The Safety of High Flight: The Effects of Hypobaric Exposure Upon the Brain – Human Single Exposure Trial at 3 years

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Disclosure Information

- **No financial relationships to disclose.**
- **No discussion of off-label use and/or investigational use in my presentation.**
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U.S. Air Force photo by A1C Zade C. Vadnais

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- KBRwyle Labs

USAF photo by A1C Bobby Cummings

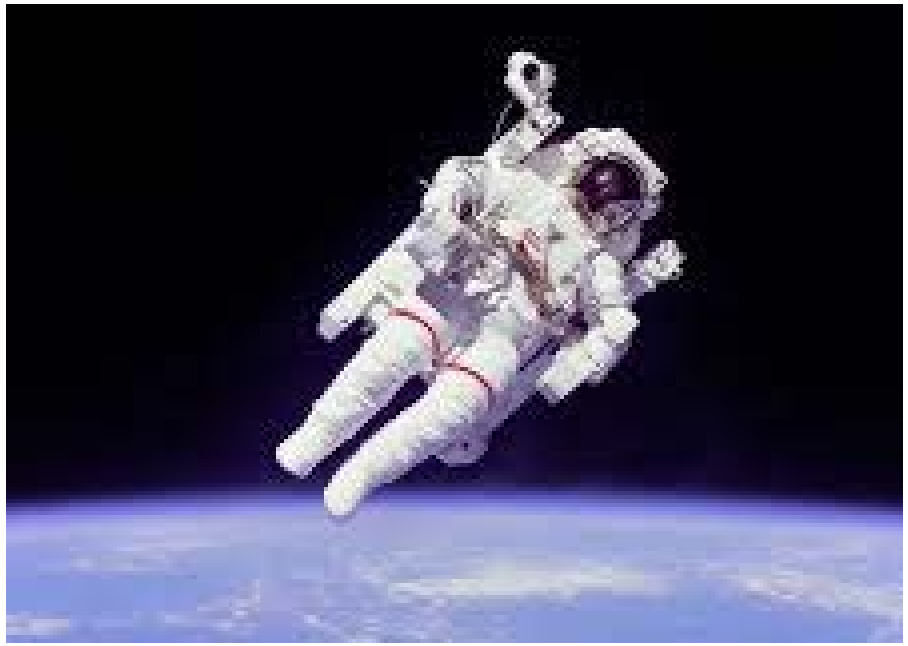
USAF photo by A1C Bobby Cummings

Overview

- **U-2 pilot and normative database study**
  - ***105 U-2 pilots, 83 Aerospace physiology chamber inside observers (AOP), 148 Controls***
- ***NASA astronaut study***
  - ***39 Astronauts***
- **Single Hypobaric Exposure Study**
  - **96 Aircrew Fundamentals Course (AFC) trainees, 65 Controls**
- **Swine studies**
- **Summary**

Background

- U-2 operates in an extreme environment
- Crew protection based on years of experience and research
- U-2 pilots and NASA astronauts <u>during EVAs</u> experience a hypobaric environment of approximately 4.3 psia
  - Pressure inside the pre CARE U-2 cockpit = EVA suit for astronauts
- Not all ISS astronauts perform EVAs; when not performing EVAs, astronauts live at 14.7 psia
- Different DCS countermeasures used by USAF and NASA



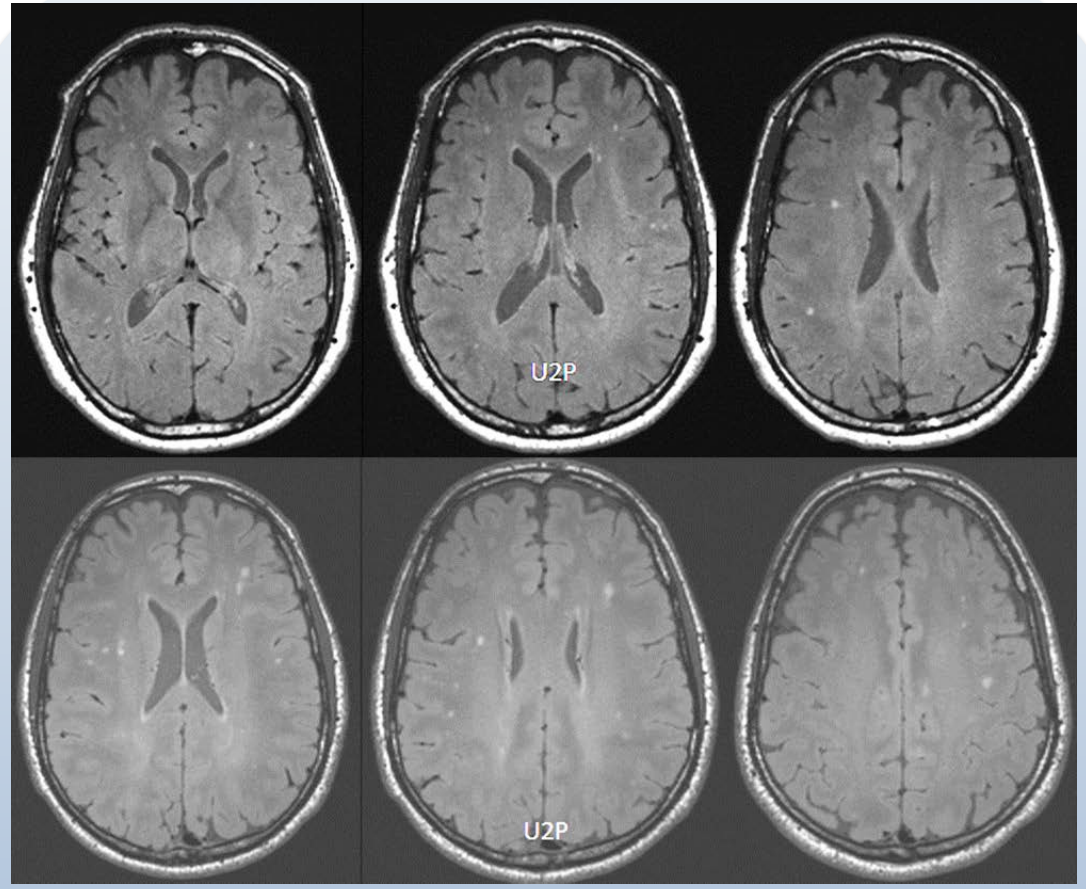
Military and Civilian Relevance

- Potential impact to anyone subjected to decompressive stress
  - High altitude drops (special forces, aircrew)
  - High altitude operations in unpressurized platforms (including rotary)
  - SCUBA divers
- Long-term neurocognitive functioning impact/disability in exposed individuals unknown
- Aeromedical transport personnel of neurological worsening in acute TBI associated with flight (human and animal studies) and in worsening with hypobaria only (swine)
- Unexplained physiologic events
  - F/A-18, F-16, F-22, F-35, T6

USAF photo by Chris Gulliford

U-2 Study – Repetitive Exposure

- Imaging began as part of evaluation for Neurologic DCS
  - 300% increase 2006-2010
  - 5 near fatalities 2009-2010
- Focal punctate white matter hyperintensities (WMH) on FLAIR MRI
- MRI highly reproducible



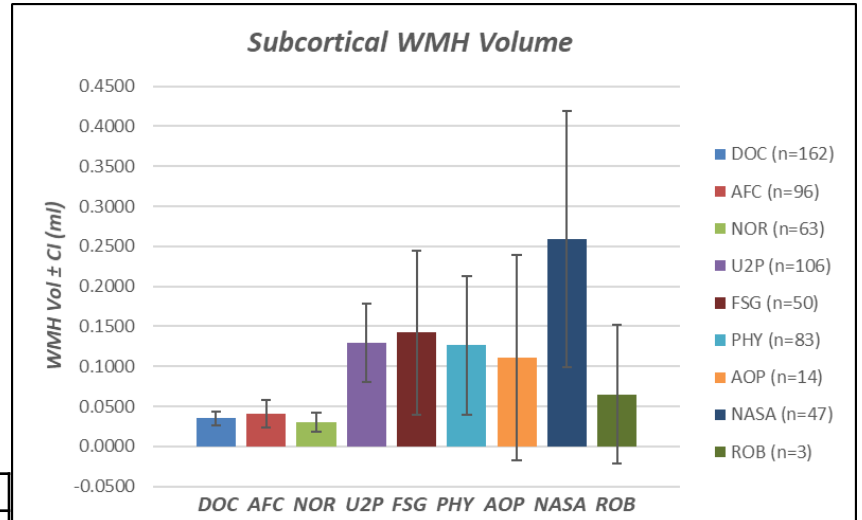
U2P and AOP, with or without NDCS

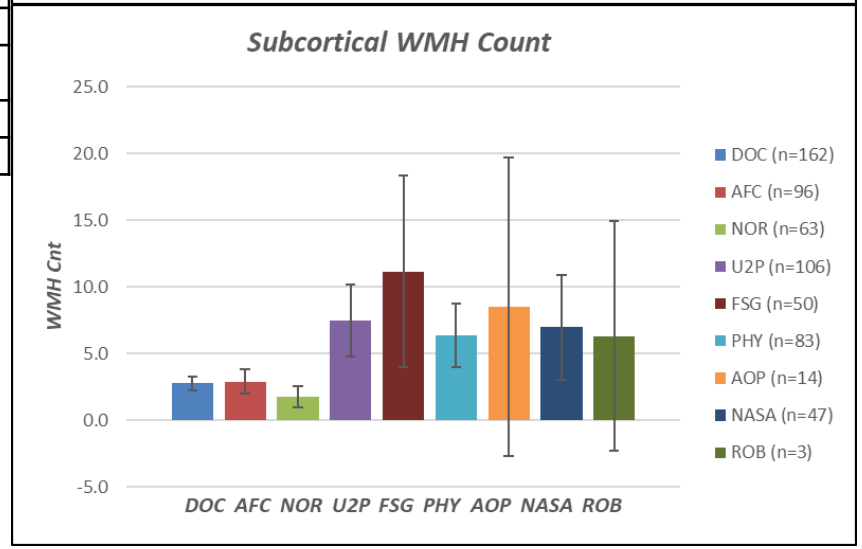
Phase 1 Repetitive Exposure White Matter Hyperintensities

- **Significantly increased subcortical WMH volume/count in U2P & AOP/PHY**
- **AFC ≈ DOC ≈ NOR**
- **U2P ≈ AOP/PHY ≈ FSG**
  - **Individual variability**
- **Volume most clinically significant**

	DOC	U2P	PHY
WMH vol (mean±CI)	0.035±0.009	0.129±0.049	0.126±0.086
WMH cnt	2.8±0.5	7.5±2.7	6.4±2.4
Mann-Whitney-Wilcoxon	DOC:PHY	DOC:U2P	U2P:PHY
WMH volume (mL)	p=0.0287	p<0.0001	p=0.4046
WMH cnt	p=0.0499	p=0.0374	p=0.9388

DOC – doctorate controls
U2P – U-2 pilots
AOP/PHY – aerospace operational physiologists
AFC – aircrew fundamental course students
NOR – combat arms students
FSG – flight surgeons
NASA – astronauts
ROB – reduced oxygen breathing device

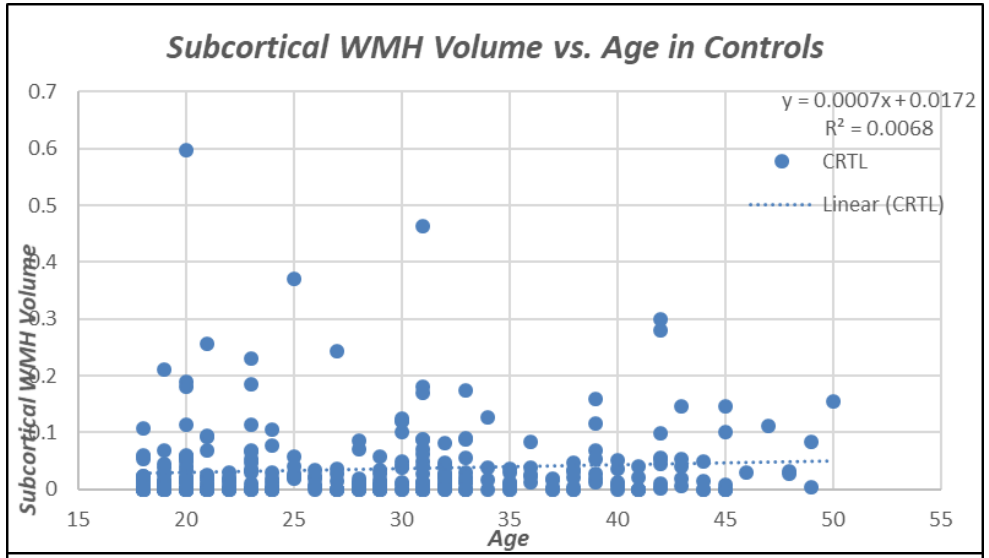


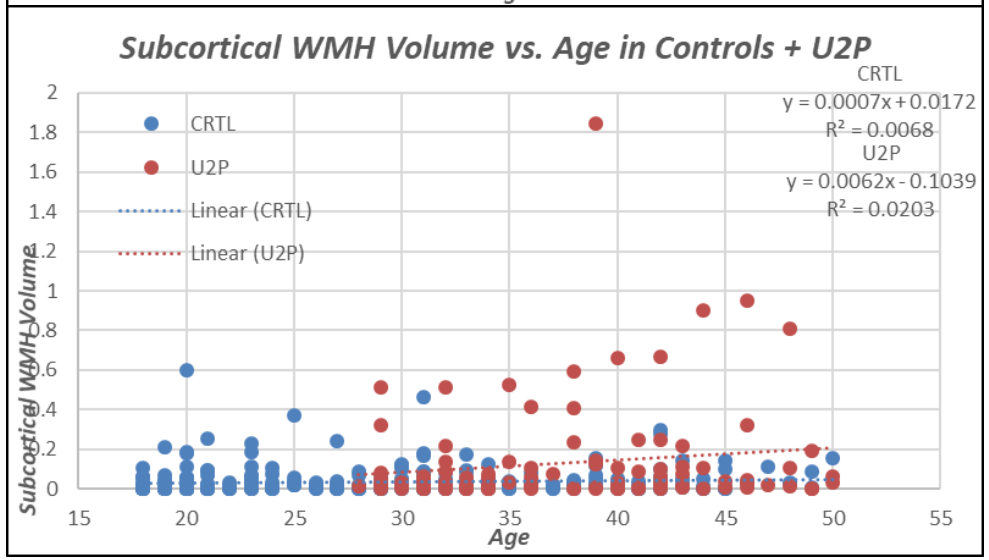


McGuire et al. Neurology 2013;81:729-735
McGuire et al. Ann Neurol 2014;76:719-726

Subcortical WMH Volume vs. Age

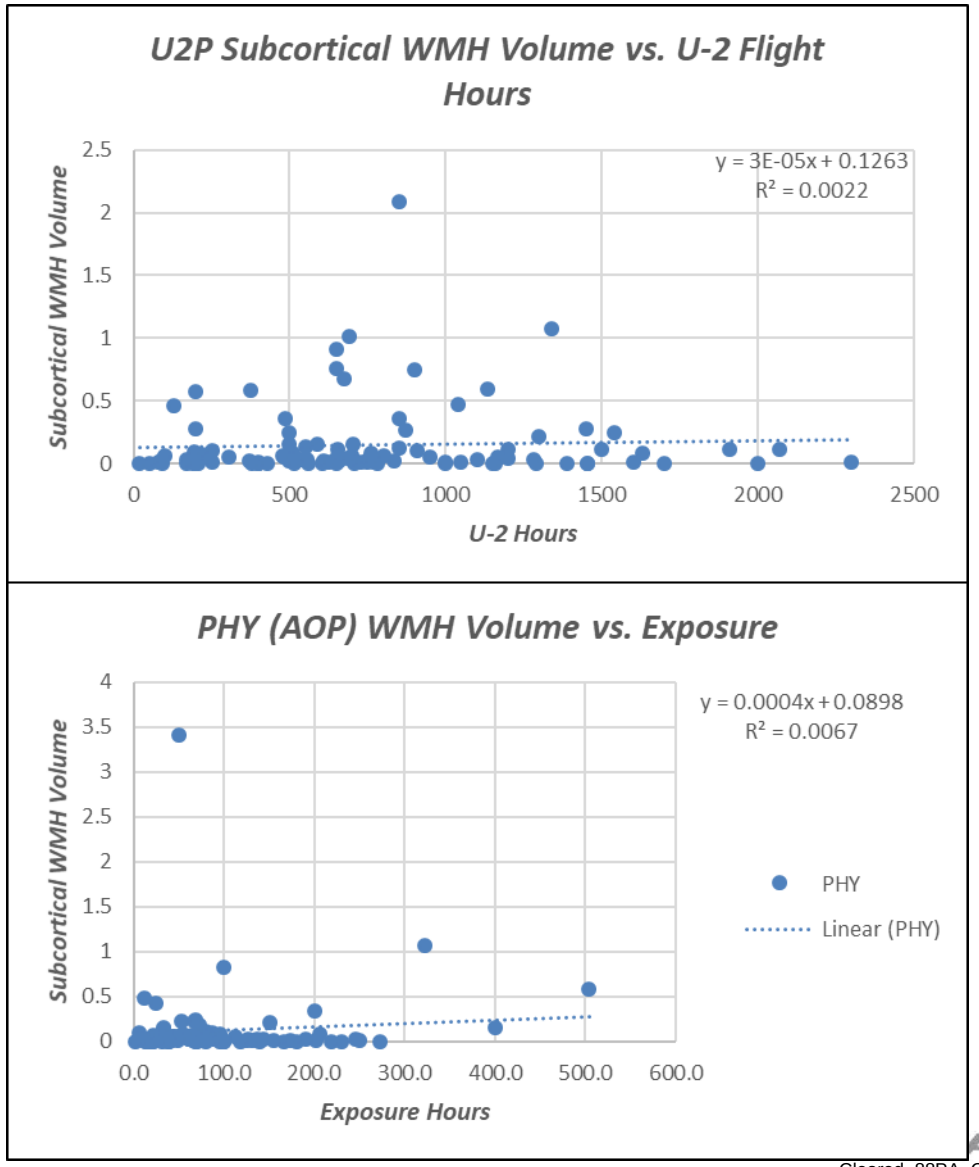
- *Subcortical WMH volume known to increase with advanced age (> ~ 60 yr)*
  - *Over age range 18-50 essentially no increase with age*
- *Increase slightly more rapid in U2P but not sufficient to account for increase in volume*
  - *Suggests not a simple factor of exposure*





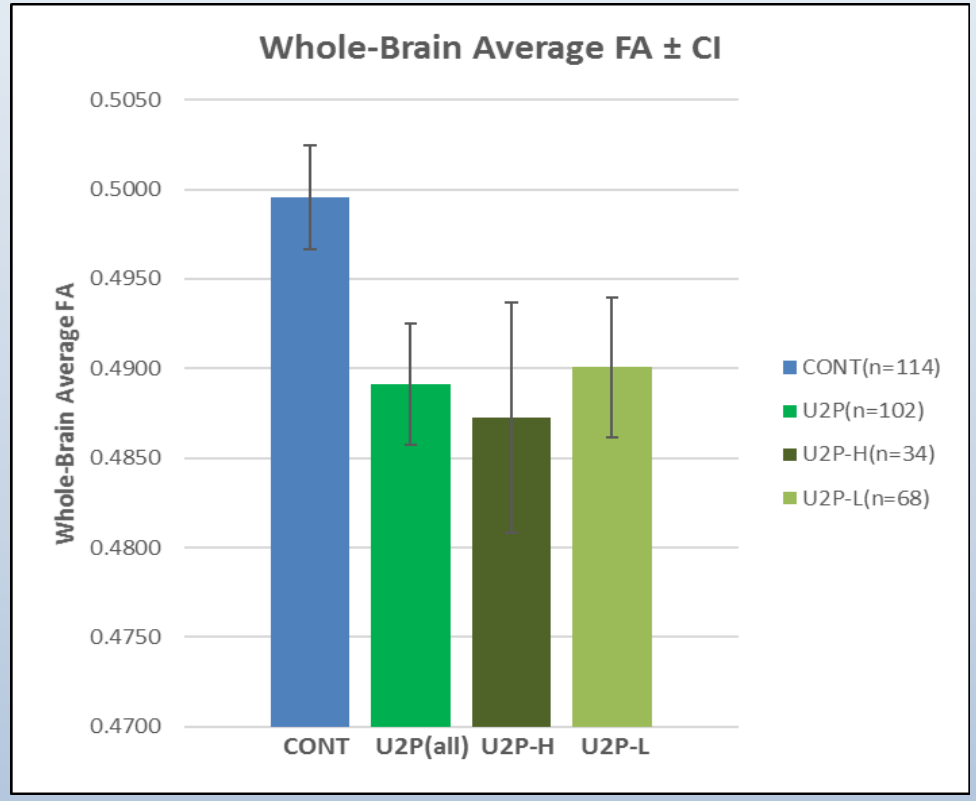
WMH Volume vs. Exposure

- *Little correlation between total hours of exposure and subcortical WMH burden*
  - *Suggests multifactorial relationship to WMH burden*
- **Mild/controlled HTN and/or hyperlipidemia not an explanation for findings in this study population**
- **No significant contributing factors**
  - **No caffeine, smoking, supplements, etc.**



Repetitive Exposure Fractional Anisotropy

- **Whole brain average FA assesses entire WM**
  - **FA believed to correlate with axonal integrity**
  - **Used ENIGMA-DTI protocol to exclude visible areas of WM injury (punctate WMH)**
  - **KS p<0.001; GLM p<0.001**
    - **Kolmogorov-Smirnov (KS)**
    - **Generalized linear model (GLM) with age as nuisance covariate**
- **Reflects ~ 2% decline in axonal integrity**
- **Decline in axonal integrity appears to track with WMH burden**
- **Results contingent upon cross calibration of scanners**
  - ***46 subjs dual imaged (r=0.85; COV=4%). Univ of Texas and Wilford Hall magnets**



McGuire et al. Aerosp Med Hum Perform. 2016.

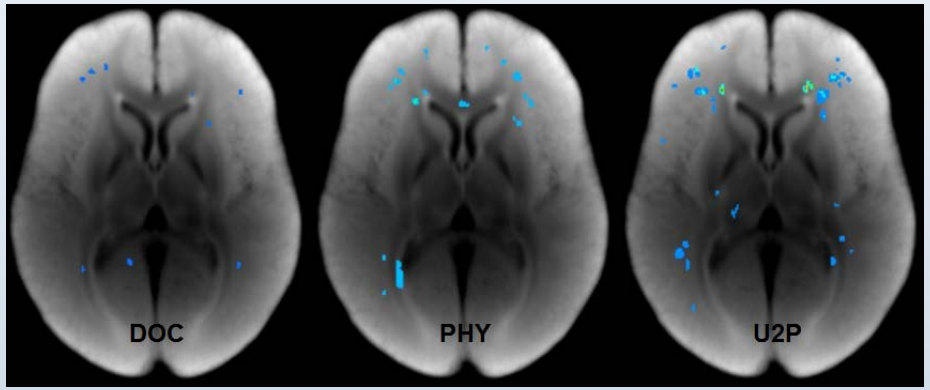
U2 Pilot Neurocognitive Differences

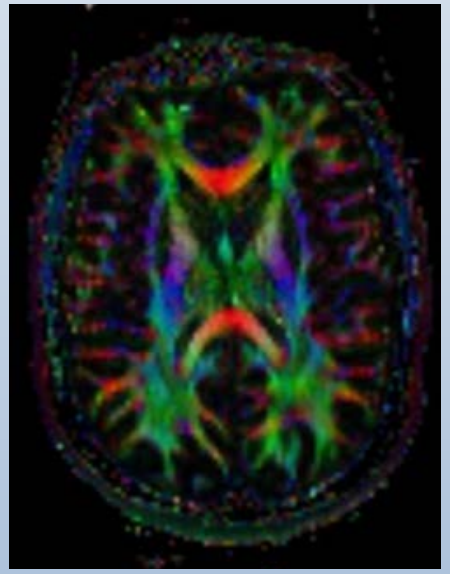
- ***Significant decrease in current computer-based Microcog testing in U2P compared to AF pilot controls***
- ***Pattern of change similar to all other neurological diseases with subcortical injury***
- ***Multiple indices indicate pilots similar at undergrad pilot training***
- ***Decrease suggests diffuse WM process***
- ***MicroCog absolute values generally decreased with greater WMH burden within the U2P population***

	MicroCog	U2P (n=93)	AFP (n=80)	t-test (2-tailed) Significance	Sidak (2-tailed) Significance
1	Attention/mental control	104.4	103.8	p=0.696	p=0.997
1	Reasoning/calculation	99.4	106.5	p<0.001	p=0.001
1	Memory	105.5	110.9	p=0.007	p=0.036
1	Spatial processing	109.1	109.1	p=0.989	p=1.000
1	Reaction time	107.3	104.8	p=0.047	p=0.216
2	Information processing speed	103.6	106.5	p=0.100	p=0.189
2	Information processing accuracy	102.1	105.8	p=0.016	p=0.032
3	General cognitive functioning	103.5	108.5	p=0.002	p=0.004
3	General cognitive proficiency	105.4	108.6	p=0.037	p=0.072

U-2 Study – Summary

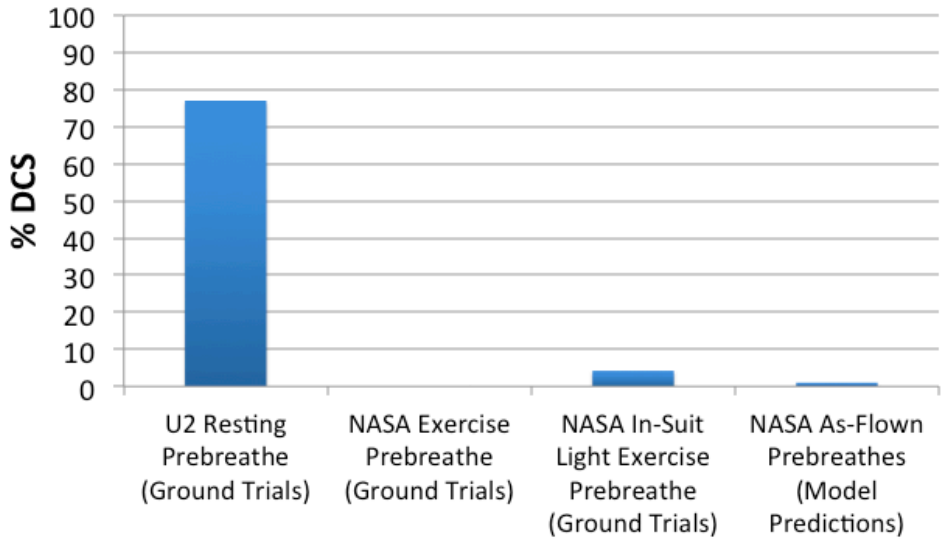
- **Recurrent exposure to nonhypoxic extreme hypobaria incites:**
  - **Focal punctate WMH on MRI**
  - **Diffuse decrement in axonal integrity on MRI (FA changes)**
  - **Acquired neurocognitive decline as measured on CBT**
    - **Corresponds to WMH burden**
- **Quantitative MRI highly reproducible**

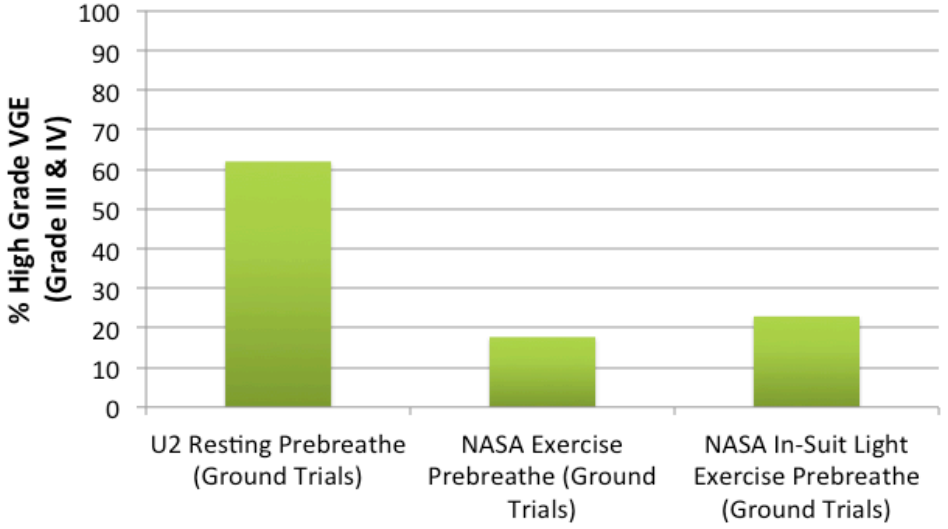




Background NASA Data

- ***Data from ground trials as well as model predictions confirm that prebreathe protocols are far more conservative (lower DCS risk) for NASA EVAs than for U-2 pilots***
- ***NASA prebreathe protocols as-flown include additional prebreathe compared with ground trials due to operational factors***
  - ***Model predictions estimate actual NASA DCS risk as-flown at 1%***
  - ***Same model predicts 67% DCS for U2 1hr resting prebreathe***

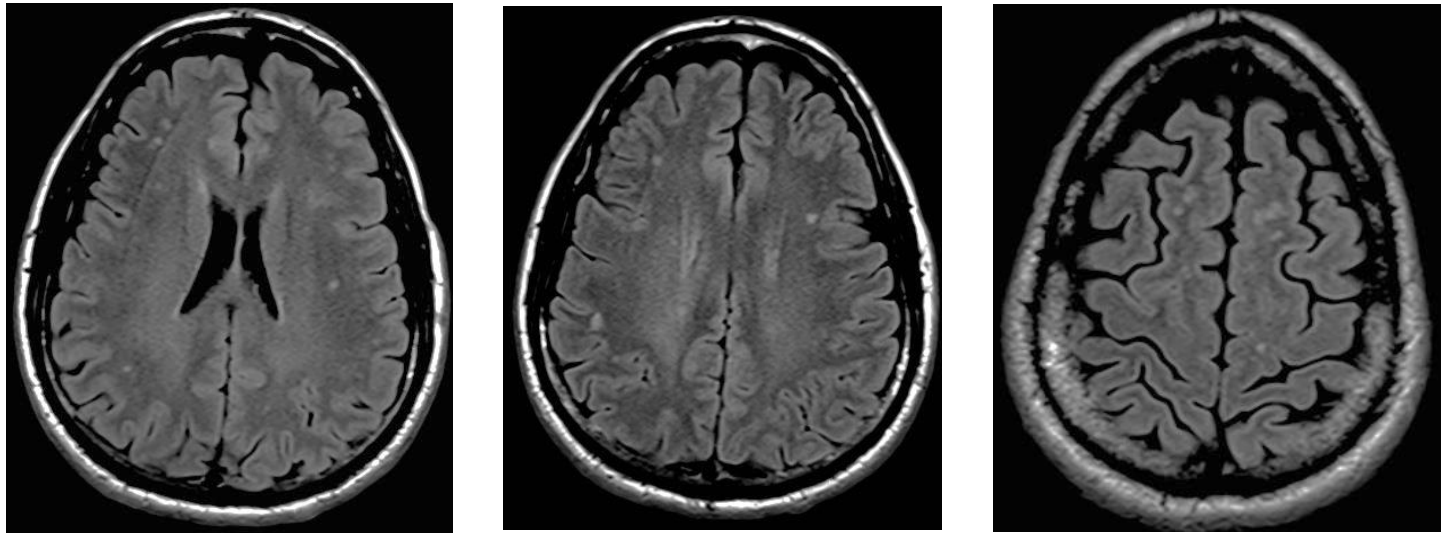




Brooks AFB data, Webb JT et al. Exercise-enhanced preoxygenation increases protection from decompression sickne
Aviat Space Environ Med 1996; 67:618-24.

Initial NASA collaboration

- ***Brain MRI scans from 39 astronauts***
  - ***41 total scans***
  - ***Post ISS or shuttle mission completion***
- ***These scans were conducted on 3 different 3T magnets, two Siemens scanners and one Philips scanner, with 12-channel head coils***
  - ***Siemens n=21; Philips n=20***
- ***De-identified MRI scans, 5 mm clinical FLAIR sequence only, were provided by NASA's Lifetime Surveillance of Astronaut Health (LSAH)***

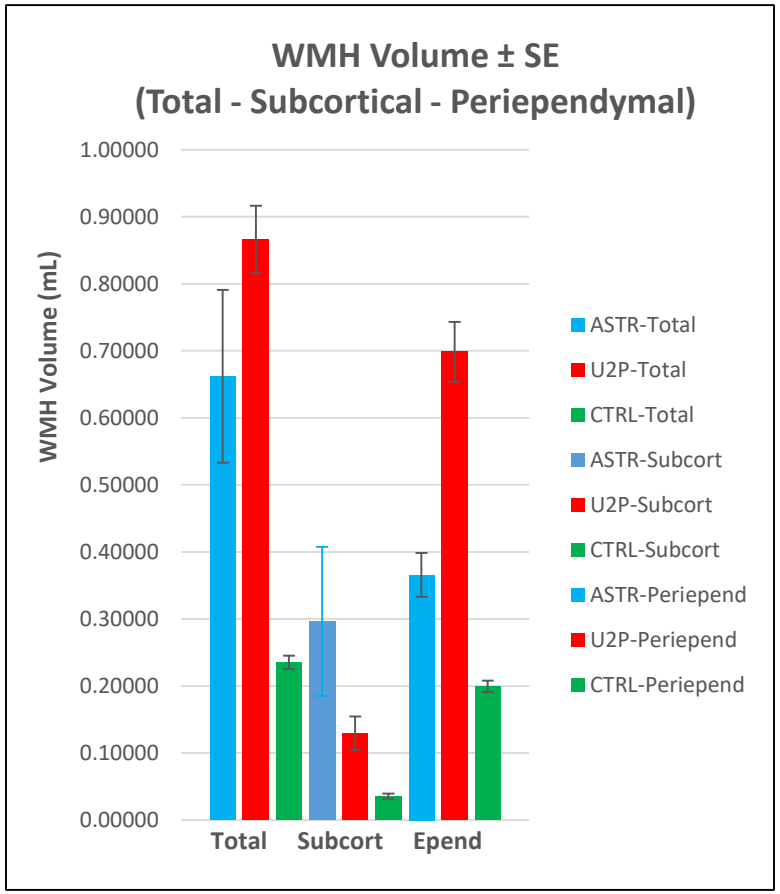


5mm slice thickness
(U2 0.8 mm)

Astronaut FLAIR Data

Our Analyses

- ***Comparison of mean WMH volume***
- ***SE = standard error***



Astronaut Summary

- *Unexplained increased WMH burden, similar to U-2 pilots*
  - *Is WMH burden in astronauts a consequence of training vs. other factors prior to entry into astronaut corps?*
  - *Exposure to hyper- and hypobaric stresses during training regimen (i.e. chamber activities including underwater/tank training)*
  - *Many exposed to prior activities including aviation (military and commercial), SCUBA diving, mountain climbing, etc.*
- *We don't have this data to be able to draw specific conclusions*
- *Recent demonstration of intracranial fluid shifts, increase in periventricular WMH, and sulcus change with reports of "mental fog" suggests a more detailed analysis of white matter integrity is warranted to understand and minimize risks in these high-performing individuals*

Single Hypobaric Exposure Study

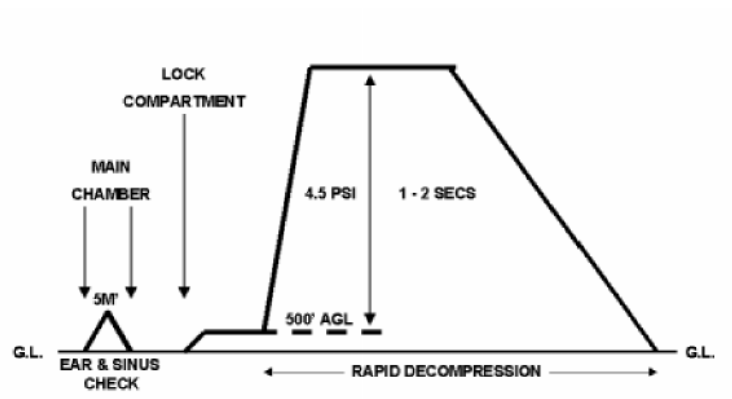
- **Hypothesis – single occupational exposure to hypobaria and/or hypoxia will be associated with transient MRI and serological changes**
  - **MRS, arterial blood flow, DTI/Q-space**
  - **Inflammatory serological markers will be up-regulated**
  - **Transient microparticle increase MAY parallel changes noted in divers**
- **Identifying transient changes with single exposure may lead to understanding the neuropathophysiology of white matter injury demonstrated in chronic hypobaric exposure**
  - **In combination with ongoing animal studies**
- **Only volunteer undergoing occupational training hypobaric and/or hypoxic exposures**

Single Exposure Study

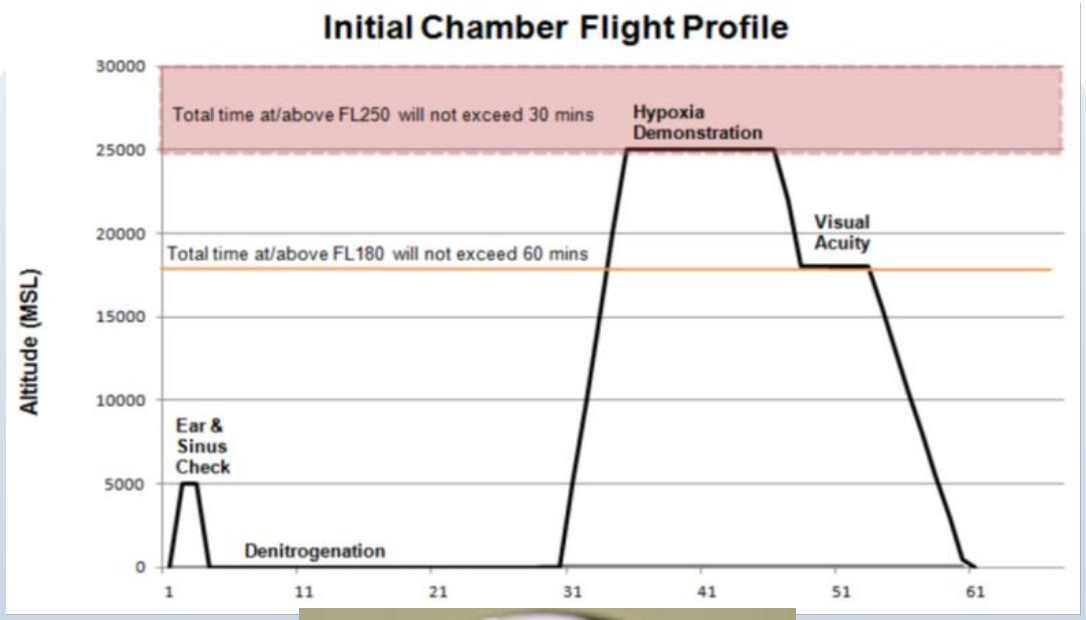
- Examine acute (MRI/serological) changes following a single exposure – all meet FCII/FCIII neurological standards
  - 1. Hypobaric-hypoxic (AFC – aircrew chamber training)
  - 2. NOR – Controls
  - 3. AOP and ROBD groups (recruitment issues)
- Protocol:
  - MRI 24 h before; 24 h after; 72 h after
  - Serological immediately before; immediately after; 24 h after; 72 h after
  - No other altitudinal exposure beginning 7 d prior
  - No alcohol beginning 7 d prior
  - Maintain normal physiological activities
    - No sleep deprivation/shift changes, etc.
- Intra-subject and cross-group comparisons

USAF Chamber Profile

- Max altitude 25,000 ft
- (7,620 m, 5.45 psi)
- 30-min denitrogenation
- Time >FL250 ≤30 min



AFI11-403 30 Nov 2012



USAF photo by Benjamin Faske.

USAF photo by Joel Martinez.

Single Exposure Study

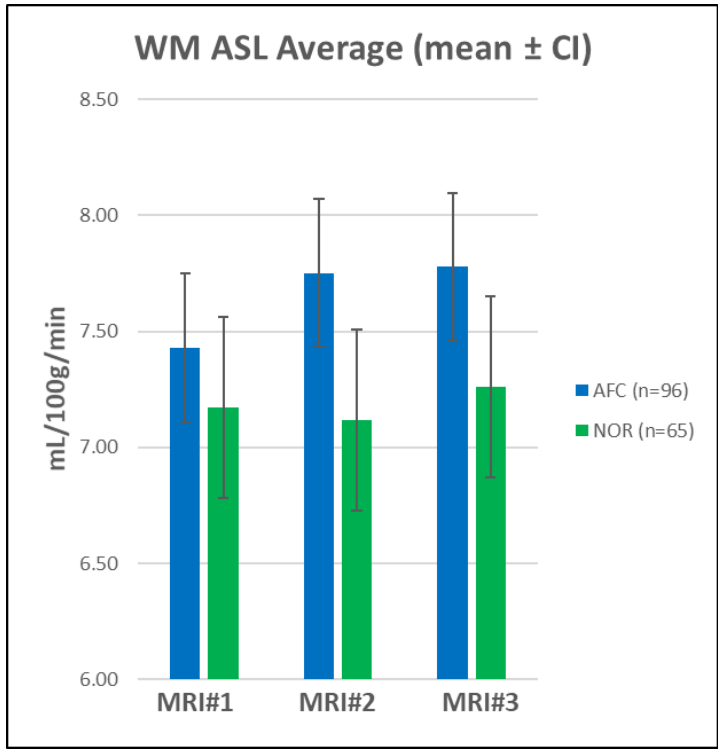
- Total of 178 total subjects
- 161 excluding AOP, ROBD
- AFC group – 96 (32F, 64M)
  - Avg. age 21.2
- NOR – 65 (6F, 59M)
  - Avg. age 22.4

Siemens 3T Verio

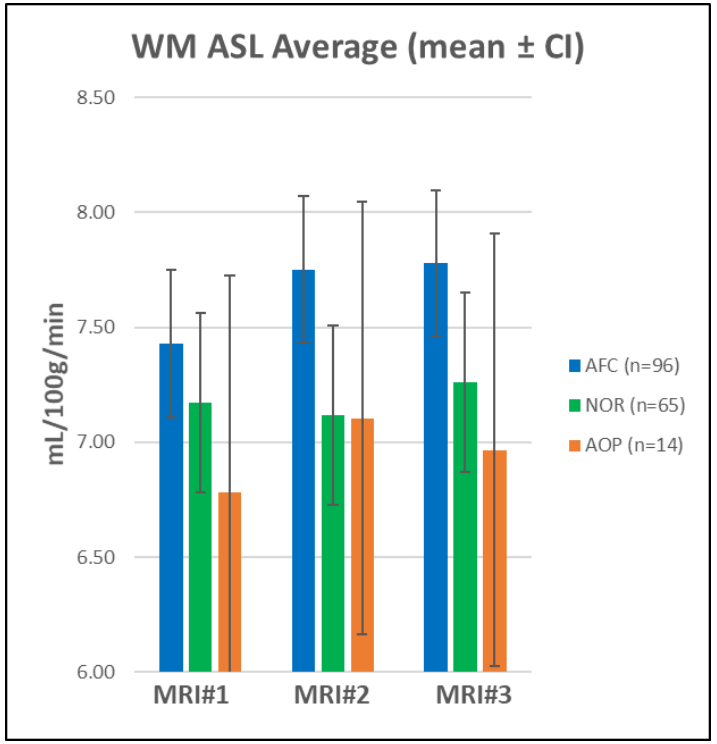
Arterial Blood Flow (ASL) – CBF

Increase in WM CBF at 24/72 h

- Significant group (AFC vs. NOR) difference
  - WM p<0.001 (Utilized generalized additive model adjusted for age and gender)

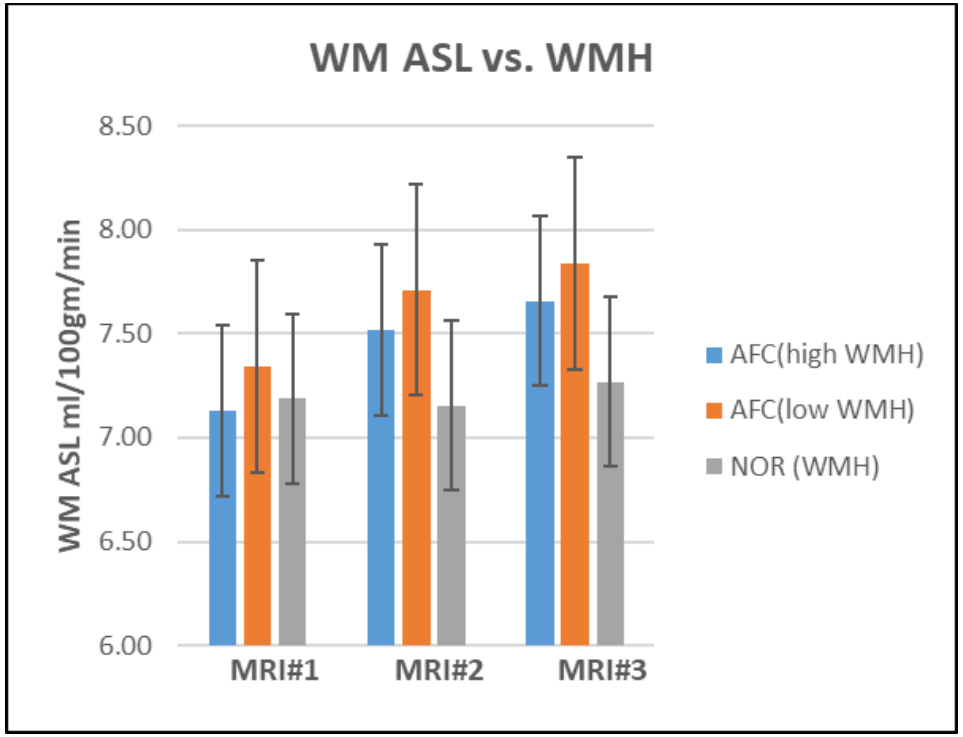


AFC	Subj #	WM
MRI#1 avg	96	7.43
MRI#2 avg	94	7.75
MRI#3 avg	96	7.78
TTEST #1-#2		0.004
TTEST #1-#3		0.009
TTEST #2-#3		0.967
NOR		
MRI#1 avg	65	7.17
MRI#2 avg	65	7.12
MRI#3 avg	60	7.26
TTEST #1-#2		0.738
TTEST #1-#3		0.363
TTEST #2-#3		0.088



Single Exposure
MR FLAIR and FA Avg

- Cerebral blood flow appears to be associated with the preexisting FLAIR WMH burden
- Higher WMH baseline associated with greater WM-ASL response to stress

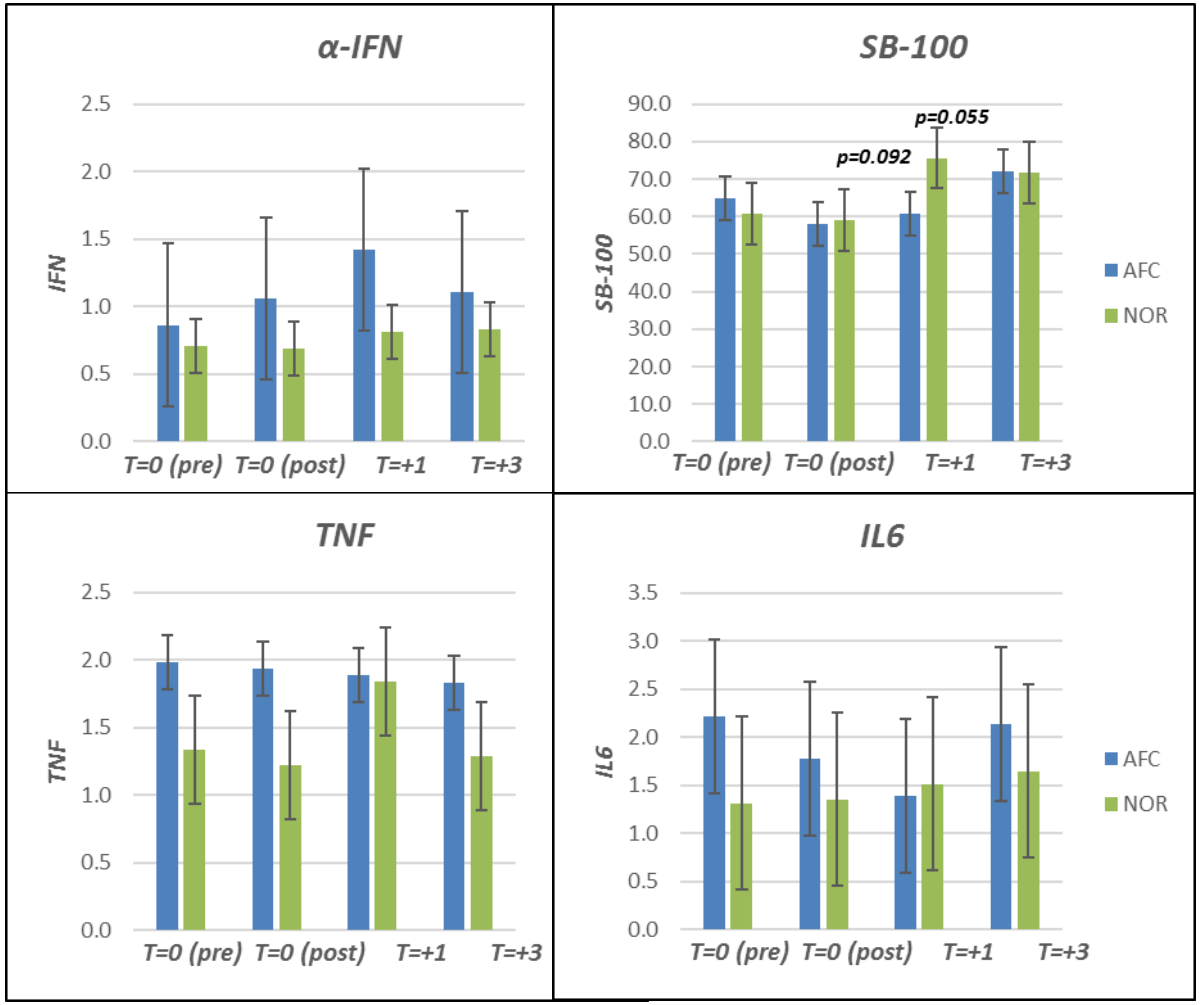


Cerebral Blood Flow

- No change in normal controls, as expected
- Approximately 5-6% increase in WM CBF
- Increase CBF reflects increased cerebral demand
  - Inflammatory, metabolic, ischemic
- Does exposure induce transient WM damage?
  - Need for adequate recovery time between exposures?
- Underlying physiological explanation remains unclear
- Duration of CBF elevation unknown
  - Ongoing duration of exposure effects study – 5 MRI data points

Single Exposure Serological Studies

- **Decrease in S100B in exposed subjects**
  - **Glial associated**
  - **Increase suggests BBB breakdown**
- **All cytokines performed by a clinical lab**
  - **(Cost; accuracy in question)**
  - ***Current research utilizing multiplex cytokine analysis and mRNA**
- **Possible systemic response to hypobaric stress**



Phase 2 Single Exposure MR Spectroscopy

- **Reproducible measurement of multiple neurometabolites with MR spectroscopy (TE30) in frontal (white matter) and anterior cingulate gyrus (mixture of white and gray matter)**
  - Glu=glutamate
  - tCho=choline
  - tNAA=n-acetylasparate
  - mI=myo-inositol
  - tCr=creatine
  - Glu+Gln=glutamate + glutamine
  - GSH=glutathione
- **tNAA reflects neurons**
- **mI reflects glia**
- **GSH reflects oxidative stress**
- **tCr reflects energy**

Metabolite	ICC	Rating (3%)	Rating (10%)
TE30 frontal lobes WM			
Frontal Mean Glu	0.816	N = 141(Low)	N = 14(High)
Frontal Mean tCho	0.886	N = 91(Low)	N = 9(High)
Frontal Mean tNAA	0.694	N = 51(Low)	N = 6(High)
Frontal Mean mI	0.745	N = 155(Low)	N = 15(High)
Frontal Mean tCr	0.565	N = 84(Low)	N = 9(High)
Frontal Mean Glu+Gln	0.818	N = 119(Low)	N = 12
Frontal Mean GSH	0.696	N = 281(Low)	N = 26(Mod)
TE30 AC GM			
AC Glu	0.763	N = 43(Low)	N = 5(High)
AC GSH	0.798	N = 87(Low)	N = 9(High)
AC tCho	0.879	N = 52(Low)	N = 6(High)
AC tNAA	0.787	N = 15(High)	N = 3(High)
AC mI	0.781	N = 44(Low)	N = 6(High)
AC tCr	0.667	N = 21(Mod)	N = 3(High)
AC Glu+Gln	0.765	(Low)	N = 4(High)

McGuire et al. Brain Behav 2017;e00759 (https://doi.org/10.1002/brb3.759)

Single Exposure MR Spectroscopy

Significant group differences

- Generalized additive model statistics
- NAA=neuronal
- mI=glial
- Cr=creatine
- Glu+Gln=glutamate + glutamine
- GSH=oxidative stress

Significant differences for:

- GSH Front 30 (p=0.029)
- Glu Front 30 (p=0.017)
- Cho AC 30 (p=0.009)
- NAA AC 30 (p=0.023)
- MI AC 30 (p=0.038)
- Cr AC 30 (p=0.008)
- GluGln AC 30 (p=0.004)

TE30 Frontal Average	*Count*	*Average Glu*	*Average Cho*	*Average NAA*	*Average mI*	*Average Cr*	*Average Glu+Gln*	*Average GSH*
AFC#1	*89*	*8.177*	*2.253*	*10.136*	*5.362*	*7.152*	*9.831*	*2.444*
AFC#2	*87*	*8.093*	*2.229*	*10.000*	*5.265*	*7.051*	*9.809*	*2.381*
AFC#3	*89*	*8.120*	*2.260*	*10.118*	*5.297*	*7.178*	*9.929*	*2.403*
AFC Paired TTEST p-value								
#1-#2		*0.435*	*0.175*	*0.110*	*0.047*	*0.130*	*0.944*	*0.170*
#1-#3		*0.481*	*0.681*	*0.826*	*0.430*	*0.654*	*0.291*	*0.523*
#2-#3		*0.884*	*0.202*	*0.292*	*0.582*	*0.091*	*0.414*	*0.604*
NOR#1	*60*	*8.356*	*2.259*	*10.170*	*5.368*	*7.251*	*10.194*	*2.470*
NOR#2	*59*	*8.206*	*2.273*	*10.195*	*5.419*	*7.191*	*10.093*	*2.471*
NOR#3	*54*	*8.259*	*2.268*	*10.095*	*5.361*	*7.184*	*10.085*	*2.460*
NOR Paired TTEST p-value								
#1-#2		*0.141*	*0.683*	*0.855*	*0.612*	*0.409*	*0.407*	*0.870*
#1-#3		*0.445*	*0.879*	*0.428*	*0.899*	*0.491*	*0.413*	*0.795*
#2-#3		*0.364*	*0.884*	*0.861*	*0.646*	*0.949*	*0.429*	*0.461*

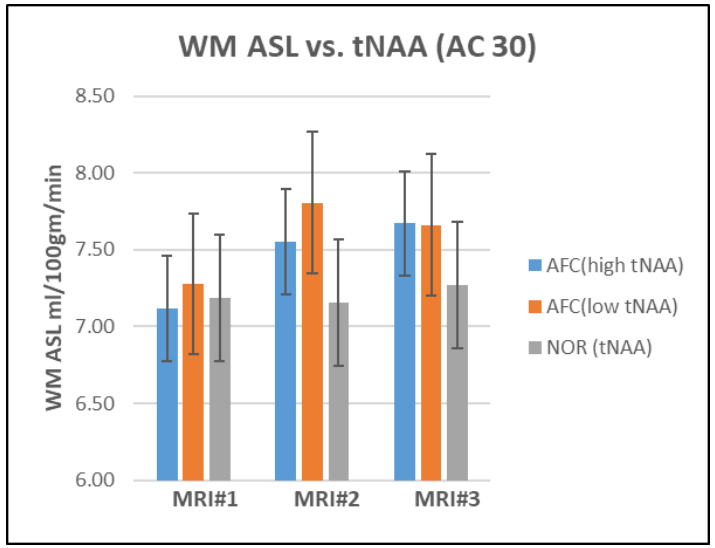
Phase 2 Single Exposure MR Spectroscopy

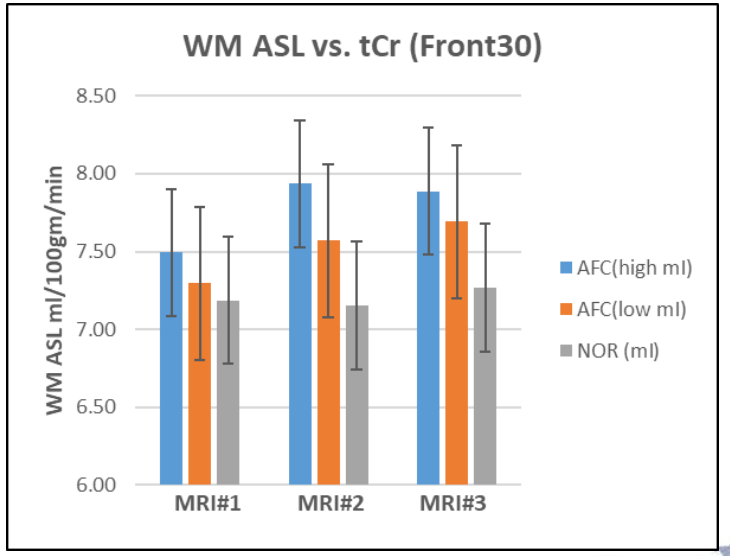
- **Cerebral blood flow increase correlates with cellular metabolite changes**

Metabolite	WM-ASL
TE30 Frontal Lobe WM	p-value
Mean Glu	0.061
Mean tCho	0.013
Mean tNAA	0.589
Mean mI	0.001
Mean tCr	0.001
Mean Glu+Gln	0.148
Mean GSH	0.122
TE30 Ant Cingulage GM	
Glu	0.05
GSH	0.011
tCho	0.611
tNAA	0.045
mI	0.641
tCr	0.37
Glu+Gln	0.018

Single Exposure MR Spectroscopy

- Cerebral blood flow is associated with cellular metabolite changes
- Higher tNAA baseline may predict smaller WM-ASL response
- Higher tCr baseline may predict greater WM-ASL response



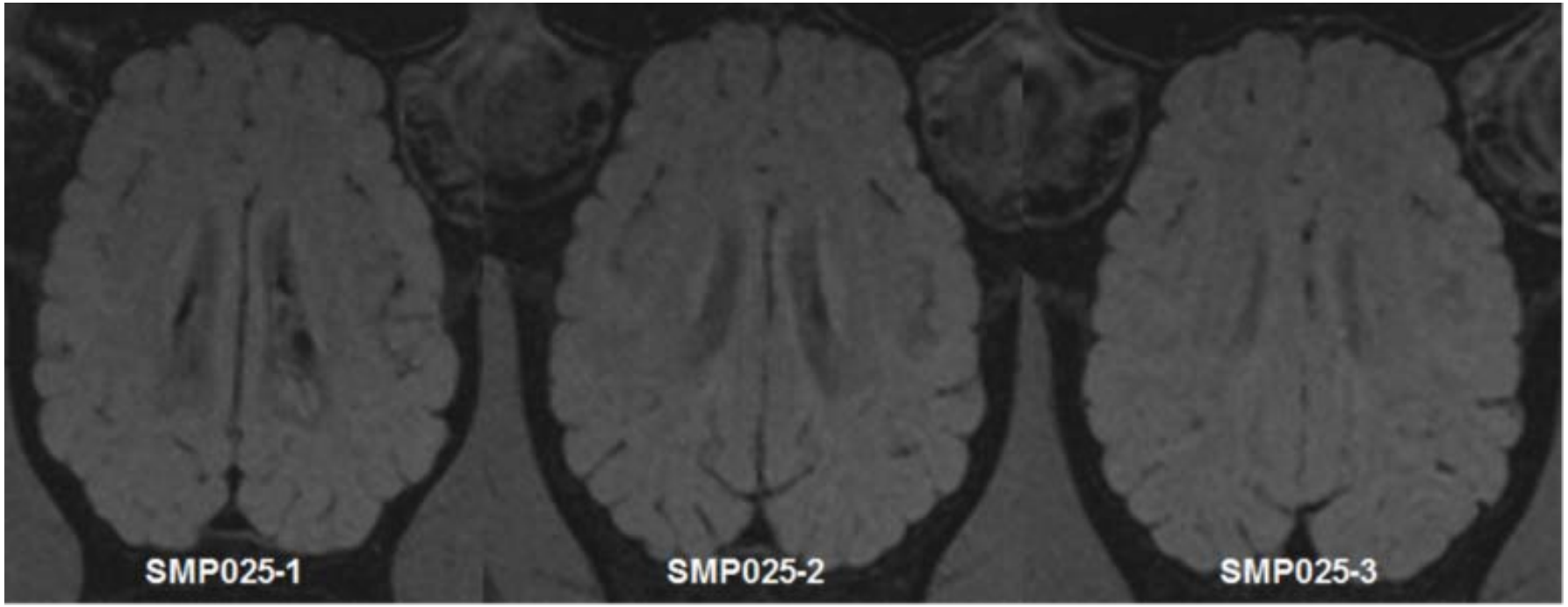


Summary

- **Single occupational exposure to a hypobaric/hypoxic environment is associated with an increase in CBF**
  - **CBF tightly regulated by cerebral metabolic demands**
  - **Hypoxic portion ~ 2-5 min (correlating with a PaO_2Sat ~ 65-75%)**
- **The degree of ASL change appears related to baseline neurocellular metabolites**
- **The greater the initial WMH burden the greater the ASL response**
  - **Is there an inherent predisposition for injury?**
- **Duration of CBF changes unknown at this time**

Swine Studies

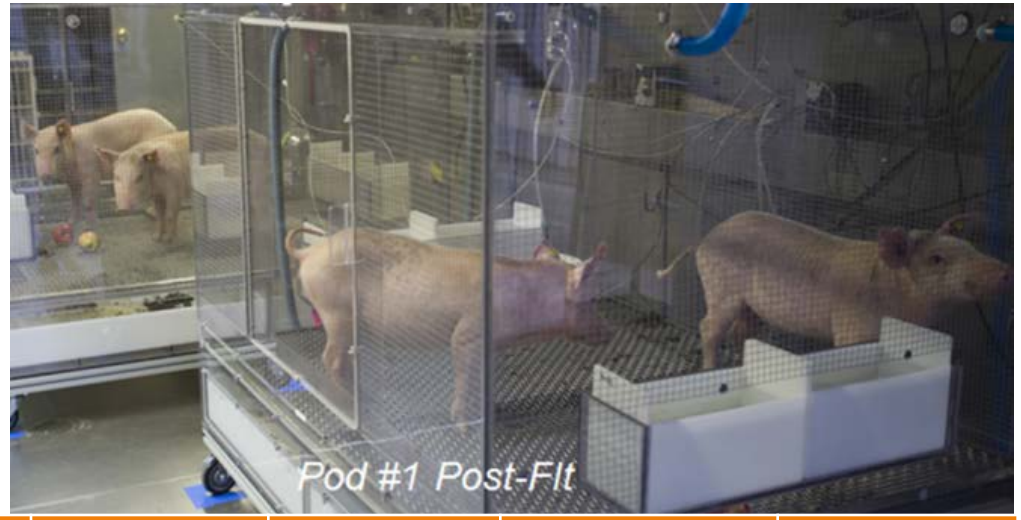
- **Develop an animal model for axonal cerebral injury following non-hypoxic hypobaric exposure utilizing advanced magnetic resonance imaging techniques**



Swine Model

Mimic U2 pilot experience

- **No sedation**
- **1 h 100% O_2 pre-breathe**
- **30 min ascent**
- **8 h at altitude**
- **30 min descent**



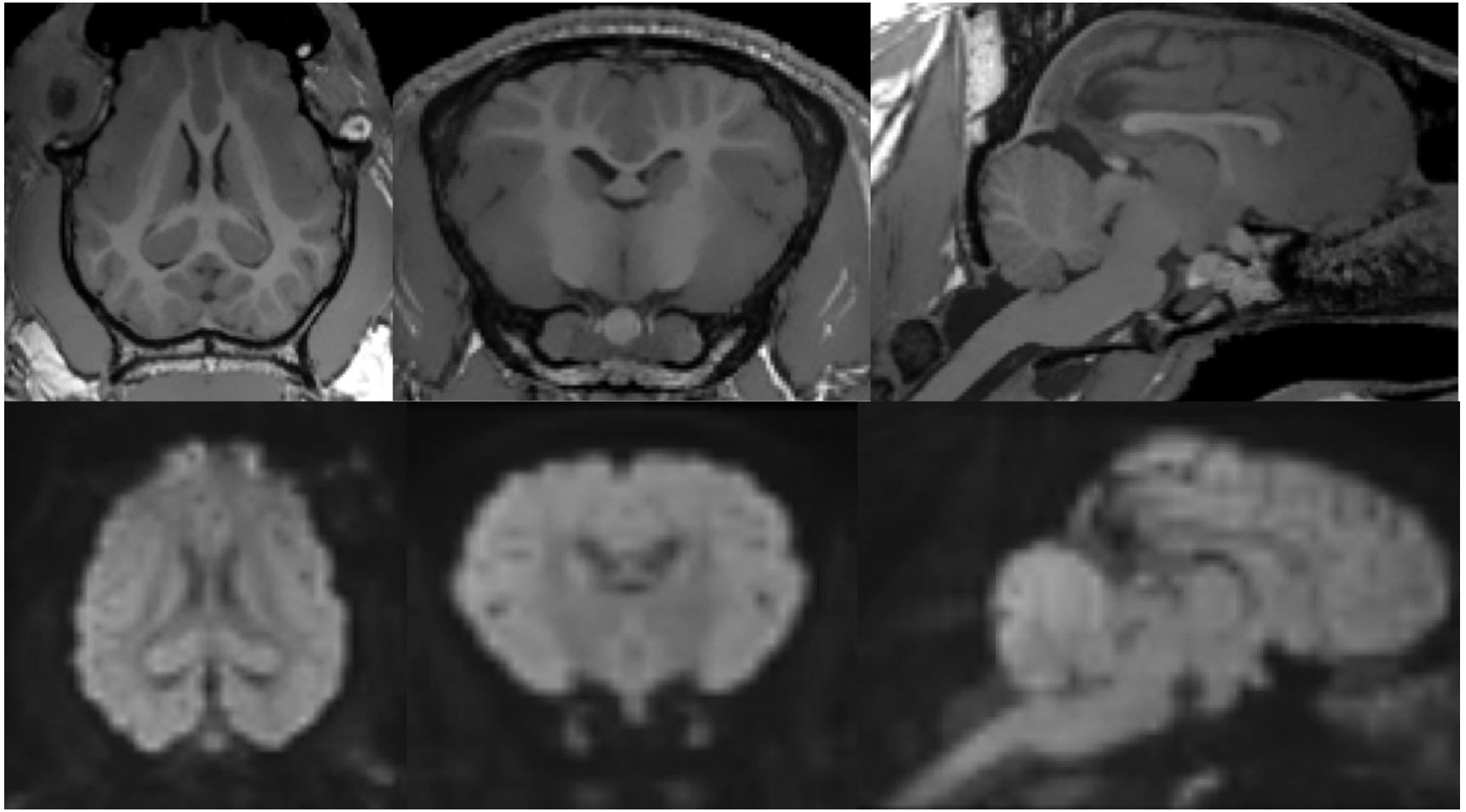
Swine Model Phase 2

MRIs obtained

- **Prior to exposure**
- **5-6h post exposure**
- **4 weeks post final exposure**
- **8 weeks post final exposure (POD 7-11)**

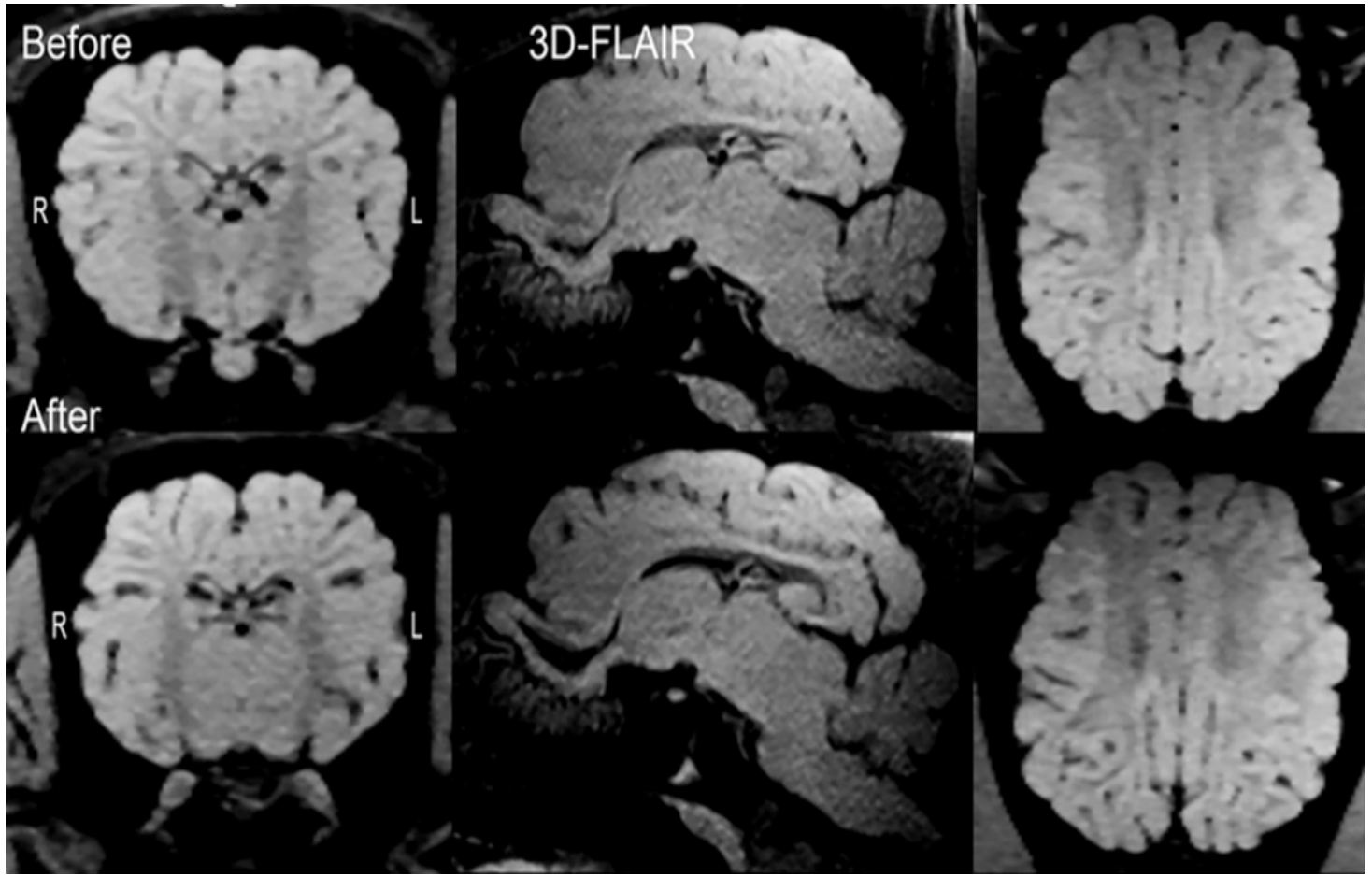
By the 4 week post-exposure MRI session, the POD 1&2 pigs were already growing too big for the head coils.
Younger animals(~8 weeks) were used for subsequent pods.

Sus Scrofa domestica Brain MRI



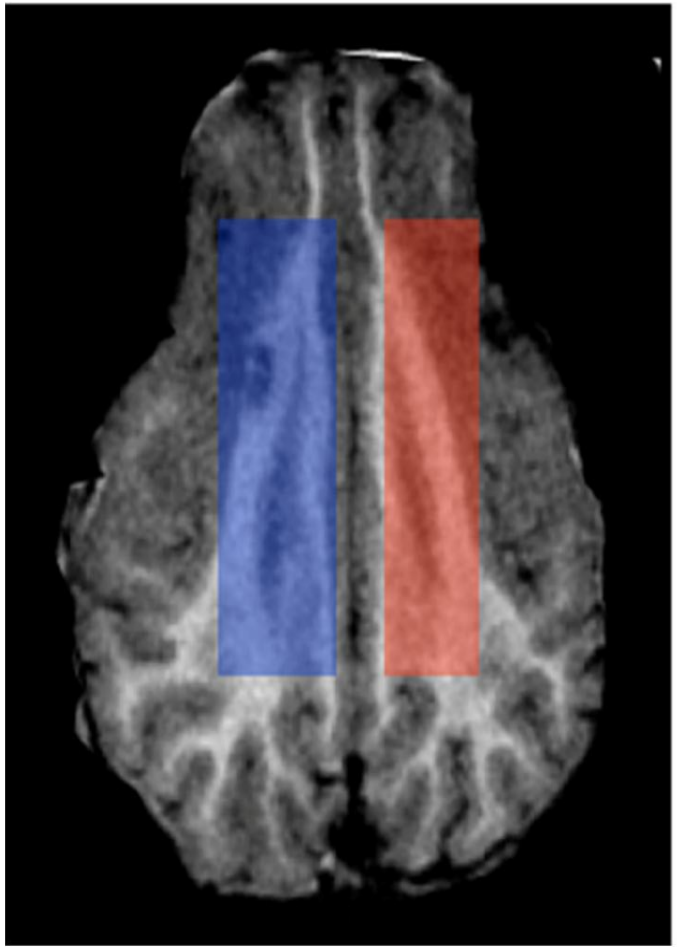
T1-weighted and DWI (avg across all b-values) images. Fully gyrified cortex with excellent gray-white matter differentiation. DWI demonstrates excellent resolution and lack of shape distortion artifact.

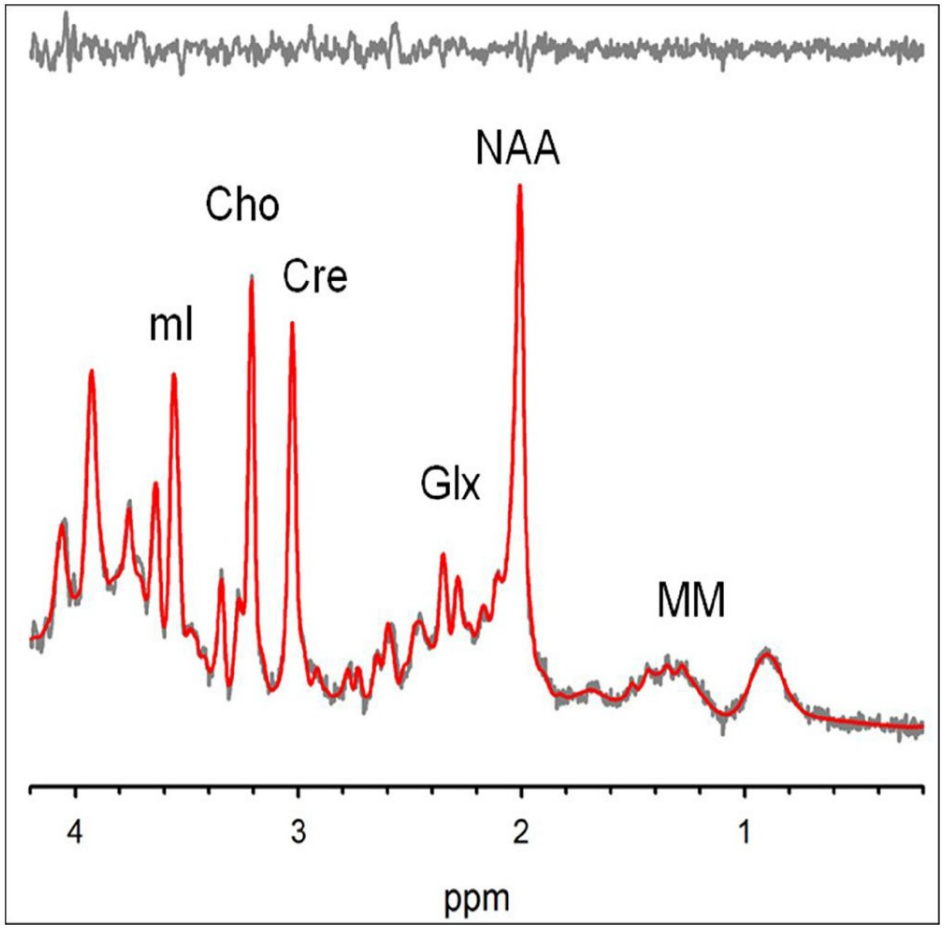
Swine FLAIR Imaging



Pre and post-exposure FLAIR imaging in 3-planes. No white matter hyperintensities.

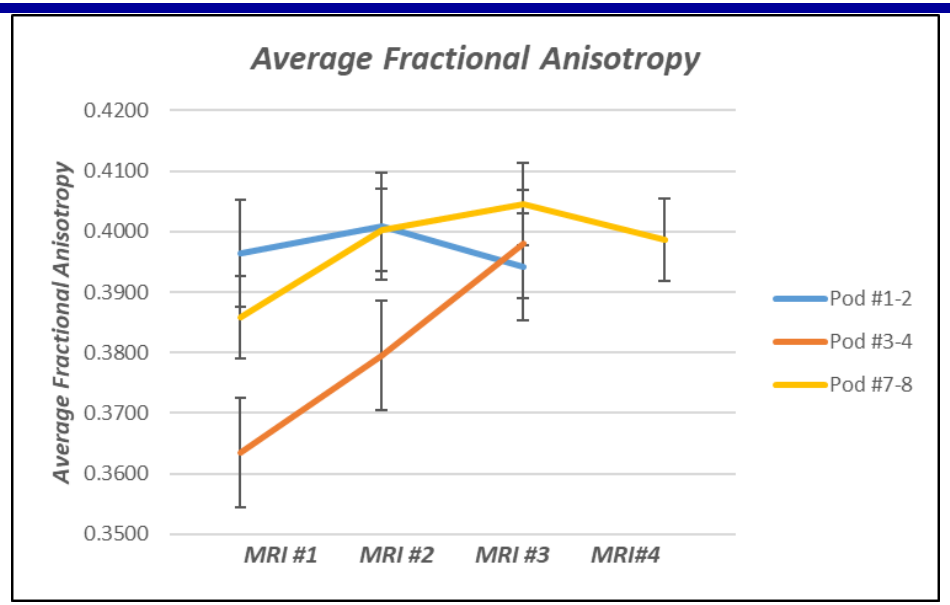
Brain Magnetic Resonance Spectroscopy Model

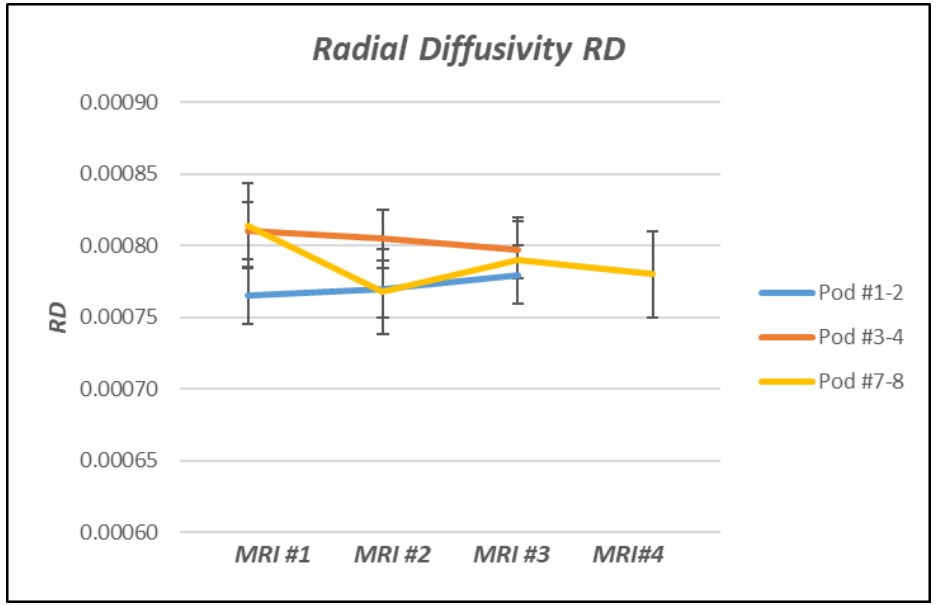




Representative place of 2 spectroscopic voxels in the pig's brain; representative spectrum of metabolite peaks identified as offset (parts per million from hydrogen frequency)

Phase 2 Results: DTI





- **Pod 1&2, six exposures over 18 days**
  - **Older animals**
- **Pod#7-8, twelve exposures over 24 days**
  - **Similar age to Pod 3&4 controls**
- **FA drops while RD increases**
  - **Suggests vasogenic (interstitial) edema**

Pathology Pending

- Need neuropathological corroboration of MRI findings
- Center for Neuroscience and Regenerative Medicine at USUHS (Dr. Dan Perl) and group
  - Analysis in progress

Summary - What We Think We Know

- ***Recurrent exposure to nonhypoxic extreme hypobaria incites:***
  - ***Focal punctate subcortical white matter hyperintensities (WMH) on MRI***
  - ***Diffuse decrement in axonal integrity on MRI***
  - ***Acquired neurocognitive decline as measured on CBT***
  - ***Clinical neurological decompression sickness is not a prerequisite for abnormalities***
- ***Single exposure to extreme hypobaria/hypoxia (routine occupational aircrew training) incites:***
  - ***Increase in white matter followed by gray matter cerebral blood flow that persists at 72 hours post-exposure on MRI***
  - ***Consistent with increased cerebral metabolic demand***
- ***Quantitative serial MRI highly reproducible***
- ***Swine model may be a viable model***

McGuire et al. Neurol 2013;81:729-735
McGuire et al. Ann Neurol 2014;76:719-726
McGuire et al. Neurol 2014;83:638-645
McGuire et al. Aerosp Med Hum Perform 2016;87:983-988
McGuire et al. Brain Behav 2017;e00759 (https://doi.org/10.1002/brb3.759)

Unknowns

- ***Pathophysiological mechanism(s)***
  - ***Relative contribution of hypobaria vs. other metabolic parameters (hyper-/hypoxemia, hyper-/hypocarbia, etc.)***
  - ***Temporal susceptibility window***
    - ***"Double-hit hypothesis"***
- ***Individual biosusceptibility***
- ***Possible mitigating/treatment strategies***
- ***Possible impact on acutely injured brain***
- ***Long-term impact on neurocognition***

QUESTIONS?