Cumulative Cyclic Exposures to 8000-ft Pressurization Equivalence and Attention Network Responses

Jennifer E. Thropp; Paul W. Buza

INTRODUCTION: The literature is equivocal regarding the degree of cognitive impairment incurred at the 8000-ft (2438 m) maximal cabin pressure altitude equivalence for commercial aircraft. This study elaborates upon the investigation of the 8000-ft limit by introducing the cumulative effects of repeated daily exposures thereof.

METHOD: Pilots completed four daily high-altitude chamber flights at both sea level and 8000 ft. During each chamber flight, attentional processing and executive function were assessed using the Attention Network Test and the antisaccade task.

RESULTS: Antisaccade task performance likely reflected a learning effect at both altitudes. Attention Network Test results, however, exhibited sensitivity to the fatigue and altitude interaction. Orienting network scores were affected by fatigue differently depending on altitude, with superior efficiency at 8000 ft compared to sea level (M = 44.9, SD = 25.0 vs. M = 29.0, SD = 18.1) in the last flight of the exposure cycle. Conflict network performance, however, suggested that while fatigue increasingly compromised executive control at both altitudes, marginally worse overall executive efficiency was observed at 8000 ft compared to sea level, notably in the last flight of the exposure cycle (M = 98.3, SD = 19.8 vs. M = 87.8, SD = 21.7).

DISCUSSION: Executive control function, as measured by inhibition of interference in reconciling conflicting stimuli, degraded as a function of cumulative exposures to mild hypobaric hypoxia, though adaptive measures possibly compensated to preserve performance to a degree. This study serves as a baseline against which longer 8000-ft exposures, including long-haul flight, can be measured.

KEYWORDS: executive control, orienting, alerting, conflict.

Thropp JE, Buza PW. *Cumulative cyclic exposures to 8000-ft pressurization equivalence and attention network responses*. Aerosp Med Hum Perform. 2019; 90(6):513–523.

The partial pressure of oxygen at a typical cruise altitude (e.g., 11,000 m or 36,000 ft) is severely inadequate for survival relative to that which occurs at sea level (e.g., 4.7 kPa vs. 21 kPa) and must be reconciled by the aircraft's onboard environmental control system.[21] U.S. Federal Aviation Regulation 25.841 requires commercial aircraft to be equipped to produce a maximal cabin altitude (CA) of 2438 m (8000 ft) under normal operating conditions,[12,21] a level judged to best satisfy both the physiological and cognitive requirements of the human and the structural and fuel requirements of the aircraft.[1] In practice, however, CA may range from 6000–9000 ft (1828–2743 m), in which aircrew blood oxygen saturation (S_pO_2) has been found to range from an average minimum of 88.6% to an average maximum of 97%.[6]

The degree of cognitive impairment resulting from the mild level of hypoxia incurred at lower altitudes such as 8000 ft has been regarded as controversial.[18] Reported impairments include increased response time on signal detection tasks, impaired learning, visual degradation under scotopic conditions, and self-reported symptoms that could jeopardize safe flight (e.g., impaired calculations and confusion).[1,23] Conversely, adaptive mechanisms may be responsible for some task improvements that have been noted, such as faster performance on card-sorting tasks and improved logical reasoning.[23] Simulated flight research has showed that while mild hypoxia might not produce significant deviations in maintaining headings and altitudes

From Embry-Riddle Aeronautical University, Daytona Beach, FL.

This manuscript was received for review in July 2018. It was accepted for publication in March 2019.

Address correspondence to: Jennifer Thropp, Embry-Riddle Aeronautical University, School of Graduate Studies, College of Aviation (COA 113), 600 S. Clyde Morris Blvd., Daytona Beach, FL 32114; throppj@erau.edu.

DOI: https://doi.org/10.3357/AMHP.5232.2019

or very high frequency (VHF) omni-directional range (VOR) tracking, more procedural errors can result.[22] Further, marginal impairment on complex decision-making tasks involving conflict resolution has been reported in subjects assessed at 8000 ft,[18] an effect that could have adverse implications for the cognitive flexibility necessary for handling unanticipated events in flight. Thus, well-learned cognitive, vigilance, and perceptual-motor tasks appear to remain intact, whereas effects on complex cognition are less certain.[18]

A well-established paradigm of attentional networks theorizes a system of neural substrates linked to the engagement of three different types of attention in task performance.[10] Alerting is necessary for achieving and maintaining attentiveness to impending stimuli and may involve frontal and parietal regions of the right hemisphere, which are activated during continuous performance and vigilance tasks. Orienting involves selecting appropriate information from sensory input as distributed in space and responding to cues indicating where to attend for pertinent information. It has been linked to the parietal and frontal lobes, frontal eye fields, superior colliculus, midbrain, and thalamus.[4] Executive control is elicited in resolving conflict among contradicting stimuli or responses, decision-making, detecting errors, and response inhibition and is linked to the anterior cingulate and lateral prefrontal cortex.[17] The Attention Network Test (ANT)[10] is a combination of the cued reaction time test and the flanker task and measures the efficiencies of these three attentional networks, thereby providing a means for assessing several neural structures. While the ANT has indicated adverse effects of extreme environments in prior studies,[3,28] there is a lack of such research regarding acute, mild hypoxia exposures.[27]

Executive control is also measured by the antisaccade task,[13] in which the subject must suppress a reflexive, automatic response (i.e., a prosaccade) toward a peripheral task-irrelevant stimulus in favor of executing a voluntary command to look in the mirror-opposite periphery (i.e., an antisaccade) toward a task-relevant stimulus.[20] Such inhibition of a dominant response is necessary for resistance to disruption or interference by task-irrelevant stimuli or responses. Task failure, however, is a result of inhibition that is too weak relative to the dominant saccadic response or is executed too slowly.[9] Saccades activate the posterior parietal cortex and the frontal and supplementary eye fields, though antisaccades do so to a greater degree than do prosaccades, and the prefrontal cortex and posterior parietal cortex are particularly tasked in generating the command to look in the direction that opposes a reflex.[25]

Administering the ANT and antisaccade task in the context of acute hypoxic exposure would assess vulnerabilities of early stages of visual information processing, attentional control, and executive functioning, which are fundamental for flight performance. The present protocol administered these two tasks to experienced pilots at an 8000-ft altitude equivalence and further induced the stressor of repeated daily exposures to this consequential mild hypoxia, as would be incurred by regional aircrew flying several times per day. These repetitive exposures were assumed to also induce a degree of fatigue. To our knowledge, the cumulative effects of cyclic exposures to an 8000-ft equivalence on attention and behavioral control have not yet been reported. Adverse effects on task performance, notably in executive function at 8000 ft, with exacerbation in later exposures, were anticipated. However, given the relatively small altitude difference between the two conditions, the effects were expected to be small.

METHODS

Subjects

Subjects were 24 pilots (21 men, 3 women) with a mean age of 25.5 yr (SD = 8.1) and an average of 745.2 total flight hours (SD = 992.6). All subjects had an FAA-valid medical certificate and were screened for additional confounding or disqualifying health issues. Neither dietary nor lifestyle restrictions were imposed prior to participation. The study protocol was approved in advance by the Embry-Riddle Aeronautical University institutional review board and all subjects provided written informed consent before participating.

Equipment

The high-altitude chamber used to produce the altitude conditions was a Class D multilock hypobaric chamber (Victoria Machine Works, Inc., Victoria, TX) measuring 3 m (10 ft) in diameter and 9.75 m (32 ft) in length. The mean temperature and humidity readings inside the chamber were 25.8°C (78.5°F) and 58.1% at sea level, and 25.6°C (78°F) and 53.3% at 8000 ft. CO_2 remained stable at 1.5 mBar. S_pO_2 was measured during each flight using finger pulse oximetry sampling at a rate of once per 5 s. The tasks were administered on laptop computers (1280 × 720 display) with responses made via keyboard.

Procedure

A within-subjects design was used, assessing two repeated-measures independent variables: simulated altitude (sea-level equivalence, termed "SL"; and 8000-ft equivalence used to represent cabin altitude, termed "CA" for the purpose of this study) and flight number (a sequence of four chamber flights at each altitude, referred to as "flights"), thereby generating eight flights termed SL1, SL2, SL3, SL4, CA1, CA2, CA3, and CA4. The SL flights served as the control condition. The mean S_pO_2 across all four flights was 98% (SD = 0.09%) at SL and 93.3% (SD = 2.7%) during CA flights.

In the CA condition, the pressure inside the chamber was gradually reduced at a rate of approximately 457 m (1500 ft) per minute until approximately 2438 m (8000 ft) equivalence was attained, at which point subjects began the tasks. All other conditions inside the chamber were consistent between altitudes. The control flights at SL were performed with the chamber doors closed and the chamber was flown to 500 ft with ventilation maintained for the same time duration as were the CA flights to minimize the perceptible difference between altitudes and blind subjects to the current altitude condition.

Each subject completed four 45-min chamber flights per day (35 min at each altitude) with a different altitude condition on each day. The order of altitude conditions was counterbalanced between the 2 d such that half of the subjects were tested in the CA condition on Day 1 and SL on Day 2, while the other half of the subjects were tested in the SL condition on Day 1 and CA on Day 2. Subjects were seated at individual laptop computers inside the chamber. Six subjects were inside the chamber at one time, in addition to one medically trained chamber tender and an experimenter. There was a break of approximately 60 min between flights. The computer-based ANT and antisaccade task were administered during each flight. The order in which the tasks were administered in each flight was counterbalanced such that the number of times each task was presented first was equally distributed among subjects as well as among each combination of altitude order and flight number.

In each trial of the ANT (see Fan et al.[10] for further detail), subjects were instructed to maintain their gaze upon a central fixation point which appeared for a variable duration. One of four warning cue types appeared and then the target appeared along with one of three flanker types. The target was an arrow pointing either left or right and appearing with spatial uncertainty (i.e., either above or below the central fixation point). Subjects were instructed to respond as quickly and accurately as possible by pressing the arrow key that corresponded with the target arrow direction.

The alerting and orienting networks were manipulated through the presentation of four different cue types (an asterisk shape) which warned of the target onset differentially:

1. No cue: Only the fixation point was visible; no alerting was provided.
2. Center cue: One asterisk appeared at the fixation point, providing a nondirectional alert; therefore, no spatial information regarding target location was provided.
3. Double cue: Two asterisks appeared simultaneously, one directly above and another directly below the fixation point; alert was therefore nondirectional, but the two cues together created a larger attentional field.
4. Spatial cue: One asterisk appeared in the same location as the impending target, thereby providing an alert with spatial information to orient attention accordingly.

To manipulate the conflict network, each target arrow was accompanied by one of three types of flanker congruence:

1. Congruent: horizontal lines with arrowheads pointing in the same direction as the target arrow.
2. Incongruent: horizontal lines with arrowheads pointing in the direction opposing that of the target arrow, thereby creating conflicting information.
3. Neutral: horizontal lines without arrowheads.

The ANT began with a practice block of 24 trials that provided response time (RT) and accuracy feedback. The task consisted of three experimental blocks, each consisting of 96 trials equally comprised of the following stimulus condition combinations presented in random orders: 4 cue types $\times$ 3 congruence types $\times$ 2 target locations $\times$ 2 target arrow orientations.

The efficiency of each attention network was calculated using the follow mean RTs (mRTs):

Alerting effect = mRT of No Cue conditions – mRT of Double Cue conditions (i.e., improvement from knowing when the target will appear).

Orienting effect = mRT of Center Cue conditions – mRT of Spatial Cue conditions (i.e., improvement from knowing when and where the target will appear).

Conflict effect = mRT of Incongruent Flanker conditions – mRT of Congruent Flanker conditions (i.e., cost incurred from conflicting information).

For alerting and orienting effects, larger values indicate greater efficiency through responding more quickly by using the cues. In the conflict effect, a larger value indicates greater time required to resolve conflict and therefore signals inefficiency.

In the antisaccade task (see Hallett[13] for further detail) subjects were instructed to maintain their gaze upon a central fixation point appearing for 800 ms. A peripheral stimulus (7.5 cm^2 box) appeared on either the left or right side of the fixation point. Subjects were instructed to quickly look on the opposite side of the fixation point, where a second peripheral box (7.5 cm^2) would then appear 250 ms later. This second box contained the target, an arrow, which was visible for 150 ms before being masked with a hash mark pattern. The target arrow was pointing in one of four directions (up, down, left, or right). Subjects were tasked with indicating the correct arrowhead direction as quickly as possible by pressing the corresponding arrow key. Failure to successfully and quickly suppress the reflexive prosaccade toward the first stimulus box and execute the antisaccade resulted in missing the arrow in the second stimulus box. The two boxes were separated by 17.5 cm, which ensured that subjects could not simultaneously distinguish the contents of both without executing a proper antisaccade. A practice block of 32 trials with accuracy and RT feedback preceded the task, which consisted of 90 trials.

Following the tasks in each flight, subjects completed the Samn-Perelli Crew Status Check,[24] in which they rated their fatigue on a scale of 1 ("fully alert, wide awake") to 7 ("completely exhausted, unable to function properly"). They also completed an abbreviated version of the Raw NASA Task Load Index,[14] in which they rated their subjective workload using a scale of 0 ("low") to 100 ("high") on six subscales (mental demand, physical demand, temporal demand, performance, effort, and frustration). On the performance subscale, high scores indicated high appraisal of task performance success. Overall workload was calculated as the average of subscale scores. **Fig. 1** shows the schematics of the ANT and antisaccade task.

Statistical Analysis

For both tasks, RT was defined as the interval [in milliseconds (ms)] between stimulus onset and response via key press and was only calculated for correct trials. Accuracy was proportion of trials with correct responses.

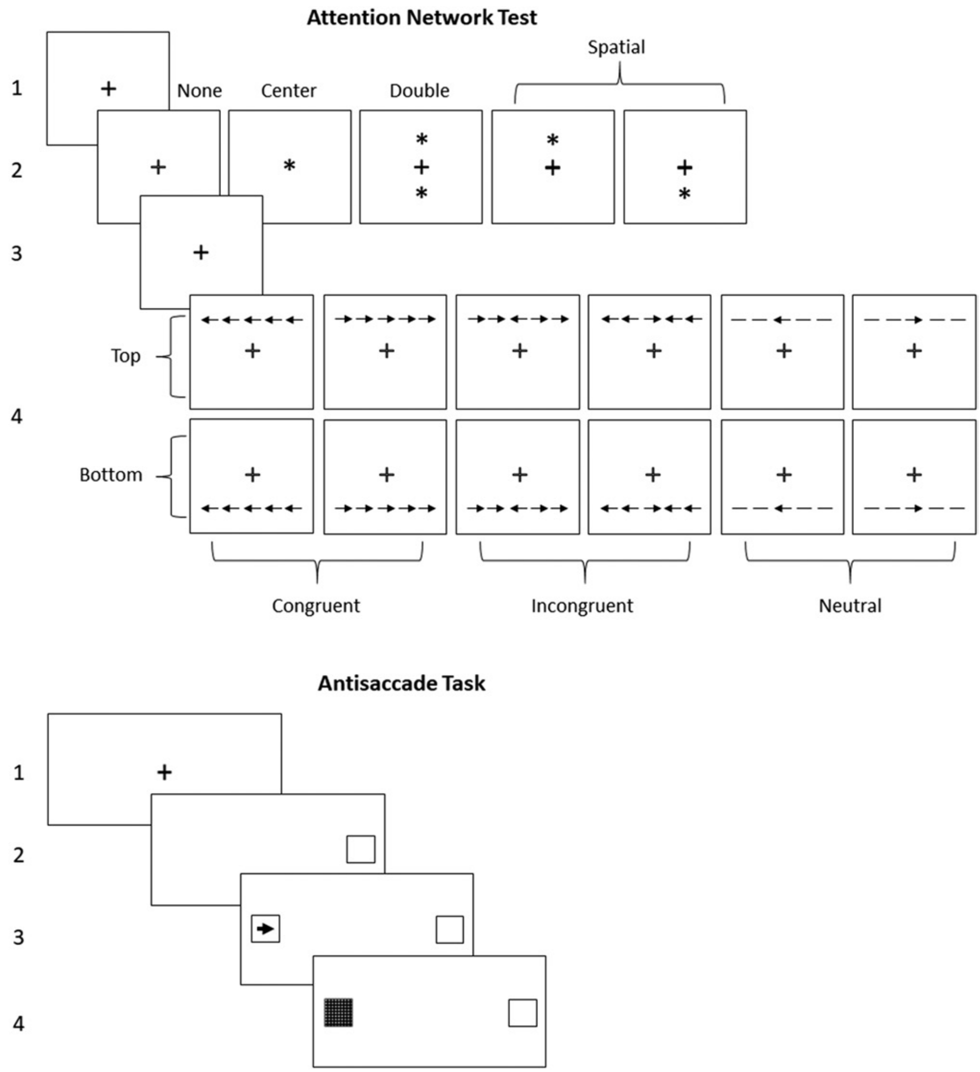

Fig. 1. Top: ANT sequence of stimulus presentation: 1) Fixation cross (400–1600 ms); 2) one of four cue types appears (100 ms); 3) fixation cross returns (400 ms); 4) target appears in one of the eight possible locations and flanker combinations (maximum of 1700 ms). Bottom: Antisaccade task sequence of stimulus presentation: 1) fixation cross (800 ms); 2) first peripheral box appears, signaling to the subject to look to the opposite side; 3) second peripheral box containing target arrow appears 250 ms later for a duration of 150 ms; 4) arrow is obscured by mask.

For the ANT, four-way 2 (Altitude: SL, CA) × 4 (Flight: 1, 2, 3, 4) × 4 (Cue: no cue, center cue, double cue, spatial cue) × 3 (Congruence: incongruent, neutral, congruent) repeated measures ANOVAs (rmANOVAs) were conducted on accuracy and RT. Two-way rmANOVAs [2 (Altitude) × 4 (Flight)] were computed for each attention network efficiency. The efficiency of each network was reported in milliseconds.

For the antisaccade task, two-way 2 (Altitude) × 4 (Flight) rmANOVAs were conducted on overall accuracy, bivalent accuracy, RT, and bivalent RT. Overall accuracy reflected correct indication of the arrowhead direction, while bivalent accuracy reflected correct indication of the orientation of the entire target arrow as either horizontal or vertical (e.g., indicating either up or down for an arrow pointing up was scored as correct). Responses exceeding 2000 ms were considered extreme and excluded from analyses.

For statistically significant rmANOVAs (defined as a P-value of < 0.05), pairwise comparisons were adjusted for multiple comparisons using Sidak post hoc tests. P-values smaller than 10^{-8} are presented as $P < 0.0000001$. The Greenhouse-Geisser test was used to correct for violations of sphericity. Effect size was calculated as partial eta squared (η_p^2).

RESULTS

Subjective Fatigue and Workload

Post-task subjective fatigue indicated a main effect of Flight [$F(3,45) = 3.659$, $P = 0.019$, $\eta_p^2 = 0.196$] with ratings that were higher for flight 3 than flight 1 ($P = 0.047$). The Altitude × Flight interaction was marginal [$F(3,45) = 2.497$, $P = 0.072$, $\eta_p^2 = 0.143$]; ratings for SL2, SL3, and SL4 exceeded that of SL1 (all $P < 0.01$), but were stable across CA flights.

Overall subjective workload ratings (**Table I**) indicated a marginal Flight × Altitude interaction [$F(1.661,34.871) = 2.969$, $P = 0.073$, $\eta_p^2 = 0.124$], indicating that at SL, subjective workload generally increased across flights, with SL2 ($P = 0.068$) and SL3 ($P = 0.051$) marginally exceeding that of SL1, while it was stable across CA flights. There was a significant main effect of Flight on the physical workload subscale [$F(3,63) = 5.457$, $P = 0.002$, $\eta_p^2 = 0.206$], with flight 3 ($P = 0.024$) and flight 4 ($P = 0.017$) exceeding flight 1. In subjective ratings of performance, the Altitude × Flight interaction was significant [$F(3,63) = 3.126$, $P = 0.032$, $\eta_p^2 = 0.130$]; appraisal of SL2 was marginally higher than SL3 ($P = 0.052$) and SL4 ($P = 0.060$), and SL1 was marginally higher than SL3 ($P = 0.069$). Appraisal of CA3 exceeded that of CA2 ($P = 0.035$).

Attention Network Test

For the alerting and orienting networks, higher scores indicate better efficiency. The alerting network indicated a significant main effect of Flight [$F(3,69) = 9.210$, $P = 0.000015$, $\eta_p^2 = 0.283$]. The mean alerting efficiencies for flight 4 ($P = 0.0003$), flight 3 ($P = 0.0018$), and flight 2 ($P = 0.00038$) all exceeded

Table I. Subjective Measures by Altitude and Flight.

ALTITUDE × FLIGHT MEAN (SD)				
		POST-TASK WORKLOAD (NASA-TLX)		
FLIGHT	POST-TASK FATIGUE	OVERALL	PHYSICAL	PERFORMANCE
SL1	2.38 (1.2)	38.2 (11.5)	25.7 (18.9)	71.6 (12.0)
SL2	3.31 (1.2)	42.1 (12.9)	30.7 (20.6)	72.5 (15.6)
SL3	3.31 (1.4)	43.5 (14.5)	34.6 (24.3)	64.3 (19.5)
SL4	3.38 (1.4)	43.5 (16.0)	32.2 (23.0)	65.2 (20.4)
CA1	2.94 (1.3)	41.1 (15.6)	24.6 (19.7)	65.9 (18.8)
CA2	3.13 (1.7)	40.5 (15.4)	30.4 (21.8)	65.0 (16.4)
CA3	3.06 (1.5)	38.1 (16.1)	30.7 (23.4)	70.2 (10.2)
CA4	3.13 (1.8)	40.8 (20.0)	32.5 (23.6)	65.7 (16.9)
MAIN EFFECTS MEAN (SE)				
SL	3.09 (0.27)	41.8 (2.6)	30.8 (4.3)	68.4 (2.8)
CA	3.11 (0.35)	40.1 (3.3)	29.5 (4.4)	66.7 (2.6)
Flight 1	2.66 (0.25)	39.6 (2.4)	25.1 (3.7)	68.8 (2.7)
Flight 2	3.22 (0.34)	41.3 (2.9)	30.5 (4.0)	68.8 (3.1)
Flight 3	3.19 (0.30)	40.8 (3.1)	32.6 (5.0)	67.3 (2.7)
Flight 4	3.34 (0.37)	42.2 (3.6)	32.4 (4.8)	65.5 (3.7)

SL: sea level; CA: cabin altitude.

that of flight 1. The orienting network indicated a significant Altitude × Flight interaction [$F(3,69) = 4.229$, $P = 0.008$, $\eta_p^2 = 0.155$]; the mean orienting efficiency in CA4 was higher than in SL4 ($P = 0.010$).

For the conflict network, higher scores indicate worse efficiency. The main effect of Altitude was marginal [$F(1,25) = 3.882$, $P = 0.061$, $\eta_p^2 = 0.144$], with the conflict effect at CA exceeding that of SL. A pairwise comparison using least significant differences indicated that the mean conflict score at CA4 was significantly greater than in SL4 ($P = 0.017$). There was a significant main effect of Flight [$F(3,69) = 9.543$, $P = 0.000024$, $\eta_p^2 = 0.293$]. Flight 3 ($P = 0.010$) and flight 4 ($P = 0.001$) both had greater conflict effects than flight 1. Flight 3 ($P = 0.029$) and flight 4 ($P = 0.012$) had greater conflict effects than flight 2. **Fig. 2** shows the pattern of attention network efficiencies per altitude and flight number.

There was a significant Cue × Congruence interaction for accuracy [$F(3.978,91.502) = 6.289$, $P = 0.00016$, $\eta_p^2 = 0.215$]. When flankers were incongruent, spatial cue accuracy exceeded that of the center and no cue conditions (both $P <$ 0.005), and double cues were more accurate than center cues ($P = 0.001$). When flankers were neutral, spatial cue accuracy exceeded that of the no cue condition ($P = 0.014$).

The main effect of Cue was significant for accuracy [$F(3,69) = 5.831$, $P = 0.001$, $\eta_p^2 = 0.202$]; spatial cue accuracy exceeded no cue ($P = 0.026$) and center cue ($P = 0.010$) accuracies, and double cue accuracy marginally exceeded center cue accuracy ($P = 0.079$). The main effect of Congruence was significant [$F(1.073,24.673) = 56.735$, $P < 0.0000001$, $\eta_p^2 = 0.712$]; congruent and neutral flanker accuracies exceeded incongruent flanker accuracy (both $P < 0.0000005$).

There was a marginal Flight × Congruence interaction for accuracy [$F(3.477,79.981) = 2.477$, $P = 0.059$, $\eta_p^2 = 0.215$] that had been significant ($P = 0.026$) prior to using the Greenhouse-Geisser test. The accuracy difference was greatest between flights when flankers were incongruent, with flight 1 exceeding flight 4 ($P = 0.016$), flight 3 ($P = 0.078$), and flight 2 ($P = 0.013$). When flankers were neutral, flight 1 accuracy exceeded flight 2 ($P = 0.030$) and flight 4 ($P = 0.053$) accuracies. When flankers were congruent, flight 1 accuracy was only marginally higher than both flight 2 ($P = 0.057$) and flight 4 ($P = 0.062$) accuracies.

The main effect of Flight for accuracy was marginal [$F(1.479,34.006) = 2.345$, $P = 0.081$, $\eta_p^2 = 0.093$]; accuracies in flight 4 ($P = 0.073$) and flight 2 ($P = 0.070$) were marginally lower than in flight 1. However, after using the Greenhouse-Geisser test, this effect became nonsignificant ($P = 0.124$). **Fig. 3** shows the mean accuracy for each cue and congruence type for each flight in the SL and CA conditions.

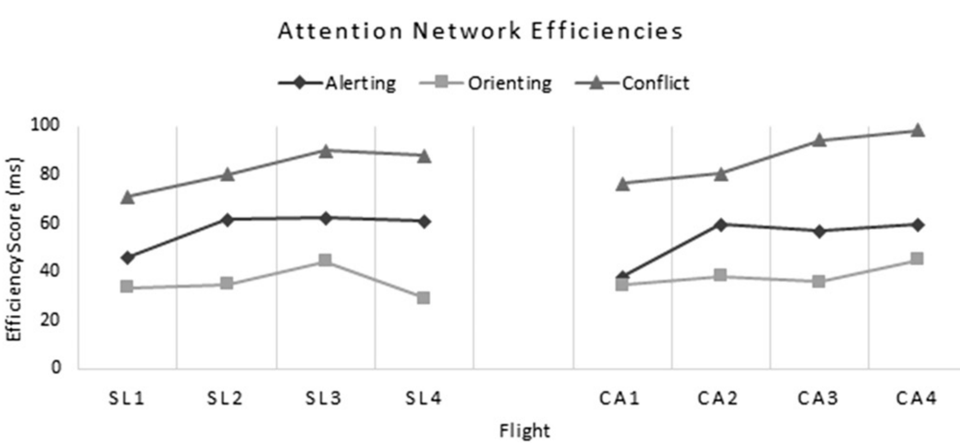

Fig. 2. Attention network efficiencies by altitude and flights. Higher alerting and orienting scores indicate greater efficiencies, while higher conflict scores indicate lower efficiencies.

For RT on the ANT, a significant Cue × Congruence interaction [$F(6,138) = 32.381$, $P < 0.0000001$, $\eta_p^2 = 0.585$] indicated that the RTs of all four cue types significantly differed from each other within each congruence type (all $P < 0.002$). There was a significant Flight × Congruence interaction for RT [$F(6,138) = 7.266$, $P < 0.0000001$, $\eta_p^2 = 0.240$]. In all flights, the RT of the incongruent flankers exceeded those of the neutral and congruent flankers (all $P < 0.0000001$), with increasing differences as flights advanced.

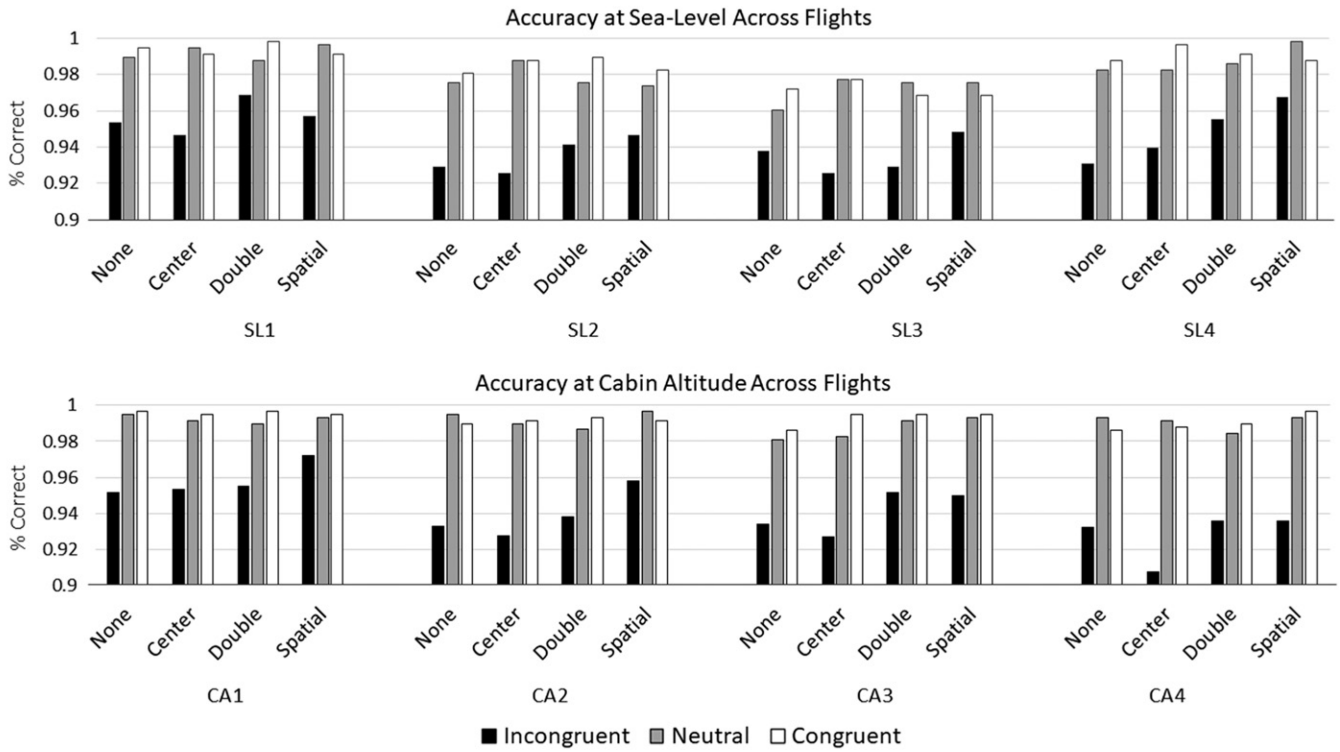

Fig. 3. Accuracy (in proportion correct) for flights at SL (top) and CA (bottom).

Additionally, congruent flanker RT exceeded neutral flanker RT in all four flights (all $P < 0.00001$).

There was a significant Flight × Cue interaction for RT [$F(4.825,110.971) = 3.402$, $P = 0.007$, $\eta_p^2 = 0.129$]. In flight 1, spatial cue RT was less than those of the other three cue conditions. In flights 2, 3, and 4, all cue pairs were significantly different (all $P < 0.003$), in addition to center cue RT exceeding double cue RT ($P < 0.006$).

A significant main effect of Flight [$F(2.360,54.286) = 5.699$, $P = 0.004$, $\eta_p^2 = 0.199$] indicated that RTs of flight 3 ($P = 0.036$) and flight 4 ($P = 0.010$) both exceeded flight 1 RT. A significant main effect of Cue [$F(2.007,46.152) = 212.604$, $P < 0.0000001$, $\eta_p^2 = 0.902$] indicated that the RTs of all pairs of cue conditions differed (all $P < 0.0005$). A significant main effect of Congruence [$F(2,46) = 566.150$, $P < 0.0000001$, $\eta_p^2 = 0.961$] indicated that the RTs of all pairs of congruence conditions differed (all $P < 0.0000001$).

Table II shows the descriptive statistics for each attention network efficiency, in addition to overall mean accuracy and RTs for each flight at each altitude. **Fig. 4** shows the mean RT for each cue and congruence type for each flight in the SL and CA conditions. Finally, **Table III** shows mean accuracy and RT values for the Congruence × Cue interaction, Flight × Congruence interaction, and main effects of Cue and Congruence.

Antisaccade Task

For overall accuracy, there was a significant main effect of Flight [$F(1.798,41.347) = 21.828$, $P < 0.0000001$, $\eta_p^2 = 0.487$]. The mean accuracies for flight 2 ($P = 0.00004$), flight 3 ($P = 0.00009$), and flight 4 ($P = 0.00024$) all exceeded flight 1 accuracy. Bivalent accuracy also indicated a significant main effect of Flight [$F(1.460,33.571) = 4.267$, $P = 0.033$, $\eta_p^2 = 0.156$], where flight 2 exceeded flight 1 ($P = 0.037$). Overall RT indicated a significant main effect of Flight [$F(3,69) = 10.965$, $P = 0.000006$, $\eta_p^2 = 0.323$]. The mean RTs for flight 2, flight 3, and flight 4 were all lower than that of flight 1 (all $P < 0.005$). **Table IV** shows mean accuracy and RT values for each flight at each altitude, as well as for each altitude and flight overall on the antisaccade task.

DISCUSSION

At both altitudes, the alerting network was characterized by initial improvement across flights before plateauing, possibly reflecting a learning effect, which is consistent with prior research involving fatigue.[16] Examination of Fig. 4 shows that after flight 1, RT for the no cue condition increased more sharply than double cue RT, suggesting that subjects benefitted from the larger attentional field created by the double cues as fatigue accrued.

Orienting scores were affected by fatigue differently depending on altitude, with superior efficiency in CA flights in the last flight of the daily cycle. At SL, center cue processing leveled off at SL3 while spatial cue processing continued to slow. Conversely, at CA, spatial cue processing quickened in the midst of decelerating center cue processing. Thus, ability to take advantage of spatial information to efficiently direct attention

Table II. ANT Network Efficiencies and Overall Performance.

	ALTITUDE × FLIGHT MEAN (SD)				
FLIGHT	ALERTING	ORIENTING	CONFLICT	OVERALL ACCURACY	OVERALL RT
SL1	46.0 (34.9)	33.5 (17.2)	71.0 (20.8)	0.981 (0.020)	502 (82)
SL2	61.4 (31.8)	35.0 (21.6)	80.0 (27.0)	0.966 (0.040)	523 (93)
SL3	62.2 (31.0)	44.4 (23.5)	90.0 (19.7)	0.960 (0.083)	538 (94)
SL4	61.0 (36.4)	29.0 (18.1)	87.8 (21.7)	0.975 (0.019)	538 (96)
CA1	37.9 (29.5)	34.5 (15.8)	76.4 (29.8)	0.982 (0.014)	507 (76)
CA2	59.4 (27.5)	38.2 (22.6)	80.5 (22.3)	0.974 (0.019)	514 (72)
CA3	56.9 (30.7)	36.0 (24.3)	94.4 (24.1)	0.973 (0.014)	521 (84)
CA4	59.6 (34.7)	44.9 (25.0)	98.3 (19.8)	0.970 (0.027)	520 (72)
	MAIN EFFECTS MEAN (SE)				
SL	57.7 (6.1)	35.4 (2.6)	82.2 (3.0)	0.971 (0.007)	525 (17)
CA	53.5 (4.7)	38.4 (3.2)	87.4 (3.7)	0.975 (0.003)	516 (15)
Flight 1	42.0 (5.0)	34.0 (2.7)	73.7 (4.6)	0.981 (0.003)	504 (16)
Flight 2	60.4 (4.5)	36.5 (3.3)	80.3 (4.1)	0.970 (0.005)	519 (16)
Flight 3	59.6 (5.6)	40.2 (4.0)	92.2 (3.8)	0.967 (0.009)	530 (18)
Flight 4	60.3 (4.7)	37.0 (3.5)	93.0 (3.7)	0.972 (0.004)	529 (16)

ANT: Attention Network Test; RT: reaction time; SL: sea level; CA: cabin altitude.

appeared more vulnerable to fatigue at SL, which contradicts a learning effect observed in orienting in prior research.[16] However, subjects' use of spatial cues improved under mild hypoxia, possibly due to short-term compensatory or adaptive measures used to maintain performance. The relative stability of subjective measures (e.g., fatigue, workload) across CA flights may support this theorized compensation.

Conflict network efficiency, in contrast, generally degraded across flights, signaling that fatigue increasingly compromised executive control. At SL, executive function degraded until plateauing at SL3. There was, however, worse efficiency in CA flights in general, wherein executive function steadily declined as a function of flight number, driven by slower processing of incongruent flankers relative to increased speed of processing congruent flankers, especially in the last flight of the day. Specifically, it appeared that in CA flights, RT was stable if not slightly expedited for congruent flankers, but gradually increased for incongruent flankers, thereby generating a high conflict network score. Across SL flights, however, RT generally increased for both flanker types. Further, the means in Fig. 3 illustrate a trend for decreasing incongruent flanker accuracy across CA flights, with the worst accuracy in CA4, whereas a U-shaped trend can be observed over time for SL flights. Mild hypoxia results in physiological compensation, which is

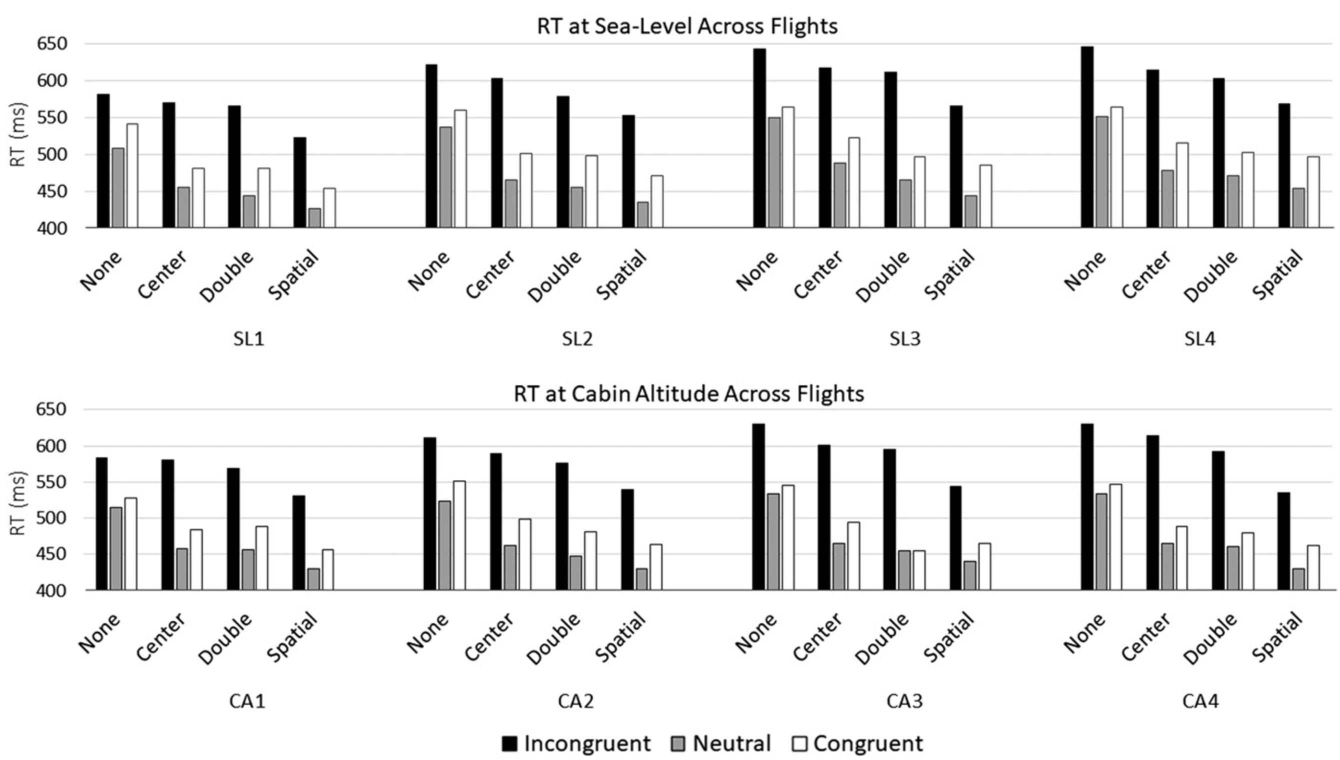

Fig. 4. RT (in ms) for each flight at SL (top) and CA (bottom).

Table III. Mean Accuracy and RT on the ANT for the Interactions and Main Effects of Congruence, Cue, and Flight.

	ACCURACY									
	PER CUE × CONGRUENCE						PER FLIGHT × CONGRUENCE			
	CUE						FLIGHT			
	NONE	**CENTER**	**DOUBLE**	**SPATIAL**	**CONGRUENCE OVERALL**		**1**	**2**	**3**	**4**
Neutral	0.984	0.987	0.985	0.990	0.986	Neutral	0.992	0.985	0.980	0.989
Congruent	0.987	0.990	0.990	0.988	0.989	Congruent	0.995	0.988	0.982	0.990
Incongruent	0.938	0.931	0.947	0.954	0.942	Incongruent	0.957	0.937	0.938	0.938
Cue Overall	0.969	0.970	0.974	0.978						
	PER FLIGHT × CUE									
Flight 1	0.980	0.979	0.983	0.984						
Flight 2	0.967	0.968	0.971	0.975						
Flight 3	0.962	0.964	0.968	0.972						
Flight 4	0.969	0.968	0.974	0.980						
	RT									
	PER CUE × CONGRUENCE						PER FLIGHT × CONGRUENCE			
	CUE						FLIGHT			
	NONE	**CENTER**	**DOUBLE**	**SPATIAL**	**CONGRUENCE OVERALL**		**1**	**2**	**3**	**4**
Neutral	531	467	457	436	473	Neutral	462	470	480	480
Congruent	550	498	489	469	502	Congruent	489	503	508	507
Incongruent	618	598	586	545	587	Incongruent	563	584	601	600
Cue Overall	566	521	511	483						
	PER FLIGHT × CUE									
Flight 1	543	505	501	470						
Flight 2	567	519	506	482						
Flight 3	577	531	519	491						
Flight 4	578	529	518	491						

RT: reaction time; ANT: Attention Network Test.
All SEs for accuracy are 0.01 or less. All SEs for RT are between 14–20 ms.

sympathetic-mediated,[5] and sustained sympathetic stimulation can result in fatigue, as seen in the general adaptation syndrome.[26] Thus, under mild hypoxia, compensatory mechanisms (see Petrassi et al.[23]) used to sustain performance may have been adequate for maintaining congruent flanker processing, but less so for the more difficult incongruent flanker processing. This pattern may serve as preliminary evidence for mild executive control inefficiency under mild hypoxia incurred at 8000 ft, consistent with previous research.[18] Further, the degradation observed in the present study appeared to be exacerbated by accruing exposures to altitude, a possible reflection of prefrontal cortex circuitry. The basal ganglia, which projects to the prefrontal cortex,[16] is a substrate of cognitive fatigue and vulnerable to hypoxic insults.[19]

Moreover, these results may indicate that the conflict and orienting networks have partially separate stores of attentional resources, an arrangement that particularly manifests under the duress of cumulative exposures to hypoxia, which diminish the already limited resources. Despite executive function appearing the most taxed in the last CA flight of the cycle, orienting concomitantly improved and was thus not encumbered by intensive simultaneous executive processing. In support of this

Table IV. Antisaccade Task Performance.

	ACCURACY		RT	
FLIGHT	**OVERALL MEAN (SD)**	**BIVALENT MEAN (SD)**	**OVERALL MEAN (SD)**	**BIVALENT MEAN (SD)**
SL1	0.835 (0.159)	0.960 (0.058)	618.69 (122.47)	643.33 (124.62)
SL2	0.887 (0.138)	0.969 (0.053)	578.19 (99.75)	591.47 (109.34)
SL3	0.889 (0.137)	0.969 (0.051)	598.37 (116.85)	612.26 (117.62)
SL4	0.885 (0.127)	0.959 (0.073)	585.75 (131.74)	602.36 (135.96)
CA1	0.803 (0.153)	0.952 (0.064)	614.16 (111.28)	634.11 (120.10)
CA2	0.870 (0.104)	0.974 (0.031)	576.10 (84.85)	594.99 (87.64)
CA3	0.898 (0.104)	0.969 (0.044)	562.01 (94.53)	579.98 (99.87)
CA4	0.890 (0.121)	0.970 (0.047)	560.57 (86.68)	575.22 (96.60)
MAIN EFFECTS	**MEAN (SE)**	**MEAN (SE)**	**MEAN (SE)**	**MEAN (SE)**
SL Overall	0.874 (0.027)	0.964 (0.011)	595.25 (22.79)	612.36 (23.53)
CA Overall	0.865 (0.022)	0.966 (0.008)	578.21 (18.36)	596.08 (19.64)
Flight 1 Overall	0.819 (0.024)	0.956 (0.009)	616.42 (20.90)	638.72 (21.39)
Flight 2 Overall	0.878 (0.021)	0.971 (0.007)	577.14 (18.11)	593.23 (19.17)
Flight 3 Overall	0.894 (0.021)	0.969 (0.008)	580.19 (20.59)	596.12 (21.19)
Flight 4 Overall	0.888 (0.023)	0.964 (0.010)	573.16 (21.83)	588.79 (23.30)

RT: reaction time; SL: sea level; CA: cabin altitude.

theory is prior neuroimaging research, which has attributed orienting and executive functioning to differing neural substrates.[4]

Decremented inhibition of interference in response to fatigue was also reported by Heaton et al.,[15] who administered the ANT three times within a 26-h period to sleep-deprived military personnel, and by Holtzer et al.[16] in their assessment of older adults. In contrast, however, Ishigami and Klein[17] administered the ANT once daily for 10 d (at approximately 8.6-d intervals) to young adults and reported learning effects in the conflict network as evidenced by shortened RTs for incongruent flankers over time.

Studies on the effects of acute hypoxia exposure on ANT performance are lacking, but long-term exposures have been assessed. Zhang et al.[28] reported that individuals who were raised at 4200 m (13,780 ft) exhibited impaired orienting and improved conflict efficiencies relative to those of subjects raised at lower altitudes of 2900 m and 3700 m (9514 and 12,139 ft). However, individuals raised at or near SL were not sampled for comparison. Barkaszi et al.[3] administered the ANT once per 6-wk cycle to subjects stationed in Antarctica (3233 m/10,607 ft). Over time, RTs decreased, which was attributed to practice; the alerting effect continually increased, indicating improvement in the use of cues; and the conflict effect decreased, indicating improved inhibition of interference. The attention networks may therefore respond differently to acute altitude exposures compared to longer exposures that permit adaptation. Further, changes in the conflict network over time appear to differ as a function of the interval between ANT administrations, in which multiple administrations per day may elicit degradation through fatigue, while greater spans can accommodate improvements through learning.

Consistent with Fan et al.,[10] incongruent flankers interfered with target processing to impair accuracy in general. The present results, however, further included a main effect for cue and an interaction between cue and congruence, possibly due to the added experimental stressors of fatigue and altitude. The interaction between cue and congruence indicated that in trials featuring the more difficult incongruent flankers, the informative spatial cues provided a significant accuracy benefit, and the double cue condition, which generated a larger attentional field, promoted higher accuracy over the center cue condition. These cue benefits waned, however, under the easier neutral and congruent flanker conditions. This interaction may suggest a degree of dependence among attention networks, as the influence of attentional field size and spatial cueing was greater when executive control was the most taxed. Finally, across cue and flanker conditions, accuracy somewhat declined as a function of exposure, an effect that has been similarly observed in prior fatigue research.[15,16]

Consistent with previous studies,[10,17] the results for RT indicated main effects of cue and congruence and an interaction between them. Resolution of incongruent flankers was especially protracted, notably when cues did not provide spatial information. These effects were consistent between SL and CA flights, and thus the dependence among networks suggested by this interaction appears robust to altitude and fatigue manipulations. RT globally increased as a function of fatigue, especially in resolving incongruent stimuli, an effect that was the most pronounced in the last two flights of the daily cycle. Conflicting information thus increasingly burdened the central executive as fatigue intensified. Together, the greater RT and reduced accuracy for incongruent flankers demonstrate that the conflict interfered with target processing and that among congruence conditions, incongruent flankers yielded the highest degree of difficulty.

The interaction between flight and cue indicated that as flights progressed, the larger attentional field generated by double cues may have provided an RT benefit over the central cues. Thus, when fatigued, the operator may benefit from distributing attentional resources across the entire field of possible target locations as opposed to directing attention to a specific location once the target appears.

In contrast to the ANT, performance generally improved on the antisaccade task as a function of time. A learning effect appears evident at both altitudes, wherein accuracy significantly improved after the first administration, with a trend of plateauing earlier in SL flights. While accuracy at SL1 was superior to CA1, accuracies in CA4 and SL4 were comparable, indicating a greater improvement under mild hypoxia as a function of time, though accuracy was slightly lower in CA flights overall. RTs also tended to shorten across flights, especially in CA flights. Flexible behavioral control in terms of saccadic movement was thus not vulnerable to mild hypoxia or fatigue in this task and, further, subjects appeared to refine skill despite these stressors. In an administration of a similar antisaccade assessment to subjects who had rapidly ascended to 3459 m (11,348 ft), Faull et al.[11] found no differences in saccadic latency. Both accuracy and latency have also shown imperviousness to 20 h of sleep deprivation.[7]

Most components of the ANT appear to have been minimally prone to practice or learning effects, but sensitive enough to render this instrument a generally useful measure of fatigue and hypoxia in aviators. Though some of the outcomes observed could imply the potential for compromised attentional allocation in flight, it is important to consider that these results were derived from a task that was purposefully designed for brevity and simplicity. An applied, flight deck-specific approach to assessing conflict resolution during the progression of cyclic 8000-ft exposures would serve as an informative next step in this line of research. Impairment of executive control could hinder resistance to distraction and other task interferences, timely decision-making, and reconciliation of discordant information (e.g., trusting instruments and automation decisions that disagree with beliefs or the senses). There thus exists particular application to responses to emergency scenarios, and the present results may contribute to our understanding of precipitating factors leading to accidents. Further, small effects found in this baseline study could become substantial in the context of other environmental and task factors. Finally, replicating this study using measures of cognitive adaptability to varying task requirements (e.g., card-sorting task) may also contribute to our understanding of decision-making during novel situations under cyclic hypoxia.

The protocol of four flights performed within 8 h was designed to model regional airline profiles where pilots often fly multiple short flights in a given shift. Prior studies involving long-haul flight with mild hypobaric hypoxia have shown disruption of circadian rhythm, possibly via disturbance of the pineal gland, as measured with melatonin and cortisol levels.[5] Future studies to assess the attention networks during longer exposures (e.g., long-haul flight) would be of benefit to better understand the physiological effects of fatigue. Further, an interesting consideration is that 8000 ft has been proposed as the pressure altitude equivalent for future suborbital spacecraft cabins,[2] and this understanding of baseline attentional performance may serve as an informative foundation in planning mission and cabin design characteristics with respect to the added complications imposed by extreme acceleration forces.

Limitations of this study include the possibility that the subjects, who were experienced pilots, might have been able to distinguish the pressure differences between the altitude conditions, and such awareness could have influenced motivational factors. Also, while the subjective assessments indicate increased fatigue as flights progressed, actual fatigue cannot be determined with the present experimental protocol. However, cognitive fatigue has been defined as failure of the sustained attention required for optimal task performance,[8] which was evidenced by most aspects of ANT performance across flights and, further, self-reported fatigue has been linked with degraded executive control performance in terms of speed and accuracy.[16] Finally, it has been argued that because both the alerting and orienting networks are elicited by cues which precede flanker presentation in the ANT, the variances of the attention network efficiencies may not be fully separable.[17] While the present investigation involved a visual version of the ANT, the ANT-Interactions employs auditory cues to manipulate the alerting network,[17] which might modulate the suspected learning effect observed and mitigate dependencies among the networks.

Mild hypoxia and fatigue are two pervasive stressors incurred by human operators in the aerospace environment. However, given the small difference between the simulated altitudes, coupled with previous research showing inconsistent effects of mild hypoxia exposure on cognition, it is reasonable that small and sometimes no differences were observed between altitude conditions. Subtle effects detected in this protocol, however insidious, could be potent in flight and other contexts. Fatigue can be demonstrated by a decline in performance over time,[16] which was evident in the orienting and conflict networks as flights progressed. Executive control function, as measured by proficiency of inhibiting interference to reconcile conflicting information, appears to be further degraded, albeit mildly, by frequent exposures to mild hypoxia. This study modeled what is seen in regional commercial aviation where pilots fly numerous short-leg flights within a given shift, which can modulate the overall factors that contribute to fatigue. Recreating an 8000-ft pressurization altitude equivalence in a high-altitude chamber further contributes to previous studies related to fatigue and serves as a fundamental baseline against which longer exposures, including long-haul flight, can be measured.

ACKNOWLEDGMENTS

Financial support: This research was funded by Embry-Riddle Aeronautical University for the operation expenses of the hypobaric chamber.

Authors and affiliations: Jennifer E. Thropp, Ph.D., M.S., Embry-Riddle Aeronautical University, Daytona Beach, FL, and Paul W. Buza, D.O., F.A.C.N., Southern Aeromedical Institute, Melbourne, FL.

REFERENCES

1. Aerospace Medical Association; Aviation Safety Committee; Civil Aviation Subcommittee. Cabin cruising altitudes for regular transport aircraft. Aviat Space Environ Med. 2008; 79(4):433–439.
2. Aerospace Medical Association Commercial Spaceflight Working Group. Suborbital commercial spaceflight crewmember medical issues. Aviat Space Environ Med. 2011; 82(4):475–484.
3. Barkaszi I, Takács E, Czigler I, Balázs L. Extreme environment effects on cognitive functions: a longitudinal study in high altitude in Antarctica. Front Hum Neurosci. 2016; 10:331.
4. Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven activation in the brain. Nat Rev Neurosci. 2002; 3(3):201–215.
5. Coste O, Beaumont M, Batéjat D, Van Beers P, Touitou Y. Effects of mild hypoxia on circadian time structure during long duration flights in man. In: Strategies to maintain combat readiness during extended deployments – a human systems approach. Proceedings of the Human Factors and Medicine Panel Symposium. Neuilly-sur-Seine (France): NATO RTO; 2005:25-1–25-14.
6. Cottrell JJ, Lebovitz BL, Fennel RG, Kohn GM. In-flight arterial saturation: continuous monitoring by pulse oximetry. Aviat Space Environ Med. 1995; 66(2):126–130.
7. Crevits L, Simons B, Wildenbeest J. Effect of sleep deprivation on saccades and eyelid blinking. Eur Neurol. 2003; 50(3):176–180.
8. DeLuca J. Fatigue, cognition, and mental effort. In: DeLuca J, editor. Fatigue as a window to the brain. Cambridge (MA): MIT Press; 2005:319–325.
9. Derakshan N, Ansari TL, Hansard M, Shoker L, Eysenck MW. Anxiety, inhibition, efficiency, and effectiveness. Exp Psychol. 2009; 56(1):48–55.
10. Fan J, McCandliss BD, Sommer T, Raz A, Posner MI. Testing the efficiency and independence of attentional networks. J Cogn Neurosci. 2002; 14(3):340–347.
11. Faull OK, Robertson J, Thomas O, Bradwell AR, Antoniades CA, Patterson KTS. The effect of acetazolamide on saccadic latency at 3459 meters. Wilderness Environ Med. 2015; 26(1):72–77.
12. Federal Aviation Administration. Pressurized cabins. Washington (DC): FAA; 2006. 14 CFR Part 25.841.
13. Hallett PE. Primary and secondary saccades to goals defined by instructions. Vision Res. 1978; 18(10):1279–1296.
14. Hart SG, Staveland LE. Development of NASA-TLX (Task Load Index): results of empirical and theoretical research. In: Hancock PA, Meshkati N, editors. Advances in Psychology: human mental workload, vol. 52. Amsterdam: North Holland Press; 1988:139–183.
15. Heaton KJ, Maule AL, Maruta J, Kryskow EM, Ghajar J. Attention and visual tracking degradation during acute sleep deprivation in a military sample. Aviat Space Environ Med. 2014; 85(5):497–503.
16. Holtzer R, Shuman M, Mahoney JR, Lipton R, Verghese J. Cognitive fatigue defined in the context of attention networks. Aging Neuropsychol Cogn. 2011; 18(1):108–128.
17. Ishigami Y, Klein RM. Repeated measurement of the components of attention using two versions of the Attention Network Test (ANT):

stability, insolability, robustness, and reliability. J Neurosci Methods. 2010; 190(1):117–128.
18. Legg SL, Hill S, Gilbey A, Raman A, Schlader Z, Mündel T. Effect of mild hypoxia on working memory, complex logical reasoning, and risk judgment. Int J Av Psych. 2014; 24(2):126–140.
19. Lieberman P, Protopapas A, Reed E, Youngs JW, Kanki BG. Cognitive defects at altitude. Nature. 1994; 372(6504):325.
20. Munoz DP, Everling S. Look away: the anti-saccade task and the voluntary control of eye movement. Nat Rev Neurosci. 2004; 5(3):218–228.
21. National Research Council, Committee on Air Quality in Passenger Cabins of Commercial Aircraft. The airliner cabin environment and the health of passengers and crew. Washington (DC): National Academy Press; 2002. [Accessed May 2018]. Available from http://nap.edu/10238.
22. Nesthus TE, Rush LL, Wreggit SS. Effects of mild hypoxia on pilot performances at general aviation altitudes. Final Report. Oklahoma City (OK): Civil Aeromedical Institute; 1997. Report No.: DOT/FAA/AM-97/9.
23. Petrassi FA, Hodkinson PD, Walters PL, Gaydos SJ. Hypoxic hypoxia at moderate altitudes: review of the state of the science. Aviat Space Environ Med. 2012; 83(10):975–984.
24. Samn S, Perelli L. Estimating aircrew fatigue: a technique with application to airlift operations. Final Report. Brooks AFB (TX): USAF Aerospace Medical Division, U.S. Air Force School of Medicine; 1982. Report No.: SAM-TR-82-21.
25. Schaeffer DJ, Amlung MT, Li Q, Krafft CE, Austin BP, et al. Neural correlates of behavioral variation in healthy adults' antisaccade performance. Psychophysiol. 2013; 50(4):325–333.
26. Selye H. The general adaptation syndrome. Annu Rev Med. 1951; 2(1):327–342.
27. Taylor L, Watkins SL, Marshall H, Dascombe BJ, Foster J. The impact of different environmental conditions on cognitive function: a focused review. Front Physiol. 2016; 6:372.
28. Zhang D, Zhang X, Ma H, Wang Y, Ma H, Liu M. Competition among the attentional networks due to resource reduction in Tibetan indigenous residents: evidence from event-related potentials. Sci Rep. 2018; 8(1):610.