ipsilateral to the affected ear

• Bilateral tinnitus
  – mHG volume substantially reduced in both hemispheres

• Also evidence for a relation between volume reduction and hearing loss
Speculations

- Reduced gray matter volume changes may represent:
  - Antecedents or consequences of tinnitus and tinnitus-related hearing loss
  - May constitute a vulnerability factor

- Raise intriguing possibility that:
  - mHG volume loss might be brought about by atrophy or programmed cell death

- Chronic hyperactivity might:
  - Generate excitotoxic levels of glutamate receptor activation sufficient to induce volumetric changes
What is Magnetic Resonance Spectroscopy?

- Non-invasive technique to measure concentrations of different chemical constituents within tissues
- Based on the same principles of MRI
- Displayed as a spectrum with peaks consistent with various chemical detected
- Functional spectra related to the underlying physiology
Why is it important?

• Identify concentrations of neurobiochemical constituents
  – N-acetyl aspartate
  – Choline
  – Creatine
  – Myo-inositol
  – Lactate

• Measure concentrations of excitatory and inhibitory neurotransmitters
  – Glutamate/glutamine
  – GABA
Metabolites and Their Function

- **NAA**: almost entirely localized to neurons (cell bodies and axons); considered a neuronal biomarker. Decreased concentrations correlate with neuron loss; as seen in tumors, ischemia, and neurodegenerative disease.

- **Creatine**: marker of aerobic energy metabolism of brain cells; present in larger concentrations in grey vs. white matter.

- **Choline**: a constituent molecule of phospholipid metabolism of cell membranes and reflects membrane turnover. Concentration is slightly greater in white vs. gray matter.

- **Myo-inositol**: marker of glial function and is an important osmotic agent regulator for cell volume.

- **Glutamate**: excitatory neurotransmitter
Develop the Use of MRS in Hearing Research

• **Primary goal:**
  – help establish metabolic and neurobiochemical biomarkers of tinnitus

• **Clarify and track disease pathogenesis**
  – establish and confirm mechanism and models
  – delineate effects of hearing loss from tinnitus
  – Adds specificity to structural and other functional MRI data

• **Correlate neurobiochemical properties with structural and functional MRI data**

• **Serve as a tool in drug discovery/development and in clinical trials**
Auditory Cortical Areas

Central Sulcus
(Fissure of Rolando, Rolandic fissure)

- Occupies central position in cortex in anterior posterior dimension
- Separates frontal from parietal lobe

Sylvian Fissure
(Fissure of Silvius, lateral fissure, lateral sulcus)

- Deep fissure on lateral aspect of each hemisphere
- Separates temporal, from parietal, from frontal lobes

(note: intersection of these lines is used as an approximate location of the most anterior aspect of auditory cortex)
Magnetic Resonance Spectroscopy

3T MRI

(8 cm$^3$ voxel)

Structure (ROI)

Function (Display of metabolites)

Relative signal intensity

Chemical Shift

Glu

Cho

Cr

NAA
Normative MRS Study of Auditory Cortex

- Participants matched for age, gender, and pure-tone hearing sensitivity (thresholds <25 dB HL; 0.25-4.0 kHz)
- Based on ANOVA
  - Main effects of age, gender and hemisphere were observed (no interactions)
  - Different metabolites were significant for each main effect

Age Matching

<50 years, n = 30
>50 years, n = 30

Gender

Age (Years)

Male
Female
Group Audiograms

- **Left ear**
  - Frequency (Hz): 250, 500, 1000, 2000, 4000
  - dB HL: 0, 20, 40, 60, 80, 100

- **Right ear**
  - Frequency (Hz): 250, 500, 1000, 2000, 4000
  - dB HL: 0, 20, 40, 60, 80, 100

- **Males**
  - **Females**

- **<50 years**

- **>50 years**
Main Effect of Age

- **Glu**
  - <50 years: 3
  - >50 years: 2

- **NAA**
  - <50 years: 2
  - >50 years: 1
Main Effect of Gender

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Male</th>
<th>Female</th>
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</thead>
<tbody>
<tr>
<td>Glu</td>
<td>3</td>
<td>2.5</td>
</tr>
<tr>
<td>NAA</td>
<td>2</td>
<td>1.8</td>
</tr>
<tr>
<td>Cre</td>
<td>1.5</td>
<td>1</td>
</tr>
</tbody>
</table>
Main Effect of Hemisphere

- **Glu**
- **NAA**
- **Cre**
- **Cho**
- **GABA**

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Left</th>
<th>Right</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glu</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>NAA</td>
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<td>1</td>
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<tr>
<td>Cre</td>
<td>1</td>
<td>0.5</td>
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<tr>
<td>Cho</td>
<td>0.5</td>
<td>0.1</td>
</tr>
<tr>
<td>GABA</td>
<td>0.1</td>
<td>0</td>
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Concentration
MRS in acute TBI

MRS in Acute TBI

• Glutamate/glutamine and choline were significantly elevated in occipital gray and parietal white matter early after injury in patients with poor long-term outcomes.

• Glx and Cho ratios predicted long-term outcome with 94% accuracy.
  – Combined with the Glasgow Coma Scale provided highest predictive accuracy (97%).
MRS in Acute TBI

- Elevated Glutamine (Glx) and Choline (Cho) were more sensitive indicators of injury and predictors of poor outcome when MRS is performed early after injury.
- Data may reflect:
  - Early excitotoxic injury (elevated Glx), and
  - Injury associated with membrane disruption (increase Cho) secondary to diffuse axonal injury.
rTMS in Tinnitus Suppression
rTMS

- Sham controlled cross-over design
  - One week actual treatment
  - One week sham treatment
- Evaluate efficacy in noise-induced tinnitus
- Determine if rTMS treatment alters the neurobiochemical constituents in auditory cortical areas
- Work in progress (Cacace)
  - Funded by Tinnitus Research Consortium
Blast-induced tinnitus: Can it be modified by somatic or other sensory/motor inputs?
Gaze-Evoked Tinnitus
Gaze Evoked Tinnitus

- Phenomenon where horizontal or vertical deviation of eye position, from a neutral head referenced position, produces a subjective aural perception
- Observed after unilateral deafferentation
- Because it can be turned on and off or modulated, it can be imaged
- Hypothesized mechanisms
  - Neural sprouting or ephaptic interactions between oculomotor and brainstem auditory pathways
  - Unmasking of silent synapses
Gaze Evoked Tinnitus

• Pure form
  – Distinguished from other forms of tinnitus; can be turned on and off with static deviation in eye position

• Other variations
  – Additional components can be added to an existing tinnitus, or
  – Existing tinnitus can be modulated (changed in pitch, loudness, or timbre) with static change in eye direction
Gaze-Evoked Tinnitus
(More common then initially anticipated)

Example Case Report

• **Case 1:**
  - 47 year old female
  - 2 cm right sided CP angle meningioma
  - Complete and acute deafferentation on affected ear
AUDIOGRAM
Case 1

Operated Ear

Non Operated ear

Frequency (kHz)

Pre-Op

Post-Op

dB HL
Auditory Perceptual and Visual-Spatial Characteristics

- Psychoacoustics
  - Pitch and loudness matches
- Visual-field testing
  - Standard perimetry
  - Modified perimetry to map the visual-spatial characteristics of gaze-evoked tinnitus
Octapus Perimeter 1-2-3
(Interzeag, Inc., Marlboro, Mass, USA)
Modified Visual Field Testing

Case 2

Degrees of Visual Field

-30 -20 -10 0 10 20 30

Tinnitus absent

Tinnitus present

Left eye

Right eye
Modified Visual Field Testing

Case 1

Degrees of Visual Field

<table>
<thead>
<tr>
<th>Pitch</th>
<th>Loudness</th>
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<tr>
<td>1350 Hz</td>
<td>82 dB SPL</td>
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<tr>
<td>940 Hz</td>
<td>87 dB SPL</td>
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<tr>
<td>246 Hz</td>
<td>79 dB SPL</td>
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<tr>
<td>1128 Hz</td>
<td>86 dB SPL</td>
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CUTANEOUS-EVOKED TINNITUS
Case Studies

• **Case 1:**
  - 66 year old female with a large glomus jugulare tumor

• **Case 2:**
  - 47 year old male with a 1.5 cm vestibular schwannoma
Case 1
(CT Scans Glomus Jugulare Tumor)

Arising from skull base
a: extending to temporal bone area
obliterating middle ear space
b & c: more superior views; tumor
extending into posterior cranial fossa
Hand area evoking tinnitus
Pitch Match

Modality: Visual
Condition: Eye gaze left

Modality: Somatosensory
Condition: Stroking left wrist

Test 1, Track 1, Descending
Test 1, Track 2, Ascending
Test 2, Track 1, Descending
Test 2, Track 2, Ascending
Case 2

1.5 cm mostly intracanalicular vestibular schwannoma
Tinnitus evoked by finger tapping
fMRI
Case 2

Cutaneous Evoked Tinnitus
(Right Hand, TP)

Slice 10  Slice 16  Slice 17  Slice 18
fMRI
Case 2

Finger Tapping
(Left Hand, subject TP)

Slice 10  Slice 16  Slice 17  Slice 18

Slice 19  Slice 20  Slice 21
Relevant References


Consequences of Blasts

Military

Humvee after IED attack, Sumarra, Iraq

Civilian

In city causalities
Animal Models

- Using shock tube exposures, neuroanatomical and neurobiochemical correlates can be ascertained
  - High resolution MRI
  - Susceptibility weighted imaging
  - Diffusion tensor imaging
New Developments in Contrast-Related Activity Dependent Functional Mapping
Manganese Enhanced MRI (MEMRI)

- During functional stimulation, Mn$^{2+}$ enters firing neurons via voltage-gated Ca$^{2+}$ channels.
- After entry into neurons, Mn$^{2+}$ is transported down axons via microtubule based fast neuronal transport.
- Mn$^{2+}$ is also paramagnetic, acts as a $T_1$-weighted contrast agent.
- Elucidate anatomical information and identify activity dependent regions of cellular activity.
MEMRI Study of Rats with Tinnitus

- In rats with behavioral evidence of tinnitus:
  - Elevated activity in auditory brainstem
    - Cerebellar parafollocculus
    - PVCN
    - IC
    - Forebrain structures showed reduced activity

- Vigabatrin (GABA agonist)
  - Shown to eliminate behavioral evidence of tinnitus

(From: Brozoski et al. 2007. Central neural activity in rats with tinnitus evaluated with manganese-enhanced magnetic resonance imaging (MEMRI). Hear Res, 228, 168-179)
Summary

- Imaging tinnitus-related activity is in its infancy
- Offers considerable potential for identifying anatomical substrate, neurobiochemical substrate and associated processes related to the tinnitus percept
- Holds considerable potential for validating and tracking treatments
- Holds considerable potential for targeted drug development and monitoring
Tinnitus verification: Animal Models

• Behavioral methods
  – Operant approaches (all variations on a theme)

• Reflex procedures
  – Gap detection startle reflex procedure
Behavioral Conditioning Models

- Conditioned lick suppression (Jastreboff et al., 1988)
- Conditioned level (food) suppression (Bauer et al., 1999; Bauer & Brozowski, 2001)
- Conditioned pole jumping avoidance (Guitton et al., 2003)
- Conditioned polydipsia avoidance procedure (Lobarinas et al., 2004)
- Conditioned two-choice left/right procedure (Hefner & Koay, 2005)
Rapid Screening Tool


Recent Updates on Tinnitus

**Gap Detection Reflex Procedure**

**Startle Only**
No Gap Trial

10 kHz background

**Startle Pulse**

**Normal Startle Reflex**

Silent gap serves as warning to inhibit reflex in normal animals

10 kHz

10 kHz

Tinnitus partially fills in silent gap, degrading its ability to inhibit reflex

10 kHz

10 kHz

10 kHz

**Tinnitus**

(Adapted from: Turner, JG. 2007. Behavioral measures of tinnitus in laboratory animals. Prog. Brain Res. 147-156.)
More Ecologically Valid Animal Model

- Assess cognitive skills
  - Spatial memory
  - Learning
  - Morris water maze
- Evaluate psychological state
  - Anxiety
  - Elevated T-maze
Locus of Imaging in Drug Development

Molecular Imaging (PET)
Functional Imaging (fMRI)

Molecular Diagnostics
Genomic Profiling

Disease
Function
Targets
Pathways
Structure

Function
Organ
Tissue
Receptors
Cellular
Genomic

(Adapted from: Borsook et al. 2006)
(Central) Auditory Processing Disorder

- Deciding what is and what is not a CAPD is a matter of arriving at a useful definition
- CAPD – a riddle wrapped in a mystery inside an enigma
- CAPD – is a modality specific perceptual dysfunction not due to peripheral hearing loss (McFarland & Cacace)
(Central) Auditory Processing Disorder

- Perceptual dysfunctions are modality specific
- Evaluation becomes a form of hypothesis testing to delineate:
  - Modality specific
  - Supramodal (attentional)
  - Poly-sensory disorders
- To accomplish this goal, multimodal testing is advocated
  - Not limited to behavioral assessment
- In TBI, identifying the specificity of the deficit is crucial
Modality Specificity

• Basic idea:
  – any test result is the product of multiple factors (perception, motivation, language abilities, decision processes, motor abilities, etc.)

• To be a useful construct:
  – (C)APD should be conceptualized as producing poor performance in tasks using auditory stimuli
  – if a relative deficit with auditory stimuli is obtained when test performance is evaluated on matched tasks in multiple modalities, like vision, then alternative explanations can be ruled out; and,
  – diagnostic significance is enhanced
Modality Specificity as a Criterion for Diagnosis

• Provides a means for distinguishing auditory perceptual abilities from more general skills
• It’s a form of hypothesis testing to distinguish modality specific auditory perceptual dysfunction from “supramodal” or “polysenory” dysfunctions
• Requires multimodal assessment
  – Use of matched tasks in multiple modalities
  – Attempt to keep all factors constant but just change modality of presentation
Auditory Processing Disorder as a Theoretical Construct

• We never actually observe an APD
• We might suspect an APD
• It is inferred across a consistent pattern of test results
• APD is *not* a “behavior”
  - it is an *abstract concept* that describes a disposition
Rationale for Evaluation (Children)

• Auditory specific perceptual deficits could underly many functional problems
  – specific reading disability
  – specific language disability
  – attention deficit disorders

• Could form the basis of therapeutic options
• Could serve as the basis for medical referral
  – tumors and/or other medical related issues related to brain abnormalities
Blast Related Injuries

• Complexities of injury mandates a more comprehensive model
• To study this concept effectively requires a paradigm shift
• Present “inclusive” methodology insufficient to arrive at a definitive diagnosis
Factors Influencing Test Performance

- Detection
- Recognition
- Discrimination
- Attention
- Memory

- Motivation
- Language Skills
- Decision Processes
- Motor Skills
Multitrait-Multimethod Framework

- Multiple tests measuring multiple traits are compared to evaluate whether a given test correlates with those measures it is theorized to be related to
- Does not correlate with those measures in which theory suggests it should not be correlated with
- Key: Multiple tests are necessary, since no single test is a pure index of the construct being measured
- Means of developing convergent and discriminate validity

Multi-modal Tasks

• Dichotic (auditory) vs. dichoptic (visual) presentation (digits)
• Span length (auditory and visual presentation of digits)
• Auditory and visual detection of digits in noise (SNR)
• Gap detection
  – Auditory vs. visual (Humes)
• Temporal order
  – Frequency, level
  – Size, orientation, color
• Pattern recognition
  – Frequency vs. color
  – Intensity vs. brightness
Design Considerations

• For studying perception:
  – Emphasize recognition vs. reproduction
    • Not interested in studying motor abilities, or sensory-motor integration
  – Simplify instructions
    • 3-interval forced choice (IFC) oddity paradigm
  – Minimize memory component
Temporal Order Thresholds
Methods/Procedure

• 3-IFC Oddity Paradigm
• Single track adaptive
  – Adaptive parameter ISI between stimulus onsets
  – 2-down, 1-up procedure
  – Threshold, 70.7% correct level of performance

• Psychometric Functions
  – Block randomized format


Forced Choice Methodology
(Advantages)

• Use of simple instructions; can be used for all tasks
• Avoids floor and ceiling effects; adapts on the 70% point on the psychometric function
• Uses recognition vs. reproduction; simplifies interpretation
3-IFC Oddity Paradigm

Alerting Interval

Stimulus Interval

Response Interval

Feedback Interval
Interstimulus Interval
(Adapting on the time dimension)

Frequency
- Short ISI

Level
- Long ISI
- Onset
Single Track Adaptive
(Stepping Rules)

• Initial ISI, 400 ms
  – 2 consecutive correct responses decreases ISI
  – 1 incorrect response increases ISI

• Initial step size, 50 ms
  – each successive reversal reduces ISI 80% of previous value
  – minimum, 1 ms (Auditory)
  – minimum, 22.4 ms (Visual)
Adaptive Tracking
(Auditory Frequency Dimension)

Session 1 (8.4 ms)
Adaptive Tracking
Auditory Frequency Dimension

Trials

TOT (ms)

0 1 2 3 4 5 6

Session 1 (18.8 ms)
Session 4 (8.4 ms)
Auditory Stimulus Dimensions
(3-IFC Paradigm)

Frequency

1st

2nd

Level

1st

2nd

---

Interval 1

Interval 2

Interval 3
Visual Stimulus Dimensions
(3-IFC Paradigm)

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MVA TBI

SWI

Z-Score (Standard units)

-2

Signal-to-noise ratio

Auditory

Visual

Signal-to-noise ratio

Frequency patterns

Color patterns

Digits

Digits

Modality

Modality
Conclusions

- Multimodal perceptual testing is one means to help delineate sensory perceptual from cognitive, linguistic and attentional disorders.
- In TBI studies, the presence of sensory modality specific effects needs closer examination.
Hyperacusis

• Methods of evaluation
• Advocate use of magnitude estimation
  – Classic form
  – Cross-modality scaling
Hyperacusis

![Graph showing Hyperacusis, Normal, and Cochlear hearing loss]

- **Hyperacusis**
- **Normal**
- **Cochlear hearing loss**

The graph illustrates the magnitude estimate of sound levels in dB SPL for different conditions.
Magnitude Estimation in Tinnitus Assessment
Auditory Manifestations of mTBI

- Application of new technology will be a driving force to help understand brain behavior relationships
- Parallel human and animal models are well suited for this application
- Complexities of blast-induced TBI highlights the need for a paradigm shift in the conceptualization, assessment, and diagnosis of (C)APD