The Impact of Blast on Balance

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Blast – why do we care

- Major issue in the military – accounts for over 90% of our battlefield injuries
- Increasingly more common in the civilian world
- Blast causes a unique injury pattern
- Exposure to blast alone can produce injuries

View

View

Blast – Physics

- Any event where individuals or those around them “feel” a pressure wave
- Damage is done largely by the pressure wave not the impulse sound

Blast is not new

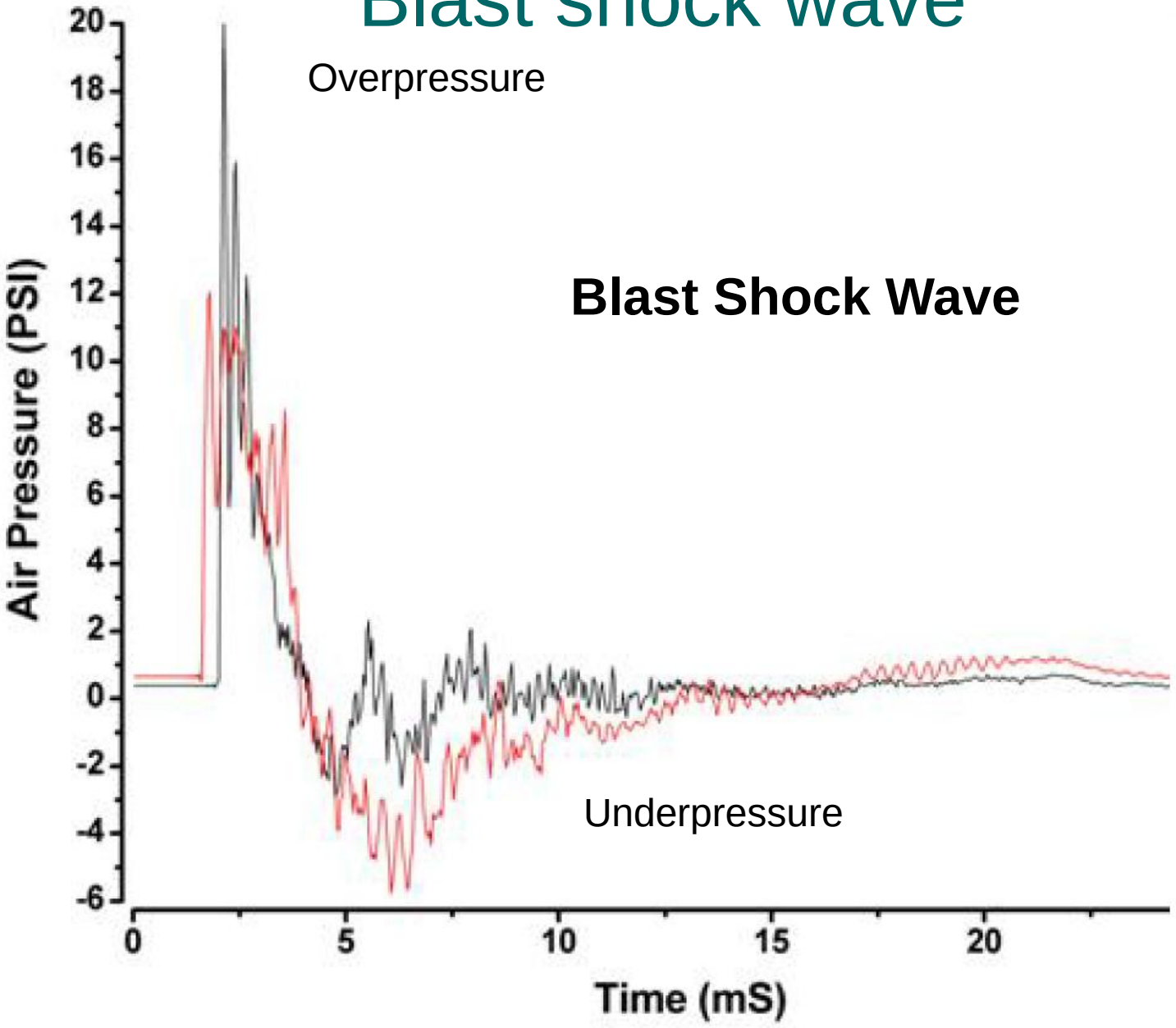
- **World War II cases neuropsychiatric setting**
- **Early symptoms included (in order)**
  - **Headache**
  - **Tinnitus**
  - **Dizziness**
  - **Tremors**
  - **"Nervousness"**
  - **Insomnia/battle dreams**
  - **Intolerance of noises**

Cramer F, Paster S, Stephenson C. Cerebral injuries due to explosion waves-"cerebral blast concussion". Arch. Neurol. Psychiat. 61 (1949) 1-20

Blast injury categories

- **Primary blast injury:** shock wave propagation through tissue
  - -***Acute acoustic trauma*** - via conductive path
  - -***Blast injury*** – Blast physics and biomaterials
- **Secondary blast injury:** shrapnel or fragments
- **Tertiary blast injury:** impact with objects in environment
- **Quaternary blast injury:** heat, electro-magnetic pulses or detonation toxins

Blast shock wave



Shock wave propagation

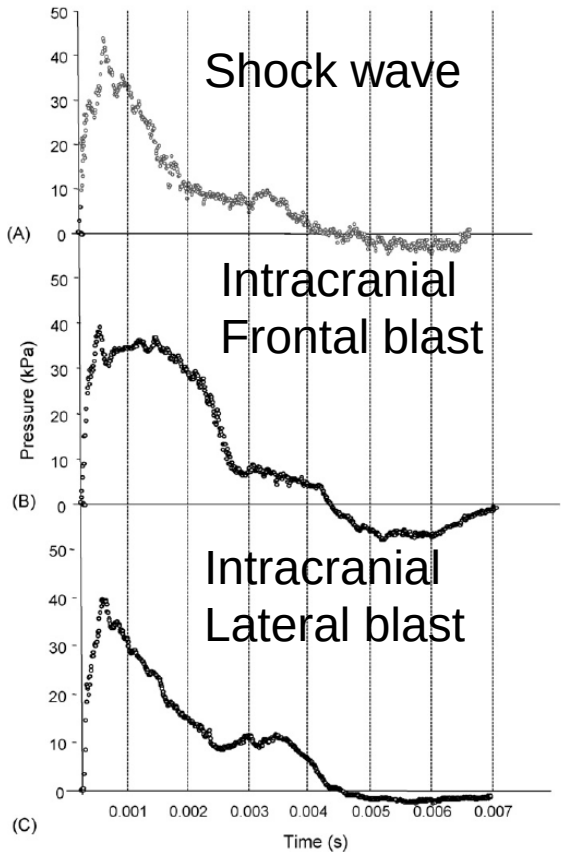


Fig. 5. (A) Pressure wave recorded in the air; (B) pressure wave recorded inside the brain of the rat placed in frontal position in a shock tube; (C) pressure wave recorded inside the brain of the rat placed in lateral position in a shock tube.

- Shock wave overpressure-underpressure sequence propagates effectively into brain case
- Rat model in shock tube

Chavko M, Koller WA, Prusaczyk WK, McCarron RM. Measurement of blast wave by a miniature fiber optic transducer in the rat brain. J. Neurosci. Methods 159 (2007) 277-281

Basic question

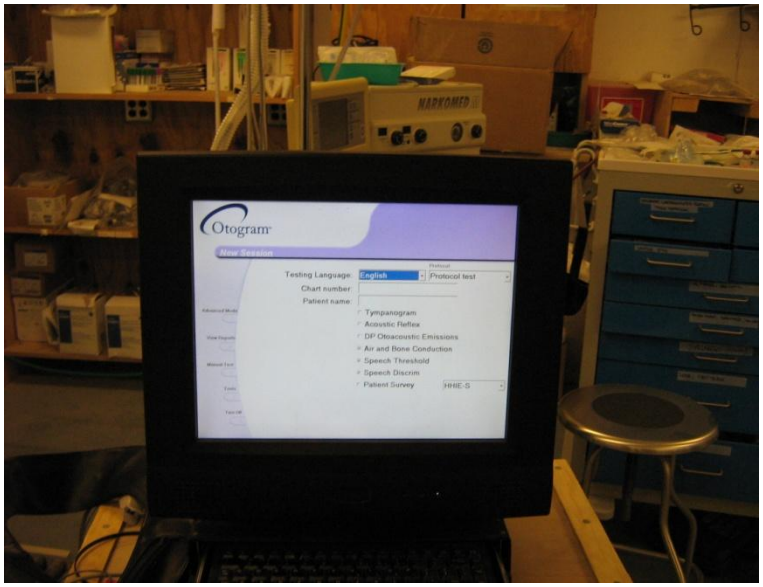
- Determine the difference in presenting symptoms of blast induced mild traumatic brain injury as a function of time
- Examine the diagnostic and management implications of these differences

Materials and Methods

- Three groups of mild traumatic brain injury (mTBI) patients divided by time of presentation
  - Acute – seen in under 72 hours from blast in Iraq
  - Sub-acute – seen 4-30 days after blast at NMCSD
  - Chronic – seen 30-360 days after blast at NMCSD
- All had mTBI secondary to blast as defined by the DoD definition of TBI (October 2007)

Materials and Methods

- Acute patients
  - **History and physical**
  - Dynamic Gait Index (DGI)
  - Hearing test (Otogram)
- Sub-acute and Chronic patients
  - **History and physical**
  - Rotational chair (details in paper)
  - Sensory Organization test (Posturography)
  - DGI
  - Hearing test
  - Standardized Instruments (details in paper)



Results

- Groups (Median age 22)
  - Acute – 81 Individuals
  - Sub-Acute – 25 Individuals
  - Chronic – 42 Individuals

Mild Traumatic Brain Injury after Blast - Symptoms Distribution

Group	Dizziness	Vertigo	Hearing Loss	Headache	PTSD
Acute	98%*	4%*	33%*	72%	2%*
Sub-acute	76%	47%	43%	76%	20%
Chronic	84%	36%	49%	82%	44%

Tinnitus – Time dependent

- Immediately after blast – Over 90% report “non-concerning” ringing
- 70% of those report tinnitus if questioned in first seven days
- Tinnitus rates drop to less than one-third from 10 days to several months
- After several months rates rise again to over 60%

Tinnitus – Issues

- Tinnitus is a pre-existing condition in many service members
- Many service members have an ear that is already “primmed” from previous noise
- Acute and subacute tinnitus can be distinguished from baseline
- Chronic cases may represent new tinnitus or return to baseline
- “Uncovering error” – rate of tinnitus is higher if you ask

Tinnitus – Changes over time

- Changes do not parallel hearing loss
  - Early on high rate of tinnitus may represent TTS
  - Reduction in subacute period may be secondary to resolution of TTS
  - Rise in rate in chronic period (difference from 2-3 months to 6-8 months post blast) does not parallel a dramatic change in hearing loss in that period of time

Explanations – Associated Conditions

- Chronic growth in tinnitus may be secondary to post-traumatic endolymphatic hydrops
- Growth of tinnitus may be related to brain changes over time after mTBI
- Growth of tinnitus may be related to repair mechanisms

Tinnitus- Unanswered Questions

- Relationship of tinnitus to central auditory processing disorder
- Relationship of tinnitus to headache syndromes
- Relationship of long term tinnitus to previous blasts or previous noise exposure
- Impact of “early intervention” on long term tinnitus

Impact of Tinnitus

- Increases disability
  - Impacts hearing ability
  - Impacts Sleep
  - Effects over sense of well being
- Impacts recovery
  - Difficult to treat
  - Reminder of disability
  - Can become a focal point

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Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

A mouse model of blast-induced mild traumatic brain injury

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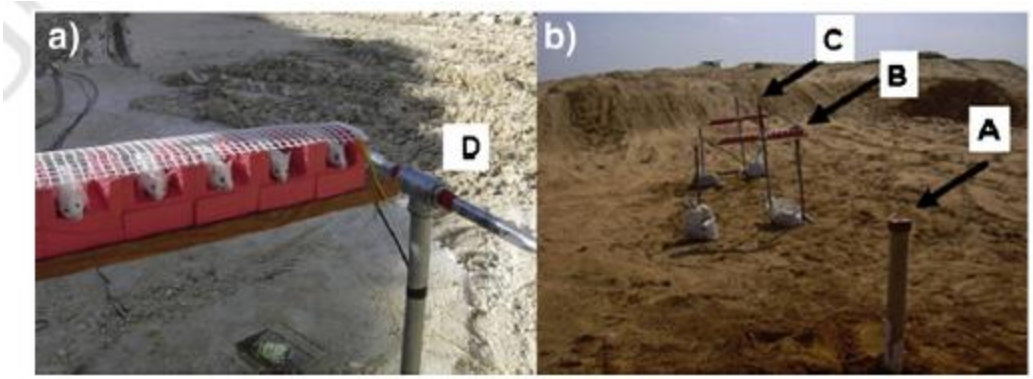


Mouse Open Field Blast Results

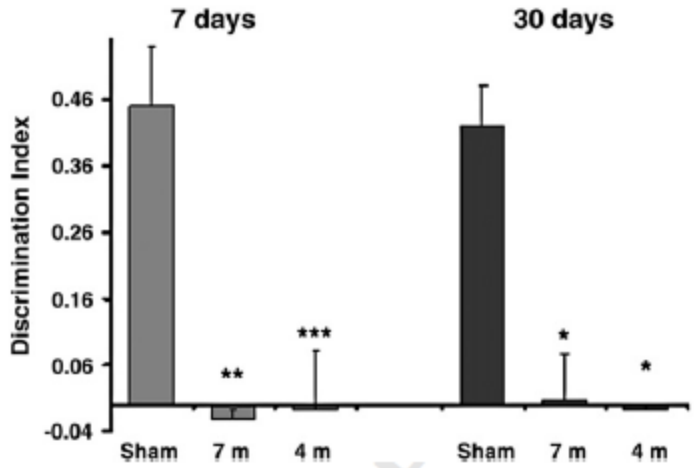


Fig. 3. The effect of blast on visual memory as assessed by the novel object recognition test. The preference for novel objects was significantly reduced in all the blast groups both at 7 days (-0.02 ± 0.01 for 7 m group, -0.008 ± 0.009 for 4 m group and 0.45 ± 0.09 for sham group) and 30 days (0.007 ± 0.07 for 7 m group, -0.008 ± 0.01 for 4 m group and 0.42 ± 0.06 for sham group). *$p<0.05$,**$p<0.01$ or ***$p<0.001$.

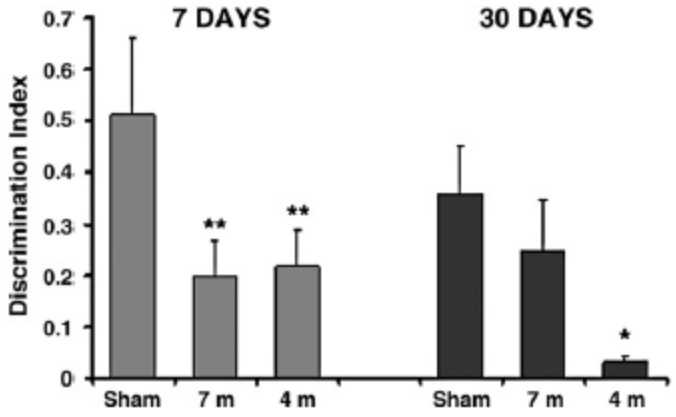


Fig. 4. The effect of blast on spatial memory as assessed by the Y-maze test. Preference for the new arm was significantly reduced in mice 7 days post blast in both groups (0.2 ± 0.07 for 7 m group and 0.22 ± 0.07 for 4 m in comparison with the sham group 0.51 ± 0.15). Similar impaired memory was found after 30 days for the 4 m group (0.033 ± 0.01 for the 4 m group and 0.361 ± 0.09 for the sham group). *$p<0.05$,**$p<0.01$ or ***$p<0.001$.

Mouse Open Field Blast Results

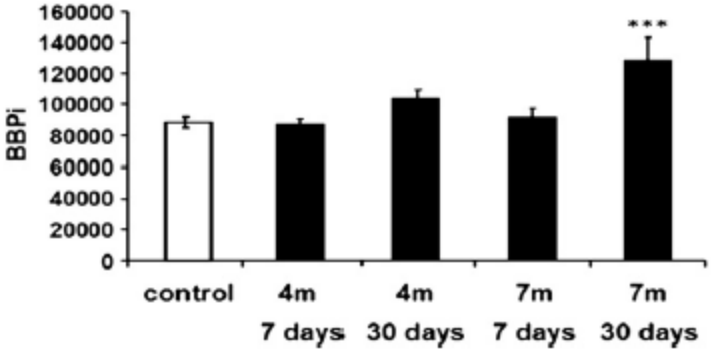
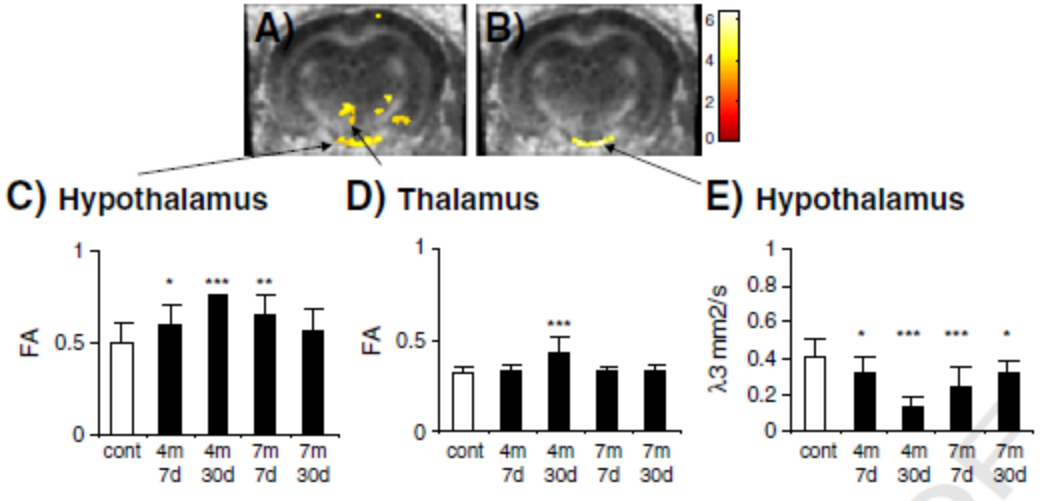
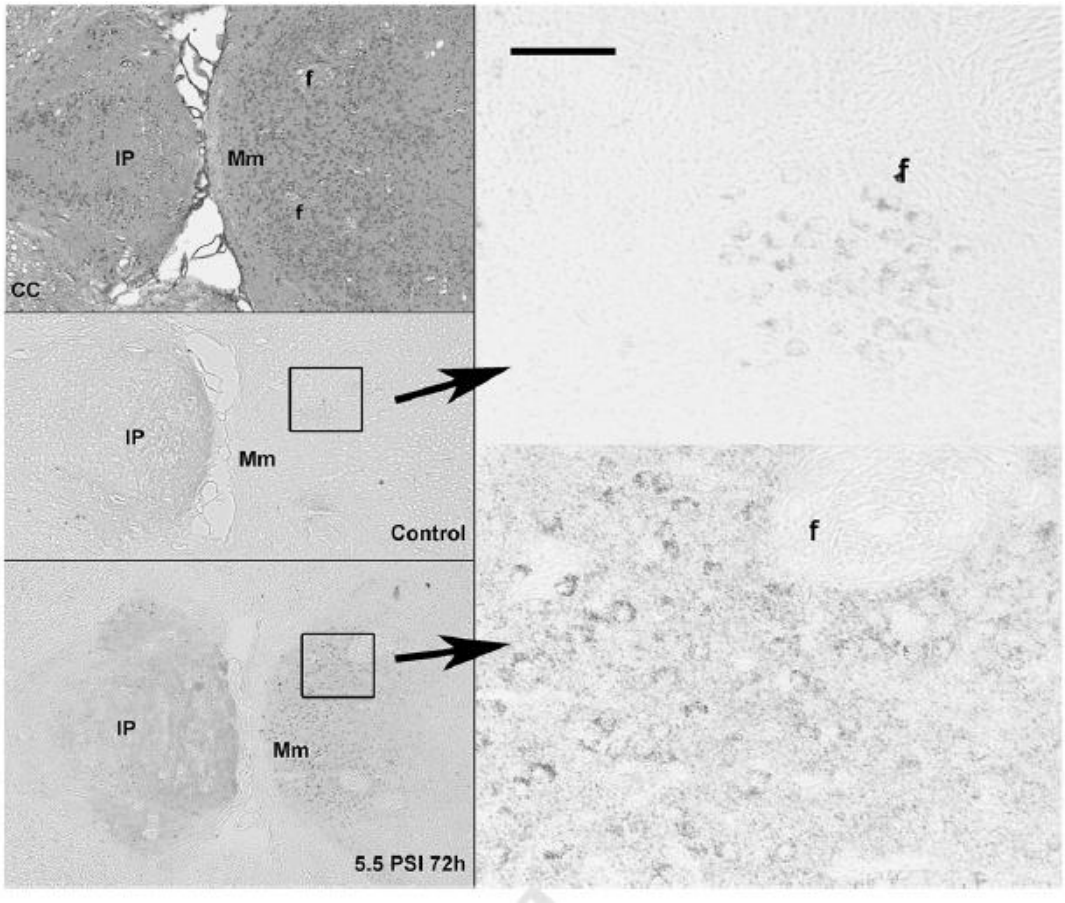


Fig. 6. Blast effect on BBB permeability index (BBPi). Permeability increased after blast-explosion at 30 days at 7 m compared with control group ($F(4,40) = 5.9$, $P < 0.001$). *** indicates significant difference between the 7 m 30 days post-blast group compared to the control group, $p < 0.001$.



Mouse Open Field Blast Results

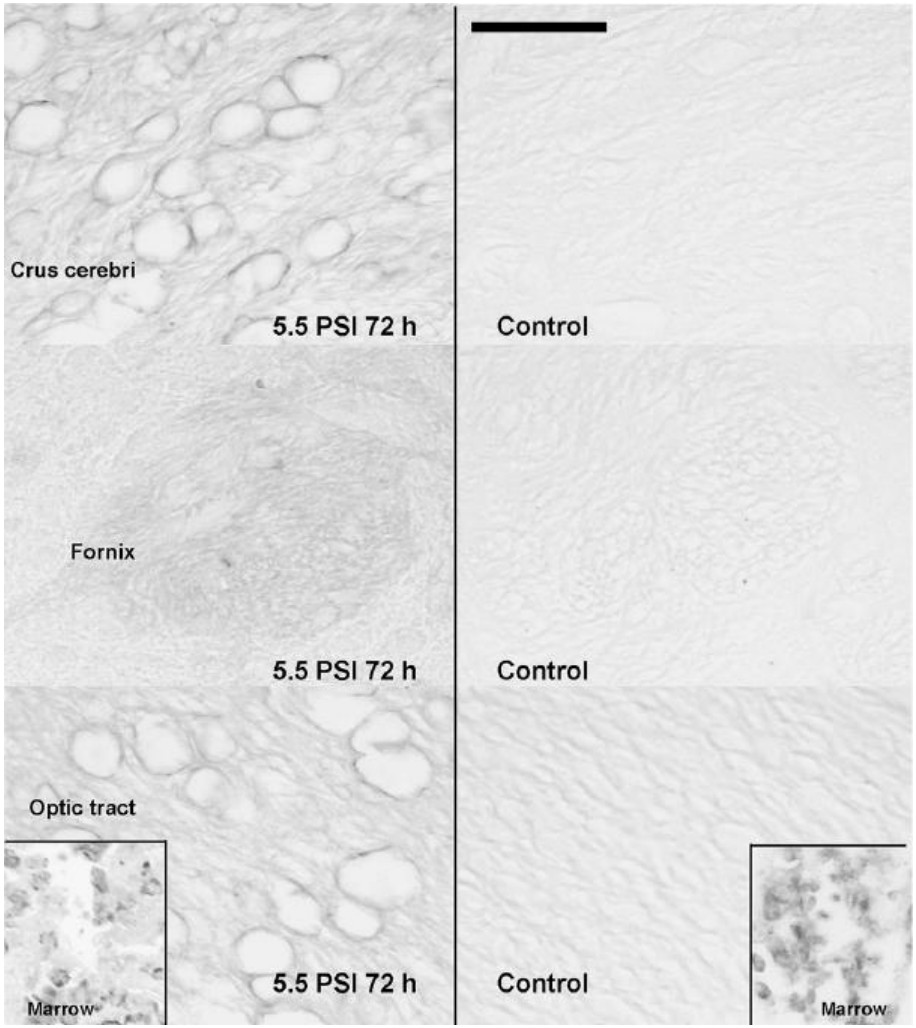
MnSOD2 upregulation in regions showing FA changes



Mouse Open Field Blast Results

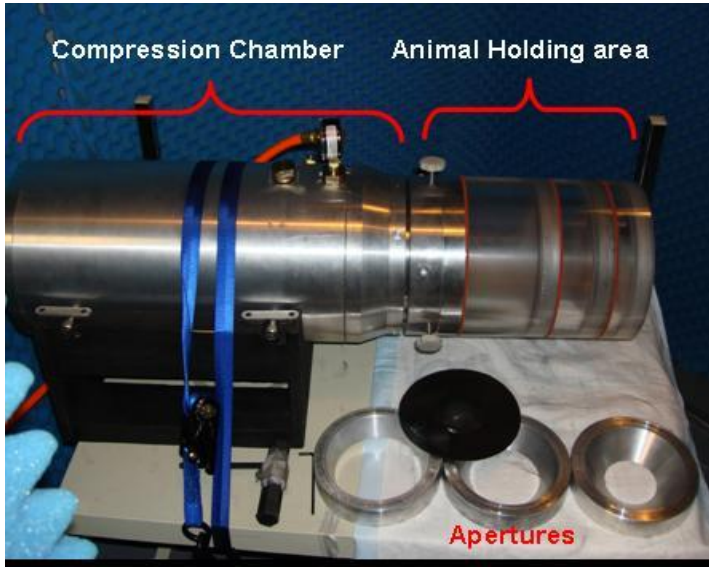
C-X-C motif chemokine receptor 3 (CXCR3) upregulation around blood vessels in fiber tracts

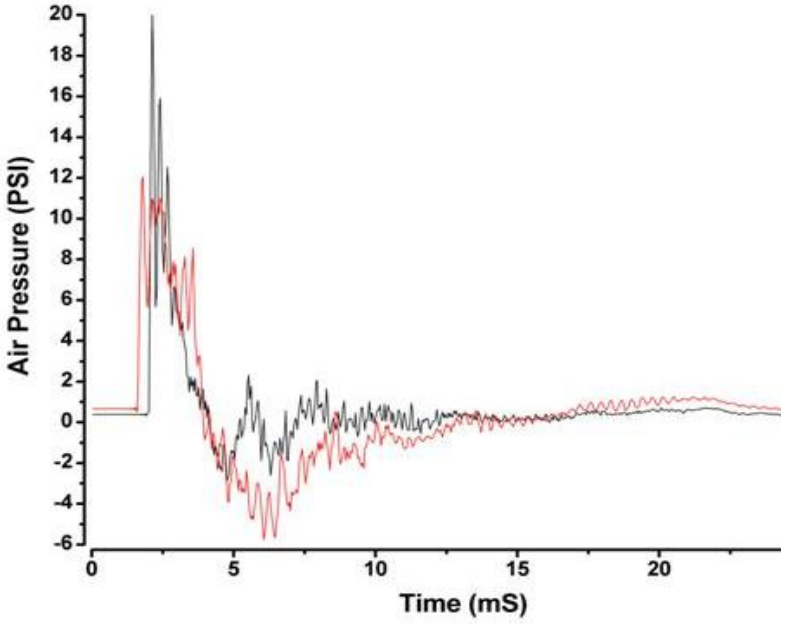
CXCR3 implicated in vascular remodeling and autoimmune disorders (e.g., thyroid disease and multiple sclerosis)



Basic Research: Blast-Induced mTBI

- Rats exposed to low intensity (10-15 PSI peak) Friedlander profile shock waves
- Behavioral tests, qRT-PCR microarrays and histopathology

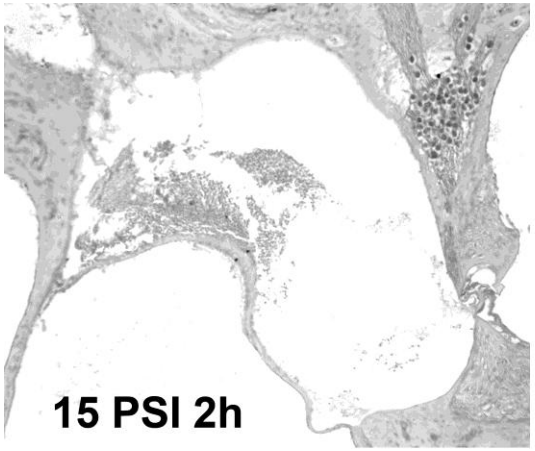


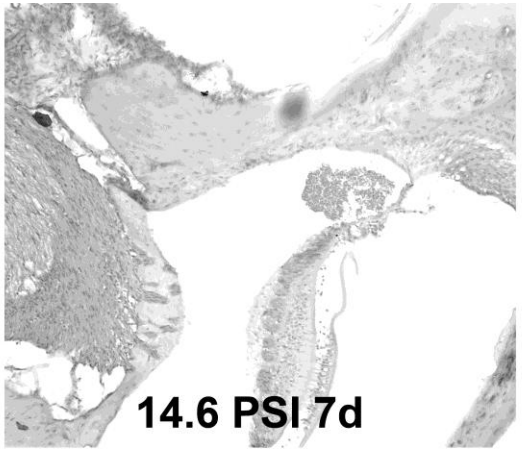


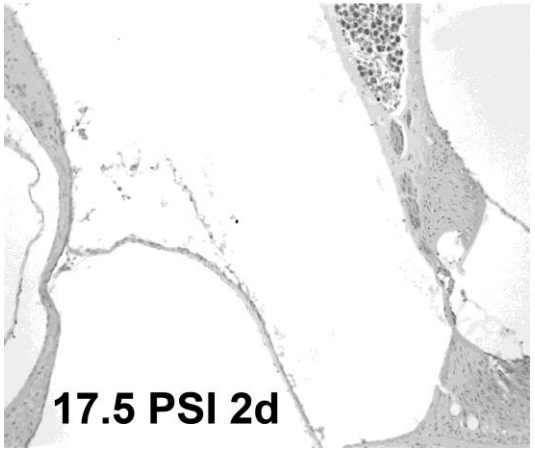
Basic Research: Blast-Induced mTBI

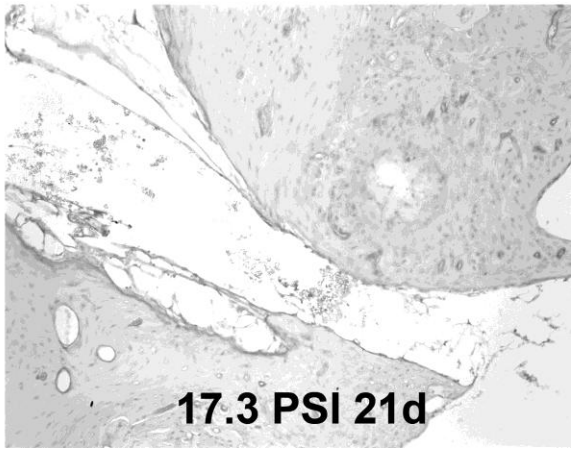
- Histopathology on decalcified whole heads: mild vascular changes and local protein extravasation but brain parenchyma appears normal
- Temporal bone evidence of vascular pathology
- qRT-PCR Arrays: Vascular wound healing pattern for 10 PSI and 15 PSI peak single exposures
  - Many vascular-associated mRNAs up-regulated (>2-fold) in exposure dependent manner at 2 h, 24 h and 72 h post-exposure

Histopathology: Rat Head





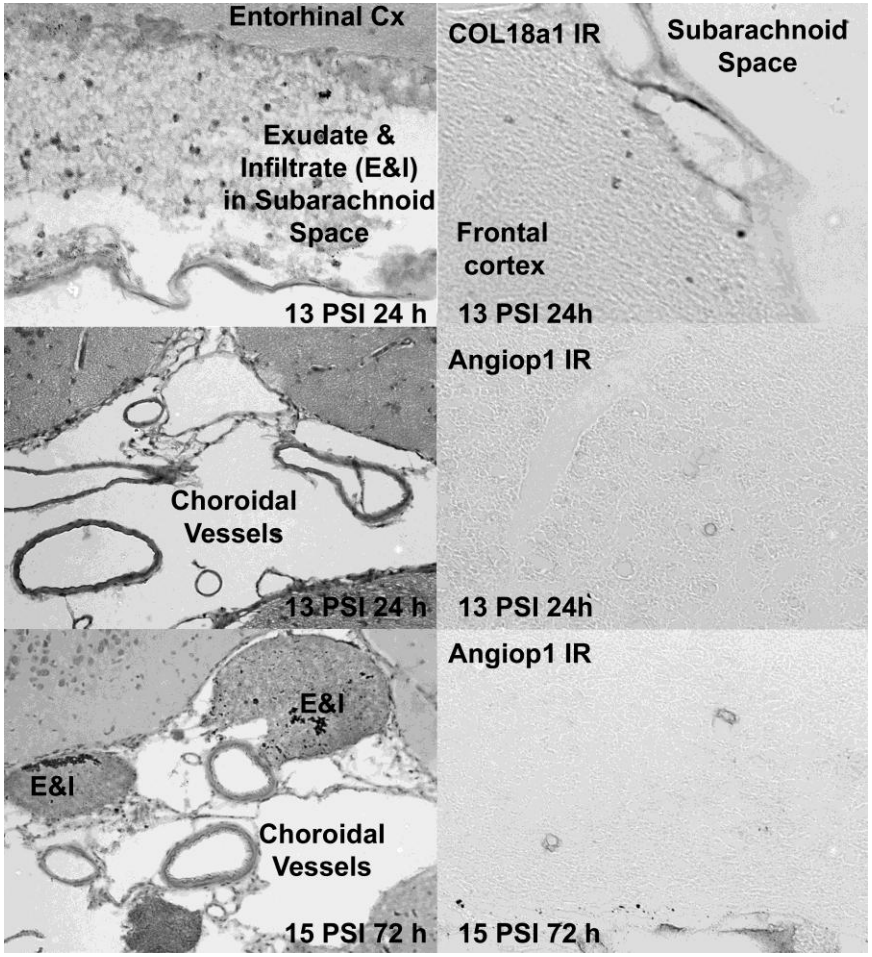




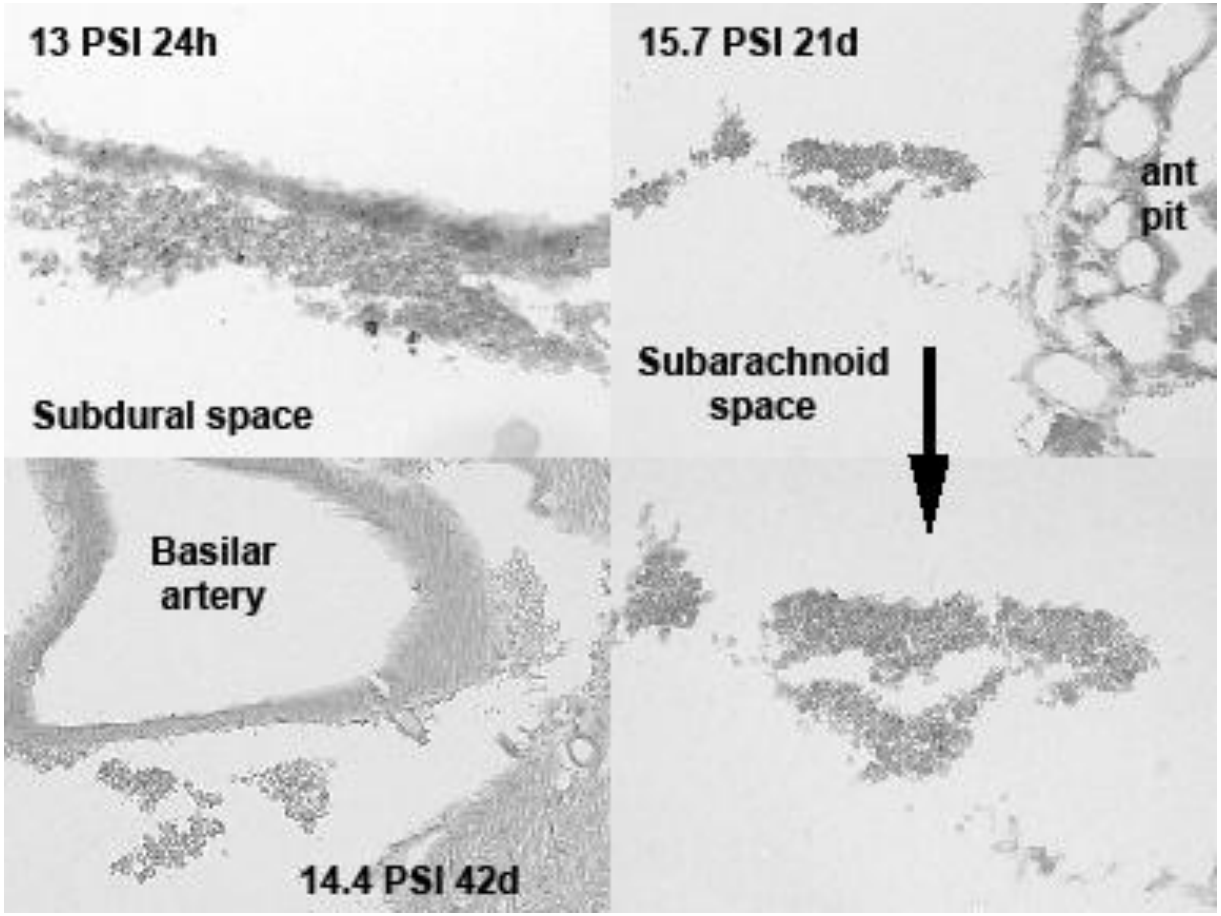
Intracranial Vascular Pathology

- Hemorrhage and emboli associated with superficial vessels
- Immunohistochemical and qPCR evidence of wound healing response
  - Scales with blast intensity

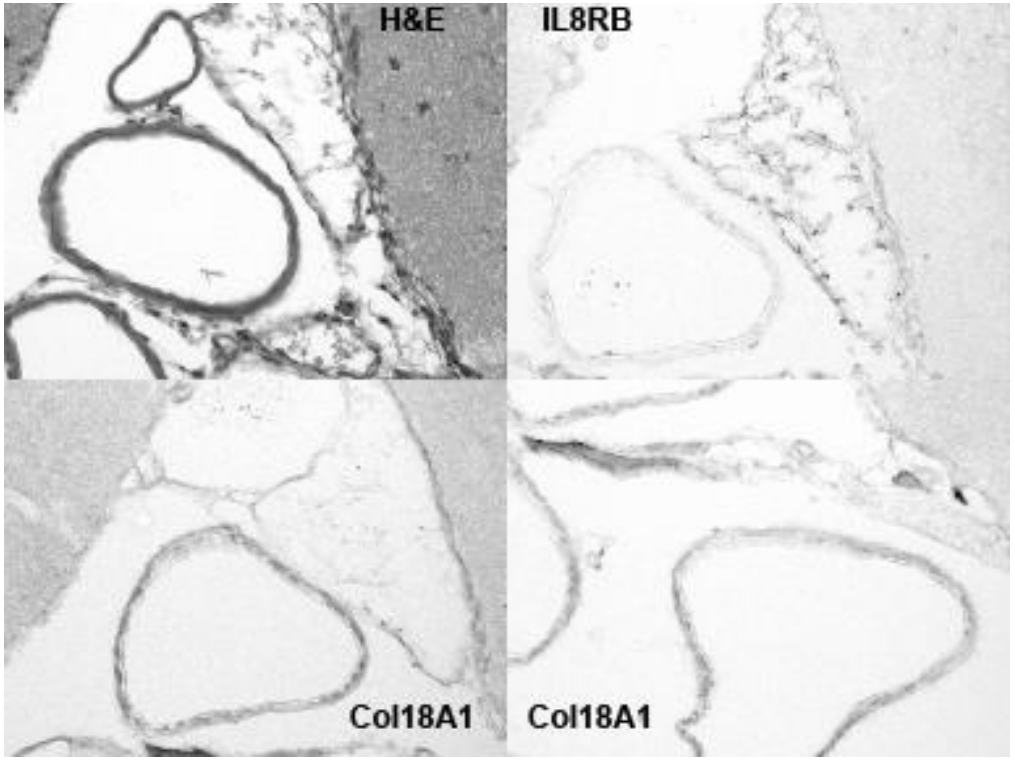
Histopathology: Rat Head



Histopathology: Rat Head

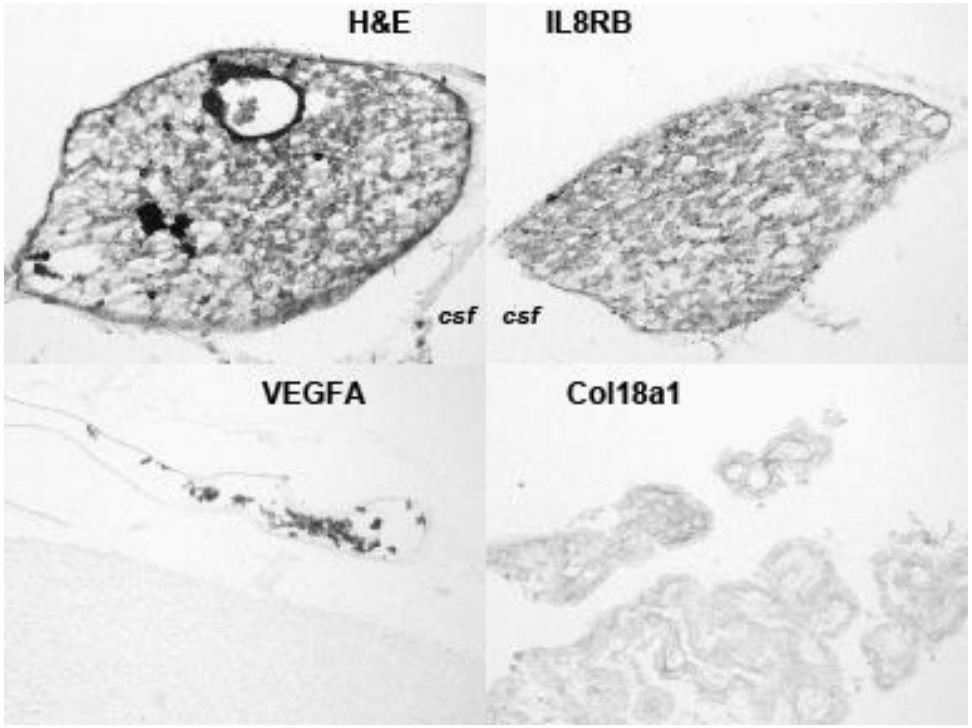


Histopathology: Rat Head



Choroidal fissure, 24 hours after single 13 PSI shock wave

Histopathology: Rat Head



Cisternal space and choroid plexus,
24 hours after single 13 PSI shock wave

Subarachnoid Space and Extensions

- Meckel's Cave
- Perilymph space in inner ear
  - Connected to pontomedullary cistern via cochlear aqueduct
  - Vestibulocochlear vein enters inferior petrosal sinus near distal opening of cochlear aqueduct
  - Reports of intracochlear hemorrhage after acoustic trauma
    - E.g., Reinis, S. Acute changes in animal ears due to simulated sonic booms. J. Acoust. Soc. Am. 60 (1976) 133-138.

Subarachnoid Hemorrhage

- Recent clinical reviews
  - McDonald et al. Nature Clin. Prac. Neurol. 3 (2007) 256- 262.
  - Sebha & Bederson, Neurol. Res. 28 (2006) 381-398.
- Vascular effects include
  - Vasospasm
  - Injury cascades (including inflammatory responses)
  - Microemboli
  - Cortical spreading ischemia

Subarachnoid Hemorrhage

- Increases in 20-hydoxyeicosatetraeinoic acid (HETE) and 5-HT in CSF in clinic and animal models
- Direct effects on vasculature via TRPV1 and 5-HT_{1B} receptors
  - Vasoconstriction of small resistance arteries
  - Neural actions at terminals and cell bodies in contact with CSF (e.g., trigeminal ganglion and vestibular ganglion, where both receptors are expressed)

Vestibular and spiral ganglia express 5HT1B, 5-HT1D and TRPV1 receptors

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Type 1 vanilloid receptor expression by mammalian inner ear ganglion cells

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Vestibular and spiral ganglia express 5HT1B, 5-HT1D and TRPV1 receptors

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BRAIN RESEARCH

Research Report

Distribution of 5-HT_{1B} and 5-HT_{1D} receptors in the inner ear

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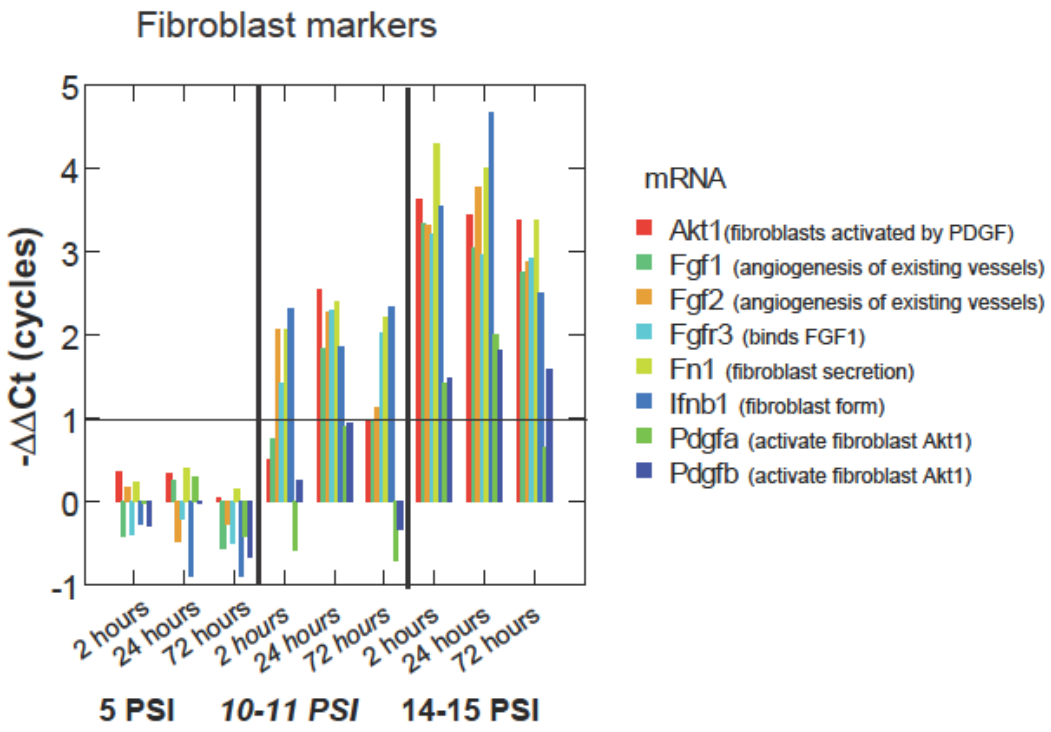
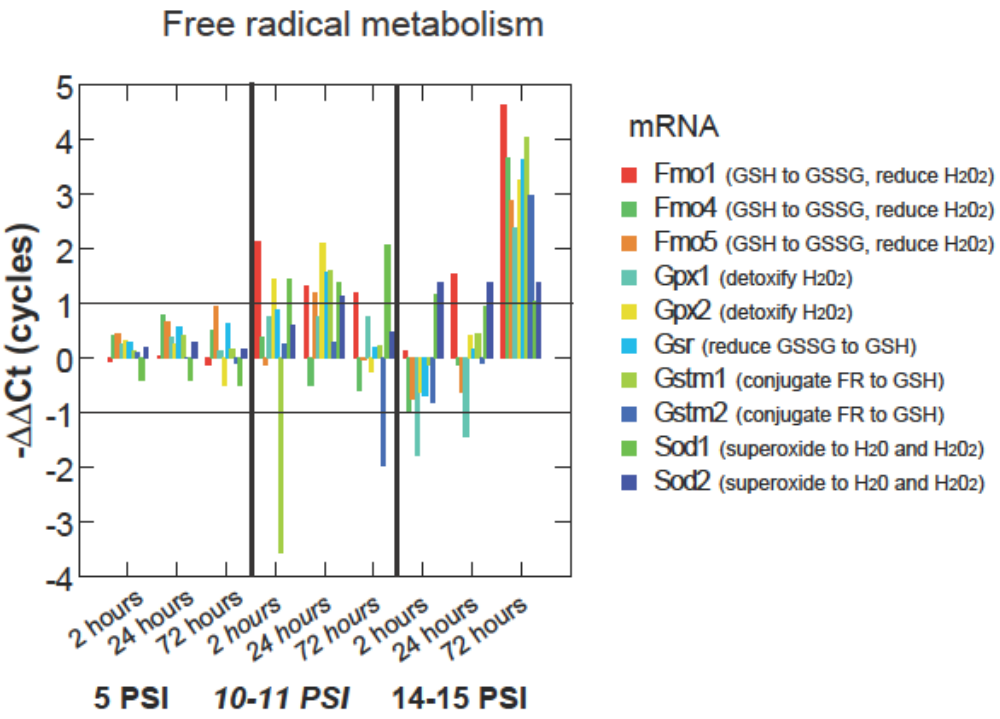
qPCR: Vascular wound pattern



qPCR: Vascular wound pattern



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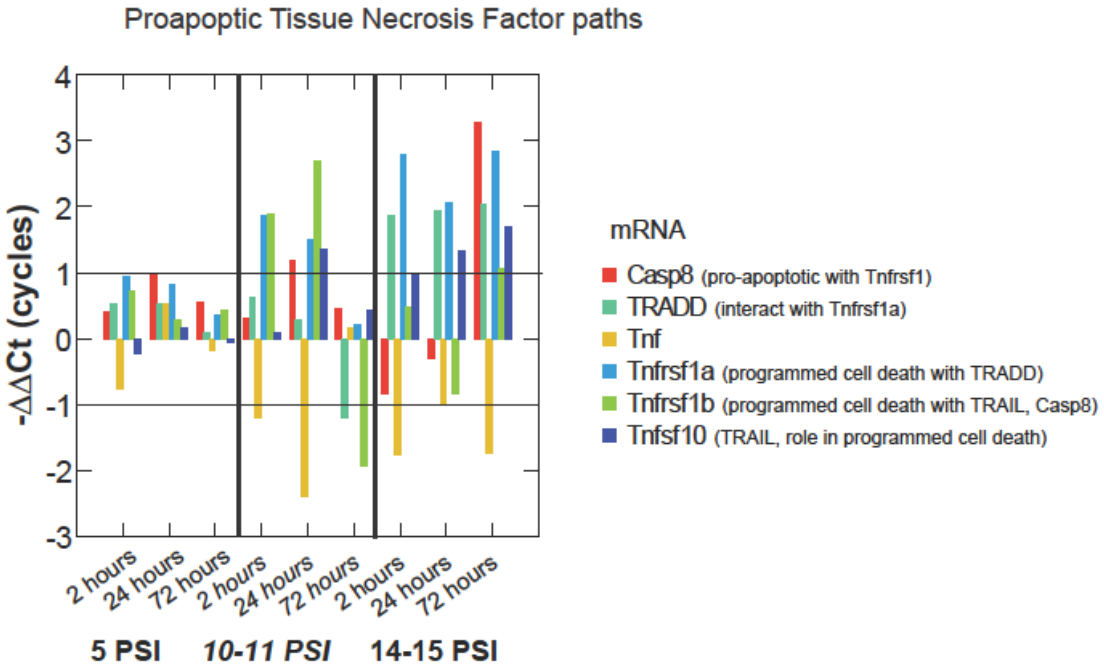
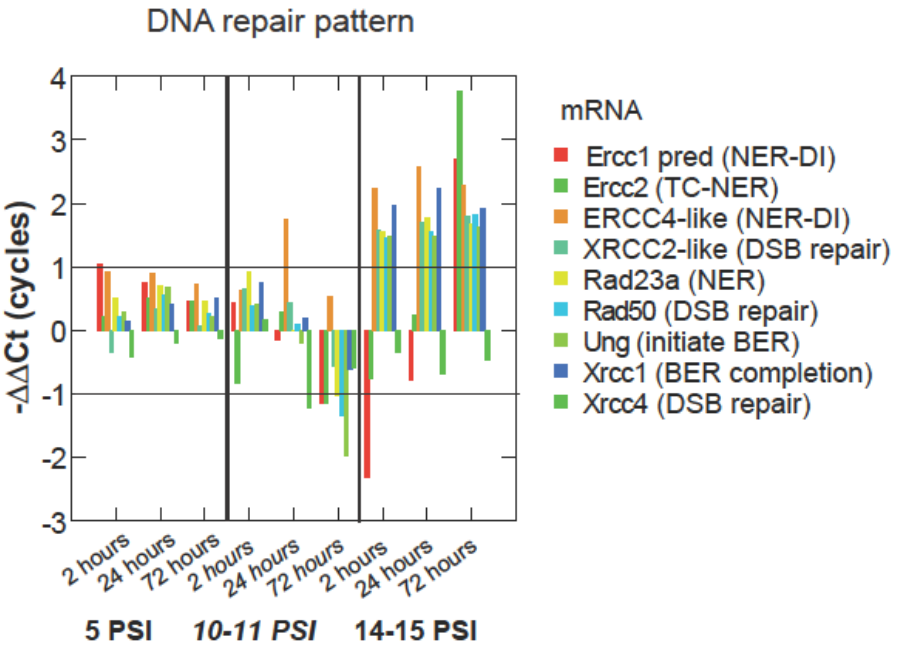


qPCR: Vascular wound pattern



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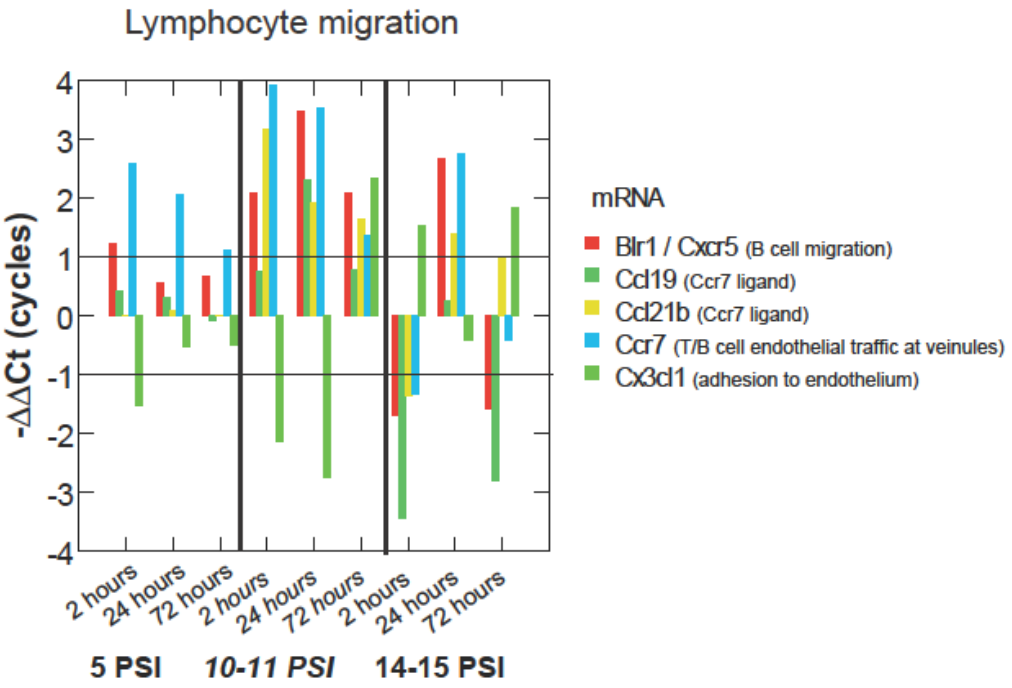
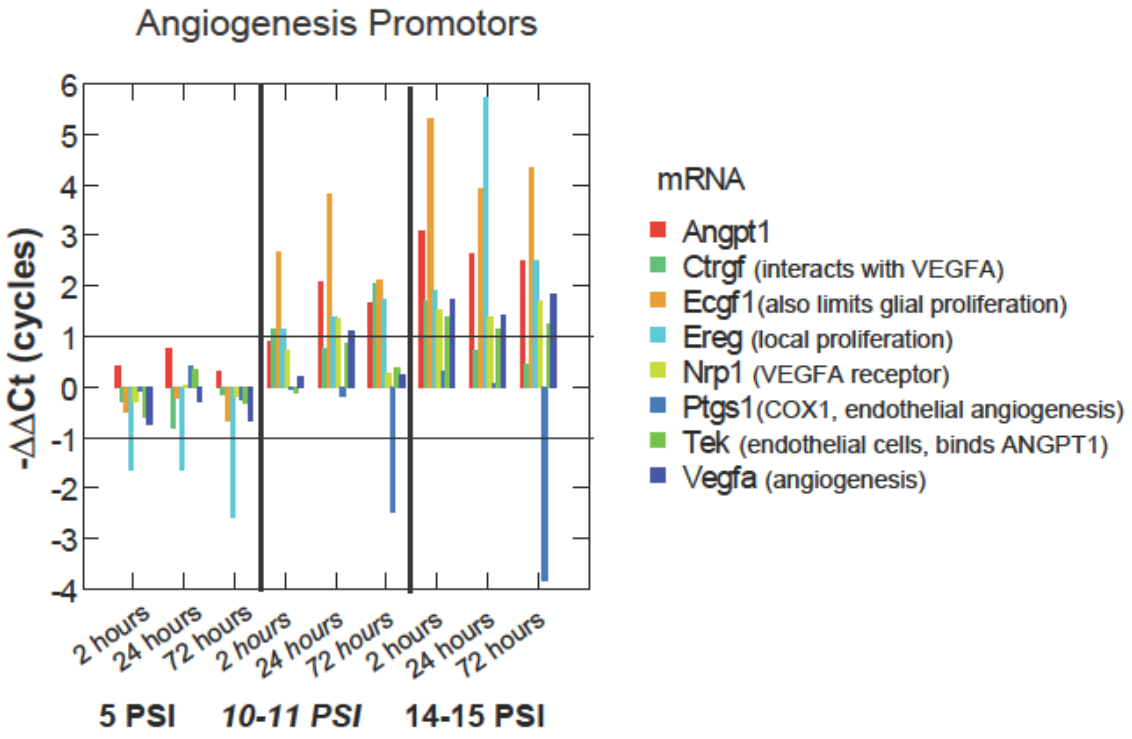
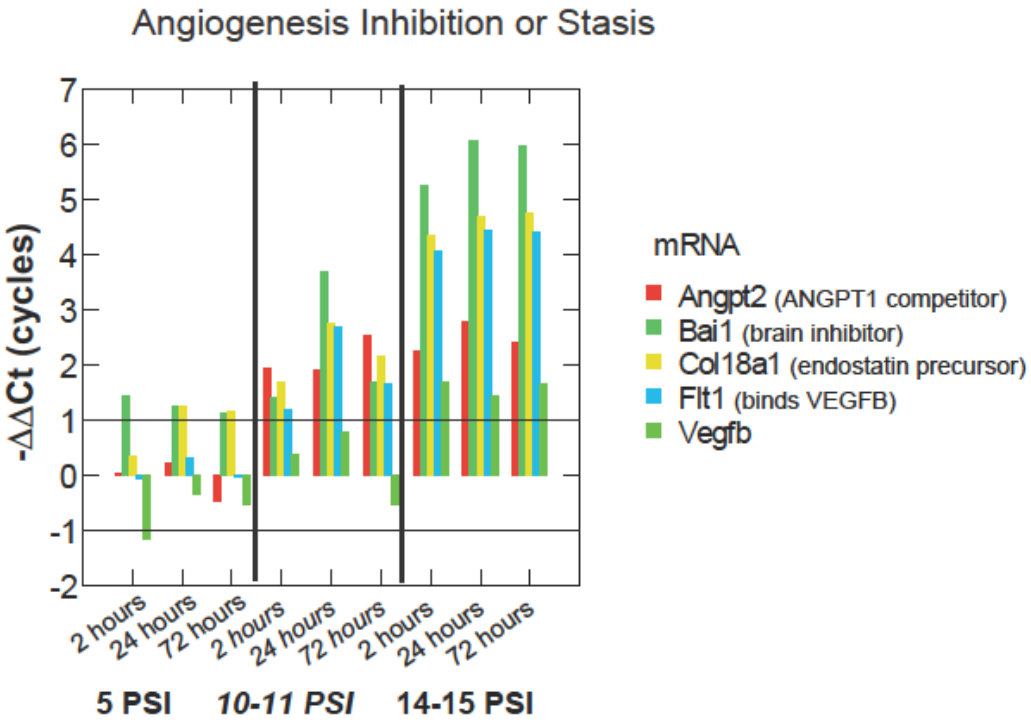


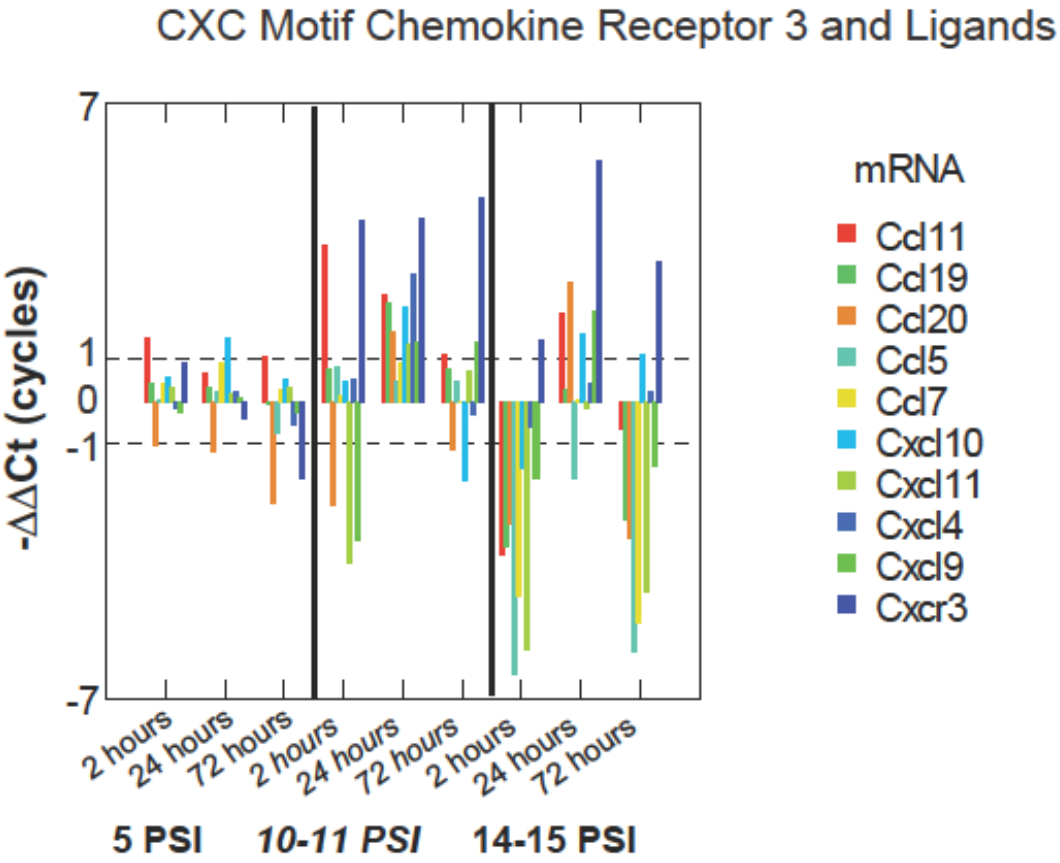
qPCR: Vascular wound pattern



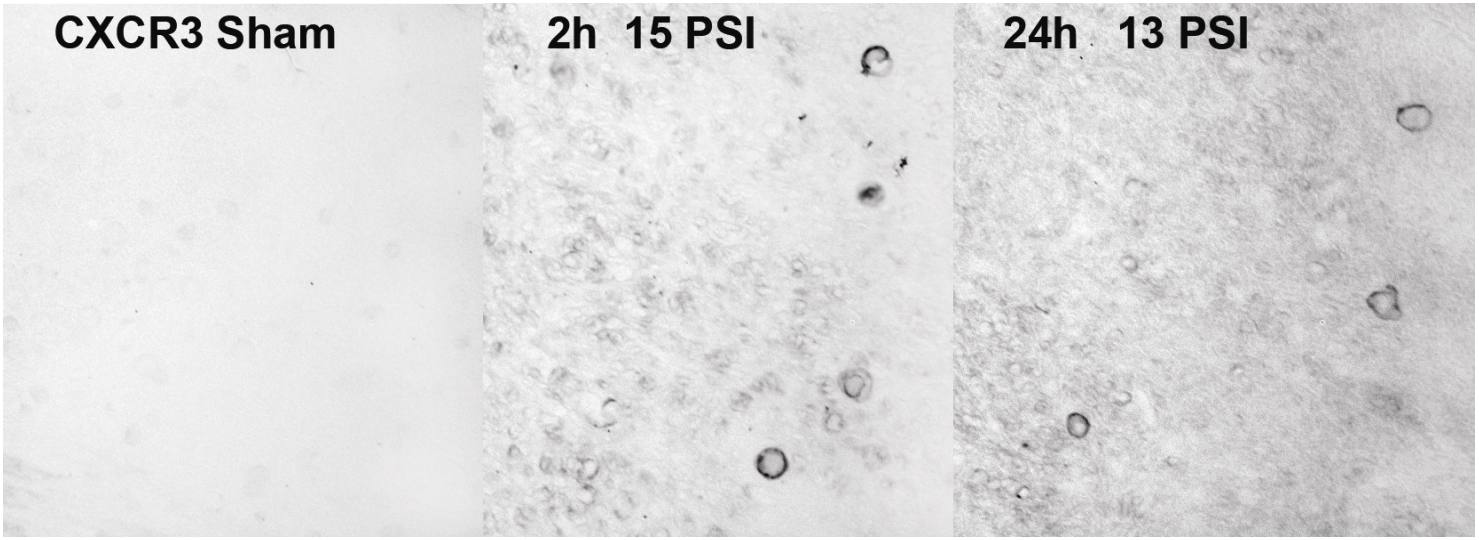
qPCR: Vascular wound pattern



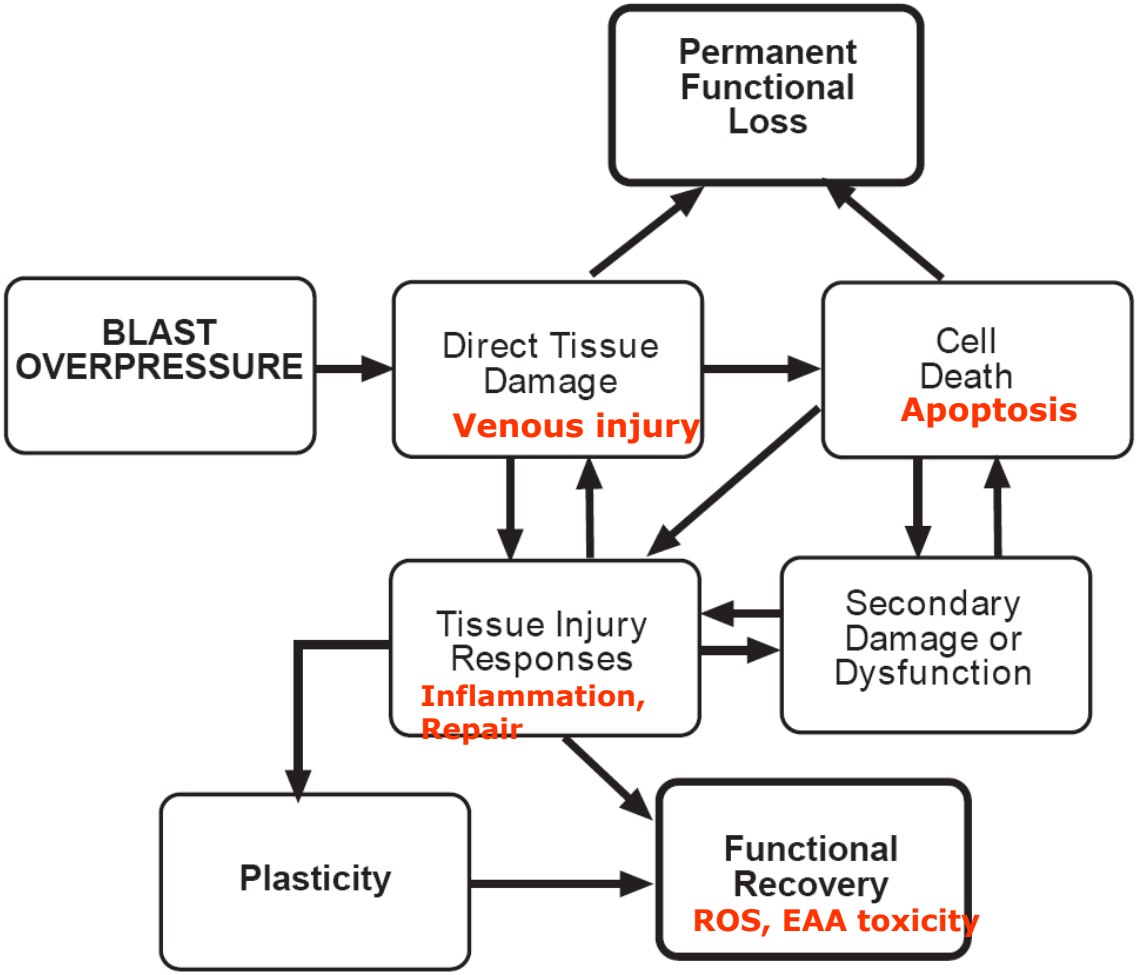
qPCR: CXC Chemokine Receptor 3



CXC Chemokine Receptor 3 Expression in Cortical White Matter



Pathophysiology – Blast Injury



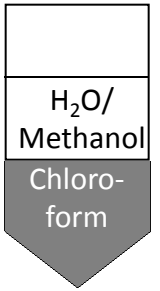
Pathophysiology – Blast Injury

- Shock wave effect
  - Microvascular injury in brain and inner ear
  - Headache and vestibular symptoms may result from persistent blood products in CSF
  - Oxidative cellular stress
  - Healing or secondary neuronal damage (e.g., dysregulation of chemokine mechanisms)

Tissue sectioning

Lipids extraction[1]

Matrix deposition



Lipids partition[2-4]

→ Fraction # 5 :
neutral phospholipids

→ Fraction # 6 :
acidic phospholipids
and sulfatides
(+ desalting on C18 columns)

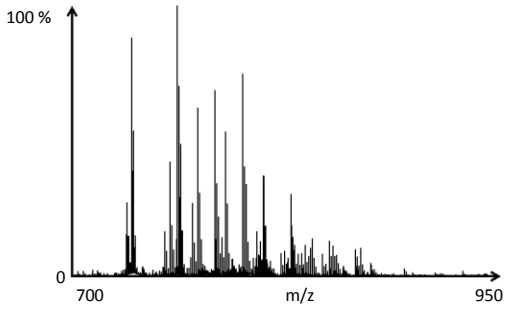
Lipids profiling with

DHA + NH_4SO_4

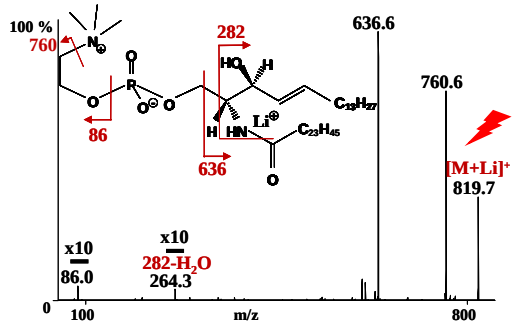
Lipids structural analysis

Lipids imaging with

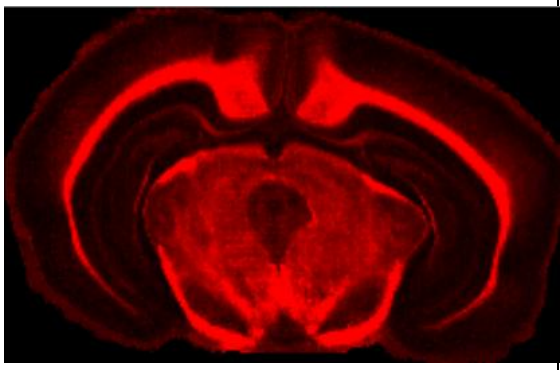
DHA + NH_4SO_4 + HFBA



MALDI LTQ MS



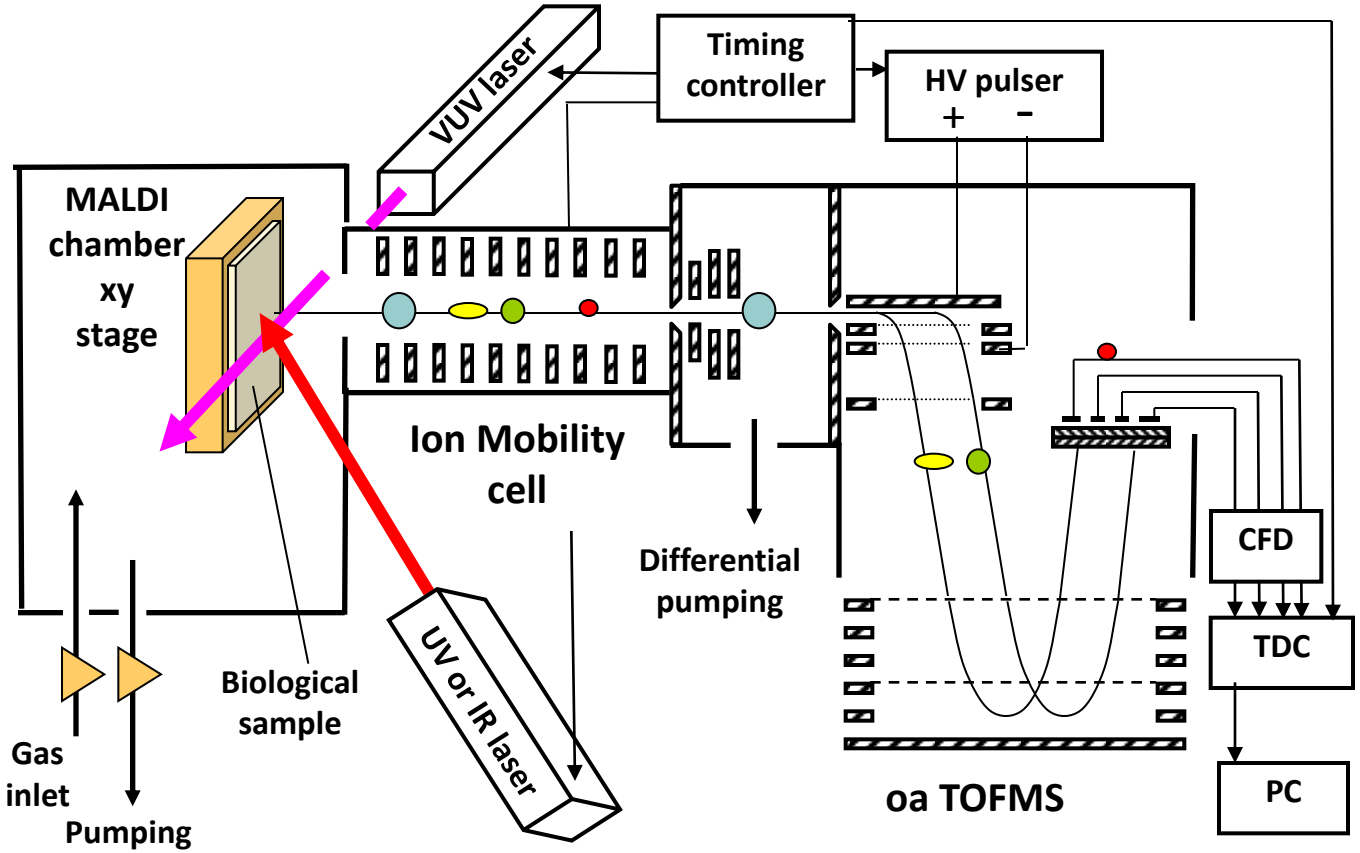
CID / PQD / HCD

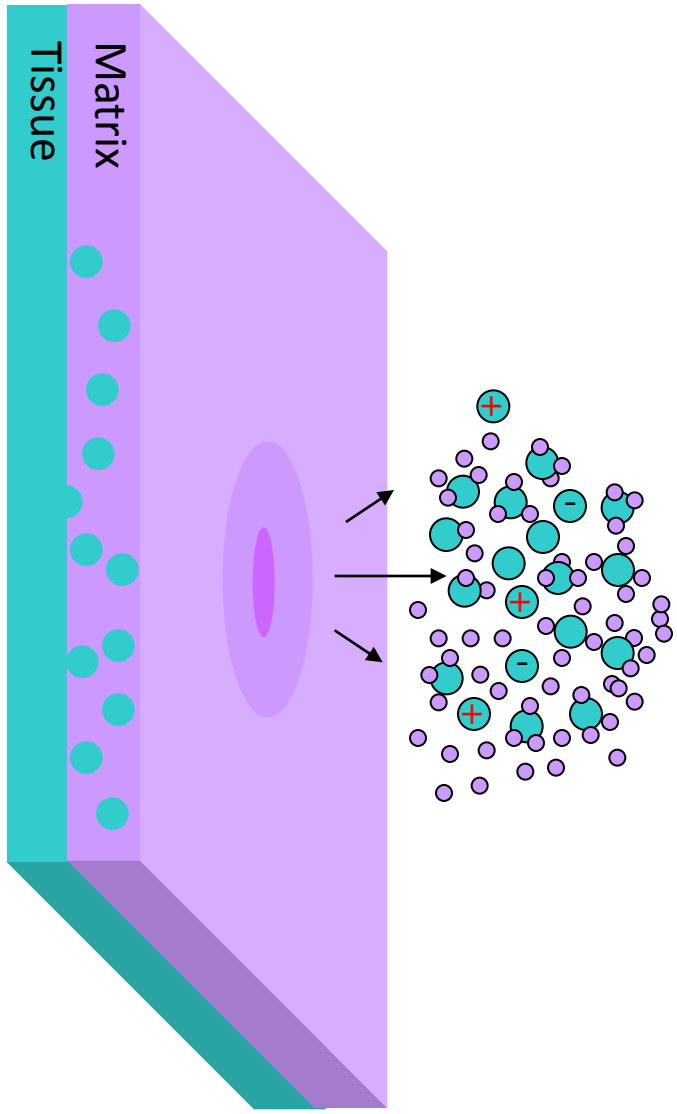


MALDI LTQ imaging

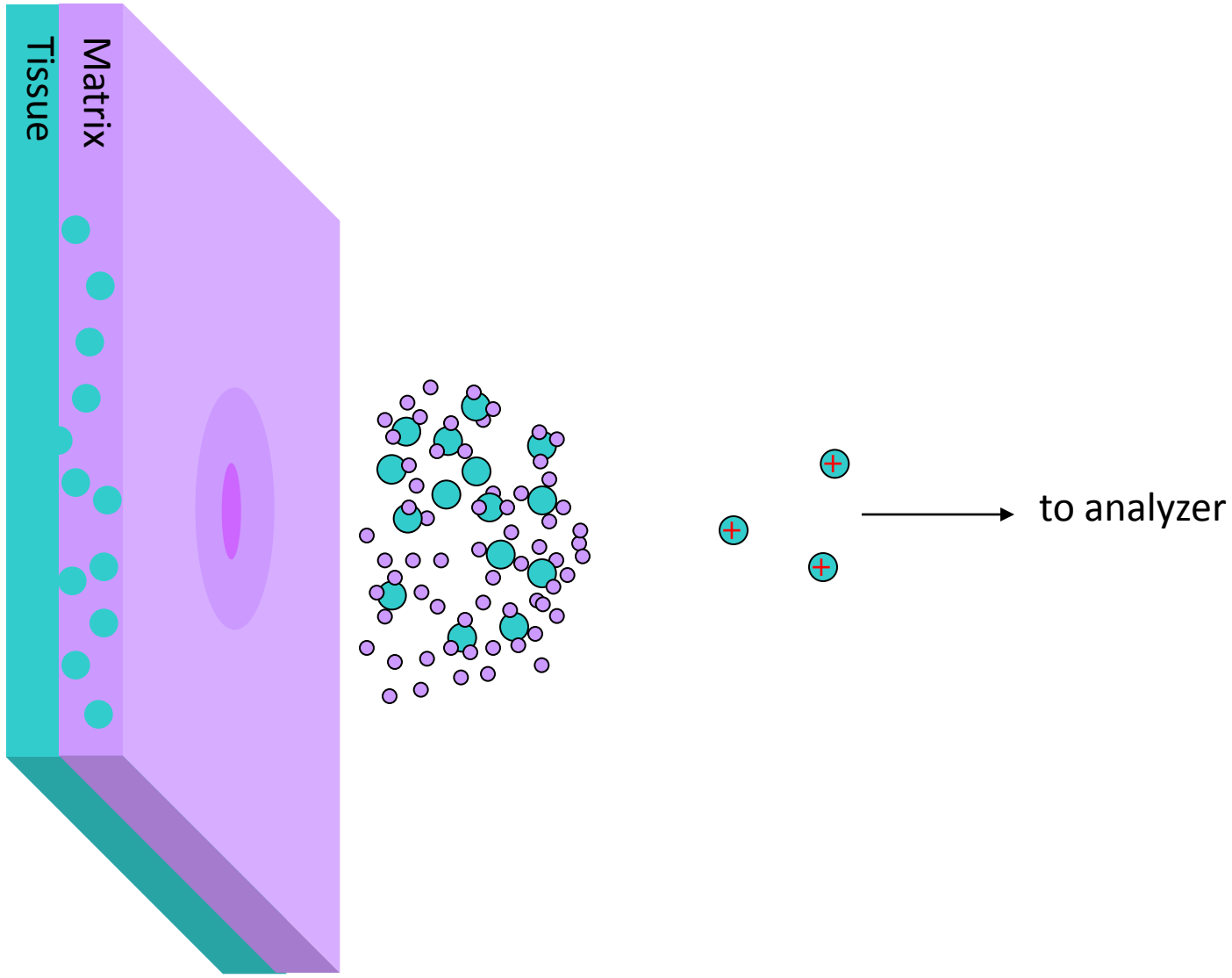
Schematic of the UV or IR/VUV MALDI- Ion Mobility-oTOFMS.

Ion mobility separates molecules according to their conformation (shape) prior to measuring their molecular weight in the mass spectrometer. VUV Photon pulse delayed hundreds of microsecond create ions from stagnant neutral plume in front of the sample.

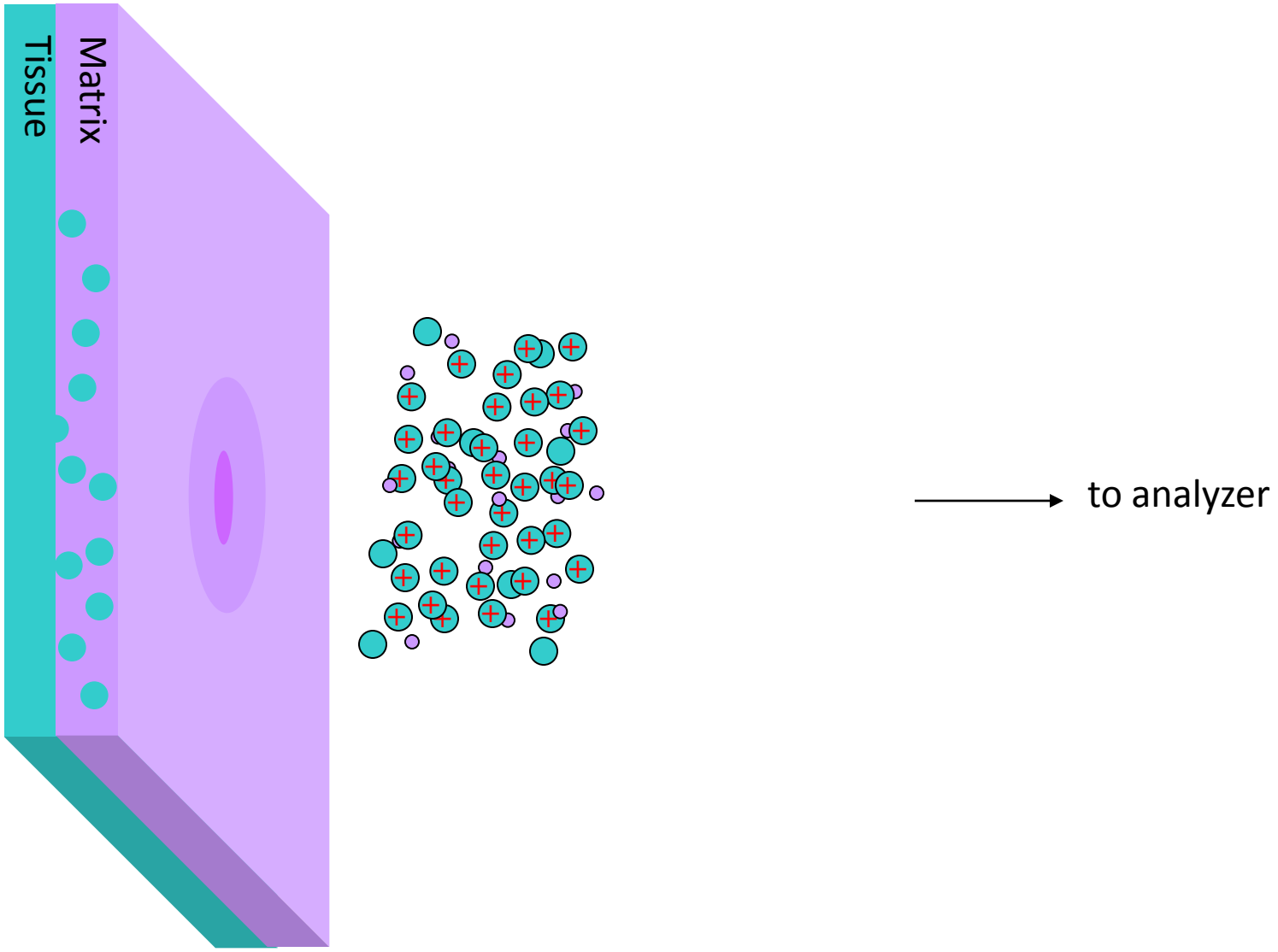




MALDI (Matrix assisted laser desorption ionization) MS

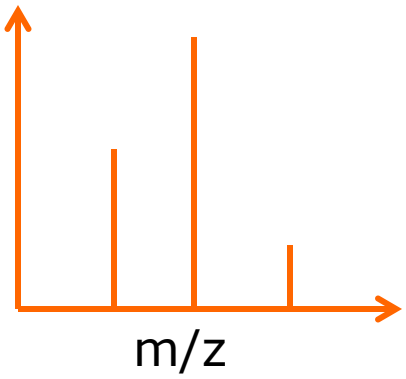


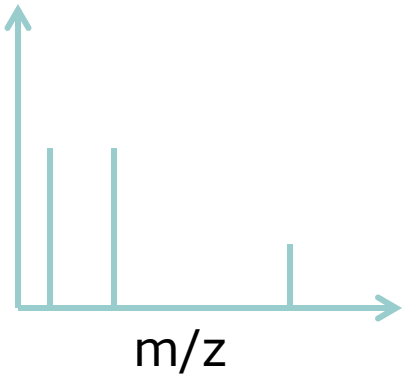
Post-ionization

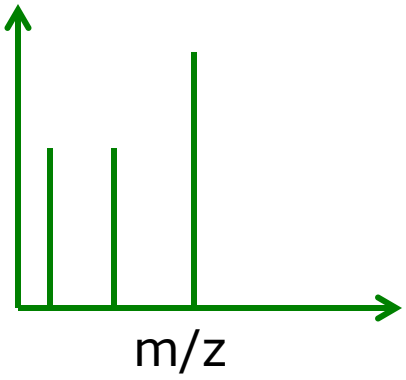


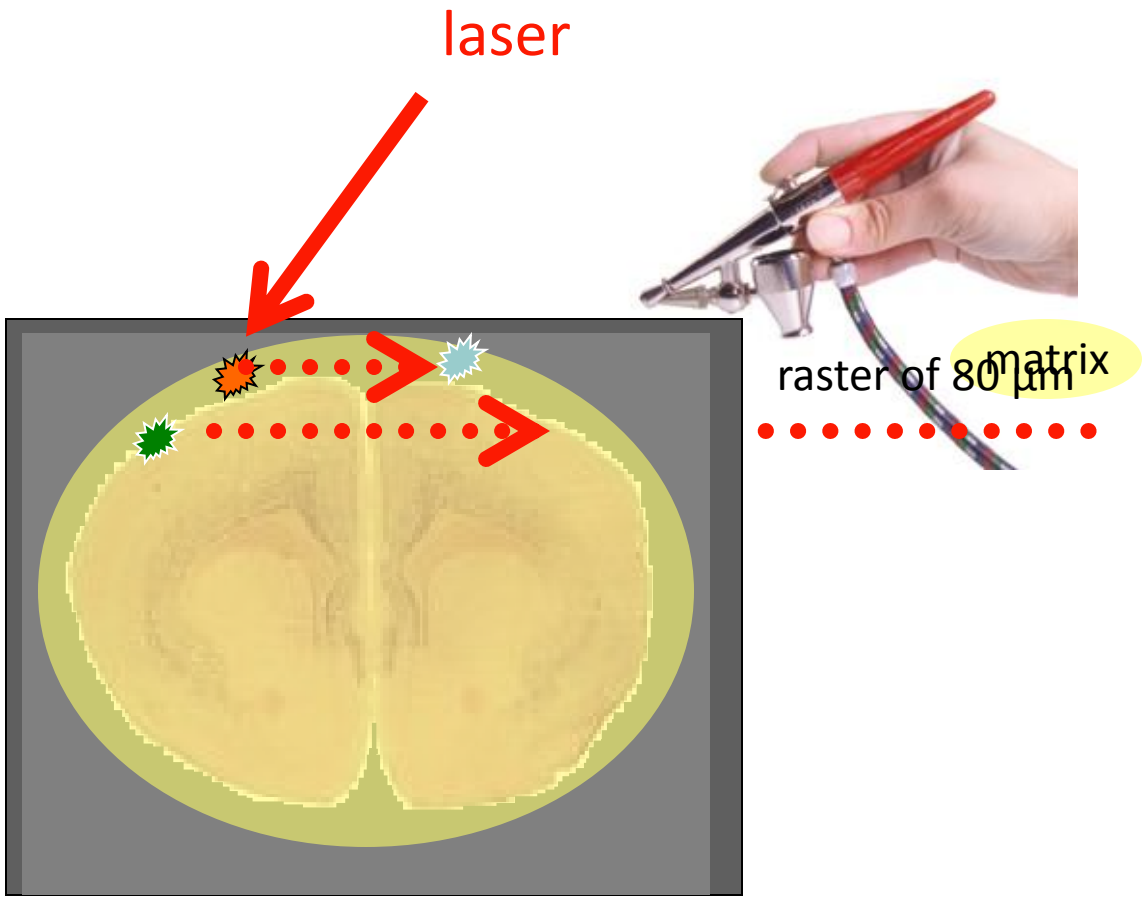
Post-ionization

Matrix deposition with an airbrush

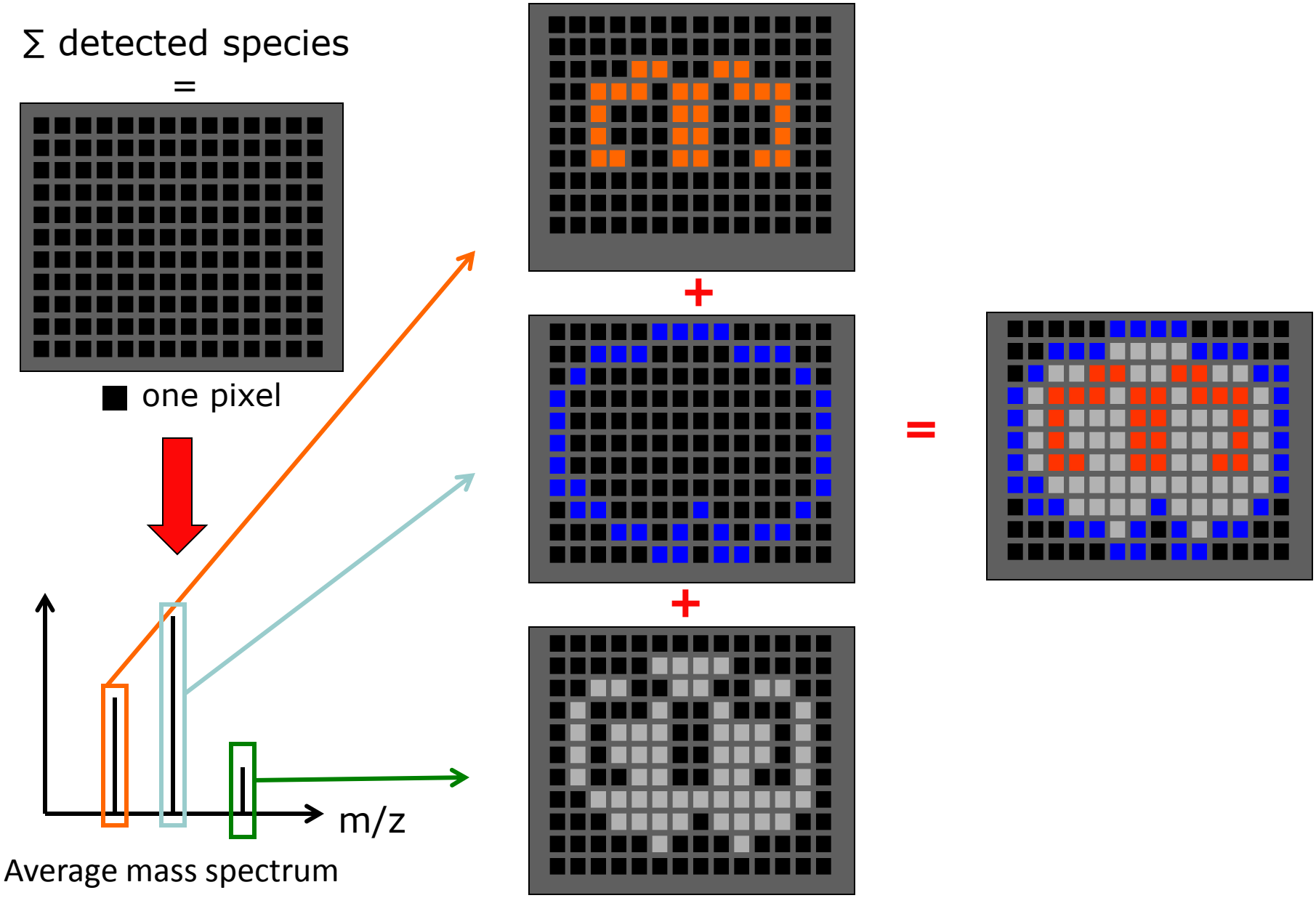








Data processing



Tissue: 16 µm rat cerebrum section

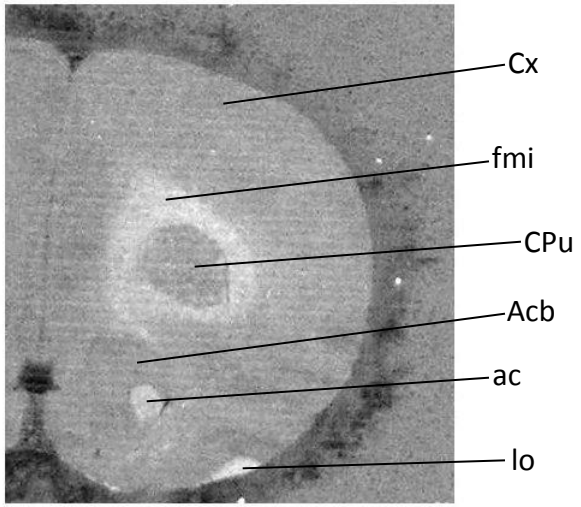
Spatial Resolution: 200 µm

Matrix: 5.5 nm gold particles

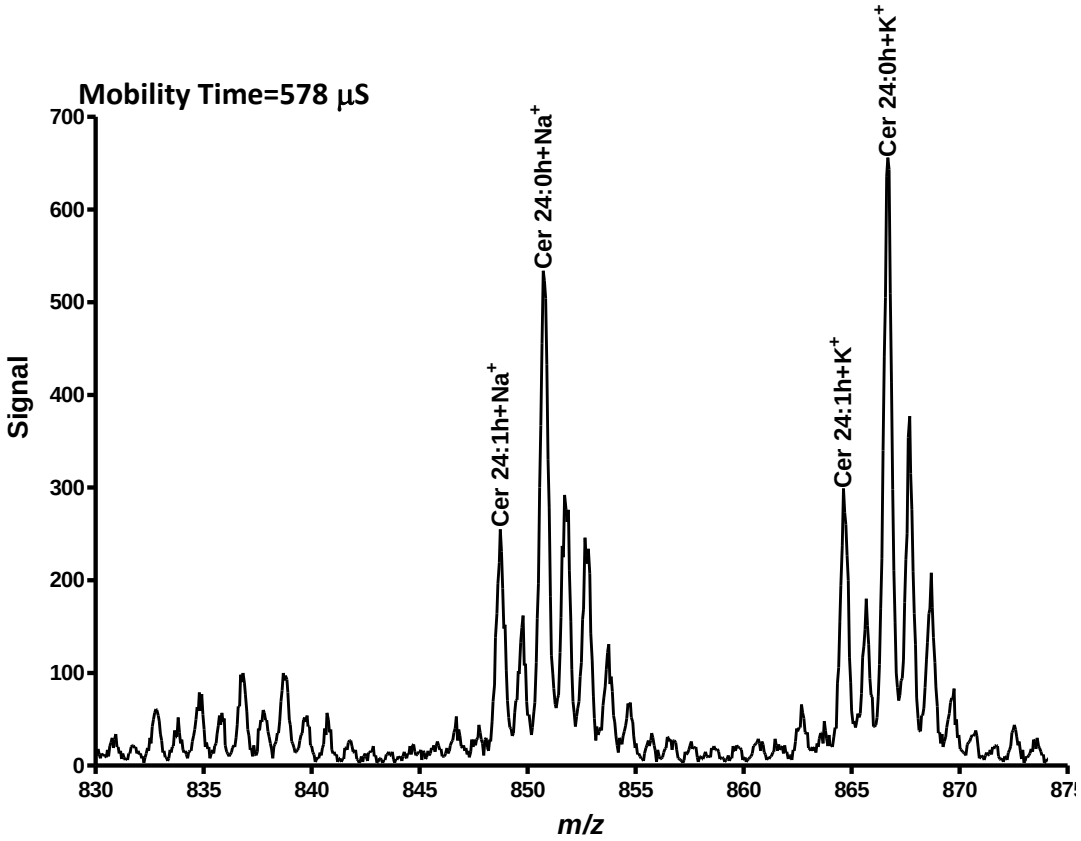
Matrix deposited by air brush.

Positive Ion Mode

Images 40x40 pixels



Cx: cortex; **fmi**: forceps minor of the corpus callosum; **Cpu**: caudate putamen (striatum); **Acb**: nucleus accumbens; **ac**: anterior commissure; **lo**: lateral olfactory tract



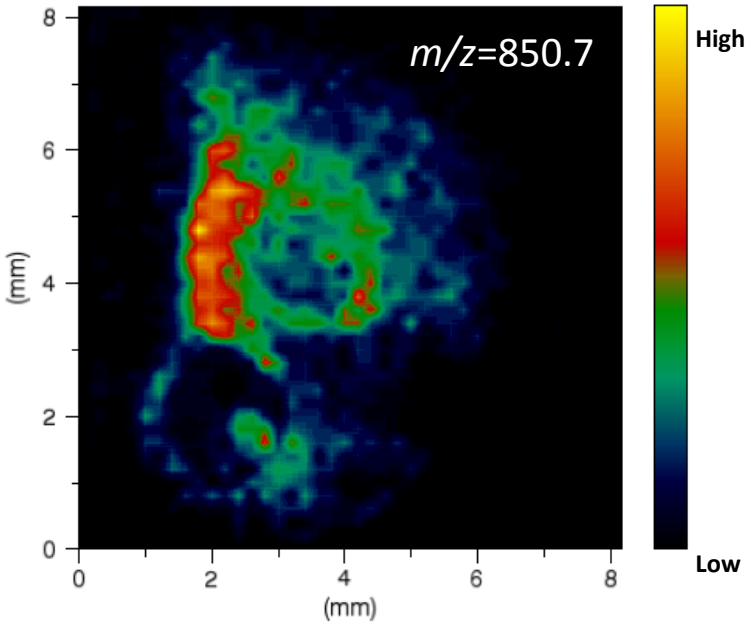


Figure 1A: 2.5 PSI Images

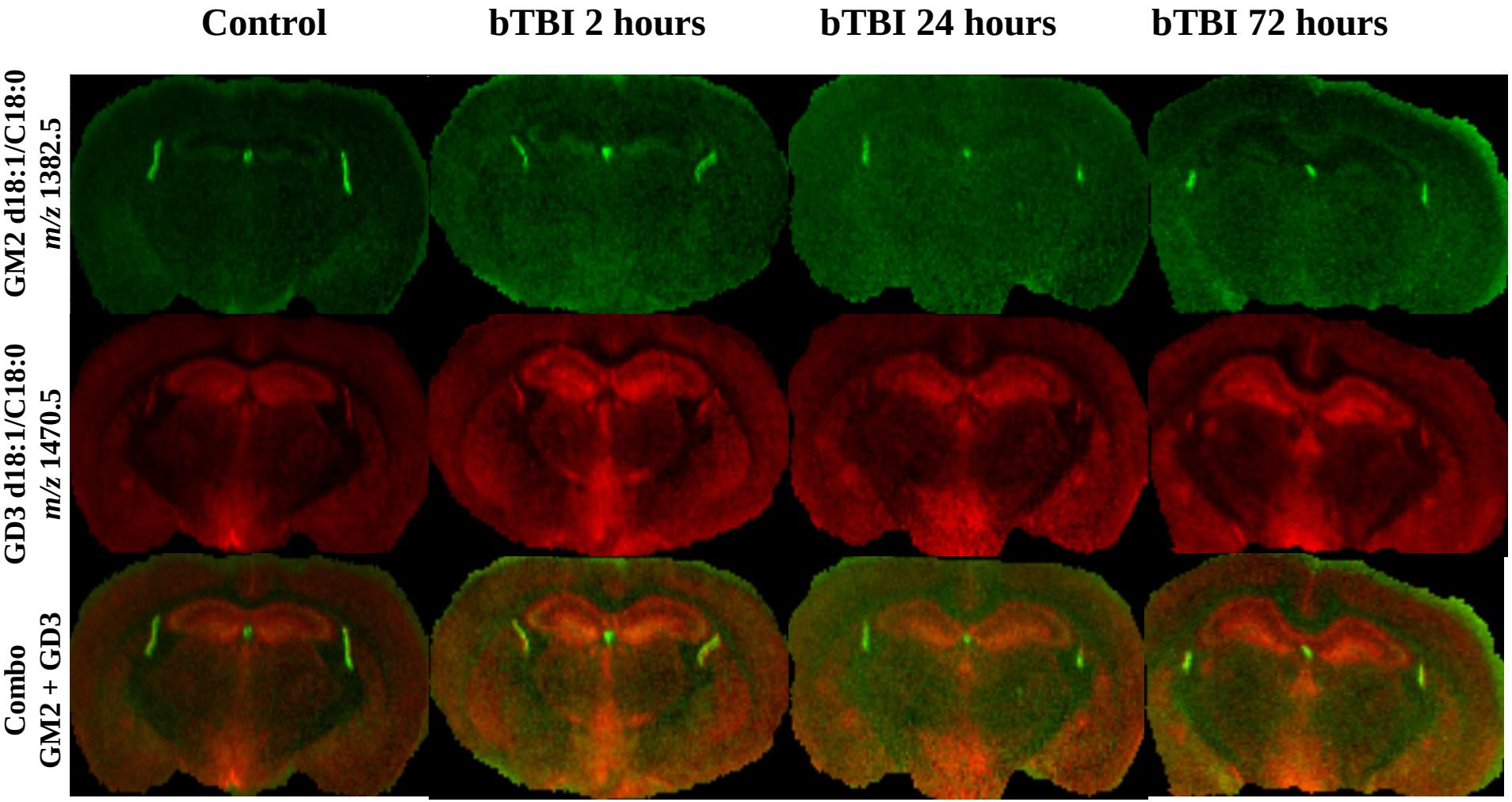
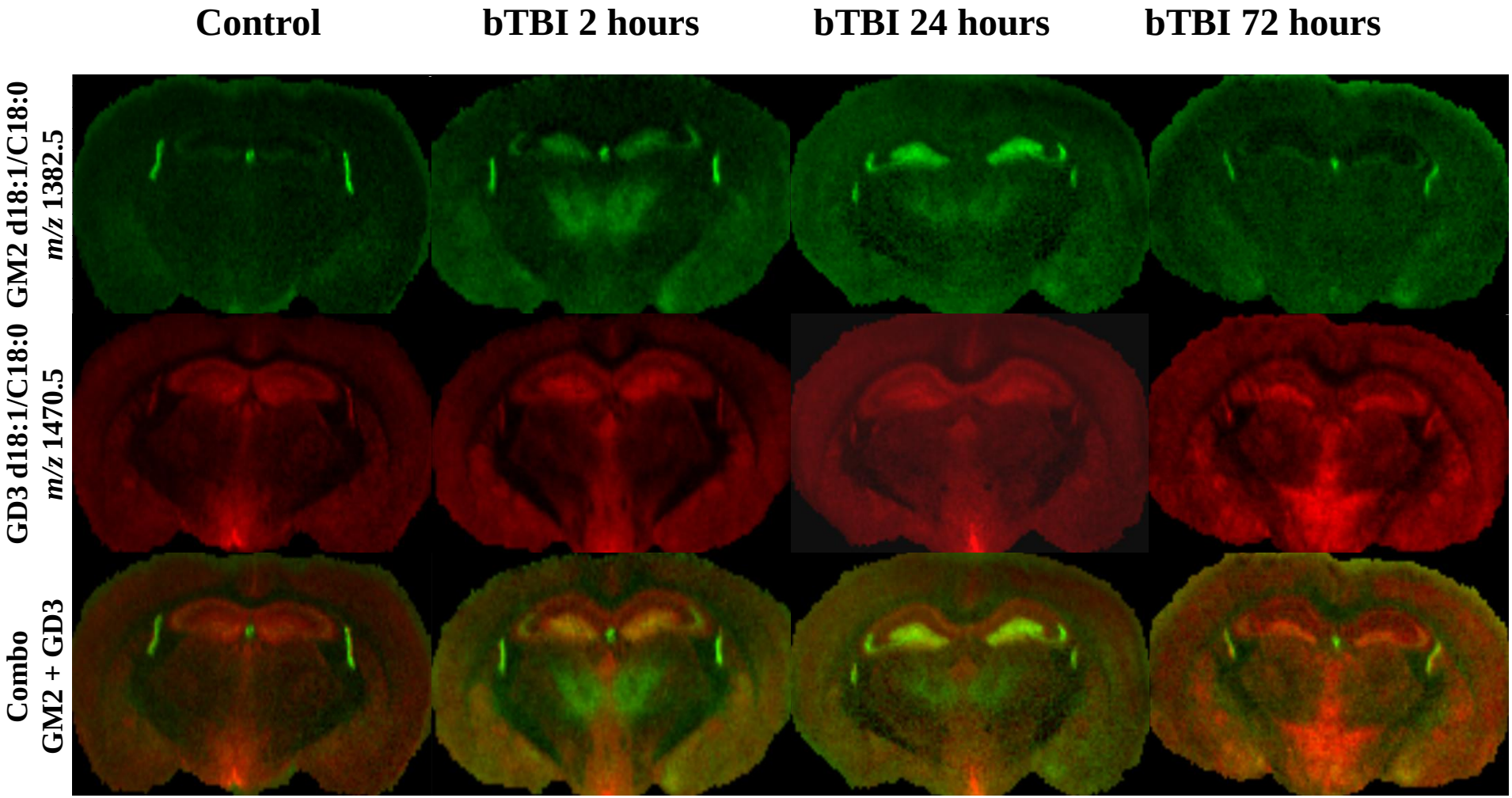
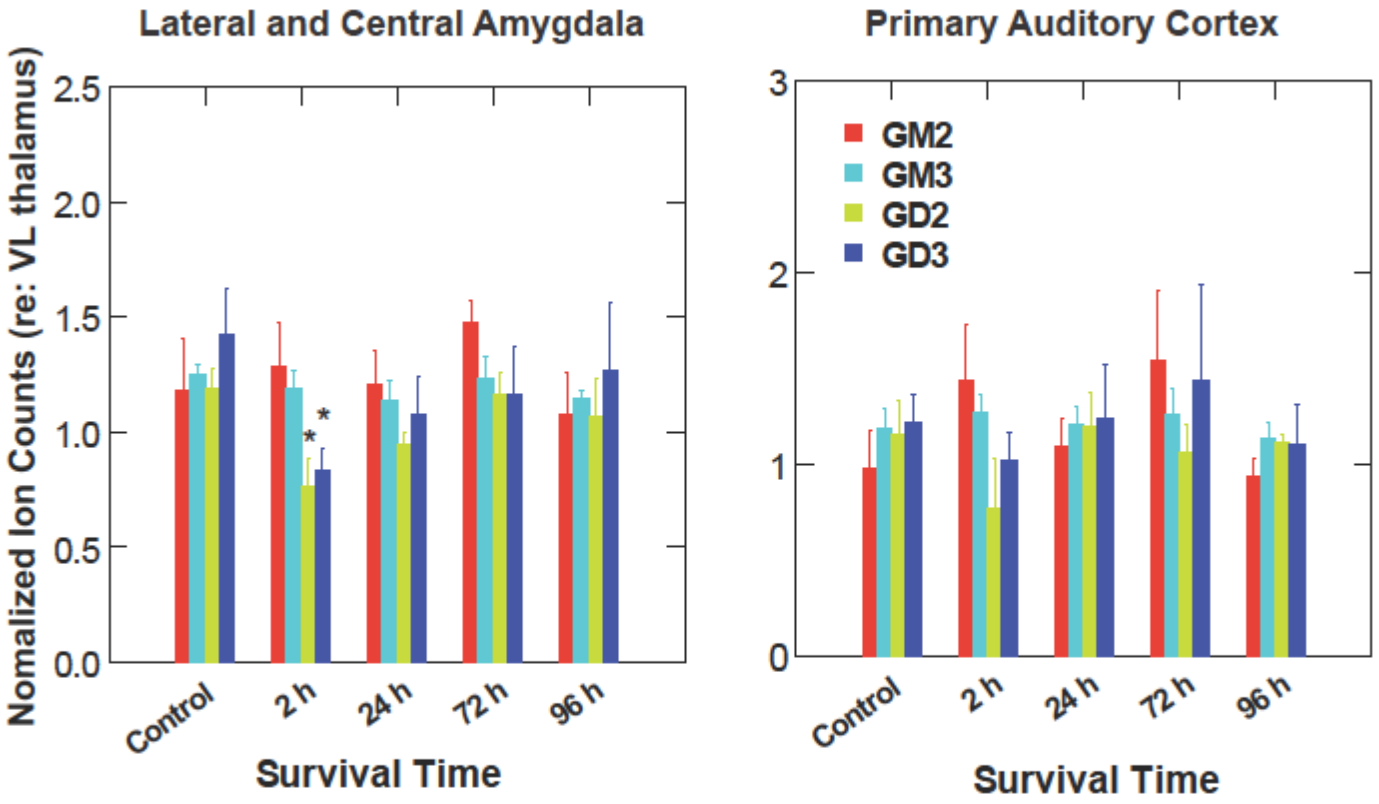


Figure 1B: 5.5 PSI images



5.5 PSI Quantitative Analysis



Pathophysiology – Blast Injury

- Shock wave effect
  - Microvascular injury in brain and inner ear
  - Headache and vestibular symptoms may result from persistent blood products in CSF
  - Oxidative cellular stress
  - Healing or secondary neuronal damage
  - Transient changes in neuronal cell membrane lipid structure