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14. ABSTRACT

Determine whether United States Air Force (USAF) U-2 pilots (U2Ps) with occupational exposure to repeated hypobaria had lower neurocognitive performance compared to pilots without repeated hypobaric exposure and whether U2P neurocognitive performance correlated with white matter hyperintensity (WMH) burden. We collected Multidimensional Aptitude Battery–II (MAB-II) and MicroCog: Assessment of Cognitive Functioning (MicroCog) neurocognitive data on USAF U2Ps with a history of repeated occupational exposure to hypobaria and compared these with control data collected from USAF pilots (AFPs) without repeated hypobaric exposure (U2Ps/AFPs MAB-II 87/83; Micro- Cog 93/80). Additional comparisons were performed between U2Ps with high vs low WMH burden. U2Ps with repeated hypobaric exposure had significantly lower scores than control pilots on reasoning/calculation (U2Ps/AFPs 99.4/106.5), memory (105.5/110.9), information processing accuracy (102.1/105.8), and general cognitive functioning (103.5/108.5). In addition, U2Ps with high whole-brain WMH count showed significantly lower scores on reasoning/calculation (high/low 96.8/104.1), memory (102.9/110.2), general cognitive functioning (101.5/107.2), and general cognitive proficiency (103.6/108.8) than U2Ps with low WMH burden (high/low WMH mean volume 0.21/0.003 cm3 and mean count 14.2/0.4). In these otherwise healthy, highly functioning individuals, pilots with occupational exposure to repeated hypobaria demonstrated lower neurocognitive performance, albeit demonstrable on only some tests, than pilots without repeated exposure. Furthermore, within the U2P population, higher WMH burden was associated with lower neurocognitive test performance. Hypobaric exposure may be a risk factor for subtle changes in neurocognition.

15. SUBJECT TERMS
White matter hyperintensities; neurocognitive change; neurologic decompression sickness; high altitude; U-2 pilot

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Lower neurocognitive function in U-2 pilots: Relationship to white matter hyperintensities

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Lower neurocognitive function in U-2 pilots

Relationship to white matter hyperintensities

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ABSTRACT

Objective: Determine whether United States Air Force (USAF) U-2 pilots (U2Ps) with occupational exposure to repeated hypobaria had lower neurocognitive performance compared to pilots without repeated hypobaric exposure and whether U2P neurocognitive performance correlated with white matter hyperintensity (WMH) burden.

Methods: We collected Multidimensional Aptitude Battery–II (MAB-II) and MicroCog: Assessment of Cognitive Functioning (MicroCog) neurocognitive data on USAF U2Ps with a history of repeated occupational exposure to hypobaria and compared these with control data collected from USAF pilots (AFPs) without repeated hypobaric exposure (U2Ps/AFPs MAB-II 87/83; MicroCog 93/80). Additional comparisons were performed between U2Ps with high vs low WMH burden.

Results: U2Ps with repeated hypobaric exposure had significantly lower scores than control pilots on reasoning/calculation (U2Ps/AFPs 99.4/106.5), memory (105.5/110.9), information processing accuracy (102.1/105.8), and general cognitive functioning (103.5/108.5). In addition, U2Ps with high whole-brain WMH count showed significantly lower scores on reasoning/calculation (high/low 96.8/104.1), memory (102.9/110.2), general cognitive functioning (101.5/107.2), and general cognitive proficiency (103.6/108.8) than U2Ps with low WMH burden (high/low WMH mean volume 0.213/0.003 cm^3 and mean count 14.2/0.4).

Conclusion: In these otherwise healthy, highly functioning individuals, pilots with occupational exposure to repeated hypobaria demonstrated lower neurocognitive performance, albeit demonstrable on only some tests, than pilots without repeated exposure. Furthermore, within the U2P population, higher WMH burden was associated with lower neurocognitive test performance. Hypobaric exposure may be a risk factor for subtle changes in neurocognition. *Neurology*® 2014;83:1–8

GLOSSARY

AFP = United States Air Force pilot; **DOC** = doctorate-degree volunteer; **MAB-II** = Multidimensional Aptitude Battery–II; **MicroCog** = MicroCog: Assessment of Cognitive Functioning; **NDCS** = neurologic decompression sickness; **USAF** = United States Air Force; **U2P** = U-2 pilot; **WMH** = white matter hyperintensity.

Neurologic decompression sickness (NDCS) is an occupational risk for high-altitude pilots[1] characterized by a variety of neurologic symptoms including confusion, disorientation, concentration problems, memory deficits, and reduced neurocognitive processing,[2] significantly affecting functional capacity.[3] In response to an increased incidence of NDCS in the United States Air Force (USAF),[4,5] research was performed that demonstrated pilots who experienced NDCS had increased volume and number of subcortical T2-weighted white matter hyperintensity (WMH) abnormalities.[6] Follow-up research reported significant elevation of WMH in high-altitude pilots without clinical symptoms of NDCS.[7] WMH are important markers of cerebral integrity in aging and brain disorders[8] linked to executive functioning,[9] processing speed, and general neurocognitive status,[9–11] and are an important predictor of increased neurocognitive decline.[12–15]

Supplemental data at Neurology.org

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

We examined the relationship between WMH and neurocognitive performance in active duty USAF high-altitude pilots. This presents a unique opportunity to study the association between WMH burden caused by occupational factors rather than aging or illnesses in high-performing individuals with optimal health, free of the cardiovascular and metabolic risk factors frequently present in individuals with significant WMH burden.[12–14,16,17] We studied the effects of occupational hypobaria on neurocognition by testing 2 hypotheses: (1) there will be a significant reduction in the neurocognitive test scores between USAF pilots (AFPs) repetitively exposed to hypobaria compared with AFPs not exposed to repetitive hypobaria, and (2) the volume and number of WMH will explain a significant proportion of the variability of the neurocognitive performance in AFPs who were occupationally exposed to repetitive hypobaria.

METHODS

Standard protocol approvals, registrations, and patient consents. The study was approved by the Air Force Research Laboratory Institutional Review Board. All participants were active duty members of the US military recruited with strict adherence to Department of Defense requirements regarding protection of human subjects in research. Participation in this study was voluntary, and commanding officers were not involved in subject participation. All participants acknowledged this was not an anonymous study and provided informed consent before testing.

Participants. All participants were between the ages of 28 and 47 years, were healthy without any history of neurologic or psychiatric disease, and had undergone annual medical examinations within 12 months of participation. All participants at the time of testing met USAF Flying Class II neurologic standards, and all pilots were on active flying status.[18] Briefly, exclusionary criteria for Flying Class II include a history of any of the following: head trauma with any loss of consciousness or amnesia; migraine headache; psychiatric or psychological disease requiring any medication or hospitalization; hypertension requiring more than a single angiotensin-converting enzyme inhibitor for control; hyperlipidemia requiring more than a single statin for control; diabetes or glucose intolerance; ischemic cardiac disease; any neurologic disease including infection, seizure, or stroke; or substance or drug abuse or dependence. Subjects were not evaluated for the presence of a patent foramen ovale because this is not a disqualifier for Flying Class II certification. Subjects were not compensated for participation, but their travel costs were reimbursed as permitted under Federal Government travel regulations.

All active duty USAF U-2 pilots (U2Ps) were invited to participate: 106 individuals agreed, exceeding a 90% participation rate. All U2Ps before flight and altitude exposure must undergo a physiologist-monitored 1-hour nitrogen degassing with 100% O_2 and then remain on 100% O_2 until returning to below 10,000-feet altitude. Hypobaric exposure during flight may be as long as 9 hours with cabin altitude of 28,000 to 30,000 feet. Exposure frequency is variable, but not more often than every third day. Sixteen (15%) reported symptoms of NDCS, with only 2 reporting more than a single episode. No episode of NDCS was associated with equipment failure or aircraft malfunction.

For structural MRI comparison, 132 active duty doctorate-degree volunteers (DOCs) matched for age and medical conditions were recruited as previously described.[7] All DOCs were healthy at the time of study, without present or past history of any medical conditions associated with WMH or disqualifying for Flying Class II certification.

For neurocognitive comparison, testing results for 83 active duty AFPs matched for age at the time of the neurocognitive assessment and on active flying status meeting Flying Class II standards were obtained from the AFP neurocognitive testing dataset via record review.

All U2Ps and DOCs underwent high-resolution MRI as previously described.[6,7] AFPs only participated in the neurocognitive assessment and did not undergo MRI. Neurocognitive assessment data were collected on U2Ps before imaging. Eighty-seven U2Ps completed the Multidimensional Aptitude Battery–II (MAB-II) and 93 completed the MicroCog: Assessment of Cognitive Functioning (MicroCog). From the USAF neurocognitive testing dataset, MAB-II assessment was available on 83, while MicroCog assessment was available on 80.

Cognitive assessment. Computer-based MAB-II and MicroCog neurocognitive assessment tests are routinely used in aircrew by the USAF. The MAB-II is a broad-based evaluation of neurocognitive ability based on the Wechsler Adult Intelligence Scale–Revised (correlation 0.91).[19,20] This is a computer-administered test that yields 3 summary scores (full-scale IQ, verbal IQ, and performance IQ) based on subtests of vocabulary, arithmetic, information, comprehension, similarities, digit symbol, picture arrangement, object assembly, picture completion, and spatial thinking. Similar to the Wechsler Adult Intelligence Scale–Revised, the MAB-II full-scale, verbal, and performance IQ scores are standardized to age with a mean of 100 and an SD of 15. Measures of reliability and construct validity for full-scale IQ have been demonstrated.[19] Results on the MAB-II may inflate IQ estimates, but this systematic bias will be present in all subjects and therefore not affect group comparisons.

The MicroCog is a computer-based neurocognitive assessment test that consists of 18 subtests used to derive 9 index scores. Level 1 indexes include the 5 domains of reaction time, memory, attention and control, reasoning and calculation, and spatial processing.[21] Level 2 indexes assess overall information processing speed and information processing accuracy, while level 3 indexes represent global neurocognitive functioning with general cognitive functioning weighing speed and accuracy equally and general cognitive proficiency weighing accuracy over speed.[22–24] MicroCog was specifically designed to provide more accurate assessment of the reaction time and processing speed when compared with other neurocognitive assessment instruments.[22] However, because MicroCog is a computer-based instrument, more comprehensive neuropsychological testing is required to draw conclusions about the general cognitive profile of subjects. Nonetheless, normative scores on the MicroCog have been established for age and education level,[22] and overall, MicroCog-derived scores show good consistency with other neuropsychological instrument batteries.[24]

MRI assessment. Structural MRI data for U2Ps were collected at the Research Imaging Institute, University of Texas Health Science Center, San Antonio, using a Siemens 3T Tim Trio scanner equipped with a 12-channel phase array coil (Siemens AG, Erlangen, Germany).[6,7] Structural MRI data for DOCs were

collected at Wilford Hall Ambulatory Surgery Clinic, Lackland Air Force Base, TX, using a Siemens 3T Verio scanner equipped with a 32-channel phase array coil. Both scanners are operated under quality control and assurance guidelines in accordance with recommendations by the American College of Radiology, and cross-calibration between scanners has been performed as previously described.[7] Briefly, 3-dimensional imaging parameters were T1 magnetization-prepared rapid-acquisition gradient echo repetition time 2,200 milliseconds, echo time 2.85 milliseconds, and isotropic resolution 0.80 mm, and fluid-attenuated inversion recovery repetition time 4,500 milliseconds, echo time 311 milliseconds, and isotropic resolution 1.00 mm. Fluid-attenuated inversion recovery images were coregistered to a common Talairach atlas–based stereotactic frame permitting normalization of brain size and hence cross-individual comparison. An experienced neuroanatomist (intrarater reproducibility $r = 0.95$) blinded to group as previously described manually traced WMH,[7] while a neuroradiologist provided oversight and clinical interpretation of MRIs. We manually counted the total number (count) of subcortical WMH and used in-house software to calculate the total volume (volume) of subcortical WMH in each lobe.

Stratification of data by WMH. U2Ps were separated into low WMH volume/count and high WMH volume/count cohorts. We selected as the stratification point the median WMH volume/count of the 132 DOC MRIs, making the assumption that healthy young to middle-aged adults lacking comorbid risk factors for WMH can serve as a representative sample for the upper- and lower-half quartile of WMH burden. We hypothesized that in the absence of hypobaric exposure, there should be no significant differences in either the burden or distribution of WMH between DOCs and U2Ps. The DOC median WMH volume was 0.013 cm^3 (mean DOCs/U2Ps 0.036/0.147 cm^3; $p < 0.001$) and median WMH count was 2 (mean DOCs/U2Ps 2.8/9.7; $p < 0.001$). Within U2Ps, there were no significant differences between high and low WMH volume/count groups in either age ($p = 0.921/0.342$) or number of U-2 flight hours ($p = 0.464/0.313$).

Statistical analysis. We used the 2-tailed Student *t* test with Sidak adjustment for multiple tests for comparison of MAB-II and MicroCog between U2Ps and AFPs. Similarly, we used the 2-tailed Student *t* test with Sidak adjustment for multiple tests for comparison of MAB-II and MicroCog within U2Ps separated into low and high WMH volume/count groups. We used the 2-tailed Student *t* test with Sidak adjustment for multiple tests for comparison of MicroCog within U2Ps separated into low-, mid-, and high-range quartile WMH volume/count, comparing each quartile individually with AFPs. Finally, we utilized Cohen *d* as a descriptive statistic to describe how substantial our findings are when utilizing the *t* test for comparing U2Ps and AFPs.

RESULTS

Demographics. Mean age for U2Ps/AFPs was 36.8 ± 5.3/33.7 ± 5.1 years, with a male/female ratio for U2Ps of 95/2 and for AFPs of 78/5. No difference was present between U2Ps and AFPs on the Air Force Officer Qualifying Test performed before commissioning ($p > 0.05$) or baseline MAB-II performed at time of entry into undergraduate pilot training (table e-1 on the *Neurology*® Web site at Neurology.org). No difference in distribution of initial assigned aircraft after undergraduate pilot training or in subsequent aircraft flown was present between U2Ps and AFPs.

Current cognitive assessment group comparisons. There were no significant differences between U2Ps and AFPs for any of the age-adjusted MAB-II measures after applying the Sidak adjustment (table 1). Performance for both groups was high when compared with population normative data, indicating that AFPs are highly functioning individuals.

In contrast, age- and education-corrected MicroCog subtests demonstrated a significant difference between U2Ps and AFPs on reason/calculation, memory, information processing accuracy, and general cognitive functioning after applying the Sidak adjustment (table 2). Regardless, performance on all measures was in the average range of function relative to pilot peers.

In the U2P cohort, the correlations between neurocognitive performance and the clinical occurrence of NDCS or the total hours or average frequency of hypobaric exposure were not significant (all $p > 0.05$).

WMH volume/count U2P comparison groups. There were no significant differences in MAB-II current performance between the low and high WMH volume/count groups after applying the Sidak adjustment (table 3). However, MicroCog results demonstrated a significant difference in reasoning/calculation, memory, general cognitive functioning, and general cognitive proficiency (count) and a trend in information processing accuracy (count and volume) after applying the Sidak adjustment (table 4). Furthermore, there were no MicroCog differences between the low-quartile U2Ps and AFPs while there were significant differences between the mid- and high-quartile U2Ps and AFPs (tables e-2 and e-3).

Cohen *d* effect. Cohen *d* values for MicroCog test results were substantial with moderate value for reasoning/calculation, mild to moderate values for memory and global cognitive functioning, and mild values for reaction time, information processing speed and accuracy, and global cognitive processing (table e-4).

DISCUSSION

Our study demonstrated that a subgroup of AFPs (U2Ps), occupationally exposed to repeated hypobaria but lacking any clinical deficits, had subtle changes on neurocognitive function, demonstrable as significantly reduced scores on several neurocognitive measures after Sidak adjustment for multiple tests, when compared to AFPs without repeated hypobaric exposure. Specifically, U2Ps had significantly lower scores on reasoning/calculation, memory, information processing accuracy, and general cognitive functioning with a nominal reduction in general cognitive proficiency. In addition, within the U2P population, higher WMH count was associated with significantly lower scores on reasoning/calculation,

Table 1 Current MAB-II comparison between U2Ps and AFP controls

MAB-II	U2Ps[a] (n = 87)	AFPs[a] (n = 83)	*p* Value, *t* test (2-tailed)	*p* Value, Sidak (2-tailed)
Verbal IQ[b]	120.7 ± 5.9	121.3 ± 6.0	0.516	0.887
Performance IQ[b]	127.5 ± 9.0	128.0 ± 6.7	0.680	0.967
Full-scale IQ[b]	125.5 ± 6.8	126.3 ± 5.5	0.442	0.826
Information[c]	67.5 ± 6.7	68.2 ± 6.0	0.459	0.998
Comprehension[c]	59.7 ± 3.5	60.3 ± 3.2	0.245	0.940
Arithmetic[c]	61.3 ± 6.2	62.9 ± 6.6	0.095	0.632
Similarities[c]	61.6 ± 4.5	62.5 ± 3.7	0.129	0.748
Vocabulary[c]	61.1 ± 5.1	61.4 ± 6.0	0.771	1.000
Digit symbol[c]	66.0 ± 9.0	69.3 ± 5.9	0.007	0.073
Picture completion[c]	65.1 ± 5.7	65.8 ± 5.8	0.421	0.996
Spatial[c]	63.2 ± 7.2	62.6 ± 6.3	0.592	1.000
Picture arrangement[c]	58.4 ± 9.1	57.4 ± 7.5	0.435	0.997
Object assembly[c]	65.9 ± 6.0	66.5 ± 4.9	0.489	0.999

Abbreviations: AFP = United States Air Force pilot; MAB-II = Multidimensional Aptitude Battery–II; U2P = U-2 pilot.
Data are mean ± SD.
[a] Age 28–47 years.
[b] Standard score.
[c] *t* Score.

memory, general cognitive functioning, and general cognitive proficiency compared with lower WMH count. In addition, these subjects showed nominally significant reduction in information processing accuracy (count and volume).

One potential limitation of this work is the use of computer-based cognitive assessment instruments rather than human-administered evaluations. An advantage of computer-based cognitive assessment is it provides for more accurate and standardized assessment of processing speed and reaction time, 2 cognitive domains of importance for military pilots. However, stand-alone computer-based testing does limit conclusions on general cognitive profile. A second potential limitation is interpretation of significance when using multiple tests, even after applying the Sidak adjustment. While Sidak adjustment attempts to correct for the probability of false positives when conducting multiple tests, this also affects the critical value for rejecting the null hypothesis. Finally, while we observed that lower neurocognitive performance in U2Ps appears to be associated with higher

Table 2 Current MicroCog comparison between U2Ps and AFP controls

Level	MicroCog	U2Ps[a] (n = 93)	AFPs[a] (n = 80)	*p* Value, *t* test (2-tailed)	*p* Value, Sidak (2-tailed)
1	Attention/mental control	104.4 ± 9.3	103.8 ± 10.8	0.696	0.997
1	Reasoning/calculation	99.4 ± 12.5	106.5 ± 10.9	<0.001	0.001
1	Memory	105.5 ± 12.5	110.9 ± 13.7	0.007	0.036
1	Spatial processing	109.1 ± 9.4	109.1 ± 9.4	0.989	1.000
1	Reaction time	107.3 ± 6.7	104.8 ± 9.2	0.047	0.216
2	IPS	103.6 ± 12.5	106.5 ± 10.5	0.100	0.189
2	IPA	102.1 ± 9.8	105.8 ± 10.0	0.016	0.032
3	GCF	103.5 ± 10.0	108.5 ± 10.6	0.002	0.004
3	GCP	105.4 ± 9.4	108.6 ± 10.2	0.037	0.072

Abbreviations: AFP = United States Air Force pilot; GCF = general cognitive functioning; GCP = general cognitive proficiency; IPA = information processing accuracy; IPS = information processing speed; MicroCog = MicroCog: Assessment of Cognitive Functioning; U2P = U-2 pilot.
Data are mean ± SD. All scores standard scores.
[a] Age 28–47 years.

Table 3 Current MAB-II comparison between U-2 pilots with high vs low WMH burden

	Lower WMH (mean count/volume 0.6/0.003 mL)		Upper WMH (mean count/volume 14.4/0.213 mL)		*p* Value, *t* test (2-tailed)		*p* Value, Sidak (2-tailed)	
MAB-II	Count (n = 31)	Volume (n = 29)	Count (n = 62)	Volume (n = 64)	Count	Volume	Count	Volume
Verbal IQ[a]	122.0 ± 4.9	122.0 ± 5.1	120.1 ± 6.2	120.1 ± 6.0	0.146	0.147	0.377	0.379
Performance IQ[a]	127.6 ± 8.9	128.7 ± 8.7	127.5 ± 9.0	127.0 ± 9.0	0.978	0.400	1.000	0.784
Full-scale IQ[a]	126.4 ± 6.6	127.0 ± 6.6	125.1 ± 6.9	124.9 ± 6.8	0.434	0.177	0.819	0.443
Information[b]	69.2 ± 4.9	69.2 ± 4.7	66.6 ± 7.2	66.7 ± 7.2	0.092	0.123	0.619	0.731
Comprehension[b]	60.3 ± 2.9	60.0 ± 3.1	59.4 ± 3.7	59.6 ± 3.6	0.318	0.654	0.978	1.000
Arithmetic[b]	61.5 ± 5.1	61.4 ± 5.8	61.2 ± 6.7	61.2 ± 6.4	0.791	0.916	1.000	1.000
Similarities[b]	61.7 ± 4.2	62.2 ± 4.3	61.5 ± 4.6	61.3 ± 4.5	0.818	0.389	1.000	0.993
Vocabulary[b]	62.8 ± 4.8	62.8 ± 4.6	60.4 ± 5.0	60.4 ± 5.1	0.042	0.041	0.349	0.342
Digit symbol[b]	68.3 ± 6.3	68.1 ± 6.5	65.0 ± 9.8	65.1 ± 9.6	0.111	0.165	0.692	0.835
Picture completion[b]	64.8 ± 5.0	65.4 ± 4.3	65.2 ± 6.0	65.0 ± 6.2	0.733	0.727	1.000	1.000
Spatial[b]	62.5 ± 7.6	63.2 ± 7.8	63.5 ± 6.9	63.1 ± 6.8	0.556	0.953	1.000	1.000
Picture arrangement[b]	57.6 ± 9.3	59.2 ± 8.5	58.8 ± 9.0	58.1 ± 9.3	0.551	0.630	1.000	1.000
Object assembly[b]	66.0 ± 5.4	66.6 ± 5.4	65.8 ± 9.0	65.6 ± 6.1	0.863	0.476	1.000	0.998

Abbreviations: MAB-II = Multidimensional Aptitude Battery–II; WMH = white matter hyperintensity.
Data are mean ± SD.
[a] Standard score.
[b] *t* Score.

WMH burden, the absence of MRI data in AFPs prevents a direct association between neurocognitive scores and WMH burden. Notably, regardless of the statistically significant differences in test performance, U2Ps continue to be on par with age- and cohort-specific normative data, indicating that the reduction in neurocognitive performance is not of immediate clinical significance.

The apparent lower neurocognitive performance in relationship to WMH burden in U2Ps is consistent with findings from cerebral aging research demonstrating an association between increased WMH burden and reduced performance on attention/processing speed,[9,11,12] possibly reflecting decreased efficiency of the affected neural network and eventual loss of function.[25] Interpretation of these associations between WMH abnormalities and neurocognition is complicated by both the nonspecific nature of sporadic WMH regions and the potential differences in the underlying pathophysiologic

Table 4 Current MicroCog comparison between U2Ps with high vs low WMH burden

		Lower WMH (mean count/volume 0.6/0.003 mL)		Upper WMH (mean count/volume 14.4/0.213 mL)		*p* Value, *t* test (2-tailed)		*p* Value, Sidak (2-tailed)	
Level	MicroCog	Count (n = 33)	Volume (n = 30)	Count (n = 60)	Volume (n = 63)	Count	Volume	Count	Volume
1	Attention/mental control	104.8 ± 6.7	104.7 ± 7.2	104.2 ± 10.4	104.2 ± 10.1	0.808	0.806	1.000	1.000
1	Reasoning/calculation	104.1 ± 11.3	101.8 ± 11.7	96.8 ± 12.3	98.2 ± 12.6	0.009	0.197	0.044	0.666
1	Memory	110.2 ± 11.0	108.8 ± 12.5	102.9 ± 12.4	103.9 ± 12.1	0.006	0.075	0.030	0.323
1	Spatial processing	111.0 ± 8.3	110.9 ± 8.3	108.1 ± 9.8	108.3 ± 9.7	0.161	0.202	0.584	0.676
1	Reaction time	108.4 ± 6.1	109.5 ± 5.4	106.7 ± 6.9	106.2 ± 7.0	0.299	0.028	0.831	0.132
2	IPS	106.7 ± 11.5	1047 ± 13.3	101.9 ± 12.5	103.0 ± 11.9	0.101	0.534	0.192	0.783
2	IPA	105.0 ± 7.9	105.2 ± 8.6	100.5 ± 10.2	100.7 ± 9.9	0.029	0.036	0.057	0.071
3	GCF	107.2 ± 8.9	106.1 ± 9.8	101.5 ± 9.8	102.3 ± 9.7	0.010	0.081	0.020	0.155
3	GCP	108.8 ± 8.6	107.6 ± 9.0	103.6 ± 9.3	104.4 ± 9.4	0.011	0.121	0.022	0.227

Abbreviations: GCF = general cognitive functioning; GCP = general cognitive proficiency; IPA = information processing accuracy; IPS = information processing speed; MicroCog = MicroCog: Assessment of Cognitive Functioning; U2P = U-2 pilot; WMH = white matter hyperintensity.
Data are mean ± SD. All scores standard scores.

mechanisms of WMH. In aging studies, increased WMH burden is associated with many insidious and chronic conditions including cerebrovascular inflammation,[16,26] small-vessel stenosis,[27] diabetes, and hypertension.[28] In addition, the associations between WMH abnormalities and neurocognitive performance are often drawn from observations in elderly and patient populations. Our study provides strong evidence that occupational hypobaria-associated WMH load may be an independent predictor of lower neurocognitive performance even among healthy and high-performing individuals, free of typical risk factors associated with elevated WMH.

Hypobaria is a known risk factor for decompression sickness that may include neurologic symptoms ranging from very mild (feeling of physical fatigue and complaints of slowed thought processes) to severe (anomia, confusion, and unresponsiveness),[2] including permanent neurocognitive decline.[3] At this time, the precise mechanisms of CNS damage due to hypobaria are uncertain. Previously, we hypothesized that CNS damage may be caused by microbubble occlusion of small arterioles, by platelet thrombi produced by accelerated coagulation in the presence of nitrogen microbubbles,[29,30] or by direct tissue damage from microparticles and activation of proinflammatory leukocytes.[7,31,32] In other words, exposure to hypobaria leads to bombardment of brain vasculature and thrombo-inflammatory damage in cerebral white matter that is visible as WMH. A significantly more uniform regional distribution of WMH across cerebral white matter in U2Ps compared with DOCs supports this hypothesis.[7] Specifically, WMH were more uniformly distributed across the cerebral white matter in U2Ps, while the lesion burden was primarily observed in frontal areas in DOCs. How this pattern of injury would lead to lower neurocognitive performance is unknown.

We believe the significant difference in neurocognitive scores between U2Ps and AFPs is caused by repeated hypobaric exposure, although we cannot exclude other environmental contributors associated with high flight including radiation injury. U2Ps showed significantly reduced scores across a broad range of neurocognitive domains compared with AFPs. In addition, finding significantly lower neurocognitive scores in U2Ps with greater vs lesser WMH burden further suggests an association between WMH burden and reduced neurocognitive performance in U2Ps. Indeed, post hoc testing revealed U2Ps from the lower WMH group did not show significant difference from AFPs. In contrast, the neurocognitive scores from the U2Ps with mid-range or high WMH burden were significantly lower (tables e-2 and e-3). The lack of MRI data on AFPs, however, prevents the direct association of WMH burden and neurocognitive performance. Nonetheless, our finding supports the hypothesis that WMH changes may, by themselves, be associated with a decline in neurocognition.[33] This is consistent with the current mechanist view of the brain as a collection of large-scale functional networks supporting higher neurocognitive functioning. However, this observation requires additional validation, and following this cohort as they age would be an important step in understanding whether or not these changes are progressively different than what is expected for a healthy, aging cohort.

Finally, despite the findings of statistical difference on neurocognitive performance, U2Ps remain very highly functioning individuals with neurocognitive scores above the average for the general public. They remain fully capable of performing the complex multitasking necessary of pilots in this challenging aircraft with no persistent behavioral abnormalities noted.[34] Similar to reports in other populations,[35] this may represent neurocognitive reserve present in these highly functioning individuals. A single U2P (excluded from all analysis) experienced neurocognitive impairment sufficient to preclude further pilot duties, but this was an unusual case not representative of the U-2 population.[3] One pilot included in this study experienced repeated episodes of headache associated with high flight and was therefore restricted to pressurized aircraft with no subsequent clinical symptoms or impairments. In addition, although 2 pilots in this study did voluntarily withdraw from the U-2 program before testing, neither one demonstrated any clinical neurocognitive deficit and both remained on active flying status medically qualified for all USAF aircraft including the U-2 without restriction. However, our findings are a cause for concern and suggest that further investigation on the long-term significance of this difference is needed.

Analysis of other MRI parameters, including spectroscopy and volumetric parameters, is ongoing in an attempt to better understand the pathophysiologic process and impact on neurostructures and performance. In addition, a reliable laboratory model for neurologic injury secondary to hypobaric exposure is under development.

This study demonstrates that U2Ps with repeated occupational exposure to hypobaria have significantly lower neurocognitive test performance compared to AFPs without repeated hypobaric exposure. Moreover, higher WMH burden was significantly associated with reduced neurocognitive performance. In addition, our study suggests that other healthy, peak-of-function, young to middle-aged populations who are at high risk of increased WMH burden, such as concussion from athletic activities, may be at risk of significantly reduced neurocognitive performance.

AUTHOR CONTRIBUTIONS

Dr. McGuire: study concept, design, performance analysis, interpretation, and principal author of manuscript. Dr. Tate and Dr. Wood: study concept, design, performance, data analyses, and critical revision of the manuscript for important intellectual content. Dr. Sladky, Dr. McDonald, and Dr. Sherman: study concept, design, performance, analysis and interpretation. Ms. Kawano: critical scientific editorial assistance. Dr. Rowland, Ms. Patel, Ms. Wright, Dr. Hong, Dr. Rasmussen, and Dr. Willis: analysis and interpretation. Dr. Kochunov: study concept, design, performance, data analyses, and critical revision of the manuscript for important intellectual content.

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