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The Combined Effects of Acute Exposure to Simulated Altitude and Moderate Intensity Aerobic Exercise on Measures of Cognition

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THE COMBINED EFFECTS OF ACUTE EXPOSURE TO SIMULATED ALTITUDE AND MODERATE INTENSITY AEROBIC EXERCISE ON MEASURES OF COGNITION

By

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The present study was conducted to examine the behavioral cognitive and neurophysiological effects of acute exposure to simulated moderate and high altitudes at rest and during exercise in an effort to delineate whether there is a level of simulated altitude beyond which cognition and neurophysiological function are impaired and whether exercise improves or worsens cognitive function during exposure to simulated altitude. Dependent variables included accuracy and reaction time on a number of behavioral cognitive tasks, and the amplitude and latency of their associated event-related potentials. Fourteen recreationally active college students (M=9, F=5) aged 18-35 participated in this study, which consisted of six experimental days, with three simulated altitude conditions: sea level (SL), simulated moderate altitude (MA; 15.4% F_IO_2, ~2400 m) or simulated high altitude (HA; 12.8% F_IO_2, ~3900 m); and two exercise conditions: rest or moderate intensity cycling exercise at 60% altitude-specific peak power output, in a randomized-order, crossover design. Simulated altitude slowed down reaction time on a number of tasks (p=0.04), while exercise improved reaction time (p=0.01), without decrements in accuracy under any condition. These effects were partially explained by alterations in associated event-related potential amplitudes and latencies, such as slower

N200 latencies with altitude ($p=0.04$) but faster latencies with exercise ($p<0.01$), as well as reduced P300 amplitude and slower latency with altitude ($p<0.01$), and reduced amplitude but faster latency with exercise ($p=0.03$). Acute exposure to simulated altitudes slows behavioral cognitive reaction time while preserving task accuracy. An acute bout of moderate intensity cycling exercise improves reaction times so that they are comparable to those achieved without exercise or altitude, at least in instances where exercise does not exacerbate the peripheral oxygen saturation drops seen with simulated altitude.

DEDICATION

I dedicate this dissertation to my loving family.

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CHAPTER 1

INTRODUCTION

Hypoxia is a condition in which the body or regions of the body are deprived of adequate oxygen supply. This may result from exposure to high altitude, where the low ambient atmospheric pressure reduces the oxygen diffusion gradient in the lungs resulting in a decline in arterial oxygen content. In addition to physical symptoms, it has been well established that exposure to high altitude causes significant impairments of behavioral cognitive functions[29,51] that are normalized over months to years of high altitude exposure.[32,35] An improved understanding of the cognitive and neurophysiological effects of acute high altitude exposure and practices that may ameliorate these effects may be vital to individuals such as aircraft pilots, rapidly deployed military personnel, and those that ascend to high altitude quickly; since each of these may experience compromised decision-making capabilities.

A number of studies have examined cognitive changes once cerebral oxygenation became compromised, as evidenced by reductions in peripheral oxygen saturation (SpO_2), which has been shown to mirror reductions in cerebral oxygenation.[5,50] These studies cover a wide range of experimental conditions ranging from actual moderate altitudes of 2700 m[10], simulated high altitudes from 4000 to 6000 m[19,22,28,34,47], and a simulated extremely high altitude equivalent to Mt. Everest at an elevation of almost 9000 m.[51] These studies also covered a wide range of acute altitude exposure durations, ranging from 10 min to 12 h, though on average, experiments tended to last 30-60 min at each selected level of altitude. Despite the wide variability of methodologies, some broad conclusions can be drawn about the effects of hypoxia on electroencephalographical (EEG) waveforms and changes in mental processing, executive functions, and psychomotor responses. Examination of event-related potentials (ERPs), predictable EEG waveforms that occur alongside reaction time and accuracy on task responses, has shown that the N100, P200, and N200 ERPs are not affected by hypoxia. The P300 component, however, appears highly sensitive to the influence of hypoxia.[11,20,31,49] It also appears that the brain waves are not as sensitive to drops in atmospheric pressure as they are to the resulting decrease in oxygen delivery.[26,31,45]

The most recent studies examining cognitive function at altitude did not utilize EEG recordings, but relied on behavioral measures of cognitive function, including paper and computer tests. These studies found significant cognitive impairments in attention, visual and working memory, concentration, executive functions, inhibitory control, and overall speed of processing with acute exposure (30 min to 24 h) to moderate and high altitudes.[2,3] Further, there is evidence that hypoxia may undercut task learning in a test-retest scenario.[46]

Despite the volume of research in this area, the large disparity in altitude methodology, assessment methods, and subject variability has made drawing definitive conclusions problematic. It is difficult to say at what level of altitude-induced hypoxia cognitive impairment begins and to what extent. The only clear evidence is that there exists an overall trend of impairment at high altitude and that this impairment seems to originate at the cortical level due to reduced cerebral oxygenation.[48]

One proposed tool for improving cognitive function and performance is exercise. It has been widely established that chronic exercise and improved physical fitness increase cognitive function in healthy populations spanning the entire life cycle.[12,13,16,37,42] In the last few decades, researchers have established that a single bout of aerobic exercise can positively affect behavioral and neurophysiological processing and performance.[44] Low and moderate intensity steady-state aerobic exercise appears most beneficial in improving reaction time[7], reducing ERP latencies[18], and increasing ERP amplitudes.[30] The best results were obtained during steady-state, moderate intensity exercise involving repetitive motion such as cycling lasting less than 60 minutes.[44] Moderate intensity cycling exercise has been associated with improved performance on executive function tasks, regardless of the presence or absence of hypoxia.[1,21] It remains unknown whether the small cognitive gains that acute exercise provides can attenuate the cognitive impairment induced by acute exposure to high altitude.

The purpose of the current study was to examine the behavioral cognitive and neurophysiological effects of acute exposure to simulated moderate and high altitudes at rest and during exercise. This was done in an effort to delineate whether there is a level of simulated altitude beyond which cognition and neurophysiological function are impaired and whether exercise improves or worsens cognitive function during exposure to simulated altitude. It was hypothesized that exposure to simulated moderate and high altitudes would impair behavioral cognitive performance and alter EEG activity during

ERPs. It was further hypothesized that an acute bout of moderate intensity aerobic cycling exercise would significantly improve behavioral cognitive performance and EEG activity compared to rest at sea level and simulated moderate and high altitudes.

CHAPTER 2

METHODS

Subjects

A total of 14 men and women between the ages of 18 and 35 y participated in this study. All subjects were screened for any health concerns that might prevent them from participating in moderate intensity exercise and cognitive testing, such as cardiovascular disease, orthopedic issues affecting capacity to exercise, mental illness as diagnosed by their physician, alcoholism or other drug dependence, and smoking status. Subjects were considered for the study if they were recreationally active, right handed, and did not have a history of physical or mental health concerns, or otherwise took any medications that might interfere with cognitive assessment, including cold and allergy medications that induce drowsiness, or any other neuroactive drugs. Additionally, subjects could not have lived at altitude (> 2100 m) for more than two years during their lifetime or spent more than two weeks at altitude over the previous six months. Subjects also agreed not to travel to altitude during the investigation. All procedures and risks were thoroughly explained to each subject and a written informed consent was obtained. All procedures within the study were approved by the University of Miami Human Subjects Research Office.

General Experimental Design

Following screening, subjects participated in six experimental trials on separate days in randomized order with at least 48 h between trials. For each trial, they rested or exercised while being exposed for a total of 60 min to one of three altitude conditions: sea level

(SL), simulated moderate altitude (MA; 15.4% F_IO_2, ~2400 m) or simulated high altitude (HA; 12.8% F_IO_2, ~3900 m). Shown in Figure 1 is a flowchart and outline of the sequence of activities in this study.

Screening

After completing a written, informed consent form, subjects underwent a screening appointment at baseline. At this time, they filled out a physical activity habits questionnaire (IPAQ, International Physical Activity Questionnaire)[6], a PAR-Q[43], a handedness questionnaire (Handedness Questionnaire[27]), and a health history questionnaire. Additionally, an assessment of body composition was conducted to provide information on the demographic make-up of the study sample through the use of an Inbody-500 (Biospace, Beverly Hills, CA). Collected information included height, weight, lean body mass, body fat percentage, and body mass index. Then, subjects participated in a familiarization trial, where they were able to practice all the computerized cognitive tests they would encounter during experimental trials. Subjects were also exposed to simulated altitude for a brief period of 15 minutes, after which they completed a Lake Louise Scale Questionnaire to determine whether they could tolerate the HA condition. Additionally, subjects completed a peak aerobic capacity (VO_{2peak}) test.

Peak Aerobic Capacity and Power Output

VO_{2peak} was assessed at SL during baseline screening using a continuous progressive exercise test to volitional exhaustion on an electromagnetically braked ergometer

(Monark Ergometric 829e, Vansbro, Sweden). Subjects pedaled at 50, 100, and 150 W for 2 min each, after which power output was increased by 30 W every 2 min until exhaustion.[15] Subjects were considered to have reached VO_{2peak} if they attained two of the following three criteria: a plateau in oxygen consumption despite an increase in workload, a respiratory exchange ratio (RER) > 1.10, and volitional exhaustion where a pedaling cadence of 50 rpm could not be maintained for more than 10 s. Expired respiratory gases were collected continuously and analyzed using an online open-circuit metabolic cart (Vmax Encore 29c, CareFusion, San Diego, CA). Pilot data previously collected in our laboratory indicated that W_{peak} declined from SL to simulated altitudes of ~1500, 2100, 2700, and 3900 m in a highly linear fashion ($r = 0.993$, $n = 5$, unpublished observation). The regression equation derived from this pilot data was used to estimate W_{peak} at MA and HA. Information from these tests was then used to set the workloads at 60% of altitude-specific W_{peak} for the subsequent experimental exercise trials.

Experimental Exercise Trials

Subjects completed a total of six experimental trials (rest and exercise at SL, MA, and HA), with at least 48 h between trials. A computerized list of all possible combinations of the six trials was generated in random order and subjects were assigned the order of their trials from this list sequentially after completing the screening appointment. Subjects were asked to record their diet for 24 h before the first experimental trial and were then asked to repeat this diet prior to each subsequent trial. Subjects were also asked to refrain from alcohol consumption and exercise for 36 h before testing and not to consume any caffeine on the day of testing. Subjects were asked to arrive at the laboratory fully hydrated, having consumed 500 ml of water before testing.

Altitude Simulation and Peripheral Capillary Oxygen Saturation

Altitude was simulated using a Hypoxico generator (HYP-123, Hypoxico, New York, NY) with high altitude adapters to provide the normobaric hypoxic condition of all MA and HA experimental trials. While subjects were prepared for EEG and ERP recording, hypoxic gas was delivered to the subject through a facemask that was sealed over the mouth and nose at a rate that exceeded ventilation. To assure that experimental conditions were met, the oxygen composition of the hypoxic gas was monitored before and after each trial with a portable oxygen monitor (Handi O_2, Maxtec, Salt Lake City, UT).

During the rest trials, subjects breathed either ambient or hypoxic air in single blind fashion for 45 min prior to cognitive testing and throughout the testing period for a total of approximately 60 min per session. During exercise trials, subjects breathed either ambient or hypoxic air in single blind fashion for 30 min at rest, then continued with the 15-min exercise portion of the trial, followed by cognitive testing. This also totaled approximately 60 min per session. SpO_2 was measured continuously in all trials using a portable dual wavelength pulse oximeter placed over the index finger of the left hand (PulseOx 300i, Konica Minolta Sensing Americas Inc., Ramsey, NJ).

EEG Setup and Procedures

All subjects reported to the Neurocognitive Kinesiology laboratory for each of six sessions to be prepared for EEG recording. They were connected to a 60-channel cap through a SynAmps2 amplifier (Compumedics USA, Charlotte, NC). Each electrode-recording site was filled with a high conductive gel until all sites exhibited electrical resistance under 5 KOhms. Additional electrodes were placed above and below the left eye and outside each lateral canthus to monitor and correct for electro-ocular artifacts (eye blinks). Two linked reference electrodes were attached to the mastoid processes. Subjects were then moved to a quiet area within the lab for cognitive testing and EEG recording.

During behavioral cognitive testing, all stimulus categories were coded on the EEG for later processing through the use of parallel ports from the SynAmps2 amplifier. All EEG data were processed offline using Neuroscan Curry Suite 7.0 (Compumedics USA, Charlotte, NC). A band-pass filter of 1-30 Hz was applied to the raw EEG. Recordings were visually inspected for "bad blocks" (stretches of activity that contained too much noise or spikes that were too large to be considered natural) that were then marked and eliminated. An electro-oculogram (EOG) was recorded for blink detection and artifact reduction. Blinks were defined as any signal on the EOG channels exceeding -150 µV to 150µV. Ocular artifacts were reduced via a covariance method. Coding of all trials was then averaged by condition (exercise and altitude levels) as well as test modality (congruent/incongruent trials of the Flanker task, target/non-target stimuli of the auditory oddball task, matched/mismatched trials of the Stroop task, and 3-Letter/5-Letter sequences of the Sternberg memory task).

Event-related potentials were recorded during performance of the cognitive battery. There are a number of components of these event-related potentials that are most commonly examined and are labeled by whether they deflect in a positive (P) or negative (N) direction from baseline (amplitude), and how long after the event they occur (latency). The most commonly examined components are the N100, P200, N200, and P300 waveforms (occurring 100-300ms after the event, on average). Due to size of each data set, ERP findings for the N100 and N200 were limited to the FZ electrode, based on task-relevant electrode areas predicted by cognitive activation.[11,32] ERP findings for the P200 and P300 were limited to the PZ electrode, for the same reasons.[26,36,45] For each ERP, latency and amplitude were identified and recorded. These values were extracted and imported into SPSS 21.0 (IBM, Armonk, NY) for statistical analysis using a peak detection algorithm.

Exercise Trials

After subjects had been fitted with the EEG cap and spent time breathing either ambient or hypoxic air, they were seated on a Monark 828e cycle ergometer (Monark Exercise AB, Vansbro, Sweden) and asked to cycle at a moderate intensity corresponding to 60% of altitude-specific W_{peak}[25] for 15 min. Subjects continued to exercise throughout the duration of the cognitive testing battery for a total of approximately 30 min of moderate intensity aerobic cycling exercise.

Cognitive Battery Setup and Procedures

For each recording session, the cognitive battery began with a short period during which baseline EEG was recorded for one minute with eyes open and one minute with eyes closed for later quantitative analysis. Subjects were asked to blink as little as possible during the eyes-open baseline condition as they focused on a static mark at the center of the computer monitor.

After this baseline recording, subjects completed four computerized cognitive function tasks in randomized order, including a modified Erikson flanker task that assesses executive cognitive function[8], an auditory oddball task that assesses the effect of stimulus novelty and significance in information processing[38], a Stroop color interference task that assesses selective attention and decision-making processes[40], and a Sternberg memory task for assessing short term memory.[39] For all behavioral tasks, both reaction time and accuracy were recorded using E-Prime 2.0 stimulus presentation software (Psychology Software Tools Inc., Sharpsburg, PA). These tasks were chosen to assess a variety of cognitive functions to be able to create a more complete picture of how various functions are affected under exposure to simulated altitude and exercise.

During the Flanker task, 100 trials of five arrows were presented to the subject, who was then asked to indicate which way the center arrow pointed. Fifty percent of the time, trials were congruent (> > > > > or < < < < <), meaning that the center arrow pointed in the same direction as the arrows flanking it; while the remaining 50% of the trials were incongruent, with the center arrow pointing in a direction opposite that of the arrows flanking it (< < > < < or > > < > >). The subject was required to respond accordingly, ignoring the distractors.

The auditory oddball task involved a repetitive auditory stimulus (1000Hz) that was infrequently interrupted by a target stimulus (2000Hz). There were a total of 100 trials each session (80% common, 20% uncommon stimuli). Subjects were asked to react by pressing a button every time they heard the target stimulus.

During the Stroop task, subjects were required to press one button when a shown word ("BLUE," "RED," "GREEN," "YELLOW," or "PURPLE") matched its color, and another button when the name of a color did not match its meaning. There were a total of 80 trials, with a 50/50 ratio of congruent versus incongruent trials.

For the Sternberg memory task, subjects were presented with a string of either three or five letters that they had to memorize. After a short pause, they were shown a new letter and were asked to indicate whether this new letter was or was not present within the original set. There were a total of 50 trials (25 three-letter sets, 25 five-letter sets) in randomized order. To avoid a learning effect from one recording session to the next, multiple versions of this test were presented in alternating order across experimental trial days.

Statistics

Results were analyzed using SPSS 21.0 software (IBM, Armonk, NY) , and are presented as Means (SD), unless otherwise indicated. A series of 2x3 (exercise by altitude) repeated measures ANOVAs were conducted to test the significance of within-subjects factors on dependent variables including reaction time and accuracy on each of the cognitive battery tests, and their corresponding ERP amplitudes and latencies. Analyses were conducted for each modality of the tasks separately, due to large variability of performance from one test modality to another (e.g. congruent trial performance vs. incongruent trial performance), which rendered all 'overall' analyses meaningless. Significance was set *a priori* at alpha < 0.05. Where appropriate, *post-hoc* analyses were conducted and Bonferroni adjustments were made to reduce the likelihood of Type II errors.

CHAPTER 3

RESULTS

Subject Characteristics

A total of 18 participants were screened for this experiment. Two subjects were excluded because they were left-handed while another two were excluded because they grew faint during hypoxia. A total of 14 subjects (9 male and 5 female) completed all six experimental trials and were included in data analyses (Table 1). Subjects were at least recreationally active, with a self-reported average of 48 ± 36 min of moderate intensity physical activity on 2.5 ± 1.9 d/wk. Apart from the two excluded participants, the highest reported Lake Louise Score was 3 indicating that hypoxia was well tolerated by the subjects. There were no significant differences in SpO_2 between rest and exercise trials at any time point. SpO_2 was significantly lower throughout rest and exercise at MA and HA compared to SL, dropping an average of 6-13% from SL to MA and HA, respectively (Figure 2).

Behavioral Cognitive Performance

Prior to analyzing the effects of exercise and altitude on behavioral cognitive performance, a one-way repeated measures ANOVA was conducted for each task to determine whether there were significant differences in performance based on test modality (congruent versus incongruent trials on the Flanker task, matched versus mismatched pairs on the Stroop task, 3-letter versus 5-letter sequences on the Sternberg memory task; Table 2). Except for accuracy on the Flanker task, task performance differed significantly across all test modalities. Therefore, all data below were analyzed separately for each test modality. Table 3 displays the main effects of exercise and altitude, as well as their interaction effects, on the response accuracy and reaction time for each behavioral cognitive task broken down by test modality. Accuracy was not affected by either altitude or exercise on any of the behavioral cognitive tasks. There was a significant effect of altitude on reaction time ($F_{(2,26)}=3.84$, $p=0.035$, $\eta_p^2=0.228$) during incongruent Flanker task trials, with a trend that for slower reaction times at MA and HA compared to SL. For the auditory oddball task, there was a significant effect of exercise on reaction time ($F_{(1,13)}=10.86$, $p<0.01$, $\eta_p^2=0.460$) with significantly faster reaction times during exercise regardless of altitude. For the Stroop task, there were significant main effects of exercise ($F_{(1,13)}=7.44$, $p=0.017$, $\eta_p^2=0.364$) and altitude ($F_{(2,26)}=3.81$ $p=0.04$, $\eta_p^2=0.226$) on reaction time whenever the color and word meanings of a trial matched. Exercise improved reaction time regardless of altitude during the Stroop task, while exposure to HA slowed reaction time down compared to SL and MA. Behavioral cognitive performance on the Sternberg memory task was not affected under any condition.

Neurophysiological Activity

Amplitude and latency of the N100 were only affected during mismatched Stroop task trials and congruent Flanker task trials. There was a significant main effect of exercise on N100 amplitude ($F_{(1,13)}=5.14$, $p=0.041$, $\eta_p^2=0.280$) and a significant main effect of altitude on N100 latency ($F_{(2,26)}=5.37$, $p=0.01$, $\eta_p^2=0.292$) during mismatched Stroop trials. Exercise increased N100 amplitude, while altitude increased latency. There was also a main effect of exercise on N100 amplitude during congruent Flanker task trials ($F_{(1,13)}=5.40$, $p=0.04$, $\eta_p^2=0.293$).

There was a significant interaction effect of altitude and exercise on P200 amplitude during incongruent Flanker task trials ($F_{(2,26)}$=3.7, p=0.04, η_p^2=0.221). Exercise generally increased P200 amplitude except at MA. There were also significant main effects of altitude ($F_{(2,26)}$=5.56, p=0.01, η_p^2=0.30) and exercise ($F_{(1,13)}$=7.39, p=0.018, η_p^2=0.362) on P200 latency during 3-Letter sequences of the Sternberg memory task. Latency was lengthened during exercise trials, as well as during MA.

There was a significant main effect of exercise on N200 amplitude during incongruent Flanker task trials ($F_{(1,13)}$=9.77, p<0.01, η_p^2=0.43). Exercise generally reduced N200 amplitude. There was also a significant main effect of altitude on N200 latency on incongruent Flanker task trials ($F_{(2,26)}$=3.70, p=0.04, η_p^2=0.221), both MA and HA significantly slowing latency compared to sea level (Figure 4). No other behavioral cognitive tasks impacted the N200 ERP.

There was a significant main effect of exercise on P300 amplitude during incongruent Flanker task trials $F_{(1,13)}$=5.46, p=0.036, η_p^2=0.297), as well as a significant main effect of altitude on P300 amplitude during matching Stroop task trials ($F_{(2,26)}$=5.71, p<0.01, η_p^2=0.305). While exercise tended to reduce P300 amplitude, so did increasing altitude. There was also a significant interaction effect of altitude and exercise on P300 latency matching Stroop task trials ($F_{(2,26)}$=3.36, p=0.05, η_p^2=0.206). Latency significantly increased with increasing altitude, but exercise reduced latency at MA and HA, though not at sea level (Figure 5).

CHAPTER 4

DISCUSSION

The aim of this study was to examine the behavioral cognitive and neurophysiological effects of acute exposure to simulated moderate and high altitudes at rest and during exercise in an effort to delineate whether there was a level of hypoxia beyond which cognition and neurophysiological function were impaired and whether exercise would improve or worsen cognitive function during exposure to hypoxia. Our primary findings were that while altitude exposure increased reaction time on some behavioral tasks, exercise improved it, making performance at MA and HA during exercise comparable to performance at SL during rest. Despite changes in reaction time, performance accuracy was not affected under any conditions. These behavioral findings were only partially supported by changes in ERPs.

For executive function tasks like the Flanker and Stroop tasks, altitude significantly reduced reaction time without affecting accuracy (Table 3). This finding agrees well with several other studies investigating the impacts of altitude on behavioral cognitive performance.[2,46] It was fully expected that the incongruent trials of the Flanker task would be more affected than the congruent trials, given that incongruent trials present more of a novel stimulus that requires greater cognitive processing and resources to handle. On the other hand, it was unusual to find significant impacts on matching Stroop trials, but not mismatched ones. After closer examination of the data, it appears that average reaction time on mismatched Stroop tasks closely approximated the allotted response window that subjects were allowed before the computer logged their lack of timely response (598 ms vs 600 ms, respectively). Therefore, it is possible that we saw a ceiling effect at work, not allowing us to capture effects that fell outside the range of our assessment. Also, given that the auditory oddball task has been shown to be sensitive to hypoxia at simulated altitudes at or above 5000 m[9,31,49], it was surprising that no altitude effect was found in the current study (Table 3). A close examination of the literature suggests that auditory oddball task performance may not be impacted until altitudes higher than those used in the current study (> 5000 m).[20] Our findings suggest that there is a dose-response of altitude on cognitive task reaction time. While executive function task reaction time, such as measured by the Flanker task, was affected as low as 2400 m (MA), another reaction time task requiring different brain functions, such as the Stroop task, which accesses the language and color processing centers of the brain, was not affected until 3900 m (HA). The Flanker and Stroop tasks are the only tests utilized in this experiment that assess high-level executive function requiring a high degree of impulse control and decision making. This may in part be why they were affected when more reflexive tasks like the auditory oddball, or memory tasks, like the Sternberg, were not. On the other hand, short term memory tasks (such as the Sternberg) have been more seldom utilized when investigating the effects of altitude, and there is some evidence that short term memory is not as sensitive to hypoxia as other cognitive modalities.[21] Based on evidence from the literature, Sternberg memory task performance would likely not be affected until altitudes above 5000 m. The evidence of our experiment suggests that different areas and modalities of cognitive function are affected differently and to varying degrees by altitude and exercise, and the exact level and magnitude of effects on each kind of behavioral cognitive performance remains to be investigated.

Exposure to MA and HA resulted in significant declines in SpO_2 compared to SL (Figure 2) with values similar to those reported in other cognition studies with similar simulated altitudes.[1,31] Surprisingly, SpO_2 did not decrease further from values at rest with the introduction of exercise at either MA or HA as has been shown in other studies.[15,23] Perhaps the moderate intensity exercise stimulus was not intense enough to provoke further drops in SpO_2. It is also possible that subjects engaged in ventilatory compensation mechanisms, increasing their tidal volume or ventilatory rate to maintain SpO_2.[4] The lack of a drop in SpO_2 during exercise may be why exercise was able to have a beneficial impact on behavioral cognitive performance, rather than impairing it. Most likely, we avoided a scenario where muscular and cerebral tissues were in direct competition for a limited arterial oxygen supply. In addition, our findings imply that cerebral oxygenation likely dropped to levels comparable to our SpO_2 data, especially since it has been previously shown that these parameters mirror one another until at least 5000 m[5] and that much of the cognitive impairment seen with simulated altitude likely stems from reductions in cerebral oxygenation.[48]

Contrary to the effects of altitude, performing 30 min of moderate intensity aerobic cycling exercise improved cognitive reaction time during the auditory oddball and Stroop tasks at SL, MA, and HA (Table 3). This agrees with much of the recent literature that postulates a general positive impact of exercise on cognitive behavioral performance at altitude[1,21,44], likely as a result of an increase in general arousal.[33] Flanker task performance, however, was not improved by exercise, which deviates from many other findings.[7,17,37,42] Most research agrees that the Flanker task is a hallmark test that covers a wide range of executive functions and has often been used as a proxy of cognitive performance. It has also been shown to be sensitive to exercise.[17,37] It is unclear why we did not find an exercise effect on Flanker task performance in this study.

This experiment demonstrates that exercise can significantly improve and ameliorate the negative effects caused by moderate and high altitude, at least for some cognitive processes. Average performance on these tasks at HA combined with exercise was similar to that achieved at SL without exercise, implying that exercise can be used as a tool to combat the deleterious effects of rapid ascent and exposure to altitude. However, this is only true so long as exercise does not negatively impact SpO_2. If the exercise stimulus becomes intense enough to lower SpO_2, it is also likely reducing cerebral oxygenation by directly competing with cerebral tissues for oxygen, which may in turn worsen behavioral cognitive performance at altitude.

To attempt to support behavioral cognitive findings, ERPs during task performance were also studied. As mentioned previously, it was reasonable to expect alterations in ERP waveforms with simulated altitude, as evidence from the literature suggests that these waveforms are sensitive to drops in oxygen availability.[26,31,45] In this experiment, the vast majority of the time these waveforms were affected neither by physical activity nor by increasing altitude and hypoxia. Additionally, most of the time altered waveforms were not reflected in changes in behavioral cognitive performance. This could indicate that there are compensatory mechanisms at work that act to resist perturbations induced by altitude and exercise. Changes in ERP amplitude and latency that are reflected in changes in behavioral cognitive performance may in turn be the result of impacts that are too large for compensatory mechanisms to counteract. An increase in signal amplitude implies a greater amount of cognitive processing power currently in use, meaning that more work is being done and more attention required for a task. An increase in latency indicates an overall neuronal slowing.[41] The N100 is a pre-attentive ERP and involved in perception of a stimulus. The P200 is also involved with attentive perception of a stimulus, and is often grouped together with the N100 as the N1-P2 complex. These ERPs are more reflexive responses to physical stimuli, while the N200 and P300 are more involved with cognitive processing. The N200 is generally elicited as a response to unusual or incongruent stimuli, when response inhibition and switching is required. There have been a number of studies that investigate the effects of altitude on ERPs, but there is evidence that the N100, P200, and N200 waveforms are generally not sensitive to alteration by hypoxia or exercise.[9,49] Many of our results fall in line with these findings. However, during Flanker task performance, N200 latency was increased at altitude; for the Stroop task, amplitude was increased by exercise (Figure 4). If one were to draw generalized conclusions based on these meager findings, the implication would be that altitude produced a slowing of neuronal processing, while exercise resulted in an increase in attentional resources required to process stimuli.

On the other hand, the P300 component is the most frequently studied ERP in executive function studies and is used as an indicator of object discrimination and classification. Higher amplitudes are indicative of greater attentive (processing) requirements of a task, while shorter latencies (more rapid onsets) are endemic of superior mental performance as opposed to longer latencies. Most modern literature agrees that the P300 ERP component is highly sensitive to alteration both due to altitude[9,11,31,49] and exercise.[14,18,30] While we did find some effects on this waveform, hardly any overlapped with changes in performance. This evidence suggests that despite a tendency for increasing altitude to increase amplitudes and latencies of the P300, which would normally indicate an increased demand for attention and an overall neuronal slowing, there could have been unmeasured compensatory mechanisms at work that prevented these waveform changes from negatively impacting behavioral performance. The only time we saw overlaps was during the Stroop task, where altitude resulted in reduced amplitudes and increased latencies, while exercise in turn reduced latencies. While altitude may have slowed neuronal processing, moderate intensity cycling exercise sped up processing, resulting in a normalization in performance (Figure 5). This further supports our finding that moderate intensity exercise can ameliorate the negative impacts of acute exposure to altitude, and that these improvements are in part due to alterations in central processes, including improved processing speed and efficiency.

These findings could have profound significance in real world situations, where people rapidly ascending to various altitudes are required to deal with the physical and cognitive impacts hypoxia induces in a very short time. This includes rapid deployment military personnel, aircraft pilots, athletes, and anyone who travels to high altitude who may experience compromised decision-making capabilities. If an acute bout of moderate intensity physical activity, performed as soon as altitude is reached, can ameliorate some of these detriments in the short term, the result could be normalized performance in a number of physical and cognitive decision-making scenarios, where rapid as well as accurate action and reaction are essential. However, these behavioral cognitive improvements generally averaged 30-50 ms. While these are statistically significant improvements, it remains questionable how applicable these benefits will be in real-life scenarios.

Limitations

To our knowledge, this study is one of only a select few that have attempted to combine elements of simulated altitude and moderate intensity exercise with behavioral cognitive testing and EEG recording. It is quite possible that the inherent nature of this experimental design has introduced a number of errors into recorded data, especially in the acquired EEG data. Because EEG is such a sensitive measure, any errant electrical signals can introduce noise. Conventionally, electroencephalography is conducted within a Faraday cage, blocking out all electric activity from outside the enclosure. However, our experimental design required the use of an electromagnetically braked cycle ergometer and an altitude simulator. Both the cycle ergometer and the EMG activity generated by working muscles groups would add additional noise. Since we did not use a Faraday cage, current from the computers used to present subjects with behavioral cognitive stimuli and to record the resultant EEG signals may have further added noise to our data, not all of which may have been eliminated in signal processing post-collection.

Additionally, the behavioral cognitive tasks chosen for this experiment demonstrated a clear ceiling effect. Most subjects performed extremely well on these tasks under all conditions, scoring well above 90%. The tasks may have simply not been difficult enough for a healthy, active, college-aged population to be impacted by simulated altitude or moderate intensity exercise. At the same time, our protocols did not deviate from those adopted as standard by the literature, and remain highly comparable to other studies.[3,14,20,47]

Future Research

As with any EEG recordings, there is a large deal of data that is never examined for the purposes of a given study. However, there are a number of factors that may be impacted by simulated altitude or exercise that we did not explore. Future efforts should investigate additional indices of neural function contained within an EEG, including spectral band power, or source localization.[28,34,47]

In addition, it is clear that varying aspects of cognitive function are affected differently by altitude and exercise. There may possibly exist a more optimal combination of exercise modality, intensity, and duration that would prove more effective at alleviating the negative effects of altitude. At the same time, the literature reinforces the choices we made in this regard, demonstrating that moderate intensity cycling exercise lasting less than 60 min is still the most effective way to elicit behavioral cognitive improvements.[24,44]

CHAPTER 5

CONCLUSION

Acute exposure to MA and HA induces a slowing in behavioral cognitive performance while preserving overall task accuracy. An acute bout of moderate intensity cycling exercise improves reaction time, resulting in speeds that are comparable to those achieved without exercise or altitude exposure. These findings are in part supported by changes in N200 and P300 ERPs. Finally, these cognitive changes were encountered within 60 min of altitude exposure and within 30 min of exercise, indicating that cognitive processes can be rapidly altered with even short-term stimuli.

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TABLES

Table 1. *Participant characteristics*.

Variable	Male (N=9)	Female (N=5)
Age	24.7(3.6)	27.6(4.4)
BMI (kg/m^2)	25.9(2.9)	26.8(5.6)
Body Fat (%)	19.9(8.3)	32.3(7.7)
VO_2peak (ml/kg/min)	42.1(8.8)	34.3(9.4)
Peak Power Output (W)	221.0(51.1)	161.4(39.4)

Values are means (SD), *n*=14. BMI, Body Mass Index, VO_{2peak}, peak oxygen consumption.

Table 2. *Effect of test modality on behavioral cognitive performance.*

A) Flanker task	**Congruent**	**Incongruent**
Accuracy (% correct)	98(2)	88(23)
Reaction time (ms)	403(43)	444(43)**
B) Stroop task	Matched	Mismatched
Accuracy (% correct)	93(3)	94(3)*
Reaction time (ms)	560(58)	586(59)**
C) Sternberg memory task	3 Letters	5 Letters
Accuracy (% correct)	95(4)	91(6)*
Reaction time (ms)	583(83)	628(81)**

Values are means (SD), *n*=14.
**p<0.05*
***P<0.01*

Table 3. *Main effects of exercise (Rest, Exercise), altitude (SL, MA, HA) and their interactions on response accuracy and reaction times on each measure of behavioral cognitive performance.*

Values are means (SD), *n*=14. SL, sea level; MA, simulated moderate altitude; HA, simulated high altitude.

**p<0.05, significant effect of altitude, different from SL*

†p<0.05, significant effect of exercise, different from Rest.

A) Flanker task		*Congruent*		*Incongruent*	
Accuracy (% correct)		***Rest***	***Exercise***	***Rest***	***Exercise***
	SL	98(3)	98(3)	90(25)	86(23)
	MA	97(4)	99(2)	89(23)	86(22)
	HA	99(2)	99(1)	89(22)	88(25)
Reaction time (ms)					
	SL	390(48)	407(48)	427(41)	440(43)
	MA	396(43)	415(56)	438(40)*	461(63)*
	HA	409(50)	402(45)	451(59)*	450(52)*

B) Auditory oddball task		***Target Response***	
Accuracy (% correct)		***Rest***	***Exercise***
	SL	95(6)	91(18)
	MA	95(6)	95(7)
	HA	95(5)	96(5)
Reaction time (ms)			
	SL	438(38)	424(51)†
	MA	436(35)	414(30) †
	HA	454(26)	418(41) †

C) Stroop task		***Match***		***Mismatch***	
Accuracy (% correct)		***Rest***	***Exercise***	***Rest***	***Exercise***
	SL	95(4)	91(8)	95(4)	92(6)
	MA	92(6)	92(6)	93(5)	96(5)
	HA	94(4)	93(4)	95(5)	93(6)
Reaction time (ms)					
	SL	560(64)	537(49) †	587(66)	567(59)
	MA	573(67)	550(62) †	596(67)	582(65)
	HA	583(80)*	558(63)*†	597(76)	588(68)

D) Sternberg memory task		***3-Letter Sequences***		***5-Letter Sequences***	
Accuracy (% correct)		***Rest***	***Exercise***	***Rest***	***Exercise***
	SL	97(5)	95(7)	92(9)	91(5)
	MA	92(9)	95(7)	90(11)	89(11)
	HA	97(4)	92(7)	89(12)	93(5)
Reaction time (ms)					
	SL	604(100)	558(133)	639(97)	597(97)
	MA	603(110)	585(77)	635(114)	632(85)
	HA	579(84)	570(92)	641(101)	623(93)

FIGURES

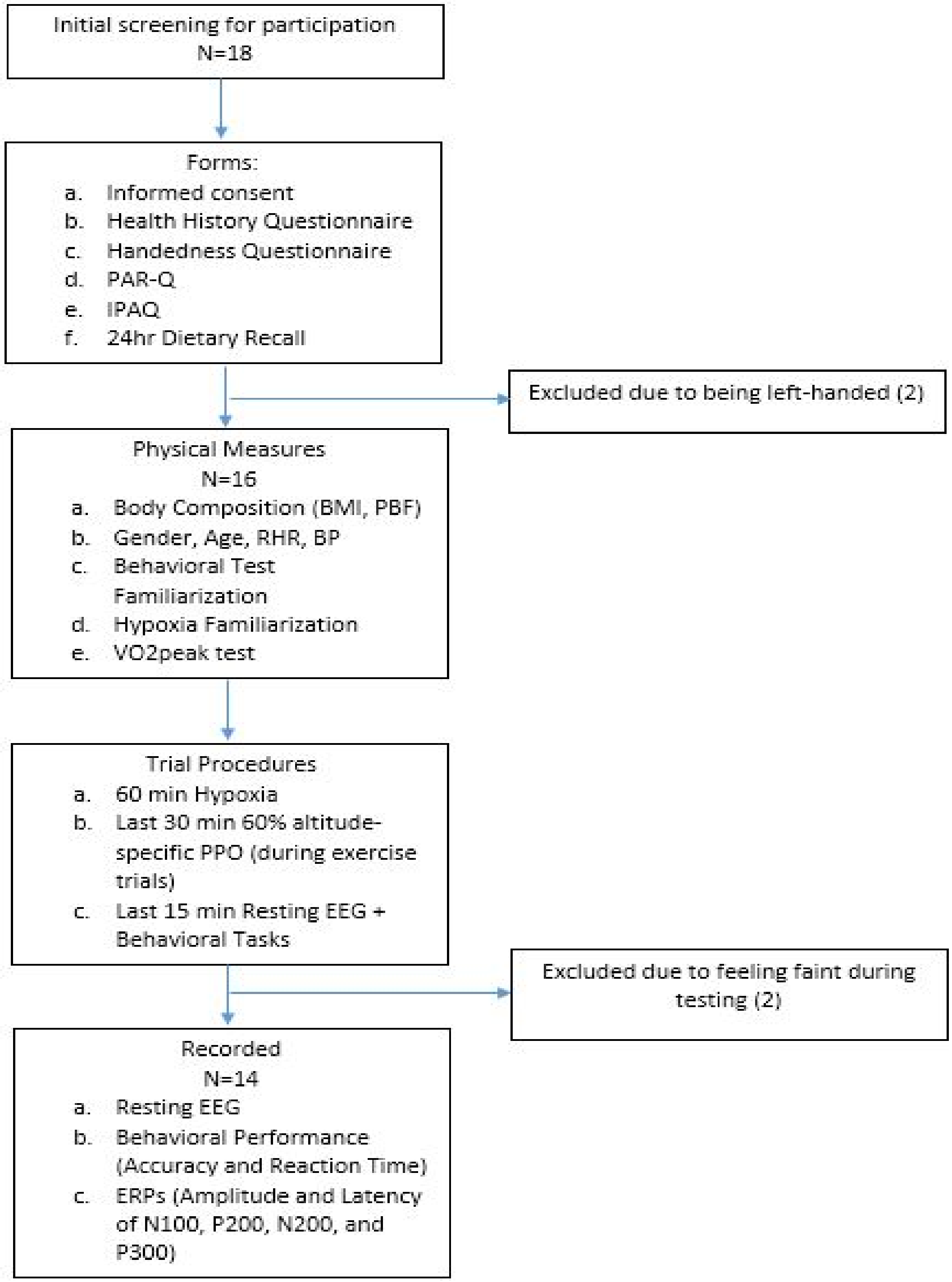
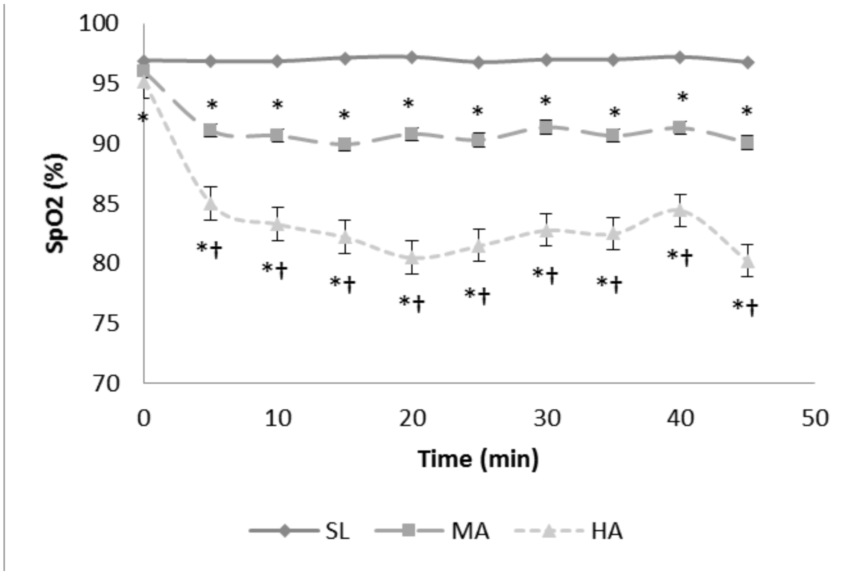


Figure 1. *Consolidated standards for participant activities.*

A.



B.

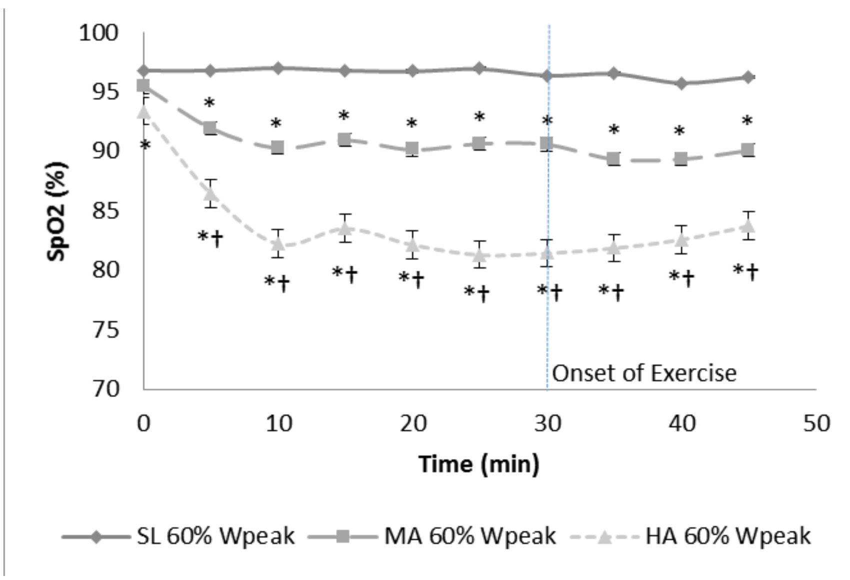


Figure 2. *Peripheral oxygen saturation during A) rest and B) exercise trials at sea level and simulated moderate and high altitudes.* Values are means ± SD, *n*=14. SL, sea level; MA, simulated moderate altitude; HA, simulated high altitude.

** $p<0.01$ significantly different from SL*

† $p<0.01$ significantly different from MA

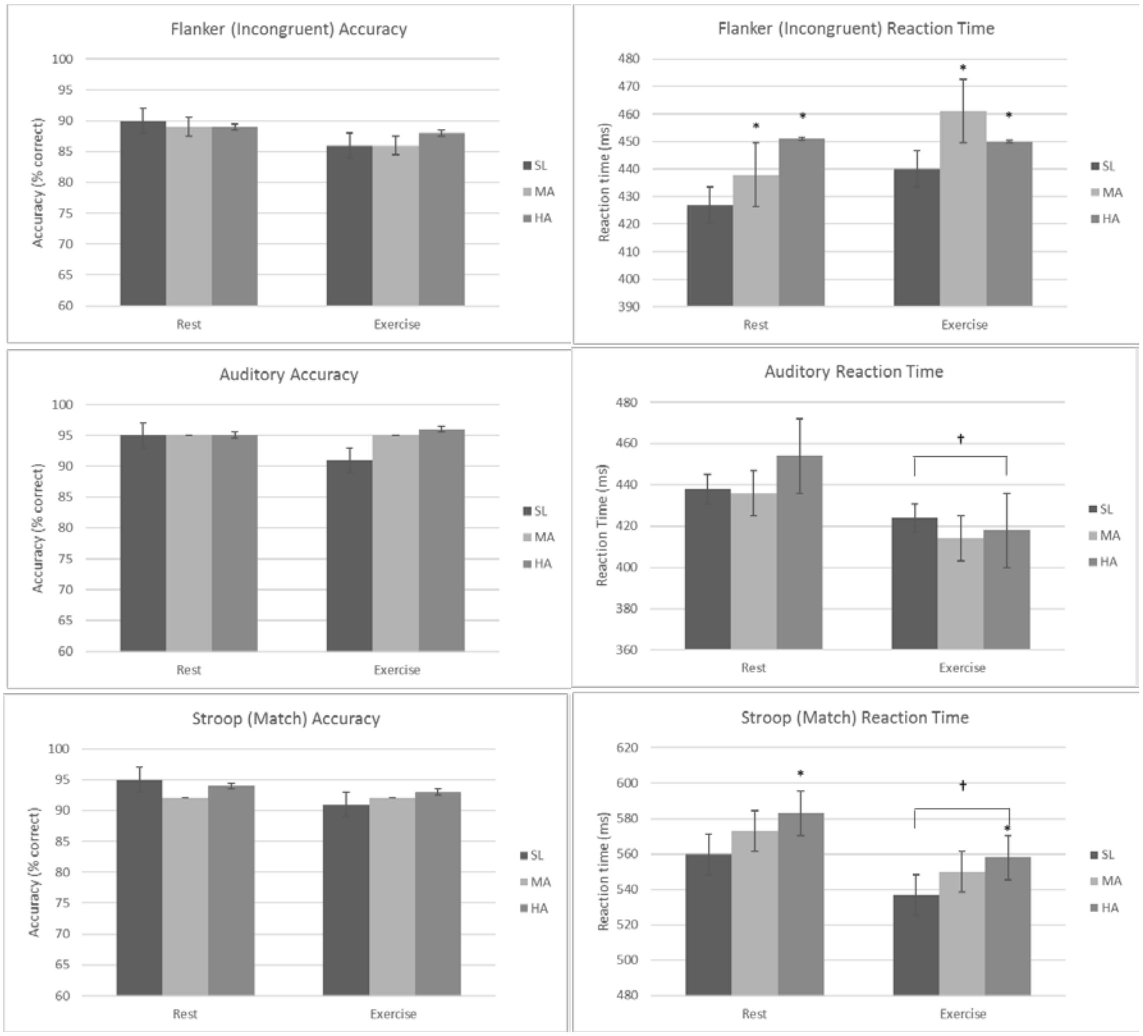


Figure 3. *Effects of exercise and altitude on behavioral cognitive task accuracy and reaction time for incongruent flanker task trials, target auditory trials, and matched Stroop trials.* Values are means ± SD, n=14. SL, sea level; MA, simulated moderate altitude; HA, simulated high altitude.
**p<0.05, significant effect of altitude, significantly different from SL*
†p<0.05, significant effect of exercise, significantly different from Rest

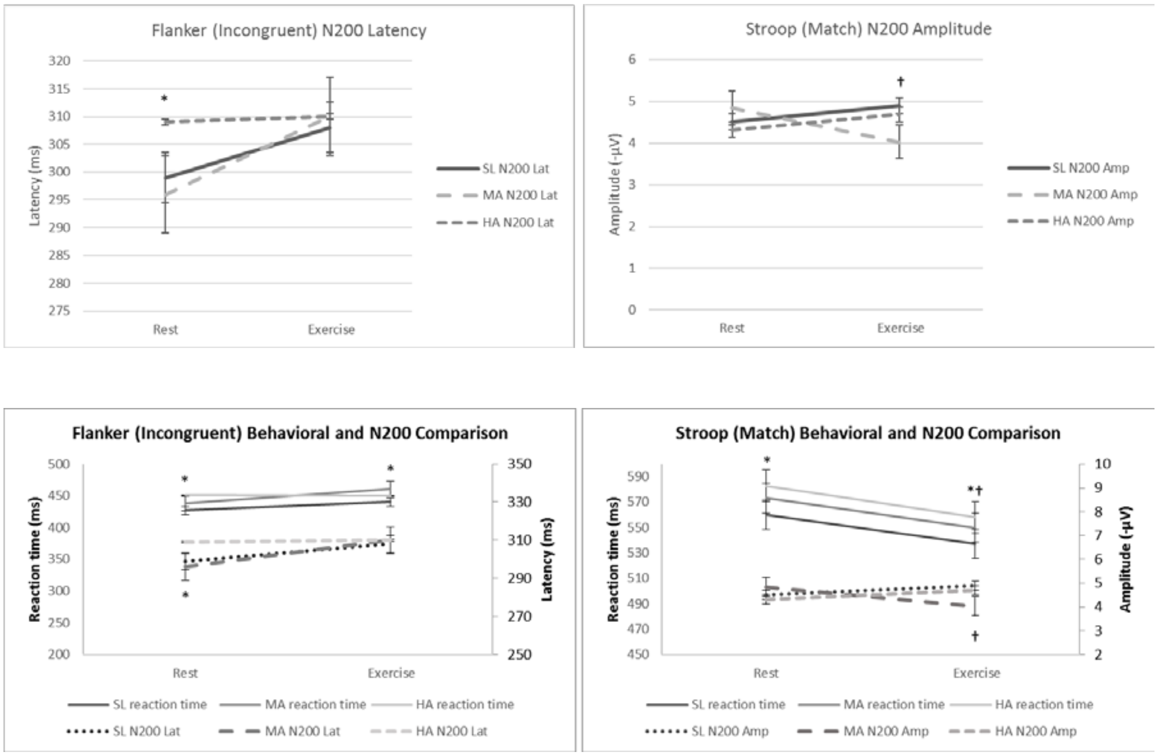


Figure 4. *Effects of exercise and altitude on N200 amplitude and latency.* Effects of exercise and altitude are displayed separately for N200 latency and amplitude changes, then overlapped with changes in cognitive behavioral reaction time (below). Values are means ± SD, n=14. SL, sea level; MA, simulated moderate altitude; HA, simulated high altitude; N200 Lat, latency of the N200 event-related potential; N200 Amp, amplitude of the N200 event-related potential.
**p<0.05, significant effect of altitude, significantly different from SL*
†p<0.05, significant effect of exercise, significantly different from Rest

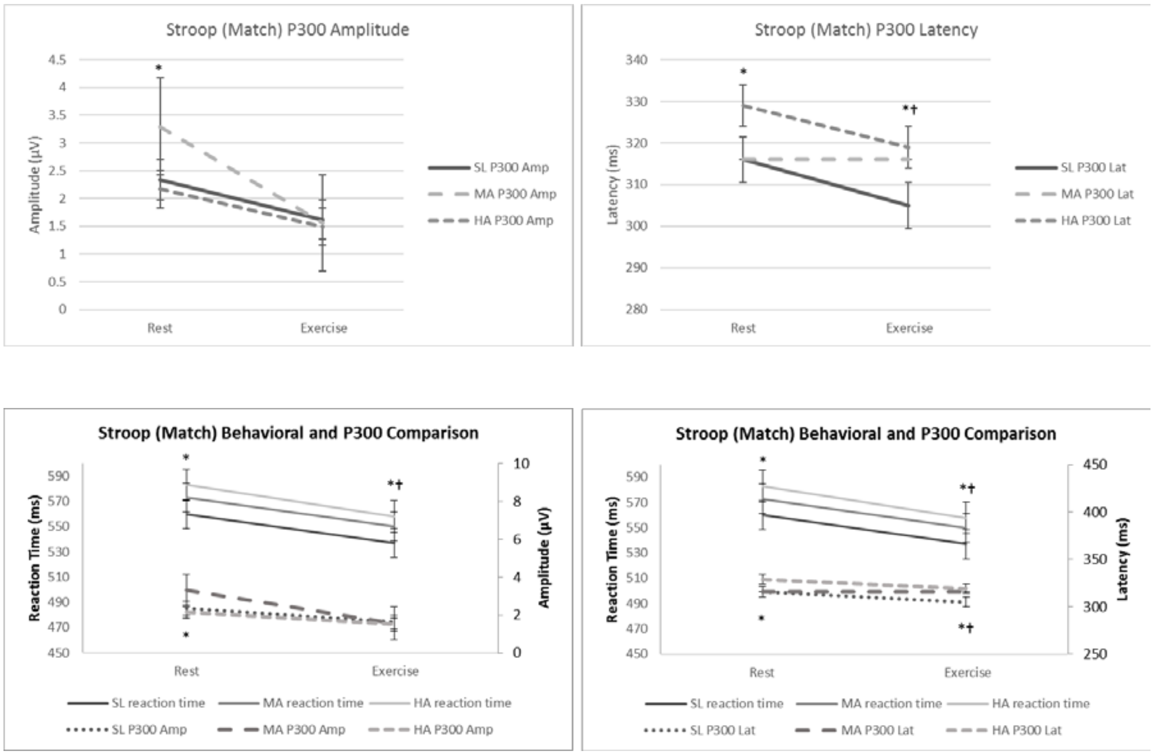


Figure 5. *Effects of exercise and altitude on P300 amplitude and latency.* Effects of exercise and altitude are displayed separately for P300 latency and amplitude changes, then overlapped with changes in cognitive behavioral reaction time (below). Values are means ± SD, n=14. SL, sea level; MA, simulated moderate altitude; HA, simulated high altitude; P300 Lat, latency of the P300 event-related potential; P300 Amp, amplitude of the P300 event-related potential.

**p<0.05, significant effect of altitude, different from SL*

†p<0.05, significant effect of exercise, different from Rest