Differential Cognitive Effects of Extended Hypoxia

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Abstract

This research investigates the impact of prolonged oxygen deprivation (approximately 40 minutes) on foundational cognitive capacities such as attention, declarative memory, and executive control. Data was analyzed from twenty one participants under normoxic and hypoxic conditions performing the psychomotor vigilance test, a paired associates task, and the change signal task. Hypoxia delayed simple visual response times and reduced response inhibition throughout the entire protocol. On the scale of minutes, false starts tended to increase across blocks when participants were hypoxic, but this effect did not carry across blocks. Finally, declarative memory performance was initially unaffected. However, after approximately 20 minutes, hypoxia nearly reversed gains from the first 20 minutes while performance under normoxic conditions continued to improve. The results show a differential susceptibility of different cognitive processes to hypoxia at different time scales and support the use of PVT as a diagnostic for decrements attributed to hypoxia.

Keywords: prolonged hypoxia; visual attention; declarative memory; executive control

Introduction

Human cognition is intimately tied to the task environment (Anderson, 1990; Gray & Boehm-Davis, 2000; Stevens et al., 2023; Tripp et al., 2009). Further, cognitive performance is also altered through exposure to environmental stressors, such as toxic chemical compounds, pharmaceuticals, and nutriceuticals.

The overarching research agenda of this work is to identify the dynamics and mechanisms of action associated with hypoxia-induced changes in physiology and cognitive performance using physiological measures and neurophysiological monitoring (fNIRS, EEG) combined with tasks closely associated with cognitive processes foundational to higher-order cognitive operations (decision-making, situation awareness, etc.). Understanding the underlying mechanisms and their dynamics will facilitate the development of prophylactics associated with cognitive decline from hypoxia. An example of this type of goal can be taken from research on caffeine's mitigating effect on cognitive performance decrements from fatigue induced through sleep deprivation (Barone & Roberts, 1996). The community's understanding of caffeine's rates of absorption, distribution, metabolism, and excretion along with its neurological mechanism of action have led to detailed integrative computational *physiocognitive* models of caffeine's mitigating effect on fatigue (Halverson et al., 2022). In the current paper, we investigate the effects of oxygen deprivation, or *hypoxia*, on foundational cognitive capacities such as attention, declarative memory, and executive control.

Hypoxic hypoxia, a state of physiological impairment caused by exposure to reduced levels of breathable oxygen, is a known risk to heath, physical performance, and cognitive performance. Commonly encountered at high altitudes, hypoxic hypoxia poses a serious threat to aviators and hikers as acute hypoxic exposure negatively impacts functions essential to the execution of procedures important to goal completion, such as maintaining altitude in an aircraft or directional heading as a hiker (Cable, 2003; Green & Morgan, 1985; Steinman et al., 2017; Temme et al., 2010). Acute hypoxic exposure adversely affects a range of neurophysiological systems including cognition, perception, and motor control (Blacker & McHail, 2021).

Impairments manifest in a wide variety of subjective, self-reported symptoms, making the investigation of hypoxia-induced performance impairment exceedingly difficult. Thus, the identification of robust cognitive, physiological, and neurological markers of hypoxic hypoxia would facilitate impairment detection and mitigation. One way to observe cognitive and performance deficits is through process and performance measures in cognitive tasks. For example, participants experiencing hypoxia have exhibited increased response time latency (Dart et al., 2017), impaired working memory (Mcmorris et al., 2017), and altered decision making (Niedermeier et al., 2017).

In the current study, we sought to expand previous research examining cognitive performance during acute normobaric hypoxia exposure by investigating impairments across tasks closely associated with foundational cognitive capacities, specifically the psychomotor vigilance (attention), paired associates (declarative memory), and change-signal (executive control) tasks. In the following sections we first present our empirical methodology followed by experiment results.

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Method

To evaluate the effects of hypoxia on foundational cognitive capacities, a within-subjects design was applied. There were two levels of normobaric oxygen exposure: normoxic and hypoxic. Each participant performed three cognitive tasks in a random order.

Participants

Thirty one male adults (M_{age} = 32.87, SD_{age} = 6.49) participated for monetary compensation. Only male participants were recruited to control for exhaled breath variation associated the ovarian cycle (Dragonieri et al., 2018; Sukul et al., 2018). All participants were recruited through flyers, online announcements, and word of mouth. Participants who completed the study received $200. The study protocol was approved by the Naval Medical Research Unit – Dayton's (NAMRU-D) Institutional Review Board in compliance with all applicable federal regulations governing the protection of human participants.

All participants self-reported normal or corrected-to-normal vision; normal hearing; no history of psychological, neurological, or other medical diagnoses; no use of tobacco in the past six months; and no excessive alcohol use. A total of 14 participants reported previously experiencing hypoxia (e.g., through previous hypoxia studies, flight crew and/or other trainings, etc.).

Ten participants data was removed from these analyses. Three withdrew at the start of the study. Seven withdrew during the study: Three participants SpO_2 fell below a preestablished safety threshold of 60%. Two participants fainted. One participant asked to stop. One participant did not complete the study due to technical issues with the equipment.

Procedure

Participants completed three visits on separate days. On the first visit, participants provided written informed consent, completed screenings to collect eligibility and demographic information, and practiced shortened versions of the tasks. After at least one week, participants completed two experimental visits in counterbalanced order of exposure condition (i.e., hypoxia and normoxia). At least 24 hours elapsed between the two experimental visits (M = 4.7 days; SD = 5.90). Both experimental visits had the same start time.

Each experimental visit took place in the Reduced Oxygen Breathing Environment (ROBE) at NAMRU-D, a normobaric hypoxia chamber. The hypoxic condition involved breathing 10.6% O_2 (17,500 ft equivalent), while the normoxic condition involved breathing 21% O_2. The participants completed five blocks of tasks per visit. During each block, participants provided breath samples and then performed the tasks. Each task was presented for 2 min each in random order. When performing the tasks, participants were seated approximately 65 cm from a 13.5" HP tablet. EEG, hypoxia symptoms questionnaire, SpO_2, blood, breath, and oral/salivary data were collected but are beyond the scope of this paper.

Tasks

Three tasks were utilized in this study: the paired associates, psychomotor vigilance, and change-signal tasks. The tasks were built in NetBeans, a development environment for Java, and were ran using Apache Ant 1.8.0.

Paired Associate Task A paired associate task (PAT) was used to investigate effects on declarative memory. On each trial, participants were presented with a symbol and their task was to respond with the associated digit. The first time in each block a symbol was shown, the digit was presented with it. Stimuli were presented in a random order for 5,000 ms, with 1,000 ms between stimulus presentations. If an error was made, the symbol-digit pair was shown as feedback for 4,000 ms but with a red font instead of the usual black font (see Figure 1, left panel).

Psychomotor Vigilance Task The Psychomotor Vigilance Task (PVT; Dinges & Powell, 1985) was used to investigate effects on visual attention. Participants saw a grey uniform background before the stimulus appeared. A red millisecond counter appeared on-screen and started to scroll up from zero until participants responded to the stimulus. Participants were instructed to hit any key on the keyboard once they saw the red number appear, to stop the counter as quickly as possible. The stimulus remained on-screen for 1,000 ms after a response was recorded, providing the participant with performance feedback. Interstimulus intervals were distributed randomly from 1,000 to 5,000 ms (see Figure 1, middle panel).

Change Signal Task The Change Signal Task (CST; Brown & Braver, 2005) was used to investigate effects on response inhibition and executive control. Participants initially saw a "Go Signal" displayed on-screen (i.e., an arrow pointed left or right). On 33% of trials, a "Change Signal" was presented after the Go Signal, which was a larger arrow above the Go Signal. This Change Signal was always in the opposite direction of the Go Signal. The participants' task was to respond by pressing the arrow key in the same direction as the Go Signal unless the Change Signal appeared, in which case they were to respond with the direction of the Change Signal arrow. The delay between the Go Signal and a Change signal (stimulus onset asynchrony) varied between 20 ms and 800 ms; the delay was determined based on a staircase procedure. The initial delay was 200 ms and decreased by 50 ms when participants successfully changed responses and increased by 100 ms when participants did not change their response. Two error conditions were presented (low and high), which only differed with respect to the shade of the arrows. Change Signal delay was calculated separately for these two conditions. A 500 ms intertrial interval was used (see Figure 1, right panel).

Auditory Task

Auditory tones were presented for the entire period the participant was performing the tasks described above. Participants were instructed to ignore the tones and to focus only on the

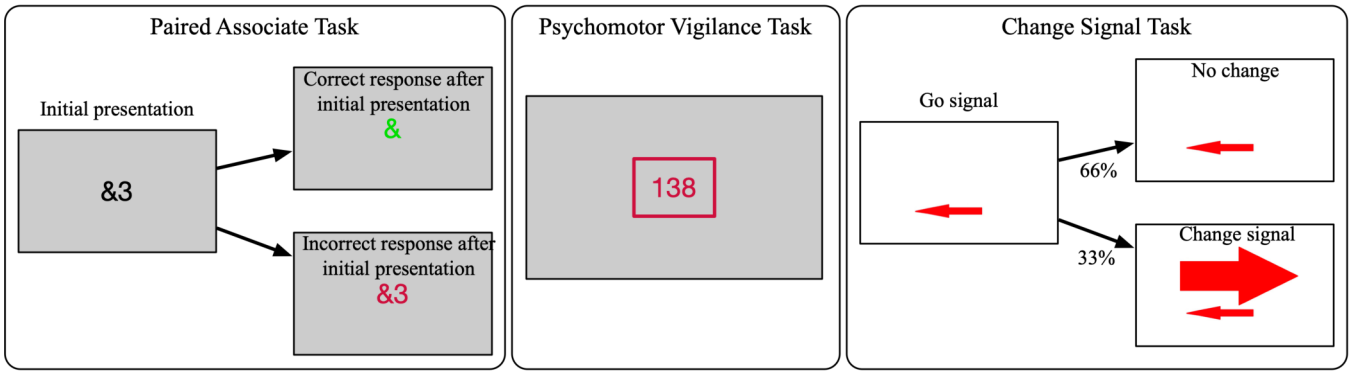

Figure 1: The three tasks presented to participants. The left pane provides the paired associated task as well as feedback provided on response to subsequent presentations of a symbol (e.g., &). The middle pane is the psychomotor vigilance task, displaying the milliseconds past the onset of the trial. The right pane provides an illustration of the change signal task and the prevalence of the change signal and how it appeared to participants.

visual tasks. The auditory tones were presented to participants every 500 ms and at 85 dB sound pressure level via Etymotic ER3-A insert earphones. The passive auditory oddball paradigm comprised a sequence of tones (n = 5,100), of which, 85% were standards (50 ms, 1,000 Hz) and 15% were deviants, where the tones either differed in duration (100 ms, 1000 Hz) or both duration and frequency (100 ms, 1,100Hz). All tones had a 5 ms rise/fall. The auditory task was included for EEG analyses and will not be discussed further.

Statistical Analyses

Linear mixed-effect models (Bates et al., 2015) were selected and fit for each dependent variable. A series of models for each dependent variable were developed by adding one effect at a time, first random and then fixed, in an order informed by the experimental design. At each step, the model with the new variable was compared against the model without using Likelihood Ratio Tests to determine if the new variable warrants inclusion. Only the final model for each dependent variable is shown in the results.

Results

The results related to hypoxia are summarized in Table 1. The details of those results, and other significant effects and interactions, are provided below.

Psychomotor Vigilance Task

The response times, false starts, and lapses were analyzed separately. In all three models, hypoxic condition, trial number, and trial number squared were evaluated as random variables, and hypoxic condition, trial number, trial number squared, and block number were evaluated as fixed, in that order. All trials after the 28th trial were removed from analysis to make comparisons comparable across participants.

Response Time This analysis was performed on error-free trials only. False starts (responses faster than 250 ms) and lapses (responses slower than 500 ms) were excluded from this analysis. The distribution of response times was somewhat non-normal and a logarithmic transformation was used to correct the distribution.

An ANOVA on the final model confirmed an effects of hypoxic condition, $F(1, 5360.6.8) = 187.94$, $p < .001$, block, $F(1, 80.3) = 13.17$, $p < .001$, and trial number squared, $F(2, 5384.0) = 47.78$, $p < .001$. As shown in Figure 2, participants responded more slowly when hypoxic ($M = 344.2$ ms, $SE = 5.5$) than when normoxic ($M = 328.2$ ms, $SE = 5.0$). No interactions with hypoxic condition contributed meaningfully to the model (all $ps > .05$).

Lapses PVT lapses, responses that take longer than 500 ms, is an important dependent variable for decreased attention in the sleep literature (Lim & Dinges, 2008). Responses were categorized as a lapse or not.

An ANOVA on the final model confirmed an effect of hypoxic condition, $\chi^2(1, N = 5892) = 14.69$, $p < .001$ and an interaction between block squared and trial, $\chi^2(1, N = 5892) = 18.28$, $p < .001$. As shown in Figure 3, participants experi-

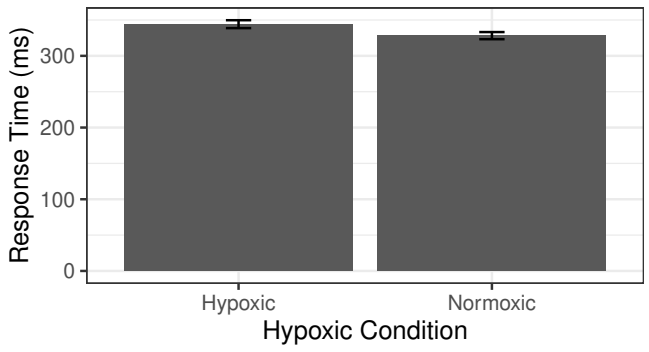

Figure 2: Observed PVT response time as a function of hypoxic condition. Error bars indicate ± 1 standard error of participant means.

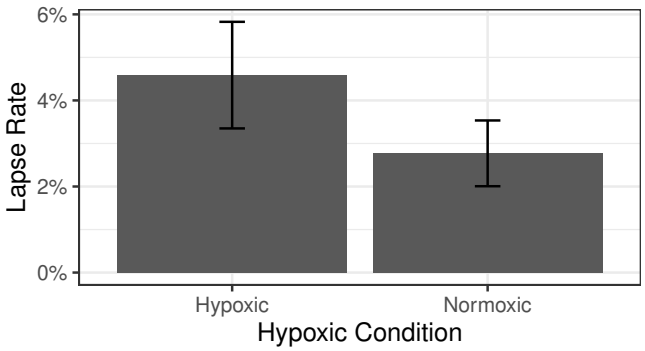

Figure 3: Observed PVT percentage of lapse trials as a function of hypoxic condition. Error bars indicate ±1 standard error of participant means.

enced more lapses when hypoxic (M = 5.6%, SE = 1.2) than when normoxic (M = 2.8%, SE = 0.8).

False Starts PVT false starts are responses that occur before the person could process the visual stimuli. These false starts include responses with a response time of less than 250 ms and responses that occur between stimulus presentations. Responses were categorized as a false start or not.

An ANOVA on the final model confirmed an interaction between of hypoxic condition and trial, $\chi^2(2, N = 5892) = 12.22$, $p < .001$. As shown in Figure 4, participants experienced more false starts when hypoxic than when normoxic, and this effect is greater in later trial.

Paired Associate Task

PAT response time and errors were analyzed separately. In both models, hypoxic condition, trial number, and trial number squared were evaluated as random variables. Block number, trial number, trial number squared, and hypoxic condition were evaluated as fixed variables, in that order. All trials after the 23rd trial were removed from analysis to make comparisons comparable across participants.

Response Times This analysis was performed on error-free trials only. Incorrect responses, false starts (responses less than 250 ms), and non-responses (responses greater than 2,000 ms) were excluded from this analysis. The distribution of response times was somewhat non-normal, and a reciprocal transformation was used to correct the distribution.

An ANOVA on the final model confirmed a main effect of block, $F(1, 651.48) = 61.30$, $p < .001$, and a main effect of trial squared, $F(2, 37.10) = 3.156$, $p = .043$. However, the effect of hypoxia and all interactions with hypoxia did not contribute meaningfully to the model (all ps $> .05$).

Errors This analysis excluded trials that were false starts (responses less than 250 ms) or non-responses (responses greater than 2000 ms). Responses were categorized as a correct response or an incorrect response.

An ANOVA on the final model confirmed an interaction between hypoxic condition and block, $\chi^2(1, N = 4553) = 5.34$, $p = .021$, and a main effect of trial, $\chi^2(1, N = 4553) = 24.81$, $p < .001$. As shown in Figure 5, participants tended to make fewer errors in the first three blocks. However, when hypoxic, participants made substantially more errors in later blocks.

Change Signal Task

Response time and errors were analyzed separately. In both models, hypoxic condition, change trial number, change trial number squared, trial number, trial number squared, and cue direction were evaluated as random variables. Block number, block number squared, change trial number, change trial number squared, trial number, trial number squared, cue direction, and hypoxic condition were evaluated as fixed variables, in that order. Change trial number cubed was also evaluated in the response time model as both random and fixed variables after change trial number squared. All trials after the 41st trial and after the 18th change trial were removed from analysis to make comparisons comparable and stable across

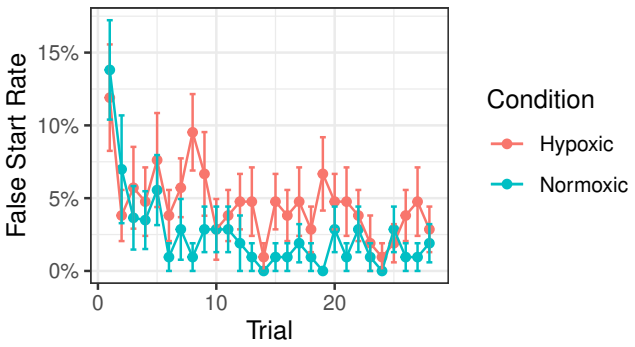

Figure 4: Observed PVT percentage of false starts as a function of hypoxic condition and trial. Error bars indicate ±1 standard error of participant means.

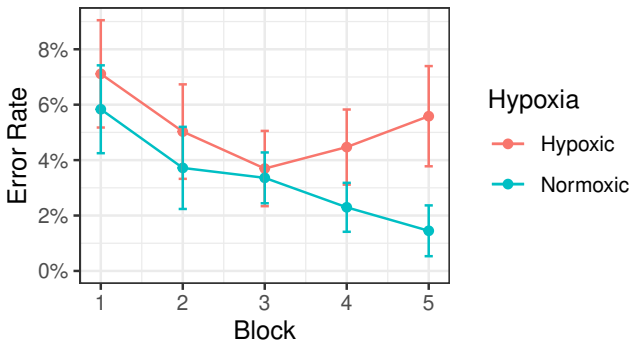

Figure 5: Observed PAT percentage of error trials as a function of hypoxic condition and block. Error bars indicate ±1 standard error of participant means.

participants.

Response Time This analysis was performed on trials in which a change signal was presented, the participant inhibited their response until the change signal appeared, and the participant responded correctly. Incorrect responses, false starts (responses less than 250 ms), and non-responses (responses greater than 2000 ms) were excluded from this analysis. The distribution of response times was non-normal, and a square root transformation was used to correct the distribution.

An ANOVA on the final model confirmed a main effect of change trial cubed, $F(3, 2127.8) = 7.47$, $p < .001$. However, the main effect of hypoxic condition and all interactions with it did not add meaningfully to the model (ps $> .05$).

Errors This analysis excluded trials that were false starts (responses less than 250 ms) or non-responses (responses greater than 2,000 ms). Responses were categorized as a correct response or an incorrect response. It should be noted that block was not used a grouping variable in this analysis because all models were singular with that grouping variable included.

An ANOVA on the final model confirmed three main effects: hypoxic condition, $\chi^2(1, N = 2863) = 4.17$, $p = .041$, block, $\chi^2(1, N = 2863) = 21.46$, $p < .001$, and trial, $\chi^2(1, N = 2863) = 4.88$, $p = .027$. Change trial was not significant, $\chi^2(1, N = 2863) = 388$, $p = .08$. All interactions with hypoxia did not contribute meaningfully to the model (ps $> .05$). As shown in Figure 6, participants tended to make more errors when hypoxic ($M = 22.3\%$, $SE = 3.8$) than when normoxic ($M = 19.3\%$, $SE = 4.0$).

Discussion

Prolonged hypoxic hypoxia can affect cognitive performance substantially, but the degree to which it affects foundational cognitive processes varies. The results of this study suggest that attention, declarative memory, and executive control are not only differentially susceptible to hypoxia but are affected on different time scales.

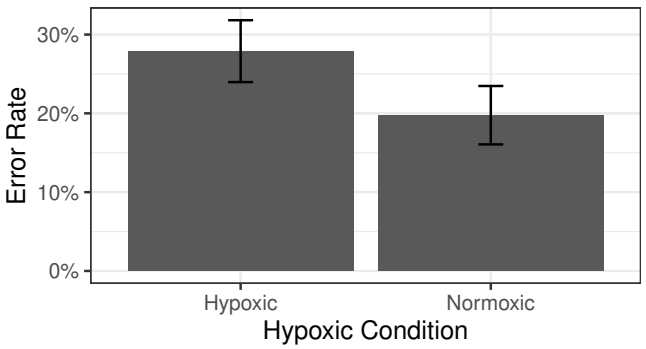

Figure 6: Observed CST percentage of error trials as a function of hypoxic condition. Error bars indicate ±1 standard error of participant means.

Task	Metric	Figure	Hypoxia Effect	*Sig*	R^2_β
PVT	RT	2	simple	$p < .001$	.035
	Lapses	3	simple	$p < .001$	.001
	FS	4	trial interaction	$p < .001$	.001
PAT	RT	—	none	—	
	Errors	5	block interaction	$p = .021$	.003
CST	RT	—	none	—	
	Errors	6	simple	$p = .041$	.002

Table 1: Summary of hypoxic effects, either simple effects (main effect of hypoxia alone) and experience/time-on-task related independent variables (trial or block) that interact with hypoxia.

Throughout the entire study, hypoxia had a significant and consistent affect on performance. Hypoxia caused an increase in visual attention response time, based on PVT response times and lapses as demonstrated in Figures 2 and 3. Both reflect a slowing resulting from hypoxia. In addition, as shown in Figure 6, hypoxia negatively affected response inhibition, making it more difficult for participants to inhibit their response to the initial arrow in the CST. What is not clear is why these effects are consistent across forty minutes. It could be that participants had an immediate and consistent decrease in performance, or it could be that the measures were not sensitive enough to detect an increasing effect of hypoxia over time.

Within blocks, at a time scale of a couple of minutes, we observed an increasing effect of hypoxia on false starts. This can be seen in Figure 4. False starts start high, regardless of exposure and then decrease less rapidly when participants are hypoxic. This could be a ceiling-effect of sorts for false starts at the start of blocks and not a true interaction. In addition, it could be that switching between tasks caused an initial perturbation of behavior that resolved quickly unrelated to hypoxia. Regardless, participants experienced more false starts in the hypoxic condition. This increase in false starts is consistent with the finding in the CST where participants were less likely to inhibit their response until the appropriate stimuli appeared.

Across blocks, we see hypoxia-induced decrements across tens of minutes with declarative memory. Participants improved in accuracy across the first two to three blocks. This improvement was facilitated by consistent pairing of digits and symbols across all trials and blocks. However, after

approximately 20 minutes in the hypoxic condition, performance decreased nearly back to baseline (block 1). What remains unclear is whether hypoxia is affecting declarative memory encoding, retrieval, or both and warrants further empirical and modeling research and development.

These findings, summarized in Table 1, can inform methods to detect and mitigate impairment due to hypoxic hypoxia. This table has been supplemented with R^2_β (Jaeger, 2017; Nakagawa & Schielzeth, 2013), a coefficient of determination that provides one way to determine effect size for linear mixed-effect models (Bates et al., 2015). This summary provides support for the use of PVT as a diagnostic tool for detecting hypoxia, especially when compared to the other metrics. First, the greatest effect size is found with measurements of PVT RT. Second, all three PVT metrics were found to be significantly affected by hypoxia. Third, the effect of hypoxia on these metrics is observed throughout the entire protocol. In contrast, as shown in Figure 5, the PAT error rate is not affected until approximately 20 minutes in the exposures used in this study. Given the early detection ability of the PVT, it could be used to warn against forthcoming memory errors with continued and prolonged hypoxia.

Given the significance of the data at an aggregate level, how do the metrics differentiate on an individual basis? While the detailed analysis of individual differences will be the focus of future research, Figure 7 shows the differences between hypoxic and normoxic performance for the five metrics found to vary significantly with hypoxic condition. The metrics that provide the strongest signal for poorer performance in the hypoxic condition, in accordance with the aggregate analyses presented above, will have more data points above the abscissa. The PVT RT and false start metrics have the most data points above or near the abscissa. That is, the PVT may provide the strongest behavioral signal for more individuals. These visualizations provide some additional support for the PVT as a diagnostic tool for detecting hypoxic effects. However, individuals are differentially susceptible to hypoxic conditions (Petrassi et al., 2012). Future research is planned to examine this data in more detail in conjunction with blood oxygen saturation values from the study.

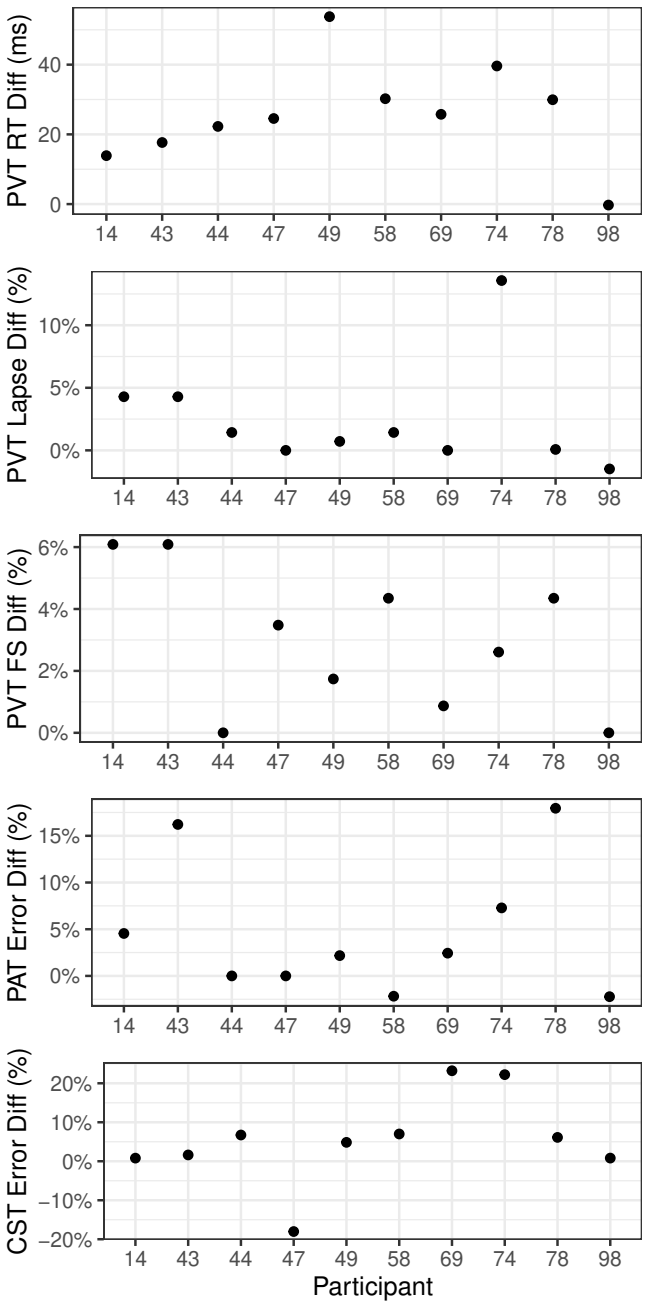

Figure 7: Differences between hypoxic and normoxic performance for each participant on each of the five metrics that showed significant differences between the two conditions. A positive value indicates worse performance in the hypoxic condition. Only participants that received the hypoxic condition first are shown.

Conclusion

This research investigated the impact of approximately 40 minutes of hypoxic hypoxia (10.6% O_2) on cognitive performance. The analysis of data from the PVT, PAT, and CST found differential effects of hypoxia on different cognitive processes. The RT and lapses in the PVT were effected throughout the protocol, showing a moderate slowing effect. PVT false starts and CST errors were also increased throughout the protocol, showing a decreased ability to inhibit responses. Greater errors for hypoxic participants only revealed themselves after about 20 minutes, showing a delayed effect on declarative memory processes. These quantitative analyses on aggregate data and qualitative analysis on individual data suggest that the PVT could provide a good behavioral diagnostic tool for hypoxia. However, planned future research, including the analysis of physiological data (like blood oxygen saturation), are needed to draw more definitive conclusions.

Acknowledgments

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