NAMRU-D-20-049 Dec-2019

NAVAL MEDICAL RESEARCH UNIT DAYTON

The Brain-Based Hypoxia Signature: A Superior Predictor of Performance

by Todd R. Seech[1], Matthew E. Funke[2], Richard F. Sharp[3], Gregory A. Light[3,4], & Kara J. Blacker[2,5]

[1]Warfighter Effectiveness Research Center, U.S. Air Force Academy, CO, USA
[2]Naval Medical Research Unit-Dayton, Wright-Patterson AFB, OH, USA
[3]Department of Psychiatry, University of California San Diego, San Diego, CA, USA
[4]VISN-22 Mental Illness, Research Education and Clinical Center, VA San Diego Healthcare System, San Diego, CA, USA
[5]The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, MD, USA

STATEMENTS

Disclaimer

The views expressed in this manuscript are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U.S. Government.

Source of Support

This work was supported by the Office of Naval Research and funded by work unit number 0601153N.

Human Research/Institutional Review Board (IRB) statement

The study protocol was approved by the Naval Medical Research Unit Dayton Institutional Review Board in compliance with all applicable federal regulations governing the protection of human subjects.

The Brain-Based Hypoxia Signature: A Superior Predictor of Performance

Todd R. Seech[1], Matthew E. Funke[2], Richard F. Sharp[3], Gregory A. Light[3,4], & *Kara J. Blacker[2,5]

[1]Warfighter Effectiveness Research Center, U.S. Air Force Academy, CO, USA
[2]Naval Medical Research Unit-Dayton, Wright-Patterson AFB, OH, USA
[3]Department of Psychiatry, University of California San Diego, San Diego, CA, USA
[4]VISN-22 Mental Illness, Research Education and Clinical Center, VA San Diego Healthcare System, San Diego, CA, USA
[5]The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, MD, USA

Abstract

The ability to detect novelty in our environment is a critical sensory function. A reliable set of event-related potentials (ERP), known as the auditory deviance response (ADR), are elicited in the absence of directed attention and indexes functionally relevant networks. The ADR consists of three peaks: mismatch negativity (MMN), P3a, and reorienting negativity (RON) that are sequentially evoked in response to unattended changes in repetitive background stimulation. While previous studies have established the ADR's sensitivity to a range of pharmacologic and non-pharmacologic interventions and are leading candidate biomarkers of perturbations of the central nervous system (CNS), here we sought to determine if ADR peaks are sensitive to decreases in breathable oxygen. Participants performed a visuomotor tracking task while EEG was recorded during two 27 minute sessions. The two sessions differed in the amount of environmental oxygen available: 10.6% O_2 (hypoxia) versus 20.4% O_2 (normoxia). ERPs were measured while a series of identical, or "standard," tones combined with occasional "oddball," tones, were presented. MMN, P3a, and RON were assessed in response to the oddball compared to the standard stimuli. Behavioral impairment during hypoxia was demonstrated by a deficit in tracking performance compared to the normoxia condition. Whereas no changes were detected in the MMN or RON, the amplitude of the P3a component was significantly reduced during hypoxia compared to normoxia, within the first 9 minutes of exposure. To our knowledge, this is the first study to demonstrate the effect of low oxygen exposure on passively elicited neural measures of early sensory processing. This study demonstrates that passively elicited EEG measures, reflecting pre-attentive auditory processing, are disrupted by acute hypoxia. Results have implications for the development of biomarkers for the non-invasive assessment of CNS perturbations.

1. Introduction

The amount of information present in the surrounding environment at any given moment far exceeds our perceptual and cognitive capacities. To cope with this surplus of sensory input, the central nervous system (CNS) seamlessly governs what information transitions from routine sensory processing to allow for the allocation of additional cognitive resources necessary for processing unexpected changes in the environment (Braff & Light, 2004). The efficiency of this early information processing can be reliably assessed using event-related potentials (ERPs). The mismatch negativity (MMN), P3a, and reorienting negativity (RON) are ERP measures that are sequentially evoked as a triphasic auditory deviance response (ADR) complex (Rissling et al., 2012), and can reliably index automatic and preattentive stages of early auditory information processing (Naatanen, Gaillard, & Mantysalo, 1978; Naatanen, Kujala, & Light, 2019; Naatanen, Paavilainen, Rinne, & Alho, 2007). The ADR is passively elicited when a series of frequently presented auditory tones (i.e., "standards") that are identical in pitch and duration (e.g., "beep, beep, beep, beep…") is occasionally interrupted by a physically deviant (i.e., "oddball") tone (e.g., "beeeeep"). The ADR requires no overt behavioral response from the participant and can be measured in the absence of directed attention, usually while participants perform some other active or passive foreground task in the visual domain.

Notably, ADR responses can be measured in rodents, non-human primates, fetuses, sleeping infants and adults, and even comatose individuals (Amann et al., 2010; Featherstone et al., 2015; Gil-Da-Costa, Stoner, Fung, & Albright, 2013; Javitt, Steinschneider, Schroeder, Vaughan, & Arezzo, 1994; Swerdlow, Powell, Breier, Hines, & Light, 2013; Todd, Harms, Michie, & Schall, 2013). The MMN response peaks at 120-200ms and is followed by a positive-going waveform, the P3a, which peaks at 250-320ms. In some cases, the P3a is followed by a negative going wave that peaks at 350-450ms known as the RON (Munka & Berti, 2006; Rissling et al., 2014; Schroger & C., 1998). While the MMN represents a preattentive sensory discrimination process, the P3a is thought to reflect a higher-order orienting or covert shifting of attentional resources to an unexpected stimulus. RON is thought to reflect a re-orienting of attention back to the foreground task, though the underlying psychological construct is less developed. Important for the current study, the ADR complex has been shown to be sensitive to a number of CNS perturbations including acute pharmacologic challenges and cognitive training interventions (Dulude, Labelle, & Knott, 2010; Hochberger et al., 2019; Kantrowitz & Javitt, 2010; Kawakubo et al., 2007; Perez, Miyakoshi, Makeig, & Light, 2019; Perez et al., 2017; Swerdlow et al., 2016). The ADR components are translational biomarkers elicited in the absence of directed attention and index functionally relevant networks, thus they are increasingly used as biomarkers in the development of interventions that target CNS dysfunction (Hochberger et al., 2019; Light & Braff, 2005; Light & Naatanen, 2013; Perez et al., 2017; Swerdlow, Bhakta, & Light, 2018).

Despite the automaticity of this novelty detection function, these processes carry a neural expenditure that requires energy, which is partially supplied through oxygen. While the average human brain represents only about 2% of one's total body weight, it accounts for approximately 20% of the oxygen consumption for the entire body (Clarke & Sokoloff, 1999). Therefore, any decrement in the amount of breathable oxygen available may impact a host of neural functions, perhaps even the earliest sensory information processes, like those measured by the ADR complex.

The condition in which an organism has insufficient environmental oxygen is known as hypoxic hypoxia (differing from hypoxia brought about by other factors, such as histotoxic

hypoxia). Notably, hypoxic hypoxia occurs in healthy individuals when they ascend to high altitude or when breathing mixtures of gases with low oxygen content (e.g., while underwater diving), particularly when using rebreather systems that control the amount of oxygen in the supplied air. For simplicity, subsequent use of the term "hypoxia" will indicate hypoxic hypoxia.

The symptoms of hypoxia depend on the severity (i.e., dose) and exposure time. In cases of altitude sickness in which hypoxia develops gradually, symptoms can include fatigue, numbness or tingling of extremities and nausea (Chapman, 2014), but specific symptoms have been shown to be highly idiosyncratic in other settings (e.g., flight training; Artino, Folga, & Swan, 2006). Despite individual differences in some symptom reports, hypoxia in general has been shown to negatively affect performance on a range of perceptual, cognitive, and motor tasks. For example, hypoxia increases pupillary response latency (Barry Fowler, White, Wright, & Ackles, 1982), changes perception of stimulus intensity (Bess Fowler, Banner, & Pogue, 1993), impairs color vision (Connolly, Barbur, Hosking, & Moorhead, 2008), and reduces reaction time (RT; Barry Fowler & Lindeis, 1992; Barry Fowler, Taylor, & Porlier, 1987; Barry Fowler et al., 1982; Shukitt-Hale, Banderet, & Lieberman, 1998). Further, hypoxia often results in decreases in working memory (Malle et al., 2013; Shukitt-Hale et al., 1994), as well as other higher-order cognitive tasks (Green & Morgan, 1985; for a review see, McMorris, Hale, Barwood, Costello, & Corbett, 2017).

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 (depending on whether eyes were opened versus closed during recording) under hypoxic compared to normoxic conditions (Kraaier, Van Huffelen, & Wieneke, 1988; Ozaki, Watanabe, & Suzuki, 1995; Papadelis, Kourtidou-Papadeli, Bamidis, Maglaveras, & Pappas, 2007; Schellart & Reits, 2001). 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.

Few studies to date have examined ERPs to investigate the influence of hypoxia on sensory and/or higher-order cognitive processing. The results of one early study of an active auditory target detection task showed evidence of a delayed latency of the P3b component to target stimuli that corresponded to a lag in RT to those auditory stimuli (Barry Fowler & Lindeis, 1992). More recently, Altbäcker et al. (2019) 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 Barry Fowler and Lindeis (1992), these components were elicited via an active target detection task while participants attended to a continuous stream of letters. The results demonstrated that the Novelty P3, 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 cognitive task, is sensitive to hypoxia.

Given that 1) the brain requires a substantial amount of oxygen to function, 2) neuroelectrical activity is notably affected by hypoxia, and 3) deficits in sensory and higher-order cognitive processes are associated with hypoxia, it is reasonable to suspect that the lower levels of background sensory processing may also be impacted by an insufficient supply of oxygen. Thus, the current study sought to examine the sensitivity of the MMN, P3a, and RON components to acute normobaric hypoxia exposure. Since these ADR components are leading candidate biomarkers for predicting and monitoring response to interventions, determining the profile and

time course of response to acute hypoxia exposure represents an important biomarker validation for future. We anticipated that this signal complex would demonstrate a reduction in all peak amplitudes during hypoxic compared to normoxic conditions. Follow up analyses were also performed to assess the relative timing of this reduction in relation to oxygen saturation (SpO_2) levels and performance on a foreground behavioral task.

2. Materials and Methods

2.1 Participants

A total of 40 healthy adults (age: *M*=29.43, *SD*=5.99; 27 males) participated for monetary compensation. All participants were recruited through flyers and online announcements. Participants who completed the study received $200. All participants enrolled in the study self-reported normal or corrected-to-normal vision, no history of psychological, neurological, or medical diagnosis, no use of tobacco in the past 6 months, and no excessive alcohol use. Participants gave written informed consent approved by the Institutional Review Board of the Naval Medical Research Unit - Dayton.

2.2 Experimental design and procedures

Participants completed two counterbalanced experimental sessions separated by an average of 8.7 days (*SD*=9.9). Testing was conducted in a Reduced Oxygen Breathing Environment (ROBE; Figure 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 the participation. During the normoxia session, participants were exposed to near sea-level 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 the experimental testing sessions, participants wore a NoninConnect Model 3230 finger-mounted pulse oximeter (Nonin Medical, Inc.) to index SpO_2 for both safety monitoring purposes and as a variable of interest.

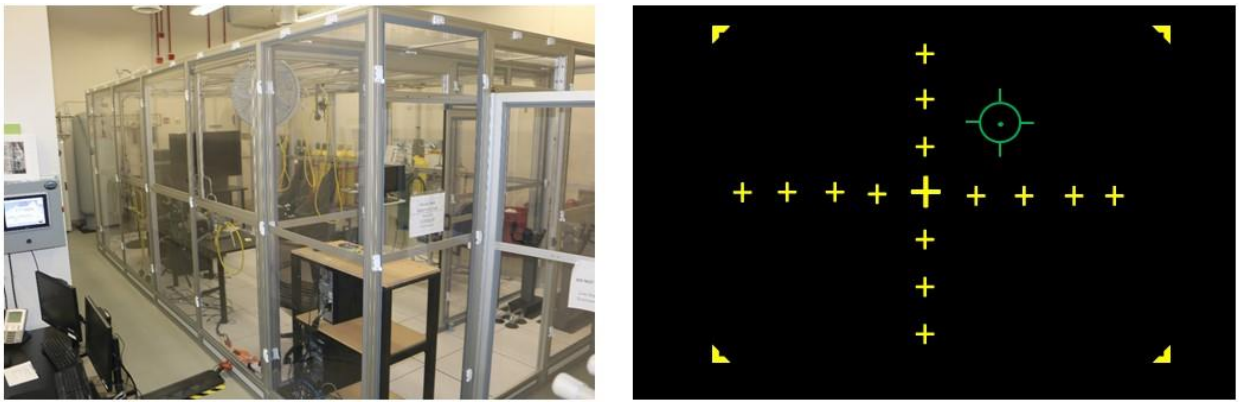

Figure 1. Left: Reduced Oxygen Breathing Environment (ROBE) where experimental sessions took place. Right: Visuomotor tracking task schematic. Participants were tasked with using a joystick to keep the green reticle in the center of the yellow crosshairs over the course of a 27 minute exposure.

2.3 Behavioral tracking task

Participants were seated approximately 90 cm from a 21" monitor and used a joystick to align an independently moving reticle (using a sinusoidal equation to provide pseudorandom motion requiring constant correction by the participant) with the center point of a crosshair displayed on the screen (see Figure 1). 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 10Hz sampling rate. Prior to their first session, participants practiced the tracking task outside the ROBE for 5 minutes to acclimate to the sensitivity of the joystick.

2.4 EEG data acquisition and analysis

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) referenced to the right mastoid (TP9) in DC mode, at a sampling rate of 1000Hz. Electrode impedance for all channels was kept below 10 kΩ.

Auditory stimuli were presented to participants at 85 dB sound pressure level via Etymotic ER3-A insert earphones. The passive auditory oddball paradigm used to elicit ADR measures comprised a sequence of tones, of which 85% were standards (50 ms, 1000 Hz, *n*=2754) and 15% were deviants (7.5%, *n*=243 per deviant type) that differed in stimulus duration (100 ms, 1000 Hz) or both duration and frequency (i.e., 'double-deviant' 100 ms, 1100 Hz). All tones had 5 ms rise/fall times and were presented with a fixed 500 ms stimulus onset asynchrony. Participants were instructed to ignore auditory stimuli while they completed the visuomotor tracking task, described above.

EEG data were processed using EEGLab and Brain Vision Analyzer. Data were down-sampled to 500 Hz and a 0.5 Hz high pass filter, and common average reference were applied for initial preprocessing. Independent Component Analysis (ICA) was applied to continuous data to minimize ocular artifacts. Data were segmented around the stimuli, -100 to 500 ms, baseline corrected, and screened for residual artifacts where segments with amplitudes exceeding ±100 μV in frontocentral electrodes (Fz, FCz, Cz) being rejected. ERP averages for standards and each deviant type were generated separately, and the resultant difference waves were low-pass filtered at 20 Hz. Waveforms were re-referenced to linked mastoids, with ADR amplitudes calculated for data across the entire 27 minute recording as well as binned into three blocks of 9 minutes. Statistical analyses were performed using SPSS v26 and focused on differences in the mean MMN (120-200 ms), P3a (250-320 ms), and RON (350-450 ms) time windows at an a priori defined electrode of interest (i.e., Fz) during hypoxia and normoxia over the three blocks of testing (each 9 minutes).

3. Results

One participant was excluded from all analyses due to below chance level performance on the visuomotor tracking task during both experimental sessions. Three additional participants dropped below our safety designation (i.e., $SpO_2\% < 60$) during the hypoxia session and the session was terminated early. Those three participants' data were included in the subsequent

analyses where possible[1]. One participant's performance data for the normoxia session was lost due to experimenter error.

3.1 Behavioral performance

Performance was measured as the amount of error (in pixels) between the reticle that the participant controlled and the stationary center target (Figure 2A). A 2 (session: normoxia vs. hypoxia) x 3 (time bin) repeated-measures ANOVA was tested on error (Figure 2). The main effect of time was not significant, $F(2,33)=1.08$, $p=0.34$. A main effect of session was significant, $F(1,34)=6.07$, $p<0.05$, $\eta_p^2=0.15$, with performance being impaired in the hypoxia session compared to the normoxia session. The session x time interaction did not reach significance, $F(2,33)=0.24$, $p=0.79$.

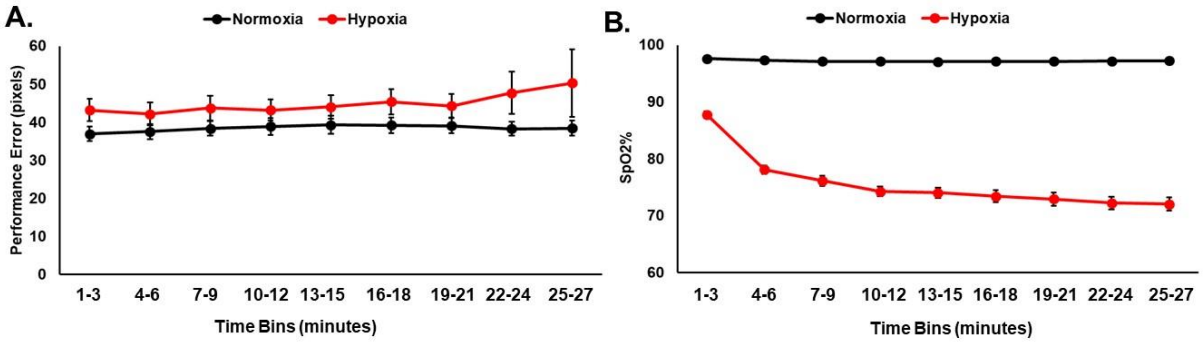

Figure 2. A) Visuomotor tracking task performance shown for hypoxia and normoxia sessions separately. Performance was significantly worse (more error) for hypoxia compared to normoxia. B) SpO_2% data shown for hypoxia and normoxia sessions separately. Error bars represent standard error of the mean.

3.2 Physiological monitoring

SpO_2 and heart rate (beats per minute; BPM) were monitored throughout the 27 minutes for both sessions. A 2 (session: normoxia vs. hypoxia) x 3 (time bin) repeated-measures ANOVA was tested on SpO_2%. Both the main effect of session, $F(1,36)=416.40$, $p<0.001$, $\eta_p^2=0.92$, and the main effect of time bin, $F(2,35)=583.33$, $p<0.001$, $\eta_p^2=0.94$, were significant with lower SpO_2% during hypoxia and in the later time bins. The session x time bin interaction, $F(2,35)=509.91$, $p<0.001$, $\eta_p^2=0.93$, was also significant, demonstrating that SpO_2% dropped over time more drastically during hypoxia compared to normoxia (Figure 2B). Descriptive statistics for SpO_2% and heart rate for both sessions are reported in Table 1.

Table 1. Means (SEM) of physiologic parameters.

[1] All analyses were tested with and without these three participants included. Excluding them did not change the direction or significance of any reported effects.

MEASURE	NORMOXIA		HYPOXIA	
AVERAGE HEART RATE (BPM)	72.98	(2.15)	87.71	(2.36)
MAX HEART RATE (BPM)	85.25	(2.27)	102.28	(2.92)
ST DEV HEART RATE (BPM)	3.55	(0.16)	5.54	(0.44)
AVERAGE SPO_2%	97.29	(0.18)	76.54	(0.82)
MIN SPO_2%	95.78	(0.28)	67.20	(0.88)
ST DEV SPO_2%	0.56	(0.04)	6.70	(0.31)

3.3 Assessment of hypoxia effects on MMN, P3a, and RON amplitudes

A 2 (session: normoxia vs. hypoxia) x 3 (time bins) repeated-measures ANOVA was tested separately for MMN, P3a, and RON amplitudes. For both MMN and RON, no significant effects of session, time bin, or session x time bin interaction were present (all Fs<1.4, all p>0.15). For P3a, significant main effects of session, $F(1,36)=18.6$, $p=0.0001$, $\eta_p^2=0.34$, and time bin, $F(2,35)=5.92$, $p<0.01$, $\eta_p^2=0.25$, were observed with reduced P3a amplitude during hypoxia and over time (Figure 3). Planned follow-up t-tests revealed P3a amplitude reduction evident in each bin, with the largest reduction present in bin 3, $t(36)=2.87$, $p<0.01$.

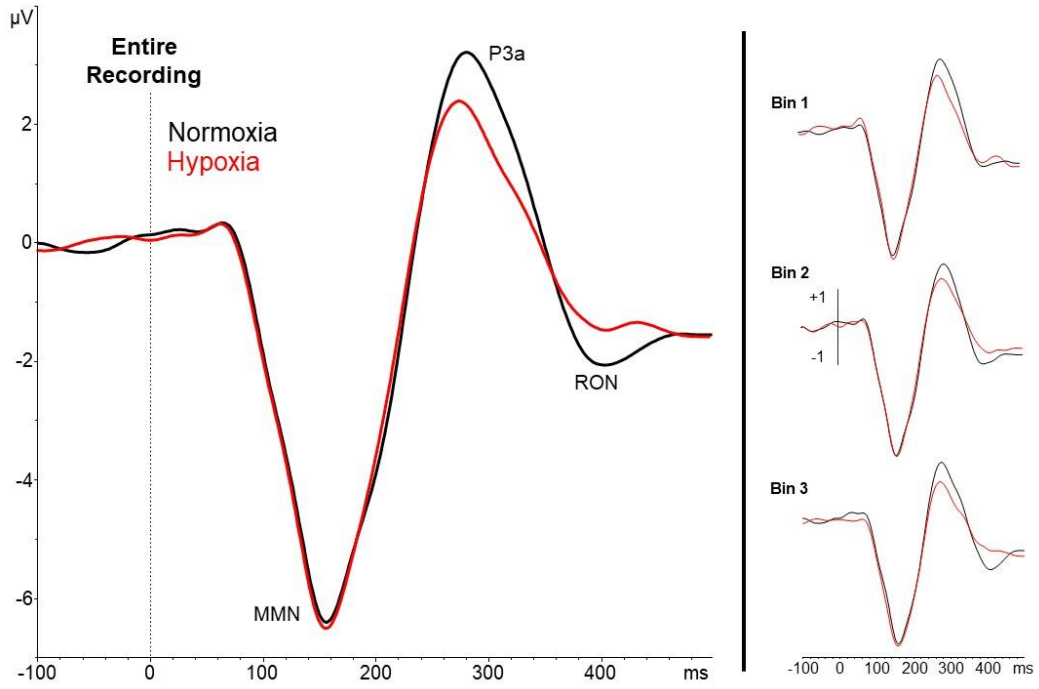

Figure 3. Grand averaged waveforms from electrode Fz for the entire 27 minute exposure (left) and the three 9 minute time bins (right). Results show a reduced amplitude P3a under hypoxic compared to normoxic conditions.

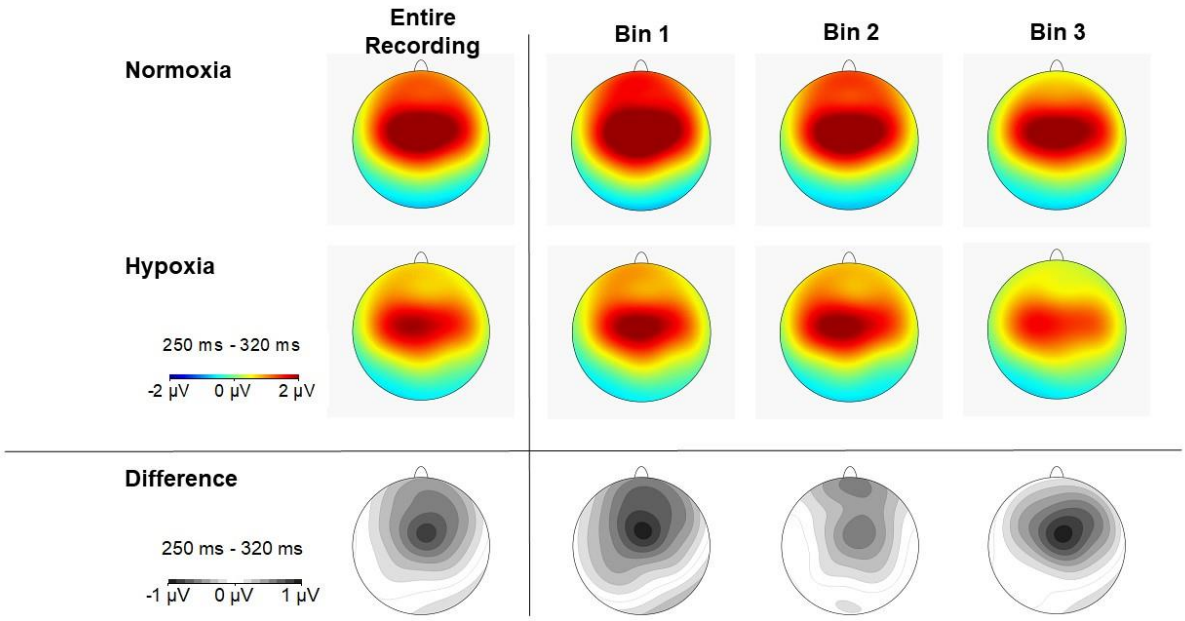

Figure 4. Scalp topography of P3a amplitude (250-320ms) in each time bin for normoxia (top row), hypoxia (middle row), and the difference between conditions (bottom row).

4. Discussion

The results of the present study demonstrate that passively elicited EEG measures, reflecting pre-attentive auditory information processing, are disrupted by acute hypoxia exposure. To our knowledge, no previous work has demonstrated the effect of low oxygen exposure on passively elicited neural measures of sensory processing. Specifically, using a passive auditory oddball paradigm in conjunction with a continuous visuomotor tracking task, a significant reduction in P3a amplitude during a hypoxic compared to a normoxic condition was observed. Importantly, this reduction was evident within the first 9 minute of the exposure and corresponded to a significant impairment in concurrent performance on a foreground behavioral task.

Previous work involving the P300 signal has shown that the P3b component, when *actively* elicited in response to a foreground target detection task, is sensitive to hypoxia exposure (Altbäcker et al., 2019; Barry Fowler & Lindeis, 1992). Whereas these prior studies have examined the P3b subcomponent in response to correctly identified task-relevant target stimuli (and required an active response on the part of the participant), the present data represent the first report showing that even *passively* elicited P3a in response to background, task-irrelevant, sensory stimuli is also disrupted by hypoxia. The finding that P3a is acutely sensitive to a non-pharmacologic CNS perturbation has implications for the use of this and related measures of early auditory information processing as biomarkers in clinical trial designs (e.g., Light & Makeig, 2015; Light & Swerdlow, 2015; Swerdlow et al., 2018). Interestingly, no changes in the earlier MMN or later RON components were detected. Future studies are needed to confirm the specificity of P3a in response to hypoxia exposure.

Low oxygen conditions represent a risk to any exposed individual due to the known impact on a variety of behavioral performance outcomes, including RT (Barry Fowler & Lindeis,

1992; Barry Fowler et al., 1987; Barry Fowler et al., 1982; Shukitt-Hale et al., 1998), perceptual sensitivity (Connolly et al., 2008; Bess Fowler et al., 1993), and higher-order cognitive functions (for a review see, McMorris et al., 2017). One particular environment where hypoxia is an ever-present threat is in tactical aviation. Current military aircraft are not equipped with a failsafe warning system to detect conditions that cause or exacerbate hypoxia. Instead, operators must recognize a broad range of idiosyncratic hypoxia symptoms, such as tingling in extremities, light-headedness, difficulty concentrating, and slowed RTs before they become incapacitated (Artino et al., 2006), which has been compared to the reliability of an intoxicated individual determining if he/she is safe to drive. Ancillary to these subjective symptoms, exposure to reduced levels of breathable oxygen has been documented to affect an operator's ability to maintain a constant airspeed, altitude, and directional heading during simulated flights (Cable, 2003; Green & Morgan, 1985). Thus, the establishment of a neural biomarker of hypoxia using the P3a would benefit research into the onset and effects of hypoxia on performance measures relevant to tactical aviation.

Here, we observed that the P3a amplitude reduction occurred in conjunction with concurrent behavioral performance. One limitation to the current study is the resolution at which we could examine the ERP effects. It is possible that the P3a reduction occurs prior to this performance deficit, but in the current study we lacked adequate resolution to detect that effect. Future studies should aim to reduce the acquisition time needed to get a reliable P3a, in order to examine the predictive potential of the component during low oxygen exposure. Novel analytic approaches may allow for a more rapid detection of changes in EEG dynamics (e.g., Lainscsek et al., 2019). Alternatively, since scalp-level ERPs represent a variable mixture of contributions from multiple brain regions, examination of source-level brain dynamics may allow for a more rapid detection of changes secondary to hypoxia or other CNS perturbations (e.g., Perez et al., 2019). A second limitation was the use of only one altitude for the hypoxia manipulation. The current results represent a first step and future studies should examine whether the reduction in the amplitude of the P3a changes with lower levels of breathable oxygen and presumably more impaired performance.

In conclusion, the current study showed for the first time that a passively elicited neural measure of sensory processing, the P3a, is sensitive to acute hypoxia exposure. The reduction in P3a amplitude during a 10.6% O_2 exposure represents a first step in exploring the utility of the P3a as a biomarker of hypoxia-related insults.

Acknowledgements

The views expressed in this article reflect the results of research conducted by the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U.S. Government. We would like to thank Grant Roush, Chelsea Levin, and Bernadette McCann for assistance with data collection.

Funding

This work was supported by Office of Naval Research award 0601153N to Naval Medical Research Unit-Dayton, with Principal Investigator LT Todd R. Seech, U.S. Navy.

Human Research/Institutional Review Board (IRB) statement

The study protocol was approved by the Naval Medical Research Unit Dayton Institutional Review Board in compliance with all applicable federal regulations governing the protection of human subjects

Conflict of Interest

The authors declare that they have no conflict of interest.

Copyright Statement

Author Contributions

TS and GL generated the idea for the study. RS programmed the auditory oddball stimuli. TS, GL, and KB designed the experiment. TS and KB collected the data. MF, GL, RS, and KB analyzed the data. KB wrote the first draft of the manuscript and TS, MF, and GL critically edited it. All authors approved the final submitted version of the manuscript.

Contribution to the Field Statement

The ability to detect change in our environment is a critical function of our sensory systems. A set of event-related brain potentials measured from the scalp is able to measure the integrity of the auditory system. These potentials, known as the auditory deviance response (ADR), are leading candidate biomarkers that are sensitive to a variety of central nervous system changes, such as drugs, traumatic brain injury, psychiatric disorders, and cognitive training. Here we assessed the ADR in response to an acute exposure to a low-oxygen environment. Within 9 minutes of breathing approximately half of the oxygen that is normally available in the

environment, individuals showed a significant reduction in one component of the ADR, specifically the P3a component. This finding is the first in the literature to show the effect of low-oxygen exposure on a passively elicited neural measure of early sensory processing. The results broaden the utility of the ADR as a biomarker for use in clinical research and may have implications for the use of detecting performance deficits in low-oxygen environments, such as tactical aviation.

References

Altbäcker, A., Takács, E., Barkaszi, I., Kormos, T., Czigler, I., & Balázs, L. (2019). Differential impact of acute hypoxia on event related potentials: Impaired task-irrelevant, but preserved task-relevant processing and response inhibition. *Physiology & behavior*.

Amann, L. C., Gandal, M. J., Halene, T. B., Ehrlichman, R. S., White, S. L., McCarren, H. S., & Siegel, S. J. (2010). Mouse behavioral endophenotypes for schizophrenia. *Brain research bulletin, 83*(3-4), 147-161.

Artino, A. R., Folga, R. V., & Swan, B. D. (2006). Mask-on hypoxia training for tactical jet aviators: evaluation of an alternate instructional paradigm. *Aviation, space, and environmental medicine, 77*(8), 857-863.

Braff, D. L., & Light, G. A. (2004). Preattentional and attentional cognitive deficits as targets for treating schizophrenia. *Psychopharmacology, 174*(1), 75-85.

Cable, G. G. (2003). In-flight hypoxia incidents in military aircraft: causes and implications for training. *Aviat Space Environ Med, 74*(2), 169-172. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12602449

Chapman, S. (2014). *Oxford handbook of respiratory medicine* (Third edition / ed.). Oxford, United Kingdom ;: Oxford University Press.

Clarke, D., & Sokoloff, L. (1999). Basic neurochemistry: molecular, cellular and medical aspects. *Lippincott-Raven: Philadelphia*.

Connolly, D. M., Barbur, J. L., Hosking, S. L., & Moorhead, I. R. (2008). Mild hypoxia impairs chromatic sensitivity in the mesopic range. *Investigative ophthalmology & visual science, 49*(2), 820-827.

Dulude, L., Labelle, A., & Knott, V. J. (2010). Acute nicotine alteration of sensory memory impairment in smokers with schizophrenia. *Journal of clinical psychopharmacology, 30*(5), 541-548.

Featherstone, R. E., Shin, R., Kogan, J. H., Liang, Y., Matsumoto, M., & Siegel, S. J. (2015). Mice with subtle reduction of NMDA NR1 receptor subunit expression have a selective decrease in mismatch negativity: implications for schizophrenia prodromal population. *Neuobiology of disease, 73*, 289-295.

Fowler, B., Banner, J., & Pogue, J. (1993). The slowing of visual processing by hypoxia. *Ergonomics, 36*(6), 727-735.

Fowler, B., & Lindeis, A. E. (1992). The effects of hypoxia on auditory reaction time and P300 latency. *Aviation, space, and environmental medicine, 63*(11), 976-981.

Fowler, B., Taylor, M., & Porlier, G. (1987). The effects of hypoxia on reaction time and movement time components of a perceptual—motor task. *Ergonomics, 30*(10), 1475-1485.

Fowler, B., White, P. L., Wright, G. R., & Ackles, K. N. (1982). The effects of hypoxia on serial response time. *Ergonomics, 25*(3), 189-201.

Gil-Da-Costa, R., Stoner, G. R., Fung, R., & Albright, T. D. (2013). Nonhuman primate model of schizophrenia using a noninvasive EEG method. *Proc Natl Acad Sci U S A, 110*, 15425-15430.

Gore, C. J., Clark, S. A., & Saunders, P. U. (2007). Nonhematological mechanisms of improved sea-level performance after hypoxic exposure. *Med Sci Sports Exerc, 39*(9), 1600-1609. doi:10.1249/mss.0b013e3180de49d3

Green, R. G., & Morgan, D. R. (1985). The effects of mild hypoxia on a logical reasoning task. *Aviat Space Environ Med, 56*(10), 1004-1008. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/4062765

Hochberger, W. C., Joshi, Y. B., Thomas, M. L., Zhang, W., Bismark, A. W., Treichler, E. B., . . . Swerdlow, N. R. (2019). Neurophysiologic measures of target engagement predict response to auditory-based cognitive training in treatment refractory schizophrenia. *Neuropsychopharmacology, 44*(3), 606.

Javitt, D. C., Steinschneider, M., Schroeder, C. E., Vaughan, H. G., Jr., & Arezzo, J. C. (1994). Detection of stimulus deviance within primate primary auditory cortex: intracortical mechanisms of mismatch negativity (MMN) generation. *Brain Research, 667*, 192-200.

Kantrowitz, J. T., & Javitt, D. C. (2010). N-methyl-d-aspartate (NMDA) receptor dysfunction or dysregulation: the final common pathway on the road to schizophrenia? *Brain research bulletin, 88*(3-4), 108-121.

Kawakubo, Y., Kamio, S., Nose, T., Iwanami, A., Nakagome, K., Fukuda, M., . . . Kasai, K. (2007). Phonetic mismatch negativity predicts social skills acquisition in schizophrenia. *Psychiatry research, 152*(2-3), 261-265.

Kraaier, V., Van Huffelen, A. C., & Wieneke, G. H. (1988). Quantitative EEG changes due to hypobaric hypoxia in normal subjects. *Electroencephalogr Clin Neurophysiol, 69*(4), 303-312.

Lainscsek, C., Sampson, A. L., Kim, R., Thomas, M. L., Man, K., Lainscsek, X., . . . Investigators, C. (2019). Nonlinear dynamics underlying sensory processing dysfunction in schizophrenia. *Proc Natl Acad Sci U S A, 116*(9), 3847-3852.

Light, G. A., & Braff, D. L. (2005). Stability of mismatch negativity deficits and their relationship to functional impairments in chronic schizophrenia. *American Journal of Psychiatry, 162*(9), 1741-1743.

Light, G. A., & Makeig, S. (2015). Electroencephalographic biomarkers of psychosis: present and future. *Biological Psychiatry, 77*(2), 87-89.

Light, G. A., & Naatanen, R. (2013). Mismatch negativity is a breakthrough biomarker for understanding and treating psychotic disorders. *Proc Natl Acad Sci U S A, 110*(38), 15175-15176.

Light, G. A., & Swerdlow, N. R. (2015). Future clinical uses of neurophysiological biomarkers to predict and monitor treatment response for schizophrenia. *Annals of the New York Academy of Sciences, 1344*, 105-119. doi:10.1111/nyas.12730

Malle, C., Quinette, P., Laisney, M., Bourrilhon, C., Boissin, J., Desgranges, B., . . . Pierard, C. (2013). Working memory impairment in pilots exposed to acute hypobaric hypoxia. *Aviat Space Environ Med, 84*(8), 773-779. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/23926651

McMorris, T., Hale, B. J., Barwood, M., Costello, J., & Corbett, J. (2017). Effect of acute hypoxia on cognition: A systematic review and meta-regression analysis. *Neuroscience & Biobehavioral Reviews, 74*, 225-232.

Munka, L., & Berti, S. (2006). Examining task-dependencies of different attentional processes as reflected in the P3a and reorienting negativity components of the human event-related brain potential. *Neurosci Lett, 396*(3), 177-181.

Naatanen, R., Gaillard, A. W., & Mantysalo, S. (1978). Early selective-attention effect on evoked potential reinterpreted. *Acta Psychol (Amst), 42*(4), 313-329. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/685709

Naatanen, R., Kujala, T., & Light, G. A. (2019). *The mismatch negativity (MMN): a window to the brain*. Oxford: Oxford University Press.

Naatanen, R., Paavilainen, P., Rinne, T., & Alho, K. (2007). The mismatch negativity (MMN) in basic research of central auditory processing: a review. *Clin Neurophysiol, 118*(12), 2544-2590. doi:10.1016/j.clinph.2007.04.026

Ozaki, H., Watanabe, S., & Suzuki, H. (1995). Topographic EEG changes due to hypobaric hypoxia at simulated high altitude. *Electroencephalogr Clin Neurophysiol, 94*(5), 349-356.

Papadelis, C., Kourtidou-Papadeli, C., Bamidis, P. D., Maglaveras, N., & Pappas, K. (2007). The effect of hypobaric hypoxia on multichannel EEG signal complexity. *Clin Neurophysiol, 118*(1), 31-52. doi:10.1016/j.clinph.2006.09.008

Perez, V. B., Miyakoshi, M., Makeig, S. D., & Light, G. A. (2019). Mismatch negativity reveals plasticity in cortical dynamics after 1-hour of auditory training exercises. *International Journal of Psychophysiology*.

Perez, V. B., Tarasenko, M., Miyakoshi, M., Pianka, S. T., Makeig, S. D., Braff, D. L., . . . Light, G. A. (2017). Mismatch negativity is a sensitive and predictive biomarker of perceptual learning during auditory cognitive training in schizophrenia. *Neuropsychopharmacology, 42*(11), 2206.

Rissling, A., Braff, D. L., Swerdlow, N. R., Hellemann, G., Rassovsky, Y., Sprock, J., . . . Light, G. A. (2012). Disentangling early sensory information processing deficits in schizophrenia. *Clinical Neurophysiology, 123*(10), 1942-1949.

Rissling, A., Miyakoshi, M., Sugar, C. A., Braff, D. L., Makeig, S., & Light, G. A. (2014). Cortical substrates and functional correlates of auditory deviance processing deficits in schizophrenia. *Neuroimage Clin, 6*(424-437).

Schellart, N., & Reits, D. (2001). Transient and maintained changes of the spontaneous occipital EEG during acute systemic hypoxia. *Aviation, space, and environmental medicine, 72*(5), 462-470.

Schroger, E., & C., W. (1998). Attentional orienting and reorienting is indicated by human event-related potentials. *NeuroReport, 9*, 3355-3358.

Shukitt-Hale, B., Banderet, L. E., & Lieberman, H. R. (1998). Elevation-dependent symptom, mood, and performance changes produced by exposure to hypobaric hypoxia. *Int J Aviat Psychol, 8*(4), 319-334. doi:10.1207/s15327108ijap0804_1

Shukitt-Hale, B., Stillman, M. J., Welch, D. I., Levy, A., Devine, J. A., & Lieberman, H. R. (1994). Hypobaric hypoxia impairs spatial memory in an elevation-dependent fashion. *Behav Neural Biol, 62*(3), 244-252. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7857247

Swerdlow, N. R., Bhakta, S., Chou, H. H., Talledo, J. A., Balvaneda, B., & Light, G. A. (2016). Memantine effects on sensorimotor gating and mismatch negativity in patients with chronic psychosis. *Neuropsychopharmacology, 41*(2), 419.

Swerdlow, N. R., Bhakta, S. G., & Light, G. A. (2018). Room to move: plasticity in early auditory information processing and auditory learning in schizophrenia revealed by acute pharmacological challenge. *Schizophr Res, 199*, 285-291.

Swerdlow, N. R., Powell, S. B., Breier, M. R., Hines, S. R., & Light, G. A. (2013). Coupling of gene experession in medial prefrontal cortex and nucleus accumbens after neonatal ventral hippocampal lesions accompanies deficits in sensorimotor gating and auditory processing in rats. *Neuropsychopharmacology, 75*, 38-46.

Todd, J., Harms, L., Michie, P., & Schall, U. (2013). Mismatch negativity: translating the potential. *Frontiers in psychiatry*, *4*, 171.