Accelerated Cerebral White Matter Aging in a Cohort of U-2 Pilots and Air Force Physiologists/Chamber Technicians

USAF photo by SSgt Ramon A. Adelan

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Col (r) Paul Sherman, MD

Integrity ★ Service ★ Excellence

Sept 20, 2018

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.***

Background

- ***Research driven by an unexplained 5-fold increased incidence of neurological decompression sickness (NDCS) in U-2 pilots associated with Mideast conflict***
  - ***U-2 pilot (U2P) imaging began 5/2011***
    - ***Increased # of white matter hyperintensities (WMH) found in U-2 pilots***
  - ***Human and animal research ongoing***
  - ***Operational changes already implemented***
- ***Funded by AF/SG thru USAFSAM/711HPW***
  - ***Critical support provided by 59MDW***
  - ***JPC5 funding for pig studies***

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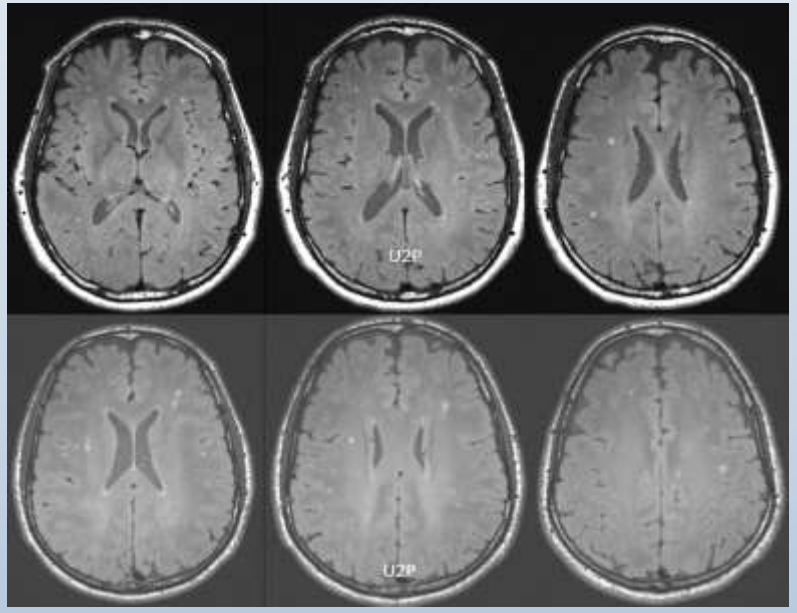
Bendrick et al. Aviat Space Environ Med. 1996; 67:199-206.
Jersey et al. Aviat Space Environ Med. 2010; 81:64-68.
Jersey et al. Aviat Space Environ Med. 2011; 82:673-828.
Hundemer et al. Aviat Space Environ Med. 2012; 83(10):968-974.

Background: WMH Lesions in Initial 50 U2P Cohort

- *50 U2Ps assessed:*
  - *12 pilots with NDCS*
  - *38 w/o h/o of NDCS*
- *Increased volume of WMH in pilots with NDCS compared to those without*
- *No change in number of WMH counts*
- *Increased number of WMH in insular subcortical regions in those pilots with NDCS*



McGuire SA, Sherman PM, Brown AC, et al. Aviat Space Environ Med. 2012; 83(12):1117-1122.

Background: Recurrent Exposure Study

- ***Hypothesis – recurrent occupational exposure to nonhypoxic hypobaria will be associated with quantitative magnetic resonance imaging (MRI) changes***

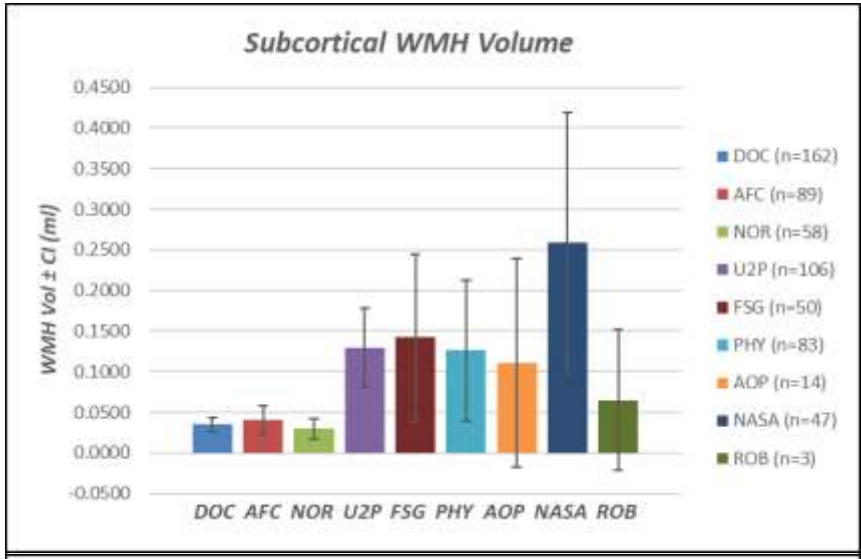
- ***Four limbs – all meet Flying Class II/III neurological standards currently on flying status (except for DOC) without any limitations***
  - ***Hypobaric (U2P pilots physically at altitude)***
  - ***Hypobaric (PHY/AOP inside safety monitors physically at sea level)***
  - ***Hypoxic (FSG – with at least one operational tour)***
  - ***Control (DOC – doctorate degree without operational tour)***
- ***Protocol:***
  - ***Single MRI***
  - ***MicroCog testing of U2P with comparison to AFP***
- ***Cross-group comparisons***
  - ***CAL – dual imaged for cross calibration of MRI machines***

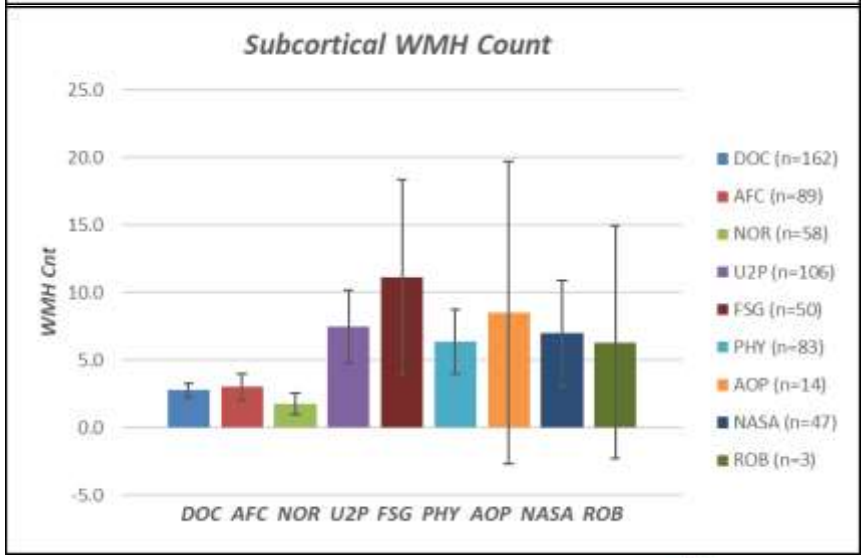
Phase 1 Repetitive Exposure WMH

- ***Significantly increased subcortical WMH volume/count in U2P & AOP/PHY***
- ***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.

Accelerated aging hypothesis

Hypothesis: We hypothesized that occupational exposure to hypobaria may lead to accelerated aging of cerebral white matter.

Null hypothesis:
Individuals occupationally exposed to hypobaria show the same aging trends as normal controls

We tested this by comparing the aging trends in U-2 pilots and Air Force physiologists/chamber technicians and age-and-health matched controls.

Test of the hypothesis:

1. ***Assemble representative datasets with focus on white matter***
2. ***Use general linear model to test for:***
   a. ***Group differences***
   b. ***Age x Group interaction term***
      - ***Significance of the Group indicates group-wise differences in the underlying marker***
      - ***Significance of the Age x Group interaction term indicates difference in the aging trends***

Methods

- ***We collected MRI data in the following:***
  - ***106 U-2 pilots:***
  - ***74 Air Force physiologists/chamber technicians (PHYS):***
  - ***125 Controls (CON) ages 28-58 years***

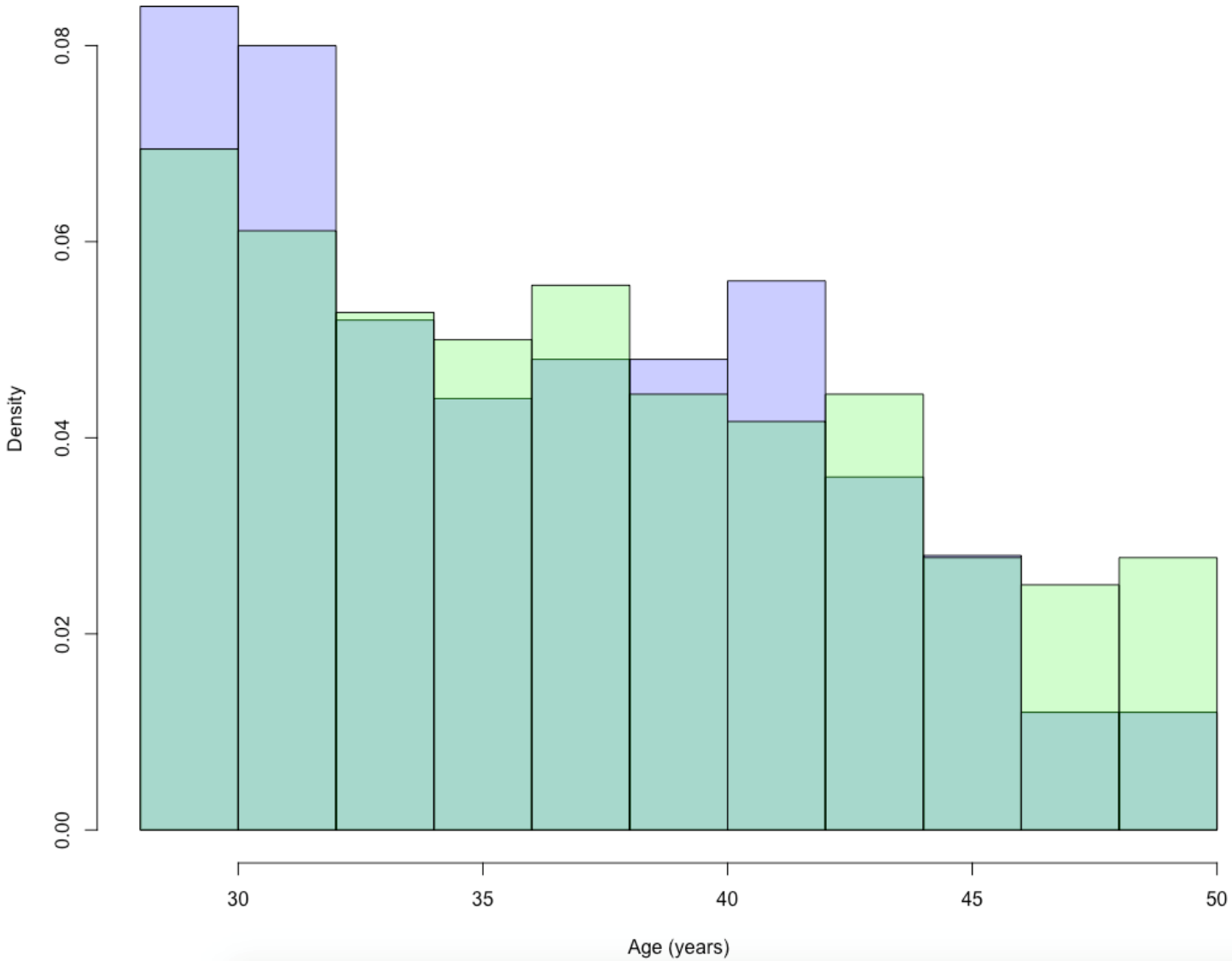
  - ***The MRI protocol consisted of a 3D T2-weighted FLuid-Attenuated Inversion Recovery (FLAIR) and diffusion tensor imaging sequences to assess the integrity of cerebral WM.***

Demographic Comparison

Control Age matched sample, 28-50 years old

Group	Average Age	Number of Subjects	Age Range
DOC	35.58 ± 5.76	125	28-50
PHY	37.70 ± 6.50	74	28-50
U2	37.68 ± 5.99	106	28-50
U2 + PHY	37.69 ± 6.19	180	28-50

Age Histogram



Purple = DOC
Green = U2+PHY

T Test Group Comparisons

Age matched Controls, 28-50 years old

Group	Age	Exposure Hours	Total FLAIR Volume	Subcortical Volume	Average FA
U2 vs. DOC	0.156	-	**2.31E-29**	**1.08E-05**	**2.60E-03**
U2 vs. PHY	0.980	**1.76E-21**	**1.94E-10**	0.954	0.080
PHY vs. DOC	0.205	-	**2.95E-03**	**0.018**	0.43
U2+PHY vs. DOC	0.113	-	**1.55E-15**	**1.50E-03**	**0.019**

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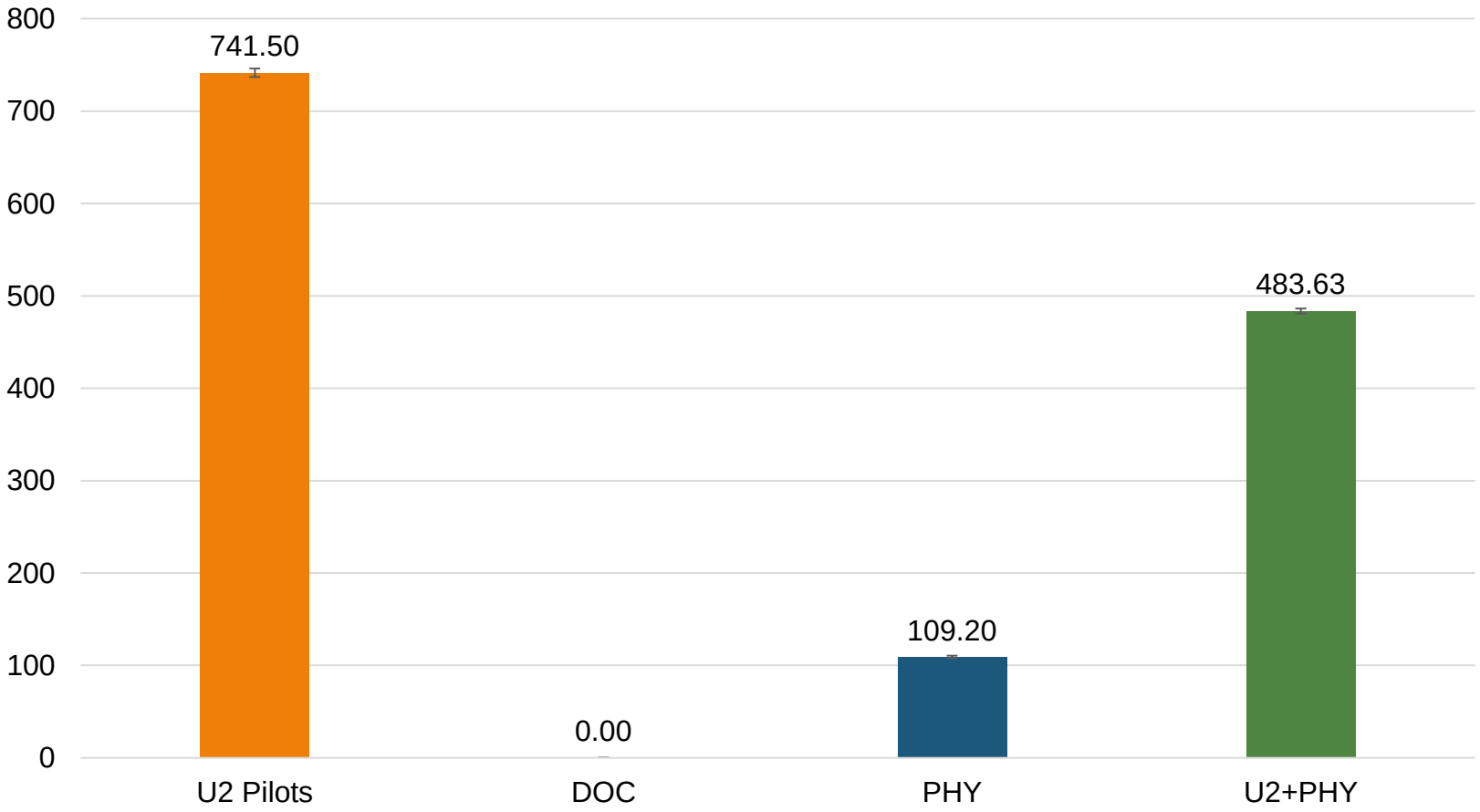
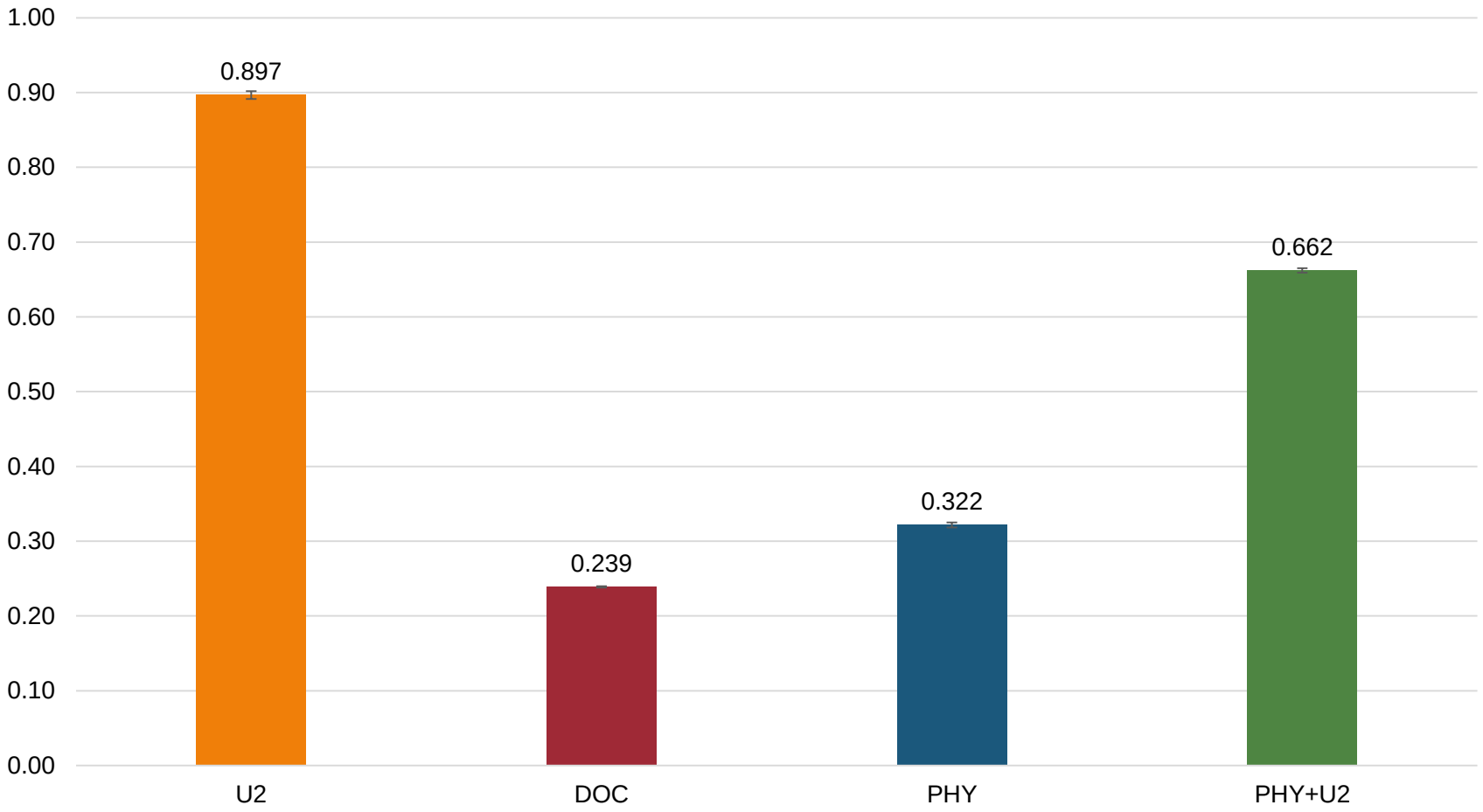
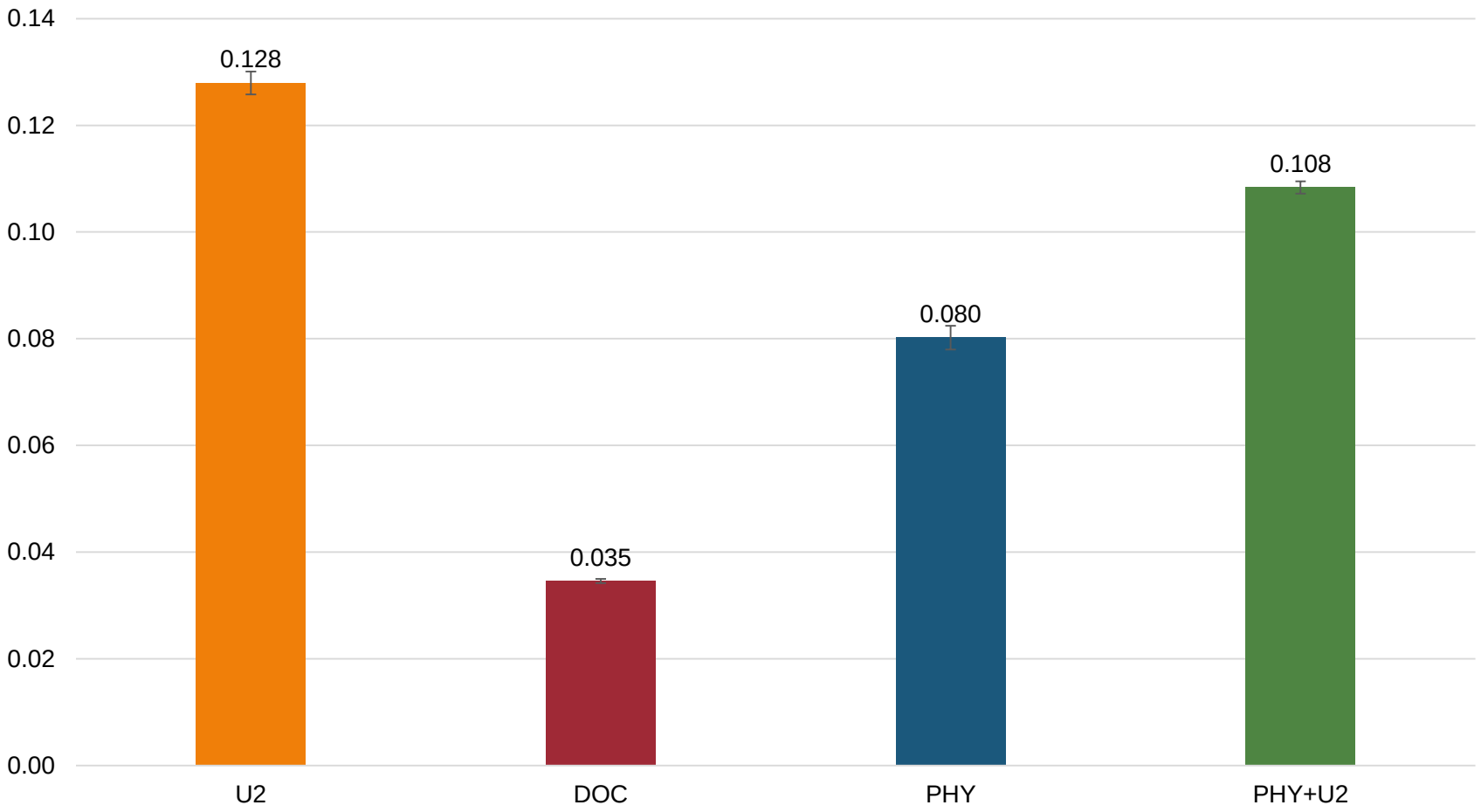


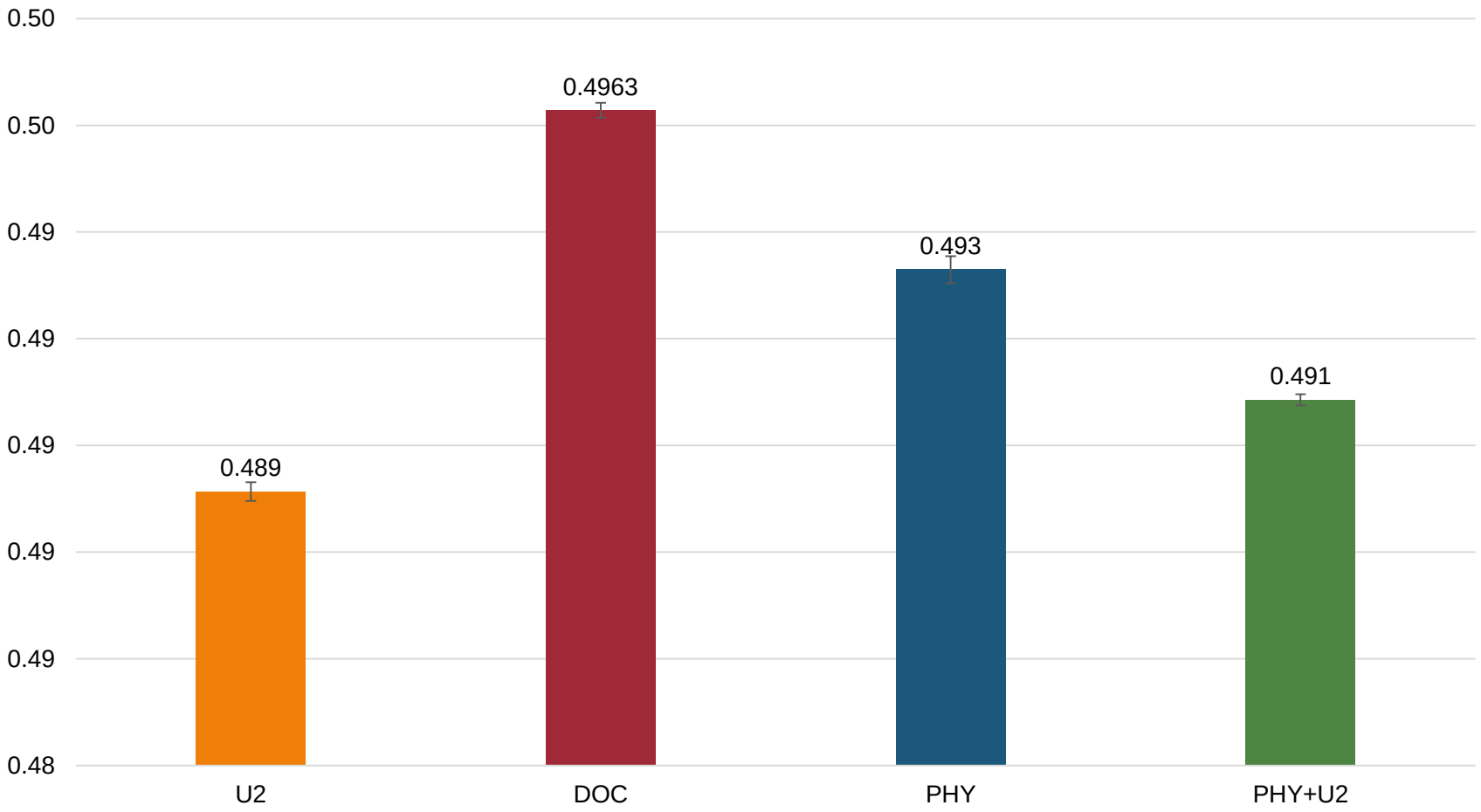
Total FLAIR Volume



Subcortical Volume



Average FA


0.50
0.50
0.49
0.49
0.49
0.49
0.49
0.48
0.4963
0.493
0.491
0.489
U2
DOC
PHY
PHY+U2

Group:Age Interaction

Null hypothesis: There is no significant differences between slopes in aging trends for white matter integrity measures.

FA/FLAIR/Volume = lm(Age:Group)

Two group comparison coded as:

Controls = 0 U2+PHY = 1

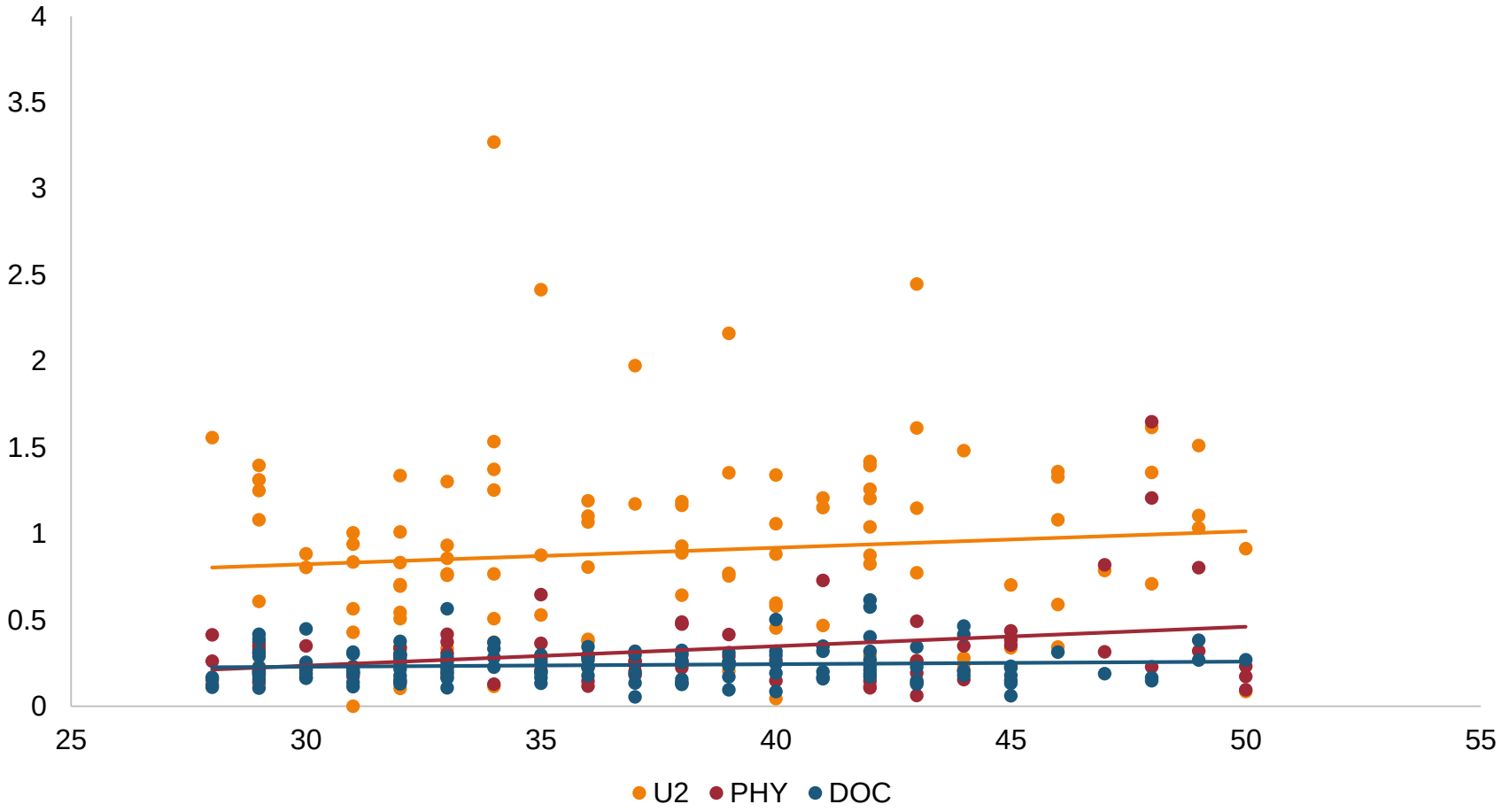
	Beta Age:Group (p value)
Total FLAIR Volume	**1.17E-02 ± 1.33E-03 (<2.00E-16)**
Subcortical Volume	**2.84E-03 ± 7.35E-04 (1.37E-04)**
Average FA	**-1.57E-04 ± 5.44E-05 (4.31E-03)**

Three group comparison coded as:

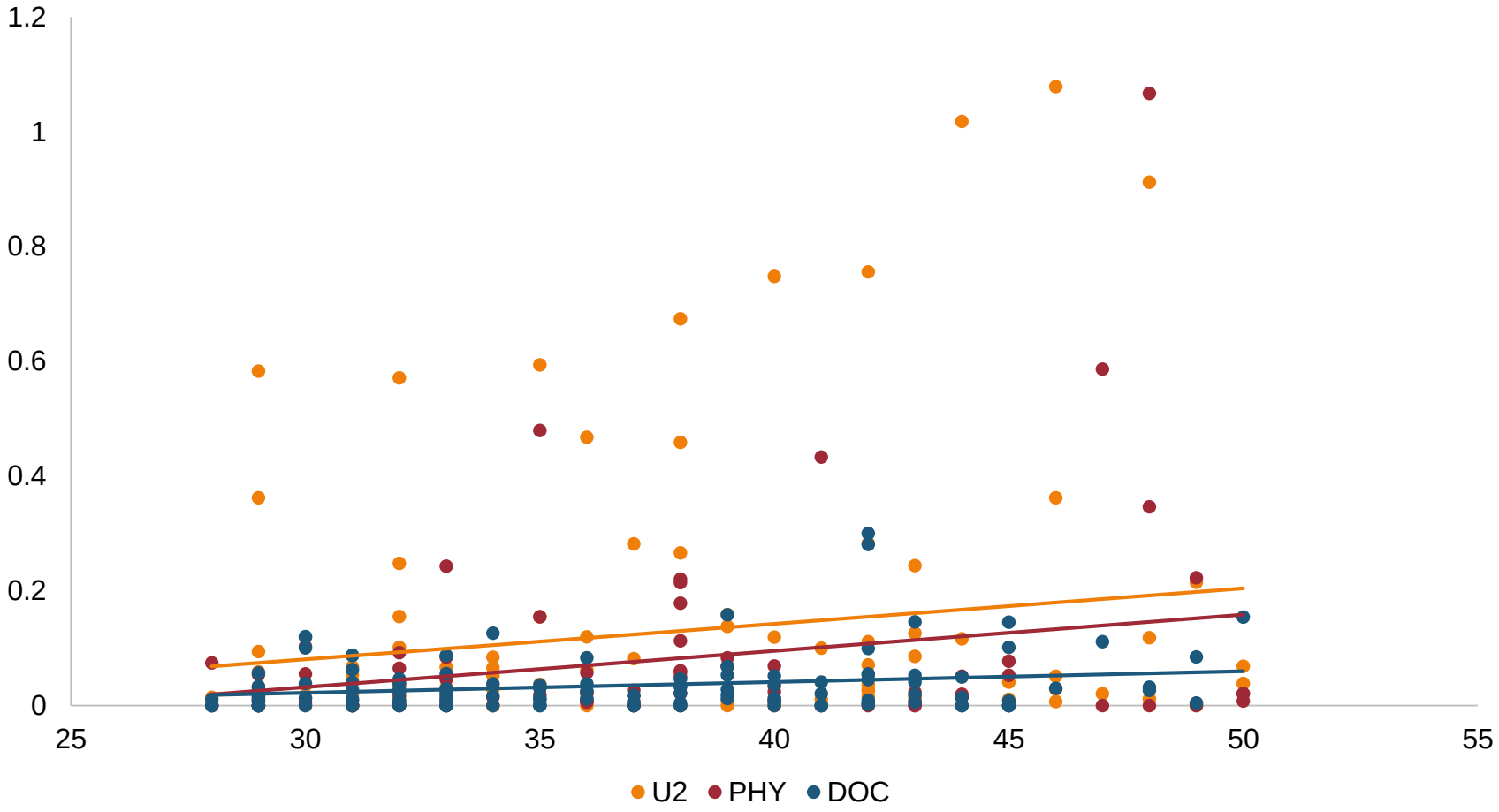
Controls = 0 PHY = 1 U2 = 2

	Beta Age:Group (p value)
Total FLAIR Volume	**8.53E-03 ± 6.95E-04 (<2.00E-16)**
Subcortical Volume	**1.44E-03 ± 4.21E-04 (7.01E-04)**
Average FA	**-1.04E-04 ± 3.10E-05 (8.95E-04)**

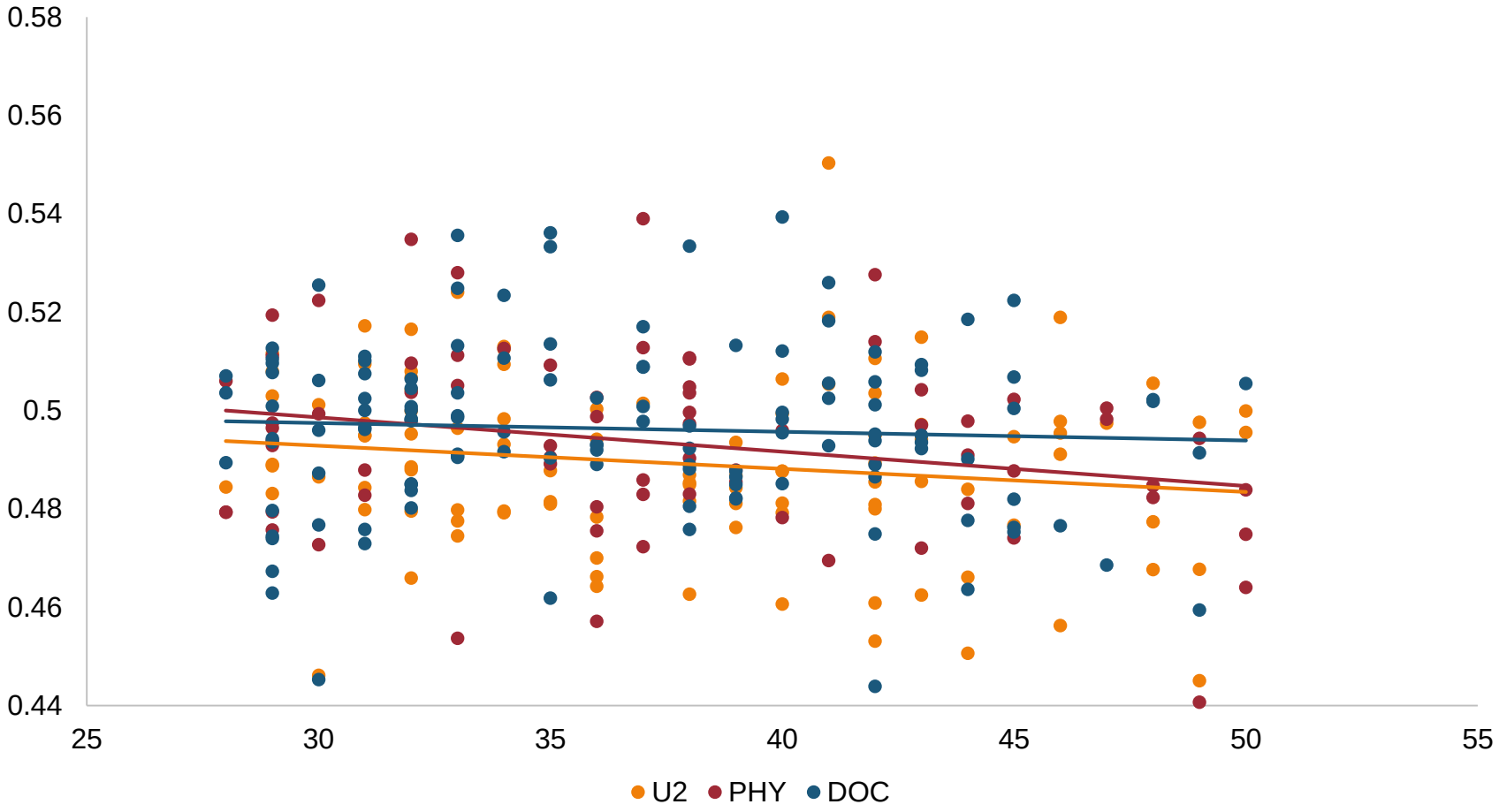
Total FLAIR Volume vs. Age



Subcortical Volume vs. Age



Average FA vs. Age

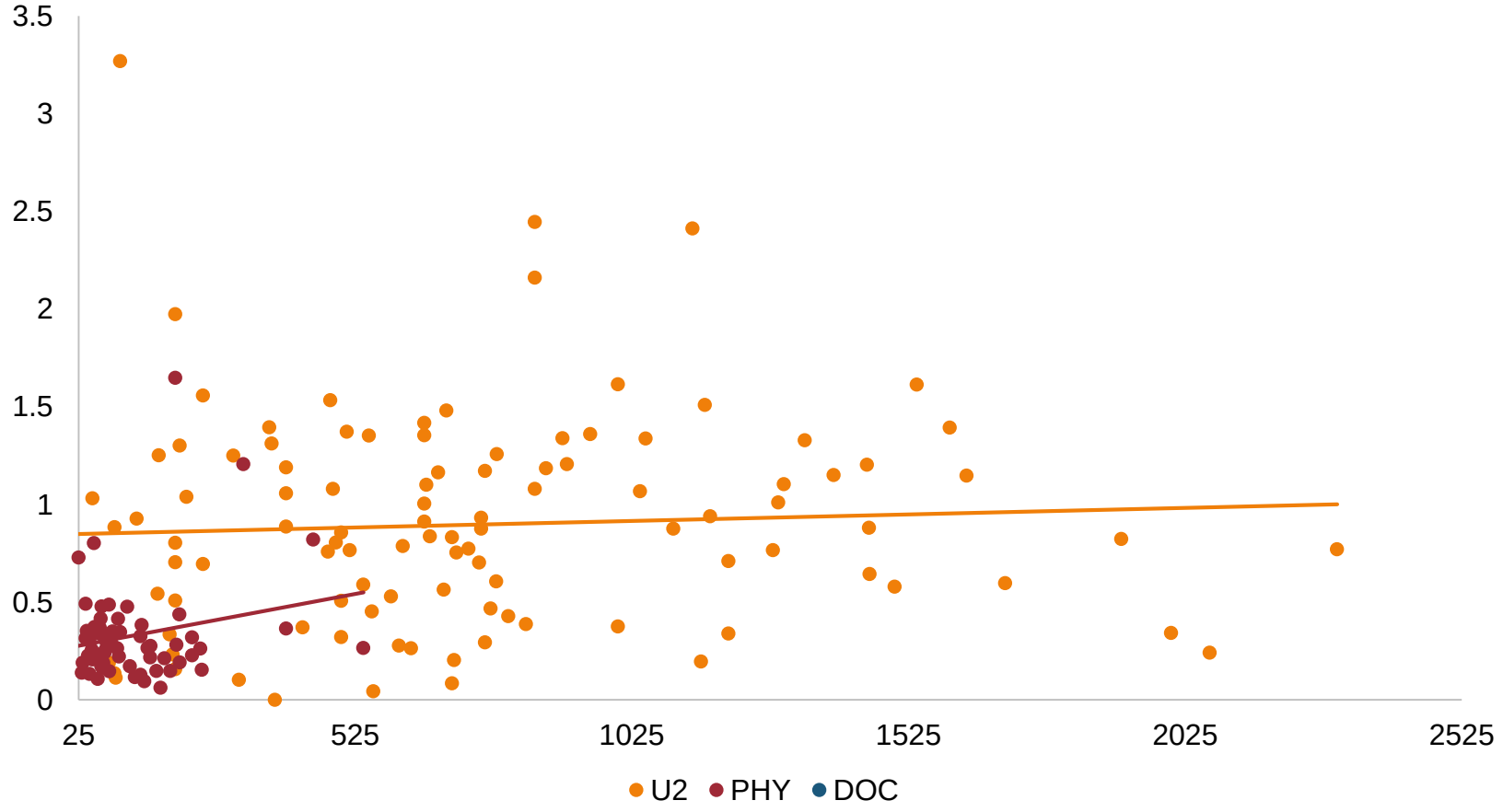


Trends with Number of Exposure Hours

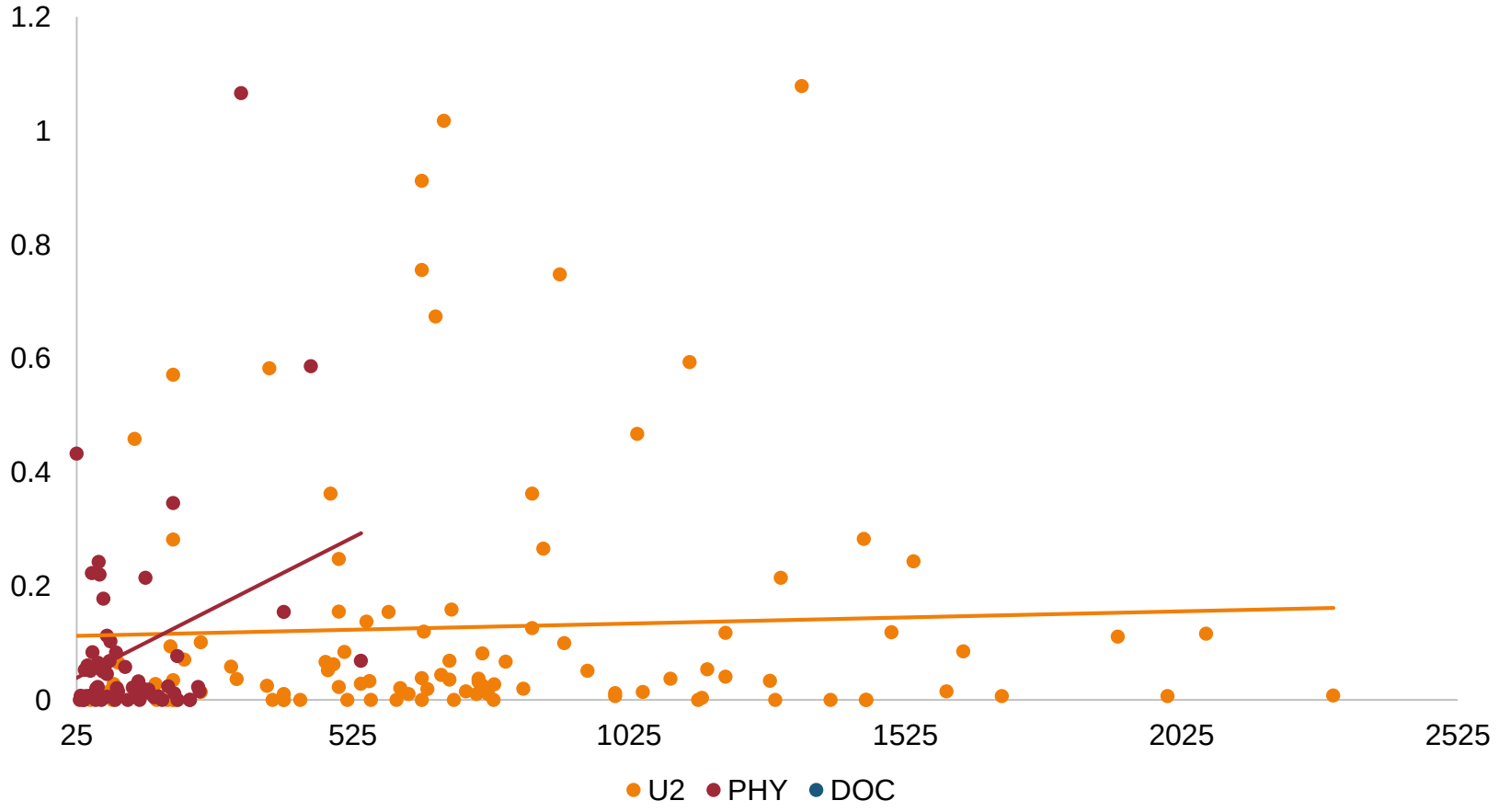
PHY vs. Number Exposure Hours

U2 vs. Number Exposure Hours

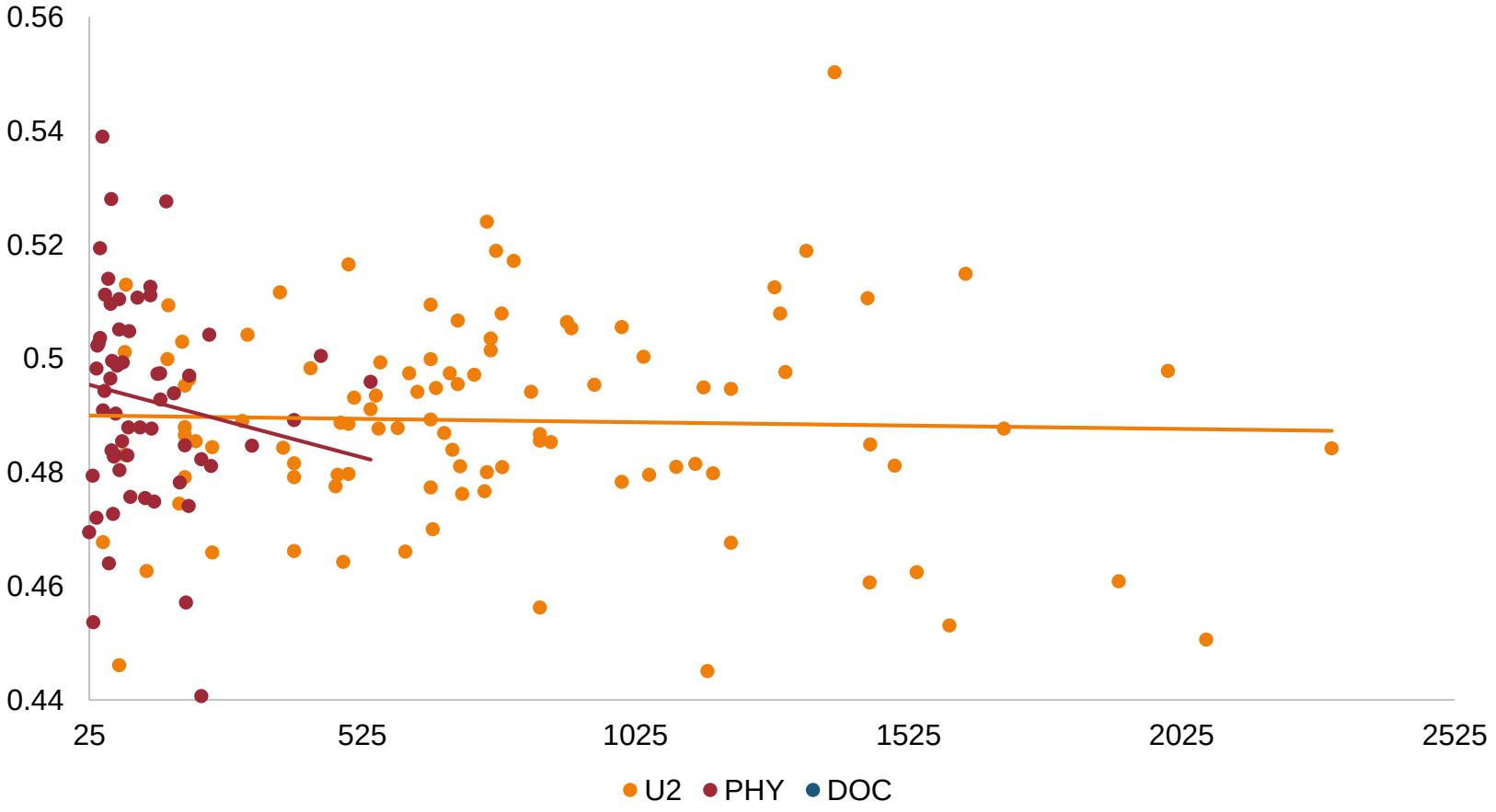
Total FLAIR Volume vs. Exposure Hours



Subcortical Volume vs. Exposure Hours



Average FA vs. Exposure Hours



Regression Results for FA vs. Age for the Control Group (NOR, AFC, DOC), U2 Pilots, and Physiologists

Tract	Controls β_{Age} ± SE (p-value)	U2 β_{Age} ± SE (p-value)	PHYS β_{Age} ± SE (p-value)
Average	-2.43E-04 ± 2.72E-04 (0.373)	**-6.25E-04 ± 2.68E-04 (0.022)**	**-7.01E-04 ± 3.20E-04 (0.032)**
Genu	**-1.29E-03 ± 4.31E-04 (0.003)**	-6.34E-04 ± 3.30E-04 (0.058)	**-1.27E-03 ± 5.52E-04 (0.024)**
Body	-1.18E-03 ± 6.92E-04 (0.091)	**-1.69E-03 ± 6.06E-04 (0.006)**	**-2.16E-03 ± 8.32E-04 (0.011)**
Splenium	1.46E-04 ± 4.01E-04 (0.716)	**-3.82E-04 ± 1.65E-04 (0.023)**	-6.34E-04 ± 4.80E-04 (0.191)
Fornix	-1.16E-03 ± 5.90E-04 (0.051)	**-1.04E-03 ± 4.09E-04 (0.013)**	-4.91E-04 ± 8.74E-04 (0.576)
Corticospinal	**1.87E-03 ± 5.97E-04 (0.002)**	-3.75E-04 ± 3.78E-04 (0.323)	1.99E-04 ± 7.21E-04 (0.783)
Internal capsule	4.39E-04 ± 3.89E-04 (0.260)	-3.71E-04 ± 3.03E-04 (0.225)	-2.64E-04 ± 4.66E-04 (0.572)
Corona radiata	-3.44E-04 ± 3.44E-04 (0.319)	-6.79E-04 ± 3.55E-04 (0.059)	**-9.35E-04 ± 4.47E-04 (0.040)**
Thalamic radiation	-5.70E-04 ± 4.44E-04 (0.201)	**-1.42E-03 ± 4.35E-04 (0.001)**	-7.42E-04 ± 5.56E-04 (0.186)
Sagittal striatum	-3.90E-04 ± 4.90E-04 (0.428)	**-1.28E-03 ± 4.81E-04 (0.009)**	-1.90E-04 ± 6.11E-04 (0.756)
External capsule	-1.33E-05 ± 3.81E-04 (0.972)	**-8.16E-04 ± 3.56E-04 (0.024)**	-3.28E-04 ± 4.39E-04 (0.457)
Cingulum	3.11E-04 ± 5.50E-04 (0.573)	**-1.09E-03 ± 5.34E-04 (0.044)**	-7.85E-04 ± 6.94E-04 (0.262)
SLF	1.12E-04 ± 4.33E-04 (0.796)	-5.21E-04 ± 3.82E-04 (0.175)	-1.59E-04 ± 5.14E-04 (0.758)
Front occip	9.06E-04 ± 5.56E-04 (0.106)	-3.62E-04 ± 4.01E-04 (0.369)	2.08E-04 ± 6.33E-04 (0.743)
Sup front occip	5.58E-04 ± 5.87E-04 (0.344)	-2.98E-04 ± 3.57E-04 (0.406)	-1.02E-04 ± 6.36E-04 (0.873)
Inf front occip	1.25E-03 ± 7.28E-04 (0.087)	-4.92E-04 ± 7.32E-04 (0.503)	5.18E-04 ± 8.38E-04 (0.538)

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Corona radiata	-3.44E-04 ± 3.44E-04 (0.319)	-6.79E-04 ± 3.55E-04 (0.059)	**-9.35E-04 ± 4.47E-04 (0.040)**
Thalamic radiation	-5.70E-04 ± 4.44E-04 (0.201)	**-1.42E-03 ± 4.35E-04 (0.001)**	-7.42E-04 ± 5.56E-04 (0.186)
Sagittal striatum	-3.90E-04 ± 4.90E-04 (0.428)	**-1.28E-03 ± 4.81E-04 (0.009)**	-1.90E-04 ± 6.11E-04 (0.756)
External capsule	-1.33E-05 ± 3.81E-04 (0.972)	**-8.16E-04 ± 3.56E-04 (0.024)**	-3.28E-04 ± 4.39E-04 (0.457)
Cingulum	3.11E-04 ± 5.50E-04 (0.573)	**-1.09E-03 ± 5.34E-04 (0.044)**	-7.85E-04 ± 6.94E-04 (0.262)
SLF	1.12E-04 ± 4.33E-04 (0.796)	-5.21E-04 ± 3.82E-04 (0.175)	-1.59E-04 ± 5.14E-04 (0.758)
Front occip	9.06E-04 ± 5.56E-04 (0.106)	-3.62E-04 ± 4.01E-04 (0.369)	2.08E-04 ± 6.33E-04 (0.743)
Sup front occip	5.58E-04 ± 5.87E-04 (0.344)	-2.98E-04 ± 3.57E-04 (0.406)	-1.02E-04 ± 6.36E-04 (0.873)
Inf front occip	1.25E-03 ± 7.28E-04 (0.087)	-4.92E-04 ± 7.32E-04 (0.503)	5.18E-04 ± 8.38E-04 (0.538)

Results

- ***Significant group by age interactions were observed for whole brain WMH volume and whole brain FA values***
- ***Analysis of regional trends demonstrated accelerated aging was limited to subcortical rather than periventricular regions***
- ***Accelerated aging in regional FA values was observed along the long-range white matter bundles originating in the frontal and parietal lobes.***
- ***No sig interaction between total WMH volume and FA values***

Summary

- ***Investigating aging in the context of hypobaric exposure; specifically focused on WM***

- ***Used a T test to assess group differences and a linear regression model to assess aging trend differences***

- ***Results***
  - ***Significant group differences for, Total FLAIR volume, Subcortical Volume and Average FA***
  - ***Linear Model:***
    - ***Significant Age:Group for Total FLAIR volume, subcortical volume, and average FA***

Conclusions

- ***Our study demonstrates that U-2/PHYS group accumulated subcortical WMH volume at a faster rate as a function of age compared to age-matched CON.***
  - ***Not a direct linear correlation to exposure hrs***
- ***This group also showed an accelerated decline in whole-brain and regional FA values.***
- ***We observed no significant interaction between total WMH volume and FA values.***
  - ***However, the FA measurements were limited to normal appearing WM to exclude the potential bias in measuring FA in a group with higher WMH load.***
- ***Overall, our findings show that occupational exposure to hypobaria may result in acceleration of cerebral aging and that increase in total WMH and decline in FA values may be independent processes.***

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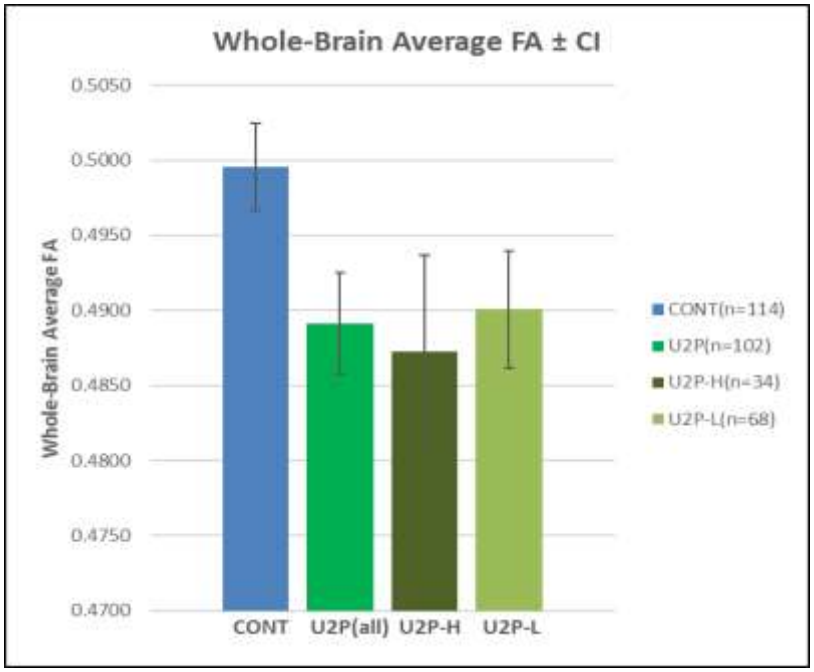
Group Comparison Regression Results for WMH

Item	U2 Pilots vs. PHYS		U2 Pilots vs. Controls		U2 Pilots + PHYS vs. Controls	
	β_{Group} ± SE (p-value)	$\beta_{Group:Age}$ ± SE (p-value)	β_{Group} ± SE (p-value)	$\beta_{Group:Age}$ ± SE (p-value)	β_{Group} ± SE (p-value)	$\beta_{Group:Age}$ ± SE (p-value)
LNFLAIR	-0.585 ± 0.572 (0.308)	0.027 ± 0.015 (0.068)	-0.344 ± 0.485 (0.479)	**0.027 ± 0.013 (0.032)**	-0.415 ± 0.354 (0.242)	**0.024 ± 0.009 (0.008)**
Total Flair Volume	-0.140 ± 0.249 (0.576)	0.009 ± 0.006 (0.154)	-0.014 ± 0.148 (0.926)	**0.009 ± 0.004 (0.018)**	-0.239 ± 0.146 (0.103)	**0.013 ± 0.004 (0.001)**
Subcortical Volume WH	-0.190 ± 0.195 (0.332)	0.004 ± 0.005 (0.417)	-0.103 ± 0.082 (0.212)	0.004 ± 0.002 (0.055)	**-0.222 ± 0.110 (0.044)**	**0.008 ± 0.003 (0.007)**
Ependymal Volume WH	0.050 ± 0.159 (0.753)	0.005 ± 0.004 (0.215)	0.089 ± 0.133 (0.505)	0.005 ± 0.003 (0.139)	-0.017 ± 0.103 (0.871)	**0.005 ± 0.003 (0.049)**

Phase 1 Repetitive Exposure Fractional Anisotropy (FA)

- ***Whole-brain average FA assesses entire WM***
  - ***FA believed to correlate with axonal integrity***
  - ***Used ENIGMA diffusion tensor imaging (DTI) protocol to exclude visible areas of WM injury (punctate WMH)***
  - ***In other words, FA is assessing normal appearing WM on fluid attenuated inversion recovery (FLAIR) to see if there is any dysfunction using DTI***
  - ***Important biomarker as it can sensitively track WM changes in both neurological and psychiatric disorders along with normal development and aging***
  - ***KS p<0.001; GLM p<0.001***
    - ***Kolmogorov-Smirnov (KS)***
    - ***Generalized linear model (GLM) with age as nuisance covariate***
- ***Decline in axonal integrity appears to track with WMH burden***



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