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Assessment of the interaction of hyperbaric N_2, CO_2, and O_2 on psychomotor performance in divers

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Freiberger JJ, Derrick BJ, Natoli MJ, Akushevich I, Schinazi EA, Parker C, Stolp BW, Bennett PB, Vann RD, Dunworth SA, Moon RE. Assessment of the interaction of hyperbaric N_2, CO_2, and O_2 on psychomotor performance in divers. *J Appl Physiol* 121: 953–964, 2016. First published September 15, 2016; doi:10.1152/japplphysiol.00534.2016.—Diving narcosis results from the complex interaction of gases, activities, and environmental conditions. We hypothesized that these interactions could be separated into their component parts. Where previous studies have tested single cognitive tasks sequentially, we varied inspired partial pressures of CO_2, N_2, and O_2 in immersed, exercising subjects while assessing multitasking performance with the Multi-Attribute Task Battery II (MATB-II) flight simulator. Cognitive performance was tested under 20 conditions of gas partial pressure and exercise in 42 male subjects meeting U.S. Navy age and fitness profiles. Inspired nitrogen (N_2) and oxygen (O_2) partial pressures were 0, 4.5, and 5.6 ATA and 0.21, 1.0, and 1.22 ATA, respectively, at rest and during 100-W immersed exercise with and without 0.075-ATA CO_2. Linear regression modeled the association of gas partial pressure with task performance while controlling for exercise, hypercapnic ventilatory response, dive training, video game frequency, and age. Subjects served as their own controls. Impairment of memory, attention, and planning, but not motor tasks, was associated with N_2 partial pressures >4.5 ATA. Sea level O_2 at 0.925 ATA partially rescued motor and memory reaction time impaired by 0.075-ATA CO_2; however, at hyperbaric pressures an unexpectedly strong interaction between CO_2, N_2, and exercise caused incapacitating narcosis with amnesia, which was augmented by O_2. Perception of narcosis was not correlated with actual scores. The relative contributions of factors associated with diving narcosis will be useful to predict the effects of gas mixtures and exercise conditions on the cognitive performance of divers. The O_2 effects are consistent with O_2 narcosis or enhanced O_2 toxicity.

diving; narcosis; nitrogen; carbon dioxide; oxygen; cognitive testing

NEW & NOTEWORTHY

N_2, CO_2, and O_2 affected cognitive performance differently. Attention, memory, and planning were more affected by N_2 than CO_2. Motor tasks were nearly unaffected by N_2. O_2 at 0.925 ATA partially rescued motor and memory reaction time impaired by 0.075-ATA CO_2. However, 1.22-ATA O_2 with 4.5-ATA N_2, 0.075-ATA CO_2, and exercise caused incapacitation with amnesia. O_2 narcosis or enhanced O_2 toxicity is postulated. Perception of narcosis was not correlated with actual scores.

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DIVING NARCOSIS IS A REVERSIBLE condition of cognitive impairment that occurs when gases are breathed at higher than atmospheric pressures. At barometric pressures >3 atmospheres of pressure absolute (ATA; 1 ATA = 1.01325 bar, 760 mmHg), air breathing consistently causes euphoria, impaired neuromuscular coordination, delays in auditory, visual, and tactile responses (84), diminished memory, and impaired concentration (3, 7, 9). Narcosis was initially recognized in caisson workers in the 19th century (9) and has been extensively researched by many contributors to the field of diving medicine (7, 10, 16, 30, 31, 44, 54, 65, 68, 83, 87). The narcotic potencies of individual gases have been attributed to their chemical characteristics, primarily lipid solubility (7, 13, 65). More recent studies suggest that pressure-dependent conformational changes occur from gas-protein binding, particularly at *N*-methyl-D-aspartate (NMDA) and GABA (A) receptors in the substantia nigra pars compacta (74, 75, 86), supporting a protein-binding theory of narcosis (73, 74). CO_2-sensitive GABAergic neurons may also play a role in central CO_2/pH chemoreception(53). Evidence exists suggesting hyperbaric nitrogen toxicity after repetitive episodes of nitrogen narcosis (57, 58, 73, 74).

The signs and symptoms of diving narcosis change depending on the partial pressures of the component gases of the breathing mixture, the environmental conditions at which they are inspired, and the unique characteristics of the diver. The impairing effects of elevated partial pressures of nitrogen (P_{N_2}) are well recognized; however, this is less true for carbon dioxide (CO_2) and oxygen (O_2). CO_2 narcosis is substantially different from that of N_2 in its threshold dose, its principal effects, and its ability to increase the risk of central nervous system O_2 toxicity (4, 20, 21, 35, 36, 49, 56, 64, 78, 88). Divers risk elevated arterial partial pressure of CO_2 (Pa_{CO_2}) from hypoventilation due to gas density-related increased work of breathing, increased physiological dead space, O_2 inhibition of the hypercapnic ventilatory response (28, 33, 34, 59, 66, 76, 82), and malfunction of CO_2-absorbent technologies in rebreathing systems. CO_2 is reported to slow cognitive performance rather than disrupt processing accuracy, in contrast to N_2 (35, 36), and may cause sudden (16), unexpected, and unrecognized (36) impairment that is independent of the effects of other inspired gases. The slope of the hypercapnic ventilatory response curve has also been reported to decrease in response to the narcotic action of N_2 on respiratory control centers (28).

Although O_2 is metabolically consumed, it is toxic to the central nervous system (CNS) when breathed at partial pressures >1.3 ATA while immersed (5, 85). O_2 is also 1.6 times more lipid soluble than N_2 and has been postulated to cause

N_2-like cognitive impairment (2, 9, 38). High inspired partial pressure of oxygen (P_{O_2}) values have been associated with performance impairment during evaluation of psychomotor performance in humans (38) and with delayed auditory induced cortical evoked potential responses in cats and humans (8). In 1967, Fenn found that raising the P_{O_2} from 0.21 to 1.0 ATA increased both the toxicity and narcotic potency of N_2, CO_2, and other inert gases in a *Drosophila* survival model (30, 31). In 1978, Hesser et al. observed that narcosis was not decreased when they substituted O_2 for N_2, concluding that O_2, N_2, and CO_2 had narcotic properties in humans (49). Linnarsson et al. concluded that CO_2 cognitive impairment was fundamentally different from that caused by the other two gases (60), a finding later supported by Fothergill et al. in 1991 (35).

In spite of prior work the factors influencing diving gas narcosis are insufficiently quantified where exercise, immersion, environmental conditions, and gas partial pressures interact. However, we hypothesized that with the proper methodology this interaction could be broken down into its component factors. Past attempts to quantify the factors influencing diving narcosis (3, 7, 22) have been limited by less realistic experimental settings, a lack of multitasking assessment tools, and individual variation in susceptibility and learning (37, 46). Moreover, no human studies have measured narcosis in the same subjects while changing inspired P_{O_2} under otherwise identical experimental conditions. Therefore our study sequentially varied the inspired partial pressures of CO_2, N_2, and O_2 in immersed exercising divers while continuously assessing cognitive performance. The testing methodology, gases, gas delivery devices, immersion setting, and exercise levels were selected to simulate divers in a physically and cognitively challenging, multitasking environment. Gas exposures were measured by continuous mass spectrometry and confirmed by arterial measurements of O_2 and CO_2 tensions at each stage of the trial.

MATERIALS AND METHODS

After Duke University Medical Center institutional review board approval, and written informed consent, the National Aeronautics and Space Administration (NASA)'s Multi-Attribute Task Battery II (MATB-II) flight simulator was used to evaluate performance and each subject's perception of their performance under 20 experimental combinations of gas partial pressures and exercise.

Test environment and safety. Forty-two male subjects were selected according to U.S. Navy age and fitness profiles (14) and tested during head-out immersion in 31.5°C [88.7°F; target value = 31.5°C; actual readings 32.3 C ± 0.8°C (SD)] water inside a 10 × 18-ft hyperbaric chamber while seated on an underwater, resistance-controllable cycle ergometer. For safety they were tethered to the chamber ceiling by a climbing harness and attended by a study team member and an in-chamber physician with full authority to stop the trial if danger to the subject was perceived. Audio and video communication was continuously maintained with the outside control, and electrocardiogram, radial arterial blood pressure, heart rate, respiratory rate, tidal volume, and end-tidal partial pressure of CO_2 ($P_{ET_{CO_2}}$), O_2 ($P_{ET_{O_2}}$), and N_2 ($P_{ET_{N_2}}$) were monitored. Hemodynamic and respiratory data were digitally captured using ADInstruments' LabChart 7 Pro software (Colorado Springs, CO) using an analog-to-digital data acquisition board connected to a dedicated study computer. Gas analysis was performed with a PerkinElmer MGA 1100 mass spectrometer (refurbished by MA Tech Services, St. Louis, MO) calibrated using three primary standard, premixed gases of known O_2, Ar, N_2, and CO_2 concentrations. Test and calibration gases were blended by Airgas (Durham, NC), and certificates of analysis were provided for each precision mix. Mouthpiece pressure was measured with a Validyne Engineering (Northridge, CA) pressure transducer and calibrated at pressures from +10 to −10 cmH_2O using a Sper Scientific (Scottsdale, AZ) electronic manometer. A Fleisch pneumotachograph and another Validyne pressure transducer were used to measure tidal volume, and calibration was performed using a Hans Rudolph 3-liter calibrated syringe (Kansas City, MO). The inspired P_{O_2}, P_{CO_2}, and P_{N_2} were confirmed using mass spectrometry during the first 15 s of each experimental stage. Immersed exercise was targeted to ~100 W at 50 revolutions of the cycle ergometer per minute (rpm) and adjusted according to subject comfort. An outside observer counted the rpm using a video monitor, and subjects were coached when necessary to maintain the proper speed and cadence. Arterial blood samples were taken 4 min into each experimental stage to confirm the gas exposures. The maximum inspired P_{O_2} was limited to 1.22 ATA to remain within the 1.3-ATA recommended upper limit for the U.S. Navy Mk 16 closed-circuit mixed gas breathing apparatus (85). At the end of the experiment all subjects and staff underwent poststudy transthoracic echocardiography to check for the presence of venous and left heart gas emboli. Subjects and staff were asked to limit physical activity and remain in telephone contact for a 24-h "bends watch" period after all hyperbaric exposures. See Appendix D of the supplemental material (available in the online version of this paper) for a description of the decompression procedures.

All subjects were tested for their intrinsic sensitivity to inhaled CO_2 by determining their hypercapnic ventilatory response (HCVR) before the experiment. HCVR was expressed as the slope of the expired gas volume in liters per minute vs. $P_{ET_{CO_2}}$ when the $P_{ET_{CO_2}}$ ranged from 55 to 65 mmHg. HCVR test procedures with O_2 as the background gas have been published elsewhere (39, 67). Before the trials all subjects reported the following: their recreational, commercial, or military dive training (yes or no), their number of lifetime dives, and their current frequency of video game play (<1 or >1 game each week) (18).

Performance tests. Performance data were generated using the MATB-II flight simulator software, a JavaScript personal computer-based program created by NASA in 1992 and revised in 2014 (77). The MATB-II has four simultaneously administered and independently scored tasks plus a built-in workload rating survey to measure perceived performance. Multitasking is required to detect and correct eight possible out-of-range values while listening for and responding to call sign-specific radio frequency-tuning requests. By varying the timing, number, and composition of the MATB-II's tasks the intensity and difficulty of the trial were configurable to purpose. The MATB-II's four tasks are as follows: *1*) TRACKING, *2*) SYSMON (system monitoring), *3*) COMM (communications), and *4*) RESMAN (resource management). TRACKING tests visual motor performance and manual dexterity using a joystick to simulate ordinance targeting or three-axis vehicle piloting. The second-by-second, root-mean-square distance in pixels from the target center to the cursor location generates a continuous TRACKING score. The SYSMON task tests attention and impulsivity by requiring the subject to attend to the status of red and green "warning" lights and four continuously moving scales. SYSMON queries requiring a response were as follows: a red light on, a green light off, and an out-of-range scale. Both the number of correct responses as well as extraneous keystrokes were recorded for each stage and scored using a methodology derived from the Test of Variables of Attention (T.O.V.A.) clinical manual (43) and adapted to the MATB-II. The T.O.V.A. is a well-validated continuous performance test used for the diagnosis of attention-deficit/hyperactivity disorder that compares a subject's errors of omission and commission to normative data. The T.O.V.A. defines errors of omission as measures of inattention or distraction. An example of an error of omission would be to fail to respond to a target before the time-out period has elapsed. Errors of omission were calculated as the number of queries minus the number of "true" responses as a percentage of the number of queries for that experimental stage. Errors of commission are

defined as measures of impulsivity or disinhibition. An example of an error of commission would be to inappropriately respond with a keystroke to a nontarget. Errors of commission were calculated as the number of "false" or incorrect keystrokes as a percentage of queries. Extremely frequent errors of commission indicate a noncompliant gaming strategy where a subject strategically responds with multiple keystrokes to randomly obtain a higher number of correct responses. This biases scoring because excessive commission errors decrease omission errors, shorten response times, and increase variability (43). Subjects employing noncompliant strategies were identified from repetitive programmatic keystroke patterns with excessive numbers of "false" responses, and those scores were not analyzed.

The COMM task tested working memory and auditory discrimination using an aircraft control tower communications scenario where a specific aircraft call sign must be recognized and both radios and frequencies must be remembered and selected. Errors of omission were also calculated for the COMM task as they were for the SYSMON task; however, because of the constraints of the joystick and software interface, calculation of errors of commission was not possible for the COMM task. The RESMAN task tested planning and problem solving using an aircraft fuel management scenario with failing fuel pumps. The normalized absolute value of the mean deviation from the target fuel level for the two virtual fuel tanks was calculated each 15 s and reported for each stage. The Workload Rating Scale (WRS) surveyed the subject's perceived performance after each experimental stage. Six questions assessed the subject's perceived degree of performance impairment, level of effort, frustration, and mental, physical, and temporal demands imposed by the previous stage. The questions were asked by the in-pool safety diver during the first 30 s of the subsequent stage. Subjects responded using hand signals showing one to four fingers for "none," "mild," "moderate," or "severe," respectively.

An external computer ran the MATB-II software, recorded the MATB-II data, projected the flight simulator screen through a chamber viewport, and operated the subject's joystick-controller and headset through an electrically isolated USB chamber penetrator and radio frequency communication device. A pressure-tolerant underwater joystick housing was designed and constructed by the Duke Hyperbaric Chamber engineering staff to allow use of the MATB-II underwater and to reduce the confounding effects of water viscosity on reaction times (23). A second external computer recorded the mass spectrometer and physiology data. An Apple iPad running FilemakerGo version 11 (filemaker.com) provided a detailed script for each individual experiment and recorded the precise time of each experimental event. A FilemakerPro version 11 database collected, stored, and synchronized the subject's personal information with his performance and physiology data during the experiment's multiple gas, pressure, and exercise conditions. All devices were synchronized to an Internet-obtained time signal (see Appendix A of the supplemental material for calculation formulas and software details).

MATB-II software configuration trials. Pilot trials were conducted to rehearse procedures and configure the MATB-II software to avoid learning and ceiling effects. These trials revealed that a performance plateau could be reliably reached using a pretrial familiarization protocol and that a high-workload configuration that employed the complete suite of MATB-II tasks was required to avoid ceiling effects (Appendix B of the supplemental material). After *pilot subject 8* the final MATB-II software configuration was fixed, and the same MATB-II events file was used for all subjects to ensure an identical sequence of MATB-II task queries. The final file contained ~180 TRACKING events, 42 SYSMON events, and 35 combined COMM and RESMAN events per data stage. We assumed that the nearly 500 MATB-II events presented over the course of the experiment precluded significant subject memorization and anticipation of event order.

Experimental stages (gas and exercise conditions). Twenty 5-min experimental stages were tested. Stages were defined by their gas partial pressures and exercise status. Gas mixtures and barometric pressures were varied to achieve inspired N_2 partial pressures ($P_{I_{N_2}}$) of 0.0, 0.79, 4.5, and 5.6 ATA, oxygen partial pressures ($P_{I_{O_2}}$) of 0.21, 1.0, and 1.22 ATA, and carbon dioxide partial pressures ($P_{I_{CO_2}}$) of 0.004 and 0.075 ATA. When 0.075-ATA CO_2 was added at sea level, the $P_{I_{N_2}}$ or $P_{I_{O_2}}$ were reduced by 0.075 ATA as needed. All subjects were tested at eight sea level stages where O_2, CO_2, and exercise were varied. The 12 hyperbaric stages were divided into 4 protocols (*protocols A-D*) to increase safety and reduce decompression time. Subjects were randomized to their protocols by blinded selection of paper labels from a hat at the time of consent.

Figure 1 shows the number of subjects in each protocol and the exercise and gas partial pressure conditions tested during each protocol stage. Table 1 shows composition of each gas and the pressure at which it was breathed. Figure 2 shows the events that occurred within each 5-min stage.

Statistical analysis procedures. Linear regression was used to model the association of arterial CO_2 (Pa_{CO_2}) and O_2 (Pa_{O_2}) partial pressures, end-tidal N_2 partial pressure ($P_{ET_{N_2}}$), and exercise with the MATB-II tasks while controlling for HCVR, diving experience, video game frequency, and age. For the noncontinuous SYSMON, COMM, and RESMAN tasks, impairment was expressed as the difference in percent error between the trial condition and a baseline reference condition, *stage 1*, "air breathing at 1 ATA without CO_2." Stage percent error was calculated for the SYSMON and COMM tasks by subtracting the number of correct responses from the number of queries and expressing that number as a percentage of the queries. For the RESMAN task the absolute value of the 15-s mean deviation from the target value was calculated and normalized using each subject's reference stage. The percent change from reference error was used as the dependent variables in a series of linear regression models that assessed the effects of gas partial pressures and exercise while controlling for individual covariates (Fig. 4). Z scores were used as the dependent variable for the continuous TRACKING task. The regressions employed directly measured end-tidal values for N_2 and arterial blood values for CO_2 and O_2. No automated procedures such as backward or stepwise elimination were used, and no attempt was made to combine the scores from the four different MATB-II tasks. The standardized regression coefficients for the factors Pa_{CO_2}, $P_{ET_{N_2}}$, and Pa_{O_2}, age, HCVR, video frequency, and dive training were plotted to illustrate the relative effects of each factor on task performance while simultaneously controlling for the effects of the other gases and conditions of the experimental stage. $P_{ET_{CO_2}}$ and Pa_{CO_2} were compared with Pearson correlation. To test for appropriate learning or residual gas effects, stage sequence was reversed for *subjects 32–38, 41*, and *42*, and the mean TRACKING values were compared for reversed vs. standard stage sequences using ANOVA.

If a subject became too narcotized to continue a specific stage, MATB-II data were analyzed up to the point of stage discontinuation. If the subject recovered and verbally consented to continuing the experiment, the remaining trial stages were attempted. Stages were excluded for MATB-II computer failure, mass spectrometer or joystick failure, or inability to clear ears requiring termination of a dive. Stages exhibiting signs of subject noncompliance such as surreptitious breathing around the mouthpiece or the strategic use of multiple anticipatory keystrokes were excluded from regression models; however, they were included in the univariable analyses (Appendix A of the supplemental material) to maintain intention to treat. Arterial-to-end-tidal differences were not temperature corrected (62). Software employed was SPSS v23 (IBM, Armonk, NY) and SAS v9.0 (Cary, NC). *P* values of 0.05 were considered statistically significant. Data storage was conducted in accordance with a Duke University Department of Anesthesiology-compliant and Duke Medical Center institutional review board-approved data management plan. All raw data and experimental notes were archived for future retrieval in individual subject folders on a firewall-protected server at Duke University Medical Center.

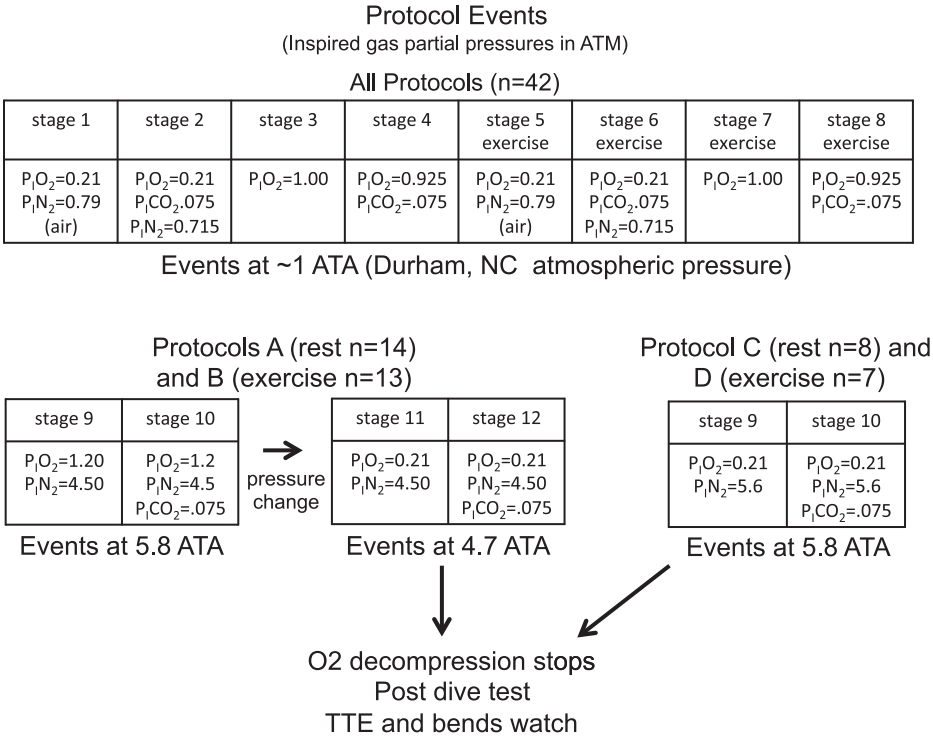

Fig. 1. Protocols, stages, inspired gas partial pressures for each stage, and barometric pressure and number of subjects in each protocol. For the fractional composition of each gas and the depth at which it was breathed, see Table 1. Stage numbers refer to the initial design order of the stages, and their conditions are unique to each protocol. TTE, transthoracic echocardiography.

RESULTS

Forty-two subjects, aged 29 ± 8.0 (SD) yr (range 19–48 yr), were studied from April 2014 through January 29, 2016. There were no significant differences among protocol assignments for the following: age, body mass index (BMI; 24.2 ± 2.0), percentage of subjects who had ever received dive training (51%), HCVR slope (1.39 ± 0.56), or percentage of subjects who reported weekly video game practice (18%). A total of 216 practice stages and 572 trial stages were attempted. Five hundred sixteen trial stages were completed and analyzed. Thirteen stages were excluded for equipment failure or ear-clearing difficulty. Eleven stages were discontinued because of unsafe levels of narcosis. Subject noncompliance was observed in 32 stages from evidence of breathing around the gas delivery mouthpiece or evidence of strategic multiple random keystrokes identified by obvious repeating patterns of time adjacent responses throughout the stage. Stage order was not a significant predictor of mean TRACKING scores ($P > 0.05$, ANOVA) indicating the absence of ongoing subject task learning or residual gas effect. There was no statistical difference in mean HCVR between subjects with and without dive training. No bubbles were observed in subjects or staff on transthoracic echo ~20 min after ending O_2 decompression (Appendix D of the supplemental material).

Arterial to end-tidal CO_2. The mean Pa_{CO_2} and $P_{ET}{}_{CO_2}$ values for rest and exercise conditions with and without added CO_2 are shown in Table 2. Arterial and end-tidal gas partial pressures at rest and exercise were correlated with arterial values ($R^2 = 0.802$, $P < 0.001$ Pearson; Fig. 3). In stages without added CO_2, exercise $P_{ET}{}_{CO_2}$ values exceeded their arterial counterparts by 3.5 mmHg [95% confidence interval (CI): 1.44, 5.54] as expected (41). When 0.075-ATA CO_2 was added to the breathing gases, the mean $P_{ET}{}_{CO_2}$ values exceeded Pa_{CO_2} by 4.02 mmHg (95% CI: 2.57, 4.56) at sea level and by

Table 1. *Stage descriptions: gas composition and barometric pressure by experimental stage*

	Gas Composition	Pressure, ATA	Verbal Description of Gas
	Sea level		
All protocols *stages 1* and *5*	79% N_2, 21% O_2	1	Air
All protocols *stages 2* and *6*	100% O_2	1	Surface O_2
All protocols *stages 3* and *7*	71.5% N_2, 21% O_2, 7.5% CO_2	1	Air with CO_2
All protocols *stages 4* and *8*	92.5% O_2, 7.5% CO_2	1	Surface O_2 with CO_2
	Hyperbaric pressures		
Protocols A and *B stage 9*	79% N_2, 21% O_2	5.8	Air at 158 fsw
Protocols A and *B stage 10*	77.7% N_2, 21% O_2, 1.6% CO_2	5.8	Air at 158 fsw with added CO_2
Protocols A and *B stage 11*	95.5% N_2, 4.5% O	4.7	158 fsw EAD N_2, normoxic P_{IO_2}
Protocols A and *B stage 12*	93.9% N_2, 4.5% O_2, 1.6% CO_2	4.7	158 fsw EAD N_2, normoxic P_{IO_2}, added CO_2
Protocols C and *D stage 9*	96.4% N_2, 3.6% O_2	5.8	200 fsw EAD N_2, normoxic P_{IO_2}

Breathing gases administered during each experimental stage are shown by fractional composition of each component gas and the overall barometric pressure at which it was administered.

Stage Events

minute 1	minute 2	minute 3	minute 4	minute 5
SYSMON COMM WRS	SYSMON COMM begin RESMAN at 90 sec	SYSMON COMM RESMAN TRACKING	SYSMON COMM RESMAN TRACKING	SYSMON COMM RESMAN TRACKING
ask WRS (perception) questions			draw ABG	

Fig. 2. Events that occurred within each 5-min stage. At both sea level and hyperbaric pressures the stages ran consecutively. To allow time for test gas wash-in and for the subjects to respond to the six WRS questions, the TRACKING task was not performed during the first 2 min, and the RESMAN (fuel tank scenario) was programmed to reset all tank levels to baseline during the first 90 s of each stage. The SYSMON and COMM tasks ran continuously. At *minute 4* an arterial blood sample (ABG) was collected to confirm CO_2 and O_2 washout and wash-in. There was a 1-h, out-of-the-water lunch break between the sea level and hyperbaric stages.

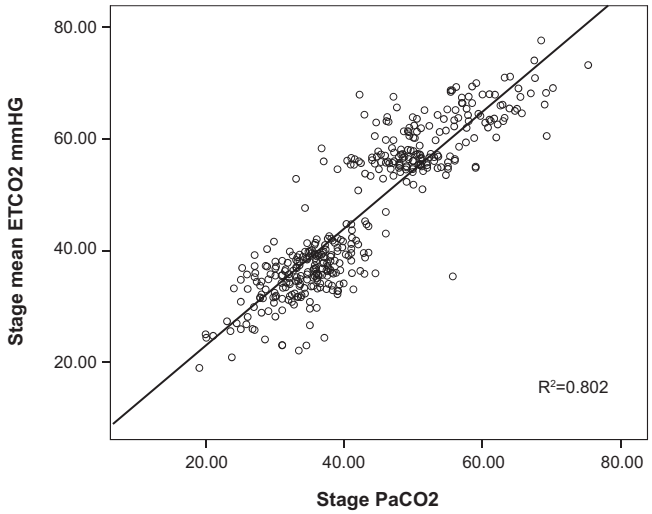

Fig. 3. Arterial to end-tidal CO_2 correlation. Stage Pa_{CO_2} (*x*-axis) drawn at *minute 4* of the 5-min experimental stage by the mean of all $P_{ET_{CO_2}}$ values recorded within 15 s before and after the precise time of the blood gas sample (*y*-axis). Values clustered to the upper right are from the absorbent failure scenarios where 0.075-ATA CO_2 was added to the test gas mix.

1 mmHg (95% CI: −2.09, 3.66) at hyperbaric pressures. During normoxic exercise at hyperbaric pressures without added CO_2, the mean Pa_{CO_2} exceeded mean $P_{ET_{CO_2}}$ by 2.79 mmHg (95% CI: −7.1, 1.5) as previously reported by Cherry et al. (17). Exercise significantly increased Pa_{CO_2} with and without added CO_2 ($P < 0.001$, ANOVA). Exercise and added CO_2 independently worsened whereas dive training and video game practice improved performance (Table 3). Table 3 shows the mean percent change from baseline MATB-II error scores when the experimental stages were grouped by exercise, added CO_2, diver training status, and video game frequency as compared by ANOVA.

Multiple-regression model for combined gas effects. Standardized regression coefficients illustrate each factor's relative contribution to error for the indicated MATB-II task. Figure 4 shows the standardized regression coefficients and *P* values when Pa_{CO_2}, Pa_{O_2}, $P_{ET_{N_2}}$, exercise, HCVR slope, dive training, video game frequency, and age were regressed against the MATB-II scores for the individual tasks. All regression ANOVA *P* values were <0.001. Because Pa_{O_2} and $P_{ET_{N_2}}$ were inversely correlated at sea level pressures ($P = 0.01$, Pearson), a significant interaction was found between Pa_{O_2} and hyperbaric pressure for motor performance (TRACKING) and the attention (SYMON) and memory (COMM) reaction times; therefore stratification by sea level and hyperbaric pressures was performed for these tasks.

Figure 4*A* shows that N_2 and exercise were strongly and significantly associated with errors of omission (attention) while the other factors tested, including CO_2, were not. Figure 4*B* shows that increased age, N_2, and video game experience were associated with errors of commission (impulsivity) whereas increased sensitivity to CO_2 as indicated by HCVR

Table 2. *End-tidal compared with arterial CO_2 by added CO_2 (absorbent failure scenario), barometric pressure, exercise, and inspired O_2 partial pressure*

Conditions				Pa_{CO_2}, mmHg			$P_{ET_{CO_2}}$, mmHg			
Absorbent Failure (+0.075-ATA CO_2)	Barometric Pressure, ATA	Exercise	PI_{O_2}	Mean	*n*	SD	Mean	*n*	SD	ET-Art CO_2
0	1	0	0.21	31.99	65	5.17	34.11	71	5.57	2.12
0	1	0	1	30.89	36	4.25	36.80	39	3.90	5.91
0	1	1	0.21	35.02	36	4.13	39.71	39	3.80	4.69
0	1	1	1	36.22	36	4.24	42.67	38	4.54	6.45
0	≥4.69	0	0.21	35.76	18	4.52	36.50	20	6.05	0.74
0	≥4.69	0	1.22	33.15	10	3.96	36.14	12	3.26	2.99
0	≥4.69	1	0.21	40.09	14	6.31	38.10	15	4.94	−1.99
0	≥4.69	1	1.22	37.50	10	3.55	37.65	12	2.88	0.15
1	1	0	0.21	48.61	34	4.09	52.72	37	2.27	4.11
1	1	0	1	47.56	34	4.99	51.87	37	2.30	4.31
1	1	1	0.21	54.95	35	6.78	59.77	37	3.60	4.82
1	1	1	1	55.08	35	6.39	59.37	37	3.93	4.29
1	≥4.69	0	0.21	50.76	17	4.76	53.86	20	5.32	3.10
1	≥4.69	0	1.22	54.91	9	4.00	53.15	12	2.81	−1.76
1	≥4.69	1	0.21	61.13	13	11.49	62.07	14	6.56	0.94
1	≥4.69	1	1.22	57.99	11	9.91	61.75	12	4.07	3.76

Arterial (Pa_{CO_2}) and end-tidal CO_2 ($P_{ET_{CO_2}}$) are compared at different conditions of added CO_2, barometric pressure, exercise, and inspired O_2 partial pressure (PI_{O_2}). ET-Art CO_2, difference between mean $P_{ET_{CO_2}}$ and Pa_{CO_2}.

Table 3. *Percent change from baseline errors by exercise, added CO_2, diver status, and video game frequency*

		Attention			Memory			
Factor	Motor: TRACKING Error	SYSMON Omission Error	SYSMON Commission Error	SYSMON Reaction Time	COMM Omission Error	COMM Reaction Time	Strategy: RESMON Error	Perception: WRS Score
Exercise +								
% change	23%	2%	−7%	0%	4%	0%	29%	1%
P value	0.000	0.055	0.310	0.604	0.084	0.002	0.419	0.000
Added CO_2 +								
% change	27%	1%	0%	0%	2%	0%	162%	0%
P value	0.00	0.23	0.99	0.39	0.47	0.00	0	0
Is diver +								
% change	−7%	−3%	6%	0%	−10%	0%	53%	0%
P value	0.06	0.01	0.39	0.68	0.00	0.86	0.128	0.516
Video weekly +								
% change	1%	0%	−11%	0%	−13%	0%	76%	0%
P value	0.86	0.79	0.19	0.90	0.00	0.28	0.064	0.367

Mean percent change from baseline MATB-II error scores is shown when the experimental stages were grouped by exercise, added CO_2, diver status, and video game frequency and compared by ANOVA. Exercise and added CO_2 independently increased error whereas dive experience and video game practice improved performance.

was associated with a decrease in error for that task. Attention (SYSMON) reaction times are shown in Fig. 4, *I* and *J*. At sea level pressures, video game practice and CO_2 sensitivity (higher HCVR) were associated with shortened reaction times. At hyperbaric pressures, increased age was associated with longer reaction times whereas dive training shortened them. Reaction times for the attention task (SYSMON) were not associated with breathing gases or exercise at either pressure condition.

Figure 4*C* shows the strength of factors associated with working memory (COMM) error. N_2 is the only factor associated with memory errors, yet the association was strong. In contrast, dive training and video game experience were strongly associated with a decrease in memory-related errors. Figure 4, *G* and *H*, shows memory-related (COMM) reaction times under sea level and hyperbaric conditions. Prolonged memory-related reaction times were associated with CO_2, exercise, and age at sea level pressures. At the hyperbaric pressures, N_2 further prolonged memory-related reaction times. As was seen with the decrease in sea level motor performance error, at sea level pressures both dive training and O_2 were associated with shorter reaction times.

Figure 4*D* shows the relative strengths of factors associated with errors of strategy and planning (RESMAN). N_2 and CO_2 were strongly associated with impairment. Reaction time is not a meaningful measurement for this task.

Figure 4, *E* and *F*, shows the relative strengths of factors associated with motor performance errors (TRACKING) at sea level and hyperbaric pressures. Under both pressure conditions, dive training was significantly associated with a decrease in motor error whereas CO_2 and exercise increased it. Age was also associated with increased motor error at hyperbaric pressures, but the small coefficients for N_2 and HCVR indicate that they were relatively unimportant influences on the performance of this task. The effect of N_2 was the smallest of all factors influencing motor error at hyperbaric pressures. O_2 was associated with a decrease in motor error at sea level, yet at hyperbaric pressures, error was increased.

Figure 4*K* shows relative strength of factors associated with the subjects' perception of their own performance (WRS). CO_2, O_2, exercise, age, and video game practice were associated with higher perceived error scores. N_2 and dive training were associated with a decreased perception of error by the subjects.

Table 4 summarizes the results of the regression analysis. Impairment of memory, memory-related reaction time, attention, and planning were all associated with N_2. In contrast, N_2 did not impair motor performance. Impaired motor and planning performance was associated with elevated CO_2 and O_2, yet O_2 improved motor performance and memory reaction times at 1 ATA. CO_2 was not associated with impairment of memory or attention confirming findings of earlier studies (35). Increased diver age was generally associated with slower reaction times and attention errors whereas dive training and recent video game practice were associated with improved scores.

Comparison of subjective vs. objective measures of performance (WRS vs. TRACKING). When the subjects' perception of their own performance (WRS) scores were analyzed by rank order, significant differences in the different experimental stages *P* were observed ($P < 0.001$, Kruskal-Wallis). However, the rank orders of the perceived and actual scores were not correlated [not significant (NS), Spearman]. Figure 5 illustrates and compares the rank order for perceived vs. actual stage performance on the motor task. The gas and exercise conditions of the 20 experimental stages are ordered from best to worst by the subjects' perceived (top to bottom, column at *left*) vs. their actual performance (column at *right*). Lines connect perceived vs. actual motor performance for the same stages.

DISCUSSION

The MATB-II simulator simultaneously tested multiple cognitively demanding tasks. Motor performance, attention, impulsivity, memory, and planning were simultaneously measured during exercise and at rest in an immersed setting. Pa_{CO_2}, $P_{ET_{N_2}}$, and Pa_{O_2} were directly measured as opposed to implied from inspired gases.

Gas effects on motor performance. Motor performance was more influenced by CO_2 and Pa_{O_2} than by N_2 (Fig. 4, *E* and *F*). As long as neither hypercapnia nor hyperoxia were present, 5.6

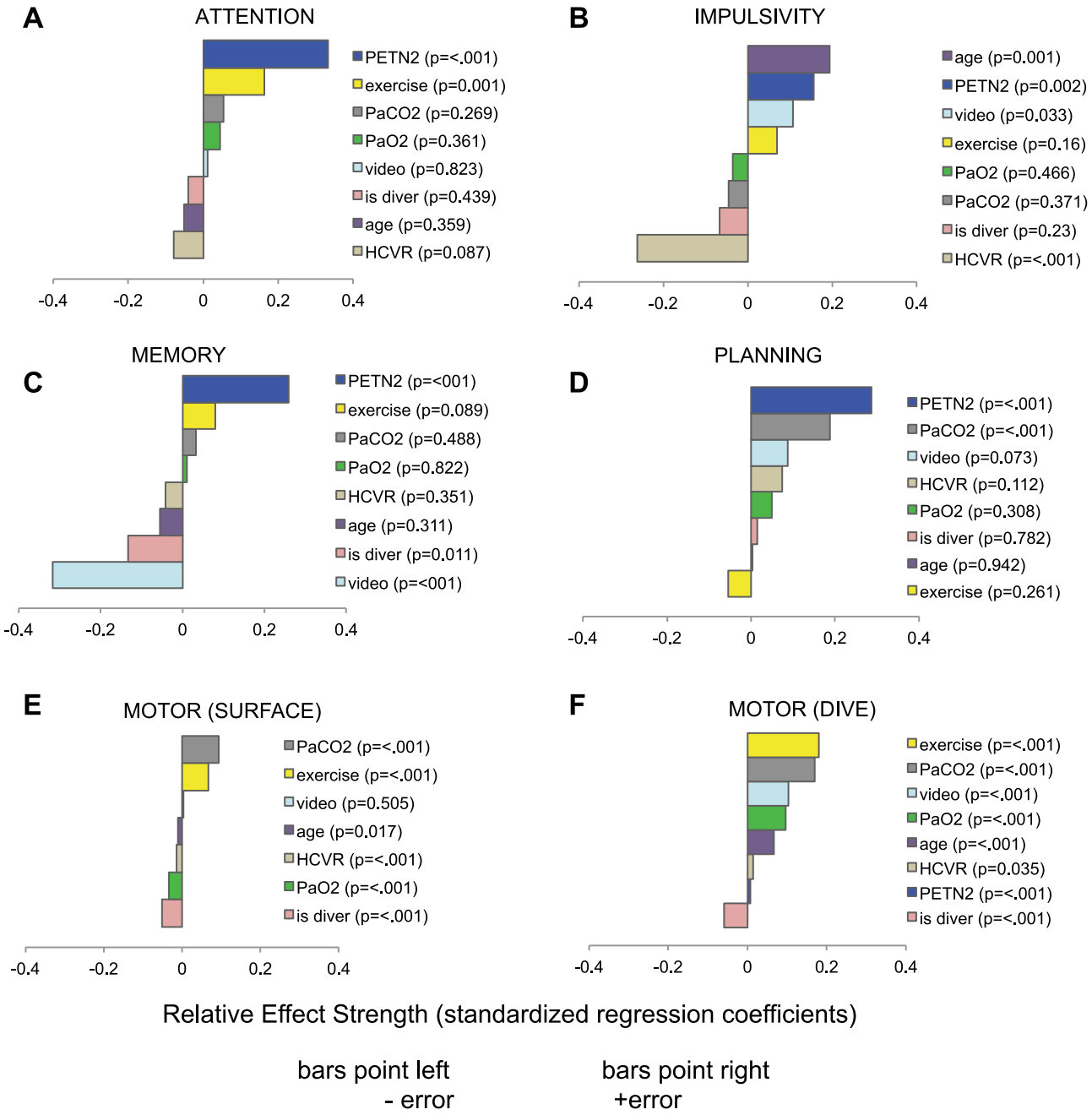

Fig. 4. Regression models for MATB-II tasks (1). *A*: SYSMON error of omission (attention). *B*: SYSMON error of commission (impulsivity). *C*: COMM error of omission (memory). *D*: RESMAN (strategy). *E*: TRACKING at 1 ATA (motor). *F*: TRACKING at hyperbaric pressures (motor). *G*: reaction time (RT) COMM at 1 ATA. *H*: reaction time COMM at hyperbaric pressures. *I*: reaction time SYSMON at 1 ATA. *J*: reaction time SYSMON at hyperbaric pressures. *K*: perception of performance.

ATA of N_2 was surprisingly well tolerated at both rest and exercise. This finding agrees with past authors including Abraini, Adolfson, Behnke et al., Case and Haldane, and Hesser et al. (1, 3, 7, 16, 48, 49), who reported that skills requiring higher-level reasoning were generally more impaired than manual dexterity during deep air dives. CO_2-associated motor impairment differed from that of N_2 in both threshold dose and principal cognitive effects. We found that acute exposure to 0.075-ATA CO_2 *1*) was sufficient to impair motor function on its own, *2*) was significantly more impairing during exercise than at rest, and *3*) was better tolerated with hyperoxia at sea level, but not at hyperbaric pressures where both N_2 and O_2 were elevated, similar to what was reported by Fenn in 1967 (30, 31) and Linnarsson et al. in 1990 (60). At sea level pressures there were no statistically significant differences among initial resting, exercising, or postdive resting motor performance (TRACKING) scores when the subjects breathed either room air or 1-ATA O_2. However, when CO_2 was added, motor error increased by 8% at rest and 43% during exercise ($P < 0.001$, ANOVA). Substituting 0.925-ATA O_2 for air

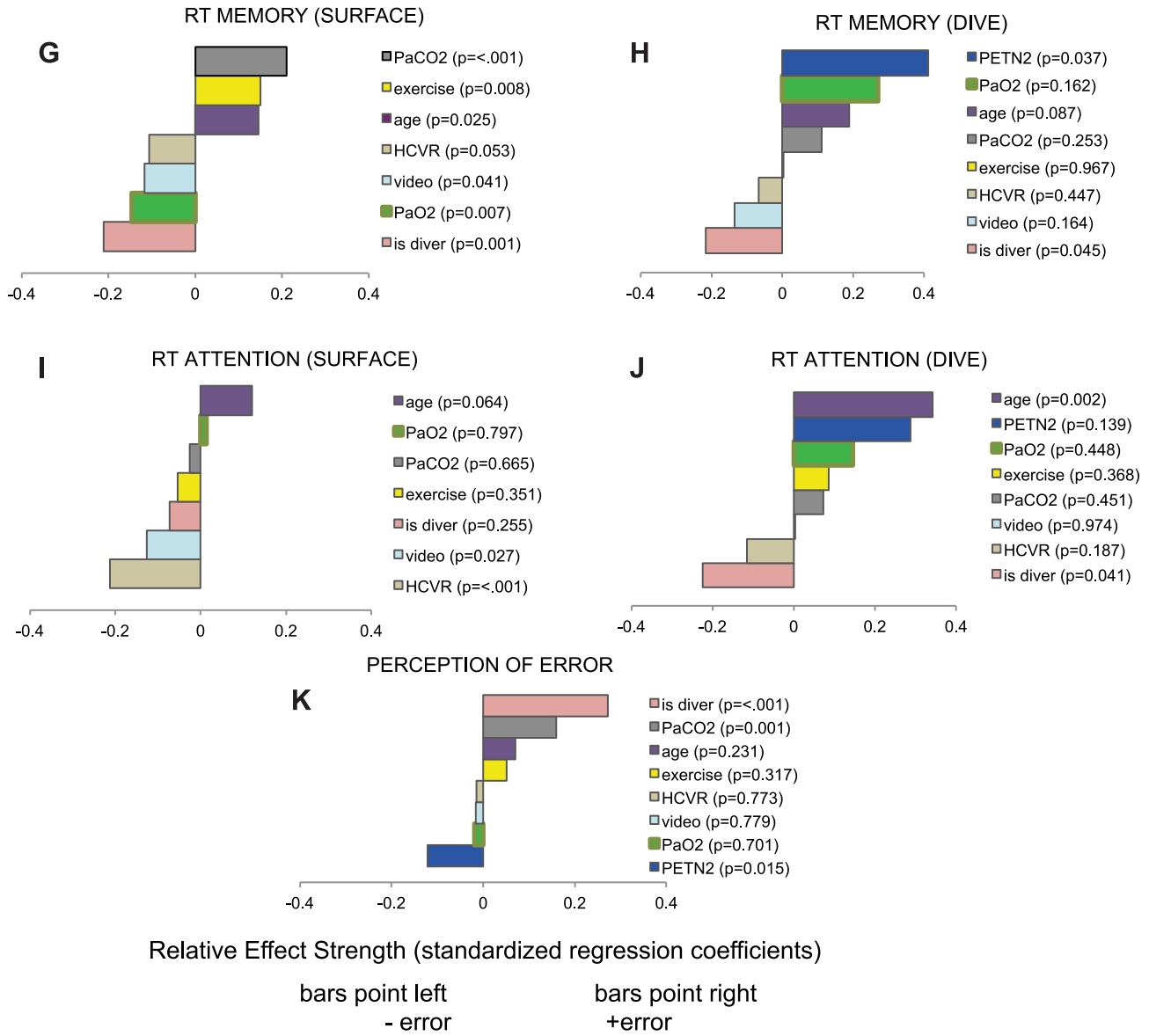

Fig. 4—*Continued*

partially corrected the CO_2-induced performance decrement and limited the increase from baseline to 8% at rest (P = NS) and to 18% during exercise ($P < 0.001$, ANOVA). Linear regression of inspired gas partial pressures against motor error while controlling for exercise, HCVR, and dive and video game experience confirmed this finding (Fig. 4*E*). These data support the findings of Gill et al., who studied resting and exercising divers at 1.3-ATA O_2 and found that it appeared to counteract CO_2-associated impairment (42). Scholey and colleagues also found that O_2 selectively improved cognitive performance and memory consolidation (80, 81).

Like Frankenhaeuser et al.'s 1963 study (38), our study inverted Hesser et al.'s 1978 design (49) to test for O_2 narcosis. We held $P_{I_{N_2}}$ constant at 4.5 ATA while changing $P_{I_{O_2}}$ to 0.21 from 1.22 ATA. Where O_2 modestly improved sea level performance under hypercapnic conditions, at hyperbaric pressures where $P_{I_{N_2}}$ was also elevated, 1.22-ATA $P_{I_{O_2}}$ significantly contributed to motor task error. In subjects performing normocapnic exercise at a constant $P_{I_{N_2}}$ of 4.5 ATA, changing $P_{I_{O_2}}$ from 0.21 to 1.22 ATA was associated with an increase in motor error of 7% over baseline (P = 0.003, ANOVA). When added CO_2 and exercise were present, the O_2 effect was amplified. During normoxic exercise at either 4.5- or 5.6-ATA $P_{I_{N_2}}$ the addition of 0.075-ATA $P_{I_{CO_2}}$ increased motor error by 35 and 97% above baseline, respectively ($P < 0.001$, ANOVA). The triple combination of exercise, hypercapnia, and hyperoxia during a 4.5-ATA $P_{I_{N_2}}$ dive caused profound and near-catastrophic loss of consciousness with amnesia. These subjects experienced a 138% increase over baseline in motor error ($P < 0.001$, ANOVA) at a $P_{I_{O_2}}$ of 1.22 ATA compared with a 35% increase over baseline at a $P_{I_{O_2}}$ of 0.21 ATA while holding all other conditions constant. This stage was also associated with a 38% completion failure rate and a fuguelike state of verbal unresponsiveness requiring physical intervention by the in-pool safety staff to remove the gas delivery mouthpiece. Although our subjects recovered within

Table 4. *Impairment profiles of breathing gases by MATB-II task*

MATB-II Task	Contribution to Error							
	Pa_{CO_2}	$P_{ET}\{\downarrow N_2\}$	Pa_{O_2}	Exercise	Diver	Age	HCVR	Video
Motor errors (sea level)	++		−	++	−−	0	0	0
Motor errors (hyperbaric)	++++	0	++++	++	−−	0	0	++
Reaction time, attention (sea level)	0		0	0	0	++	−−−−	−−−
Reaction time, attention (hyperbaric)	0	0	0	0	−−−−	++++++	0	0
Reaction time, memory (sea level)	++++		−−−	+++	−−−−	++++++	−−−−	−−
Reaction time, memory (hyperbaric)	0	+++++++	0	0	−−−−	++++++	0	0
Attention omission errors	0	++++++	0	+++	0	0	0	0
Impulsivity commission errors	+++	0	0	0	0	++++	−−−−−−	++
Memory omission errors	0	++++++	0	0	−−	0	0	−−−−−−
Strategy combined error	++++	++++++	0	0	0	0	0	−−

Summary of regression findings showing the relative strength of each predictor variable's contribution to error based on their standardized regression coefficients. Diver, subject had prior dive training; HCVR, hypercapnic ventilatory response; video, played video games at least weekly.

45 s of breathing chamber air, all reported some amnesia for this stage. This observation recalls the "semi loss of consciousness" described by Phillips in 1932 in 17 of 58 deep dives [210–330 ft of sea water (fsw)] (69). We hypothesize that the experimental conditions of our study may have lowered the threshold for CNS O_2 toxicity. As suggested by Lambertsen et al. in 1955 (56), the cerebrovasodilator effects of 0.075-ATA PI_{CO_2} and exercise may be sufficient to overcome the cerebrovasoconstrictive effects of the hyperbaric O_2 at 1.22 ATA and allow increased O_2 delivery to the brain permitting the development of CNS O_2 toxicity at lower than expected O_2 partial pressures. Evidence for this interpretation exists from Fenn's work on *Drosophila* (30, 31), Demchenko and colleagues' work on O_2 toxicity and CNS blood flow (24–27, 40, 45), and Pilla et al.'s reports on hyperoxic hyperpnea (70). Matott et al. suggested that the increased firing rates of CO_2-sensing neurons in the caudal solitary complex of the brain stem (63) could be a preconvulsive signal. The adverse cognitive changes we observed could be another early sign.

Gas effects on attention, impulsivity, memory, and planning. In contrast to the non-N_2-sensitive motor performance task, attention-requiring tasks and working memory were highly N_2 sensitive, yet tolerant to elevations in CO_2 and O_2. This is consistent with the findings of Fothergill and colleagues, who reported a slowing of performance with CO_2 rather than a disruption of processing accuracy compared with N_2, which produced impairment in both speed and accuracy (34, 35). We also found this to be true for planning tasks (RESMAN), impulsivity measurements (SYSMON errors of commission), and memory (COMM)-associated reaction time. The attention- and memory-related errors of omission showed significant impairment at 5.6-ATA PI_{N_2} in the regression analysis. Moreover, this impairment occurred both with and without added CO_2 or exercise (Fig. 4, *A* and *C*). Memory errors were also significantly increased during the lower,

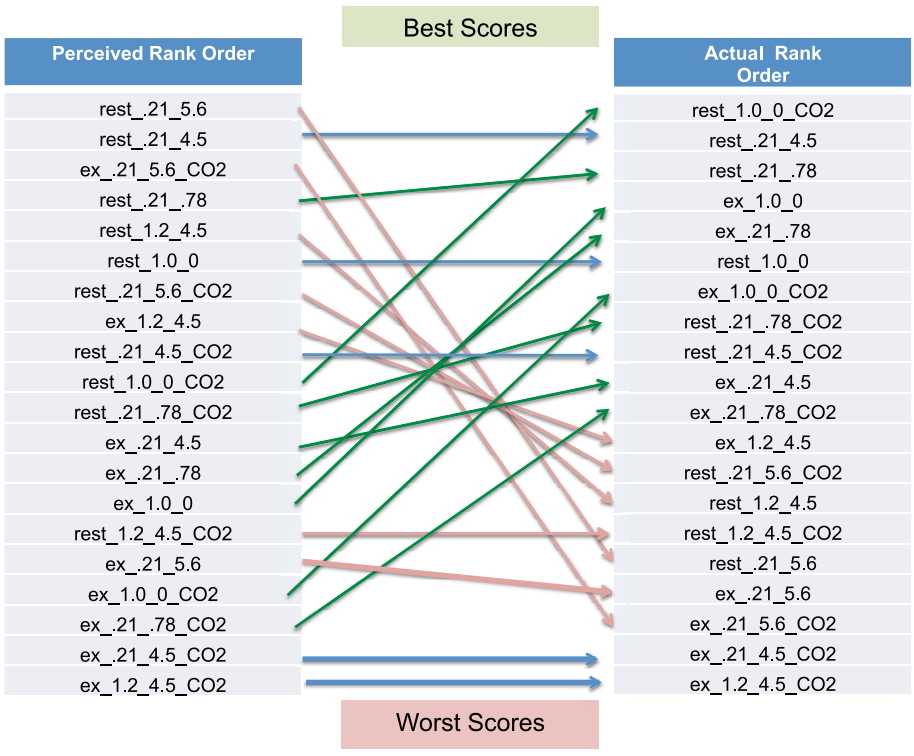

Fig. 5. Perception vs. performance of TRACKING task. The two columns of experimental stages were ordered from best (top) to worst (bottom) by the subjects' perceived performance as obtained from the Workload Rating Scale (column at *left*) and their actual performance from the MATB-II TRACKING task (column at *right*). Stage naming convention: exercise state_PI_{O_2}_PI_{N_2}_CO_2. Pink lines indicate actual performance better than, blue lines the same as, and green lines worse than perceived performance.

4.5-ATA $P_{I_{N_2}}$ stages. For staff safety reasons, 5.6-ATA $P_{I_{N_2}}$ was not tested at 1.22-ATA $P_{I_{O_2}}$; however, at 4.5-ATA $P_{I_{N_2}}$ the error scores for both the attention and memory tasks were increased by >100% at the higher $P_{I_{O_2}}$ when $P_{I_{N_2}}$ and $P_{I_{CO_2}}$ were held constant. Similar to what was observed for motor performance, the triple combination of exercise, hypercapnia, and hyperoxia during a 4.5-ATA $P_{I_{N_2}}$ dive was associated with highest recorded univariate impairment scores for both attention and memory (Appendix A of the supplemental material). Planning was also sensitive to CO_2 and N_2 (Fig. 4*D*). Greater diver age was associated with impairment in motor performance, impulsivity, and reaction times. Age was not associated with increased errors in memory or strategy (Fig. 4). N_2 was associated with slowed reaction time for tasks requiring memory, yet not for the simple attention-requiring task of responding to a warning light or scale.

Factors affecting perception of impairment. Although a recent study suggests that self-assessment may not be impaired in the depth range of 108–137 fsw (33–42 m) (50), we found that the subjects' perception of their performance did not match actual multitasking performance as measured by the MATB-II. This finding is in agreement with past findings regarding subjective reports of narcosis adaptation (11, 46, 47, 54). Narcosis is known to blunt the perception of pain (55) and to affect arousal-related emotional responses to events during hyperbaric exposure (37, 61). Figure 5 shows that although exercise, O_2, and CO_2 were perceived as impairing, elevated $P_{ET_{N_2}}$ decreased the perception of impairment, an assumption not supported by the actual scores. If narcosis adaptation is subjectively perceived but performance remains impaired, then both mission success and diver safety will be compromised (9).

Future directions. Future work should define the lower threshold for CO_2-related impairment. In this study, 0.075-ATA $P_{I_{CO_2}}$ in air was well tolerated for short periods of time with less impairment of memory- and attention-related tasks than for motor performance. However, a test of the acute effects of $P_{I_{CO_2}}$ in the 0.01–0.4-ATA range is needed along with an evaluation of the effects of temperature, exercise (34, 36), and medications (72). Hypercarbia is recognized earlier and perceived to be greater during cold water immersions compared with warm water (36). The observation that high P_{O_2} impaired performance is also intriguing. Whether this is due to narcosis or O_2 toxicity remains unanswered and warrants further investigation using independent measures of O_2 toxicity such as heart rate variability (24) and electroencephalography. Novel neuroscience techniques that employ detailed signal processing and mathematical modeling of EEG signals (12, 19, 71, 79) may improve the measurement, the prediction, and ultimately the control of diving gas narcosis.

Study limitations. Longer experimental stages may be indicated. Subjects can overcome impairing effects of sleep deprivation on the MATB-II within short-duration testing periods, and a similar adaptive response may be present for narcosis testing (29). For this reason the results of our acute testing should not be compared with research on chronic indoor CO_2 levels (78). Furthermore, although diving narcosis should not last beyond the actual exposure time, studies show that even subtle residual effects may be carried forward from one condition to the next (6). These residual effects may induce bias from stage order, and although we saw no effect of stage order on the TRACKING task, this source of bias remains a possibility. Finally, although all of our subjects were tested at approximately the same time of day, circadian rhythms influence cognitive testing (15, 52). Correlation of test scores with physiological indexes that more accurately monitor mental workload may be helpful (51, 78).

Conclusions. 1) A $P_{I_{N_2}}$ of 5.6 ATA [200-fsw nitrogen equivalent air depth (EAD)] is well tolerated for the motor tasks. Piloting a vehicle or performing a well-learned motor sequence may be resistant to N_2's impairing effects at these pressures or less.

2) Impairment of memory, attention, and planning is seen at 4.5-ATA $P_{I_{N_2}}$. Attention to detail, remembering commands, or plotting a new course of action in an emergency will be adversely affected.

3) At sea level pressures an inspired P_{CO_2} of 0.075 ATA impairs motor and planning performance, but not memory or attention. The threshold for $P_{I_{CO_2}}$-related motor impairment should be obtained. Adverse effects of CO_2 on motor function and planning at sea level are attenuated at 0.925-ATA $P_{I_{O_2}}$.

4) At hyperbaric pressures both O_2 and CO_2 are associated with additional impairment where the $P_{I_{N_2}}$ is 4.5 ATA or greater. An inspired P_{CO_2} of 0.075 ATA additionally impaired all tasks when $P_{I_{N_2}}$ was held constant. When both $P_{I_{N_2}}$ and $P_{I_{CO_2}}$ were held constant, a $P_{I_{O_2}}$ of 1.22 ATA was associated with severe psychomotor and cognitive impairment compared with a $P_{I_{O_2}}$ of 0.21 ATA. Characterization of this interaction requires further investigation to determine if this finding represents O_2 narcosis or potentiation of CNS O_2 toxicity.

5) A positive training effect is apparent. Under hyperbaric conditions, experienced divers performed better than nondivers.

6) Diver perception of impairment did not correlate with objective measurements and may lead to overconfidence. Dive training and N_2 were significantly associated with a perception of decreased error.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

J.J.F., B.D., M.J.N., B.W.S., P.B.B., R.D.V., and R.E.M. conception and design of research; J.J.F., B.D., M.J.N., E.A.S., C.P., B.W.S., S.A.D., and R.E.M. performed experiments; J.J.F., I.A., R.D.V., and R.E.M. analyzed data; J.J.F., B.D., M.J.N., I.A., B.W.S., R.D.V., and R.E.M. interpreted results of experiments; J.J.F. prepared figures; J.J.F. and B.D. drafted manuscript; J.J.F., B.D., M.J.N., B.W.S., P.B.B., R.D.V., and R.E.M. edited and revised manuscript; J.J.F., B.D., M.J.N., B.W.S., P.B.B., R.D.V., and R.E.M. approved final version of manuscript.

REFERENCES

1. **Abraini JH.** Inert gas and raised pressure: evidence that motor decrements are due to pressure per se and cognitive decrements due to narcotic action. *Pflugers Arch* 433: 788–791, 1997.
2. **Ackerman MJ, Spencer JW.** Brain stimulation in rats exposed to hyperbaric environments. *Undersea Biomed Res* 3: 369–378, 1976.

3. **Adolfson J.** Deterioration of mental and motor functions in hyperbaric air. *Scand J Psychol* 20: 26–32, 1965.
4. **Arieli R, Arieli Y, Daskalovic Y, Eynan M, Abramovich A.** CNS oxygen toxicity in closed-circuit diving: signs and symptoms before loss of consciousness. *Aviat Space Environ Med* 77: 1153–1157, 2006.
5. **Arieli R, Shochat T, Adir Y.** CNS toxicity in closed-circuit oxygen diving: symptoms reported from 2527 dives. *Aviat Space Environ Med* 77: 526–532, 2006.
6. **Balestra C, Lafere P, Germonpre P.** Persistence of critical flicker fusion frequency impairment after a 33 mfw SCUBA dive: evidence of prolonged nitrogen narcosis? *Eur J Appl Physiol* 112: 4063–4068, 2012.
7. **Behnke AR, Thomson RM, Motley EP.** Physiologic effects of breathing air at four atmospheres' pressure. *Am J Physiol* 112: 554, 1935.
8. **Bennett P.** The narcotic effects of hyperbaric oxygen. In: *Proceedings of the Fourth International Congress on Hyperbaric Medicine*. Tokyo: Igaku Shoin, 1969, p. 74–79.
9. **Bennett PB, Rostain JC.** Inert gas narcosis. In: *Bennett and Elliott's Physiology and Medicine of Diving*. London: Saunders, 2003, p. 304–322.
10. **Boycott AE, Damant GC, Haldane JS.** The prevention of compressed-air illness. *J Hyg (Lond)* 8: 342–443, 1908.
11. **Brauer RW.** Acclimation to nitrogen narcosis: a review. In: *Nitrogen Narcosis: Proceedings of a Workshop Held 15–16 December 1983, Santa Barbara Medical Foundation Clinic, Santa Barbara*, edited by Hamilton RW Kizer KW. Bethesda, MD: Undersea Medical Society, 1985, p. VII 1–9.
12. **Brown EN, Lydic R, Schiff ND.** General anesthesia, sleep, and coma. *N Engl J Med* 363: 2638–2650, 2010.
13. **Brubakk AO, Ross JA, Thom SR.** Saturation diving; physiology and pathophysiology. *Compr Physiol* 4: 1229–1272, 2014.
14. **Bureau of Naval Personnel (BUPERS).** *SEAL/EOD/SWCC/DIVER/AIRR Physical Screening Testing Standards and Procedures*. Millington, TN: BUPERS, 2013. (MILPERSMAN 1220-410 (a) OPNAVINST 6110.1J)
15. **Caldwell JA, Caldwell JL.** Fatigue in military aviation: an overview of US military-approved pharmacological countermeasures. *Aviat Space Environ Med* 76: C39–C51, 2005.
16. **Case EM, Haldane JB.** Human physiology under high pressure: I. Effects of nitrogen, carbon dioxide, and cold. *J Hyg (Lond)* 41: 225–249, 1941.
17. **Cherry AD, Forkner IF, Frederick HJ, Natoli MJ, Schinazi EA, Longphre JP, Conard JL, White WD, Freiberger JJ, Stolp BW, Pollock NW, Doar PO, Boso AE, Alford EL, Walker AJ, Ma AC, Rhodes MA, Moon RE.** Predictors of increased Pa_{CO_2} during immersed prone exercise at 4.7 ATA. *J Appl Physiol* 106: 316–325, 2009.
18. **Chiappe D, Conger M, Liao J, Caldwell JL, Vu KP.** Improving multi-tasking ability through action videogames. *Appl Ergon* 44: 278–284, 2013.
19. **Ching S, Brown EN.** Modeling the dynamical effects of anesthesia on brain circuits. *Curr Opin Neurobiol* 25: 116–122, 2014.
20. **Clark JM.** Oxygen toxicity. In: *Physiology and Medicine of Hyperbaric Oxygen Therapy*, edited by Neuman TS Thom SR. Philadelphia, PA: Saunders, 2008, chapt. 23, p. 527–563.
21. **Clark JM, Lambertsen CJ.** Pulmonary oxygen toxicity: a review. *Pharmacol Rev* 23: 37–133, 1971.
22. **Cousteau J.** *The Silent World*. London: Hamilton, 1953.
23. **Dalecki M, Bock O, Schulze B.** Cognitive impairment during 5 m water immersion. *J Appl Physiol (1985)* 113: 1075–1081, 2012.
24. **Demchenko IT, Gasier HG, Zhilyaev SY, Moskvin AN, Krivchenko AI, Piantadosi CA, Allen BW.** Baroreceptor afferents modulate brain excitation and influence susceptibility to toxic effects of hyperbaric oxygen. *J Appl Physiol (1985)* 117: 525–534, 2014.
25. **Demchenko IT, Luchakov YI, Moskvin AN, Gutsaeva DR, Allen BW, Thalmann ED, Piantadosi CA.** Cerebral blood flow and brain oxygenation in rats breathing oxygen under pressure. *J Cereb Blood Flow Metab* 25: 1288–1300, 2005.
26. **Demchenko IT, Moskvin AN, Krivchenko AI, Piantadosi CA, Allen BW.** Nitric oxide-mediated central sympathetic excitation promotes CNS and pulmonary O_2 toxicity. *J Appl Physiol (1985)* 112: 1814–1823, 2012.
27. **Demchenko IT, Zhilyaev SY, Moskvin AN, Piantadosi CA, Allen BW.** Autonomic activation links CNS oxygen toxicity to acute cardiogenic pulmonary injury. *Am J Physiol Lung Cell Mol Physiol* 300: L102–L111, 2011.
28. **Fagraeus L, Hesser CM.** Ventilatory response to CO_2 in hyperbaric environments. *Acta Physiol Scand* 80: 19A–20A, 1970.
29. **Fairclough SH, Venables L, Tattersall A.** The influence of task demand and learning on the psychophysiological response. *Int J Psychophysiol* 56: 171–184, 2005.
30. **Fenn WO.** Interactions of oxygen and inert gases in *Drosophila*. *Respir Physiol* 3: 117–129, 1967.
31. **Fenn WO.** Physiological effects of high pressures of nitrogen and oxygen. *Circulation* 26: 1134–1143, 1962.
33. **Florio JT, Morrison JB, Butt WS.** Breathing pattern and ventilatory response to carbon dioxide in divers. *J Appl Physiol* 46: 1076–1080, 1979.
34. **Fothergill DM, Carlson NA.** Effects of N_2O narcosis on breathing and effort sensations during exercise and inspiratory resistive loading. *J Appl Physiol* 81: 1562–1571, 1996.
35. **Fothergill DM, Hedges D, Morrison JB.** Effects of CO_2 and N_2 partial pressures on cognitive and psychomotor performance. *Undersea Biomed Res* 18: 1–19, 1991.
36. **Fothergill DM, Taylor WF, Hyde DE.** Physiologic and perceptual responses to hypercarbia during warm- and cold-water immersion. *Undersea Hyperb Med* 25: 1–12, 1998.
37. **Fowler B, Ackles KN, Porlier G.** Effects of inert gas narcosis on behavior: a critical review. *Undersea Biomed Res* 12: 369–402, 1985.
38. **Frankenhaeuser M, Graff-Lonnevig V, Hesser CM.** Effects on psychomotor functions of different nitrogen-oxygen gas mixtures at increased ambient pressures. *Acta Physiol Scand* 59: 400–409, 1963.
39. **Fraser JA, Peacher DF, Freiberger JJ, Natoli MJ, Schinazi EA, Beck IV, Walker JR, Doar PO, Boso AE, Walker AJ, Kernagis DN, Moon RE.** Risk factors for immersion pulmonary edema: hyperoxia does not attenuate pulmonary hypertension associated with cold water-immersed prone exercise at 4.7 ATA. *J Appl Physiol (1985)* 110: 610–618, 2011.
40. **Gasier HG, Demchenko IT, Allen BW, Piantadosi CA.** Effects of striatal nitric oxide production on regional cerebral blood flow and seizure development in rats exposed to extreme hyperoxia. *J Appl Physiol (1985)* 119: 1282–1288, 2015.
41. **Gelfand R, Lambertsen CJ, Peterson RE.** Human respiratory control at high ambient pressures and inspired gas densities. *J Appl Physiol Respir Environ Exerc Physiol* 48: 528–539, 1980.
42. **Gill M, Natoli MJ, Vacchiano C, MacLeod DB, Ikeda K, Qin M, Pollock NW, Moon RE, Pieper C, Vann RD.** Effects of elevated oxygen and carbon dioxide partial pressures on respiratory function and cognitive performance. *J Appl Physiol* 117: 406–412, 2014.
43. **Greenberg LM, Kindschi CL, Dupuy TR, Hughes SJ.** *T.O.V.A. Clinical Manual: Test of Variables of Attention Continuous Performance Test*, edited by Company TT. Los Alamitos, CA: TOVA, 2007.
44. **Grover CA, Grover DH.** Albert Behnke: nitrogen narcosis. *J Emerg Med* 46: 225–227, 2014.
45. **Gutsaeva DR, Moskvin AN, Zhiliaev S, Kostkin VB, Demchenko IT.** Nitric oxide and carbon dioxide in neurotoxicity induced by oxygen under pressure [in Russian]. *Ross Fiziol Zh Im I M Sechenova* 90: 428–436, 2004.
46. **Hamilton K, Laliberte MF, Fowler B.** Dissociation of the behavioral and subjective components of nitrogen narcosis and diver adaptation. *Undersea Hyperb Med* 22: 41–49, 1995.
47. **Hamilton K, Laliberte MF, Heslegrave R.** Subjective and behavioral effects associated with repeated exposure to narcosis. *Aviat Space Environ Med* 63: 865–869, 1992.
48. **Hesser CM, Adolfson J, Fagraeus L.** Role of CO_2 in compressed-air narcosis. *Aerosp Med* 42: 163–168, 1971.
49. **Hesser CM, Fagraeus L, Adolfson J.** Roles of nitrogen, oxygen, and carbon dioxide in compressed-air narcosis. *Undersea Biomed Res* 5: 391–400, 1978.
50. **Hobbs M, Higham PA, Kneller W.** Memory and metacognition in dangerous situations: investigating cognitive impairment from gas narcosis in undersea divers. *Hum Factors* 56: 696–709, 2014.
51. **Hsu BW, Wang MJ, Chen CY, Chen F.** Effective indices for monitoring mental workload while performing multiple tasks. *Percept Mot Skills* 121: 94–117, 2015.
52. **Hunt MG, Bienstock SW, Qiang JK.** Effects of diurnal variation on the Test of Variables of Attention performance in young adults with attention-deficit/hyperactivity disorder. *Psychol Assess* 24: 166–172, 2012.
53. **Iceman KE, Corcoran AE, Taylor BE, Harris MB.** CO_2-inhibited neurons in the medullary raphe are GABAergic. *Respir Physiol Neurobiol* 203: 28–34, 2014.
54. **Kiessling RJ, Maag CH.** *Performance impairment as a function of nitrogen narcosis. Rep US Navy Exp Diving Unit* 3–60: 1–19, 1960.

55. **Kowalski JT, Seidack S, Klein F, Varn A, Rottger S, Kahler W, Gerber WD, Koch A.** Does inert gas narcosis have an influence on perception of pain? *Undersea Hyperb Med* 39: 569–576, 2012.
56. **Lambertsen CJ, Ewing JH, Kough RH, Gould R, Stroud MW, 3rd.** Oxygen toxicity; arterial and internal jugular blood gas composition in man during inhalation of air, 100% O_2 and 2% CO_2 in O_2 at 3.5 atmospheres ambient pressure. *J Appl Physiol* 8: 255–263, 1955.
57. **Lavoute C, Weiss M, Risso JJ, Rostain JC.** Mechanism of action of nitrogen pressure in controlling striatal dopamine level of freely moving rats is changed by recurrent exposures to nitrogen narcosis. *Neurochem Res* 37: 655–664, 2012.
58. **Lavoute C, Weiss M, Sainty JM, Risso JJ, Rostain JC.** Post effect of repetitive exposures to pressure nitrogen-induced narcosis on the dopaminergic activity at atmospheric pressure. *Undersea Hyperb Med* 35: 21–25, 2008.
59. **Linnarsson D, Hesser CM.** Dissociated ventilatory and central respiratory responses to CO_2 at raised N_2 pressure. *J Appl Physiol* 45: 756–761, 1978.
60. **Linnarsson D, Ostlund A, Sporrong A, Lind F, Hesser CM, Hamilton RW.** Does oxygen contribute to the narcotic action of hyperbaric air? *Undersea Biomed Res* 16, *Suppl* 1: 7316, 1990.
61. **Lofdahl P, Andersson D, Bennett M.** Nitrogen narcosis and emotional processing during compressed air breathing. *Aviat Space Environ Med* 84: 17–21, 2013.
62. **Losa-Reyna J, Torres-Peralta R, Henriquez JJ, Calbet JA.** Arterial to end-tidal P_{CO_2} difference during exercise in normoxia and severe acute hypoxia: importance of blood temperature correction. *Physiol Rep* 3: e12512, 2015.
63. **Matott MP, Ciarlone GE, Putnam RW, Dean JB.** Normobaric hyperoxia (95% O_2) stimulates CO_2-sensitive and CO_2-insensitive neurons in the caudal solitary complex of rat medullary tissue slices maintained in 40% O_2. *Neuroscience* 270: 98–122, 2014.
64. **Meissner HH, Franklin C.** Extreme hypercapnia in a fully alert patient. *Chest* 102: 1298–1299, 1992.
65. **Miller KW.** The opposing physiological effects of high pressures and inert gases. *Fed Proc* 36: 1663–1667, 1977.
66. **Mitchell SJ, Cronje FJ, Meintjes WA, Britz HC.** Fatal respiratory failure during a "technical" rebreather dive at extreme pressure. *Aviat Space Environ Med* 78: 81–86, 2007.
67. **Moon RE, Cherry AD, Stolp BW, Camporesi EM.** Pulmonary gas exchange in diving. *J Appl Physiol* 106: 668–677, 2009.
68. **Petri NM.** Change in strategy of solving psychological tests: evidence of nitrogen narcosis in shallow air-diving. *Undersea Hyperb Med* 30: 293–303, 2003.
69. **Phillips AE.** Recent research work in deep sea diving. *Proc R Soc Med* 25: 693–703, 1932.
70. **Pilla R, Landon CS, Dean JB.** A potential early physiological marker for CNS oxygen toxicity: hyperoxic hyperpnea precedes seizure in unanesthetized rats breathing hyperbaric oxygen. *J Appl Physiol (1985)* 114: 1009–1020, 2013.
71. **Purdon PL, Sampson A, Pavone KJ, Brown EN.** Clinical electroencephalography for anesthesiologists: part I: background and basic signatures. *Anesthesiology* 123: 937–960, 2015.
72. **Reini SA, Fothergill DM, Gasier HG, Horn WG.** Propranolol's potential to increase survival time in a disabled submarine. *Aviat Space Environ Med* 83: 131–135, 2012.
73. **Rostain JC, Lavoute C.** Dopamine, neurochemical processes, and oxygen toxicity at pressure. *Compr Physiol* 6: 1339–1344, 2016.
74. **Rostain JC, Lavoute C.** Neurochemistry of pressure-induced nitrogen and metabolically inert gas narcosis in the central nervous system. *Compr Physiol* 6: 1579–1590, 2016.
75. **Rostain JC, Lavoute C, Risso JJ, Vallee N, Weiss M.** A review of recent neurochemical data on inert gas narcosis. *Undersea Hyperb Med* 38: 49–59, 2011.
76. **Salzano JV, Camporesi EM, Stolp BW, Moon RE.** Physiological responses to exercise at 47 and 66 ATA. *J Appl Physiol* 57: 1055–1068, 1984.
77. **Santiago-Espada Y, Myer RR, LAtorella KA, Comstock JR.** *The Multi-Attribute Task Battery II (MATB-II) Software for Human Performance and Workload Research: A User's Guide*. Hampton, VA: NASA, 2011. (NASA/TM–2011–217164)
78. **Satish U, Mendell MJ, Shekhar K, Hotchi T, Sullivan D, Streufert S, Fisk WB.** Is CO_2 an indoor pollutant? Direct effects of low-to-moderate CO_2 concentrations on human decision-making performance. *Environ Health Perspect* 120: 1671–1677, 2012.
79. **Schneider S, Cheung JJ, Frick H, Krehan S, Micke F, Sauer M, Dalecki M, Dern S.** When neuroscience gets wet and hardcore: neurocognitive markers obtained during whole body water immersion. *Exp Brain Res* 232: 3325–3331, 2014.
80. **Scholey AB, Moss MC, Neave N, Wesnes K.** Cognitive performance, hyperoxia, and heart rate following oxygen administration in healthy young adults. *Physiol Behav* 67: 783–789, 1999.
81. **Scholey AB, Moss MC, Wesnes K.** Oxygen and cognitive performance: the temporal relationship between hyperoxia and enhanced memory. *Psychopharmacology (Berl)* 140: 123–126, 1998.
82. **Sherman D, Eilender E, Shefer A, Kerem D.** Ventilatory and occlusion-pressure responses to hypercapnia in divers and non-divers. *Undersea Biomed Res* 7: 61–74, 1980.
83. **Shilling CW, Willgrube WW.** Quantitative study of mental and neuromuscular reactions as influenced by increased air pressure. *U S Nav Med Bull* 35: 373–380, 1937.
84. **Simpson DM, Harris DJ, Bennett PB.** Latency changes in the human somatosensory evoked potential at extreme depths. *Undersea Biomed Res* 10: 107–114, 1983.
85. **Supervisor of Salvage and Diving (SUPSALV).** *U.S. Navy Diving Manual*. Washington, DC: Naval Sea Systems Command, 2011, p. 18-14 (18-16 Change A).
86. **Vallee N, Rostain JC, Risso JJ.** How can an inert gas counterbalance a NMDA-induced glutamate release? *J Appl Physiol (1985)* 107: 1951–1958, 2009.
87. **Vann RD, Butler FK, Mitchell SJ, Moon RE.** Decompression illness. *Lancet* 377: 153–164, 2011.
88. **Warkander DE, Norfleet WT, Nagasawa GK, Lundgren CE.** CO_2 retention with minimal symptoms but severe dysfunction during wet simulated dives to 6.8 atm abs. *Undersea Biomed Res* 17: 515–523, 1990.