

# **The Evaluation of a Mobile Device to Measure Ataxia with High Altitude Exposure**

by

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## **Abstract**

To our knowledge, no study has used an assessment of ataxia and a finger-tapping task on a mobile device to monitor acclimatization to hypoxia. This research evaluated the utility of this tool in assessing human acclimatization to hypoxia while monitoring the development of acute mountain sickness (AMS).

This study used a single-blinded repeated-measures randomized crossover design. Subjects experienced a familiarization trial at a simulated altitude of 2000m, a high altitude simulating 4200m and a sham condition simulating 250m. Measurements of AMS, pulse oxygen saturation and performance of the finger-tapping task were completed immediately prior to, and five minutes, four hours, and twelve hours following entrance to the chamber. Fifteen healthy male and female subjects were recruited from the Vancouver area. Subjects were between the ages of 19 and 25 years old. Subjects had not traveled to an altitude of 3000m or higher in the three months prior to testing. Subjects were excluded if they had any cardiovascular or pulmonary conditions.

A repeated-measures ANOVA was performed to analyze if significant results were found for reaction time and accuracy of the finger-tapping task. Accuracy of the finger-tapping task worsened over the exposure to hypoxia, however, error rate and response time were not affected based on this simulated altitude alone. All other measures, including symptom questionnaires and pulse oxygen saturation suggest that these subjects had normal responses to altitude.

Based on these findings, it appears that finger-tapping tasks that focus on measures of accuracy may be useful during an exposure to hypoxia.

## **Preface**

The research presented in this dissertation was conducted in the Environmental Physiology Laboratory of the University of British Columbia (UBC). UBC's Clinical Research Ethics Board (H15-02093) approved the methods used in this study. A manuscript of this work has not yet been published. This study was conducted as part of a collaboration between Dr. Michael Koehle, Dr. Jean-Sébastien Blouin and Dr. Walter Karlen. Dr. Koehle was the principal investigator of this work. Dr. Koehle and Elliott Boake developed the concept for the project. Dr. Koehle, Dr. Blouin and Dr. Karlen collaborated to develop the study design and assisted in data analysis. Elliott Boake was solely in charge of data collection.

## Table of Contents

Abstract .....	ii
Preface.....	iii
Table of Contents .....	iv
List of Tables .....	vi
List of Figures.....	vii
Acknowledgements .....	viii
Dedications .....	ix
Introduction.....	1
Acclimatization .....	1
Altitude Illness .....	3
Altitude Illness Treatment .....	5
Subjective Determination of Acclimatization .....	7
Objective Determination of Acclimatization .....	9
Standing Balance .....	11
Cognition .....	21
Purpose and Objectives .....	29
Methods .....	30
Subjects .....	35
Sample Size .....	36
Experimental Protocol .....	36
Statistical Analysis .....	39
Results .....	42

Discussion .....	67
Introduction .....	67
Cardiovascular .....	68
Cognition .....	69
Balance .....	75
Limitations .....	78
Future Directions for Developers .....	81
Conclusion .....	82
References .....	84
Appendix.....	90

## List of Tables

1. Balance and Acute Mountain Sickness .....	13
2. Development of Ataxia with Hypoxia .....	22
3. Cross-Over Design .....	37
4. Lake Louise Score means and standard deviations .....	42
5. Significant Interaction Effects for Lake Louise Score .....	43
6. SpO <sub>2</sub> means and standard deviations .....	44
7. Significant Interaction Effects for Pulse Oxygen Saturation .....	45
8. Heart Rate means and standard deviations .....	45
9. BESS Single Leg Stances .....	47
10. Significant Interaction Effects for BESS Single Leg Stance Foam Surface .....	48
11. Numeric Trail Making Test .....	49
12. Coordination Test Accuracy of First Shape .....	50
13. Coordination Test Accuracy of Third Shape .....	50
14. First 10 Sets of Coordination Test – Response Time of First Shape .....	51
15. First 10 Sets of Coordination Test – Accuracy of Second Shape .....	51
16. Last 10 Sets of Coordination Test – Errors .....	53
17. Significant Interaction Effects for Errors in Coordination Test .....	53
18. Significant Interaction Effects for Log Transformation of Response Time to First Shape in Coordination Task .....	55
19. Response Time Test – Reaction Time .....	57
20. Response Time Test – Accuracy .....	60
21. First 10 Sets of Response Time Test – Movement Time .....	61
22. Non-significant Pearson Correlation Assessments .....	63
23. Most Important Statistical Findings .....	66

## List of Figures

1. Trail Making Test – Numeric Version .....	32
2. Trail Making Test – Alphanumeric Version .....	32
3. Coordination Test .....	34
4. Response Time Test .....	34
5. Timeline of Measurements .....	38
6. Lake Louise Score over time and condition .....	43
7. Pulse Oxygen Saturation over time and condition .....	44
8. Heart Rate over time and condition .....	46
9. BESS Single Leg Stance on Firm Surface .....	47
10. BESS Single Leg Stance on Foam Surface .....	48
11. First 10 Sets of Coordination Test – Accuracy of Second Shape .....	52
12. Last 10 Sets of Coordination Test – Errors grouped by condition .....	53
13. Last 10 Sets of Coordination Test – Errors grouped by sleep quality .....	54
14. Last 10 Sets of Coordination Test – Errors grouped by sleep quality .....	54
15. Log Transformation of Response Time of the First Shape grouped by sleep quality .....	55
16. Log Transformation of Response Time of the First Shape grouped by sleep quality .....	56
17. Response Time Test – Reaction Time .....	57
18. Response Time Test – Movement Time .....	58
19. Response Time Test – Response Time .....	59
20. Response Time Test – Accuracy .....	60
21. First 10 Sets of Response Time Test – Movement Time .....	62
22. ROC curve for LLS and log transformation of response time to first shape ..	64
23. ROC curve for LLS and change in response time to first shape from baseline	65

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I also received support from many of my peers throughout this process who helped me move through various hurdles. Additionally this research would not have been possible without the generous time volunteered by my research assistants and of course the participation of our subjects.

I would finally like to thank all my friends and both of my families, Boake and Browne for sharing this experience with me.

## **Dedications**

I would like to dedicate this dissertation to those who have been influential in my life. Lise and Stephen are my friends and parents they have always been supportive and available to help me make the big decisions in my life. They have taught me how to enjoy the world and how to work hard.

# **Introduction**

## **Acclimatization**

As altitude increases, the availability of oxygen decreases. The decrease in ambient partial pressure of oxygen is mirrored by a fall of inspired oxygen (Imray, Booth, Wright, & Bradwell, 2011). The body makes physiological adjustments to hypoxia with a process called acclimatization. Not all individuals will acclimatize at the same rate or to the same degree. Failure to acclimatize to hypoxia marks the onset of altitude illness. The rate of ascent and absolute altitude are equally important in determining an individual's ability to acclimatize (Imray et al., 2011). An individual who has acclimatized to a certain elevation above sea level might be able to continue to ascend without symptoms. On the contrary, an individual ascending much more rapidly, exposed to lower elevation may develop severe altitude illness.

The goal of acclimatization is to maintain homeostatic levels of oxygen supply to tissues and organs of the body (Bärtsch & Saltin, 2008). During an acute exposure to hypoxia, ventilation and heart rate will increase (Bärtsch & Saltin, 2008). In hypoxic exposures lasting longer than 24 hours, plasma volume is reduced, presumably to increase its oxygen carrying capacity by volume (Bärtsch & Saltin, 2008). A continued increase in ventilation has been seen up to 14 days after the initial exposure to hypoxia (Bärtsch & Saltin, 2008). This continued increase in ventilation, which increases arterial oxygen saturation during the first two weeks, is attributed to an increased sensitivity of peripheral chemoreceptors (Bärtsch & Saltin, 2008). Peripheral chemoreceptors include

the aortic and carotid bodies, which are found in the arch of the aorta and in the wall of the left and right common carotid artery respectively (McArdle, Katch, & Katch, 2007; Tortora & Derrickson, 2009). Peripheral chemoreceptors respond to hemodynamic changes in oxygen, carbon dioxide and pH (McArdle, Katch, & Katch, 2007; Tortora & Derrickson, 2009). Fluctuations in arterial oxygen saturation ( $S_aO_2$ ) can be monitored using a pulse oximeter, which estimates  $S_aO_2$  and heart rate.

A significant amount of research has been conducted to identify risk factors that are associated with an increased likelihood of poor acclimatization to hypoxia. However much of the research is mixed whether factors such as sex, history of smoking, physical fitness, and body mass index have predictive capacity for the development of altitude illness (Hackett & Roach, 2001; Mahomed et al., 2016; Wagner et al., 2006; Vinnikov, Brimkulov, & Blanc, 2015; Wu et al., 2015). Resident altitude, history of altitude illness, and age, on the other hand, have been shown to be predictors of acclimatization (Honigman et al., 1993; Wagner et al., 2006). Permanent residents from altitudes below 900 m have been found to be 3.5 times more likely to acclimatize poorly to high altitude when compared to residents from altitudes above 900 m (Honigman et al., 1993). Individuals who have previously experienced AMS were twice as likely to develop it again (Leichtfried et al., 2015; Mandolesi et al., 2014; Schneider, Bernasch, Weymann, Holle, & Bärtsch, 2002; Wagner et al., 2006; Wagner, Teramoto, Knott, & Fry, 2012). It is believed that with increasing age there is decreasing brain size. Researchers who evaluated total brain volume change over a 2 year period in 199 middle aged (38.1-82.9 years) subjects found a atrophy rate of 0.23% per year (Takao, Hayashi, & Ohtomo,

2012). Brain atrophy in older individuals allows for greater amount of brain swelling before leading to impaired cognitive function (Wagner et al., 2006). Due to an increased capacity for brain swelling those individuals who are older tend to acclimatize at a faster rate than their younger counterparts. However, this has been disputed by research that found no significant difference in age between those subjects who do develop AMS and those who do not (MacInnis, Rupert, & Koehle, 2012a; Richalet & Lhuissier, 2015).

### **Altitude Illness**

Insufficient acclimatization to altitude can lead to the development of altitude illness. High altitude illness manifests in a variety of conditions and severities. Most illnesses associated with hypoxia affect the brain, these conditions are referred to as cerebral altitude illness. However pulmonary edema may also develop due to hypoxic exposure. The spectrum of altitude illnesses associated with cerebral effects includes acute mountain sickness (AMS) and high altitude cerebral edema (Basnyat, 2005). High altitude pulmonary edema is a form of altitude illness associated with fluid leakage in the lungs. Cerebral altitude illness is characterized by non-specific symptoms, such as, headache, gastrointestinal upset, dizziness, insomnia and fatigue. Subjective measures are commonly used to monitor acclimatization, however, objective measures of the development of altitude illness are useful as they may help to rule out the diagnosis of other conditions commonly mistaken for altitude illness such as alcohol hangover, carbon monoxide poisoning, dehydration or subarachnoid hemorrhage (MacInnis, Rupert, & Koehle, 2012b; Van Roo, Lazio, Pesce, Malik, & Courtney, 2011).

Acute mountain sickness typically develops after 6 to 12 hours of exposure to an altitude of 2500m or higher (Hackett & Roach, 2001; Imray et al., 2011). The prevalence of AMS is between 10-42% at an altitude of 3000m but increases to 40-60% at 4000m (Bärtsch & Saltin, 2008; Hackett & Roach, 2001; Mairer, Wille, & Burtscher, 2010; Wilson, Newman, & Imray, 2009). Acute mountain sickness is characterized as a collection of non-specific symptoms, such as, headache, loss of appetite, nausea, insomnia, dizziness, and peripheral edema (Bärtsch & Saltin, 2008). The non-specific nature of this condition can make it difficult to differentiate from other possible conditions. Conditions such as acute psychosis, arteriovenous malformation, brain tumour, carbon monoxide poisoning, central nervous system infection, dehydration, diabetic ketoacidosis, exhaustion, hangover, hypoglycemia, hyponatremia, ingestion of toxins, drugs or alcohol, migraine, seizure, stroke, transient ischemic attack, as well as viral or bacterial infection have all been mistakenly diagnosed as AMS in the past (Hackett & Roach, 2001).

High altitude cerebral edema is considered end-stage AMS and typically develops after 24 hours or more of AMS (Fiore, Hall, & Shoja, 2010; Hackett & Roach, 2001). More severe than AMS, high altitude cerebral edema is characterized by ataxia, altered mental status, clouded consciousness, impaired mental capacity, drowsiness, stupor, and neurological dysfunction (Bärtsch & Saltin, 2008; Imray et al., 2011). High altitude cerebral edema is much less prevalent at altitudes of 4000m (seen in 1% of individuals) when compared with AMS (Bärtsch & Saltin, 2008).

While AMS and high altitude cerebral edema occur along a continuum of conditions associated with poor acclimatization to hypoxia, high altitude pulmonary edema is associated with poor acclimatization unrelated to cerebral dysfunction. AMS is not a prerequisite for high altitude pulmonary edema (Fiore et al., 2010). High altitude pulmonary edema is caused by an increase in pulmonary vasoconstriction leading to increased pulmonary capillary pressure (Bärtsch, Mairbäurl, Maggiorini, & Swenson, 2005; Fiore et al., 2010). Increased pulmonary capillary pressure causes fluid leakage into the alveoli and interstitial space impairing gas exchange (Fiore et al., 2010). High altitude pulmonary edema rarely occurs at altitudes below 3000 m above sea level and typically develops after 2-5 days of altitude exposure (Bärtsch & Saltin, 2008). In the early stages of high altitude pulmonary edema, individuals will experience decreased exercise capacity, cough, and dyspnea, which is defined as painful or labored breathing (Bärtsch & Saltin, 2008). As the condition develops it can be diagnosed by dyspnea at rest, cough, weakness, decreased exercise performance, chest tightness, and at least two of the following: crackles, wheezing, central cyanosis, tachypnea or tachycardia (Fiore et al., 2010). Although high altitude pulmonary edema is very serious, its incidence is very low. Approximately 4% of individuals ascending at 600 m per day will experience high altitude pulmonary edema (Imray et al., 2011).

### **Altitude Illness Treatment**

Altitude illness is prevalent in those travelling to high altitudes: approximately 25% of travelers to Colorado ski areas, 50% of travelers to the Himalaya, and 85% of those who fly directly to Everest basecamp will experience AMS (Fiore et al., 2010).

Despite its high prevalence, treatment of altitude illness is relatively simple. For all types of altitude illness, descent remains the best treatment (Luks et al., 2010). Symptoms of altitude illness will typically resolve with a descent of 300-1000 m (Fiore et al., 2010; Hackett & Roach, 2001; Luks et al., 2010). If individuals with altitude illness are in an area with a medical facility, the use of supplemental oxygen and pharmacological agents such as carbonic anhydrase inhibitors or glucocorticoids can be used to improve oxygenation and rapidly relieve altitude illness (Imray et al., 2011; Luks et al., 2010).

Acetazolamide, a carbonic anhydrase inhibitor, causes bicarbonate diuresis by way of renal carbonic anhydrase inhibition (Imray et al., 2011). Bicarbonate diuresis results in mild renal metabolic acidosis, which stimulates ventilation, thus improving oxygenation (Basnyat, 2005; Imray et al., 2011; Leaf & Goldfarb, 2006). Acetazolamide is most often prescribed in doses between 125 mg to 250 mg administered one to two times per day (Imray et al., 2011). Although acetazolamide helps to improve acclimatization it may not prevent altitude illness if ascent is too rapid (Imray et al., 2011). Carbonic anhydrase inhibitors are used as a first line prevention and treatment against AMS (Fiore et al., 2010).

Glucocorticoids such as dexamethasone are believed to modulate sympathetic activation, reduce capillary permeability, reduce the release of proinflammatory cytokines, and lower pulmonary artery pressure (Bärtsch & Swenson, 2013; Eide & Asplund, 2012; Imray et al., 2011). Dexamethasone is often prescribed in doses of between 4 mg to 8 mg administered every 6 to 12 hours (Fiore et al., 2010).

Dexamethasone is used to prevent and treat AMS, high altitude cerebral edema, and

high altitude pulmonary edema, however the potential for adverse effects limits its role in prevention (Bärtsch & Swenson, 2013; Eide & Asplund, 2012; Fiore et al., 2010). When dexamethasone is used as prophylaxis, it can cause hyperglycemia, psychosis, as well as suppress adrenal function and lead to glucocorticoid toxicity (Bärtsch & Swenson, 2013; Eide & Asplund, 2012). Additionally, since it does not directly improve acclimatization, once the use of dexamethasone is initiated, cessation of therapy while still at altitude can cause a relapse of altitude illness (Eide & Asplund, 2012).

Supplemental oxygen and pharmacological agents such as acetazolamide and dexamethasone should be used to improve oxygenation if an individual is developing altitude illness. Treatment and descent from altitude should be continued until the individual has increased their SpO<sub>2</sub> to 90% or greater (Luks et al., 2010). Further ascent should only be undertaken once all symptoms have been alleviated (Imray et al., 2011).

### **Subjective Determination of Acclimatization**

Altitude illness is a potentially life threatening condition that often occurs in remote locations at high altitude (Hackett & Roach, 2001). Because this condition typically develops in remote areas, tools have been developed which can be used to monitor the development of altitude illness. The most common method of monitoring acclimatization is by using subjective questionnaires that ask the subject to rate the severity of commonly occurring symptoms. The two questionnaires most often used are the Environmental Symptom Questionnaire (ESQ) and the Lake Louise Score (LLS). The ESQ is comprised of a list of eleven symptoms, which include: light-headedness,

headache, dizziness, sensations of faintness, visual symptoms, coordination, weakness, nausea, appetite, sick, and feeling hungover (Dellasanta, Gaillard, Loutan, & Kayser, 2007). Subjects rate these symptoms from 0 to 5 where 0 represents the absence of a symptom and 5 represents the extreme presence of a symptom (Beidleman, Muza, Fulco, Rock, & Cymerman, 2007). The rating for each symptom is multiplied by a weighting factor and summed (Sampson, 1983). The summed score is divided by a predetermined denominator to calculate a composite ESQ score (Sampson, 1983). Originally the ESQ was developed with 67 questions, however, Beidleman and her colleagues (2007) were able to show that a shortened 11-question version is equally as accurate in measuring the incidence of acute mountain sickness.

The most commonly used questionnaire for assessing acclimatization to high altitude is the Lake Louise Score (LLS) (Van Roo et al., 2011). The test is comprised of only 5 symptoms: headache, fatigue/weakness, dizziness/lightheadedness, difficulty sleeping, and gastrointestinal upset (Kayser et al., 2010). Subjects rate their symptoms on a scale from 0 to 3 where 0 represents the absence of a symptom and 3 represents a very severe symptom (Kayser et al., 2010). A subject is considered to have AMS if their LLS exceeds 3 in the presence of a headache (Kayser et al., 2010).

In an effort to make the monitoring of acclimatization as fast and accurate as possible, researchers have tried to determine if the use of a visual analog scale produces similar results compared to a numerical rating system. A visual analog scale presents the user with a symptom and a blank line next to it, the user places a mark along the line, which represents the absence of a symptom to the left and very severe symptoms to the

right. Van Roo and colleagues (2011) determined that not only did the use of a visual analog scale produce similar results to the standard LLS it also allowed for subjects to easily rate changes in their symptom severity on a smaller time scale.

The LLS is the closest tool we have to a gold standard. Unfortunately specific sensitivities, specificities and accuracies are not available in the literature and diagnosis of acute mountain sickness still relies on the best judgement of the medical professional. The non-specific nature of many of the commonly occurring symptoms can make it difficult to rely on subjective questionnaires to diagnose acute mountain sickness with good certainty. It is common for poor nutrition, dehydration, impaired circulation or infection to produce similar symptoms when compared to acute mountain sickness (Hackett & Roach, 2001). To improve the correct diagnosis of acute mountain sickness, clinicians should consider using more objective measures of acclimatization in conjunction with subjective questionnaires.

### **Objective Determination of Acclimatization**

Researchers have made use of heart rate monitoring to assess the degree of acclimatization. O'Connor and colleagues (2004) observed that AMS was worse in those subjects who had a higher mean heart rate (O'Connor, Dubowitz, & Bickler, 2004). Specifically, subjects who had a heart rate between 71-80 bpm had 1.4 times increased odds of developing AMS compared to subjects who had a heart rate of less than 71 bpm (O'Connor et al., 2004). While Wagner and colleagues did not find this relationship between heart rate and AMS they did find that those who were successful summiteers

had lower heart rates as compared to those who failed to reach the summit (Wagner et al., 2012).

Pulse oximetry is another tool commonly used to objectively assess acclimatization. Pulse oximetry estimates arterial hemoglobin saturation which is the percentage of hemoglobin binding sites occupied by oxygen at any given time (Luks & Swenson, 2011). Oxygen saturation changes as a function of the inspired partial pressure of oxygen, therefore with increasing altitude, oxygen saturation decreases (Luks & Swenson, 2011). Those individuals who are able to maintain or minimize their decrease of SpO<sub>2</sub>, especially following exercise, could be less likely to develop AMS (Karinen, Peltonen, Kähönen, & Tikkanen, 2010; Mandolesi et al., 2014).

Arterial hemoglobin saturation changes with exposure to hypoxia. Studies have shown that with an acute exposure to hypoxia, oxygen saturation can drop by up to 5.75% per 1000 m between 2000 and 6000 m (Burtscher & Flatz, 2004). The decline in pulse oxygen saturation is progressive and explained by ventilation. Ventilation abruptly increases within five minutes of hypoxic exposure, and then ventilation will decrease for 30 minutes before reaching steady state (Richard & Koehle, 2012). This process is referred to as hypoxic ventilatory decline (Richard & Koehle, 2012). Pulse oxygen saturation mirrors this process by not reaching steady state until after 30 minutes (Richard & Koehle, 2012).

Large decreases in oxyhemoglobin within an hour in hypoxia may have predictive power of whether an individual is likely to develop AMS (Imray et al., 2011; Karinen et al., 2010; Loeppky et al., 2008; Mandolesi et al., 2014). In contrast, some studies have

not found this relationship between pulse oximetry and AMS or even the likelihood of summit success (Wagner et al., 2012).

## **Standing Balance**

While subjective questionnaires such as the LLS and ESQ have become a common assessment tool in the diagnosis of AMS in the scientific literature, their use is problematic in the differential diagnosis of other possible conditions (MacInnis, Rupert, & Koehle, 2012b). Conditions such as dehydration, carbon monoxide poisoning, alcohol hangover, migraine or subarachnoid hemorrhage can be misdiagnosed as acute mountain sickness (MacInnis, Rupert, & Koehle, 2012b). The use of more objective evaluations associated with altitude illness such as measures of balance can help rule out commonly mistaken pathologies.

Ataxia is defined as incoordination in the absence of significant weakness and results from disorders of the cerebellum or cerebellar pathways (Bird et al., 2011). Measurable disturbances in the performance of voluntary motor actions which may affect the limbs, trunk or gait mark the development of ataxia (Johnson, Simmons, & Wright, 2005a). The accepted diagnosis of high altitude cerebral edema includes neurological deficits, which cause ataxia and lead to poor coordination and balance. The literature is inconclusive concerning whether ataxic deficits can be identified in less severe forms of altitude illness such as AMS (Bärtsch & Saltin, 2008; Imray et al., 2011). If ataxia is present in AMS it might be in relation to hypoxia alone as opposed to edema.

Literature on balance and hypoxia can be grouped into two categories: studies that show *a correlation* between the development of poor balance and acute mountain sickness and studies that show *no correlation* between poor balance and acute mountain sickness (Table 1).

<b>Balance &amp; Hypoxia</b>	<b>Author</b>	<b>Intervention</b>	<b>Result</b>
<i>Correlated</i>	Hydren et al. 2013	Examine the impact of high altitude exposure on balance and other performance parameters on a group of 11 early teens at 2828 m for 6 days	Balance and AMS (LLS) improved over 3 through 6 days of exposure to altitude
<i>Correlated</i>	Johnson et al. 2005a	AMS (LLS) and balance scores on a wobble board were compared to results taken at altitude during a 19 day trek (1345, 1600, 3300, 4650, and 5005 m)	Subjects with AMS had a significantly greater number of contacts (errors) on the wobble board as compared to those without AMS
<i>Correlated</i>	MacInnis, Rupert & Koehle 2012	BESS and AMS (LLS) were assessed at 4380 m after a 48 hour ascent from below 2000 m	Subjects with AMS scored significantly higher on mBESS and BESS when compared to subjects without AMS
<i>Uncorrelated</i>	Baumgartner, Eichenberger, & Bartsch 2002	22 subjects performed static posturography at 450 m and at 4559 m after a 24 hour ascent	No difference in ataxia between subjects with or without AMS (ESQ)

**Table 1. Balance and Acute Mountain Sickness**

<b>Balance &amp; Hypoxia</b>	<b>Author</b>	<b>Intervention</b>	<b>Result</b>
<i>Uncorrelated</i>	Cymerman et al. 2001	19 subjects were measured for postural stability on a force plate over a 24 hour continuous exposure to a simulated 4300 m	No significant correlations were found between AMS (ESQ) and postural stability
<i>Uncorrelated</i>	Johnson et al. 2005b	23 subjects performed the Sharpened Romberg Test at 150 m as well as during an 8 day ascent to 5260 m	Lack of a correlation between ataxia and AMS (LLS) below 5260 m
<i>Uncorrelated</i>	Baumgartner & Bartsch 2002	Using short-term oxygen inhalation to assess improvements in static posturography and AMS (ESQ) of 20 subjects after an overnight stay at 4559 m	Impairments in balance need more time to recover when compared to symptoms of AMS

**Table 1. Balance and Acute Mountain Sickness**

Hydren et al. (2013) followed a youth ski camp of athletes from below 450m who were training for six days between 3328 m and 3802 m, and sleeping at 2828 m. Measures of balance, power, quickness, flexibility, strength endurance and  $\text{VO}_2\text{max}$  were assessed during a week-long camp. Eleven athletes (mean age of 13 years) participated in the study. Balance was measured by using the Y-Balance Test that has the subject reach for a maximum distance with one leg in 3 directions while balancing on their dominant foot. During this task the balance foot has to remain on the floor and hands must remain on the hips. Scores are given by a sum of all three distances divided by leg length. Y-Balance improved on day 3 through 6, a main effect between days was found ( $p < 0.001$ ). AMS scores assessed by the LLS were highest on day 1 immediately after skiing, with three subjects reporting 5, 6, and 7 however by 4:30 pm those values changed to 2, 4, and 6 respectively. After the third day no subjects reported a headache and no AMS scores were reported greater than 2, indicating decent acclimatization to the current altitude. Performance of the Y-Balance task improved after subjects had been acclimatizing for 3 days. During acclimatization AMS scores also decreased suggesting a relationship between improvements in balance and recovery from AMS.

Johnson et al. 2005a developed a balance board that sat on a metal plate. When the edge of the board made contact with the plate a buzzer would sound and the number of contacts were recorded. They assessed wobble board balance and LLS on twenty subjects as they took part in a trek to 5005 m. Measurements were made at 1345 m, 1600 m, 3300 m, 4650 m, and 5005 m. Johnson et al (2005a) found a correlation between AMS and balance. At 4650m the 8 subjects who had AMS also had

a greater number of contacts on the wobble board ( $4.3 \pm 4.6$ ) as compared to subjects who did not develop AMS ( $1.1 \pm 1.8$ ). This trend was also seen at 5005 m where subjects with AMS ( $4.5 \pm 3.3$ ) continued to have greater number of contacts when compared to subjects without AMS ( $2.0 \pm 3.3$ ). These results leads to the conclusion that there is likely a relationship between poor balance and AMS as diagnosed by the LLS.

MacInnis and colleagues (2012) used a standardized measure of balance called the Balance Error Scoring System (BESS) as well as a modified version of the BESS (mBESS) to evaluate the relationship between balance and AMS at altitude (4380 m). The BESS consists of three static stance positions; a feet-together double leg stance, a non-dominant single leg stance, and a non-dominant leg behind tandem stance which was performed twice: once on a firm surface, and once on a foam surface. Failure to maintain the stance is counted as an error. The mBESS test was similar to BESS however it was only performed on a firm surface. They measured 37 subjects, most subjects completed the full BESS ( $n=27$ ) and a small group ( $n=10$ ) only completed the modified version. Subjects with AMS scored significantly higher on mBESS ( $6.6 \pm 3.5$ ) as compared to those without AMS ( $2.7 \pm 1.7$ ) ( $p = 0.018$ ). The difference between subjects with ( $19.2 \pm 8.0$ ) and without AMS ( $10.4 \pm 6.0$ ) was greater when using the full BESS assessment due to the addition of tests using the foam pad ( $p = 0.001$ ). Additionally, the correlations between mBESS as well as BESS and LLS were significant (mBESS  $r = 0.413$ ,  $p = 0.011$ : BESS  $r = 0.606$ ,  $p < 0.001$ ). The results of this investigation suggest that the BESS would be useful in conjunction with the LLS because the LLS alone may mistakenly diagnose other pathologies as acute mountain sickness.

Despite the findings by Hydren et al. (2013), Johnson et al. (2005a), and MacInnis et al. (2012), other experiments have failed to detect a relationship between poor balance and AMS. Baumgartner, Eichenberger and Bartsch (2002) assessed posturography and AMS of 22 subjects by using the ESQ at baseline (450 m) and at altitude (4559 m). Subjects were transported to an altitude of 3200 m. After staying overnight at 3200 m subjects then hiked to 4559 m. Sway velocity was measured within 3 hours of arrival at 4559 m. Posturography was analyzed while standing with feet 7 cm apart on a force plate for 20 seconds. Subjects were instructed to look straight ahead and keep their arms at their sides. The force plate determined overall sway velocity, sway velocity in the anteroposterior and mediolateral direction with eyes open and eyes closed. At altitude, the overall sway velocity and sway velocity in the mediolateral direction increased, indicating postural instability. Postural instability was not different between subjects with or without AMS. Additionally, the investigators were unable to find a correlation between posturographic parameters and arterial blood gas. Therefore, although balance seemed to deteriorate with hypoxia, this study did not show any correlation between balance and AMS as assessed by the ESQ. This is possibly because standing on a firm surface did not challenge the balance system enough.

Cymerman and colleagues (2001) assessed balance with the performance of both a static stance with eyes open and closed as well as a dynamic task performed with eyes open. Subjects stood on a force plate with feet 25 cm apart. The goal of the static task was to minimize any movements, while the dynamic task involved tracking a moving target in a circle on a computer monitor. During the dynamic task subjects

controlled the position of cursor on a two-dimensional computerized target and tried to keep the cursor in the centre of the target. The static and dynamic produced a computerized score, which was based on the timed sum of absolute distances from the central reference point. Nineteen subjects were assessed over a continuous 24-hour exposure to a simulated altitude of 4300 m after an ascent rate of 610 m/min. When subjects performed the eyes-open test after 3 hours of exposure to hypoxia, postural instability increased by 30% ( $p = 0.002$ ). This effect persisted until the end of the 24-hour exposure (21%,  $p = 0.036$ ). The eyes-closed task showed similar results with increased postural instability after 3 hours (25%,  $p < 0.001$ ) followed by a further increase of postural instability until the end of the exposure (31%,  $p < 0.001$ ). The dynamic test showed no significant difference over the entire exposure. Although instability developed over the exposure of hypoxia, this was not found to correlate with severity of AMS assessed by ESQ. The lack of relationship could be accounted for by the small changes seen in postural stability with hypoxic exposure due to the fact that a double leg firm surface stance does not challenge balance as much as other balance tests.

Johnson et al. (2005b) measured balance with the Sharpened Romberg Test. The Sharpened Romberg Test directs an individual to stand with their feet heel-to-toe in a straight line (tandem stance), hands are placed on the opposing shoulders and eyes are closed for 60 seconds. Failure to maintain this position is an indication of a failed test. If the first trial has no errors, the test is complete, however, if errors occur in the first trial, the task is performed three more times for a total of four trials. Measurements were taken from 23 subjects at 150 m, 3610 m, 4750 m, and 5260 m. Portions of the group

experienced abnormal performance of the Sharpened Romberg Test at 3610 m (43%), 4750 m (23%), and at 5260 m (43%); however, this was not correlated with the presence of AMS as assessed by the LLS. The sensitivity of the Sharpened Romberg Test at predicting the development of AMS, which is a measure of true positive findings, was found to be 71% at 3610 m and 60% at 5260 m. The specificity of the Sharpened Romberg Test at predicting which individuals will not develop AMS, which is a measure of true negative findings, was found to be 69% at 3610 m and 89% at 5260 m. Johnson et al. (2005b) did not show a significant relationship between LLS and balance assessed by the Sharpened Romberg Test.

Baumgartner and Bartsch (2002) gave supplemental oxygen to 20 subjects exposed to 4559m. Posturography was analyzed while standing with feet 7cm apart on a force plate for 20 seconds. Subjects were instructed to look straight ahead and keep their arms at their sides. Sway velocity was calculated for trials both with eyes open and eyes closed. With inhalation of supplemental oxygen, balance measurements remained unchanged, whereas the ESQ scores decreased from  $1.2 \pm 0.1$  to  $0.6 \pm 0.1$ . This finding led Baumgartner and Bartsch (2002) to suggest that ataxia is caused by a different mechanism than AMS and that ataxic symptoms may need more time to recover than other indicators of AMS. Baumgartner and Bartsch (2002) further suggested that ataxia might be caused by cerebral edema whereas AMS might be caused by dilation of cerebral arteries, which recover at a faster rate. Alternatively they might not have shown decrements in balance in hypoxia due to the simplicity of their balance task. A

double leg firm surface stance might not be an appropriate challenge to the balance system to show changes in hypoxia.

While the research is inconclusive about the time course development of AMS and balance impairments, many researchers support the notion that both balance and AMS are affected by hypoxia. The mechanisms by which instability and altitude illness develop may differ. This time-dependent relationship may exist because of differing rates of acclimatization of these systems. While Hoshikawa et al. (2010) did not take measurements of AMS, they did study instability at a simulated altitude of 5000 m before and after an expedition to 8201 m. This group found that instability at altitude improved after the 84-day expedition, which corresponded to enhanced SpO<sub>2</sub>. Hoshikawa's results suggest that exposure to high altitude enhanced their subject's ability to tolerate hypoxia made evident by improved stability and enhanced SpO<sub>2</sub>.

Cymerman et al. (2001) did not show a correlation between AMS and balance however they suggested that the loss of balance might precede the onset of AMS. They explain that the changes found in balance were very small and these would likely occur before AMS has sufficient time to develop. MacInnis and colleagues (2012) proposed that because Cymerman et al. (2001) and Baumgartner, Eichenberger, and Bartsch (2002) used ESQ, instead of LLS, to measure AMS their methods might not be sensitive enough to show a correlation between AMS and balance. MacInnis and colleagues (2012) identified that balance methods using tandem stance such as the Sharpened Romberg Test used by Johnson et al. (2005b) may not be sensitive enough to show differences in balance when compared to baseline.

We must be cautious when making conclusions based on the literature, as most of the available research used different measures of balance and altitude illness making it hard to translate findings between studies. With that said, the studies that show a correlation between balance and AMS tend to use the LLS for the diagnosis of AMS. Studies that do not show a correlation between balance and AMS either used ESQ or balance tasks that do not challenge the balance system such as double leg stance, firm surface stance and Sharpened Romberg Test. It has been suggested that the ESQ is not as sensitive as the LLS when assessing acute mountain sickness (Dellasanta et al., 2007). Tandem stance balance tests such as the Sharpened Romberg test fail to show differences at altitude when compared to baseline which brings into question their use as a measurement of acclimatization (MacInnis, Rupert, & Koehle, 2012b). Collectively, these studies support the notion that further research needs to be done comparing AMS (as assessed by LLS) to balance methods including tasks that do not use a tandem stance.

## **Cognition**

The definition of ataxia is poor coordination in the absence of significant weakness; in the early stages of ataxia this can manifest as clumsiness in the hand and finger (Bird et al., 2011; T. Wu et al., 2006). While some studies used the performance of a balance task to assess ataxia at high altitude, other researchers have used the performance of a cognitive task (Table 2). The best performance of a coordinated task relies on rhythm, posture, and equilibrium (Hatakenaka, 2012)

Author	Intervention	Result
Asmaro et al. 2013	35 subjects were assessed using Digit Span Task, Stroop Test and Trail Making Test at sea level as well as after 30 minutes of simulated altitudes of 5334 m and 7620 m	Impairments were seen in all tests at all altitudes.
Davranche et al. 2016	11 subjects assessed using choice reaction test after being flown to 4350 m and tested immediately as well as over 4 days	Choice reaction time increased by 29 ms immediately but was not detectable after 2 days at altitude. Error rate was twice as high as compared to baseline for duration of exposure to altitude.
Dykiert et al. 2010	10 subjects were assessed for AMS (LLS) and a 4 choice reaction time task on 21 occasions from sea level to 5,565 m over a 20 day trek	Reaction time became impaired above 4000 m which had a strong correlation with AMS development
Fowler et al. 1987	6 subjects were given low oxygen mixtures to reduce SaO <sub>2</sub> to hypoxic levels and response time was measured over a 60 minute trial	Response time slowed significantly at an SaO <sub>2</sub> of 82% which corresponds to an altitude of 3000 m
Kida and Imai 1993	38 subjects were tested in a decompression chamber where reaction time to an auditory stimulus was recorded during 45 minute exposures to sea level, 3000 m, 4000 m, 5000 m, and 6000 m	12 subjects showed no change in reaction time at high altitude, 20 subjects showed significant decrements in reaction time at 5000 and 6000 m, 6 subjects displayed abrupt changes in reaction time at 4000 m but were unable to complete the test

**Table 2. Development of Ataxia with Hypoxia**

Author	Intervention	Result
MacKintosh et al. 1988	20 subjects were assessed for reaction time on two expeditions that lasted 20 days and reached an elevation of 5000 m	The positive correlation between reaction time and altitude was strongest for those subjects with symptoms of AMS and non significant for subjects with no symptoms
Paul & Fraser 1994	14 subjects were assessed for serial choice reaction time during a 6 hour ascent from sea level to 1524 m, 2438 m, 3048 m and 3658 m	Reaction time increased by 15ms from 1524 m to 2438 m
Phillips, Hørning and Funke 2015	19 subjects were assessed for reaction time at sea level and as well at after a 30-minute exposure to simulated 5486 m	Reaction time was affected by the hypoxic exposure and did not return to baseline until 24 hours post exposure
Turner 2015	22 subjects were assessed using the CNS Vital Signs Test at a simulated altitude of 5500 m after 90-minute exposure	All parameters indicated impairments as compared to baseline; 20% neurocognitive index, 30% composite memory, 34% verbal memory, 23% visual memory, 36% processing speed, 20% executive function, 24% psychomotor speed, 10% reaction time, 19% complex attention, 18% cognitive flexibility

**Table 2. Development of Ataxia with Hypoxia**

Asmaro and colleagues (2013) assessed short-term and working memory with the Digit Span Task, cognitive flexibility and selective attention with the Stroop Test, as well as executive function with the Trail Making Test. Thirty-five subjects were tested at baseline as well as after 30 minutes of simulated altitudes 5334 m and 7620 m. Impairments were seen in all tests and all altitudes relative to baseline.

Davranche and colleagues (2016) had subjects perform a congruent and incongruent choice reaction test. Subjects would focus on a target and a shape would appear at a fixed distance on either the left or the right side of the target. Subjects had to react by pressing a button that responded to the shape but not the side the shape appeared relative to the target. Eleven subjects were evaluated at sea level as well as immediately after being flown to 4350 m where they remained for 4 days. Choice reaction time increased by 29 ms immediately after the arrival to altitude ( $p < 0.01$ ), however this difference was no longer significant after 2 days at altitude. Decision error rate for congruent trials increased to twice that of baseline at altitude and remained elevated for the duration of the experiment ( $p < 0.01$ ).

Dykiert and colleagues (2010) assessed choice reaction time at altitude while also measuring AMS using the LLS. Ten subjects were measured on 21 occasions both at sea level and during a hike to 5565 m. Reaction time was determined by using an Eagle Choice Reaction Time box, which included four small lamps and four push buttons (Eagle CRT box, Eagle Designs, Edinburgh, Scotland). Subjects were instructed to choose the corresponding button related to the correct lamp and push it as quickly and accurately as

possible. Lamps would light up at random intervals between one and three seconds. Each testing set would consist of eight practices followed by 40 trials. Four choice reaction times showed a significant effect above 4000 m, which correlated strongly with severity of AMS. Reaction time at 1992 m ( $261\text{ms} \pm 35$ ) was 28 ms ( $\pm 10.42$ ) faster than reaction time at 5565 m ( $289\text{ ms} \pm 33$ ). Dykiert et al. (2010) found a relationship between AMS and reaction time; an increase of 2ms for reaction time was associated with a one-point increase of the LLS. This is the only group to assess both reaction time and LLS.

Fowler et al. (1987) measured the response time of 6 subjects while giving a low oxygen mixture to lower  $\text{SaO}_2$ .  $\text{SaO}_2$  was lowered from 86%, which is the equivalent of 2700m, down to 72%, which is the equivalent of 3,474m. Response time was measured as the time it took to react to an illuminated disk and touch the appropriate disc with a wand. Reaction time measurements during this task slowed significantly (25 ms) from an  $\text{SaO}_2$  of 86% (436 ms) when compared to an  $\text{SaO}_2$  of 82% (461 ms). This response comes at a lower altitude than the Dykiert study. In the Dykiert study, subjects were exposed to real altitude meaning their bodies could adjust by changing the rate of ventilation to improve arterial oxygen saturation. Fowler et al. (1987), however, exposed individuals to simulated hypoxia in a shorter period of time (60 minutes). Hypoxia was determined by arterial oxygen saturation. Because of the relatively rapid onset of hypoxia and the inability to respond physiologically, subjects were more likely to show impairments in response time earlier in the exposure.

Kida and Imai (1993) performed a hypobaric hypoxia chamber study on 38 subjects and found both responders (n=26) and non-responders (n=12) to hypoxia. Reaction time was measured as the speed a subject could react by pressing a microswitch in response to an auditory stimulus. Reaction time was measured at sea level, 3000 m, 4000 m, and 5000 m. Non-responders had no change in reaction time to any altitude. Responders showed a significant increase in reaction time with a simulated altitude of 5000 m that persisted at 6000 m. Those subjects most affected by hypoxia (n=6) had abrupt increases in reaction time at a simulated altitude of 4000 m, however these subjects were unable to complete the rest of the trials due to the severity of their altitude illness. Kida and Imai's results support the correlation between decrements of reaction time with increasing hypoxia because the majority (68%) of their subjects were responders.

Mackintosh et al. (1988) measured reaction time of 20 subjects on expeditions to 5008 m or 4790 m. Subjects responded to a light cue by pressing a buzzer to assess reaction time. Reaction time was significantly greater above 5000 m ( $246\text{ms} \pm 16$ ) compared to below 5000 m ( $236\text{ms} \pm 80$ ). AMS was assessed by a visual analogue score of common symptoms. The correlation between altitude and reaction time was only significant for those subjects who had the most severe AMS on the first and second expedition ( $r = 0.69, p < 0.025$ ;  $r = 0.40, p < 0.05$ ). Subjects who had intermediate AMS (n = 13) showed a positive trend between reaction time and altitude ( $r = 0.42, r = 0.28$ ) however these results were not statistically significant. Mackintosh and colleagues'

(1988) results support the previously mentioned studies that found a correlation between reaction time decrements and hypoxia, however only significant correlations were only found with those subjects who developed severe AMS.

Paul and Fraser (1994) had 144 subjects perform serial choice reaction time tasks at sea level and at altitudes of 1524 m, 2438 m, 3048 m, and at 3658 m. The serial choice reaction time task was performed on a 61 x 61 cm board with five push-buttons arranged in a pentagon shape 20cm apart from each other. LED lights mounted adjacent to the push-buttons cue the subject as to which button to push. The subjects' reaction time increased over the exposure from 1524 m (540 ms) to 3658 m (555 ms) and this was mirrored by decreasing SaO<sub>2</sub> (from 95% to 86%). This study showed a time course relationship between decrements in coordination and SaO<sub>2</sub> that occurs with increasing hypoxia. It is important to note that this was not the main relationship evaluated for this study and that reaction time values were approximated to the nearest 10 ms based on the included graphs.

Phillips and colleagues (2015) assessed the reaction time of 19 military personnel at sea level and at a simulated altitude of 5486 m. Simple reaction time was measured as the time it took a subject to remove their finger from one key and press another in response to a stimulus. Choice reaction time required the subject to remove their finger from one key and press one of three keys in response to a stimulus. The mean simple reaction time at simulated altitude (362 ms) was found to be comparably slower to that at baseline (337 ms), which paralleled similar studies. The decrement in reaction time (25

ms) did not return to baseline until 24 hours after the 30-minute hypoxic exposure. This was confirmed by repeated-measures ANOVA for simple reaction time and choice reaction time. Phillips and colleagues (2015) have demonstrated that abrupt exposures to hypoxia can induce decrements in reaction time, requiring as many as 24 hours for recovery.

Turner and colleagues (2015) evaluated 22 subjects after 90-minute exposure to a simulated altitude of 5500m. They used a battery of tests called the CNS Vital Signs. CNS Vital Signs includes seven tests; verbal memory, visual memory, finger tapping, symbol digit coding, Stroop, test of shifting attention and continuous performance test. CNS Vital Signs produces a composite score of a variety of indexes and parameters. Turner found all parameters to be impaired at altitude; 20% neurocognitive index, 30% composite memory, 34% verbal memory, 23% visual memory, 36% processing speed, 20% executive function, 24% psychomotor speed, 10% reaction time, 19% complex attention, 18% cognitive flexibility.

In summary, the research that has examined the relationship between altitude and reaction time has consistently shown increasing reaction time with increasing hypoxia. Each study used a different reaction time task, meaning that the time taken to complete each task varied both at baseline (236-540 ms) and in hypoxia (246-555 ms). The decrement in performance of each task was relatively similar ( $20 \text{ ms} \pm 8$ ). This suggests that, regardless of the nature of the reaction time task, it is reasonable to expect a decrement in reaction time of approximately 20 ms during a hypoxic exposure.

Existing literature is inconclusive as to the pathophysiology of the increase in reaction time and its association with hypoxic exposure.

## **Purpose and Objectives**

Existing literature regarding ataxia and acute mountain sickness is inconclusive. Ataxia research has been grouped into two categories either balance-related research or reaction time research. Balance research is less conclusive, with some studies showing a correlation between balance and AMS (Hydren et al., 2013; Johnson, Simmons, & Wright, 2005a; MacInnis, Rupert, & Koehle, 2012b) and others showing no correlation (Baumgartner & Bärtsch, 2002; Cymerman, Muza, Beidleman, Ditzler, & Fulco, 2001; Johnson, Wright, Beazley, Harvey, Hillenbrand, Imray, Birmingham Medical Research Expeditionary Society, 2005d). Most of the research in this field supports the notion of a time-course relationship between the development of balance impairments and the development of AMS. As mentioned above, reaction time and AMS studies show very consistent decrements in hypoxia regardless of the specific nature of the task. Our research sought to investigate if ataxia early in the onset of altitude illness could be monitored by finger tap accuracy.

To our knowledge, no study has used an assessment of ataxia as evaluated by finger tap accuracy and reaction time using a cognitive task on a mobile device to monitor acclimatization to hypoxia. Our research evaluated the utility of this tool in

assessing human acclimatization to hypoxia, while monitoring the development of AMS. This research compared our novel coordination task to pulse oximetry, BESS and LLS.

The objectives of this study were to 1) Test the effect of hypoxic exposure on inter-response intervals, movement time, reaction time, response time, time to completion and tapping accuracy of novel coordination tasks over time. (2) Test the correlation between reaction time and time to completion of a novel coordination task and arterial oxygen saturation, heart rate, performance of BESS, and LLS. (3) Test the correlation between tapping accuracy of novel coordination tasks and arterial oxygen saturation, heart rate, performance of BESS, and LLS.

We hypothesized that (1) Coordination (as measured by a finger tap accuracy and delay) during hypoxic exposures is impaired compared to sham exposures. (2) Reaction time of a novel coordination task positively correlates with heart rate, performance of BESS, and LLS, as well as, negatively correlates with arterial oxygen saturation. (3) Tapping accuracy of a novel coordination task positively correlates with arterial oxygen saturation, as well as, negatively correlates with heart rate, performance of BESS, and LLS.

## **Methods**

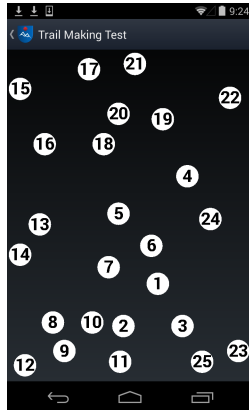
This study used a single-blind repeated measures randomized crossover design. Subjects were randomly assigned to one of two groups: the first group underwent the following order of exposures: familiarization visit, sham, and then hypoxia exposures. The

second group underwent a familiarization visit, then the hypoxia exposure, followed by the sham exposure (see Table 3). This was done to familiarize the subjects since previous work has shown an decrease in severity of AMS symptoms from the initial exposure to the sham condition (MacInnis, Rupert, & Koehle, 2012b). Measurements of balance, heart rate, pulse oxygen saturation, development of AMS, reaction time, movement time, response time and tap accuracy were taken at four time points during each trial: prior to exposure, 5 minutes, 4 and 12 hours into the hypoxic exposure.

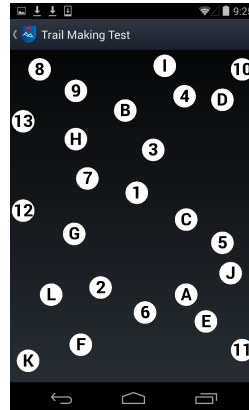
AMS Monitor is an Android™-based application which measures pulse oximetry, LLS, barometric elevation, orientation, memory, concentration as well as coordination. This application was developed as an undergraduate engineering student capstone project. The project was undertaken by a group of five computer and electrical engineering students from UBC. The supervisors for this project were Dr. Walter Karlen, a post-doctoral engineering fellow at the University of British Columbia, now Assistant Professor at ETH Zurich, as well as, Dr. Michael Koehle from the Environmental Physiology Laboratory in the School of Kinesiology at the University of British Columbia. The current study is an extension of the research recently performed under the supervision of Dr. Karlen (Bünter 2015). Our research elaborates on the previous study by increasing the repetitions of each cognitive task as well increasing the duration of the hypoxic exposure.

For the purpose of this experiment the AMS Monitor application was performed on an HTC® Nexus 9 Tablet. The tablet screen size of this device was 22.6cm across with a

resolution of 2048 x 1536 pixels. When using the application itself the Trail Making Test used a 9.6 cm x 9.6 cm area of the screen, the Coordination Test used 9.6 cm x 9.6 cm and The Response Time Test used 13.5 cm x 15.7 cm.



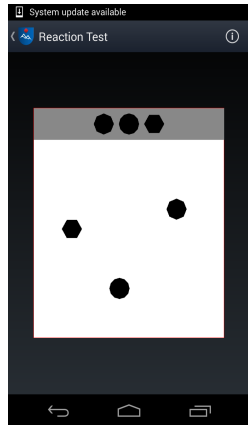
**Figure 1. Trail Making Test – Numeric Version**



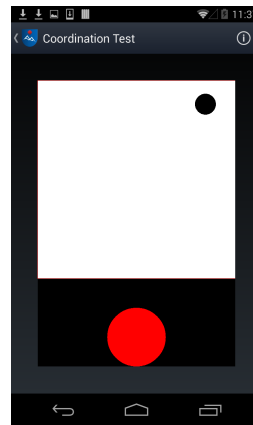
**Figure 2. Trail Making Test – Alphanumeric Version**

AMS Monitor measured coordination with a cognitive task through three distinct modules. The Trail Making Task had subjects connect dots in a particular order. There was a numeric and alphanumeric version of this task (Figure 1 & 2). The main outcome for this module was time to completion. The second module was the Coordination Test. In this test three shapes appeared in a queue in a specific order, these shapes then appeared in the space below the queue (Figure 3). The subject was required to tap all three shapes in the correct sequence. The time taken to tap the first shape comprises the **first response time** (Schmidt & Lee, 2011). The elapsed time to move from the first shape

to the second and from second to third comprises the **inter-response intervals**. The length of time it took to complete the entire task comprises the **full response time** (Schmidt & Lee, 2011). Tapping accuracy for all three taps is measured as displacement in millimetres from where the finger is placed and the actual centre of the shape. The third module was the Response Time Test, once the module has started; a dot appeared on the screen at random time intervals (Figure 4). The user was required to move from a home position, tap the target as rapidly as possible and return back to home. Tapping accuracy was determined as the magnitude of the distance from the centre of the target to where the centre of pressure of the finger tap measured in millimetres. **Reaction time** was measured as the time in milliseconds between when the target appears and when the finger leaves the home position (Schmidt & Lee, 2011). **Movement time** was measured as the difference in time between when the finger leaves home and taps the target (Schmidt & Lee, 2011). **Response time** was calculated as the sum of movement time and reaction time (Schmidt & Lee, 2011).



**Figure 3. Coordination Test**



**Figure 4. Response Time Test**

Secondary outcomes included Balanced Error Scoring System (BESS), heart rate, arterial oxygen saturation and LLS. BESS consists of a series of three static stance positions; a feet-together double leg stance, a non-dominant single leg stance, and a non-dominant leg behind tandem stance, which were performed both on a firm surface as well as on a foam surface. Subjects were instructed to close their eyes and rest their hands on their iliac crests for twenty seconds. Errors were recorded during this twenty-second interval. Errors included: opening their eyes, removing their hands from their hips, flexing or abducting their hips by more than 30 degrees, exaggerated lateral flexion or changing their foot position. Errors were totalled and recorded for each stance. All tests were graded externally by a blinded kinesiologist with daily clinical experience grading BESS tests.

Heart rate and arterial oxygen saturation were measured using a Nonin pulse oximeter (Nonin 9600, Nonin Medical Inc, Plymouth MN). The pulse oximeter uses light

emitting diodes of specific wavelengths (660 and 940 nm). This light passes through the vascular bed of the finger (Luks & Swenson, 2011). The difference between the amount of emitted light and the light received represents arterial oxygen saturation (Luks & Swenson, 2011). While taking these measures of oxygenation, a Nonin pulse oximeter also measures heart rate determined by pulsatile flow rates (Luks & Swenson, 2011).

The LLS is a commonly-used questionnaire for assessing the development of altitude illness (Van Roo et al., 2011). The LLS has the subject rate 5 symptoms: headache, fatigue/weakness, dizziness/lightheadedness, difficulty sleeping and gastrointestinal upset (Kayser et al., 2010). Symptoms were rated in terms of severity from 0 to 3 where 0 represents the absence of a symptom and 3 represents a very severe symptom (Kayser et al., 2010). Individuals are considered to have AMS if their score exceeds a total of 3 with the presence of a headache (Kayser et al., 2010).

## **Subjects**

Fifteen healthy subjects were recruited from the Vancouver area (7 male, 8 female). Subjects were between 19 and 25 years of age (mean age of 22.7 years ( $\pm 2.0$ )). Subjects had not traveled to an altitude of 3000m or higher in the three months prior to testing. The subjects were excluded if they had cardiovascular or pulmonary conditions such as uncontrolled congestive heart failure, severe COPD, pulmonary hypertension or sickle cell disease (Fiore et al., 2010).

## **Sample Size**

The difference in reaction time between sea level and altitude was used as the primary outcome for sample size determination. In previously published studies, this decrement in reaction time ranged from 10 to 30 ms (Davranche et al., 2016; Dykiert et al., 2010; Fowler, Elcombe, Kelso, & Porlier, 1987; Mackintosh, Thomas, Olive, Chesner, & Knight, 1988; Paul & Fraser, 1994; Phillips, Hørning, & Funke, 2015). Research performed by Dykiert and colleagues (2010) was most similar to the current research study. Dykiert measured four choice reaction time over 21 occasions at altitudes ranging from 1992 m to 5565 m. The decrement in reaction time at altitude as compared to baseline was 28 ms. An effect size was calculated as the difference between the mean reaction times reported at baseline and at altitude divided by the standard deviation of the baseline measurements. An alpha error probability of 0.05 and power of 0.8 were used. A difference between two dependent means (matched pairs) statistical test was performed using an effect size of 0.81, an alpha error probability of 0.05 and a power of 0.8 on G\*Power software (G\*Power, Heinrich Heine Universität Düsseldorf). The results of this calculation were a critical t value of 1.81 and a total sample size of 11. For our study to detect a similar change of 10% in reaction time over a 12-hour exposure to a simulated altitude of 4200m, we recruited 15 subjects.

## **Experimental Protocol**

Participants came to the laboratory in pairs on three different occasions; a familiarization trial, a sham trial, and a hypoxic trial. During each of these trials subjects

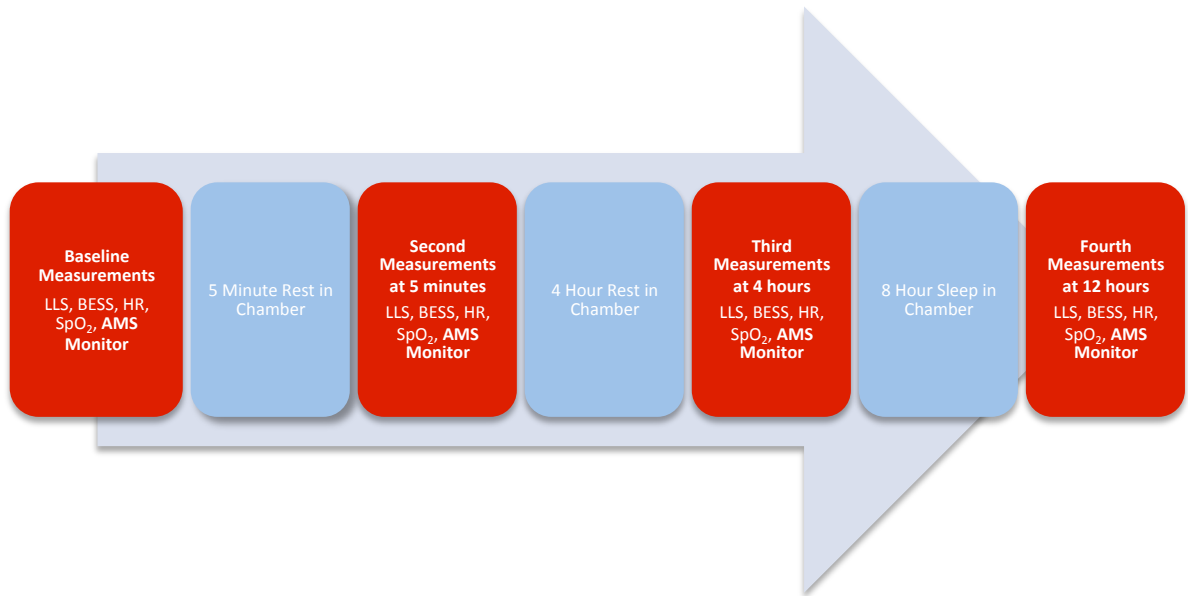
entered a normobaric hypoxic chamber (Colorado Exercise Systems, Colorado Altitude Training, Louisville CO), which simulated altitudes from sea level up to 4200m. Subjects were constantly monitored for saturation of oxygen using a Nonin pulse oximeter (Nonin 9600, Nonin Medical Inc., Plymouth MN). One group of subjects completed the familiarization trial followed by the hypoxic and then the sham trial while the other group completed the familiarization trial followed by the sham and then the hypoxic trial (Table 3).

Group Number	Trial 1 Condition	Trial 2 Condition	Trial 3 Condition
Group 1	Familiarization	Hypoxic	Sham
Group 2	Familiarization	Sham	Hypoxic

**Table 3. Cross-Over Design**

After being informed of the procedures, subjects read and signed a consent form. The subjects' arterial oxygen saturation and heart rate were measured and they completed the LLS, BESS, and coordination task. The subjects then entered the altitude chamber set either to a familiarization intermediate altitude of 2000 m, a hypoxic high altitude of 4200 m or a sham altitude to simulate sea level. After 4 hours of exposure to the chamber, all four tasks were repeated. The subjects then slept in bunk beds for eight hours during which the researcher monitored saturation of oxygen. If a subject's oxygen saturation fell below 60% they were removed from the chamber. Previous research in this chamber completed with 11-hour exposures found that the lowest SpO<sub>2</sub> readings were 79.8% ( $\pm 4$ ) and subjects have never needed medical attention (MacInnis et al.,

2014). In the present study no subject's pulse oxygen saturation fell below 60%, therefore no subject needed to be removed. After eight hours, subjects repeated all four tests before exiting the chamber.



**Figure 5. Timeline of Measurements**

Recent research in our laboratory has shown that subjects have symptoms following their first exposure in the chamber even in the sham condition (MacInnis et al., 2014). The crossover nature of Trials 2 and 3 allowed us to determine if there was a continued effect from the chamber exposure that persists due to unfamiliarity or to hypoxia alone. If there were an unfamiliarity effect, the subjects exposed to the sham on their second trial would produce worse outcomes as compared to those subjects who are exposed to sham on their third trial.

## Statistical Analysis

A 3 x 2 (Time x Condition) factorial repeated measures within-subject ANOVA was used on all measures taken during the study. The three time points were 5 minutes, 4 and 12 hours into the exposure and the two conditions represented altitudes of sham (250 m), and hypoxia (4200 m) intervention. This allowed us to analyze our data for main effects and interactions of all measures during every visit to the laboratory. This statistical analysis grouped data based on either time or altitude and analyzed the results for significant differences. When significant main effects were found a Tukey post hoc HSD test would determine between which pairs these differences lay. Similarly pair-wise comparisons were performed to find significant pair differences after an interaction effect was found.

The BESS was analyzed as a total sum score as well as partitioned into each individual component. We decomposed the BESS in order to determine if there were specific components that were more useful than others. A similar process was undertaken by previous researchers from our laboratory group (MacInnis, Rupert, & Koehle, 2012b).

The Coordination Test contained 48 sets within one test, meaning that subjects performed this task for approximately ten minutes. The Response Time Test contained 64 repetitions within one test, similarly, subjects performed this task for approximately ten minutes. Due to the length of time it took to complete these tasks, we analyzed the normality of frequency distributions of these measures to see if performance changed

within a test. In the Coordination Test, the tap accuracy measures for each shape were largely normally distributed, 12% of all sets were not considered normally distributed. Reaction time was normally distributed in 21% of the trials. The second and third inter-response intervals were normally distributed 20% and 18% of the trials respectively. The full response time was normally distributed 34% of the trials. In the Response Time Task, response time was normally distributed 85% of the trials. Low normality of some measures indicated that outliers were skewing our means. In order to mitigate the effect of outliers, data were analyzed based on the first ten sets within each test as well as the last ten sets within each test. Additionally, log transformations of data sets were performed to reduce the effect of outliers.

Although hypoxia was our main intervention, sleep quality can also effect cognitive measurements. Those measurements that appeared to get worse before sleep and improve after sleep were analyzed by sleep quality as assessed in the LLS. In this way we will be able to determine the effect of sleep quality on certain measurements.

Pearson correlation assessments were performed to test how related measurements that changed based on altitude condition were to each other. We evaluated the relationship between LLS and the log transformation of reaction time of the first shape of the Coordination Test, foam single leg stance of the BESS and tapping accuracy of the Response Time Test. Another set of correlations was conducted between pulse oximetry and the same three measurements.

Receiver operator characteristic curves (ROC) were used to measure the validity of a diagnostic test against a gold standard (Kumar & Indrayan, 2011). Although there is no true gold standard for determining the presence or absence of acute mountain sickness, for the purpose of this analysis, we used the LLS as our gold standard. ROC curves take an input dichotomous variable (in this case whether the individual has been diagnosed with acute mountain sickness) as well as a continuous variable. We used this technique to test response time against acute mountain sickness. Specifically, our continuous variables were the change in response time to the first shape from baseline and the log transformation of the response time to the first shape. ROC curves plot sensitivity on the y-axis and one minus specificity on the x-axis. Sensitivity or true positive rate represents the number of cases where an individual has been diagnosed as sick divided by the actual number of sick individuals (Kumar & Indrayan, 2011). Specificity or true negative rate is the number of cases where an individual has been diagnosed as not sick divided by the actual number of not sick individuals. One minus specificity or false positive rate is the number of times someone is incorrectly diagnosed as sick divided by the total number of non-sick individuals (Kumar & Indrayan, 2011). The output of an ROC curve analysis is the area under the curve (AUC), cutoff threshold values, specificity and sensitivity. AUC represents the effectiveness of this tool to accurately diagnose a condition. AUC can range from 0.5 (which would suggest that the test is no more effective than chance alone) to 1.0 (which would suggest that the test can perfectly differentiate those with the condition from those without it) (Kumar & Indrayan, 2011). AUC values ranging from 0.5-0.7 are considered to have low accuracy, 0.7-0.9 moderate

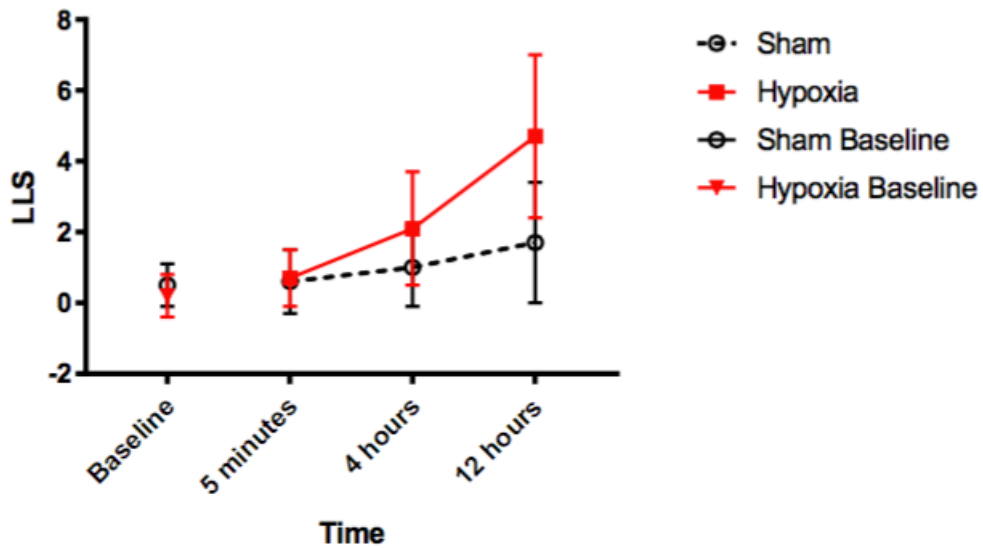
accuracy, above 0.9 high accuracy (Streiner & Cairney, 2007). To determine the other three outputs, one must evaluate the results and find the point at which sensitivity and specificity are highest. This point will also correspond with a specific cut off threshold.

## Results

In terms of LLS, main effects were found for time ( $p < 0.001$ ,  $F=25.39$ ) and altitude ( $p < 0.001$ ,  $F=35.48$ ). For the LLS, there was also a significant interaction effect for time\*altitude ( $p < 0.018$ ,  $F=5.54$ ) with significant differences found in sham between 5 minutes and 12 hours (+1.1), in hypoxia between 5 minutes and 4 hours, in hypoxia between 5 minutes and 12 hours (+1.4), in hypoxia between 4 hours and 12 hours (+2.5), at the 4-hours time point between sham and hypoxia (+1.1) and at the 12-hour time point between sham and hypoxia (+2.9). The elevated LLS in the sham condition was mostly due to increases in the fatigue and weakness component of the score. These results are outlined in Table 4 & 5 and Figure 6.

	<i><b>Baseline</b></i>	<i><b>5 minutes</b></i>	<i><b>4 hours</b></i>	<i><b>12 hours</b></i>
<b>Sham</b>	0.5 ( $\pm 0.6$ )	0.6 ( $\pm 0.9$ )	1.0 ( $\pm 1.1$ )	1.7 ( $\pm 1.7$ )
<b>Hypoxia</b>	0.2 ( $\pm 0.6$ )	0.7 ( $\pm 0.8$ )	2.1 ( $\pm 1.6$ )	4.7 ( $\pm 2.3$ )

**Table 4. LLS means and standard deviations**



**Figure 6. Lake Louise Score over time and condition**

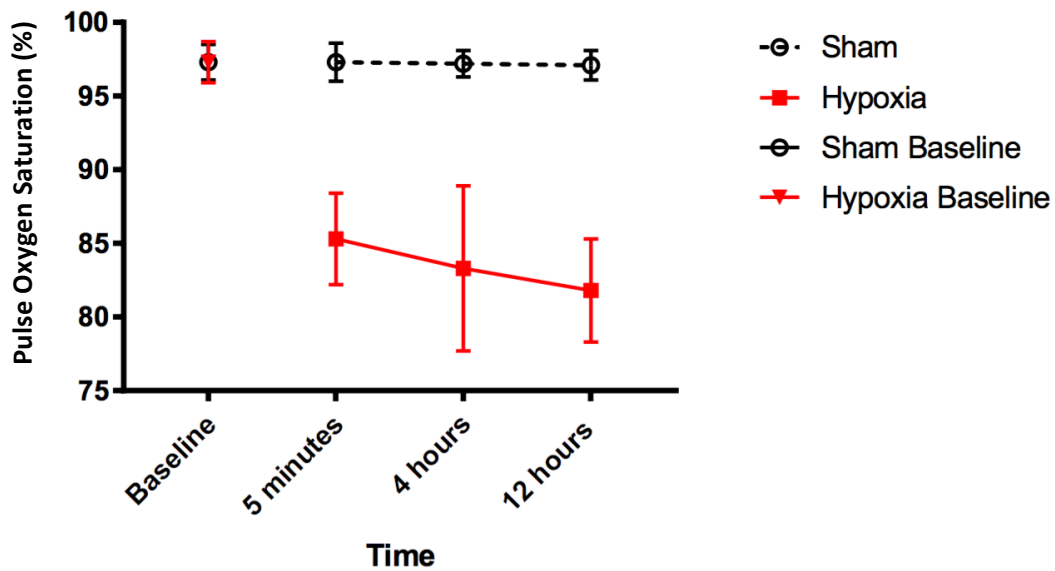
Altitude	Time	Mean Difference	Significance
Sham	5 min & 12 hours	1.13	p<0.05
Hypoxia	5 min & 4 hours	1.40	p<0.01
Hypoxia	5 min & 12 hours	3.93	p<0.001
Hypoxia	4 hours & 12 hours	2.53	p<0.001
Hypoxia & Sham	4 hours	1.13	p<0.01
Hypoxia & Sham	12 hours	2.93	p<0.005

**Table 5. Significant Interaction Effects for Lake Louise Score**

Pulse oxygen saturation produced significant main effects of time ( $p<0.01$ ,  $F=7.11$ ) and altitude ( $p<0.001$ ,  $F=244.29$ ). An interaction effect was also found ( $p<0.05$ ,  $F=7.14$ ) with significant differences found in hypoxia between 5 minutes and 12 hours (-3.5%), at the 5-minute time point between sham and hypoxia (-12.0%), at the 4-hour time point between sham and hypoxia (-13.9%) and at the 12-hour time point between sham and hypoxia (-15.3%). These results are outlined in Table 6 & 7 and Figure 7.

	<i>Baseline</i>	<i>5 minutes</i>	<i>4 hours</i>	<i>12 hours</i>
<b>Sham</b>	97.3% ( $\pm 1.2$ )	97.3% ( $\pm 1.3$ )	97.2% ( $\pm 0.9$ )	97.1% ( $\pm 1.0$ )
<b>Hypoxia</b>	97.3% ( $\pm 1.4$ )	85.3% ( $\pm 3.1$ )	83.3% ( $\pm 5.6$ )	81.8% ( $\pm 3.5$ )

**Table 6. SpO<sub>2</sub> means and standard deviations**



**Figure 7. Pulse Oxygen Saturation over time and condition**

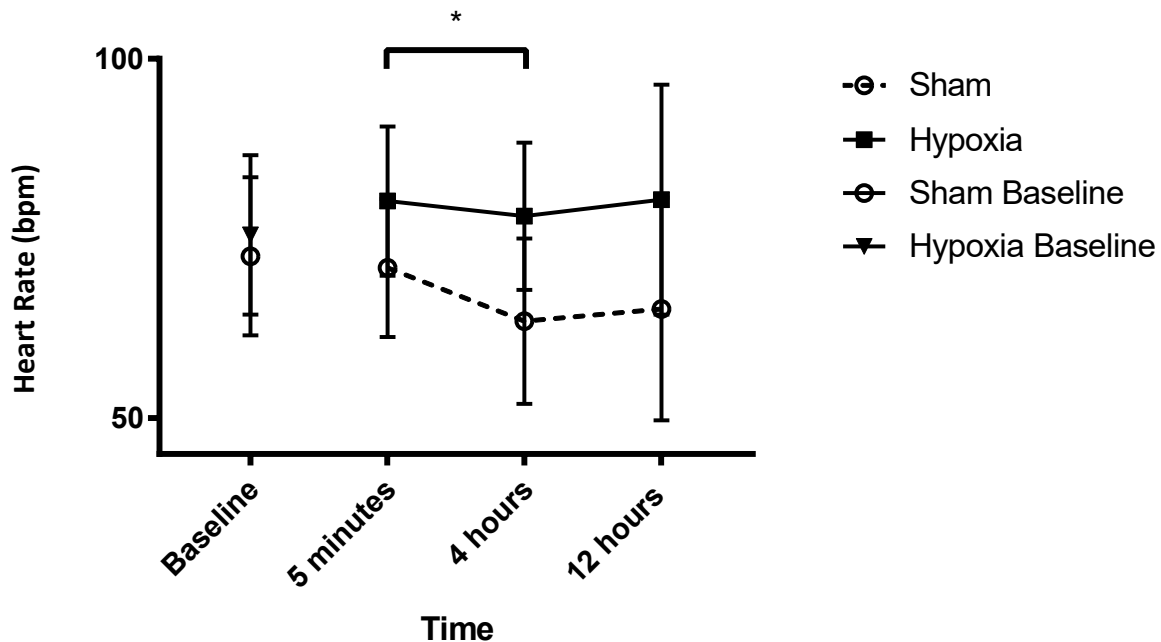
<b>Altitude</b>	<b>Time</b>	<b>Mean Difference</b>	<b>Significance</b>
Hypoxia	5 min & 12 hours	3.51	p<0.005
Hypoxia & Sham	5 min	11.96	p<0.001
Hypoxia & Sham	4 hours	13.92	p<0.001
Hypoxia & Sham	12 hours	15.32	p<0.001

**Table 7. Significant Interaction Effects for Pulse Oxygen Saturation**

Heart rate decreased over time with significant differences between 5 minutes and 4 hours (-4.71 bpm)(p<0.05, F=6.64). Heart rate was also significantly elevated at altitude (+13.01)(p<0.01, F=10.05). No interaction existed for heart rate. These results are outlined in Table 8 and Figure 8.

	<b><i>0 minutes</i></b>	<b><i>5 minutes</i></b>	<b><i>4 hours</i></b>	<b><i>12 hours</i></b>
<b>Sham</b>	72.5 bpm (±11.0)	70.9 bpm (±9.6)	63.5 bpm (±11.5)	65.2 bpm (±15.5)
<b>Hypoxia</b>	75.5 bpm (±11.1)	80.2 bpm (±10.4)	78.1 bpm (±10.3)	80.4 bpm (±16.0)

**Table 8. Heart Rate means and standard deviations**



	Pairwise Comparison	Mean Difference	Significance
*	Significance between 4 hours and 5 minutes	4.7	p<0.01

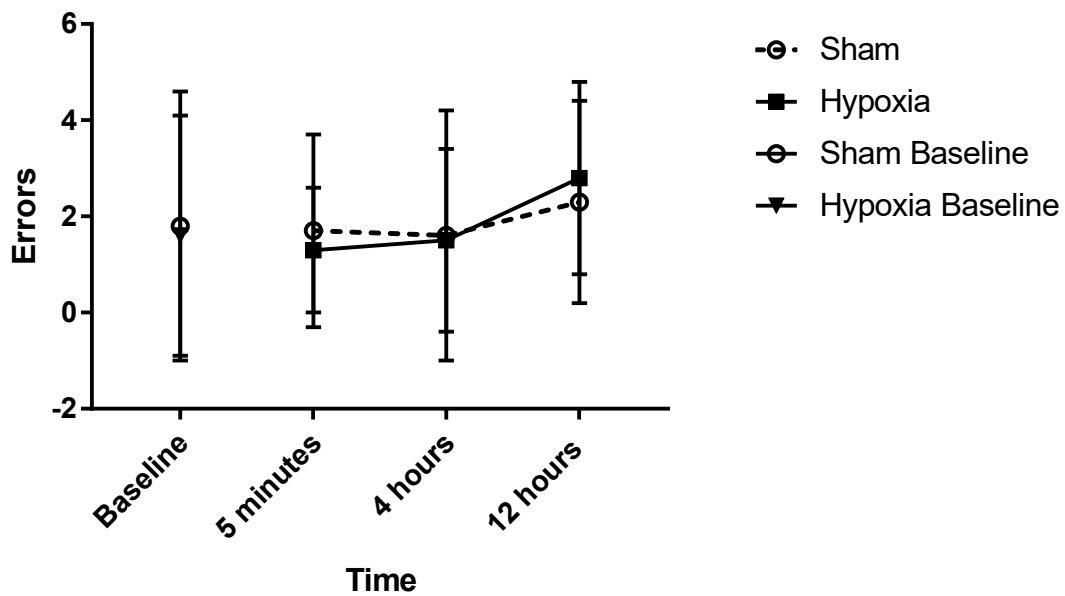
**Figure 8. Heart Rate over time and condition**

Significant differences for the tandem and double leg and total BESS scores were not found when analyzed based on time or altitude. Significant differences were detected for single leg stance of BESS. The firm surface single leg stance increased significantly over time ( $p<0.01$ ,  $F=7.22$ ) with significant differences between 5 minutes and 12 hours (+1.10), 4 hours and 12 hours (+1.03). The single-leg stance performed on the foam surface produced a significant interaction effect ( $p<0.05$ ,  $F=5.02$ ) with significant differences found in the hypoxia condition between 5 minutes and 4 hours (+1.5), 5 minutes and 12 hours (+1.6), as well as at the 5-minute time point between

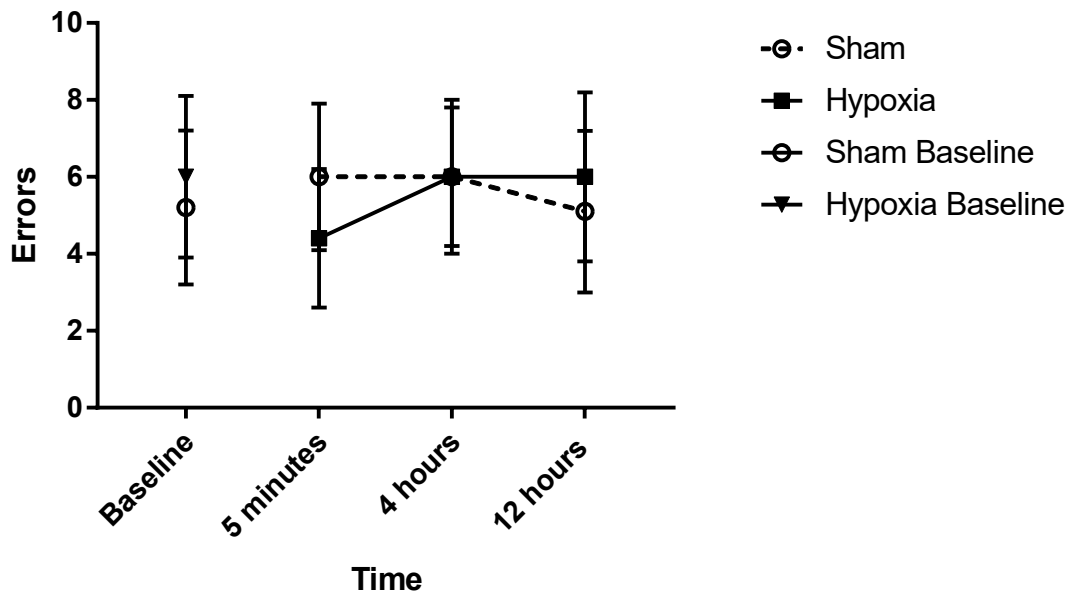
sham and hypoxia (+1.6). These results are outlined in Table 9 & 10 as well as Figure 9 and 10.

		<i>Baseline</i>	<i>5 minutes</i>	<i>4 hours</i>	<i>12 hours</i>
<b>Firm Surface</b>	<b>Sham</b>	1.8 ( $\pm 2.8$ )	1.7 ( $\pm 2.0$ )	1.6 ( $\pm 2.6$ )	2.3 ( $\pm 2.1$ )
	<b>Hypoxia</b>	1.6 ( $\pm 2.5$ )	1.3 ( $\pm 1.3$ )	1.5 ( $\pm 1.9$ )	2.8 ( $\pm 2.0$ )
<b>Foam Surface</b>	<b>Sham</b>	5.2 ( $\pm 2.0$ )	6.0 ( $\pm 1.9$ )	6.0 ( $\pm 2.0$ )	5.1 ( $\pm 2.1$ )
	<b>Hypoxia</b>	6.0 ( $\pm 2.1$ )	4.4 ( $\pm 1.8$ )	6.0 ( $\pm 1.8$ )	6.0 ( $\pm 2.2$ )

**Table 9. BESS Single Leg Stances**



**Figure 9. BESS Single Leg Stance on Firm Surface**



**Figure 10. BESS Single Leg Stance on Foam Surface**

Altitude	Time	Mean Difference	Significance
Hypoxia	5 min & 4 hours	1.53	p<0.01
Hypoxia	5 min & 12 hours	1.60	p<0.01
Hypoxia & Sham	5 min	1.60	p<0.05

**Table 10. Significant Interaction Effects for BESS Single Leg Stance Foam Surface**

Time to completion of the numeric trail-making task increased significantly over time as outlined in Table 11 with significant differences between 5 mins and 12 hours (+2.27)(p<0.05, F=5.98). The alpha-numeric trail-making test produced no significant results based on altitude or time.

	<b><i>Baseline</i></b>	<b><i>5 minutes</i></b>	<b><i>4 hours</i></b>	<b><i>12 hours</i></b>	<b><i>Mean Condition after Baseline</i></b>
<b>Sham</b>	19.0 sec ( $\pm 2.9$ )	17.5 sec ( $\pm 2.5$ )	18.5 sec ( $\pm 3.7$ )	20.3 sec ( $\pm 3.9$ )	18.8 sec
<b>Hypoxia</b>	20.4 sec ( $\pm 5.2$ )	17.0 sec ( $\pm 3.3$ )	18.2 sec ( $\pm 4.5$ )	18.7 sec ( $\pm 3.4$ )	18.0 sec
<b>Mean Time</b>	19.7 sec	17.3 sec	18.4 sec	19.5 sec	

**Table 11. Numeric Trail Making Test**

The Coordination Test assessed response time and accuracy. When assessing parameters of the Coordination Test no significant differences were found for time or error rate. However, accuracy of tapping the first shape decreased over time with significant differences between 5 minutes and 4 hours ( $+0.12$ ), 5 minutes and 12 hours ( $+0.12$ )( $p < 0.005$ ,  $F = 8.88$ ). Additionally, accuracy of tapping the third shape decreased over time with significant differences between 5 minutes and 4 hours ( $+0.15$ )( $p < 0.005$ ,  $F = 8.84$ ). These results are outlined in Table 12 and 13.

	<b><i>5 minutes</i></b>	<b><i>4 hours</i></b>	<b><i>12 hours</i></b>	<b><i>Mean Condition after Baseline</i></b>
<b>Sham</b>	2.1 mm ( $\pm 0.3$ )	2.1 mm ( $\pm 0.2$ )	2.2 mm ( $\pm 0.3$ )	2.2 mm
<b>Hypoxia</b>	2.0 mm ( $\pm 0.2$ )	2.2 mm ( $\pm 0.3$ )	2.2 mm ( $\pm 0.2$ )	2.2 mm
<b>Mean Time</b>	2.1 mm	2.2 mm	2.2 mm	

**Table 12. Coordination Test Accuracy of First Shape**

	<b><i>5 minutes</i></b>	<b><i>4 hours</i></b>	<b><i>12 hours</i></b>	<b><i>Mean Condition after Baseline</i></b>
<b>Sham</b>	2.3 mm ( $\pm 0.2$ )	2.4 mm ( $\pm 0.2$ )	2.4 mm ( $\pm 0.2$ )	2.4 mm
<b>Hypoxia</b>	2.4 mm ( $\pm 0.2$ )	2.5 mm ( $\pm 0.3$ )	2.4 mm ( $\pm 0.2$ )	2.5 mm
<b>Mean Time</b>	2.4 mm	2.5 mm	2.4 mm	

**Table 13. Coordination Test Accuracy of Third Shape**

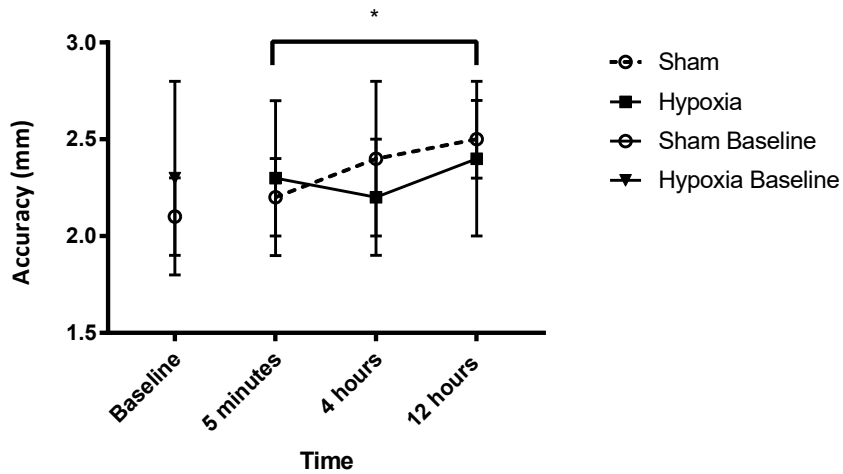
When all measures were evaluated looking only at the first ten tap sets, a significant difference was found for response time of the first shape over time that was not produced when evaluating all sets ( $p < 0.005$ ,  $F = 10.41$ ). Response time to the first shape increased between 5 minutes and 12 hours (+345.28) and 4 hours and 12 hours (+303.95). Finger tap accuracy of the second shape also decreased significantly over time when analyzing only the first 10 sets ( $p < 0.05$ ,  $F = 4.87$ ). Finger tap accuracy decreased significantly between 5 minutes and 12 hours (+0.17). These results are outlined in Table 14 and 15 as well as Figure 11.

	<i>Baseline</i>	<i>5 minutes</i>	<i>4 hours</i>	<i>12 hours</i>
<b>Sham</b>	1293.5 ms ( $\pm 253.8$ )	1307.0 ms ( $\pm 249.0$ )	1271.7 ms ( $\pm 284.5$ )	1680.9 ms ( $\pm 384.1$ )
<b>Hypoxia</b>	1612.2 ms ( $\pm 883.8$ )	1279.2 ms ( $\pm 274.6$ )	1397.1 ms ( $\pm 362.9$ )	1595.8 ms ( $\pm 629.9$ )

**Table 14. First 10 Sets of Coordination Test - Response Time of First Shape**

	<i>Baseline</i>	<i>5 minutes</i>	<i>4 hours</i>	<i>12 hours</i>
<b>Sham</b>	2.1 mm ( $\pm 0.2$ )	2.2 mm ( $\pm 0.2$ )	2.4 mm ( $\pm 0.4$ )	2.5 mm ( $\pm 0.2$ )
<b>Hypoxia</b>	2.3 mm ( $\pm 0.5$ )	2.3 mm ( $\pm 0.4$ )	2.2 mm ( $\pm 0.3$ )	2.4 mm ( $\pm 0.4$ )

**Table 15. First 10 Sets of Coordination Test – Accuracy of Second Shape**



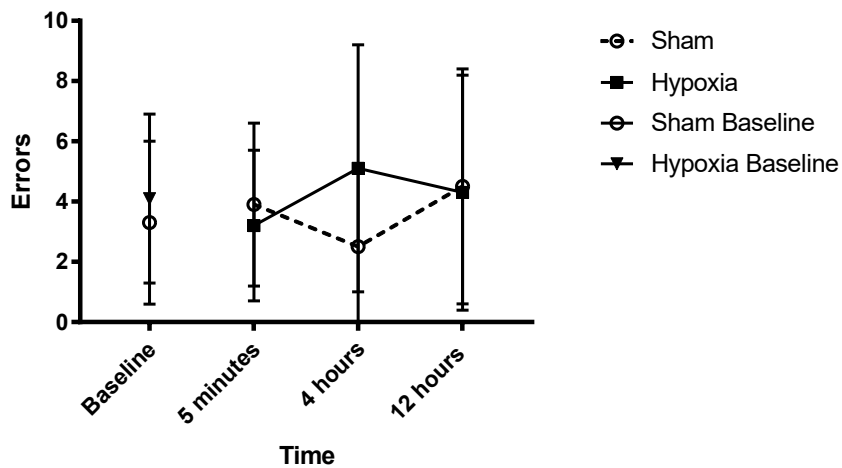
	Pairwise Comparison	Mean Difference	Significance
*	Significance between 12 hours and 5 minutes	0.171	p<0.05

**Figure 11. First 10 Sets of Coordination Test – Accuracy of Second Shape**

When all measures were evaluated looking only at the last ten tap sets, there was a significant increase in the number of errors made based on the interaction between the effect of altitude and time ( $p<0.05$ ,  $F=6.29$ ). The significant differences of this interaction were in the sham condition between 5 minutes and 4 hours (+2.0 errors) as well as at the 4 hour time point between sham and hypoxia (+2.6 errors). These results are outlined in Table 16 and 17 as well as Figure 12. The unique nature of this trend stimulated further investigation. Figure 13 and 14 below show errors when grouped by sleep quality.

	<i>Baseline</i>	<i>5 minutes</i>	<i>4 hours</i>	<i>12 hours</i>	<i>Mean Condition after Baseline</i>
<b>Sham</b>	3.3 ( $\pm 2.7$ )	3.9 ( $\pm 2.7$ )	2.5 ( $\pm 2.5$ )	4.5 ( $\pm 3.9$ )	3.6
<b>Hypoxia</b>	4.1 ( $\pm 2.8$ )	3.2 ( $\pm 2.5$ )	5.1 ( $\pm 4.1$ )	4.3 ( $\pm 3.9$ )	4.2
<b>Mean Time</b>	3.7	3.6	3.8	4.4	

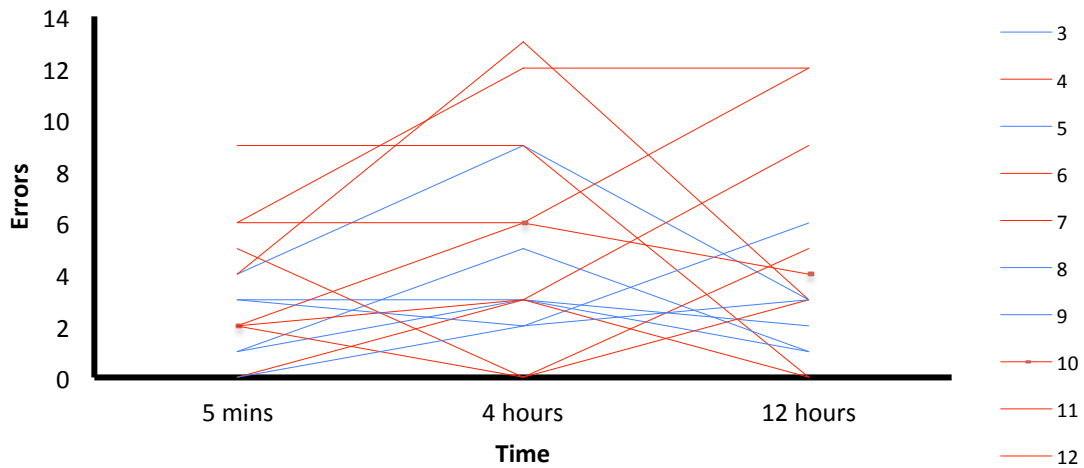
**Table 16. Last 10 Sets of Coordination Test - Errors**



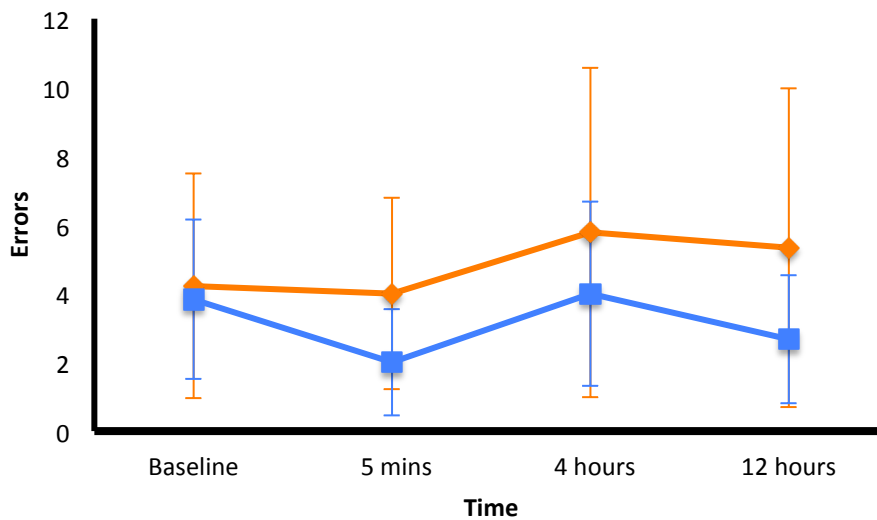
**Figure 12. Last 10 Sets of Coordination Test – Errors grouped by condition**

<b>Altitude</b>	<b>Time</b>	<b>Mean Difference</b>	<b>Significance</b>
Sham	5 min & 4 hours	2.0	p<0.05
Hypoxia & Sham	4 hours	2.6	p<0.01

**Table 17. Significant Interaction Effects for Errors in Coordination Test**



**Figure 13. Last 10 Sets of Coordination Test – Errors colored by sleep quality (red poor sleep, blue good sleep)**



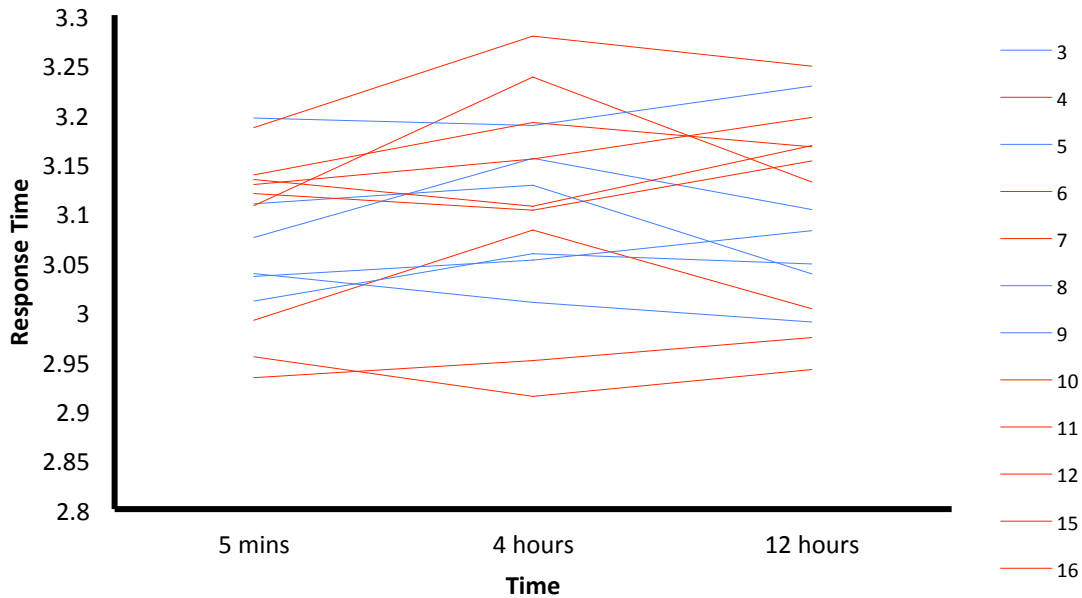
**Figure 14. Last 10 Sets of Coordination Test – Errors grouped by sleep quality (orange poor sleep, blue good sleep)**

After performing log transformations an interaction effect of time and altitude was found for the response time of the first shape ( $p < 0.05$ ,  $F = 4.33$ ) with significant differences in sham between 4 hours and 12 hours ( $+0.05$ ), in hypoxia between 5

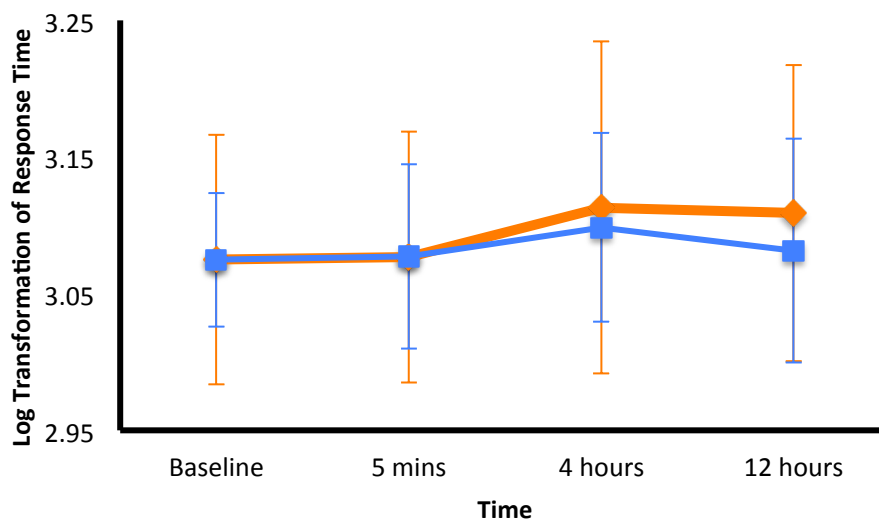
minutes and 4 hours (+0.03) and at the 4-hour time point between sham and hypoxia (+0.04). These results are outlined in Table 18. The unique nature of this trend stimulated further investigation. The figures below show response time when grouped by sleep quality that is outlined in Figure 15 and 16.

Altitude	Time	Mean Difference	Significance
Sham	4 hours and 12 hours	0.05	$p < 0.05$
Hypoxia	5 min and 4 hours	0.03	$p < 0.05$
Hypoxia & Sham	4 hours	0.04	$p < 0.05$

**Table 18. Significant Interaction Effects for Log Transformation of Response Time to First Shape in Coordination Task**



**Figure 15. Log Transformation of Response Time of the first shape grouped by sleep quality (red is poor sleep, blue is good sleep)**

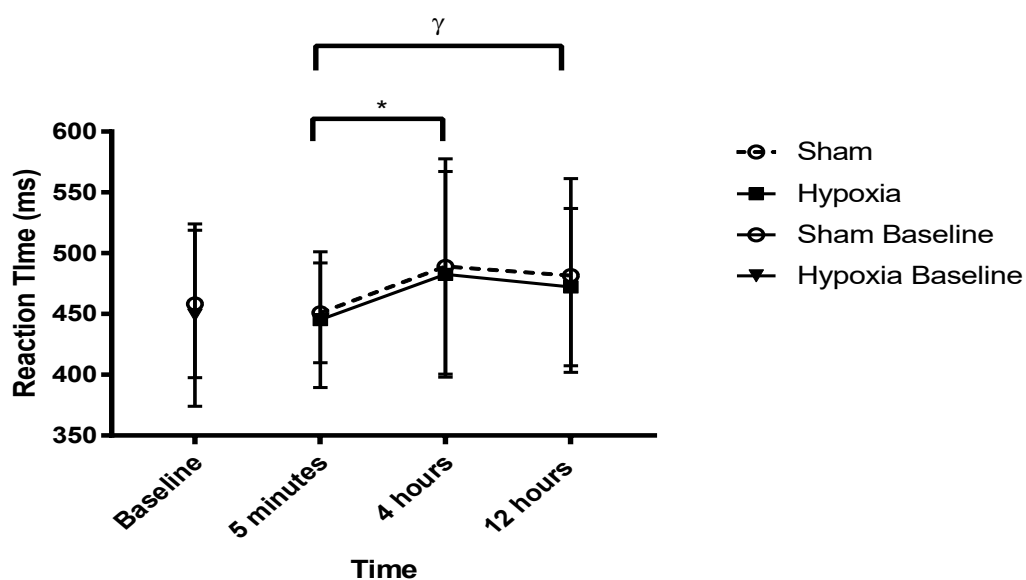


**Figure 16. Log Transformation of Response Time of the first shape grouped by sleep quality (orange poor sleep, blue good sleep)**

The Response Time Test assesses reaction time, movement time and response time of a simple reaction task. Reaction time increased significantly over time as outlined in Table 19 and Figure 17 ( $p < 0.005$ ,  $F = 11.40$ ). Reaction time increased significantly between 5 minutes and 4 hours (+37.71 ms) and 5 minutes and 12 hours (+28.74 ms). Movement time increased significantly over time as outlined in Figure 18 ( $p < 0.01$ ,  $F = 8.11$ ). Movement time increased significantly between 5 minutes and 12 hours (+45.85 ms) and 4 hours and 12 hours (+45.90 ms). Response time increased significantly over time as outlined in Figure 19 ( $p < 0.005$ ,  $F = 11.41$ ). Response time increased significantly between 5 minutes and 4 hours (+36.10 ms) and between 5 minutes and 12 hours (+66.33 ms) ( $p < 0.05$  and  $p < 0.005$  respectively).

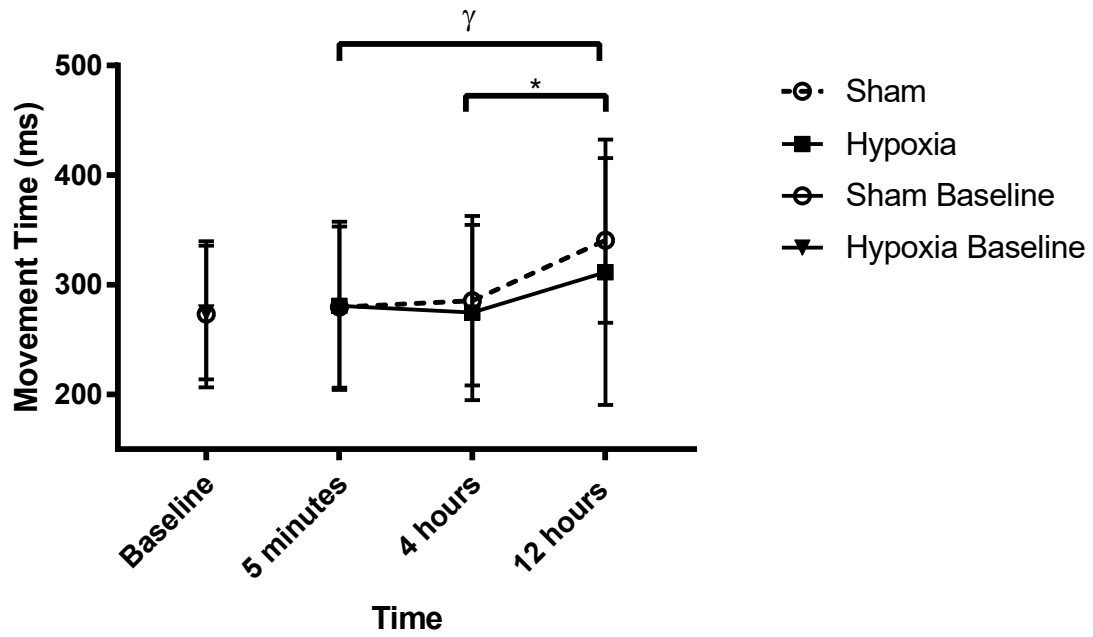
	<i>Baseline</i>	<i>5 minutes</i>	<i>4 hours</i>	<i>12 hours</i>	<i>Mean Condition after Baseline</i>
<b>Sham</b>	458.3 ms ( $\pm 60.6$ )	450.9 ms ( $\pm 41.1$ )	489.1 ms ( $\pm 88.6$ )	481.6 ms ( $\pm 79.7$ )	473.9 ms
<b>Hypoxia</b>	449.0 ms ( $\pm 75.0$ )	445.3 ms ( $\pm 55.9$ )	482.6 ms ( $\pm 84.5$ )	472.1 ms ( $\pm 64.7$ )	466.7 ms
<b>Mean Time</b>	453.7 ms	448.1 ms	485.9 ms	476.9 ms	

**Table 19. Response Time Test – Reaction Time**



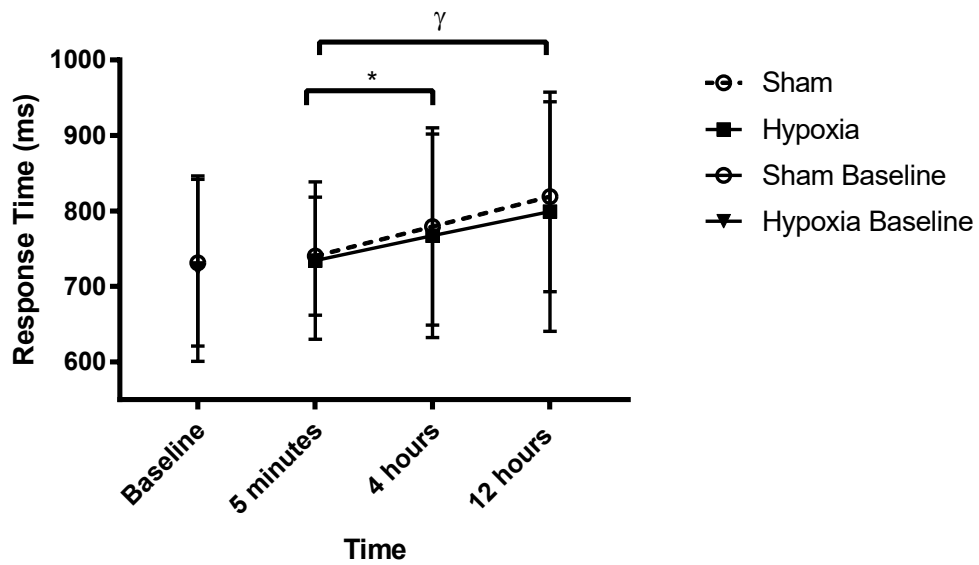
	<b>Pairwise Comparison</b>	<b>Mean Difference</b>	<b>Significance</b>
γ	Significance between 12 hours and 5 minutes	28.7 ms	p<0.01
*	Significance between 4 hours and 5 minutes	37.7 ms	p<0.01

**Figure 17. Response Time Test - Reaction Time**



	Pairwise Comparison	Mean Difference	Significance
$\gamma$	Significance between 12 hours and 5 minutes	45.9 ms	$p < 0.005$
*	Significance between 12 hours and 4 hours	45.9 ms	$p < 0.005$

**Figure 18. Response Time Test - Movement Time**



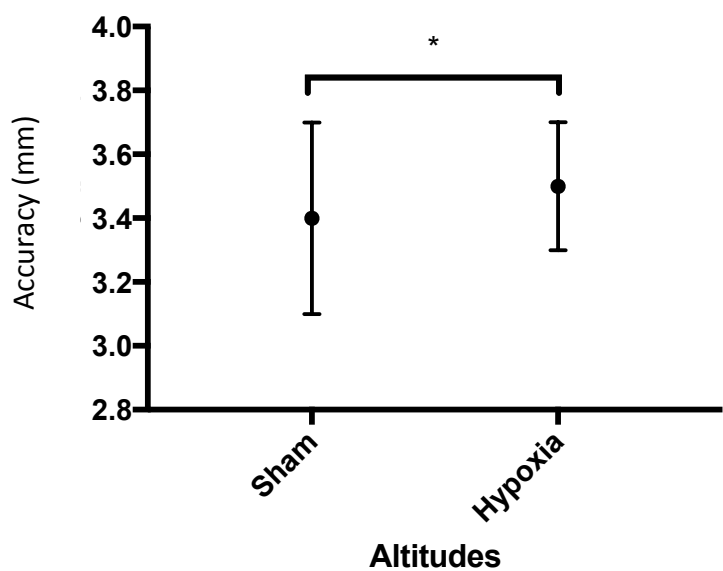
	Pairwise Comparison	Mean Difference	Significance
*	Significance between 5 minutes and 4 hours	36.1 ms	p<0.05
γ	Significance between 5 minutes and 12 hours	66.3 ms	p<0.005

**Figure 19. Response Time Test - Response Time**

Finger tap accuracy of the Response Time Test decreased significantly on trials at altitude (+0.19) as compared to as outline in Table 20 and Figure 20 ( $p<0.05$ ,  $F=5.07$ ). However, this significant difference was only present when the raw value was analyzed and not present when the changes from baseline were analyzed which contrasts the measures of time discussed above.

	<i>Baseline</i>	<i>5 minutes</i>	<i>4 hours</i>	<i>12 hours</i>	<i>Mean Condition after Baseline</i>
<b>Sham</b>	3.1 ( $\pm 0.9$ )	3.2 ( $\pm 0.8$ )	3.3 ( $\pm 1.0$ )	3.6 ( $\pm 1.3$ )	3.4
<b>Hypoxia</b>	3.3 ( $\pm 0.8$ )	3.5 ( $\pm 1.1$ )	3.6 ( $\pm 1.1$ )	3.5 ( $\pm 0.9$ )	3.5
<b>Mean Time</b>	3.2	3.4	3.5	3.6	

**Table 20. Response Time Test – Accuracy**



	<b>Pairwise Comparison</b>	<b>Mean Difference</b>	<b>Significance</b>
*	Significance between Hypoxia and Sham	0.19	p<0.05

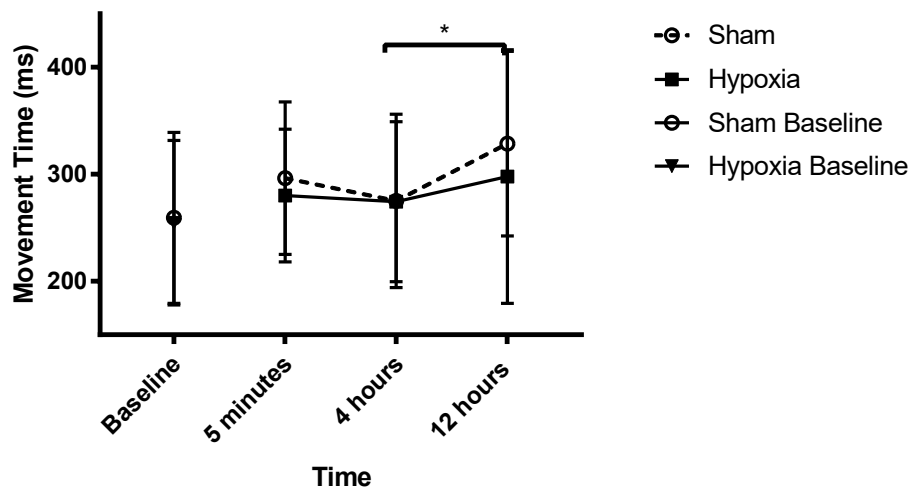
**Figure 20. Response Time Test – Accuracy**

Unlike the Coordination Test in which data was not normally distributed, in the Response Time Test 85% of frequency distributions were normal, outliers did not skew these data sets. Therefore log transformations were not necessary based on the strong normality of this data. Data sets were however analyzed based on the first ten and last ten sets within each test to determine if boredom, effort or fatigue might have affected the results.

The movement time of the first ten sets was the only parameter in the first or last ten sets to increase significantly with time ( $p < 0.05$ ,  $F = 6.30$ ). Movement time decreased significantly between 4 hours and 12 hour (-38.6 ms). These results are presented in Table 21 and Figure 21.

	<i><b>Baseline</b></i>	<i><b>5 minutes</b></i>	<i><b>4 hours</b></i>	<i><b>12 hours</b></i>	<i><b>Mean Condition after Baseline</b></i>
<b>Sham</b>	259.3 ms (79.9)	296.4 ms (71.2)	275.0 ms (81.0)	328.6 ms (86.3)	300.0 ms
<b>Hypoxia</b>	254.7 ms (76.9)	280.1 ms (61.9)	274.4 ms (74.8)	297.9 ms (118.5)	284.1 ms
<b>Mean Time</b>	257.0 ms	288.3 ms	274.7 ms	313.3 ms	

**Table 21. First 10 Sets of Response Time Test - Movement Time**



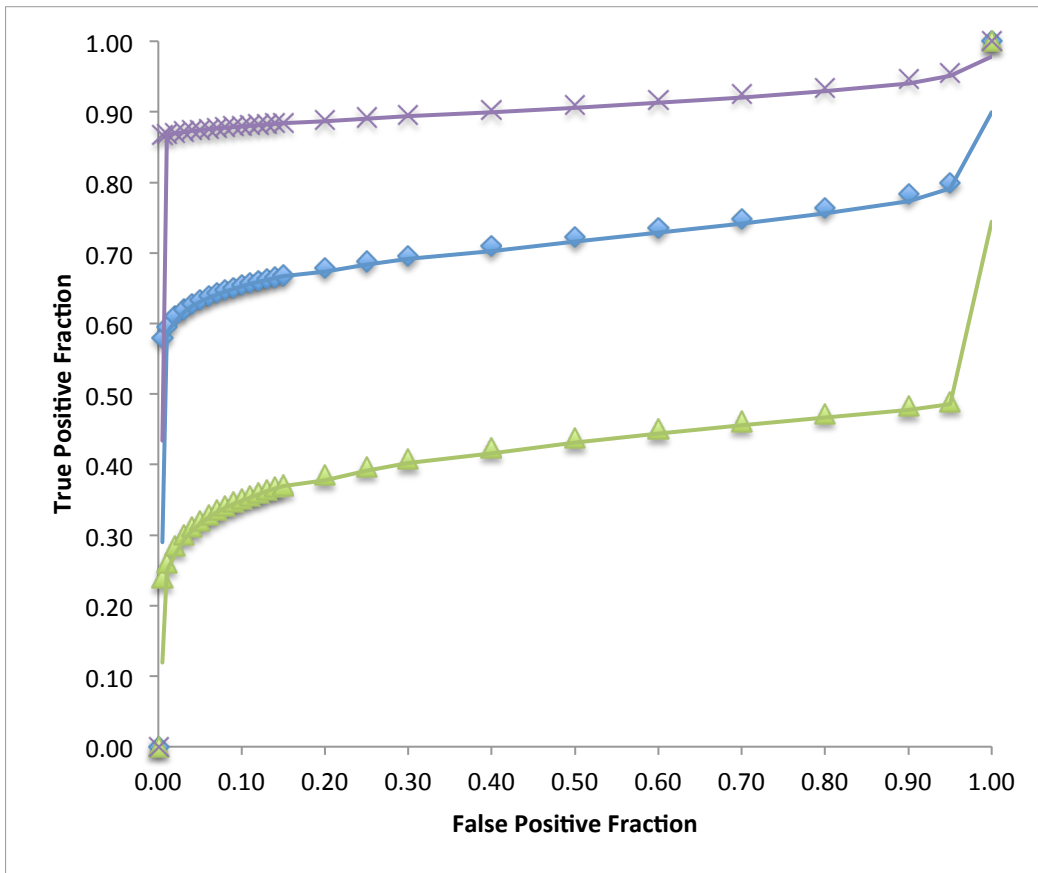
**Figure 21. First 10 Sets of Response Time Test - Movement Time**

In addition to repeated measures ANOVAs a series of Pearson correlations were performed. We analyzed correlations between LLS and the log transformation of reaction time of the first shape, foam single leg stance of BESS and accuracy of response time test. Another set of correlations were conducted between pulse oximetry and the log transformation of reaction time of the first shape, foam single leg stance of BESS and accuracy of response time test. All Pearson correlations were found to be insignificant based on their R and p values. These results can be found in the Table below (Table 22).

<b>Pearson Correlation Assessment</b>	<b>R Value</b>	<b>P Value</b>
LLS compared with Log Transformation of First Response Time of the Coordination Test	0.13	0.23
LLS compared with Single Leg Foam Stance - BESS	0.12	0.25
LLS compared with Accuracy of Response Time Task	-0.02	0.82
Pulse Oxygen Saturation compared with Log Transformation of First Response Time of the Coordination Test	0.09	0.41
Pulse Oxygen Saturation compared with Single Leg Foam Stance - BESS	0.11	0.28
Pulse Oxygen Saturation compared with Accuracy of Response Time Task	0.07	0.50

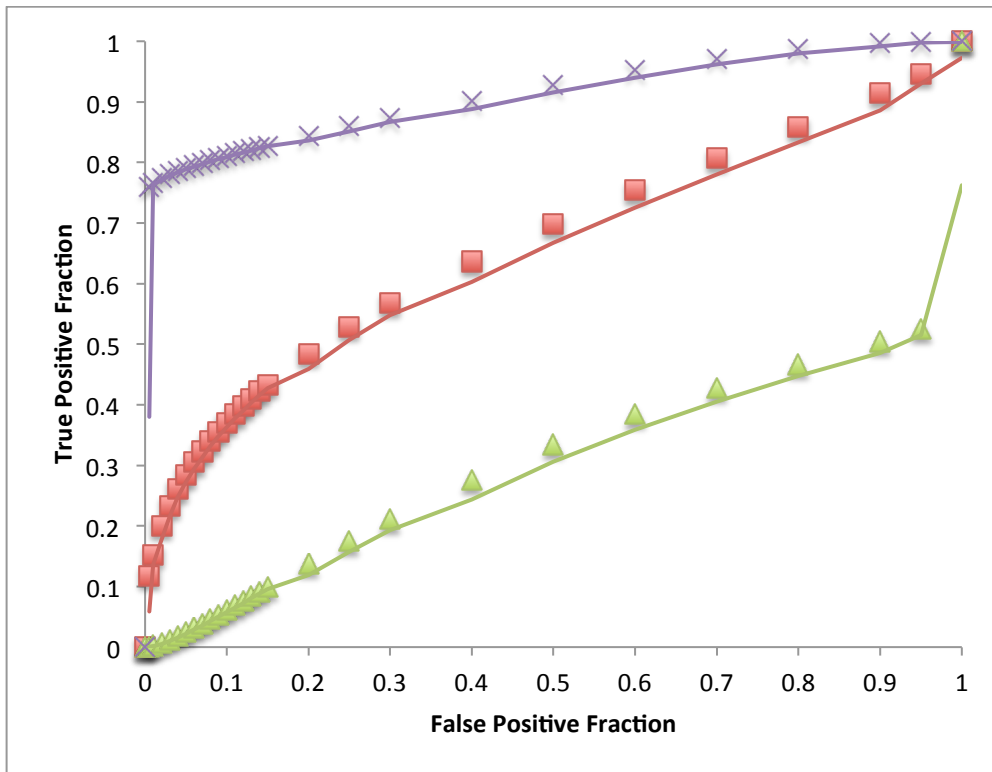
**Table 22. Non-significant Pearson Correlation Assessments**

Two receiver operator characteristic (ROC) curves were made to measure the validity of coordinated tasks performed on a tablet as a diagnostic test against a gold standard (Kumar & Indrayan, 2011). For the purposes of this analysis AMS as diagnosed by the LLS was our gold standard although we do realize that to date there is no true gold standard test for AMS.



**Figure 22. ROC curve for LLS and log transformation of response time to first shape**

In the figure above, the log transformation of response time to first shape had an area of 0.71, which is considered moderate accuracy to detect acute mountain sickness. Using a threshold log transform response time of 3.12, the sensitivity and specificity were 0.636 and 1.00, respectively. Therefore, using this threshold, this test is moderate at case detection, but would have a low false positive rate.



**Figure 23. ROC curve for LLS and change in response time to first shape from baseline**

In the figure above, the change in response time to the first shape from baseline had an area of 0.66, which is considered low accuracy to detect acute mountain sickness. Using a threshold change in response time of 15.78ms, the sensitivity and specificity were 0.545 and 0.50, respectively. Therefore, using this threshold, this test is poor at case detection, and has low true positive and true negative rates.

Test	Significant Finding
Lake Louise Score	Time, Altitude, Time*Altitude
Pulse Oxygen Saturation	Time, Altitude, Time*Altitude
Heart Rate	Time, Altitude
BESS FSL	Time*Altitude
Response Time Task – Accuracy	Altitude
Coordination Task - Log Transformation of Response Time	Time*Altitude
Coordination Task - Errors	Time*Altitude

**Table 23. Most Important Statistical Findings**

## Discussion

### Introduction

To our knowledge, no study has explored the utility of a neurocognitive test on a mobile device to monitor acclimatization to hypoxia. Our objective was to test the effect of hypoxic exposure on inter-response intervals, movement time, response time, time to completion and finger tap accuracy of novel cognitive tasks over time. We sought out to evaluate correlations between reaction time and time to completion of novel coordination tasks and pulse oxygen saturation, heart rate, performance of BESS and the LLS. We also sought out to evaluate correlations between finger tap accuracy of novel coordination tasks and pulse oxygen saturation, heart rate, performance of BESS and LLS. We successfully assessed the effect of hypoxia on inter-response intervals, movement time, response time, time to completion and finger tap accuracy of our novel tasks. However the limited number of significant results of these measurements meant that no significant correlations were found between our measurements.

This discussion will begin by outlining how LLS increased, heart rate remained elevated and oxygen saturation decreased in hypoxia. We will also discuss how finger tap accuracy of a coordinated task decreased while response time, cognitive errors and balance did not show as clear of a relationship to hypoxia.

The LLS, our measure of AMS severity, increased over time in both sham and hypoxia conditions. The mean LLS was higher after 12 hours in hypoxia ( $4.7 \pm 2.3$ ) when compared to sham ( $1.7 \pm 1.7$ ). In addition, there was a combined effect of an increase in LLS over time as well as condition. The difference over time during the sham exposure

suggests that the LLS may also be sensitive to comfort, sleep quality and fatigue (MacInnis et al., 2014). The non-specific nature of this test is what guided the direction of this study.

### **Cardiovascular**

As outlined in the introduction, in hypoxia the oxygen content in the environment decreases, as such pulse oxygen saturation decreases rapidly. Oxygen saturation in this study decreased by 12% ( $97.3\% \pm 1.36$  to  $85.3\% \pm 3.25$ ) within five minutes of simulated hypoxia, while during sham it remained unchanged for the duration of the exposure. Pulse oxygen saturation continued to drop by 3.5% after 12 hours in hypoxia ( $81.8 \pm 3.5\%$ ). This progressive decline of pulse oxygen saturation is thought to relate to ventilation and is termed the hypoxic ventilatory decline as outlined in the literature (Richard & Koehle, 2012). Richard et al. (2014) exposed subjects to hypoxia for 6-hour durations and found that pulse oxygen saturation did not reach steady-state until 30 minutes after the onset of exposure (Richard et al., 2014). Similarly in our research, pulse oxygen saturation was significantly lower after 4 hours and 12 hours than at 5 minutes into the exposure.

In our study, heart rate was increased in hypoxia and remained elevated over the course of the exposure, whereas heart rate decreased over time in the sham condition. Acute hypoxia is thought to be an activator of sympathetic activity through a reflex response initiated by chemoreceptors (Lumb 2005). This response results in elevated heart rate and blood pressure (Hackett & Roach, 2001; Imray et al., 2011; Saito, Mano, Iwase, & Koga, 1988). The increase in sympathetic tone leads to redistribution of blood

to the vital organs through peripheral vasoconstriction and an increase of organ perfusion from an increase of cardiac output (Lumb 2005).

## **Cognition**

Cognitive function in our study was measured as reaction time, response time, error rate and finger tap accuracy. Performance of tasks such as the Response Time Test and the Coordination Test rely on skills such as motor coordination, working memory and tracking. Tasks of this nature have been known to rely on structures in the frontal lobe (Asmaro, Mayall, & Ferguson, 2013). Zakzanis and colleagues performed fMRI while subjects completed a trail making task and identified activation of the left hemisphere of the frontal lobe (Zakzanis, Mraz, & Graham, 2005). These complex tasks require effort and attention and are vulnerable to impairment in hypoxia (Taylor, Watkins, Marshall, Dascombe, & Foster, 2016). In hypoxia, motor dysfunction is due to disturbances in visual, motor and cerebellar processing (Silber, 2000). Through the evaluation of cognition by the performance of various cognitive tasks, three notable results were found; finger tap accuracy, response time and error rate (1., 2., 3.).

1. Finger tap accuracy as measured by the deviation from a target has not been studied extensively in the literature. Gerard and colleagues drove subjects from sea-level to 3000 m and simulated 5000 m using normobaric hypoxia (Gerard et al., 2000). Cognitive tasks were performed the morning after arrival and deviation from the target increased at a simulated altitude of 5000 m when compared to 3000 m. In our study, deviation from the target during the Response Time Test increased during the exposure to hypoxia. It is difficult to directly compare our results with those by Gerard et al.

(2000) because of a difference in units, however, given that both studies found decreased finger tap accuracy in hypoxia, this supports the utility of finger tap accuracy as a method to monitor acclimatization.

2. The nature of tasks used in the literature to measure reaction time varies, as does use of the term reaction time. What is commonly termed Choice Reaction Time relates most closely to what we refer to as response time in the Coordination Test. Choice reaction time, as detailed in Table 2, has been observed to increase by a mean of 24ms in hypoxia (Davranche et al., 2016; Dykiert et al., 2010; Fowler et al., 1987; Paul & Fraser, 1994; Phillips et al., 2015). Of these studies, that of Fowler et al. (1987) and Phillips et al. (2015), were the only two studies to use simulated altitude (i.e. normobaric hypoxia), while the rest of the studies were performed in the field. Hypoxic exposure of these studies ranged from 2438 m to 5486 m and durations from 30 minutes to 20 days. Not all research has found an increase in choice reaction time in hypoxia. Kida and Imai found that of 32 subjects, 12 subjects showed no change in choice reaction time compared to baseline when their subjects were exposed for 45 minutes to a simulated altitude of 6000m. Our results were not normally distributed, as such we chose to analyze our results by the log transformation of the response time. In our study, there was no significant difference in the response time of the Coordination Test based on condition. However, when we analyzed a subset of the data, the response time to the first shape, an interaction effect was found. The trends of these response times under sham and hypoxic conditions are perplexing. In the sham condition, response time remained low at the 5-minute and 4-hour time point but the next

morning increased above baseline values. In the hypoxia condition, response time was similar to the sham condition at 5 minutes but increased at 4 hours and then decreased slightly the morning after. These results contradict the findings from previous studies that would predict a continued increase in the response time over the duration of a hypoxic exposure.

The effect of fatigue might be able to explain differences in response time of our results with those found in the literature. Fatigue has been known to increase the duration and variability of response time. Lorist et al. (2005) used a computer-based response time test. Response time increased by 22 ms after subjects had performed the task for 2 hours (Lorist, Boksem, & Ridderinkhof, 2005). In other research that utilized a 50-minute cognitive task, response speed variability increased over the duration of the task (Steinborn, Flehmig, Westhoff, & Langner, 2010). Due to the trends seen in our results and the interaction effect found based on time and hypoxia, it is reasonable to assume that fatigue may have played a large role. When we view the response time over the course of each trial we see it increase in value and standard deviation regardless of condition. Increased variability and our small sample size make it difficult to find a significant difference in response time.

Given that under both conditions the response time was very similar at the 12-hour time point, we also analyzed the response time when grouped for sleep quality as rated in the LLS questionnaire. Under this classification, poor sleepers had a larger increase in response time regardless of altitude and response time improved after sleep for all subjects. This finding suggests that the response time in this study may be more

closely related to sleep quality than hypoxia and that sleep might have a restorative impact on response time. Decreased performance of coordinated tasks after poor sleep is supported in the literature. Taheri and colleagues measured choice reaction time after one night of sleep deprivation (Taheri & Arabameri, 2012). Subjects had to respond to a visual stimulus by tilting a joystick. Taheri found an increase in choice reaction time by 37 ms after one night of sleep deprivation. Our task involved more choice as well as movement time in comparison with Taheri's experiment. Due to the differences in our measurements, incompatibility of units and the intervention of hypoxia as compared to sleep deprivation it is difficult to make a direct comparison. However, the trends seen in both studies suggest that poor sleep quality impaired response time of our task similar to the performance decrement seen in the choice reaction task by Taheri and colleagues. Therefore the interaction effect of response time of our task might be explained by the combined effect of hypoxia, fatigue and sleep quality.

3. Cognitive errors have been known to increase by 2-3 times their baseline level when at altitude (Davranche et al., 2016; Kourtidou-Papadeli et al., 2008; Nelson, 1982). Davranche et al. (2016) found a two-fold increase (3.5 to 6) in errors made during a congruent and incongruent visual task 4 hours after helicopter ascent from sea level to 4350m. Papadeli et al. (2008) used a multitask flight simulator including components of tracking, monitoring, communicating and fuel management. Papadeli et al. (2008) found a threefold increase in errors when subjects performed the same task in normobaric hypoxia simulating 2438m as compared to baseline. Nelson found a nearly threefold increase (7-20) in errors made during a maze task when their subjects ascended to an

altitude of 5000m on day 25 of a 35-day trek to Denali. In our study, errors made in selecting the correct shape during the Coordination Task were not significantly different based on condition alone. An interaction effect was found for the number of errors made during the last ten sets of the Coordination Test. In hypoxia, errors increased at the 4-hour time point ( $3.2 \pm 2.5$  to  $5.1 \pm 4.1$ ) however this increase did not persist at the 12-hour time point. In the sham condition, errors decreased at the 4-hour time point but increased to the same level as hypoxia the morning after. This pattern is not consistent with the previous literature which would predict an increased error rate in hypoxia at all time points as compared to sham. One possible explanation for this discrepancy could be that our task might have been too simple to challenge the regions of the brain most affected by hypoxia. The error rate peaked at the 4-hour time point in hypoxia, there were 4.06 errors. In contrast, research in hypoxia by both Kourtidou-Papadeli et al. (2008) and Nelson et al. (1982) demonstrated 13 and 20 errors, respectively. Meanwhile, Davranche et al. (2016) demonstrated an error rate similar to the present study (mean of 6 in hypoxia). In contrast to our research, however, the congruency and incongruency of the task in their experiment incorporated a response inhibition component. It appears that this inhibition component made the cognitive requirements of their task demanding enough to show a significant difference in hypoxia. In addition to perplexing trends in the data of this research, we also found that the variability increased over time in the hypoxia condition. An increased standard deviation combined with the small sample size may have obscured the effect that hypoxia might have had on cognitive errors.

Our Coordination task had the user tap three shapes in a specific order 48 times (sets) which was repeated at 4 different time points during each experiment. Interestingly, we only saw significant error trends in the last ten sets of the Coordination Task. This finding might be either due to the length of time necessary to complete the task or a Type 1 error (incorrect rejection of null hypothesis, false positive). In the present study, the order of cognitive tasks was randomized. The time required to complete each task varied, The Trail Making Task would take less than one minute for each version (numeric and alpha-numeric), The Coordination Task would take approximately 10 minutes and The Response Time Task would also take approximately 10 minutes. Due to the length of time required to complete these tasks, subjects would anecdotally report being bored or mentally fatigued. We suspect that a lack of motivation, boredom, and mental fatigue towards the end of the task might explain why error rate only became significant in the final ten sets. When grouped based on good or poor sleep, a clearer distinction was found. Poor sleepers produced more errors at every time point while those that reported a good sleep had fewer errors, indicating a potential restorative effect on errors made. Cognitive errors related to fatigue do not appear to be well studied in the literature. However, based on our results we speculate that the number of errors may be more related to fatigue and sleep quality and that the simplicity of our task may not have stressed cognitive function enough to detect a difference in hypoxia.

## **Balance**

Afferent inputs for postural reflexes come from the eyes, vestibular system and proprioceptors (Johnson, Simmons, & Wright, 2005b; Shumway-Cook & Horak, 1986). Efferent inputs originate from skeletal muscle and are integrated in the brainstem and spinal cord (Johnson, Simmons, & Wright, 2005b; Shumway-Cook & Horak, 1986). These inputs are integrated by the cerebellum, the pons and midbrain (Johnson, Simmons, & Wright, 2005b).

The research evaluating the effect of hypoxia exposure on balance and posture is conflicting. Not all studies have found a relationship between the development of acute mountain sickness and impaired balance (see Table 1 of the introduction). Furthermore, the literature does not have a clear consensus with regard to impaired balance in hypoxia independent of altitude illness. Previous studies have found an increase in postural sway by 56 cm/s and a 30% increase postural instability in hypoxia (real altitude of 4559m after a 24-hour ascent, simulated altitude of 4300m over a 24-hour exposure respectively)(Baumgartner, Eichenberger, & Bärtsch, 2002; Cymerman et al., 2001). In contrast, some researchers have not found any significant change in balance while subjects were exposed to real altitudes of 4559m and 5260m, respectively (Baumgartner & Bärtsch, 2002; Johnson, Simmons, & Wright, 2005b). In a study by Johnson et al. (2005), they found that only 43% of the subjects had impaired balance in hypoxia during an 8-day ascent to 5260m (Johnson, Wright, Beazley, & Harvey, 2005c).

Previous research on balance performed by our research group has used BESS to quantify postural stability. Iverson & Koehle (2013), assessed balance on a large

population (n=1,236), normative data demonstrated that total BESS scores were  $11.3 \pm 4.8$  for the 20-29 age category. MacInnis et al. (2012) required 27 subjects to complete the BESS after a 48-hour ascent to 4380m (MacInnis, Rupert, & Koehle, 2012b). No sea-level measurements were performed in this study and participants were divided based on AMS diagnosis. MacInnis et al. (2012) found that in those subjects who developed AMS, the total BESS score was  $19.2 (\pm 8.8)$  while for those without AMS, the score was  $10.4 (\pm 6.0)$ . Koehle et al. (2010) conducted a similar study to ours using the same hypoxic chamber (Koehle et al. 2010). They tested 14 subjects over a 7-hour exposure at a simulated of 4500m. The BESS scores increased significantly after one and three hours of exposure to hypoxia. However, by the third hour, the standard deviation was quite large, suggesting a varied response (baseline  $9.57 \pm 2.93$ , 1 hour  $15.07 \pm 3.87$ , 3 hours  $25.14 \pm 18.58$ ). Brown et al. (2013) also performed a similar experiment to ours, testing 20 subjects in the same hypoxic chamber at 4500m (Brown et al. 2013). The subjects performed 12 BESS tests over a 5-hour hypoxic exposure. Their baseline total BESS score was  $10.10 \pm 5.4$  but, increased slightly in hypoxia and peaked 2.5 hours after initial exposure at  $11.89 \pm 4.7$  (not statistically significant). In our study, total BESS was not significantly different based on hypoxia or sham alone ( $12.8 \pm 6.69$  and  $10.8 \pm 4.44$  respectively), these values are consistent with published normative data for this age category (Iverson and Koehle, 2013).

When the components of the BESS were examined individually, a significant difference was found for the single leg stance on the 10 cm thick foam pad, which produced an interaction effect of time by hypoxia. During the sham condition, this score

improved overnight, while in hypoxia it deteriorated over the duration of the exposure. While the single leg foam BESS scores in our results were slightly increased the morning following hypoxic exposure it was not significantly different.

Thus, studies performed in the field or laboratory environments have inconsistently shown impaired balance in hypoxia. Only two of these cited studies had the BESS scores rated by blinded experts (the current study, and that of Brown et al. 2013). For the other two studies (by MacInnis et al. 2012 and Koehle et al. 2010), the investigators assigned the BESS scores in an unblinded fashion. Blinding increases the accuracy of measurements taken in the study by removing potential confirmation bias by the rater. Additionally, the use of expert raters as opposed to investigators who were less familiar with the BESS test would increase the reliability of the BESS scores. Brown et al. (2013) found that athletic trainers had a much lower inter-rater reliability compared to experienced raters (0.59 compared to 0.75). The inter-rater reliability of the evaluators used in the current study (0.88) was comparable to the inter-rater reliability found by Brown and colleagues (unpublished data).

The duration and magnitude of the hypoxic exposures may have played a role on the limited effect that hypoxia had on cognitive function and balance. Similar studies to the current research have evaluated performance of cognitive tasks at altitudes of 4200m and found non-significant differences when compared to baseline (Johnson, Simmons, & Wright, 2005b; Kida & Imai, 1993; Kourtidou-Papadeli et al., 2008; Nelson, 1982; Silber, 2000). In contrast, hypoxic exposures at 5000m or greater altitudes has been shown to provoke clearer impairments in coordination (Gerard et al., 2000; Kida &

Imai, 1993; Kourtidou-Papadeli et al., 2008; Nelson, 1982; Silber, 2000). These studies used variable rates of ascent ranging from 100m/day (Kida & Imai, 1993) to 3800m in one day (Gerard et al., 2000). The research by Nelson et al. (1982), Kida and Imai (1993), and Gerard et al. (2000) actually compared performance of cognitive tasks at 3000-4000m to performance at 5000m. Nelson et al. (1982) found that the number of errors made during a maze task was non-significant at 3810m but there was a threefold increase in error rate when the task was performed at 5000m. Gerard et al. (2000) compared performance of a trail-making task and a pegboard task at 3200m and 5000m and found that trail making task was 5 seconds slower at 5000m and pegboard performance was 2.5 seconds slower at 5000m. Kida and Imai (1993) found that the number of subjects who demonstrated a significant change in reaction time increased from 6 to 20 when simulated altitude was increased from 4000 to 5000m. Additionally, while much of the literature on balance demonstrates impairments in hypoxia, there is little consensus on the required level and duration of the hypoxia. Research performed by Wu et al found that ataxia is usually not detectable until 24-48 hours into the hypoxic exposure (Wu et al., 2006). Therefore, another possible explanation for the lack of strong relationship between hypoxia and balance and cognitive function in the present study might be due to a low simulated altitude and short duration of exposure.

## **Limitations**

One potential limitation of this study is the nature and length of the selected cognitive assessments. When we assessed errors made during the hypoxic exposure, the difference was not large enough to demonstrate an effect based on condition alone.

Other research that was able to demonstrate larger differences used considerably more complex tasks such as congruent and incongruent tasks that result in mental inhibition (Davranche et al., 2016) complex flight simulators (Kourtidou-Papadeli et al., 2008) or intricate mazes (Nelson, 1982).

The second limitation of this study was an inconsistency of scheduling of the subjects. Subjects were free to schedule trials at their convenience. In some cases, the 4-hour time point measurements would be done after the time they typically go to sleep or 12-hour time points might be done before they normally wake up. Subjects should be arriving at the lab at the appropriate time so that measurements taken before they go to sleep are done closer to their actual bedtime. Alternatively this limitation could be addressed by running the study exclusively during the day in this way the researchers could control for the restorative effect sleep might have had on measurements in this study.

The third limitation was a lack of standardization of cognitive workload before arriving at the lab. We asked subjects to refrain from exhaustive exercise, however, we made no effort to standardize cognitive workload. Due to the time of year the study was being conducted, some subjects had been studying for exams, which may have placed additional mental fatigue or stress on the individual, independent of demands of the study. Future research conducted in this population should consider extraneous cognitive demands such as exam schedules. Researchers should ensure that the subjects are not visiting the laboratory close to their course exams so as not to introduce confounding mental fatigue prior to arrival to the laboratory.

The fourth limitation was a lack of blinding of investigators. Although BESS raters were blinded, no other researchers were blinded to the condition on any given trial. As explained in the discussion, a lack of blinding can introduce bias by the researcher, which could influence the manner in which the participants perform cognitive tasks or questionnaires in a favorable way that might support the research objectives. However, since a strong relationship was not seen between the cognitive tasks and the hypoxia, these objectives were not met, and the potential bias introduced by having the investigators unblinded was likely not significant.

The fifth and final limitation is the method of hypoxic exposure. While similar, hypobaric hypoxia and actual altitude exposure are not identical to normobaric hypoxia (Boos et al., 2016; Richard & Koehle, 2012). Several studies have shown that pulse oxygen saturation is lower and AMS incidence is higher in hypobaric than normobaric hypoxia (Boos et al., 2016; Richard & Koehle, 2012). Perhaps, under hypobaric conditions, with lower oxygen saturation, and hence arterial oxygen concentration, there is a more profound hypoxic stimulus, however any such effect would be modest. Furthermore, the setting itself has been known to cause discomfort to subjects due to unfamiliarity of the environment, the noise and sharing the space with another research participant. MacInnis et al. (2014) demonstrated this effect by showing a small mean increase in LLS after 12 hours in the chamber in the sham condition. To address these limitations, further research should replicate the current study, but replace normobaric exposure with hypobaric hypoxia and increase the simulated altitude to 5000m or

higher, while at the same time have the participants remain in this chamber for at least 24 hours.

### **Future Directions for Developers**

To continue in the pursuit of developing convenient digital solutions to evaluate the response to hypoxia, future developers should consider modifying the task to increase its sensitivity. We believe that increasing the cognitive difficulty of the task would increase the differences of performance in hypoxia. Perhaps one such modification to the Coordination Test would be to prevent a subject from continuing to view the specific order of shapes while being able to tap them. Asking subjects to perform the task without a reference would stress working memory more than the present test, and could lead to greater sensitivity. Additionally, the Coordination Test could be more difficult if subjects were not cued when shapes had been correctly tapped. This modification would also stress working memory more than the original version and additionally it would inhibit the subject's ability to simply guess the correct order which is more possible with the present version. Initially we had expected to see large differences in the performance of a simple task in hypoxia. Further challenging the working memory more might show larger differences in the performance of these tasks as previous research has shown decrements in working memory in hypoxia (Asmaro et al., 2013).

It is well known that the cerebellum is impaired in hypoxia (Bird et al., 2011). The cerebellum integrates various inputs allowing us to produce coordinated voluntary actions. To further stress the cerebellum in the Response Time Test, the target could

move from its initial position once the finger has left the starting position, requiring the subject to make a corrective movement mid-flight. This additional challenge for the cerebellum might show larger decrements in hypoxia than the original version.

Outside of modifications to the mobile application, additional measures of balance could be included. The BESS was convenient to perform, however only one component was found to change significantly in hypoxia. While measures of balance performed on a force plate can be cumbersome to perform in the field, the use of small accelerometers might be more feasible, yet more accurate than the BESS evaluation. An accelerometer placed around the chest could measure sway during standing balance. The outcomes from this tool could include sway variability, medial/lateral as well as anterior/posterior sway. In this way, balance could be evaluated more objectively throughout the day without inconveniencing a climber.

## **Conclusion**

We sought out to test the utility of a smart device application-based cognitive test as a tool for the evaluation of acclimatization to hypoxia. Over a 12-hour exposure to a simulated altitude of 4200m, measurements such as LLS, heart rate and pulse oxygen saturation responded as expected, while balance as measured by BESS was not impaired. Finger tap accuracy did become impaired during exposure to hypoxia, however, neither the error rate nor the response time was deleteriously affected at this simulated altitude and duration. Further research is necessary to develop an appropriate smart device-based cognitive assessment to monitor acclimatization to hypoxia and altitude illness. Future researchers should consider the cognitive difficulty

of the task and focus on finger accuracy, as this was the outcome that produced the most significant result in our research.

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## Appendix

Subject	Sex	Age
1	Male	24
2	Male	22
3	Female	25
4	Female	25
5	Male	21
6	Female	22
7	Male	20
8	Male	22
9	Female	24
10	Male	19
11	Female	24
12	Female	24
13	Female	24
14	Male	20
15	Female	25

**Table 24. Subject Gender and Age**