Deficits in Visual Processing During Hypoxia as Evidenced by Visual Mismatch Negativity

Kara J. Blacker; Todd R. Seech; Matthew E. Funke; Micah J. Kinney

INTRODUCTION: Hypoxia is an ever-present threat in tactical aviation and gained recent attention due to its putative role in physiological episodes. Previous work has demonstrated that hypoxia negatively impacts a variety of sensory, cognitive, and motor systems. In particular, the visual system is one of the earliest systems affected by hypoxia. While the majority of previous studies have relied on self-report and behavioral testing, the use of event-related potentials as a novel tool to monitor responses to low oxygen in humans has recently been investigated. Specifically, ERP components that are evoked passively in response to unattended changes in background sensory stimulation have been explored.

METHOD: Subjects ($N = 28$) completed a continuous visuomotor tracking task while EEG was recorded. During the tracking task, a series of "standard" color checkerboard patterns were presented in the periphery while occasionally a "deviant" color checkerboard was presented. The visual mismatch negativity (MMN) component was assessed in response to the deviant compared to the standard stimuli. Subjects completed two sessions in counterbalanced order that only differed by the oxygen concentration breathed (10.6% vs. 20.4%).

RESULTS: Results demonstrated a significant reduction in the amplitude of the visual MMN under hypoxic compared to normoxic conditions, showing a 50% reduction in amplitude during hypoxia. Our results suggest that during low-oxygen exposure the ability to detect environmental changes and process sensory information is impaired.

DISCUSSION: The visual MMN may represent an early and reliable predictor of sensory and cognitive deficits during hypoxia exposure, which may be of great use to the aviation community.

KEYWORDS: hypoxia, event-related potentials, mismatch negativity, visual processing.

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Hypoxia is generally recognized as one of the most serious and frequently encountered risks in aviation medicine. Currently, military aircraft have warning systems only for the oxygen concentration provided upstream in the life support system. The gas reaching the pilot is not tested, and there are no warnings of other conditions that may cause or exacerbate hypoxia in the cockpit. Thus, the risk of low-oxygen exposure is ever-present in tactical aviation and the current standard of practice is to have pilots undergo hypoxia training to facilitate identification of hypoxia or hypoxia-like symptoms.[2] However, the symptoms of hypoxia are broad ranging and idiosyncratic, with the most commonly reported symptoms being lightheadedness, dizziness, mental confusion, visual impairment, and tingling.[30]

Despite individual differences in symptom experiences and reporting, hypoxia has been routinely shown to negatively impact a number of perceptual, cognitive, and motor systems that are critical to various performance outcomes. For example, exposure to a low-oxygen environment leads to increases in response time (RT) latency,[6–8] and this deficit has been shown to persist for up to 2 h postexposure.[25] Hypoxia has also been shown to negatively impact performance on higher-order cognitive tasks, such as working memory.[19] One of the most noted and pronounced effects of hypoxia is on the visual system,

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specifically resulting in changes to the perception of light intensity[6] and the impairment of color vision.[3,4]

Moreover, it has been established that the electrical activity of the brain is sensitive to its oxygen supply. Some studies have shown changes in resting state spectral EEG activity, such as increased delta and/or theta power, as well as changes in alpha power under hypoxic compared to normoxic conditions.[15,23] While these studies demonstrate the sensitivity of resting state EEG measures to hypoxia, the reported changes in spectral power provide little insight into the specific underlying perceptual or cognitive functions that are affected.

Alternative to resting state EEG, event-related potentials (ERPs) have been used for decades to elucidate various aspects of sensory, cognitive, and motor processes that underlie human thought and behavior.[16] Few studies to date have examined ERPs to investigate the influence of hypoxia on sensory or higher-order cognitive processing. The results of one early study using an active auditory target detection task showed evidence of a delayed latency of the P3b component that corresponded to a lag in RT.[7] More recently, Altbäcker et al.[1] assessed the sensitivity of three variants of the P300 component (i.e., Target P3, No Go P3, and Novelty P3) to hypoxia evoked in response to a modified continuous performance task. Similar to that found by Fowler and Lindeis,[7] these components were elicited via an active auditory target detection task while subjects attended to a continuous stream of letters. The results demonstrated that the Novelty P3 amplitude, but not the other components, was significantly decreased under hypoxic compared to normoxic conditions. These two previous studies suggest that the P300 component, when elicited in response to an active foreground auditory task, is sensitive to hypoxia.

Furthermore, a recent study demonstrated for the first time that passively elicited ERPs, reflecting preattentive auditory processing, are disrupted by acute hypoxia.[26] In this study, a classic "oddball" paradigm was used whereby a series of frequently presented auditory tones (i.e., "standards") that were identical in pitch and duration (e.g., "beep, beep, beep, beep…") were occasionally interrupted by a physically deviant (i.e., "oddball") tone (e.g., "beeeeep"). Subjects were presented with these stimuli and instructed to ignore them while performing a central visuomotor tracking task. Three sequentially evoked ERP measures occur in response to these auditory stimuli: the mismatch negativity (MMN), the P3a, and the reorienting negativity (RON). These ERPs reliably index automatic and preattentive stages of early auditory information processing.[20,21] This type of passive oddball paradigm and the subsequent ERPs derived in response to those auditory stimuli have been shown to be sensitive to a number of central nervous system perturbations including acute pharmacologic challenges and cognitive training interventions.[11,12] Seech et al. found a significant reduction in the amplitude of the P3a during a hypoxic exposure compared to normoxic conditions.[26] The P3a is thought to reflect a higher-order orienting or covert shift of attention to the unexpected, deviant stimulus.[27,28]

This previous study demonstrated the feasibility of using passively elicited ERPs to index sensory deficits during hypoxia. Seech et al. used an auditory paradigm because there is a robust clinical literature to support the influence of central nervous system perturbations on the MMN, P3a, and RON in the auditory domain.[26] However, the visual system is more sensitive to hypoxia than the auditory system. The visual system is sensitive to its oxygen supply at multiple levels including the retina, photoreceptors, and cortical and subcortical pathways. Estimates of visual system projections throughout the cortex are thought to be in the hundreds, with interactions beyond the visual cortex into areas such as frontal, temporal, parietal lobes, and midbrain.[18] Thus, cortical insults either from injury or hypoxia are more likely to lead to a visual perception deficit.[3,9] Additionally, unique metabolic requirements for the visual system result in consumption both in light and darkness. Cone photoreceptors, which enable color vision, consume more energy than rods, as rods do not saturate in bright light. In total, visual processing ranks as one of the highest energy- and oxygen-demanding systems of the brain.[29]

Given the visual system's known sensitivity to hypoxia, in the current study we sought to use a visual oddball paradigm to elicit a visual MMN component and test the effects of hypoxia on this passively elicited visual ERP. The MMN has been demonstrated in a number of sensory modalities, including visual, olfactory, and somatosensory.[16] In the visual domain, the MMN has been elicited using a variety of stimulus features including contrast, shape, color, size, motion direction, form, orientation, and spatial frequency.[14,24] A visual MMN has more recently been found in response to pattern violations in visual stimuli.[5] Similar to the classic auditory MMN, the visual MMN has been shown to be impaired in certain clinical populations, such as bipolar disorder.[17] In our previous study, we found a reduction in the amplitude of the auditory P3a during a passive oddball paradigm when acute hypoxia was induced.[26] Given the greater sensitivity of the visual system, the current study sought to replicate and extend this previous work with a passive visual oddball paradigm. We predicted that hypoxia would elicit a reduction in the amplitude of the visual MMN compared to normoxic conditions.

METHODS

Subjects

A total of 28 healthy adults (age: $M=28.86$, $SD=7.56$; 21 men) participated for monetary compensation. Our sample contained many more men than women, which is reflective of both the overall military community and specifically the military aviation community. All subjects were recruited through flyers and online announcements. Subjects who completed the study received $200. The study protocol was approved by the Naval Medical Research Unit – Dayton's Institutional Review Board in compliance with all applicable federal regulations governing the protection of human subjects. All subjects self-reported normal or corrected-to-normal vision, no history of psychological, neurological, or medical diagnosis, no use of tobacco in the past 6 mo, and no excessive alcohol use. Subjects

all had normal color vision as tested binocularly with the Waggoner Computerized Color Vision Test (Waggoner Diagnostics) under ambient room illumination. Two subjects' EEG data were lost due to experimenter error and one subject dropped below the oxygen saturation safety criteria and did not complete the hypoxia session. These data were not included in subsequent analyses.

Procedures

Subjects completed two counterbalanced experimental sessions separated by an average of 6.5 d (SD = 11.3). Testing was conducted in a Reduced Oxygen Breathing Environment (ROBE; **Fig. 1**), which simulates the oxygen concentrations of high altitudes without the risks associated with reduced barometric pressure found in altitude chambers or other hypoxia replication devices. The two experimental sessions differed only in the oxygen content found within the testing chamber on the days of participation. Each exposure lasted 27 minutes. During the normoxia session, subjects were exposed to near-equivalent room air (20.4% O_2), while during the hypoxia session, they were exposed to a 10.6% O_2 mixture (i.e., environmental equivalent of ~17,500 ft). Throughout both testing sessions, subjects wore a NoninConnect Model 3230 finger-mounted pulse oximeter (Nonin Medical, Inc., Plymouth, MN) to index peripheral oxygen saturation (S_pO_2) for both safety monitoring purposes and as a variable of interest.

Subjects were seated approximately 90 cm from three 21-in monitors. A visuomotor tracking task was presented on the center monitor and subjects used a joystick to align an independently moving reticle (using a sinusoidal equation to provide pseudorandom motion requiring constant correction by the subject) with the center point of a crosshair displayed on the screen (see Fig. 1). The tracking task and peripheral visual stimuli (described below) were both programmed in and controlled by Unity software (Unity Technologies, Frederick, MD). Performance on this task was assessed as the difference or error in pixels between the center of the reticle and the center of the crosshair display, which was recorded at a 10 Hz sampling rate. Prior to their first session, subjects practiced the tracking task outside the ROBE for 5 min to acclimate to the sensitivity of the joystick.

EEG data were recorded continuously in the ROBE from 64 electrodes covering the whole scalp with approximately uniform density using an elastic electrode cap (ActiCHamp, Brain Products GmbH, Gilching, Germany) referenced to the right mastoid (TP9) in DC mode, at a sampling rate of 1000 Hz. Electrode impedance for all channels was kept below 10 kΩ.

Visual stimuli were presented bilaterally on peripheral 21-in monitors (Fig. 1). Physically isoluminant red/black and green/black checkerboards were used as stimuli, which subtended a visual angle of 16.26° overall and 8.13° per checkered box. The peak wavelength for red (x = 0.6559, y = 0.3350) and green

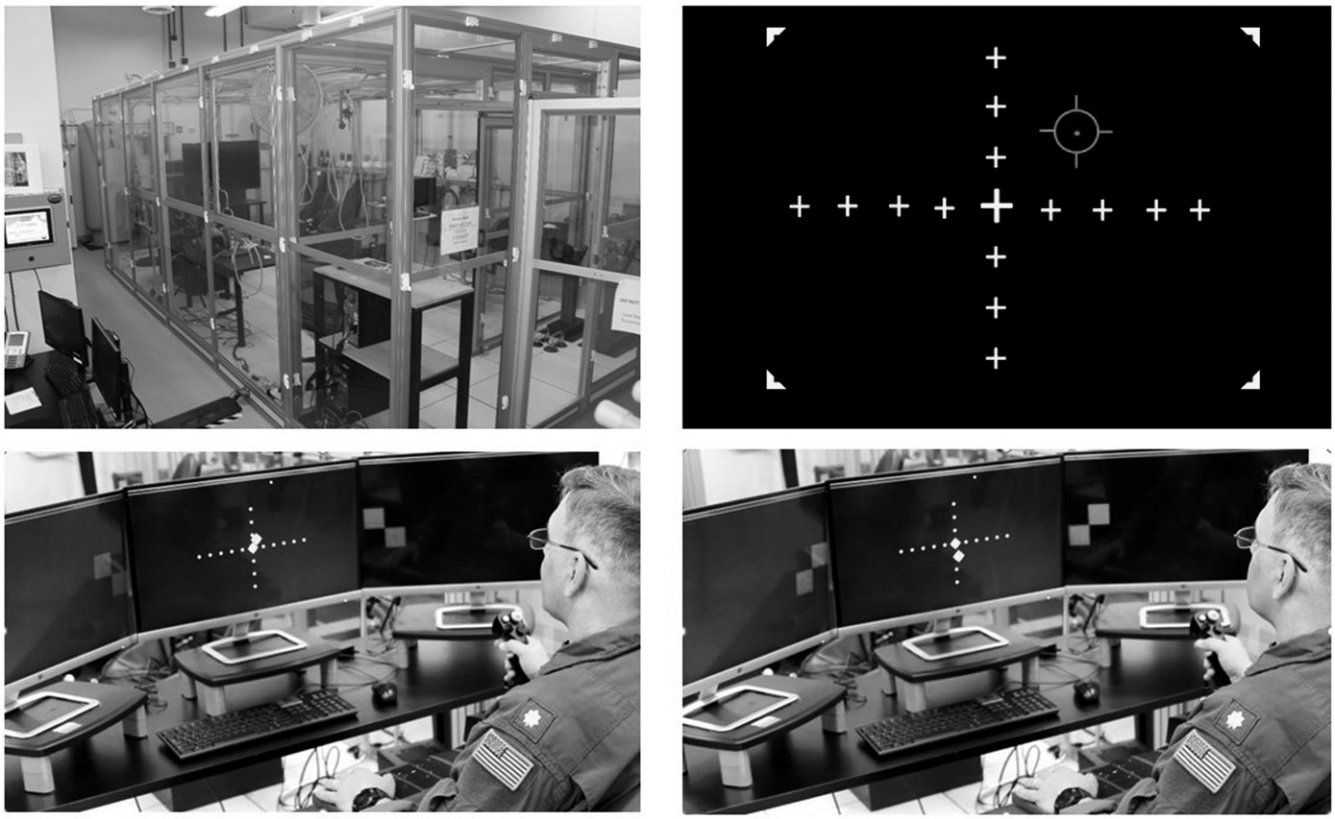

Fig. 1. Top left: Reduced Oxygen Breathing Environment (ROBE) where experimental sessions took place. Top right: Visuomotor tracking task schematic. Subjects were tasked with using a joystick to keep the grey reticle in the center of the white crosshairs over the course of a 27 min exposure. Bottom: three monitor setup with central tracking task and peripheral checkerboard stimuli. (Photos Courtesy of NAMRU-Dayton.)

(x = 0.3102, y = 0.5812) monitor colors were 612 nm and 532 nm, respectively, as measured by a Photo Research PR640 Spectroradiometer. Checkerboard patterns were presented for 100 ms with a 500-ms interstimulus interval and were located 29.7° from the center. Subjects were presented with the "standard" color checkerboard for 90% of trials ($N = 2082$) and the "deviant" color checkerboard for 10% of trials ($N = 232$). Red and green were counterbalanced for use as standard and deviant across subjects.

EEG data were processed using the Fieldtrip software package.[22] Data were segmented into epochs covering the time from 100 ms before to 500 ms after the onset of each bilateral checkerboard stimulus presentation. After trial epochs were created, data were low-pass filtered at 20 Hz, and rereferenced using a common average reference. Independent components analysis (ICA) was performed on epoched data and the eye blink component and lateral eye movement components were removed for every subject. After ICA, EEG waveforms from frontal electrodes (i.e., Fp1, Fp2) were visually inspected to identify voltage fluctuations typical of gross motor movements (amplitude > 75 μV). Trials containing these types of artifacts were rejected entirely. Any subject who lost > 35% of total trials due to artifact rejection was excluded from any subsequent analyses ($N = 1$). The remaining included subjects ($N = 24$) lost an average of 5.9% (SD = 8.9) of trials for the normoxia session and 4.7% (SD = 4.3) for the hypoxia session due to artifact rejection (range: 0–34%). After artifact rejection, average waveforms were calculated for standard and deviant trials separately and then difference waves were created as standard minus deviant. Difference waves were then subjected to parametric *t*-tests to compare between sessions.

Previous work has established that the visual MMN has two distinct neural generators located in the visual cortex and prefrontal cortex.[10,13] Therefore, MMN amplitude was examined for two a priori groups of electrodes based on this previous work. Posterior electrodes were chosen as PO8, PO4, POz, PO7, O1, O2, and Oz and frontal midline electrodes were chosen as Fz, FCz, and Cz.

RESULTS

Performance was measured as the amount of error between the reticle that the subject controlled and the stationary center target (**Fig. 2**). A 2 (session: normoxia vs. hypoxia) × 9 (time bin) repeated-measures ANOVA was tested on error. Neither the main effect of time [$F(8,16) = 1.729$, $P = 0.094$] nor the main effect of session [$F(1,23) = 0.063$, $P = 0.804$] reached significance. However, the session × time interaction was significant [$F(8,16) = 2.309$, $P = 0.022$, $\eta_p^2 = 0.091$]. Post hoc paired-samples *t*-tests with a Bonferroni correction for multiple comparisons (i.e., 0.05/9 = 0.0056) showed that no time bin reached statistical significance.

S_pO_2 was monitored throughout the 27 min for both sessions. A 2 (session: normoxia vs. hypoxia) × 9 (time bin) repeated-measures ANOVA was tested on S_pO_2. Both the main

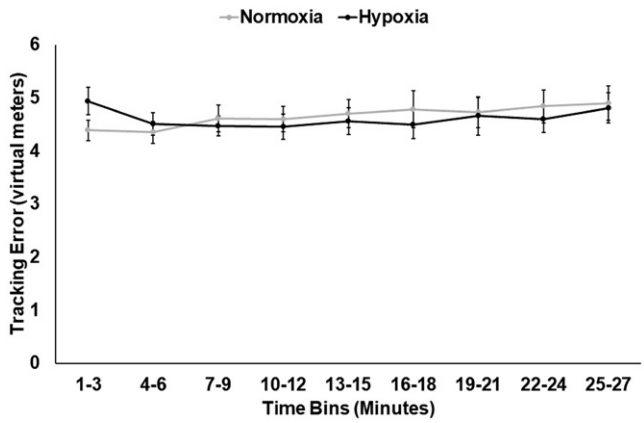

Fig. 2. Visuomotor tracking task performance over time for each session separately. Tracking error was measured in Unity units, which are arbitrary units that correspond to virtual meters. Error bars represent SEM.

effect of session [$F(1,22) = 203.380$, $P < 0.001$, $\eta_p^2 = 0.902$] and the main effect of time bin [$F(8,15) = 66.343$, $P < 0.001$, $\eta_p^2 = 0.751$] were significant with lower S_pO_2 during hypoxia and in the later time bins. The session × time bin interaction [$F(8,15) = 61.775$, $P < 0.001$, $\eta_p^2 = 0.737$] was also significant, demonstrating that S_pO_2 dropped over time more drastically during hypoxia compared to normoxia (**Fig. 3**).

Two separate parametric *t*-tests on amplitude were conducted on the electrode groups of interest. At the posterior electrodes (**Fig. 4A**) there was a significant reduction in the amplitude of the MMN (i.e., 170–185 ms) for the hypoxia compared to the normoxia session [$t(23) = 2.206$, $P = 0.0376$]. At the frontal midline electrodes (**Fig. 4B**) there was also a significant reduction in the amplitude of the MMN (i.e., 185–200 ms) for the hypoxia compared to normoxia session [$t(23) = 2.244$, $P = 0.0348$]. Due to the use of a common average reference, the polarity of the MMN is negative for posterior electrodes and positive for frontal electrodes (**Fig. 4C**).

While the above approach using a difference wave of the average response to standard and deviant stimuli is typical in the MMN literature, it does introduce the issue of comparing averages from unequal trial numbers. As the paradigm is

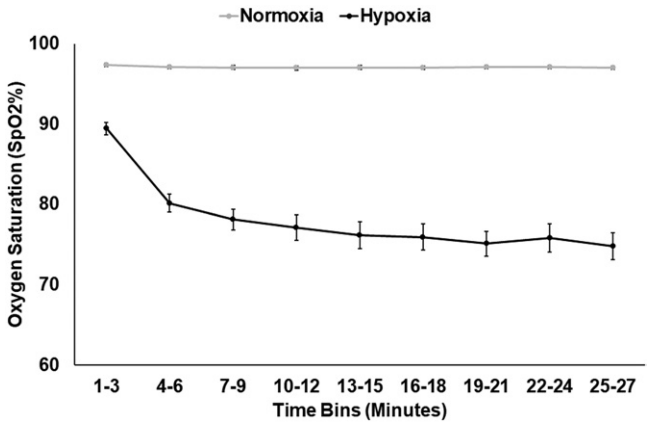

Fig. 3. Oxygen saturation (S_pO_2%) over time for each session separately. Error bars represent SEM.

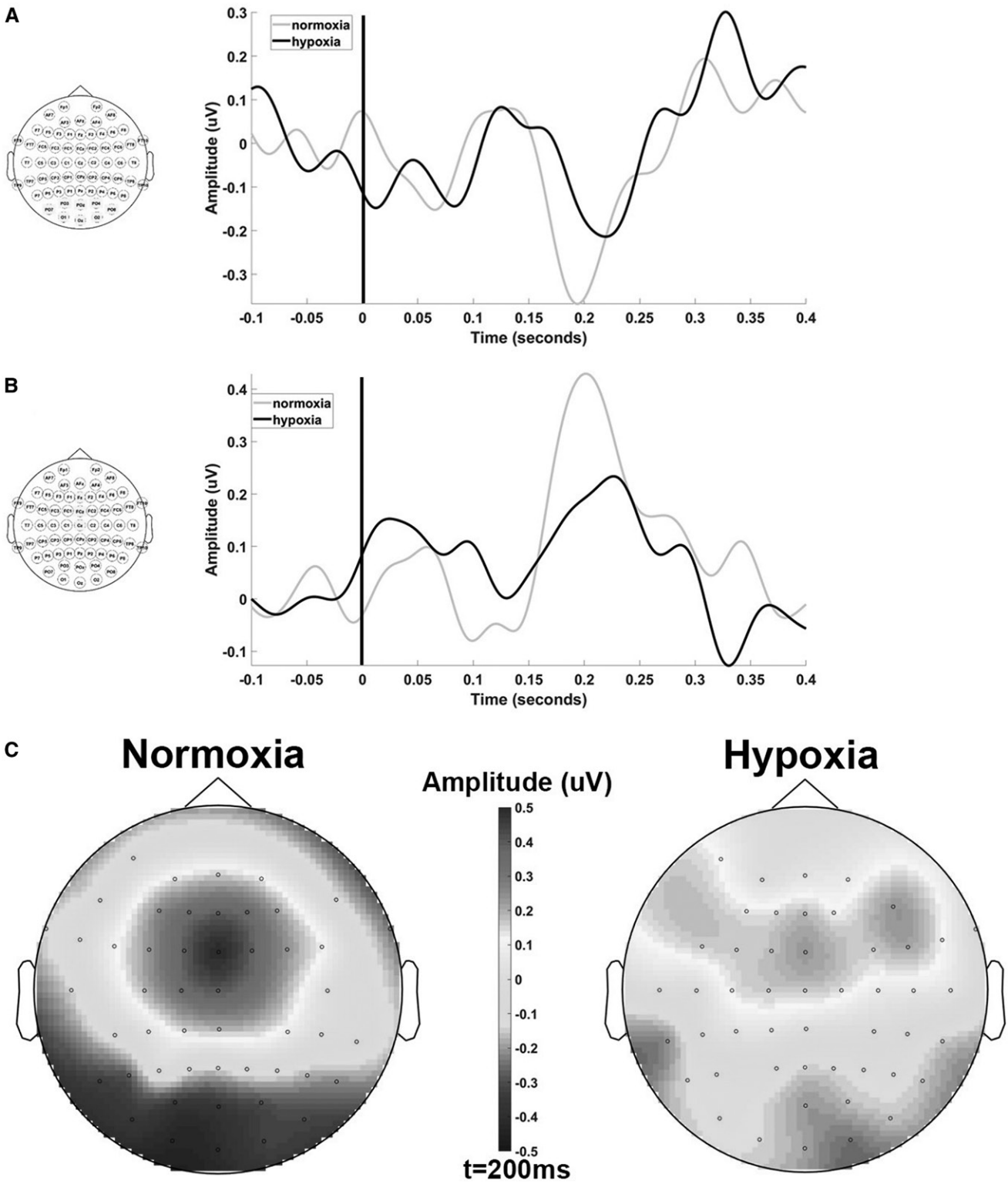

Fig. 4. ERP difference waveforms (standard – deviant) for each experimental session for A) a group of posterior electrodes and B) a group of frontal midline electrodes. C) Group average scalp maps of MMN amplitude at 200 ms poststimulus for normoxia (left) and hypoxia (right) sessions. The use of a common average reference results in a polarity reversal between posterior and frontal sites.

designed, there are far more standard stimuli to average across compared to deviant stimuli. To ensure that this approach did not unduly affect our results, we selected a random sample of standard stimuli and averaged across those. For each subject, we randomly selected a subset of standard stimuli in the same amount as their final count of deviant trials to create equal trial counts for averaging. With this approach, our parametric *t*-tests from above were retested. At frontal electrode sites, there

remained a significant reduction in the amplitude of the MMN during hypoxia compared to normoxia [$t(23) = 2.536$, $P = 0.0184$]. However, at posterior electrode sites, the reduction in amplitude only showed a trend for a reduction during hypoxia compared to normoxia [$t(23) = 1.608$, $P = 0.122$]. **Table I** has descriptive statistics for the peak amplitude of the difference wave for each of these approaches, the peak amplitude for the standard and deviant responses separately, as well as the latency of the MMN peak amplitude.

DISCUSSION

In the current study, we sought to extend previous work using passively elicited ERPs to assess sensory deficits during acute hypoxia. While previous work had shown a deficit in auditory processing during low-oxygen exposure,[26] here we demonstrated that visual processing is also disturbed during acute hypoxia and can be detected using ERPs. Specifically, we found a reduction in the amplitude of the visual MMN component when subjects were exposed to 10.6% O_2 (~17,500 ft equivalent) compared to when breathing ambient 20.4% O_2. The visual MMN was elicited by standard and deviant colored checkerboards being presented in subjects' peripheral vision while attending to a centrally presented visuomotor tracking task. The passively elicited nature of these neural responses is promising for future development in understanding how hypoxia impairs various sensory systems and ultimately flight-relevant performance.

In our group's previous study, we found a reduction in the amplitude of the P3a during hypoxia using an auditory oddball paradigm.[26] Here using a visual paradigm, we observed a reduction in the MMN component during hypoxia. The MMN reflects a preattentive sensory discrimination process, which occurs earlier in the sensory processing stream compared to the P3a. This earlier effect for visual stimuli compared to auditory stimuli is consistent with the previous work showing that the visual system is particularly sensitive to its oxygen supply[29] and is robustly impacted by hypoxia.[3,9] Thus, our results demonstrate that the visual system is impaired at a very early, preattentive stage of processing under low-oxygen conditions.

The use of a passive, versus active, ERP paradigm to detect hypoxia is critical because it represents a method for potential development of an early warning system for pilots and aircrew. At the very least, passive ERP paradigms allow for an independent measure of sensory functioning in addition to other performance variables (i.e., the visuomotor tracking task used here), which may facilitate better understanding of how and when someone is impaired during a low-oxygen exposure. Furthermore, the use of visual stimuli to elicit a passive neural response during hypoxia is potentially more advantageous for use during inflight performance. Auditory stimuli would likely interfere with necessary communication between aircrew, friendly assets, and air traffic control. In the current study, we were able to elicit the visual MMN using peripheral stimuli that were relatively unobtrusive and allowed the individual to remain focused on their primary task, which may also allow for future integration into helmet mounted displays.

Interestingly, in the current study we did not observe a robust effect of hypoxia on performance. Tracking task error did not significantly differ between the hypoxia and normoxia conditions. In our previous study,[26] we used a similar task and saw more marked changes in performance; however, we used a different version of the task here to accommodate the visual oddball stimuli into the same program. It is possible that our lack of effects here were due to changes in the movement parameters of the reticle or sensitivity of the joystick. This lack of a performance effect further supports the sensitivity of the visual MMN to hypoxia as it demonstrates that the passively elicited neural signal is disrupted even when overt performance may not be impaired. A long-term aim of this work is to use EEG to develop an early detector of hypoxia prior to flight crew impairment. The current study represents a first step toward that aim.

The current study had a few limitations worth discussing. First, the resolution of the ERP data is lower than that of our behavioral performance and physiological measures. While we can examine performance and S_pO_2 on a relatively short time scale (i.e., here we used 3 min epochs), the ERP data does not lend itself to this fine-grained division. Indeed, we noticed here that there was much greater variation in the visual MMN than we had previously found using the auditory paradigm. Thus, while visual stimuli may be preferable from a practical standpoint, the resulting signal seems to be noisier than the auditory responses. However, in the previous auditory findings,[26] the trial count for standard and deviant trials used for the difference waveforms was not equated, as it was done here. It is possible that implementing the approach here to compare

Table I. Descriptive Statistics for Amplitude and Latency.*

	NORMOXIA				HYPOXIA			
	Fz		Oz		Fz		Oz	
	MEAN	SEM	MEAN	SEM	MEAN	SEM	MEAN	SEM
MMN Amplitude (difference wave)	0.685	0.097	−0.625	0.143	0.587	0.129	−0.538	0.108
MMN Latency (difference wave)	204.04	5.63	203.92	6.29	205.92	6.14	201.25	6.69
Standard Amplitude (all trials)	0.294	0.080	−0.765	0.140	0.278	0.083	−0.597	0.133
Standard Amplitude (randomly sampled trials)	0.394	0.100	−0.907	0.136	0.563	0.123	−0.722	0.166
Deviant Amplitude	0.705	0.106	−1.078	0.146	0.583	0.131	−0.782	0.171

* Amplitude values are peak amplitude between 150–250 ms in uV. Latency is at the peak amplitude in milliseconds. Values are shown for a single frontal electrode (Fz) and a single posterior electrode (Oz). SEM: standard error of the mean.

like-sized samples of trials via random sampling of standard trials would have increased the variation in the auditory waveforms. Future work might focus on additional visual ERP components that may have a more robust signal to noise ratio while preserving the passive nature of the task. A second limitation was the use of only one altitude for the hypoxia manipulation. Future studies should examine the sensitivity of these passively elicited ERPs to several gradations of low-oxygen concentrations.

In conclusion, our current study demonstrated for the first time that a passively elicited visual ERP is disrupted during hypoxic versus normoxic conditions. This experimental approach may provide the first steps to developing an early warning system for hypoxia in the cockpit using EEG. While many additional technological advances are needed to field this concept operationally, we have established the feasibility of detecting hypoxia using passive neural signals now in two sensory modalities.

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