AltitudeOmics: Decreased reaction time after high altitude cognitive testing is a sensitive metric of hypoxic impairment

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Humans experiencing hypoxic conditions exhibit multiple signs of cognitive impairment, and high altitude expeditions may be undermined by abrupt degradation in mental performance. Therefore, the development of psychometric tools to quickly and accurately assess cognitive impairment is of great importance in aiding medical decision-making in the field, particularly in situations where symptoms may not be readily recognized. The present study used the Defense Automated Neurobehavioral Assessment (DANA), a ruggedized and portable neurocognitive assessment tool, to examine cognitive function in healthy human volunteers at sea level, immediately after ascending to an elevation over 5000 m, and following 16 days of acclimatization to this high altitude. The DANA battery begins with a simple reaction time test (SRT1) which is followed by a 20-min series of complex cognitive tests and ends with a second test of simple reaction time (SRT2). Tabulating the performance scores from these two tests allows the calculation of an SRT change score (dSRT=SRT1–SRT2) that reflects the potential effect of mental effort spent during the 20-min testing session. We found that dSRT, but not direct SRT in comparison to sea-level baseline performance, is highly sensitive to acute altitude-related performance deficits and the remission of impairment following successful acclimatization. Our results suggest that dSRT is a potentially useful analytical method to enhance the sensitivity of neurocognitive assessment. *NeuroReport* 25:814–818 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Introduction

The partial pressure of oxygen reduces exponentially with increasing altitude and leads to hypoxia, an underlying cause of cognitive and physiological impairment at high altitude. In general, the severity of impairment is a function of both altitude and the rate of ascent, where moderate altitudes (< 2000 m) and slow elevation gains induce little decrement compared with extreme altitudes (> 6000 m) and rapid ascension, which have more severe effects and can result in loss of consciousness or death [1].

Rapid ascent to high altitude results in a number of impairments in cognitive performance (see [2] for review), although it should be noted that fatigue and other travel-related factors must be accounted for before attributing impairment to hypoxia alone [3]. Impairments due to hypoxia have been observed in short-term memory [4], long-term memory and verbal expression [5], attention [6,7], and reaction time [8,9]. Because of the potential impact of these impairments upon high altitude expeditions, the develop-ment of field-deployable tools to aid the assessment of hypoxia-induced cognitive impairment is highly relevant to medical decision-making in these scenarios.

In this report, we analyzed an unexamined feature of the neurocognitive data collected from healthy human volunteers on an expedition to Mt Chacaltaya in Bolivia [10]. Cognitive performance was assessed in this study using the Defense Automated Neurobehavioral Assessment (DANA), a software package of public domain cognitive tests that runs on the Android platform. DANA was originally developed as a means of rapidly assessing cognitive changes following mild traumatic brain injury/concussion in deployed service members exposed to blasts, and its reliability has been previously validated in a number of extreme environments [11]. The DANA test battery includes two administrations of a simple reaction time (SRT) task: one at the beginning and one at the end of the ~20-min test session. To investigate the hypothesis that the second measurement of reaction time might reveal an effect of mental fatigue on cognitive performance, we tabulated a dSRT score to compare throughput, a measure of cognitive efficiency, between the two reaction time administrations. Here we show that performance decreases across DANA testing as a function of acute exposure to hypoxic conditions, an

altitude-related decrement that resolves following successful physiological acclimatization to high altitude.

Methods

Volunteer subjects

As part of the AltitudeOmics study on the physiological signatures of altitude acclimatization [10], DANA was administered to a group of volunteers at sea level (SL) and at 5260 m atop Mt Chacaltaya near La Paz, Bolivia. The study was performed according to the Declaration of Helsinki and was approved by the Institutional Review Boards of the University of Colorado and the University of Oregon, as well as the Human Research Protection Office of the US Department of Defense. The detailed methods for the overall study are summarized here and described elsewhere [10]. Before giving written and verbal consent to participate, each volunteer was informed of the possible risk and discomforts involved in the study. From a pool of 79 volunteers, a total of 24 were recruited under strict criteria including birth at a low elevation (< 1500 m), physical fitness, and general health characteristics (not pregnant or lactating, no prescription drug use, and no history of migraine, loss of consciousness, smoking, cardiovascular abnormality, or pulmonary dysfunction). Of the recruited participants, three dropped out of the study because of medical reasons apart from altitude sickness (e.g. gastrointestinal illness), resulting in a total of 21 participants (12 male, nine female; mean age 20.8 years, range 19–23 years). The constraints of the study, including strict inclusion/exclusion criteria, travel costs, and subject travel availability, produced a small and relatively homogenous sample.

The experiment proceeded according to the following timeline: first, the participants underwent baseline testing at SL (Eugene, Oregon, USA) ~1 month before traveling to Bolivia. After an overnight flight to El Alto (4050 m), the participants immediately descended to Corocio (1525 m) where they rested for 48 h to limit the effects of jet lag. Next, pairs of participants were driven to the top of Mt Chacaltaya (5260 m) over a period of 3 h. During the drive, supplemental oxygen was provided to each participant through either a mask or a nasal cannula (2 l/min) to allow an assessment of acute change upon reaching the destination altitude. After the ascent, one member of each pair immediately began testing, whereas the other continued to breathe supplemental oxygen for 2 h until his/her turn for testing. The assessment was repeated after 16 days of acclimatization at 5260 m, which included descents to La Paz (3800 m) over the first 4 days. A final round of sea-level (SL) testing was conducted ~3 months after returning from Bolivia to collect data from participants who missed the initial SL testing.

DANA administration

The DANA test battery includes the following tests: SRT1, code substitution (simultaneous), procedural reaction time, spatial discrimination, go/no-go, code substitution (delayed), match to sample, and Sternberg memory search. The ~20-min test battery ended with a second administration of simple reaction time (SRT2) according to methodology introduced by Bleiberg *et al.* [12]. The test battery was administered on a Trimble Nomad handheld computer (Android version 2.1; Trimble, Sunnyvale, California, USA). Performance in the tests administered between SRT1 and SRT2 was analyzed elsewhere [10]; for the present purposes, the intervening test battery between the two SRT administrations may be thought of as providing a cognitive challenge to the participant, which we hypothesized to have a negligible effect upon SRT2 under normal conditions.

Each SRT administration consisted of 40 trials with a random intertrial interval (600–3000 ms). Each trial began when a yellow target appeared on a black screen. The participant was instructed to tap the target as soon as it appeared and was asked to perform the task as quickly and accurately as possible. The participants completed four practice trials with feedback before commencing the portion of the test from which data were collected.

Data analysis

Throughput was calculated as follows for each SRT administration per participant:

$$\text{Throughput} = \frac{\text{Correct trials}(\%)}{\text{Correct trial median reaction time (ms)}} \times 60000\left(\frac{\text{ms}}{\text{min}}\right)$$

If the percentage of incorrect trials (i.e. failing to respond within 900 ms or responding in anticipation of the cue) exceeded 33% for any SRT administration, whether because of suboptimal effort, illness, or sleep deprivation, the participant was excluded from the analysis ($n = 2$). A two-way, repeated measures analysis of variance was used to analyze global effects on throughput. Pairwise comparisons were examined using Bonferroni-corrected paired *t*-tests (significance at $P < 0.05/4 = 0.0125$), and effect sizes were calculated with Cohen's *d*. Because the average throughput from the two SL administrations was not significantly different (unpaired *t*-test, $P = 0.51$), the second administration was used for the baseline comparison as it included complete datasets from all of the participants. All analyses were carried out using MATLAB R2013b (Mathworks, Natick, Massachusetts, USA).

Results

Participant performance in a simple reaction time test was assessed at the beginning (SRT1) and end (SRT2) of a 20-min DANA testing session at SL, following an ascent to 5260 m (ALT1), and after 16 days of acclimatization to this altitude (ALT16; Fig. 1). A two-way, repeated measures analysis of variance with the factors altitude (SL, ALT1, or ALT16) and administration (SRT1 or SRT2) revealed significant main effects of altitude ($F = 15.96$, $P < 0.0001$)

Fig. 1
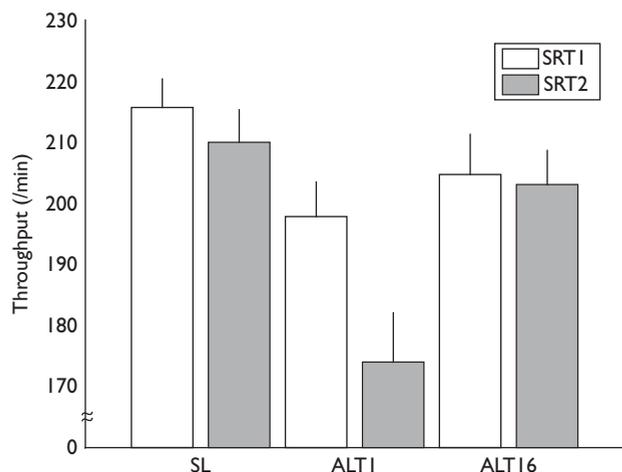
Throughput in a simple reaction time (SRT) task as a measure of cognitive performance during acute altitude exposure, after acclimatization, and at sea level (SL). SRT was administered before (SRT1) and after (SRT2) cognitive loading with DANA testing. Following acute altitude exposure (ALT1), both SRT1 and SRT2 performance decreased, with a particular decrement in the second administration. Following two weeks of acclimatization (ALT16), performance in the SRT task approximated sea level (SL) scores. Error bars represent SE from the mean. DANA, Defense Automated Neurobehavioral Assessment.

Fig. 2
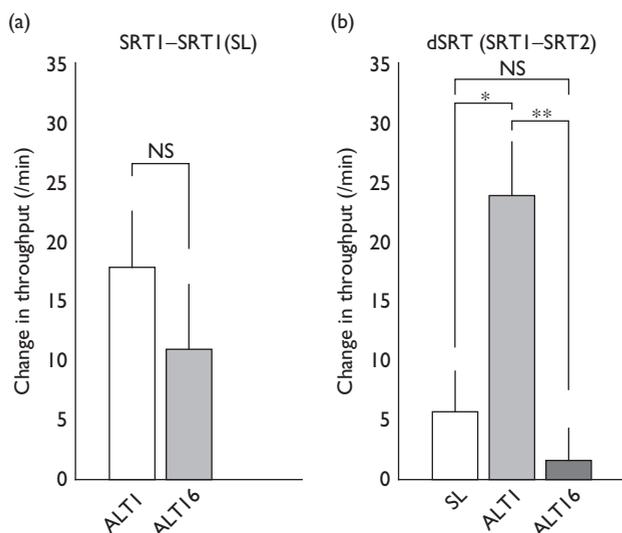
Quantification of altitude and exertion-related performance changes. (a) Simple reaction time (SRT) performance during acute altitude exposure (ALT1) and following two weeks of acclimatization (ALT16) was compared with sea-level (SL) performance. There was no significant difference between ALT1 and ALT16 when compared with SL throughput. (b) Change in SRT performance across DANA testing was compared for each time point. A marked decrease in throughput was observed at ALT1, whereas ALT16 showed an indistinguishable difference from SL. *$P < 0.005$, **$P < 0.001$. DANA, Defense Automated Neurobehavioral Assessment.

and administration ($F = 22.02$, $P < 0.0005$), as well as a significant interaction of these terms ($F = 11.37$, $P < 0.0005$) upon SRT throughput.

Post-hoc testing detected no difference between SRT1 and SRT2 throughput at SL ($P = 0.43$). This finding was corroborated by additional analysis of a previously collected dataset [11], in which a similar, ~15-min version of DANA was administered to groups of healthy volunteers in a variety of extreme climates (desert, jungle, aboard a ship, and at high altitude postacclimatization). Paired t-tests comparing throughput in SRT1 versus SRT2 failed to reach significance in any of these climates (all P's > 0.05), supporting the conclusion that the intervening tests in the DANA battery do not adversely impact SRT performance in healthy humans under these conditions.

To quantify the apparent altitude-induced impairment in reaction time, we first examined SRT performance by comparing against baseline values, a method favored by many neurocognitive assessment protocols [13,14]. Each participant's SL 'baseline' SRT1 throughput was subtracted from the SRT1 throughput values at ALT1 and ALT16. On average, participants showed a throughput decrease of 17.85 ± 4.71/min (mean $\pm$ SE) at ALT1 and 10.97 ± 5.45/min at ALT16 compared with SL baseline. A paired t-test revealed that this baseline comparison measure failed to show a significant difference between ALT1 and ALT16 ($P = 0.24$; Fig. 2a).

A second comparison, dSRT, was calculated as the difference in each participant's SRT1 and SRT2 throughput scores at each time point (SL, ALT1, and ALT16). These comparisons revealed that SRT2 throughput decreased at the end of DANA testing by an average of 23.87 ± 4.52/min at ALT1, 1.63 ± 2.71/min at ALT16, and 5.71 ± 3.42/min at SL, showing a significant difference between ALT1 and ALT16 ($P < 0.001$) and between ALT1 and SL ($P < 0.005$; Fig. 2b). In addition, the dSRT comparisons produced much larger effect sizes than the baseline comparison (dSRT ALT1 vs. ALT16 $d = 0.95$, ALT1 vs. SL $d = 0.75$; baseline $d = 0.28$).

Discussion
In accordance with previously collected evidence from healthy human volunteers [11], no difference was detected between SRT1 and SRT2 throughput at SL. These results support the hypothesis that DANA testing does not induce sufficient cognitive loading to alter psychomotor performance in healthy participants under normal inspired oxygen and barometric pressure. However, a comparison of performance in the two SRT administrations unmasked a robust altitude-dependent effect of cognitive exertion upon psychomotor efficiency. The difference score dSRT (SRT1 throughput − SRT2 throughput) shows a significant relationship with acute altitude exposure: a marked decrease in throughput

following cognitive testing emerges after ascent from SL. However, following 16 days of acclimatization to high altitude, throughput scores resemble those seen at SL: SRT1 and SRT2 performances are indistinguishable. These results are in agreement with complementary physiological and cognitive data that were simultaneously collected from the same participants [10]. In contrast, the baseline comparison measure failed to show a significant difference between ALT1 and ALT16. These results indicate that in this context, comparison against baseline was not sensitive to the cognitive effects of acute hypoxia and subsequent acclimatization. Further, the dSRT comparison produced a much larger effect size than the baseline comparison, indicating that dSRT is a robust metric by which cognitive impairment may be quantitatively assessed.

A similar post-testing decrease in reaction time was reported by Bleiberg *et al.* [15] in a study on fatigue in postpolio patients. In this study, an Automated Neuropsychological Assessment Metrics (ANAM) battery [12] was used with a configuration similar to DANA: an SRT task was presented both at the beginning and at the end of a battery of more complex cognitive tests. The participants began the morning with a complete ANAM battery, underwent a 1-h comprehensive functional medical evaluation including motor testing and other fatiguing activities, and then completed a second round of the ANAM battery. Although less than a quarter of the postpolio participants showed a decrement in SRT1, over 50% showed decreased performance in SRT2, a difference which was highly statistically significant. Together with the present results, these data indicate that performance in an SRT task after cognitive loading may be a highly sensitive means for observing cognitive impairment. However, the parameters (e.g. length, difficulty, repetition, etc.) of the testing battery that are responsible for the observed results are yet to be identified. It could be the case that a more condensed assessment may be sufficient to reveal cognitive impairment; alternatively, greater sensitivity to impairment may be achievable using an optimized test battery.

Although the observed decrement in SRT performance upon acute hypoxia exposure could be interpreted as motor fatigue rather than cognitive impairment *per se*, we note that several of the other reaction time tasks interleaved within the test battery did not show a significant difference between SL and ALT1 [10]. Taken together, these results indicate that decreased motor output alone cannot explain the change in performance; however, more research is required to investigate the complex interaction of cognitive and motor processing under these conditions.

Conclusion
Comparing SRT performance at the beginning and end of a DANA test battery provides a more robust and reliable indication of hypoxia-induced cognitive impairment

than the typically used comparison against baseline performance. Because SRT throughput does not decrease across testing under normal conditions, these results suggest that calculating the dSRT score is a promising analytical method that may aid neurocognitive assessment in situations where appropriate baseline data are not available.

Conflicts of interest
Emma B. Roach, Corinna E. Lathan, and Lawrence Wolpert are employed by AnthroTronix Incorporated, developer of the DANA tool.

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