Biomarker and Biometric Indices of Cognitive Decrements due to Physical Exhaustion

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Abstract. State of the art sensors and diagnostic tools are continuously being researched, tested, and procured for every piece of high tech equipment in the Air Force while the most critical asset, the Airman, lacks diagnostics to analyze physiological well being and cognitive performance. Eighteen active duty Air Force males completed a physical exhaustion task on a treadmill while performing two cognitive tasks and while having various biometrics and biomarkers collected. We found that while physiological variables exhibited reliable indices of physical exertion, biological changes were found to be more related to cognitive changes.

Keywords: Biomarkers, Physical Exhaustion, Cognitive Performance, Biometrics.

1 Introduction

Sensors and diagnostic tools are continuously being researched, tested, and procured for every piece of high tech equipment in the Air Force while the most critical asset, the Airman, lacks diagnostics to analyze physiological well being and cognitive performance. Heat stress, hydration levels, and cognition are largely self-assessed or visually assessed by a fellow Airman without any quantitative metric. Froom, Caine, Shochat, & Ribak [1] reviewed 500 helicopter accidents and found that high ambient temperatures were related to helicopter accidents due to human error with the highest risk occurring at 35ºC or more. This finding motivated studies to identify the physiological and cognitive effects of heat stress. One way to induce heat stress is through a

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physical exhaustion profile. This specifically applies to the military population due to the amount of load they carry during combat fighting, approach marches, and emergency procedures that require a high level of physical activity. Some of the physiological effects of heat stress due to physical exhaustion coupled with protective clothing include changes in heart rate, oxygen consumption, and increased core temperature [2]. The objective of the present study is to identify biometrics and biomarkers that exhibit changes in physical or mental ability during a physical exhaustion profile to provide a predictive monitoring tool for intervention.

Simple stimulus and response cognitive tasks do not appear to be affected by physical exhaustion [3]. However, more complex cognitive tasks have been shown to deteriorate due to physical exertion including arithmetic, short-term memory, long-term memory, attention, and visual information processing [3; 4; 5; 2]. A more consistent finding is that cognitive performance during physical exertion shows an inverted-U trend with performance improving as arousal increases, but returning to baseline or deteriorating toward the end of a physical exhaustion profile [6]. A summary of studies reveal improved performance when mental performance is assessed during physical profiles of moderate durations, while post assessments of mental ability of moderate durations show "no effect," or deterioration, supporting the inverted-U possibility [7].

A large body of research has identified physiological and biomarker relationships to resilience of physical exertion or "physiological toughness." Toughness is defined as a distinct reaction pattern to stress, mental or physical, that characterizes animals and humans who cope effectively [8]. The process, as reported by Miller [9] is that

"the sympathetic nervous system-adrenal medulla system springs into action quickly and efficiently, while the pituitary-adrenal cortex systems remains relatively stable. As soon as the emergency is over, the adrenaline response abates quickly to baseline, while the cortisol response remains low. It is thus the smoothness and efficiency of the physiological arousal pattern that characterizes the toughness response." [8].

Human studies have supported Dienstbier's "Physiological Toughness" model. Urinary adrenaline and noradrenaline spikes have been shown to predict performance on a 2-hour radar screen monitoring task [10]. Norwegian Army paratroopers who exhibited greater catecholamine spikes also demonstrated better performance on a jump task [11]. The speed of catecholamine decline back to baseline levels is also a significant predictor of performance [12]. Finally, high baseline catecholamine levels (as indicative of high chronic base rates) have been shown to predict poorer psychological judgment and more health problems [13; 14].

Prolonged exercise may yield other biological and physiological predictors of performance during physical exhaustion. Meeusen, Watson, Hasegawa, Roelands, & Piacentini [15] explain that prolonged exercise influences the metabolism of monomines (e.g., serotonin, dopamine). In particular, the increased brain serotonergic activity may augment lethargy and loss of drive, resulting in a reduction of motor unit recruitment [16]. Studies in both rats and humans provide valid evidence that brain 5-HT (serotonin) activity increases during prolonged exercise and that this response is associated with fatigue [17] and loss in performance [18].

The neuropeptide orexin-A was examined as a possible predictor of performance deficits due to a loss of alertness due to physical exhaustion. Orexin-A has been shown to produce arousal, increased attention, increased muscle tone, and to counter the effects of narcolepsy [19]. While changes in supplemented orexin-A levels have only been found to influence mental performance during sleep deprivation [19], naturally produced levels of orexin A were investigated as an exploratory biomarker. It was hypothesized that orexin-A levels would fluctuate along with changes in performance on the Psychomotor Vigilance Task.

2 Methods

Seventeen active-duty males with a median age of 29 participated in this research. This study was approved by the 711 Human Performance Wing Institutional Review Board. All participants provided informed consent prior to study inclusion. All participants attended 4 sessions. Days 1 and 2 were training days and took no longer than one hour. Day 3 (one hour) was a baseline testing day that included a baseline blood draw, a final cognitive training, the Maximal Oxygen Uptake Test, and a test version of the cognitive test. Day 4 (approximately 2 hours) was centered on a modified-Astrand Treadmill protocol designed to induce physical exhaustion. During this treadmill protocol, blood draws were taken, lactate was collected, the cognitive test

Table 1. Detailed procedures for the experimental testing session

Day 4 Procedures
Dexa Scan
Physiological Monitoring Attachment
Subjective Affect Baseline
IV Placement/Blood Draw (BD2)
PVT
Lactate Sample
Treadmill Protocol 0-3 Min T1 (Physio/Cognitive) 9-12 Min T2 (Physio/Cognitive) 18-21 Min T3 (Physio/Cognitive) 27-30 Min T4 (Physio/Cognitive) Exhaustion Final (Physio/Cognitive)
Lactate Sample
Post Blood Draw (BD3)
PVT
10 Min Recovery Blood Draw (BD4)
Physiological Monitoring Detachment

was administered, and a physiological monitoring device was worn for continuous assessment. A 50lb weighted vest was worn to simulate the carry-load experienced by ground troops and first responders. The night prior to Day 4, all participants were required to wear an activity watch to ensure at least 6 hours of rest. All four days were completed within 2 weeks. The details of the procedures for Day 4 are shown below followed by even greater detail of the modified-Astrand Treadmill protocol. The remainder of this paper will discuss the experimental details, procedures, and results for Day 4 only.

Table 2. The implemented modified-Astrand treadmill protocol

Stage	Speed (MPH)	Grade (% Incline)	Interval Time (Min)	Time (Min)	Test
1	3.2	0	3	3	NovaScan (T1)
2	3.2	6	2	5	
3	3.2	10	2	7	
4	3.2	10	2	9	
5	3.2	2	3	12	NovaScan (T2)
6	3.2	8	2	14	
7	3.2	10	2	16	
8	3.2	10	2	18	
9	3.2	2	3	21	NovaScan (T3)
10	3.2	10	2	23	
11	3.2	8	2	25	
12	3.2	12	2	27	
13	3.2	2	3	30	NovaScan (T4)
14	3.2	10	2	32	
15	3.2	12	2	34	
16	3.2	14	2	36	
17	3.2	16	2	38	
18	3.2	18	2	40	
19	3.2	20	2	42	
20	3.2	exhaustion			
21	3.2	2	3	45	NovaScan Final

Wrist Activity Monitors: Wrist monitors (Ambulatory Monitoring, Inc) were used to track sleep/activity rhythms in a relatively unobtrusive fashion. The wrist monitors (which are battery-powered devices about the size of a wrist watch) were used to ensure that subjects obtained adequate sleep prior to the time at which they report to the laboratory for testing. Subjects were required to wear the monitor beginning at 6:00pm and to continue wearing the monitor until the subject arrived at the laboratory for testing. They were required to get at least 6 hours of continuous rest.

DEXA: Subjects' body fat composition percentages were estimated by employing a technique known as Duel Energy X-Ray Analysis (DEXA). DEXA scanning is a low-dose whole-body x-ray used to precisely measure body composition (bone, muscle, and fat). Subjects wear athletic clothing, and lie on a table while a scanner arm passes over them from head to toe for approximately five minutes.

Subjective Affect: Subjective affect was measured via the Visual Analog Scale (VAS) [20]. The VAS requires that participants indicate the points on different lines that correspond to how he/she feels along the specified affect continuum at the time at which the test is taken. The adjectives included in the VAS are as follows: Alert, Anxious, Irritable, Energized, Confident, Jittery, Sleepy, and Talkative. The VAS was verbally administered following each NovaScan test.

Physiological Metrics: The BioHarness™ (Zephyr) was implemented to non-invasively monitor and collect selected physiological data associated with the autonomic nervous system activity. The basic unit consists of a belt that includes imbedded fabric sensors/electrodes for monitoring ECG and calculating heart rate and heart rate variability, respiration rate, and chest skin temperature.

Modified Astrand Treadmill Running Protocol (shown in Table 2): Subjects began at a slow running speed of 3.2 mph with a 0% grade for 3 minutes. There are 24 stages and each stage lasts 2-3 minutes. Speeds remained constant as the incline increased to a grade that ranged between 2% and 16%. The cognitive test was administered at the first 0% grade portion as well as each 2% grade. The cognitive testing portions lasted 3 minutes and included the subjective affect scale. The task was presented in front of the participants on a 21" screen. A wireless mouse was attached to the front right area of the treadmill display (left if left handed).

NovaScanTM: This test represents a special adaptation of the "multi-tasking" approach. The NTI ATS™ implementation of NovaScan uses two of the individual tests further described below (Manikin; [21] and Continuous Memory; [22]). In each, a task (e.g., Manikin) appears on the screen and the subject must perform the task for some period of time. At irregular intervals, this task is replaced by another task (e.g., Continuous Memory), and the subject must process this for some period of time. When that task is again replaced with the first (Manikin) task, the subject must remember the demands of the second task (Continuous Memory) while again performing the first. This alternation continues for some defined period of time or number of presentations. In addition to these demands, the subject must monitor a dial in which the pointer is moving at a constant rate, but in an inconsistent manner (the Dial Task). The subject must detect when the dial has gone into a "danger" zone. To do this, the subject must establish a scan rate for the dial that optimizes the opportunity to detect a danger indication, while allowing time to optimally process the other tests. This paradigm therefore approximates complex real-world tasks where two or more basic cognitive or psychomotor requirements must be attended to, and an optimal multiplexing strategy must be adopted based on current experience. The Manikin is a spatial orientation task and the Continuous Memory test is a test of working memory. The accuracy metric is comprised of the total number correct for both tasks divided into the total number of trials. The reaction time metric represents a total reaction time for correct responses divided by the total number of correct trials.

The Psychomotor Vigilance Task (PVT): The PVT [23] measures how well one can focus attention and respond to a cue given at different times on a screen. A hand-held device displays numbers counted up by milliseconds in a window. The numbers are presented for up to 1 minute during which subjects are to respond by pressing a

button. This test lasted 10 minutes and was administered prior to the Maximal Treadmill Protocol and immediately following the Maximal Treadmill Protocol.

Blood Sampling: All blood samples taken during the experimental session (Session 4) were collected via a peripheral intravenous (IV) cannula placed on an accessible forearm or antecubital vein by a certified medical technician, using standard antiseptic procedures and BD vacutainers. For each sample, five ml of blood was collected into a serum separator tube (SST) and allowed to clot for 30 min at room temperature. Tubes were centrifuged 10 min at 1000 x g. Serum was removed, separated into 200 µl aliquots, and stored at -80 degrees C. Blood biomarkers of interest include brain derived neurotrophic factor (BDNF), orexin A, serotonin, adrenaline, and noradrenaline.

Capillary Blood Lactate: All finger punctures occurred prior to the start of the treadmill exhaustion test and following the last cognitive test session on the treadmill once the treadmill has stopped. Within 60 seconds, the test result of blood lactate concentration appeared in the test meter display. The technician then recorded blood lactate concentration levels on the appropriate data collection form. A small sterile bandage was placed over the finger after each procedure.

3 Results

The participant sample yielded a median height of 70 inches, 186 pounds, body mass index (BMI) of 25.8, and a physical training (PT) score of 96. Verification of induced fatigue was examined with a two-tailed paired t-test (N = 17) to determine if the pre to post change was significantly different from 0. These results are shown in Table 3. For each variable there was a significant pre to post change. Since the purpose of the analysis was to indicate possible relationships that need to be further studied, a liberal approach to statistical testing was used. All comparisons used an alpha of .05, with no familywise error level adjustments.

Table 3. Biological, subjective, and performance indices of fatigue

	Pre Treadmill		Post Treadmill		Change from Pre to Post		Two-Tailed Paired t-test	
Dependent Variable	**Mean**	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**	**t**	**p**
Lactate (mg/dL)	2.09	0.29	6.75	0.79	4.65	0.83	5.60	0.0001
Fatigue Rating	3.12	0.51	6.32	0.58	3.21	0.57	5.64	0.0001
PVT Mean RT (ms)	248.27	5.47	262.59	7.46	14.32	4.64	3.09	0.0071

Figure 1 shows the U-shaped performance curve for cognitive performance. T1-T2 revealed a significant increase in accuracy [$t(16) = -2.31$, $p = .034$] and a decrease in reaction time [$t(16) = 2.45$, $p = .026$]. T1-T3 revealed a further increase in accuracy [$t(14) = -2.98$, $p = .010$] and decrease in reaction time [$t(14) = 3.77$, $p = .002$]. T1-T4 also showed a significant increase for accuracy [$t(11) = -2.48$, $p = .031$], but no significant decrease in reaction time. Finally, T1-Final showed a significant decrease in reaction time [$t(16) = 5.20$, $p = .000$].

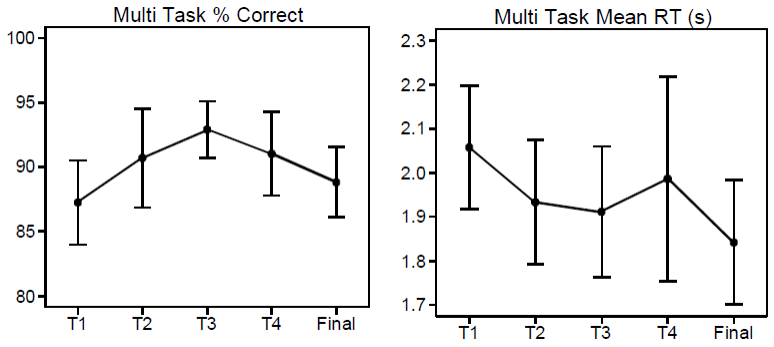

Fig. 1. Means and errors bars for cognitive performance accuracy (percent correct) and reaction times (sec) for participants completing all tasks (N = 12)

All physiological variables increased steadily throughout the treadmill protocol. Paired t-test results are shown in Table 4. Physiological load refers to a participant's heart rate against their maximal heart rate. Mechanical load refers to a participant's kinematic output based on peak acceleration magnitudes (paired t-tests were also run on assessed biomarkers). All biomarker variables were logged for analysis to help normalize the data. The first blood draw (BD2) was compared to the post treadmill blood draw (BD3), a blood draw 10 minutes post treadmill (BD4), and a blood draw 20 minutes following the treadmill protocol (BD5). BD2-BD3 revealed significant increases in BDNF [$t(15) = -5.94$, $p < .001$], serotonin [$t(15) = -3.68$, $p = .002$], adrenaline [$t(15) = -6.34$, $p < .001$], and noradrenaline [$t(15) = -5.79$, $p = .000$].

Table 4. Paired t-test results for physiological changes as a function of time on the treadmill

Dependent Variable	Level 1	Level 2	Level 1		Level 2		Difference Level 1 - 2		Two-Tailed Paired t-test		
			Mean	SEM	Mean	SEM	Mean	SEM	n	t	p
Heart Rate (bpm)	T1	T2	79.84	2.50	138.60	6.08	-58.76	5.66	16	-10.39	0.0001
	T1	T3	80.77	2.36	150.99	5.34	-70.22	5.88	14	-11.94	0.0001
	T1	T4	82.88	2.59	160.47	3.94	-77.58	4.63	11	-16.77	0.0001
Breath Rate (brpm)	T1	T2	21.23	1.08	30.05	1.70	-8.83	1.39	16	-6.34	0.0001
	T1	T3	21.32	1.23	34.25	1.64	-12.93	1.42	14	-9.13	0.0001
	T1	T4	21.40	1.46	35.51	1.83	-14.11	1.61	11	-8.77	0.0001
Heart Rate Variability	T1	T2	96.67	10.24	23.89	3.76	72.78	11.88	14	6.13	0.0001
	T1	T3	90.47	7.10	13.70	4.49	76.77	10.16	12	7.55	0.0001
	T1	T4	88.08	7.88	8.74	1.42	79.34	7.25	9	10.94	0.0001
Core Temperature (deg)	T1	T2	98.05	0.19	98.75	0.16	-0.70	0.05	16	-13.54	0.0001
	T1	T3	98.10	0.21	99.48	0.14	-1.38	0.10	14	-13.42	0.0001
	T1	T4	98.25	0.25	100.07	0.14	-1.81	0.14	11	-12.84	0.0001
Physio Load	T1	T2	1.77	0.43	25.00	3.37	-23.23	3.26	16	-7.12	0.0001
	T1	T3	1.98	0.46	71.09	6.52	-69.11	6.45	14	-10.72	0.0001
	T1	T4	1.90	0.46	127.71	11.71	-125.82	11.60	11	-10.85	0.0001
Mechanical Load	T1	T2	2.12	0.38	5.75	0.64	-3.63	0.59	16	-6.12	0.0001
	T1	T3	2.19	0.42	11.03	1.41	-8.84	1.41	14	-6.28	0.0001
	T1	T4	2.18	0.54	16.60	2.55	-14.43	2.61	11	-5.54	0.0002

BD2-BD4 revealed elevations for BDNF [t(14) = -2.50, p = .026] and adrenaline [t(14) = -4.30, p = .001]. Though noradrenaline levels were not significantly elevated after 10 minutes as compared to the baseline blood draw, levels were significantly lower than the post treadmill blood draw. Levels of orexin A did not significantly change as compared to the baseline blood draw.

Pearson correlations were computed for physiological, biological, and demographic variables to help determine relationships with changes in cognitive performance. Several significant correlations emerged.

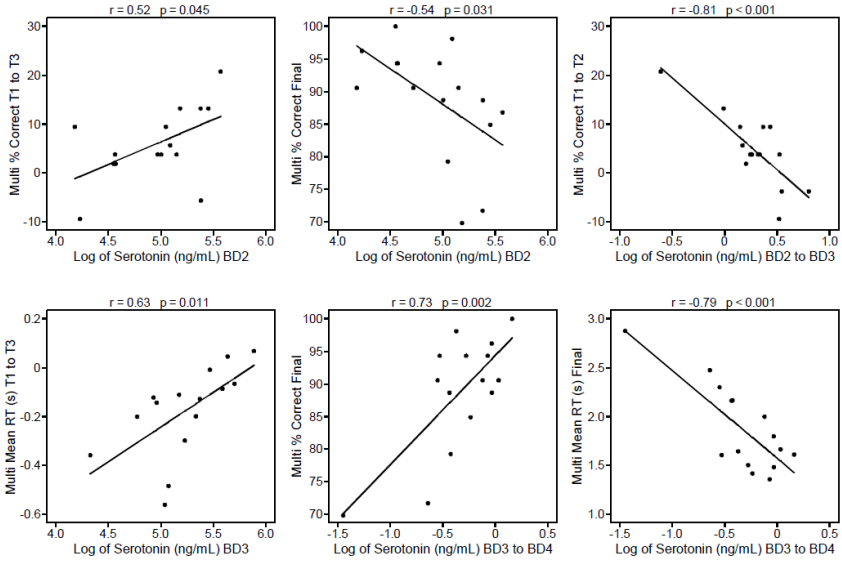

Fig. 2. Correlation results for changes in serotonin levels and changes in performance

Figure 2 above describes six significant correlations between serotonin and cognitive performance. Baseline serotonin levels positively correlated with increases in accuracy during the treadmill task (r = 0.52, p = .045) as well as decreases in accuracy from pre to post treadmill (r = -0.54, p = .031). Increases in serotonin post treadmill as compared to baseline levels revealed a high correlation with less accuracy during the treadmill (r = -0.81, p = .001). In addition, high levels of serotonin post treadmill were related to longer reaction times during the treadmill exercise (r = 0.63, p =.011). Finally, elevated serotonin levels 10 minutes post treadmill as compared to right after the treadmill were related to greater accuracy from start to completion (r = 0.73, p = .002), as well as faster reaction times from start to completion (r = -0.79, p = .000).

Additional significant correlations are shown in Figure 3 below. Increases in orexin A levels following the treadmill exercise as compared to baseline are related to less accuracy from start to finish (r = -0.61, p = .021), while increases in orexin A levels 10 minutes post treadmill compared to post treadmill are related to greater accuracy from start to finish (r = 0.59, p = .021). Higher baseline adrenaline levels are associated with less accuracy during the treadmill exercise (r = -.74, p = .001). Individuals

who had larger reaction time gains from pre to post treadmill performed the best from start to completion (r = 0.62, p = .008). Greater changes in lactate were found to be related to less accuracy during the treadmill exercise (r = -0.66, p = .008). Finally, breath rate changes from beginning to end were found to be related to greater accuracy at the end (r = 0.78, p =.005).

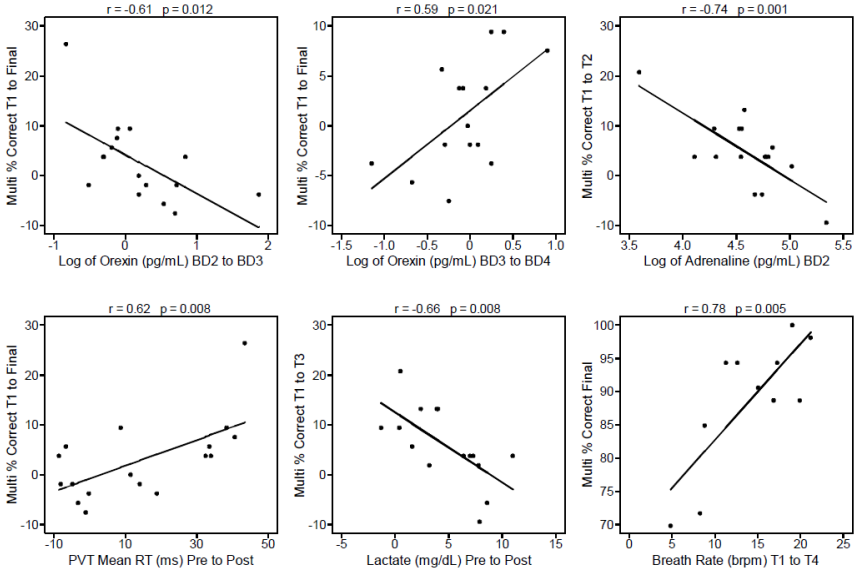

Fig. 3. Correlation results for changes in orexin A, adrenaline, PVT, lactate, and breath rate with changes in performance

4 Discussion

This effort was an exploratory study with the objective of identifying significant trends in biomarkers and biometrics during physical exhaustion. The results of this study and planned follow-on studies may lead the development of physiological or biological sensors that could signal the potential for poor decision making under heat stress and physical fatigue. The current results showed that a sample of healthy physically fit active duty males generally experienced fatigue following a modified-Astrand treadmill protocol. Fatigue is exhibited by significant increases in lactate, subjective fatigue ratings, and increases in reaction time the PVT. During the treadmill exercise, participants demonstrated an increase in accuracy and a decrease in reaction time for a multitasking test that involved spatial orientation and working memory skills. Toward the end of the treadmill exercise, performance dropped back to baseline levels supporting the finding of a U-shaped effect of physical exercise on cognitive performance [7]. Also throughout physical exertion, heart rate, breath rate, estimated core temperature, physiological load and mechanical load steadily

increased. Heart rate variability steadily decreased. Finally, all biomarkers assessed, with the exception of orexin A, increased as a function of the treadmill exercise.

Elevated serotonin baseline levels were found to be related to early rises in performance as well as greater decreases in accuracy at the end of the treadmill exercise. This may be due to early resource expenditure. Serotonin is believed to influence central fatigue, or fatigue related to the central nervous system [18]. Increased brain serotonergic activity may augment lethargy and a loss of motivation [15]. Those beginning the exercise with elevated serotonin may reach levels of fatigue faster than those with low baseline levels. Increases during the exercise were also found to be related to poor performance early in the exercise. Higher post-treadmill serotonin levels were also found to be related to slower reaction times early in exercise. In general, serotonin increases following exercise are related to poor performance. Finally, those who exhibited elevated serotonin levels 10 minutes following the treadmill exercise performed the best from the beginning to completion for both accuracy and reaction times. This relationship may be due to a pacing of mental resources and physiological control, where increases occur following the physiological stress. These results show the potential for a real-time sensor of serotonic changes to indicate changes in central fatigue that may lead to working memory and spatial orientation performance decrements.

Orexin A increases also showed a relationship with poor accuracy from the beginning to completion. Orexin- produces arousal, increased attention, and increased muscle tone [24; 25; 26; 27]. Thus, this result is contrary to expected findings. Increases in orexin A 10 minutes after the treadmill exercise exhibited a relationship with higher accuracy from the beginning to completion. It is possible that increases in orexin A may indicate greater mental effort (recruiting neural resources), thus performance that is poor compared to individuals who do not need to tap into neural resources. More research needs to be conducted to explore orexin A and its association with mental performance.

Higher baseline adrenaline levels were found to be related to poor accuracy during the beginning of the exercise. This finding is consistent with Baum's [13] that high baseline catecholamine levels have been shown to predict poorer psychological judgment. High baseline levels may be indicative of chronic levels of stress and catecholamine depletion when needed during increased exercise. Adrenaline spikes were not found to be related to increased performance as expected. This may be due to the lack of stress that is inherent in the cognitive task. Dienstbier [28] explained that catecholamine enhancement effects from exercise may not occur when mental coping is not particularly taxing.

Other relationships include increased reaction time for a psychomotor vigilance task with improved performance from beginning to completion on the treadmill. Because the PVT is administered following the treadmill exercise, it may be that resource depletion is occurring later, as in the finding that larger increases at the end are related to better performers as well. The finding that lactate increases are negatively related to early increases in performance also supports the trend that better mental performers sustain their effort, rather than expend their mental resources early. Changes in breath rate also exhibited a relationship with improved accuracy from

beginning to completion. This may be an indicator of steady increases in expended effort.

In conclusion, while physiological variables exhibited reliable indices of physical exertion, biological changes were found to be more related to cognitive changes. Serotonin revealed consistent and reliable patterns of cognitive ability throughout the physical exertion profile. The potential for serotonin to serve as a real-time indicator of central fatigue (as a function of physical exertion) should be further explored.

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