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Association of Cognitive Performance with Time at Altitude, Sleep Quality, and Acute Mountain Sickness Symptoms

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ABSTRACT

Objective: It is well documented that cognitive performance may be altered with altitude ascent, but the association of various cognitive performance tests with symptoms of Acute Mountain Sickness (AMS) is not well understood. Our objective was to assess and compare cognitive performance during a high altitude expedition using several tests and report the association of each test with AMS, headache, and quality of sleep. **Methods:** During an expedition to Mount Everest, three cognitive tests (Stroop, Trail Making, the RCAT, an in-house developed motor accuracy test) were used along with a questionnaire to assess health and AMS. Eight team members were assessed pre-expedition, post-expedition and at several time points during the expedition. **Results:** There were no significant differences ($p>0.05$) found between scores taken during the three time points on Basecamp and the post expedition scores for all three tests. Changes in the Stroop test scores were significantly associated with the odds of AMS ($p<0.05$). The logistic regression results show that the percent change from baseline for Stroop score ($\beta = -5.637$; $p = 0.032$) and Stroop attempts ($\beta = -5.269$; $p = 0.049$) are significantly associated with the odds of meeting the criteria for AMS **Conclusion:** No significant changes were found in overall cognitive performance with altitude, but a significant relationship was found between symptoms of AMS and performance in certain cognitive tests. This research shows the need for more investigation of objective physiologic assessments to associate with self-perceived metrics of AMS to gauge effect on cognitive performance.

Key Words: Cognitive Performance; Hypoxia; Altitude; AMS; Cognition; Expedition

1. Introduction

Moderate hypoxia has been shown to induce changes in visual, motor, somatosensory, and mental function. Performance in intelligence tests, reaction time, speech comprehension, hand steadiness, and visual contrast discrimination are some of the mental functions that have been shown to be negatively impacted(1-3). Hypoxia affects individuals' ability to perform word association tests along with causing abnormal test responses (4). The effects of hypoxia go as far as inducing auditory and visual hallucinations(5) and have even been documented to induce feelings of depersonalization and out of body experiences (6). Visual function changes with hypoxia include narrowing of the visual field (7)(8), and vision blurring with worsening levels of hypoxia causing failure of the entire retina and total loss of vision (9) .

Over the years, stories of climbers not being able to perform simple mental tasks have become part of the literature documenting cognitive changes at altitude. Although it is well known that cognitive performance is impaired with altitude ascent, the exact nature and timing of these changes are not clear. Each year altitude-related hypoxia affects thousands of aviators, both military and civilian, and causes complications in rapid high-altitude troop deployments (11). In addition, many workers at extreme altitudes, and even recreational climbers and tourists suffer from Acute Mountain Sickness (AMS). Assessing possible cognitive degradation with altitude ascent is complex due to the multitude of factors that accompany altitude ascent. Lack of sleep, headache, and AMS with

accompanying symptoms can all affect cognition, and isolating their effect from actual hypoxia can be difficult (10).

There are a variety of different tests used in the literature to detect cognitive function changes with hypoxia and/or altitude. They focus on the observation of the changes in motor and executive function, memory, response time, and hand-eye coordination. The sheer variety of tests available to researchers, along with the inherent variability within tests, may be a reason why there is debate in the literature on whether cognitive degradation occurs at certain elevations (10, 12-15). Additional complications are added when taking into account variation in individual physiology. The difficult nature of field expeditions and the possible differences with controlled environmental chamber studies also does not help with the consistency of results. Hence, the focus of this research expedition was to assess the degradation in cognitive performance with multiple tests and examine the relationship to the physiological consequences of high altitude, specifically AMS, headache, and quality of sleep.

Several tests such as the Stroop Color-Word and the Trail Making Test have been "grandfathered in" as standards for testing cognitive function. We decided to take a fresh approach and design a real-time cognitive assessment tool (RCAT) to examine changes in motor executive function, specifically speed, hand-eye coordination, and response time. The objective was to use the test in tandem with other tests normally used for altitude performance, and determine which tests were possibly better suited for detection of the specific symptoms accompanying altitude exposure. The test is designed (See Appendix A

for more information) to take advantage progress in mobile technology with the intention of future deployment and use in the field.

In the present expedition to Mount Everest Base Camp (5500m/17300ft), cognitive function was examined alongside changes in physiology that occur with altitude. The first objective was to use Stroop, Trail Making, and the RCAT to examine any changes in cognitive function that occur with graded exposure to altitude. The second objective was to use continuous monitoring to examine AMS, headache, as well as quality of sleep. The third objective was to report the association of each cognitive performance test with AMS, headache, and quality of sleep.

METHODS:

Subjects: During the course of the expedition eight subjects were monitored and tested. The experimental procedures were approved by the Mayo Clinic Institutional Review Board and each subject provided written informed consent prior to participation. Average subject demographics were as follows (AVG ± SD): Age 35 ± 10 years, Height 181 ± 5 cm, Weight 86 ± 8 kg, BMI 26 ± 2 kg/m^2. Before this expedition, four of the eight subjects had experienced high altitude (2500-3500 m) or greater.

Study Design: Figure 1 shows the ascent timeline to Everest Basecamp as well as the other altitudes along the trek at which expedition testing was performed. All members were tested before the climb, at three time points at base camp, and upon return. To minimize the effect of learning, subjects were asked to perform each test for approximately 20 minutes before collecting the baseline data.

Cognitive Testing: Three tests were used to evaluate cognitive performance. In each session, all tests were administered in a randomized sequence with a maximum of a one minute break in between tests. Subjects were asked to take thee of each test type and were isolated during gameplay to minimize the effect of distractions.

Stroop Color-Word Test: In this test subjects are asked to identify the color of the text and associate it with the proper text that spells the answer. Colors and text often contradict to

increase confusion and demand more focus from the subject. The version we programmed for use on Android tablets lasted for one minute and awarded one point for a correct response and subtracted one point for an incorrect response. The data tracked documented each choice and reported patterns in the errors made (e.g. incorrect text selection vs. incorrect color identification). Metrics recorded were final score, number of choices made, correct choices made, incorrect choice made, time for each choice, and type of error (color mismatch vs. word mismatch).

Trail Making Test: This test is divided into Trail A and Trail B. In Trail A, subjects are asked to connect numbers 1 to 20 in sequence using a tablet pen. In Trail B, letters are factored in so the order is 1A, 2B, 3C and so on. The programmed version times subjects and reports duration to complete each sequence as well as dwell time of each transition.

Rapid Cognitive Assessment Tool (RCAT): The RCAT was designed to test speed, accuracy, and response time. The basic premise is to click spawning squares according to prompts based on color. The game lasts one minute and reports metrics every tenth of a second. The overall score is determined by speed, accuracy, and response time. For a detailed description of the development and design, please see Appendix A.

AMS, Headache and Sleep Quality Assessment: In addition to regular physiological and cognitive monitoring, subjects were weighed every morning and asked to take a modified Lake Louise survey for AMS along with other factors. The AMS survey was given using a programmed Android tablet questionnaire with each question weighed on a 4-point scale. When subjects highlighted a choice, a small description appeared to assist them in

understanding the scale. Other questions asked about food intake, headache, and quality of sleep. All categories were tracked over the course of the expedition and analyzed for correlation with cognitive scores.

Data Analysis: Data gathered from cognitive tests of eight subjects was analyzed with R (R Foundation for Statistical Computing, Vienna, Austria). Data was analyzed with several objectives. The first objective was to determine whether testing was repeatable within a testing session. The second objective was to determine if cognitive function changes could be detected over the course of the expedition. Cognitive scores for each test were analyzed and compared across different expedition time points (see Figure1): pre-expedition, multiple basecamp time points, and post-expedition. The second objective was to determine if there was any association between cognitive function and AMS, quality of sleep, or presence of headache.

An ANOVA was used to look for repeatability of performance within subjects for each test. A repeated measures ANOVA and student T-test was used to examine difference between performances pre-expedition, multiple basecamp time points, and post-expedition. Data for each testing session was then compared with AMS symptom data (total AMS score, headache, and sleep disturbance) using a univariate logistic regression, specifically examining the association of cognitive performance with the odds of symptom presence at multiple expedition time points. P-values of less than 0.05 were considered significant.

RESULTS:

Eight subjects were analyzed for cognitive performance pre-expedition, at base camp, and post-expedition. Better performances on the Stroop and RCAT register as higher scores, while the Trials A and B register as lower times due to the shorter time it takes to complete the test (time to completion is the outcome variable). Descriptive statistics for all the raw scores are shown for each test in Table 1. To normalize for the large differences in individual performance and skill, scores were assessed as percent change from baseline for all tests.

A repeated measures ANOVA showed that there was no significant difference in the variation between repeated attempts in a given RCAT testing session ($0.19 < p < 0.87$), confirming that the developed test was reproducible. For more information on work showing test reproducibility, see Appendix A Section IV.

Figure 2 and 3 show a series of boxplots comparing performance of Stroop, RCAT, and Trials A and B performance at baseline, three Basecamp time points, and post-expedition. Both raw scores (Figure 2) and percent change in score (Figure 3) are represented. There were no significant differences ($p>0.05$) found between scores taken during the three time points on Basecamp and the post expedition scores for all three tests). However, there were large amounts of individual variation in performance on a day-to-day basis. The RCAT, Stroop, Trial A, and Trial B showed a standard deviation of 13%, 19%, 13%, and 17% respectively across all time points during the expedition.

To investigate the large amount of individual variation, we examined the relationship between individual performance and specific symptoms (AMS, headache, sleep disturbance). The logistic regression results (Table 2) show that the percent change from baseline for Stroop score (β = -5.637; p = 0.032) and Stroop attempts (β = -5.269; p = 0.049) are significantly associated with the odds of meeting the criteria for AMS. A 50% increase in score is associated with reduced odds of AMS by 93% and 94% respectively.

DISCUSSION:

In the present study, eight members of a research expedition to Mount Everest Base Camp (5500m) were monitored and assessed for cognitive function, AMS, sleep quality, and headache. Cognitive function was tracked using three different tests: Stroop, Trail Making, and an in-house designed RCAT. There was no significant difference between scores at any of the Basecamp time points and those acquired post expedition. However, some test scores were associated with changes in subject perceived presence of headache, AMS, or lack of sleep. The Stroop Test performances decreased significantly with self-reported AMS symptoms and with headache trending. The RCAT scores trended towards poorer performance with headache. Trial A performance also trended towards poorer performance self-reported AMS.

Published studies examining cognitive performance with hypoxia and altitude have use widely heterogeneous methods and techniques to reach the conclusions this research is based on. Articles documenting cognitive deficiencies in early aviation and altitude research show a gradual degradation of cognitive prowess starting at 2500m with a sharp drop off in performance at approximately 5000m (16, 17). However, more recent literature points towards no significant cognitive impairments in simulated gradual exposures to altitudes below 7000m (13, 18) (19). Field studies show more conflicted results (13-15, 20, 21) with some groups showing a change in cognitive function and others showing little or no change. For example, Harris et al (13) used CogState to evaluate cognitive performance at 5100m, and showed no impairments in individuals or the group as a whole, but at Base Camp of Kangchenjunga (5350m) Pagani et al (15) showed decrement in a memory task

they had developed. Moreover, differences between chamber and expedition testing are apparent even when using the same cognitive test. Evans and Witt reported decreased performance in the Digit Symbol Substitution Test at 4300m(20), but Kennedy et al used the same test and saw no changes with gradual decompression up to 8845m (18).

There are many complications incurred when comparing findings from different expeditions with their own unique conditions and techniques of varying complexity (even individual cognitive tests like the Stroop have different versions). In addition, there is an added layer of complexity when taking into account the wide variation in individual physiologic responses to altitude. Thus, isolating the effects of altitude and hypoxia on cognition is even more difficult given the multitude of factors that can influence cognitive performance.

In a review for the 1967 USARIUM symposium "Biomedicine of High Terrestrial Elevations", McFarland (16) nicely outlines the difficulties of interpreting cognitive performance during expeditions: "The subtle influence of hypoxia may often be masked by changes in the learning process or by "trying harder"." In the interpretation of the results he notes that "Motivation is an extremely difficult variable to control." He goes on to list numerous other hard to control factors that demand caution when interpreting expedition results: smoking, alcohol, drugs, diet, temperature extremes, and clothing. Attention, fatigue, nausea, mood, headache, and lack of sleep are a few critical factors that are amplified in a field expedition where subjects are likely facing many challenges. In such situations, rather than just altitude and hypoxia causing the decline in cognitive function, it is likely that an amalgam of conditions can cause a disturbance in cognitive performance.

In an attempt to dissect the specific causes of cognitive degradation during this expedition, AMS, headache, and quality of sleep were assessed along with cognitive function. Our analysis found that drops in Stroop test performance were associated with subjects' reporting symptoms of AMS. Although it is simple to conclude that people who believe they have such symptoms would be inclined have their concentration and cognitive performance impacted, the effects of AMS and symptoms on cognitive function is controversial. Aquino Lemos et al (22) correlated multiple cognitive performance tests, including the Stroop, to REM sleep patterns to show the effects of decreased sleep quality on cognitive performance. Virues-Ortega et al (23) believe that AMS is a "sufficient but not necessary condition for altitude neurophysiological impairment". Some studies revealed no significant correlation between AMS symptoms and cognitive functions (24), while others reported participants who developed AMS showed more cognitive impairment (14) (25). In the absence of such AMS symptoms, it could be concluded that gradual acclimation to high altitude may not induce cognitive degradation, similar to what was seen in simulated gradual exposures to altitudes below 7000m (18, 19).

It is important to note that assessing AMS and symptoms relies on individual reporting, so any association between cognitive performance and symptoms is in fact dependent on subject perceived mental state. Clearly there is a need for more objective metrics to gauge in tandem with cognition. In a good first step, Aquino Lemos et al (22) observed REM sleep patterns to get a more objective assessment of sleep quality. In a similar manner, pairing objective physiological metrics such as heart rate variability and

EEG with AMS and symptoms may help elucidate the driving mechanisms behind cognitive degradation at altitude.

Equally important to achieve an understanding of the mechanisms of cognitive degradation at altitude is teasing out the effect of disparate individual physiologic responses to hypoxia on cognitive function. In an ongoing study investigating real-time cognitive function under the effects of normobaric hypoxia while monitoring forehead NIRS, oxygen saturation, cerebral blood flow, and gas exchange, our findings suggest that forehead NIRS is a crucial predictor of cognitive performance (26). Further analysis of cerebral blood flow and other metrics may help uncover the physiological underpinnings behind cognitive degradation during hypoxia.

Limitations

There are several limitations to this study that echo the sentiments expressed by McFarland and others conducting environmental altitude research. The first and key limitation is that a field study offers limited control over circumstances normally easily manipulated in a lab environment. Testing a subject who was sleeping in an extremely cold tent is very different from testing a subject who is well rested and used to their normal routine. Solar chargers and limited use of a hydro-generator were available, but constant supply of power for electronic testing was also an issue that had to be planned around. Battery is quickly depleted in the cold, and laptops and tablets had to be kept in researcher sleeping bags to ensure functionality the next day. The chaotic nature of the environment did not always lend itself to ideal conditions for subject cognitive testing. Compared to conducting a hypobaric chamber study, the lack of control in the field is a limitation, but it also is a more accurate reflection of the reality of the effects of altitude experienced by climbers, operators, and sojourners.

Although there were expected complications during the field testing, there were other limitations in aspects unrelated to field issues. We had limited control over the period of time post-expedition when subjects were tested. The majority of the group was tested approximately one week after return, but some members crept into the two week time period. During the course of the expedition subjects occasionally played the cognitive tests when bored or being competitive. The total time each person spent outside of actual testing did not amount to over twenty minutes, but this could have contributed to an increased learning effect (an aspect of the RCAT we strived to minimize by design, see Appendix

A). This learning effect could account for a portion of the improved scores in the post expedition reporting.

Of importance is the inherent variability in such cognitive tests (see Appendix A Section IV), which, when combined with our small sample size of eight, can also account for some of the difference seen in cognitive performance. To combat this we used the individualized scores represented as a percent of baseline to make comparisons. However the combination of high testing variability and small sample size negatively impacts the statistical power of this study.

CONCLUSIONS:

There are a couple of notable implications of the study. In this small field study of travelers ascending to high altitude, we found no significant change in overall cognitive performance with altitude but a significant relationship between symptoms of AMS and performance in certain cognitive tests. Further investigation with larger sample sizes may reveal additional associations that did not meet our significance criteria in this analysis. Moreover, this research highlighted the need for more investigation into less subjective physiologic metrics that can be associated with perceived metrics of AMS. There is also a strong need for new robust tools that are to quote Harris et al (13) “portable, easy to interpret, rapid, and provide clinically relevant, individualized information.”

Combining metrics such as heart rate variability and oxygen saturation with cognitive performance and self-assessed AMS could help build a more robust field

diagnosis tool for cognitive impairment. This goal is made more realistic by the advancements in mobile monitoring technology in recent years. Furthermore, cognitive tests can more easily be modified or designed for the integrative electronic environment that we are now in (27). Using the knowledge gained from research to improve the accuracy of tests while catering to the interface of mobile devices will be crucial for creating semi-automated in-field assessments of cognition useable by the non-research population.

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AUTHOR CONTRIBUTIONS

Study concept and design (AI, RW, BJ); obtaining funding (AI, BJ); acquisition of the data(AI, BT, DS, BJ); analysis of the data(AI, NH, RW); drafting of the manuscript(AI, NH); critical revision of the manuscript(AI, NH, RW,BT,BJ); and approval of final manuscript(AI,NH,RW,BT,DS, BJ)

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Disclosures: AI RW and BDJ report a patent 14/572,280 pending, and a patent 61/916,940 pending.

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FIGURE LEGENDS

Figure 1: Ascent timeline for the expedition from Kathmandu to base camp and back. Testing days are marked by large squares and trek days by small squares. The post testing was done in the United States after the expedition.

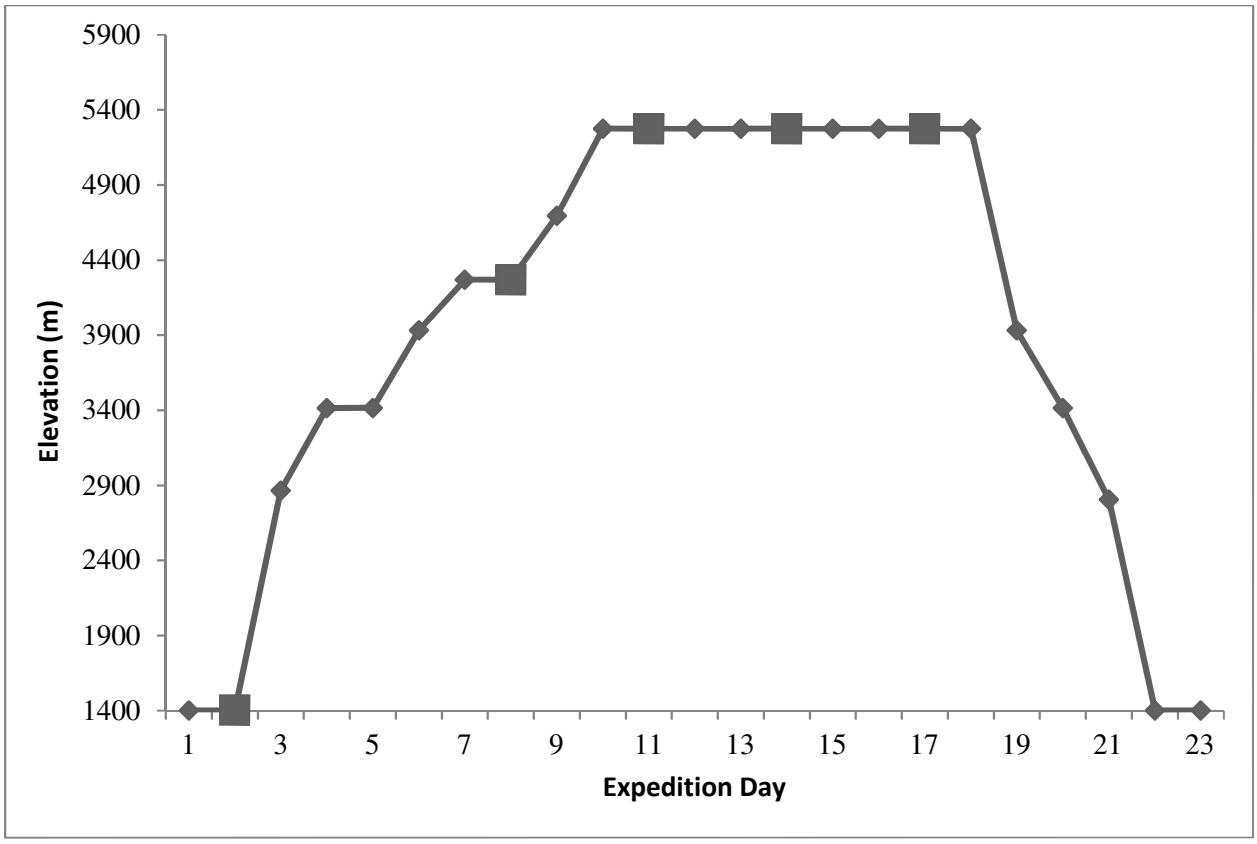
Figure 2: Series of boxplots comparing performance of Stroop, RCAT, and Trials A and B performance at baseline, three Basecamp time points, and post-expedition. The unit of measurement here is the raw score (or time in seconds in the case of the Trials) of each test.

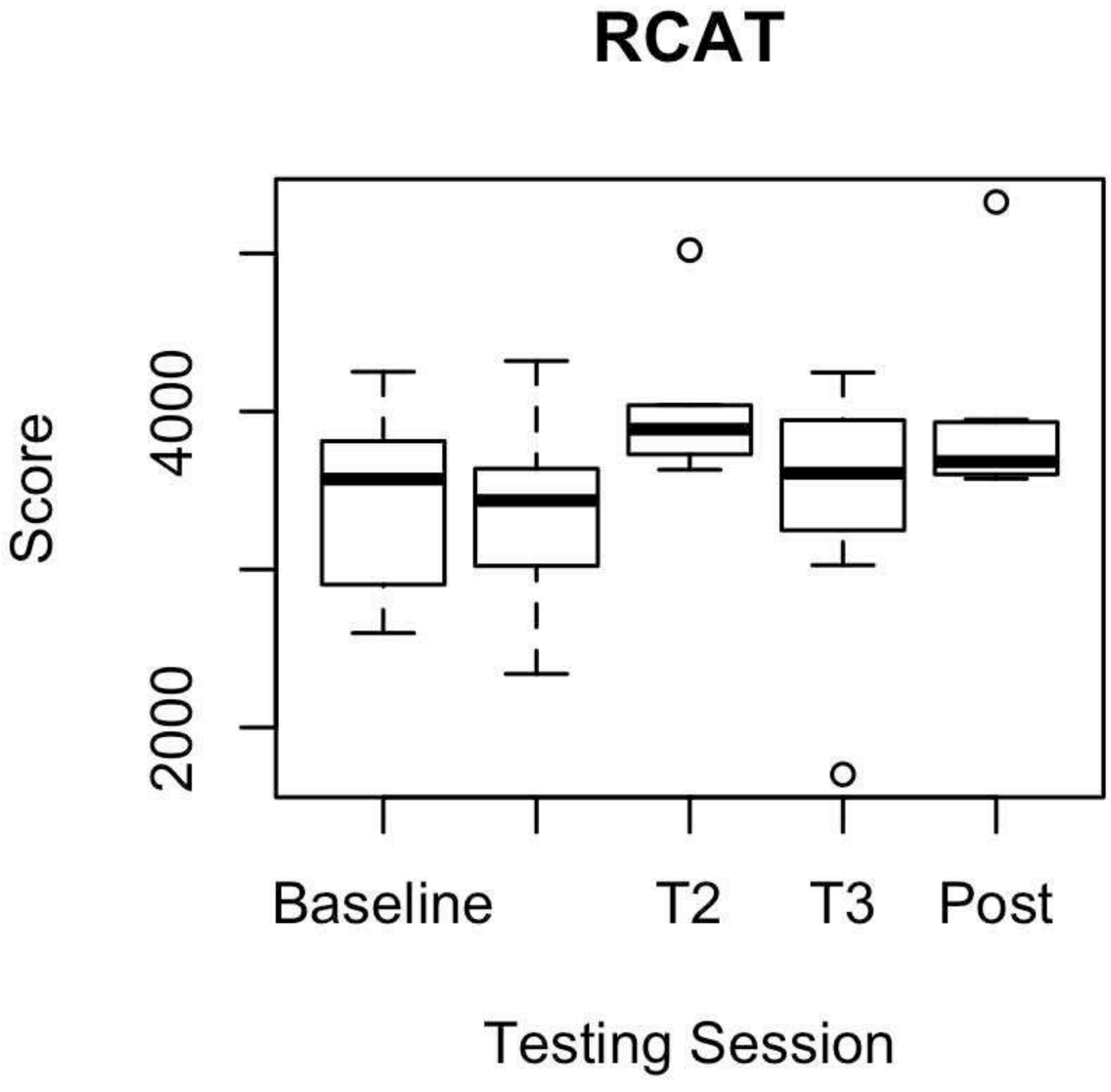
Figure 3: Series of boxplots comparing performance of Stroop, RCAT, and Trials A and B performance at baseline, three Basecamp time points, and post-expedition. The unit of measurement here is the percent change from baseline for each test.

Table 1: Test scores for each testing session shown in mean (standard deviation) format. RCAT and Stroop are represented as raw scores, with Stroop also showing total number of attempts per game. Trial A and Trial B are shown in time taken in seconds.

Table 2: Univariate logistic regression: association (β) of various cognitive metrics with the odds of reported AMS symptom (Quality of Sleep, Headache, and AMS Score). The numbers are the regression coefficients, and they describe the strength of the relationship

between the scores and the log-odds of the outcome. A significant relationship ($p<0.05$) is indicated by *.


5900
5400
4900
4400
3900
3400
2900
2400
1900
1400
Elevation (m)
1
3
5
7
9
11
13
15
17
19
21
23
Expedition Day


RCAT
Score
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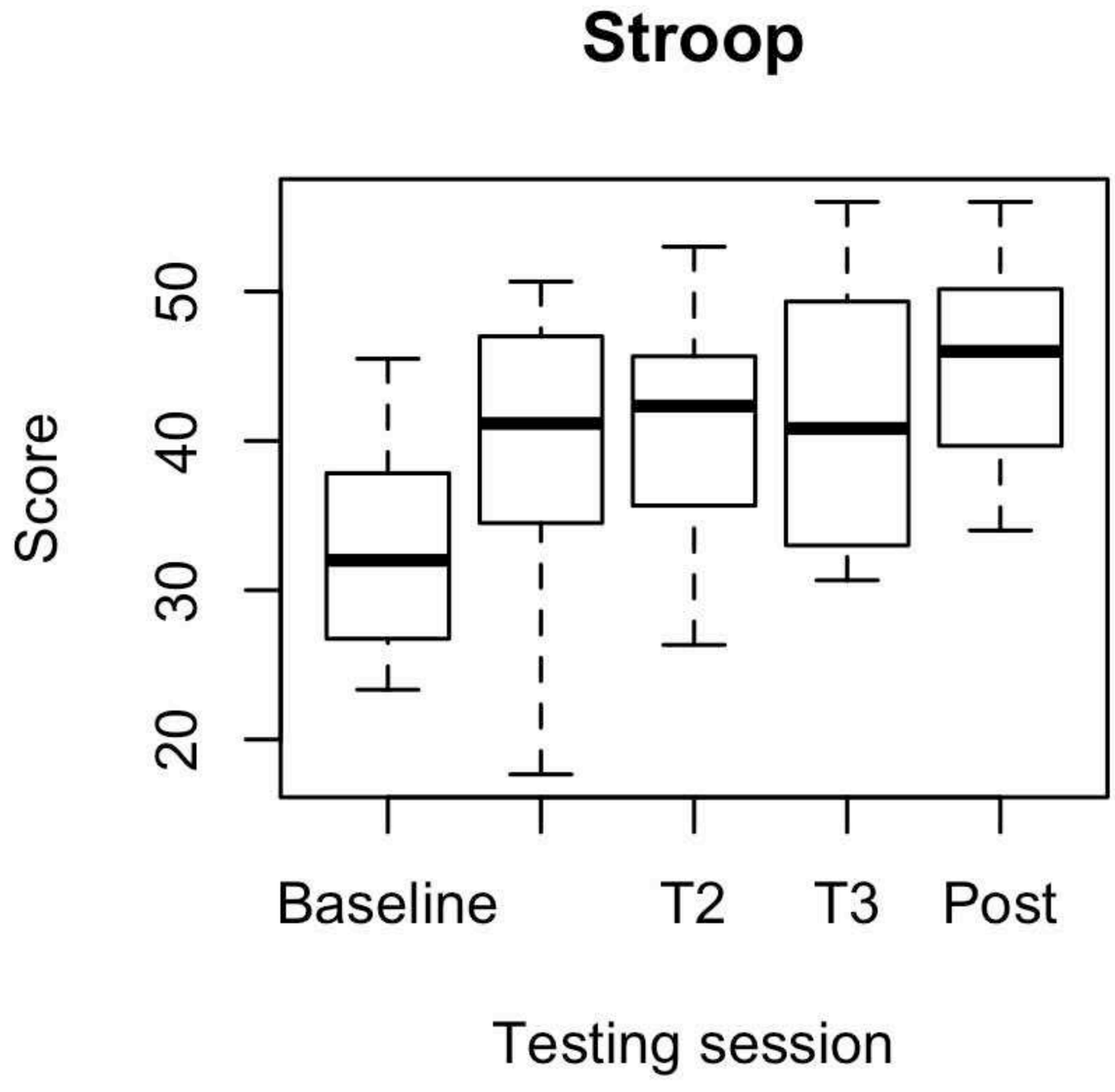
4000
Baseline
T2
T3
Post
Testing Session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Score
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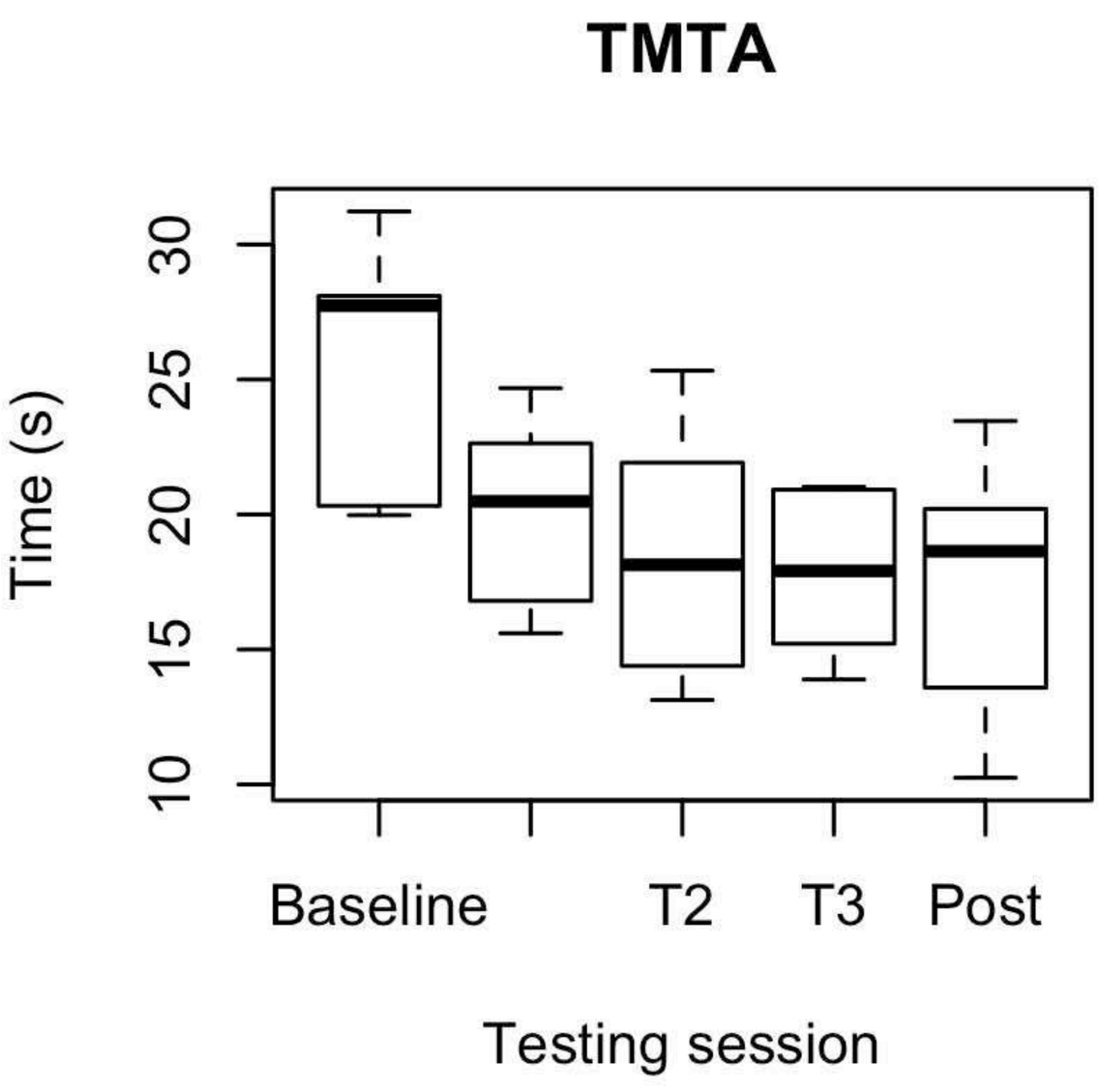
30
40
50
Baseline
T2
T3
Post
Testing session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Time (s)
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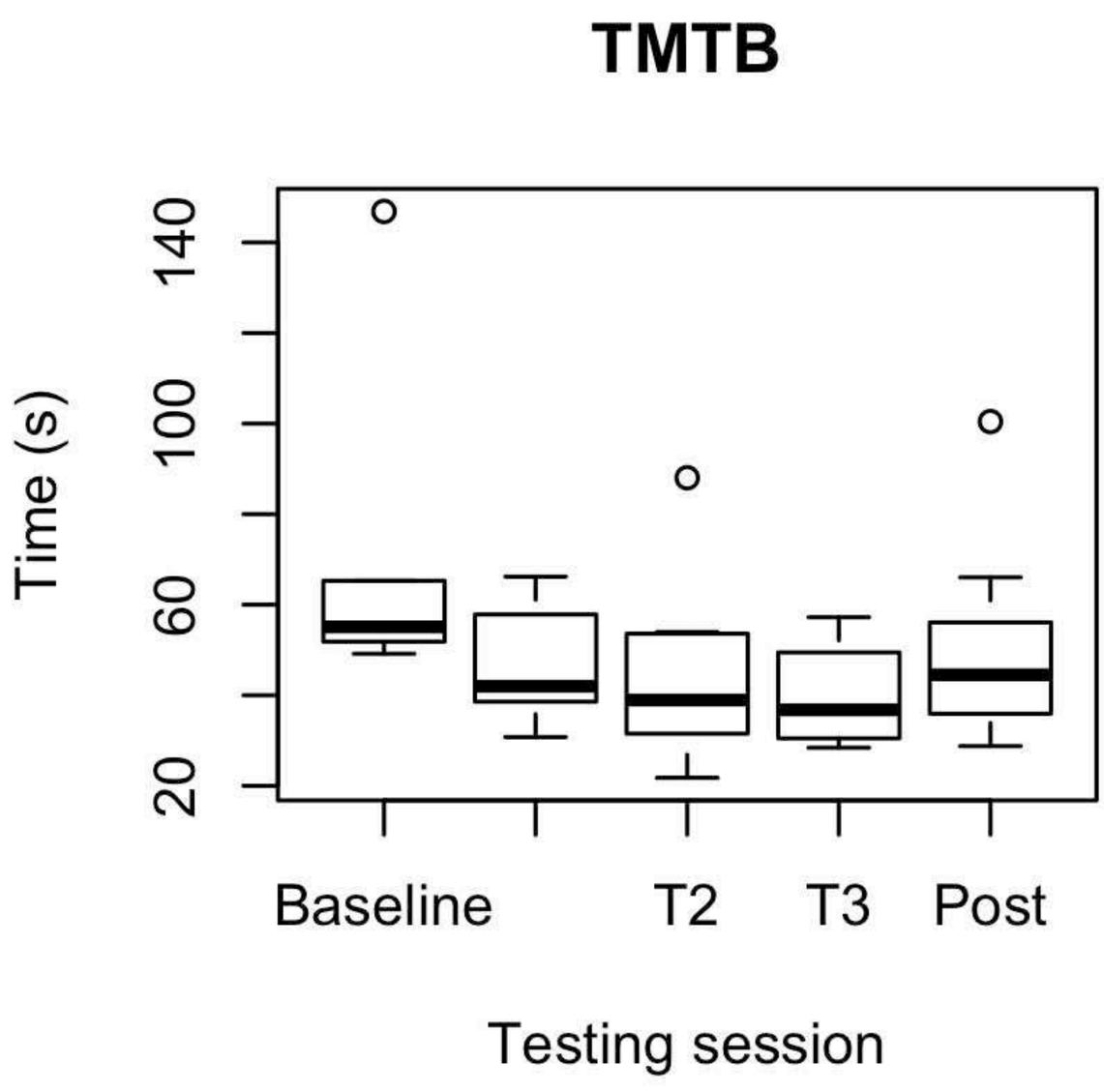
15
20
25
30
Baseline
T2
T3
Post
Testing session


TMTB
Time (s)
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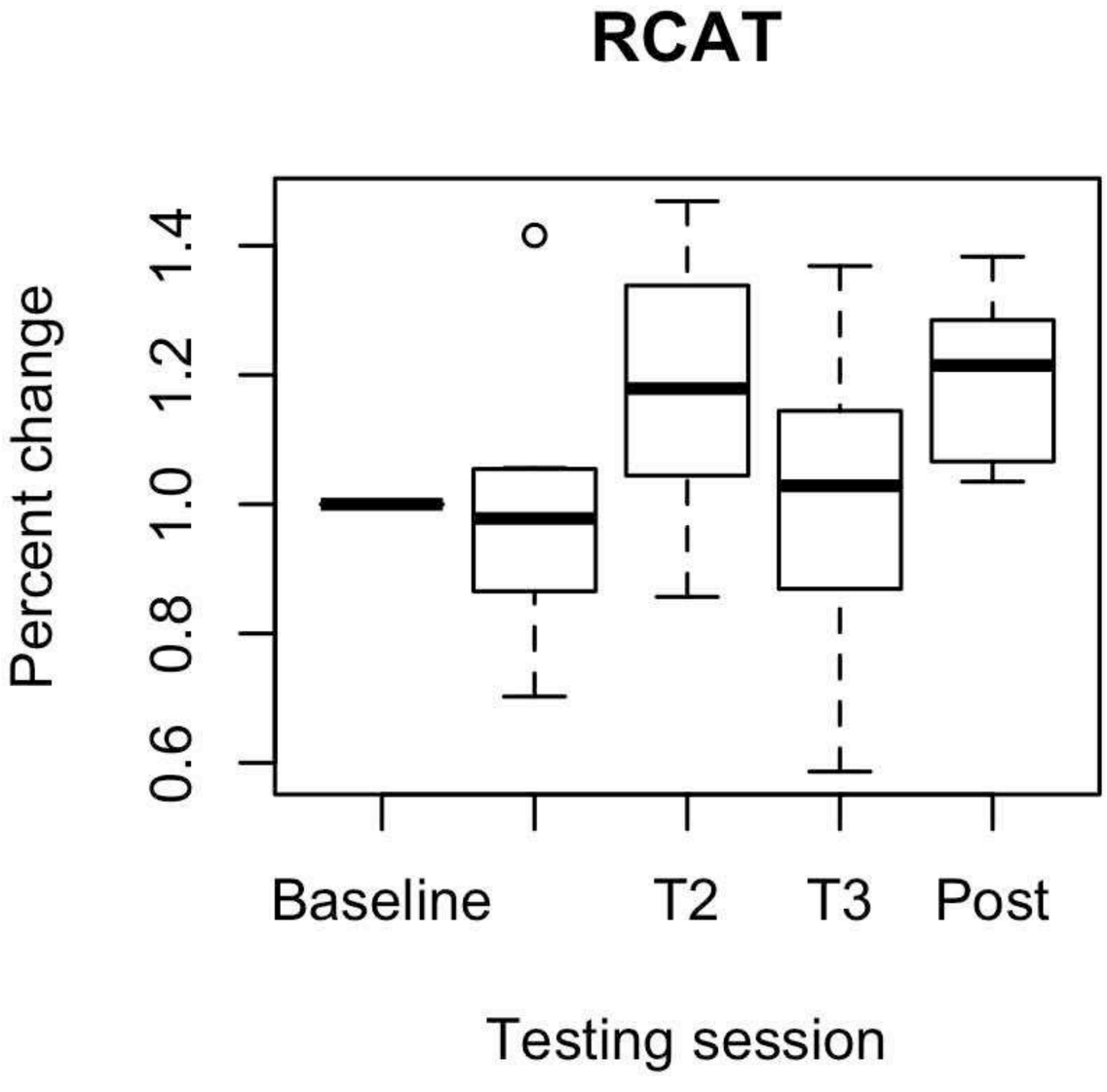
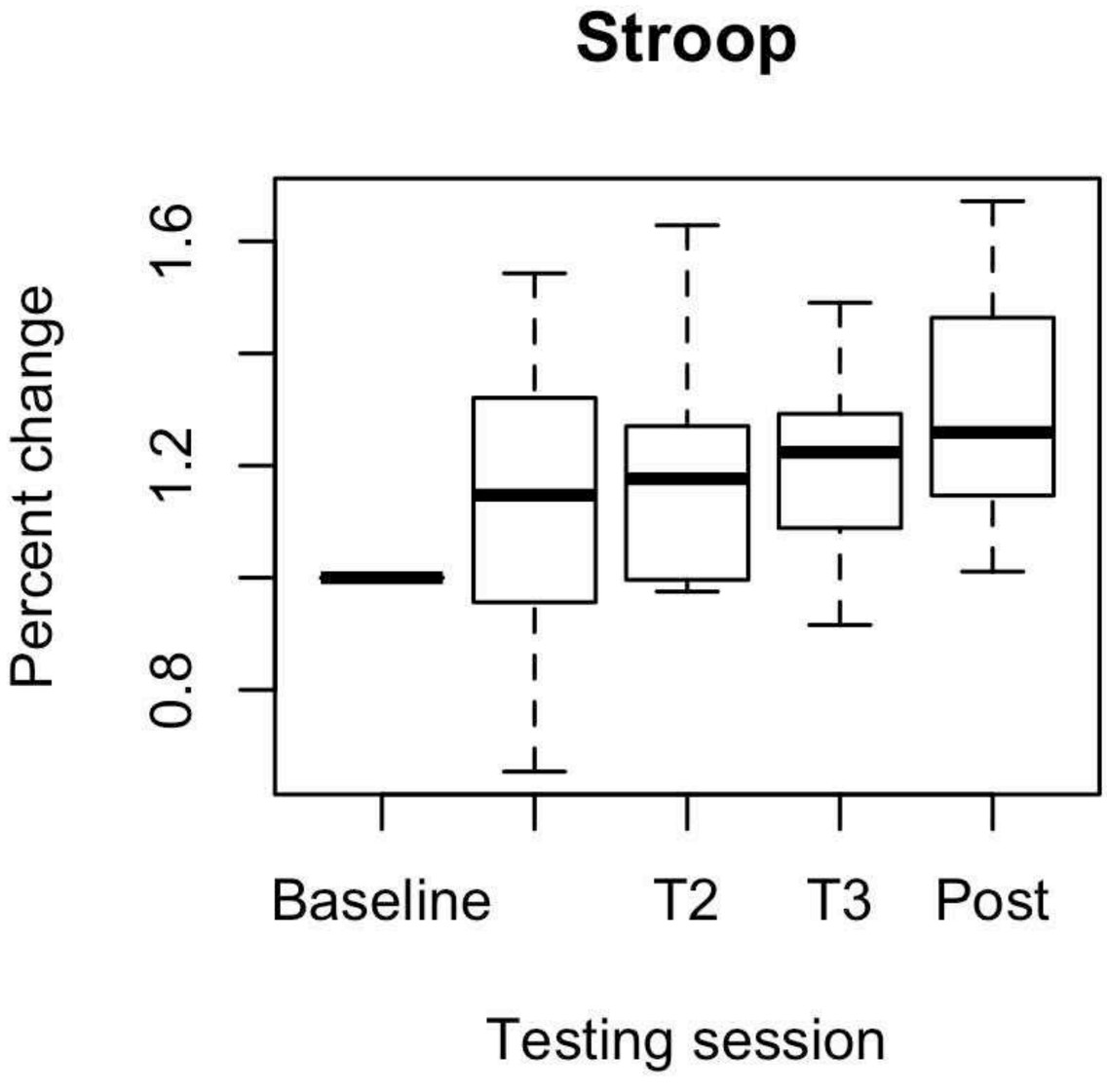
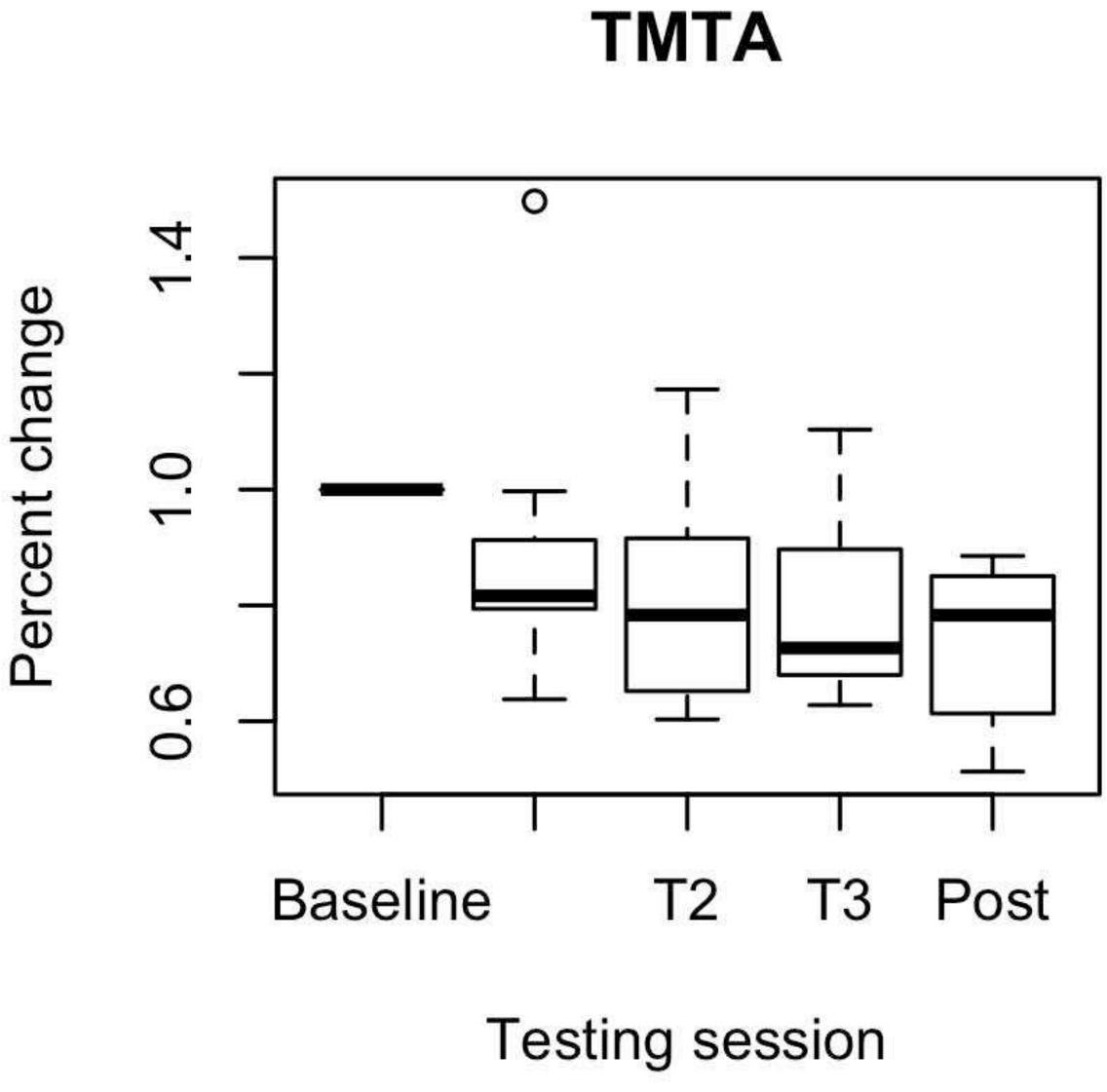
60
100
140
Baseline
T2
T3
Post
Testing session


RCAT
Percent change
0.6
0.8
1.0
1.2
1.4
Baseline
T2
T3
Post
Testing session


Stroop
Percent change
0.8
1.2
1.6
Baseline
T2
T3
Post
Testing session


TMTA
Percent change
0.6
1.0
1.4
Baseline
T2
T3
Post
Testing session

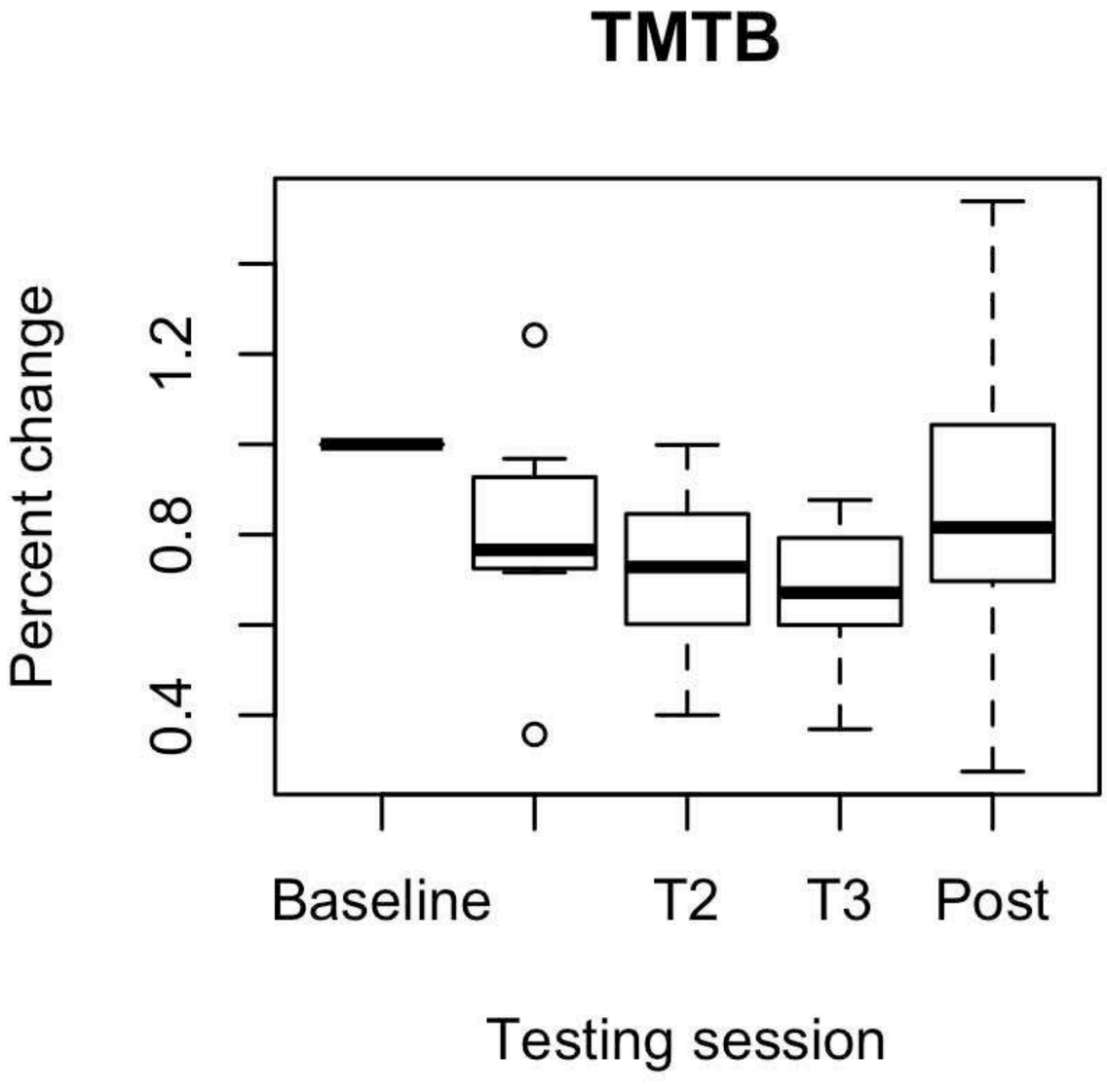

TMTB
Percent change
0.4
0.8
1.2
Baseline
T2
T3
Post
Testing session

Table 1: Test scores for each testing session shown in mean (standard deviation) format. RCAT and Stroop are represented as raw scores, with Stroop also showing total number of attempts per game. Trial A and Trial B are shown in time taken in seconds.

Time Point	Stroop		RCAT	Trail A	Trail B
	Attempts	Score	Score	Time	Time
Baseline	33.52 (7.31)	31.81 (7.99)	3127.78 (948.89)	25.47 (5.05)	73.64 (41.37)
T1	44.54 (10.20)	39.21 (10.72)	3356.50 (584.08)	20.01 (3.31)	46.72 (12.68)
T2	43.17 (8.08)	40.83 (8.38)	3995.52 (443.73)	18.42 (4.46)	44.74 (20.66)
T3	43.87 (9.49)	41.63 (9.41)	3444.38 (794.51)	17.87 (2.96)	39.89 (11.14)
Post	47.05 (8.28)	45.10 (7.69)	3950.15 (625.67)	17.13 (4.82)	51.11 (24.91)

Table 2: Univariate logistic regression: association (β) of various cognitive metrics with the odds of reported AMS symptom (Quality of Sleep, Headache, and AMS Score). The numbers are the regression coefficients, and they describe the strength of the relationship between the scores and the log-odds of the outcome. A significant relationship ($p<0.05$) is indicated by *.

AMS	Stroop		RCAT	Trail A	Trail B
Symptoms	Attempts	Score	Score	Time	Time
AMS Score	-5.637*	-5.269*	-1.281	3.075	1.090
Headache	-3.289	-3.702	-3.062	1.589	-0.527
Sleep	0.712	-0.572	-0.504	1.461	-1.136