A Novel Method to Measure Transient Impairments in Cognitive Function During Acute Bouts of Hypoxia

Koji Uchida; Sarah E. Baker; Chad C. Wiggins; Jonathon W. Senefeld; John R. A. Shepherd; Max R. Trenerry; Zachary A. Buchholtz; Haider R. Clifton; David R. Holmes; Michael J. Joyner; Timothy B. Curry

INTRODUCTION: Exposure to low oxygen environments (hypoxia) can impair cognitive function; however, the time-course of the transient changes in cognitive function is unknown. In this study, we assessed cognitive function with a cognitive test before, during, and after exposure to hypoxia.

METHODS: Nine participants (28 ± 4 yr, 7 women) completed Conner's Continuous Performance Test (CCPT-II) during three sequential conditions: 1) baseline breathing room air (fraction of inspired oxygen, $F_IO_2 = 0.21$); 2) acute hypoxia ($F_IO_2 = 0.118$); and 3) recovery after exposure to hypoxia. End-tidal gas concentrations (waveform capnography), heart rate (electrocardiography), frontal lobe tissue oxygenation (near infrared spectroscopy), and mean arterial pressure (finger photoplethysmography) were continuously assessed.

RESULTS: Relative to baseline, during the hypoxia trial end-tidal (-30%) and cerebral (-9%) oxygen saturations were reduced. Additionally, the number of commission errors during the CCPT-II was greater during hypoxia trials than baseline trials (2.6 ± 0.4 vs. 1.9 ± 0.4 errors per block of CCPT-II). However, the reaction time and omission errors did not differ during the hypoxia CCPT-II trials compared to baseline CCPT-II trials. During the recovery CCPT-II trials, physiological indices of tissue hypoxia all returned to baseline values and number of commission errors during the recovery CCPT-II trials was not different from baseline CCPT-II trials.

DISCUSSION: Oxygen concentrations were reduced (systemically and within the frontal lobe) and commission errors were increased during hypoxia compared to baseline. These data suggest that frontal lobe hypoxia may contribute to transient impairments in cognitive function during short exposures to hypoxia.

KEYWORDS: executive function, altitude, NIRS, cognitive test.

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A constant supply of oxygen is essential for normal cognitive processes, and it has been demonstrated that highly concentrated oxygen can acutely enhance cognitive performance.[4,11] Conversely, low concentrations of oxygen (i.e., hypoxia) can cause a reduction in cognitive performance.[2,13,15] This reduction in cognitive performance is a chief concern in occupations that involve duties in hypoxic environments such as aerial space or high terrestrial altitude, particularly among aircraft pilots in whom a reduction in cognitive performance can have serious and potentially fatal implications.[3] In laboratory settings, impairments in cognitive function generally occur while breathing fractions of inspired oxygen (F_IO_2) that closely simulate inspired oxygen partial pressures equivalent to altitudes of ~4572 m (15,000 ft) or more.[8,13]

Various cognitive functions are inhibited due to hypoxia, including indices imperative for safe and successful flight performance such as maintaining air speed and altitude,[14] accurately identifying targets,[3] performing arithmetic tasks[1] and central executive tasks,[17] and more generally executive function.[2,9] Given the fast navigation speeds of aircrafts at altitude, the transient impairments in executive function can quickly and directly increase risk of serious and/or fatal accidents.[10] Thus, a highly sensitive method for early detection of these impairments in executive function is needed to mitigate and

From the Departments of Anesthesiology and Perioperative Medicine, Psychiatry and Psychology, and Physiology and Biomedical Engineering, Mayo Clinic, Rochester, MN.

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Address correspondence to: Timothy B. Curry, Ph.D., Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, MN; curry.timothy@mayo.edu.

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prevent hypoxia-related accidents. Accordingly, it is important to understand how cognitive function changes from the onset of hypoxic exposure until deterioration of cognitive function. However, there are limited data describing cognitive adaptations during the onset of hypoxia,[2,12,14] and these data may have broad implications for mitigating safety risks during hypoxia.

Accordingly, the objective of this study was to determine transient impairments in cognitive function during acute bouts of hypoxia using a short-duration cognitive task. To our knowledge, this is the first study to focus on transient changes of executive function during hypoxia using a cognitive task with high temporal resolution. We hypothesized that: 1) exposure to low fraction of inspired oxygen (11.8%) would induce systemic and frontal lobe hypoxia; 2) executive function would be impaired during hypoxia; and 3) the reduction in executive function could be detected with a short-duration (140 s) cognitive task.

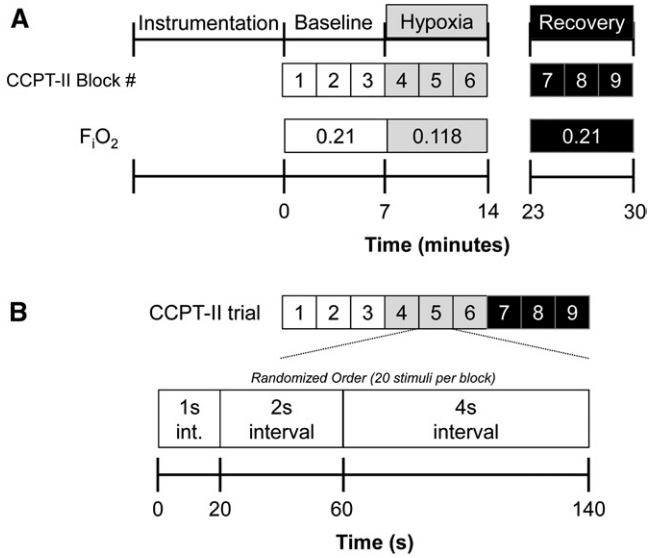

Fig. 1. Schematic of the experimental protocol. A.) Schematic showing the experimental session and B.) one block of the Conner's Continuous Performance Test II (CCPT-II).

METHODS

Subjects

Nine healthy, young participants (two men and seven women; age, 28 ± 4 yr; weight: 67.8 ± 7.6 kg; height: 166 ± 8 cm) completed the study. All subjects were right-handed, nonsmoking, nonobese (BMI $< 30\ kg \cdot m^{-2}$), normotensive (resting systolic blood pressure: 113 ± 12 mmHg and diastolic blood pressure: 63 ± 10 mmHg), healthy adults. Prior to involvement, each participant provided written informed consent. All experiments/procedures were approved by the Institutional Review Board at Mayo Clinic and were in accordance with the Declaration of Helsinki.

Procedure

Participants completed one experimental session. Participants abstained from food for 8 h and abstained from caffeine, alcohol, and vigorous exercise for 24 h prior to the experimental session. Upon arriving to the laboratory in the morning and after consent, height and weight were measured, BMI was calculated, and blood pressure was auscultated. Participants then consumed a standard breakfast—260 kcal energy bar and 250 mL of water—at least 30 min prior to the initiation of experimental measurements.

Following instrumentation and familiarization (as described below and depicted in **Fig. 1**), participants performed two sets of the Conner's Continuous Performance Test (CCPT-II). Each set of the CCPT-II included six blocks (140 s each; 14 min total) and the two sets of the CCPT-II were initiated at minute 0 and minute ~16. Thus, in total 12 blocks of the CCPT-II were performed under the following conditions: 1) baseline (blocks 1-3); 2) hypoxia (blocks 4-6); 3) transition period (blocks 7-9); and 4) recovery (blocks 10-12), as described below. The first three blocks of the CCPT-II (blocks 1–3) were baseline measures, performed while breathing room air (F_IO_2 = 21.0%). Immediately after completing the third block of the CCPT-II, a two-way nonrebreathing switching valve was flipped to a gas reservoir (meteorological balloon) containing hypoxic air (11.8% oxygen, balance nitrogen). The subsequent three blocks of the CCPT-II (blocks 4–6) were performed while inspiring the hypoxic air (F_IO_2 = 11.8%). After completing the sixth block of the CCPT-II, the next set of the CCPT-II was initiated after a ~2 min break to reinitiate the software and perform the standard familiarization trial of the CCPT-II (as described below). Because there was interindividual variability in the duration of this break period, the hypoxic air was continuously inspired until 3 min after cessation of the sixth block of the CCPT-II and on average the seventh block of the CCPT-II was performed for 1 min while inspiring hypoxic air. At minute 17, the two-way switching valve was flipped to room air. Participants continued the CCPT-II until minute 30.

During the first three blocks of the second set of the CCPT-II (blocks 7–9), hypoxic air was inspired for ~1 min and end-tidal expiration concentrations of oxygen remained suppressed for ~6 min. Because blocks 7–9 represent a physiological transition period from hypoxia back to normoxia, which had substantial interindividual variability, blocks 10–12 were analyzed as the recovery period (see Fig. 1A).

Materials

Two sets of the CCPT-II (12 blocks total) were performed by participants as a cognitive test. As described elsewhere,[5,18] the CCPT-II is used for the evaluation of attention, as well as the response inhibition component of executive function. Briefly, participants were instructed to press the spacebar key on a standard QWERTY keyboard when any letter appeared on a standard laptop computer monitor (14-inch monitor placed approximately 1.5 m away at eye level) except the letter "X". In the case of the letter "X", participants were instructed to not press the spacebar key. Each letter appeared in the same font, size, and position on the computer monitor for 250 ms. All participants were naive to the CCPT-II and were provided

standard instructions for completion of the CCPT-II including to perform the test "as quickly and accurately as possible." There were two primary types of errors that were possible during the CCPT-II test—commission and omission errors. In the instance that the letter "X" appeared on the monitor and the participant pressed the spacebar, this was considered a commission error. In the instance that any letter except "X" appeared and the participant failed to press the spacebar key, this was considered an omission error. Reaction time was measured from the point at which any letter appears on the screen until the spacebar key was pressed.

The CCPT-II required precisely 140 s for completion of one individual block. Each trial of the CCPT-II encompassed three subblocks of 20 trials (presentation of one letter). The three subblocks differed in the duration of the interstimulus interval, which lasted 1, 2 or 4 s between stimulus/letter. The three subblocks of different interstimulus interval were presented in a random order within each block. Within each subblock of 20 trials the letter "X" appeared only twice, thus, for each CCPT-II block (consisting of three subblocks), there were six possible commission errors. The number of commission errors, omission errors and average of reaction time in each trial were obtained from conventional analyses report of the CCPT-II (see Fig. 1B).

As a familiarization, participants rested semisupine in a hospital bed throughout the experimental protocol. After instrumentation (as described below), participants rested quietly for 10 min. To prevent a learning effect, participants then completed a standard familiarization trial of the CCPT-II which included presentation of 10 letters for each of the 3 possible blocks (1, 2, and 4 s interstimulus interval)—i.e., 50% of the standard CCPT-II block. After familiarization, participants began the first CCPT-II trial.

As an instrumentation, participants wore a mask connected to a two-way nonrebreathing valve for administration of gases and to allow for continuous measurement of expired volume (Universal Ventilation Meter, Ventura, CA), breathing frequency, and inspired/expired oxygen and carbon dioxide (Cardiocap/5, Datex-Ohmeda, Louisville, CO). Heart rate (HR) and peripheral oxygen saturation (S_pO_2) were monitored with electrocardiography and pulse oximetry, respectively (Cardiocap/5). Arterial blood pressure (BP) was monitored noninvasively using finger photoplethysmography (Nexfin, Edwards LifeSciences Corporation, Irvine, CA). During hypoxia, participants breathed air from a gas reservoir (meteorological balloon) containing hypoxic air (11.8% oxygen, balance nitrogen) that simulated ~4572 m (15,000 ft) of terrestrial altitude.

Frequency domain, multidistance near-infrared spectroscopy (NIRS) (Oxiplex TS, ISS Inc., Champaign, IL) was used in vivo to noninvasively estimate the volume of heme-O_2 carriers (tissue oxygenation) in the frontal lobe.[6] The device probe was placed on the surface of the forehead approximately 2 cm above the left eyebrow. The device probe was affixed with an elastic headband that covered the probe completely to prevent ambient light from disrupting signal acquisition, and the headband was tightly secured to prevent movement of the probe relative to the forehead throughout the experimental protocol. Changes in local oxygenated ([OxyHb+Mb]) and deoxygenated ([DeoxyHb+Mb]) hemoglobin/myoglobin concentrations were obtained using the multidistance spectrophotometer. Briefly, in this technique a near-infrared light is transmitted by fiber optic cable to a photon detector at standard distances from the light sources (2.0, 2.5, 3.0, and 3.5 cm). Each of the four light sources emit light at two different wavelengths (8 total diodes), 690 nm and 830 nm, corresponding to the absorbance and reduced scattering coefficients of [OxyHb+Mb] and [DeoxyHb+Mb], respectively. Based on the absorption and scattering coefficients of light at each wavelength (Beer-Lambert Law), OxyHb+Mb and DeoxyHb+Mb concentrations were then calculated. Total hemoglobin and myoglobin ([Total Hb+Mb]) concentration was calculated by adding the concentrations of OxyHb+Mb and DeoxyHb+Mb, and tissue saturation (rSo_2) was calculated as the quotient of [OxyHb+Mb] (numerator) and [Total Hb+Mb] (denominator) multiplied by 100%. Data were digitized (5 Hz) by an analog-to-digital converter (Analog Output Module, ISS Inc., Champaign, IL) and transmitted online to the data acquisition software (PowerLab, AD Instruments, Colorado Springs, CO).

Statistical Analysis

Expired airflow, end-tidal partial pressure of oxygen ($P_{ET}o_2$), end-tidal partial pressure of carbon dioxide ($P_{ET}co_2$), HR, finger plesmography, and NIRS data were collected using a 16-channel analog-to-digital data acquisition system (PowerLab, ADInstruments, Colorado Springs, CO), sampled at 1000 Hz, then recorded using compatible software (LabChart 8.1.13, ADInstruments). Prior to statistical comparisons, assumptions of normality were confirmed with Shapiro-Wilks tests and assumptions of homoscedasticity were confirmed with Levene's Test. The number of omission errors was not considered a Normal distribution according to the Shaprio-Wilks test ($P = 0.020$). Additionally, the number of commissions errors did not have equal variance (i.e., heteroscedasticity) according to the Levene's Test ($P = 0.018$), and thus, was analyzed using a nonparametric statistical test—Friedman repeated measures ANOVA on ranks and the Dunnett's test.

For all other data (normal and homoscedastic data), to determine the changes between conditions (baseline, hypoxia, recovery), separate univariate analyses of variance (ANOVAs) were used. One-way repeated measure ANOVA with Bonferroni post hoc tests were used for comparison within the group and between the groups. The a priori level of significance for all statistical comparisons was $P < 0.05$ except post hoc testing with Bonferroni corrections ($P < 0.025$), and all the analyses were performed in IBM Statistical Package for Social Sciences version 25 (SPSS, IBM Corp., Armonk, NY). Data are reported as mean ± SD in the text and displayed as mean ± SEM in the figures.

RESULTS

Physiological indices of tissue oxygenation, blood pressure, minute ventilation, and heart rate during baseline (minute

0–7), the first minute of the hypoxia stimulus (minute 7), the last minute of the hypoxia stimulus during the CCPT-II (minute 14), and the mean during the hypoxia stimulus during the CCPT-II (minute 7–14) are displayed in **Table I**. Relative to baseline and as expected, there were relative reductions in tissue oxygenation while inspiring hypoxic air ($F_IO_2 = 0.118$), including a 45% reduction in end-tidal partial pressure of oxygen ($P_{ET}O_2$; $P < 0.001$), 6% reduction in end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$; $P < 0.001$), 9% reduction in peripheral capillary oxygen saturation (S_pO_2; $P < 0.001$), and 10% reduction in frontal lobe oxygen saturation (rSO_2; $P < 0.001$). Additionally, heart rate (HR) increased by 16% ($P = 0.006$) and minute ventilation ($\dot{V}_E$) increased by 10% ($P = 0.009$) while inspiring hypoxic air; however, there was no change in mean arterial pressure (MAP; $P = 0.494$). The physiological changes while inspiring hypoxic air were progressive and the changes were larger in magnitude at minute 14 compared with minute 7, including the reductions in $P_{ET}O_2$ ($P < 0.001$), $P_{ET}CO_2$ ($P = 0.017$), S_pO_2 ($P < 0.001$) and rSO_2 ($P < 0.001$), and the increases in HR ($P = 0.004$).

These physiological indices reverted to baseline values during the recovery period, and thus, there were no differences between baseline and recovery for $P_{ET}O_2$, $P_{ET}CO_2$, S_pO_2 and rSO_2, HR, $\dot{V}_E$, or MAP (all, $P > 0.05$) (Table I).

During each condition (baseline, hypoxia, and recovery), three blocks of the CCPT-II were performed. Each index of cognitive function (reaction time, commission errors, and omission errors) did not differ between the three trials within each condition; therefore, the data were aggregated between the three blocks for analyses. Mean reaction time was not different between the three conditions (baseline vs. hypoxia vs. recovery, $P = 0.381$; **Fig. 2A**). Similarly, the mean number of omission errors did not differ between the three conditions ($P = 0.814$; **Fig. 2B**). However, the mean number of commission errors was greater during hypoxia compared to baseline ($P = 0.031$; **Fig. 2C**). There were no differences in commission errors between the other conditions (baseline vs. recovery, $P > 0.05$). **Fig. 3** displays the time-resolved results of CCPT-II and Fig. 2 displays the aggregate data. Data for the transition period are similar to the recovery period and are not displayed in Fig. 2.

For each block of CCPT-II, there were three distinct interstimulus intervals (1, 2, or 4 s) with 20 stimuli/letters each. The number of commission and omission errors did not differ between the three interstimulus intervals ($P > 0.361$). However, the reaction time was less (i.e., faster) during the sub-blocks with the shortest interstimulus interval (1 s) compared to 4-s interstimulus interval ($P < 0.001$). There were no interactions of interstimulus interval and hypoxia. Thus, although the reaction time differed between distinct interstimulus interval subblocks, these differences were not exacerbated during the hypoxia CCPT-II blocks.

DISCUSSION

The primary finding of this study was that executive function was impaired during an acute bout of hypoxia as assessed during a continuous cognitive performance test. Using a continuous test starting at the onset of hypoxia allowed for a better understanding of the time course of change in cognitive function during hypoxia. These data may have broad implications for mitigating safety risks, particularly during the early stages of hypoxia exposure.

As far as we know, this is the first study which focused on time-resolved changes of executive function during acute hypoxic exposure. With the fast navigation speeds in aircraft, cognitive impairments can quickly and directly increase the risk of serious accidents. Therefore, understanding the time-course of the transient changes in cognitive function is important as it may mitigate risk of aircraft accidents. These data demonstrate continuous and progressive impairments of cognitive and physiological indices within several minutes of exposure to hypoxia. These data confirmed the cognitive deterioration within 7 min and improved the time resolution of a cognitive test considerably. These data support our hypothesis that exposure to an acute bout of hypoxia deteriorates executive function, and that it is, in fact, plausible to detect these abrupt changes with acute hypoxic exposure. Although we confirmed a transient change of executive function, a potential weakness of the study is a relatively low time resolution (~7 min) for fast navigation speeds of aircrafts at altitude. Future investigations may interrogate executive function with greater time resolution by using a higher number of stimuli or lower interstimulus interval during a test of cognitive function to elucidate more

Table I. Physiological Responses to Fraction of Inspired Oxygen.

	BASELINE	HYPOXIA (11.8% F_IO_2)					RECOVERY
VARIABLE (UNITS)	min 0–7	min 7–14	Δ HYPOXIA - BASELINE (%)	min 7	min 14	Δ min 14 – min 7(%)	min 23–30
$P_{ET}O_2$ (mmHg)	106 ± 3	58 ± 3*	-45	74 ± 4	52 ± 4‡	-30	104 ± 3†
$P_{ET}CO_2$ (mmHg)	34 ± 3	32 ± 2*	-6	34 ± 3	32 ± 3‡	-5	33 ± 3†
$\dot{V}_E$ (L·min^{-1})	8.5 ± 2.2	9.7 ± 1.7*	10	9.8 ± 2.0	9.1 ± 2.3	-5.7	8.3 ± 2.3†
HR (bpm)	68 ± 11	79 ± 10*	16	72 ± 12	82 ± 9‡	15	67 ± 12†
MAP (mmHg)	87 ± 10	88 ± 10	1	87 ± 10	89 ± 11	3	88 ± 10
S_pO_2 (%)	99 ± 1	90 ± 3*	-9	98 ± 1	85 ± 4‡	-13	99 ± 1†
rSO_2 (%)	73 ± 8	66 ± 9*	-10	72 ± 8	66 ± 9‡	-9	73 ± 8†

$P_{ET}O_2$, end-tidal partial pressure of oxygen; $P_{ET}CO_2$, end-tidal partial pressure of carbon dioxide; $\dot{V}_E$, minute ventilation; HR, heart rate; MAP, mean arterial pressure; S_pO_2, peripheral capillary oxygen saturation; rSO_2, frontal lobe oxygen saturation. Data are displayed as mean ± SD.

* Denotes change from baseline, $P < 0.05$. † Denotes change from hypoxia; ‡ denotes change from min 7, $P < 0.05$.

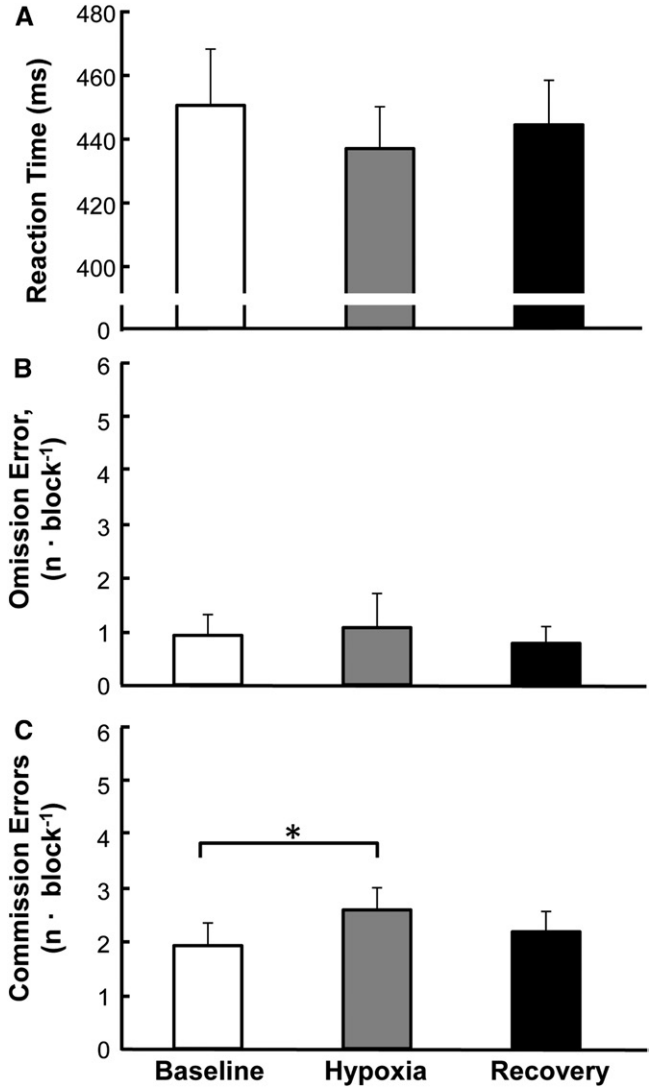

Fig. 2. Aggregate reaction time and errors during the CCPT-II. Group data for A.) reaction time, B.) omission errors, and C.) commission errors for Baseline, Hypoxia and Recovery state during the Conner's Continuous Performance Test II (CCPT-II). Group data are displayed as mean ± SE; *denotes increase from baseline; $P < 0.05$.

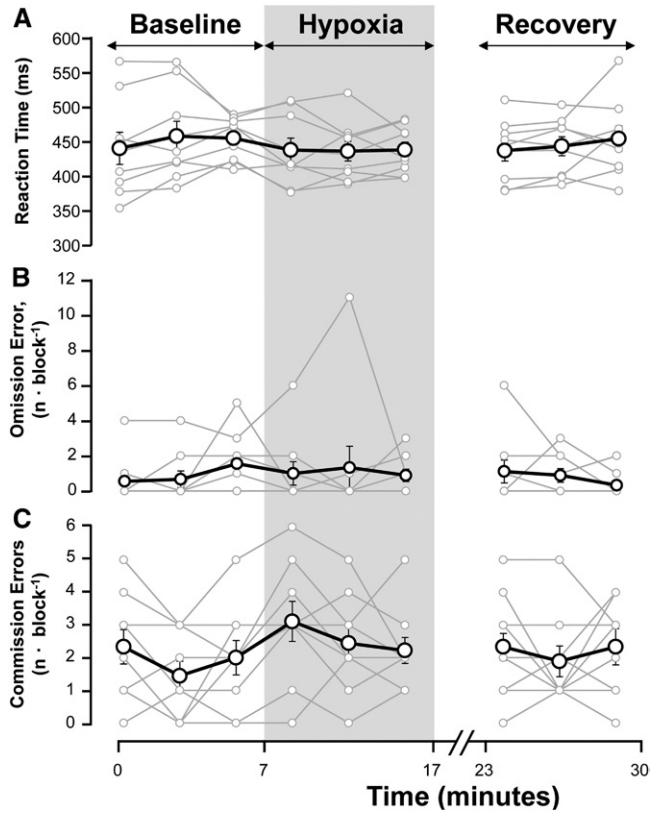

Fig. 3. Time-resolved reaction time and errors during the CCPT-II. Group (black) and individual (gray) A.) reaction times, B.) omission errors, and C.) commission errors during measurement. Group data are displayed as mean ± SE.

precise changes of cognitive function during hypoxia. Also, actual flight in the cockpit requires multitasking such as targeting or teamworking, which use various regions of the brain. Hence, the impact of hypoxia might differ between in the cockpit and a single cognitive test in this study. If we could adopt a continuous multitasking cognitive test, we would be able to evaluate the initial deterioration of flight performance during acute bouts of hypoxia more precisely.

In the present study, we used a simple Go/No-go test and we demonstrated a similar decline in systemic oxygen (S_pO_2) and frontal lobe oxygenation (rSO_2) as reported previously in similar studies interrogating peripheral[3,7,17] and cerebral tissues.[3,17] A recent meta-analysis by McMorris et al.[8] showed that a reduction in P_aO_2 to a level less than 60 mmHg resulted in worsened cognitive performance. Similarly, we found that the number of commission errors, which indicate failure to inhibit an incorrect response, significantly increased during hypoxia ($P_{ET}O_2 = 58$ mmHg). Thus, our data align with this recent meta-analysis even during transient hypoxia. The mechanisms contributing to cognitive deterioration are unknown. However, the frontal lobe is primarily responsible for executive function,[16] thus, we posit that hypoxia within the frontal lobe is a contributing factor to impaired executive function. In conclusion, acute exposure to low fraction of inspired oxygen (11.8% oxygen) resulted in a transient decline in executive function observed during the hypoxic stimulus which quickly recovered when room air was inspired.

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Authors and affiliations: Koji Uchida, M.D., Ph.D., Sarah E. Baker, Ph.D., Chad C. Wiggins, Ph.D., Jonathon W. Senefeld, Ph.D. John R. A. Shepherd, M.D.,

Zachary A. Buchholtz, B.A., Michael J. Joyner, M.D., and Timothy B. Curry, M.D., Ph.D., Department of Anesthesiology and Perioperative Medicine, Mayo Clinic Rochester, MN; Max R. Trenerry, Ph.D., Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN; and Haider R. Clifton, Ph.D., and David R. Holes, Ph.D., Department of Physiology and Biomedical Engineering, May Clinic, Rochester, MN.

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