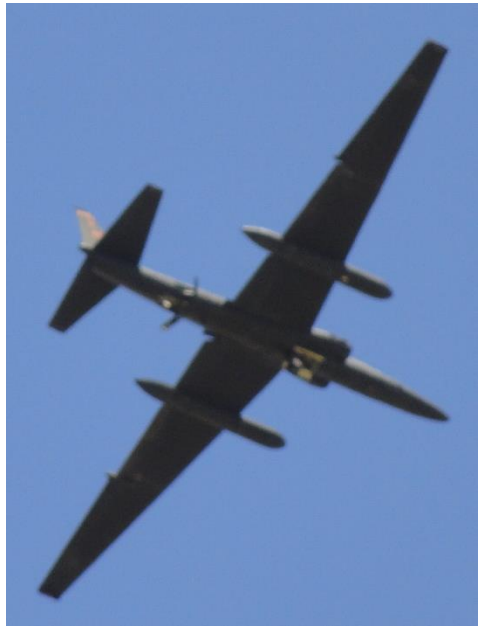
# *Increased CBF Related to High Altitude Exposure – MRI Assessment of Aircrew in the Hypobaric Environment*



***Col(ret) Paul M. Sherman, MD***

***14 Sep 2017***

***Integrity ★ Service ★ Excellence***

# Disclaimer

***The views expressed are those of the authors and do not necessarily reflect the official policy or position of the Air Force, the Department of Defense, or the U.S. Government***

Radiologist/Neuroradiologist
Prior Senior Flight Surgeon

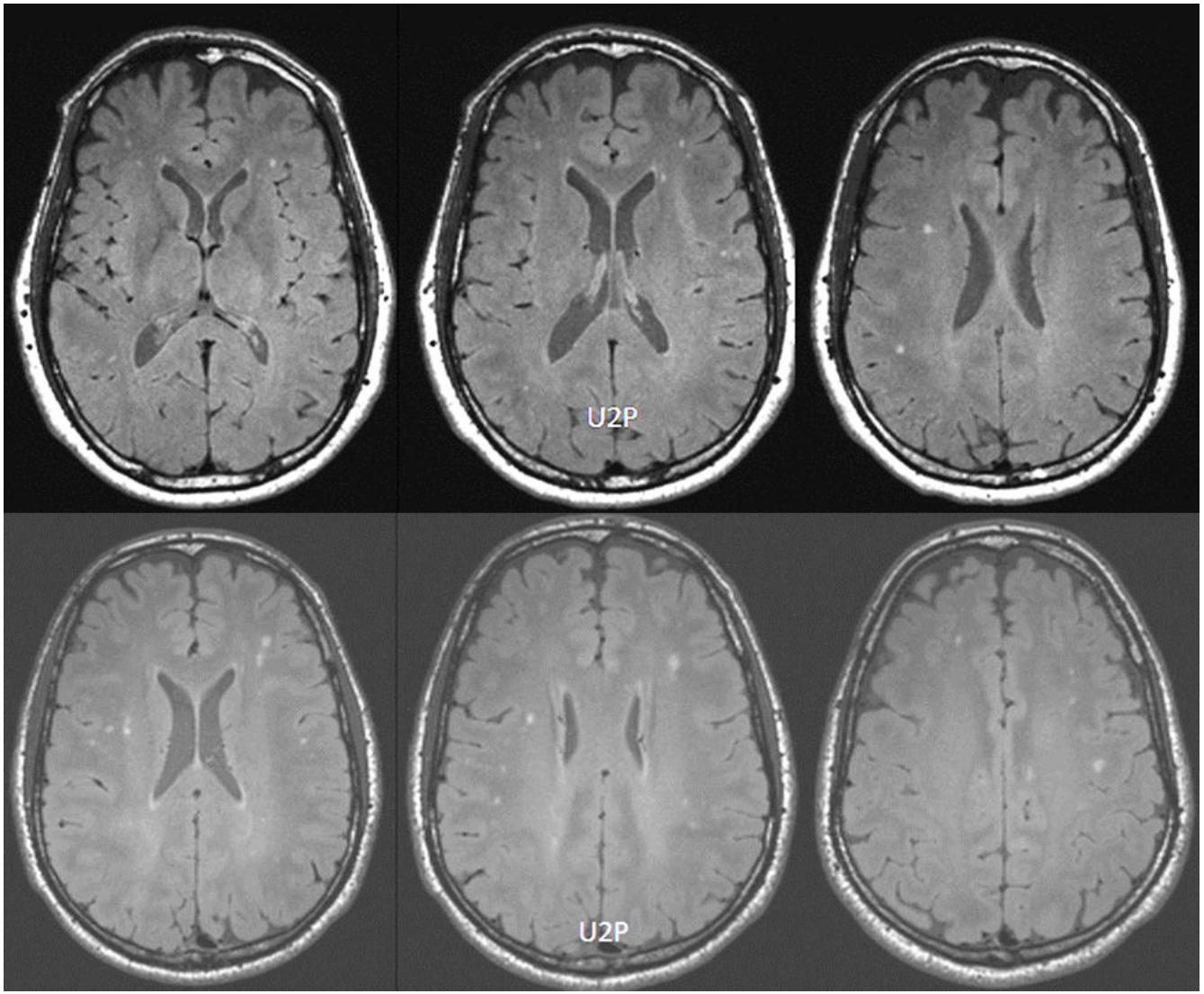
U.S. Air Force photo by A1C Zade C. Vadnais

# Neurologic Decompression Sickness (NDCS) Background

- *Increased incidence of NDCS associated with recent conflict*
- *1955-1998 no "reported" type II*
  - *1996 anonymous survey 75.5% during career noted DCS*
- *2002-2009 16 confirmed NDCS events (5 near-fatal)*
- *1994-2005*
  - *DCS risk 0.076%/flight*
  - *0-5 cases/yr*
  - *10 type II/12 yr*
- *2006-2010*
  - *300% increased rate of NDCS*
  - *DCS risk 0.23%/flight*
  - *6-10 cases/yr*
  - *22 type II/5 yr*
- *Research prompted by 5 near fatalities (2009-2010)*
  - *U2P imaging began 5/2011*

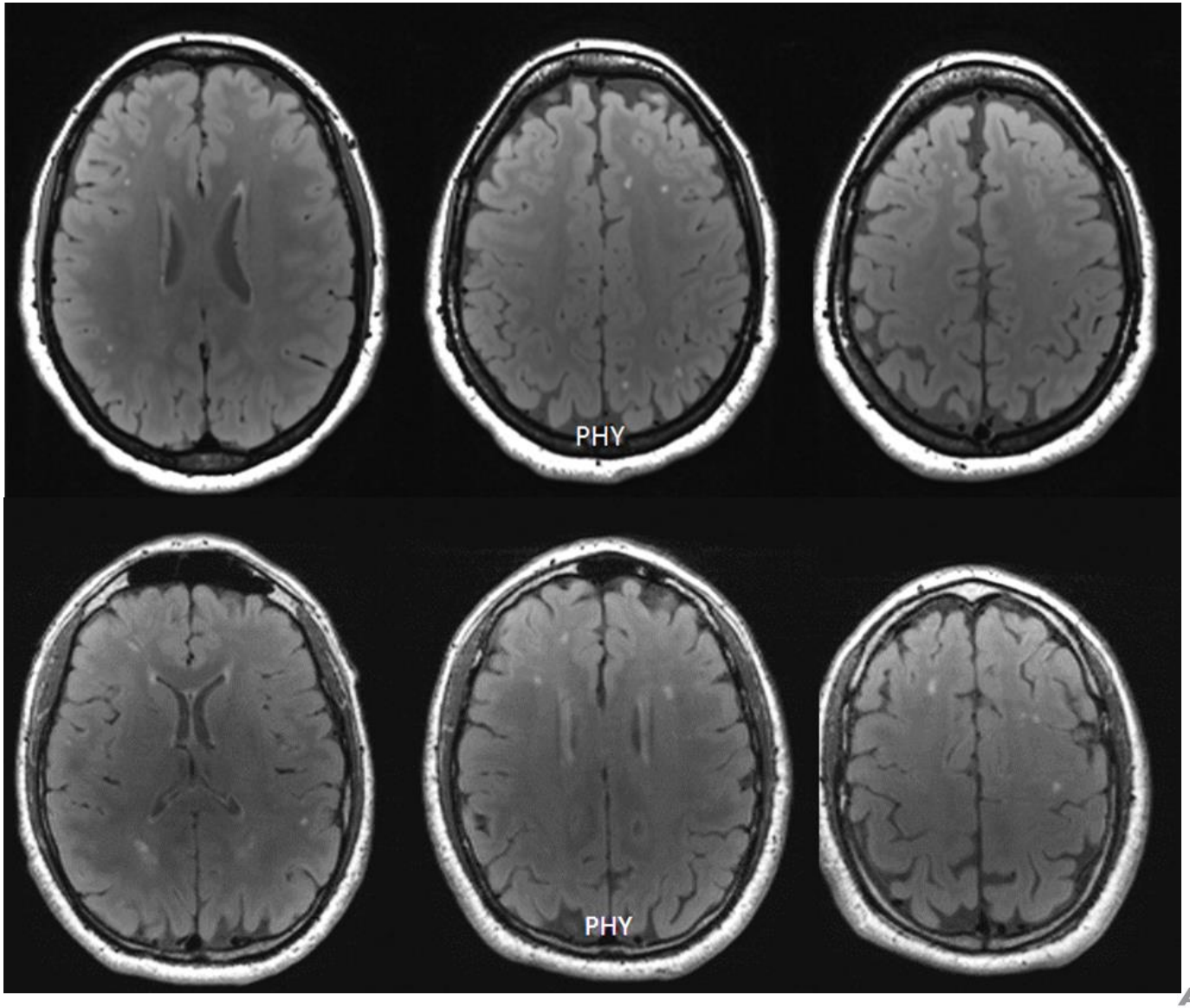
*Bendrick et al. Aviat Space Environ Med 1996; 67:199-206*
*Jersey et al. Aviat Space Environ Med 2010;81:64-8*
*Jersey et al. Aviat Space Environ Med 2011;82:673-828*
*Hundemer et al. Aviat Space Environ Med 2012;83:968-74*

# MRI in U2P (U-2 Pilots) With & Without Clinical NDCS




Phase 1 #s:
U2: 106
AOP/ PHY: 83
Controls/ Docs: 162

# MRI in AOP (Chamber) With & Without Clinical NDCS

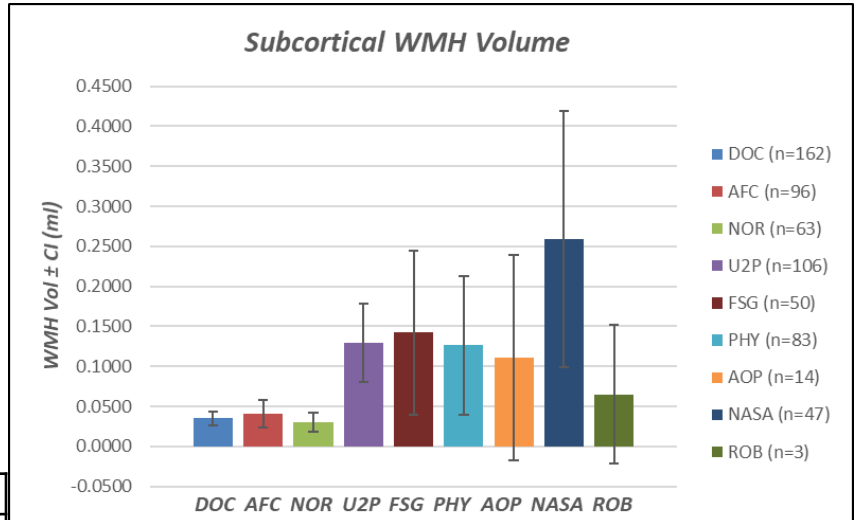


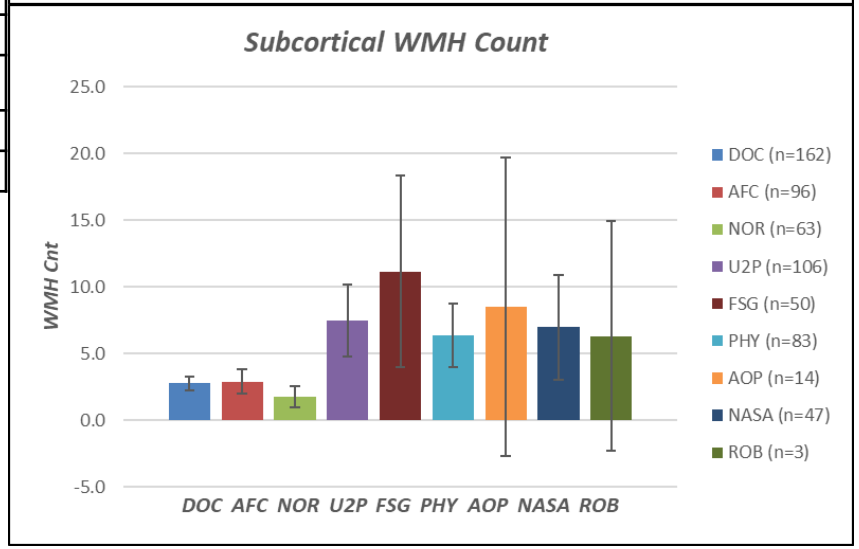
# Phase 1 Repetitive Exposure White Matter Hyperintensities

- *Significantly increased subcortical white matter hyperintensity (WMH) volume/count in U2P & AOP/PHY*
- *AFC ≈ DOC ≈ NOR*
- *U2P ≈ AOP/PHY ≈ FSG*
  - *Individual variability**
- *Volume probably more 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*

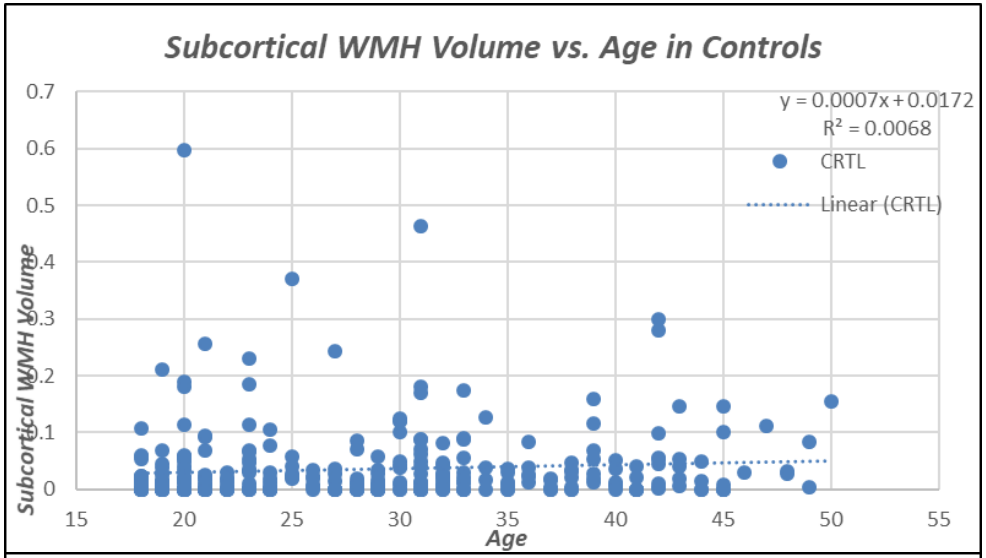


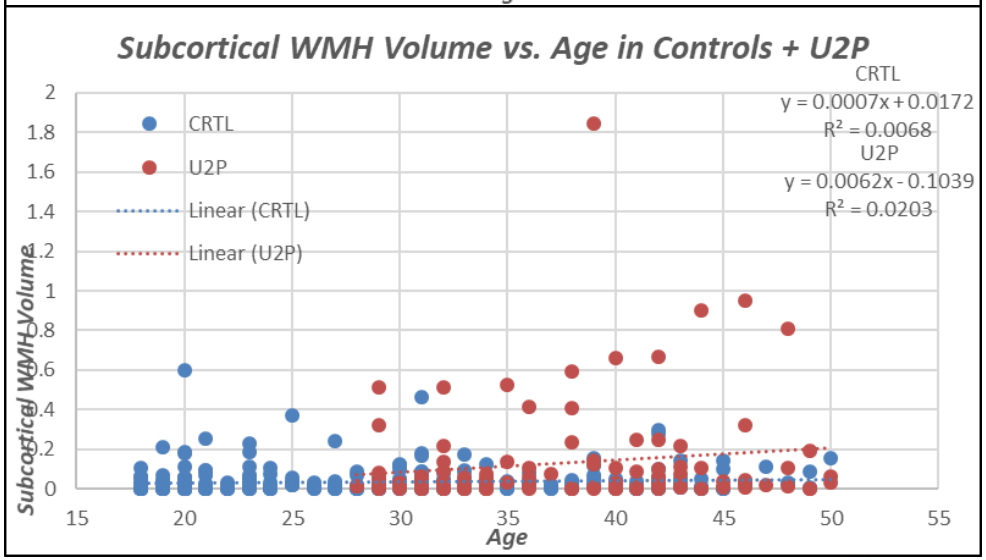




*McGuire et al. Neurology 2013;81:729-735*
*McGuire et al. Ann Neurol 2014;76:719-726*

# Subcortical WMH Volume vs. Age

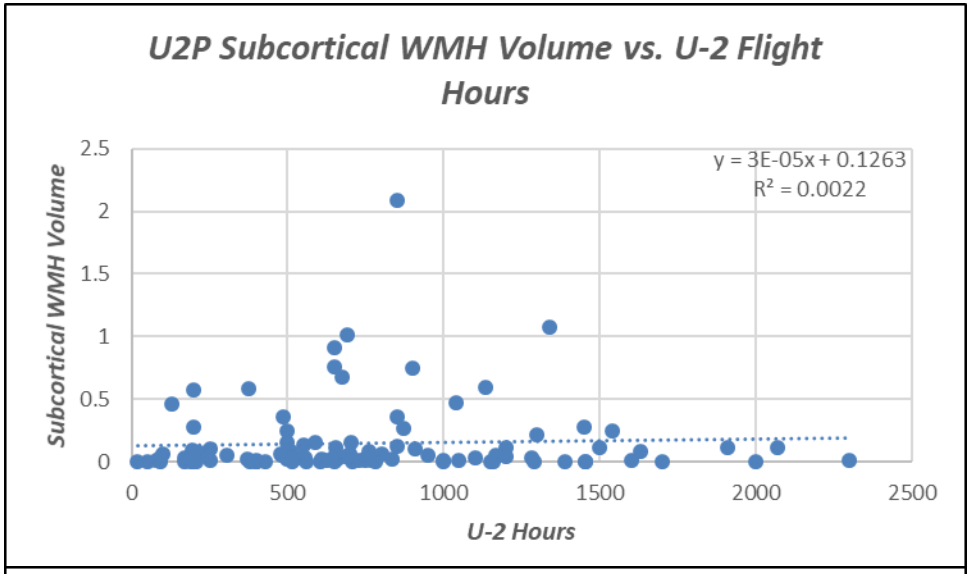
- ***Subcortical WMH volume known to increase with advanced age (> ~ 60yr)***
  - ***Over age range 18-50 essentially no increase with age***
- ***Increase slightly more rapid in U2P but not sufficient to account for increase in volume***
  - ***Suggests not a simple factor of exposure***

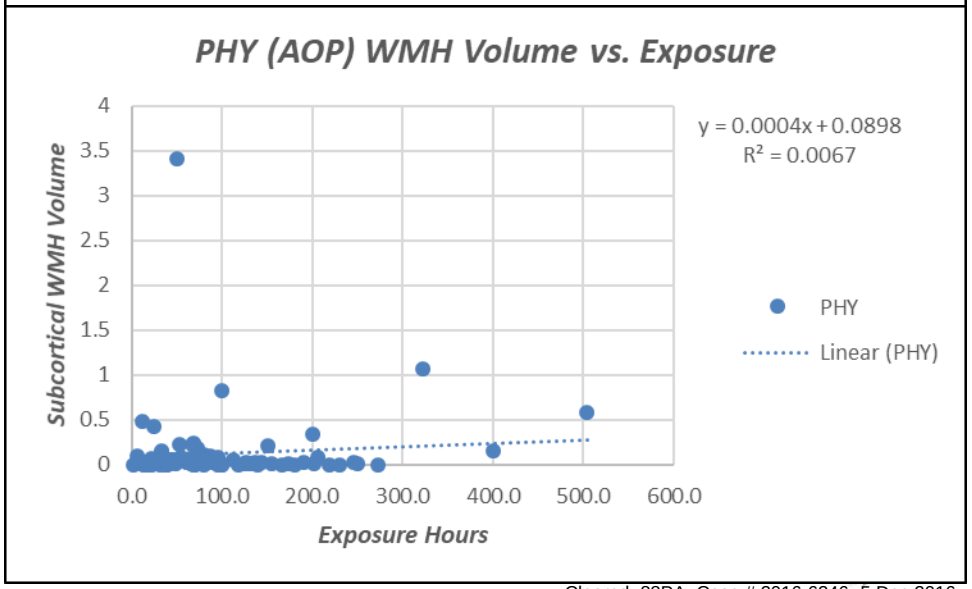


# WMH Volume vs. Exposure

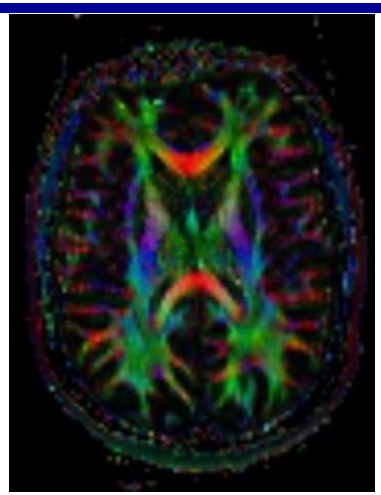
- ***Little correlation between total hours of exposure and subcortical WMH burden****
- ***Suggests multi-factor relationship to WMH burden***

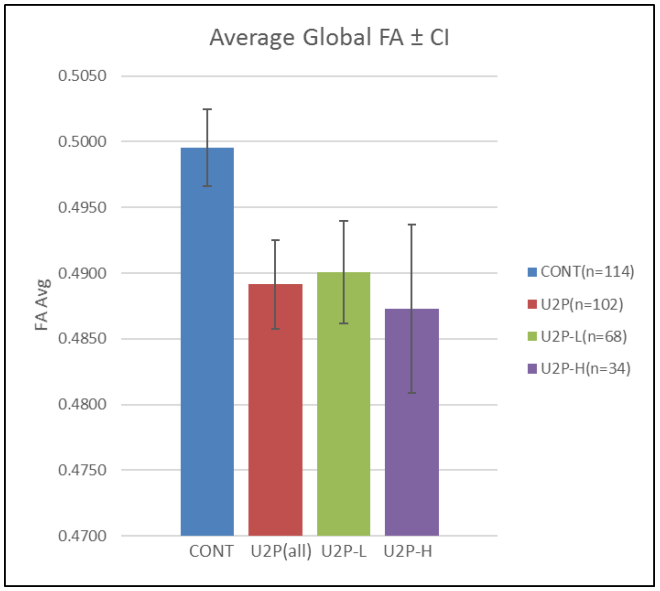


# Phase 1 Repetitive Exposure Fractional Anisotropy

- ***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 MRI scanners***
  - ***46 subjs dual imaged (r=0.85; COV=4%)***






***McGuire et al. Aerosp Med Hum Perform 2016; 87:983-988***

# Phase 1 Repetitive Exposure 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 measures indicate pilots similar at UPT*
- *Decrease suggests diffuse white matter process*

| | 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 |

*McGuire et al. Neurology 2014;83:638-645*

# Phase 1 Repetitive Exposure Neurocognitive Differences

- ***MicroCog absolute values generally decreased with greater WMH burden within the U2P population (nonsignificant trends)***

| Level | MicroCog (current) | Lower WMH Burden | | Upper WMH Burden | | t-test (2-tailed) Significance | | Sidak (2-tailed) Significance | |
|---|---|---|---|---|---|---|---|---|---|
| | | Count (n=36) | Volume (n=33) | Count (n=65) | Volume (n=68) | Count | Volume | Count | Volume |
| 1 | Attention/mental control | 105.8 | 105.9 | 105.0 | 105.0 | p=0.702 | p=0.697 | p=0.998 | p=0.997 |
| 1 | Reasoning/calculation | 104.8 | 102.8 | 97.5 | 98.8 | p=0.006 | p=0.150 | p=0.032 | p=0.557 |
| 1 | Memory | 109.8 | 108.5 | 103.3 | 104.2 | p=0.010 | p=0.103 | p=0.093 | p=0.420 |
| 1 | Spatial processing | 110.4 | 110.3 | 108.3 | 108.4 | p=0.271 | p=0.344 | p=0.795 | p=0.878 |
| 1 | Reaction time | 108.5 | 109.6 | 107.0 | 106.5 | p=0.255 | p=0.030 | p=0.771 | p=0.143 |
| 2 | Information processing speed | 106.8 | 105.0 | 102.7 | 103.7 | p=0.109 | p=0.609 | p=0.206 | p=0.847 |
| 2 | Information processing accuracy | 105.2 | 105.3 | 100.8 | 100.9 | p=0.035 | p=0.037 | p=0.069 | p=0.072 |
| 3 | General cognitive functioning | 107.4 | 106.4 | 102.2 | 103.9 | p=0.014 | p=0.105 | p=0.028 | p=0.200 |
| 3 | General cognitive proficiency | 109.0 | 108.0 | 104.2 | 104.9 | p=0.019 | p=0.154 | p=0.037 | p=0.285 |

# Phase 1 Repetitive Exposure Summary

- *Acquired increase in discrete subcortical WMH lesions*
  - *Presumably reflects permanent glial scarring in WM*
- *Acquired decrease in FA in normal appearing WM (U2P & ? PHY)*
  - *Reflects axonal integrity loss – segregates with WMH burden*
- *Acquired decrease in neurocognitive functioning*
  - *Decrease corresponds to degree of WMH burden*
  - *Includes speed of processing and executive functioning*
  - *Corresponds to diffuse axonal injury pattern*
- *Complex pathophysiological process*
  - *Intensity of exposure (frequency, duration, physical activity, etc.)*
  - *Individual biovariability and susceptibility*
- *Relative contribution from hypobaria and/or pre-breathe hyperoxia unknown*

# Single Exposure Study

- ***Hypothesis – single occupational exposure to hypobaria and/or hypoxia will be associated with transient MRI and serological changes***
  - ***Earliest MRI changes will be in MRS, DTI/Q-space, and arterial blood flow***
  - ***Transient microparticle increase will parallel changes noted in divers***
  - ***Inflammatory serological markers will be up-regulated***

- ***Permanent MRI change is associated with recurrent and frequent nonhypoxic hypobaric exposure***

# Single Exposure Study

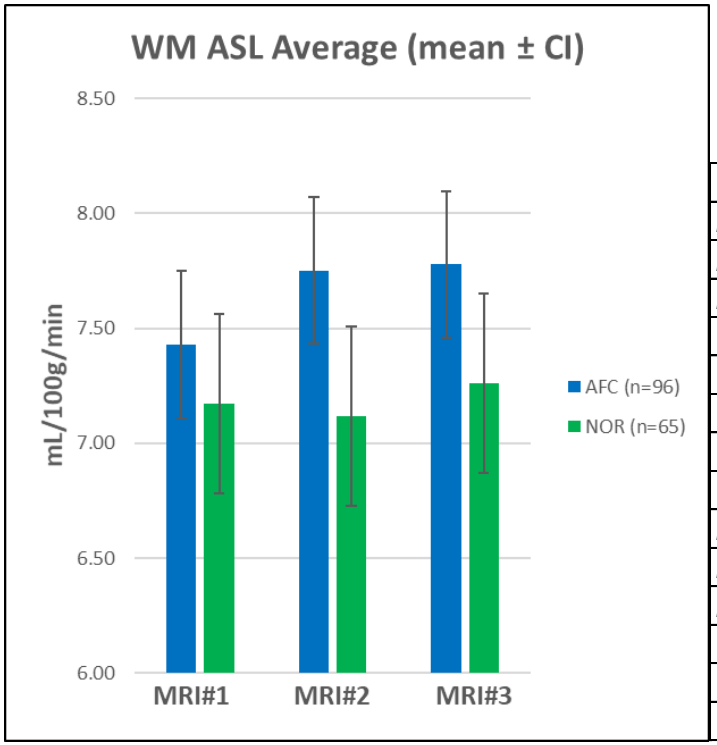
- *Four limbs – all meet FCII/FCIII neurological standards*
  - *Hypobaric-hypoxic (AFC traditional aircrew chamber training)*
  - *Hypobaric (AOP inside safety monitors)*
  - *Hypoxic (ROBD – reduced $O_2$ breathing device)*
  - *Control (NOR)*
- *Protocol:*
  - *MRI 24 h before; 24 h after; 72 h after*
  - *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*
- *Intra-subject and cross-group comparisons*

# Single Exposure Study

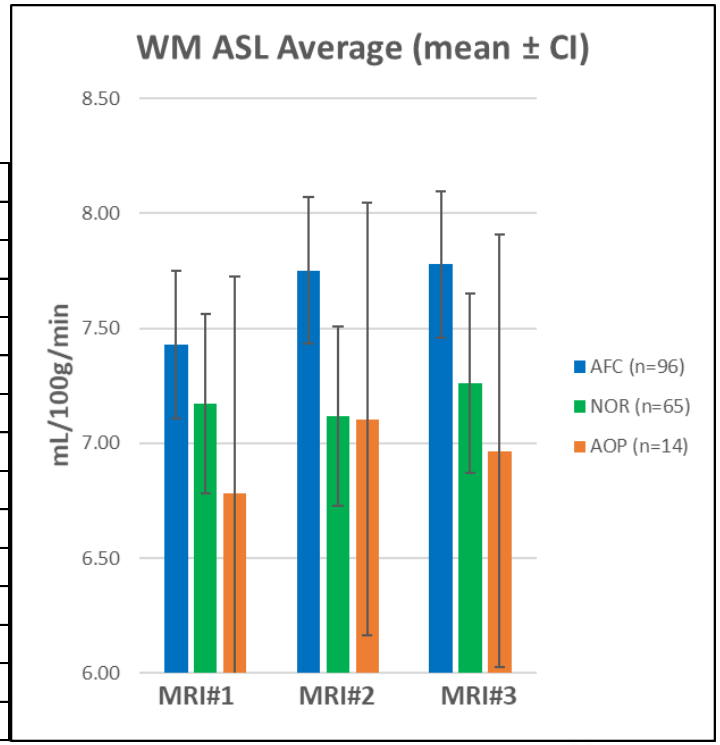
- *Study began Sep 2014, just closed to recruitment in Aug 2017*
- *Original goal: 50 subjects in each of the 4 limbs*
  - *Focus changed to AFC and NORM after realization of recruitment limitations*
- *Total imaged: 186*
- *AFC group: 96*
  - *65 males, 31 females*
- *NORM group: 73*
  - *66 males, 7 females*
- *AOP: 14*
  - *7 males, 7 females*
- *ROBD: 3*
  - *3 males*
- *Phase 1 and 2 studies: 536 subjects imaged*

# Phase 2 Single Exposure Arterial Blood Flow (ASL)

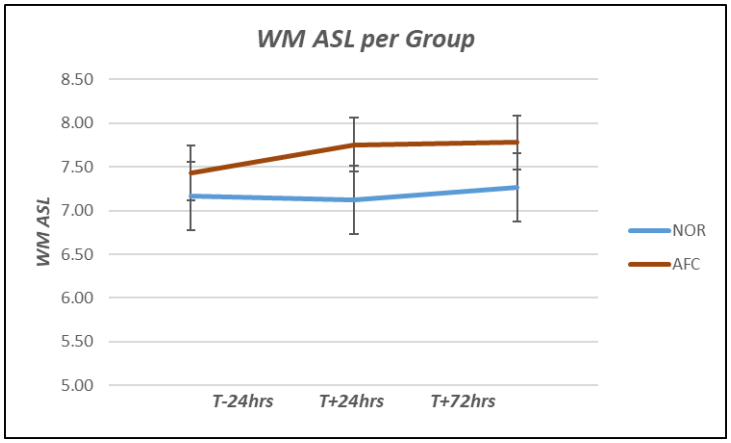
- *Increase in WM CBF at 24/72hr (WM ↑ possibly precedes GM ↑)*
  - *Significant group (AFC vs. NOR) difference*
    - *WM p<0.001 (Utilized generalized additive model adjusted for age and gender)*
- *Potentially similar change in AOP group ("n" too small for assessment)*

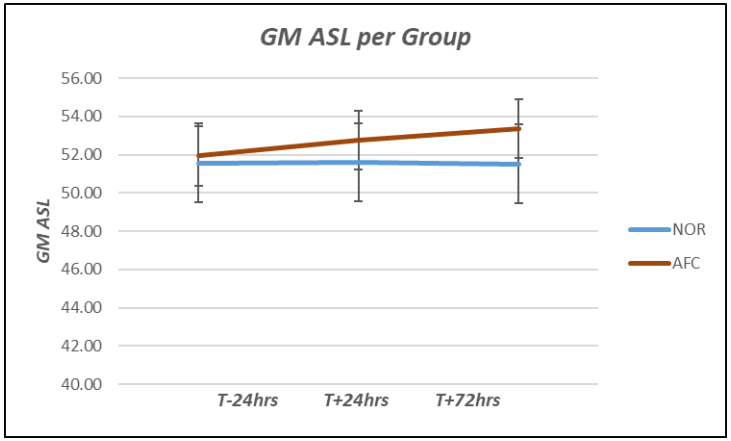



| AFC | Subj # | WM |
|---|---|---|
| MRI#1 avg | 96 | 7.43 |
| MRI#2 avg | 94 | 7.75 |
| MRI#3 avg | 96 | 7.78 |
| TTEST #1-#2 | | 0.004 |
| TTEST #1-#3 | | 0.009 |
| TTEST #2-#3 | | 0.967 |
| | | |
| NOR | | |
| MRI#1 avg | 65 | 7.17 |
| MRI#2 avg | 65 | 7.12 |
| MRI#3 avg | 60 | 7.26 |
| TTEST #1-#2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



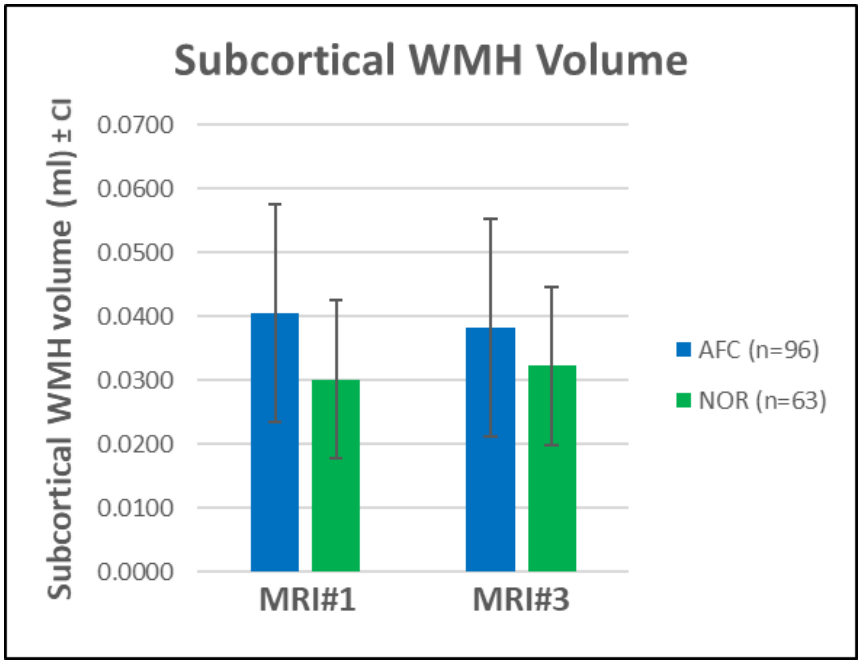
# ASL

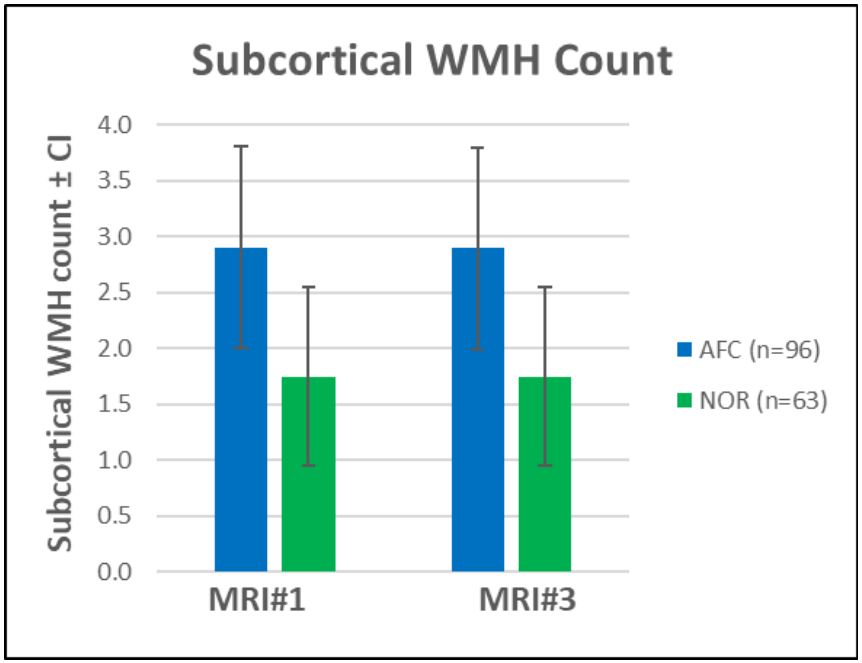

WM ASL per Group
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
WM ASL
T-24hrs
T+24hrs
T+72hrs
NOR
AFC


GM ASL per Group
56.00
54.00
52.00
50.00
48.00
46.00
44.00
42.00
40.00
GM ASL
T-24hrs
T+24hrs
T+72hrs
NOR
AFC

# Phase 2 Single Exposure WMH Burden

- ***No significant difference for subcortical WMH FLAIR group difference***
- ***A single exposure does not increase WMH burden***
  - ***Repetitive exposure in U-2 pilots demonstrates apparent acquired increased subcortical WMH burden***



# Phase 2

- ***Metabolic changes demonstrated with MRS***
  - ***Will be discussed by Dr. McGuire***
- ***Challenges with serology***

- ***No additional airframe /pilots imaged to date***
  - ***USN study to image F/A-18 pilots will begin later this year***

# Summary

- ***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***
- ***Single exposure to extreme hypobaria (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***

- ***Additional MRI findings will be discussed by Dr. McGuire***

# Aerospace Relevance

- ***Recurrent unexplained physiological events effecting all 4th and 5th generation fighter aircraft (F-16, F/A-18, F-22, F-35)***
- ***Anecdotal reports from CCAT personnel of unexplained neurological worsening in acute TBI warriors associated with A/E flights***
- ***Unexplained increased white matter hyperintensity (WMH) burden in astronauts***
- ***Long-term neurocognitive functioning impact/disability in exposed individuals***
- ***Poorly defined risk factors***

- ***Potentially impacting any warrior subjected to decompressive stress***
  - ***High altitude drops (SFO, aircrew)***
  - ***High altitude ops in unpressurized platforms (rotary, etc.)***
  - ***SCUBA divers***