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# Neuropsychological assessment in extreme environments

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**Abstract**

In this paper, we summarize studies that used ANAM tests to assess the effects of environmental stressors. The findings document performance changes resulting from conditions relevant to military operational medicine. These conditions included radiation exposure, toxins, high altitude, undersea conditions, Marine basic training, advanced military training, and fatigue. The results of these studies demonstrate that ANAM detects cognitive changes in extreme environments.


*Keywords:* Extreme environments; Radiological; Toxins; Diving medicine; Neuropsychology; Altitude; Fatigue advanced military training

Humans often function in difficult and demanding environments or in situations that are less than optimal. These environments may involve extreme temperatures, sleep deprivation, toxic exposures, or changes in normal ambient pressure which occur at altitude or with undersea activity. In these cases, extreme environments are a result of deliberate choices such as exploring space or the ocean depths. In other cases, extreme environments result from adverse circumstances, including war or accident. There is frequently no alternative to placing humans in environments where their effectiveness and, in many cases, survival, depends upon their ability to perform at the highest cognitive level. The ability to predict acute cognitive changes, detect the onset of cognitive deterioration, and monitor the residual effects of exposure is critical in these types of situations. Measuring the effects of extreme environments on cognition motivated the development of automated, repeatable, neurocognitive test batteries within the Armed Forces. In the present article we review data from studies using ANAM to study the effects of varied stressors. The review includes the effects of radiation, toxins, high altitude, undersea conditions, and high stress military operations on cognitive performance as measured with ANAM. These studies clearly demonstrate that ANAM is capable of quantifying the effects of extreme environments on cognitive functioning. ANAM also provides an estimate of the size and type of cognitive changes that occur in these settings.

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## 1. Assessment of cognitive changes following exposure to radiation or toxins

Residual cognitive effects are a concern after exposure to radiation and toxic substances. In the following section, changes in cognitive performance following a nuclear accident, and exposure to toluene and depleted uranium are described. Though not directly supportive of or related to military operational medicine, the results of a nuclear accident can be interpreted in light of today's war on terrorism and the possibility of the detonation of a small nuclear device as a tool for terrorism. The results of each study demonstrate that ANAM is capable of detecting and quantifying cognitive functioning changes following exposure to neurotoxins.

### *1.1. Radiation*

To assess the effects of exposure to varying levels of ionizing radiation on neurocognitive abilities, Gamache, Levinson, Reeves, Bidyuk, & Brantley (2005) conducted a 4-year longitudinal study in and near Chernobyl, Ukraine. Participants were volunteers who resided in Ukraine during and after the Chernobyl Nuclear Power Plant accident that occurred 26 April 1986. From 1995 to 1998, a subset of selected ANAM measures, which had been translated into Ukrainian, was administered annually to a control and three radiation exposure groups. Controls ($n = 31$) were healthy volunteers who resided in Ternopil, 450 km east of Chernobyl. The personnel that were exposed to radiation consisted of three groups: eliminators, forestry workers, and agricultural workers. The eliminators ($n = 36$) were Chernobyl decontamination and reconstruction workers who went into the area immediately and shortly after the disaster; they resided in a hospital in Kiev during the study. Forestry workers ($n = 29$) resided and worked in the Ovruch forest, 25–30 km southwest of Chernobyl. Agricultural workers lived and worked in the village of Razumnitsia, approximately 150 km south of Chernobyl.

Analyses were performed using accuracy and efficiency (throughput) scores for both across-time and between-group comparisons. Correlations were also calculated between neurocognitive performance and levels of radiation, which were obtained for the individuals in the three exposure groups. Analyses of 1995 test results (Gamache et al., 2005) indicated that the eliminators were significantly and globally more impaired on measures of neurocognitive performance as compared to the controls. Further, forestry and agricultural workers were impaired on many cognitive tests. Analyses of the 1996 data revealed that neurocognitive performance of personnel in the exposed groups had worsened compared to their 1995 results.

Analyses of 1997 data (Gamache et al., 2005) indicated that the neurocognitive performance of the eliminators and forestry workers continued to worsen, and the forestry workers who resided only 25–39 km from ground zero also began to appear globally impaired. The performance of the agricultural workers also declined over the first 3 years of the study, although not nearly as much as that of the other two exposed groups.

The analyses of the 1998 data (Gamache et al., 2005) indicated that the performance of the three exposure groups was leveling off on some of the measures, but continued to decline on others. The performance of the agricultural workers was asymptotic on most measures. Statistically significant correlations between levels of radiation dosage and cognitive performance averaged over the 4 years of the study were observed on 18 of 20 test scores for the combined exposed groups. The overall results suggested the existence of clinically meaningful neurotoxic effects of ionizing radiation, with the magnitude of the effects being significantly correlated with amount of exposure. Further, the results demonstrated the predictable declination of cognitive performance over the lifespan of the series of studies.

### *1.2. Toluene*

Rahill et al. (1996) used ANAM to study the effects of toluene on cognitive performance. These investigators also used SynWork, a multi-task developed by Elsmore (1994) that can be administered within the ANAM test system. In their study, Rahill and colleagues exposed six healthy subjects to either 100 ppm toluene, or air for the control condition, for 6 h in a double blind randomized fashion. Exposures included 30 min of exercise at a level that quadrupled minute ventilation. Exposures were separated by at least 14 days. Toluene was measured in blood and in exhaled air before, during, immediately after exposure, and at 1 and 2 h post exposure. Lung functioning was measured before exposure and immediately after. Following exercise, the mean blood toluene level was 1.5 $\mu$g and the mean toluene level in exhaled air was 28 ppm. During toluene exposure, the composite score from SynWork, which reflects the subject's overall performance on four tasks presented simultaneously, was significantly lower than under the control condition.

There was a 10% reduction in this score during the final hour of toluene exposure. With respect to ANAM measures, mean response time increased under the toluene condition for Sternberg memory search, running memory, procedural response time, and spatial processing. Decrements secondary to toluene exposure were also noted for the Sternberg throughput score.

### 1.3. Depleted uranium

McDiarmid et al. (2000) used the ANAM to examine the effects of depleted uranium (DU) upon cognitive performance. DU is a byproduct of the uranium enrichment process, and because of its high-density, availability, and the relatively low cost, the military employs DU in projectiles and in armor. It is approximately 60% as radioactive as natural uranium (McDiarmid et al., 2000).

Soldiers wounded in DU-related friendly fire incidents potentially suffered exposure as a result of inhalation or being wounded with this material. During Operation Desert Storm, 15 Bradley fighting vehicles and 9 Abrams tanks were mistakenly fired upon and struck by munitions containing DU.

The health effects of concern related only partially to DU's relatively low intensity radiologic toxicity (McDiarmid et al., 2001) which is caused by high-energy, but poorly penetrating Alpha emissions. Internalized DU delivers irradiation doses to tissue in immediate contact with it. This effect is a function of contact time, particle solubility, and rate of elimination. However, there has been no convincing evidence for an increased risk of lung cancer in miners exposed to uranium (McDiarmid et al., 2001). Likewise, while bone is known to be an important long-term storage depot for uranium, no increased bone cancer rate has been reported in uranium-exposed cohorts (McDiarmid et al., 2001). As with other heavy metals, there is a particular focus on the kidney along with the respiratory system (McDiarmid et al., 2000).

It appears uranium's chemical toxicity is the principal concern for war veterans. Some crew members surviving these friendly fire instances were left with shrapnel in muscle and soft tissue. These survivors have been followed medically at the VA Medical Center in Baltimore to assess potential untoward health effects. To date, 71 veterans participating in this health-monitoring program have been assessed from one to five times at the Baltimore VA.

Neurocognitive assessment has been part of this general health risk assessment. ANAM has been employed along with traditional test measures as a means of monitoring potential cognitive changes related to exposure to DU. Neurocognitive data have been analyzed in two ways. Veterans exposed to DU were divided into high and low exposure groups based on the amount of uranium found in their urine (exposure levels reported in previous research). When veterans were divided into high and low exposure groups, there was no statistically significant difference in their performance either on traditional or computerized measures. No relationship was found between traditional neurocognitive measures and urine uranium values using regression techniques and controlling for psychiatric distress and estimated premorbid intellectual functioning. The current plan at the Baltimore VA is to continue following DU-exposed veterans to monitor them for health problems potentially related to DU exposure including the longitudinal analysis of neurocognitive data to assess potential changes in functioning over time.

## 2. Cognitive effects at high altitude

In civilian and military applications, the time course of a disorder greatly influences the impact and costs associated with that disorder. The time course may also suggest ways to treat the disorder or understand the mechanism of insult. Banderet, Kane, & Muza (2002) investigated subjective symptoms and cognitive test performance associated with high altitude exposure. This effort was part of a larger double blind, cross-over study to assess the role of leukotrienes in high altitude sickness (Muza et al., 2001; Muza, Kaminsky, Fulco, Banderet, & Cymerman, 2004).

The investigators hypothesized that: (1) the time courses of cognitive performance decrements and symptoms of acute mountain sickness (AMS) would be different; i.e., cognitive performance impairments would occur soon after ascent to altitude and be greatly improved after 12 h; (2) adverse changes in cognitive performance and symptoms would be decreased by the drug treatment, montelukast. The investigators used a subset of ANAM measures employed by NASA for use in space flight called the Spaceflight Cognitive Assessment Tool for Windows (WinSCAT) (Kane, Short, Sipes, & Flynn, 2005). The WinSCAT battery was designed to assess the neurocognitive status of astronauts especially during long duration missions. The WinSCAT battery of ANAM tests includes code substitution, code substitution delayed memory, running memory, mathematical processing, and delayed matching to sample. The investigators used

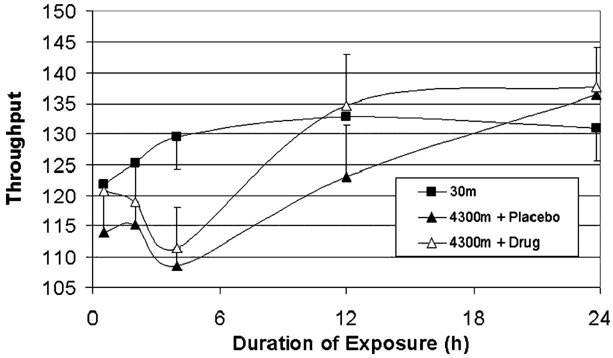


Fig. 1. Running memory throughput by time at altitude.

WinSCAT's throughput scores as their measure of cognitive performance. They also used a computerized 67-item version of the environmental symptoms questionnaire (nine factors) to measure symptoms of AMS.

Cognitive test performance and symptoms of AMS were assessed during the two non-contiguous 48 h periods (24 h at 30 m followed by 24 h at 4300 m). Eleven volunteers were treated with montelukast (Singulair$^{TM}$) or placebo in a cross-over design. During each 24 h period, starting at ~09:00 h, subjects were assessed after 0.5, 2, 4, 12, and 24 h.

Cognitive performance impairments were evident on all tasks beginning 0.5 h after ascent and increased through 4 h. At 12 and 24 h, effects did not differ from data collected at 30 m. These trends were most marked for the code substitution and the running memory tasks where maximal impairments were 15–20% less than the 30 m baseline values. Impairments on mathematical processing and delayed matching to sample were not as marked or distinct as those for code substitution and running memory. On all WinSCAT tasks, the greatest performance decrements were seen at the 4 h mark. This is illustrated in Fig. 1 showing running memory throughput performance across the time course for each of the study's test conditions.

Treatment with montelukast did not improve cognitive performance. The symptoms of AMS were delayed after ascent to high altitude. They occurred after 6 h; they increased in intensity, and were at maximum severity 12 h after ascent. Cognitive data were consistent with those obtained in an earlier study (Banderet & Shukitt-Hale, 2002) in demonstrating the cognitive effects at altitude appeared independent of AMS, i.e., the AMS-C factor on the ESQ was not associated with cognitive performance.

In this study using WinSCAT, the running memory and code substitution tasks appeared more sensitive than the other two performance tasks for assessing cognitive performance decrements after ascent to 4300 m. Decrements in cognitive performance were seen after initial ascent (0.5, 2, and 4 h) and recovered following time at altitude. Cognitive deficits appeared to resolve by 12 h. Since the authors did not assess subjects between 4 and 12 h, they could not state precisely when test performances returned to normal.

Impairments in cognitive performance had a rapid onset (0–0.5 h) and they recovered before the expression of AMS symptoms. These immediate impairments in cognitive performance with relatively rapid recovery (<12 h) suggest that they are likely mediated by hypoxia. Further studies must be conducted to determine if bold pre-treatment strategies can prevent impairments in cognitive performance within the first 4–12 h after ascent to high altitude.

## 3. Cognitive assessment in undersea medicine

In an effort to adapt ANAM as an assessment tool for US Navy diving medicine, a 3-year effort was conducted at the Navy Experimental Diving Unit (NEDU) between 1998 and 2000. A subset of selected ANAM measures, termed the ANAM Diving Medical Subset (ANAM-DMS), underwent validation studies (Lowe, Reeves, & Kane, in press) and normative data were established (Lowe & Reeves, 2002). The ANAM-DMS subset included: subject demographics, Stanford sleepiness scale, simple reaction time, code substitution, code substitution with both short and long delayed memory, delayed matching to sample, running memory, and mathematical processing. The ANAM-DMS was used in studies of deep saturation diving (Lowe & Reeves, 1999, 2001), exposure to warm water diving (Lowe, Reeves, & Long, 2002) and accelerated decompression/escape from a disabled submarine (Lowe & Reeves, 2000).

### 3.1. Saturation deep diving

In 1998, NEDU performed a simulated dive to the depth of 1000 feet of salt water (fsw) in their ocean simulation facility (OSF) to examine selected physiological, medical, and neuropsychological events. Lowe and Reeves (1999, 2000) assessed cognition in nine diver-subjects during a pre-dive baseline, at 500 fsw during compression, twice at the storage depth of 1000 fsw, at the 600 fsw level and the 200 fsw level during decompression, and then at the surface post-dive. The greatest effects (impairments) appear to have occurred between the pre-dive and 500 fsw level for accuracy, response time and throughput scores on the delayed matching to sample and code substitution long delay memory tasks. Also observed were decreased response time and throughput scores on code substitution immediate memory and a slowing of simple reaction time. Though the decrements were present at 1000 fsw for the above measures, none was greater then that at 500 fsw. The most interesting result from this study was demonstrated on the fourth day at 1000 fsw, when these measures all returned to baseline levels. This acclimation, like that seen at altitude, continued through each successive assessment concluding with the post-dive measurement.

Data obtained from ANAM demonstrated some cognitive changes associated with saturation deep diving; however, the underlying mechanisms remain to be determined. Possible reasons for these changes include the effects of pressure, the gas mixture, workload, the hyperbaric environment, or a combination of these factors. This study also demonstrated the capability to assess an individual in a hyperbaric chamber, thus providing the medical diving community with a method and means of tracking recovery from a diving insult while the individual is receiving a recompression treatment.

### 3.2. Water temperature

In 1999, NEDU began to look at the effects of warm water on divers, both physiologically and cognitively. A study by Lowe et al. (2002) examined five water temperatures, 78, 92, 94, 96, and 101 °F, under a work condition (peddling a bicycle at 80% Vo2max) or a rest condition. Again, the ANAM-DMS was used to assess diver cognitive performance before and after the dive.

There were significant decreases in accuracy scores on all three parts of the code substitution test (code substitution, code substitution short delay memory, code substitution long delay memory) that were independent of both water temperature and working mode. Mean reaction time and throughput remained relatively unchanged, except for a marginally significant improvement in mean reaction time for code substitution short delay memory. Running memory accuracy and throughput each demonstrated a significant decline from pre-dive to post-dive, and again this decrease was independent of water temperature and work mode. Matching to sample throughput showed diving-related decrements that were also independent of water temperature and work mode. However, mean response time for matching to sample increased marginally with diving and demonstrated a significant temperature interaction with the greatest increase in response time seen at the 96.5 °F water temperature. There were no significant changes in simple reaction time or mathematical processing.

Only water temperature interacted with matching to sample mean reaction time. Other trends were not noted. However, the statistical power for the tests was low due to small sample sizes and unequal groupings of subjects at each test matrix (temperature and work mode). Resolution of effects could be improved with a larger sample. As mentioned, diving-related cognitive changes are subtle and statistical power is an important factor in their detection. Future studies could benefit from the inclusion of a control group to aid in differentiating the effects of fatigue and water temperature.

Another limitation of this study was that medical termination criteria used to discontinue a diver's participation in the study impacted data collection. The diver would remain in the matrix condition until the maximum time elapsed (8 h resting mode, 4 h working mode), or until voluntary termination of the trial. Divers are very competitive and they often would not terminate until physiologically required to do so (core body temperature might reach a critical medical threshold or they would pass out). Some individuals who reached their physiological threshold subjectively reported dramatic cognitive changes, such as confusion and hallucinations. However, assessment of these divers was not possible until they were medically stable. The recommended solution for this was to conduct periodic in-water assessments so that cognitive functioning could be obtained as the diver's condition began to deteriorate.

### 3.3. Accelerated decompression procedures

Between 1998 and 2000, NEDU conducted a series of mixed gas (nitrogen and oxygen, Nitrox) saturation dives that simulated the environment on a disabled submarine that had pressurized to a theoretical depth of 2–3 atm (33–66 fsw).

These dives specifically explored accelerated decompression procedures for bringing submariners back to surface while safely providing therapeutic decompression. These studies were conducted over three phases, testing various decompression parameters (treatment gas exposure, frequency of air break, air break durations, and schedules based on decompression models).

Currently approved Navy procedures require a gradual decompression from saturation of at least 33 h. It is desirable to reduce this time to approximately 6 h to match the technical capabilities of the current disabled submarine rescue vehicle (DSRV). The human body is considered to be fully saturated after exposure to pressure of 72 h. Using 100% (>95%) humidified oxygen as a treatment gas, the goal of 6–8 h decompression was successfully achieved. Phase II examined recomputed decompression schedules based on existing models. The change between phases I and II resulted in slightly longer exposures to humidified oxygen. ANAM-DMS was used to assess potential cognitive changes associated with the use of these different air mixtures during rapid assent.

The ANAM-DMS was administered at baseline and following each decompression. Lowe and Reeves (2000, in press) and Lowe, Reeves, & Kane (2000) reported on two of the three phases. There were a total of 48 Navy divers in phase one and 73 participants in phase II. For phase I, mean response times for code substitution long delay memory and delayed matching to sample, and the accuracy measure for mathematical processing, demonstrated non-significant changes in performance from baseline. Mean response time and throughput for running memory, mean response time for mathematical processing, and code substitution long delay accuracy all demonstrated significant decrements for the phase I group.

During phase II, all three measures (mean response time, accuracy and throughput) for code substitution long delay memory, showed non-significant decrements from baseline. The accuracy measure for mathematical processing and the mean response time for simple reaction time showed non-significant decrements. Matching to sample yielded the only significant decrements in performance on both the mean response time and throughput.

The ANAM-DMS instrument was sensitive to diving-related insults. However, since the ANAM-DMS was being evaluated for possible use as a screening tool, treatment decisions during these studies were based on medical criteria and on the subject presenting with symptoms of decompression sickness (DCS). However, Lowe, Southerland, & Reeves (1999) and Reeves, Lowe, & Levinson (2001) presented a case that reported with cognitive symptoms requiring treatment for DCS. As a member of the saturation dive team for the disabled submarine project, the subject received a baseline and a post-dive assessment. An increase in performance scores was noted on all traditional test measures post-dive. This finding is similar to pre- and post-dive comparisons of group performance where all measures had significant increases in performance except for Trail Making Form B, which showed a trend toward improved performance. During the post-dive medical physical examination, no symptoms were reported. The next day, the diver reported symptoms including a decrease in peripheral vision, lack of sustained concentration and a general mental slowness. The results of the neurological exam by the attending physician were within normal limits. Based upon the presentation of the symptoms, a US Navy treatment table six was completed with full resolution. A review of the post-dive ANAM-DMS results showed statistically significant performance decrements from baseline on delayed matching to sample as evidenced by an increase in mean response time of 1790.053–2396.113 ms and a decrease in mean throughput from 29.76 to 23.60. By comparison, the peer group had a non-significant increase in mean reaction time from 1740.810 to 1792.992 ms and a non-significant decrease in throughput from 33.288 to 32.841. Two days post-treatment the diver completed a follow-up assessment that showed performance on delayed matching to sample better than baseline; mean reaction time decreased to 1701.023 ms and the mean throughput increased to 35.62.

Although it would be ideal to obtain cognitive assessment data immediately before treatment of a symptomatic diver, this was not possible due to time constraints and the urgency to treat DCS upon presentation of any symptoms. However, this case was of interest since delayed matching to sample appeared sensitive to dive effects in the above studies and in this case may have been prodromal to the onset of more apparent DCS.

## 4. Cognitive changes during Marine basic training

Basic training is inherently stressful. Fatigue, physical and mental stress are the primary issues. Gastaldo, Reeves, Levinson, and Wenger (2001) studied Marine Corps recruits during basic training and established norms for this “young adult” population. These investigators employed a customized subset of an earlier MS DOS version of ANAM to assess 197 Marine Corp recruits. This ANAM subset consisted of the Stanford sleepiness scale, the Walter Reed

Mood Scale-2, code substitution with immediate and delayed memory, Sternberg memory search, and two versions (80 and 160 items) of the running memory continuous performance task, digit set comparison, logical reasoning, matching to sample, mathematical processing, spatial processing, and simple reaction time tasks repeated up to three times. Approximately 1 month later, retest data were collected on 50 of these individuals. Normative data for females ($n = 83$) and males ($n = 114$) and retest data were obtained from this study.

Gastaldo et al. (2001) also followed 14 recruits who displayed symptoms associated with delusional hyponatremia during training. The Marine Corps normative data were used to assess the effects of this malady on the group as a whole and to provide a clinical basis for evaluating each case. For the 14 hyponatremia cases, a one sample *t*-test was used to assess differences between these cases and the normative group. During the initial assessment, which occurred within 24 h of the onset of heat stress symptoms, mean throughput scores on eight tests and mean accuracy scores on three tests were significantly lower for the 14 cases as compared to controls. These scores returned to normal at follow-up, 1–4 weeks post treatment. Gastaldo et al. (2001) noted that the pattern of performance deficits was similar to that exhibited by the traumatic brain injury (TBI) patients presented by Levinson and Reeves (1996). However, unlike the TBI patients, the hyponatremia cases returned to normal levels at retest.

## 5. Cognitive changes during high stress military exercises

Military personnel perform critical cognitive tasks in operational environments with high levels of stress. Operational stress involves extended cycles of alternating stress and recovery, and stress intensities vary from mild to intense. Effective leadership requires the ability to predict when cognitive deterioration is likely to occur, the amount of decrement that will occur, and the types of changes that will occur. The availability of tools to detect when significant deterioration has occurred is also important. Military training provides the opportunity to examine the relationship between cognitive performance and stress in a setting similar to operational environments. The ANAM battery was used in a series of studies that examined the effects of operational stress on military personnel cognitive performance. Harris, Hancock, and Harris (2005) examined the cognitive effects of an extreme training environment, the Navy Survival, Evasion, Resistance, and Escape (SERE) School at Brunswick, ME. Navy and Marine personnel cognitive performance was assessed using the ANAM before and after 7 days of intense field training. Simple response time increased 10.4 ms after training, but other cognitive tasks were stable following completion of the experience. Post-study debriefing suggested that a significant degree of recovery may have occurred during the 3 h between the end of training activities and assessment, raising the question of whether larger changes may have been present during training. A more detailed analysis of the data indicated that although average performance was at baseline levels, participants had an apparent inability to maintain performance as time-on-task increased. Spatial processing and logical reasoning performance on items near the end of these scales was less accurate; code substitution, logical reasoning, and the running memory continuous performance task response time became longer as the end of each test approached. Results suggested that increased simple response time is an early indicator of impairment in stressful situations, that the inability to maintain performance is the initial cognitive performance change, and that military personnel cognitive performance recovers rapidly following periods of stress.

A second SERE training study at Ft. Bragg was initiated to assess potential stress induced cognitive changes more immediate to the intensive training experience. The time between the end of training activities and assessment was decreased to less that 1 h, performance was assessed after a more intense training program, and a second post-stress assessment was added the following day, 12 h after the end of training (Harris, Hancock, & Morgan, 2005). Simple response time increased approximately 20 ms immediately after training (twice the increase in the previous study), and average response time to selective complex tasks increased immediately after training. The response times of two sensitive tasks in the initial study, spatial processing and logical reasoning, increased in the second study but the most pronounced change immediately following stress was increased memory response times. Cognitive performance returned to baseline levels after 12 h in which sleep and nutritional deficits were addressed.

To clarify the apparently dynamic nature of stress-related cognitive performance changes, two ANAM studies were conducted during simulated infantry combat exercises (Harris, 2004; Harris & Hancock, 2003). A subset of ANAM tests was administered to soldiers before the exercises began to establish a pre-stress baseline and periodically during the simulated combat exercise to examine the effects of training. Test measures were administered on a PDA (ANAM Readiness Evaluation System, ARES), which allowed assessments to be conducted in the field during missions. The results confirmed the dynamic nature of stress and cognitive changes related to stress. Although all soldiers were participating in the same exercise, the environmental and workload varied significantly. One company operated along the first section of a road in an area with heavy underbrush and steep, rocky ridges, and was at the point of attack. Continuous movement by these soldiers was required during a series of engagements, and because no breeze penetrated the woods, there was little relief from the 90+ °F heat. The other company defended a pass further along the road, which the invading force never reached. This group did not move, and with little underbrush on their ridge, they benefited from any breeze that occurred. Although one might expect cognitive deficits in soldiers involved in the more demanding mission, no complex task change was noted in either group. Following a 27 h mission at the end of the week the only cognitive performance change noted was a 9.2 ms increase in simple response time. Thus ANAM data were consistent with operational performance observations that indicated the average soldier was not significantly impaired at the stress levels present during the training exercise.

Although conclusions based upon one individual must be viewed with caution, assessment of a soldier immediately following a potentially serious medical event suggested that ANAM detected the acute effects of stress. His simple response time increased (30 ms) his performance of complex ANAM tasks was rapid, but inaccurate. Although cognitive assessment during emergencies is difficult, the results suggest that the ANAM may provide a valuable tool to assess the effect of stressful events upon individuals.

ANAM was employed again during infantry exercises the following year. The environmental conditions and mission demands of the participating soldiers were similar to the high stress training during the previous study but training duration was increased. Assessments carried out during initial operations revealed that soldiers' simple response time had increased 13.4 ms from their pre-exercise level and response time on three information processing tasks, logical reasoning, spatial processing, and the 6-item Sternberg task, increased. There was no indication of decreased accuracy. Information processing response time returned to baseline levels at the end of the 5-day exercise, but post-exercise accuracy on two tasks, logical reasoning and mathematical processing, were below baseline levels. After a 27-h operation during the second week of training, simple response time was approximately 21 ms above baseline, approximately twice the 9.2 ms post-assault change observed in the first infantry study. Logical reasoning and mathematical processing response times were also greater after the operation than at baseline level.

Taken together, data from these studies suggests that changes in simple response time is an early indicator of cognitive impairment, and that the likelihood of complex tasks impairment increases as simple response time increases. ANAM changes during field operations appear to reflect operational stress, with increased response times following periods of high operational demands. Complex cognitive task performance did not appear to be affected in the above studies until simple response time increases approached 15 ms above baseline. Accuracy was maintained during periods of high operational tempo but accuracy decrements were noted during a low demand period following a 5-day operation. Cognitive performance appears to be resistant to the effects of stress, but when conditions are sufficiently demanding to produce cognitive changes, all cognitive functions do not appear to be affected equally.

## 6. Fatigue and cognition

As noted above, WinSCAT is a special implementation of ANAM designed to assess the cognitive health of astronauts. In a NASA sponsored study, French, Neville, Eddy, Storm, and Flynn (1999) evaluated the sensitivity of WinSCAT to one of the pre-dominant stresses facing astronauts, fatigue induced by sleep deprivation and circadian disruption. Two groups of eight US military pilots (ages 30–40) participated in this study of the performance effects of 46 h of sleep deprivation—a period that extended over two circadian performance nadirs. In addition to WinSCAT, four cognitive performance tests typically used in fatigue research were performed repetitively during the sleep deprivation period. WinSCAT was performed every 6 h up to the 36th hour of sleep deprivation.

In their initial analysis, French et al. (1999) analyzed only the six scores from the WinSCAT battery that appeared in the early versions of the battery as immediate feedback to the astronauts. The feedback includes both accuracy and reaction time scores. For all tests, sleep deprivation's greatest effect was on response time. With respect to the WinSCAT tests, mathematical processing exhibited significant fatigue-related decrements on the last three of the six trials, following 23 h of wakefulness. Running memory and matching to sample showed significant decrements on two of the trials, after 23 and 29 h awake. Of all the tests, only running memory demonstrated an effect on response accuracy, and the effect was associated with 23 and 29 h of wakefulness. In contrast, two of the comparison tests demonstrated sensitivity on 21% of the trials and another on only 17% of the trials. WinSCAT was found to be sensitive to fatigue early ($\leq$23 h) and late (35 h) into the sleep deprivation period.

Table 1
Number of impaired scores by participant at various hours of sleep deprivation

| Group | 11 h | 17 h | 23 h | 29 h | 35 h | 42 h |
|---|---|---|---|---|---|---|
| 1 | 0 | 0 | 0 | 0 | 1 | 0 |
| 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 0 | 0 | 1 | 0 | 0 | |
| 1 | 0 | 1 | 0 | 1 | 0 | 0 |
| 2 | 0 | 0 | 1 | 2 | 1 | 1 |
| 2 | 0 | 0 | 1 | 2 | 2 | 0 |
| 2 | 2 | 1 | 2 | 2 | 1 | |
| 3 | 1 | 3 | 3 | 3 | 3 | |
| 3 | 1 | 2 | 4 | 4 | 2 | |
| 3 | 0 | 0 | 3 | 3 | 1 | 1 |
| 3 | 1 | 0 | 0 | 4 | 2 | 0 |
| 3 | 0 | 2 | 4 | 4 | 1 | 4 |

Since the analysis of French and his colleagues focused on selected accuracy and response time scores, Kane et al. (2005) reanalyzed these data using throughput scores. With respect to throughput scores, significant decrements in performance were noted at 23, 29, and 35 h of sleep deprivation for running memory and delayed matching to sample; at 29 and 35 h for mathematical processing.

Kane et al. (2005) also analyzed individual change scores using the reliable change index method (Jacobson & Truax, 1991) to look for individual differences in fatigue responses among the study participants. For this study, participants took WinSCAT 10 times to control for practice and to obtain a baseline before entering the study conditions of continued wakefulness. However, operationally, WinSCAT is given six times before flight with the final three administrations serving as baseline. Consequently, Kane and Short used throughput scores obtained during trials four through six to compute the RCI then tabulated the number of scores for each participant that fell outside of the expected range at each test interval.

Table 1 presents data obtained from 11 to 42 h of wakefulness. Values in the table represent the number of scores falling in the impaired range based on the RCI at each test interval. Four of the five WinSCAT scores were included. Data from the code substitution delayed memory test was not included due to concerns about proactive interference when this test is repeated at short intervals. Participants fell into three groups. The first group performed well throughout the entire study and had from zero to one score impaired despite being awake an extended time without sleep. Group 2 evidenced periods of marginal performance with two scores in the impaired range at different time points. Group 3 demonstrated the most severe changes in performance having three or four tests below expectations based on the RCI. Not all subjects completed all trials.

The above study assessed fatigue brought about by sleep deprivation. Law, Kane, Ashburn, Kim, and Deuster (2003) assessed fatigue brought about by physical exercise. These investigators studied 20 healthy moderately to highly physically fit males (ages 22–40, education 15–20 years). All participants took repeated trials of WinSCAT to stabilize baseline performance. During the experimental portion of the study, WinSCAT was administered before and after a load carriage (30% bodyweight backpack) exercise endurance (70% Vo2max × 2 h) treadmill test. Participants were given two trials (tyrosine and placebo experimental trial conditions) separated by at least a week. Four subjects produced invalid data on the experimental study trials (administration/equipment errors), leaving a final study sample size of $n = 16$ (ages 20–45, education 16–20 years). Dexamethasone (DEX) suppression classification of high or low stress responders was based on degree of change in adrenocorticotrophin hormone (ACTH) levels collected before and immediately after the treadmill stress test, approximately 8 h after DEX ingestion. WinSCAT scores showed deterioration due to exercise fatigue, however, no differences were found between subjects based on their DEX response or when attempting to use tyrosine as a countermeasure.

## 7. Conclusions

The necessity and benefits of exploring harsh environments are very real. It is sometimes necessary to send humans into space, deep-sea environments, extremely cold or hot environments, and settings that are contaminated with hazardous materials. Humans are often required to perform complex cognitive functions while in these extreme environments. Knowledge of the immediate effects of these conditions on cognitive functioning and the long-term neuropsychological consequences of exposure are needed to intelligently manage personnel in these demanding situations. In military settings, the Warfighter must perform cognitively demanding tasks during long, sustained missions. The operation tempo in Iraq and the resulting fatigue illustrate this problem.

In this paper we reviewed studies using ANAM to assess changes in cognition associated with different stressful conditions. The purpose was to bring together and summarize work for diverse conditions and environmental stressors. In general, ANAM measures appeared sensitive to effects of various conditions and diverse environmental stressors. These findings are not surprising since ANAM is an outgrowth of efforts within DoD to develop automated test batteries for assessing human performance and many ANAM tests had been used in previous batteries.

There are two basic questions of military relevance for all studies of environmental stressors. The first is to characterize the expected effects of a stressor on a group of individuals. The second is to develop methods of identifying when a given individual is showing appreciable changes in performance and cognition. Most ANAM research efforts were classical studies looking for group effects in response to an environmental stressor. It is well understood, however, that there is significant variability in individual's response to stressors. Work has begun within the ANAM community to study individual change measures and to explore statistical techniques for identifying when a specific individual develops cognitive decrements that are a cause of concern. The saliency of this effort is evident from the individual case report noted in this review by Lowe and his colleagues where the possibility existed that changes in cognition were prodromal of DCS. It is also noteworthy that in the reanalysis of WinSCAT fatigue data done by Short and Kane presented above, that not all individuals showed the same effects from sleep deprivation. Addressing the second question involving the assessment of individual change will likely require approaches that combine collecting reference group norms with specific statistical methods of assessing significant change for an individual. Substantial work remains to be done in assessing individual change. The reader is referred to the paper in this special issue by Roebuck-Spenser and colleagues which discusses change score issues.

With respect to ANAM, data are now available pertaining to diverse stressors including atmospheric pressure, various aspects of fatigue, psychological stress, and toxic insults. Data support the use of ANAM to detect deterioration in cognitive performance and to monitor recovery. Other papers in this journal issue address the use of ANAM in the study of cognitive changes secondary to disease and injury. Hence, current data appear to support the use of ANAM as an assessment tool contributing to the medical blueprint of the Warfighter. Information from ANAM provides a characterization of cognitive performance in extreme environments so that human performance guidelines can be established for operating in hostile environments.

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## References

Banderet, L. E., Kane, R. L., & Muza, S. R. (2002). Time course of cognitive performance after ascent to 4300 m. Presented at APA's annual midyear symposium, division 19. *Military Psychology*.

Banderet, L. E., & Shukitt-Hale, B. (2002). *Cognitive performance, mood, and neurological status at high terrestrial elevation*. *Textbook of military medicine: Medical aspects of harsh environments* (Vol. 2, pp. 729–763). Washington, DC: Borden Institute.

Elsmore, T. (1994). SYNWORK 1: A pc-based tool for assessment of performance in a simulated work environment. *Behavioral Research Methods, Instruments, and Computers*, *26*, 421–426.

Gamache, G. L., Levinson, D. M., Reeves, D. L., Bidyuk, P. I., & Brantley, K. K. (2005). Longitudinal neurocognitive assessments of Ukrainians exposed to ionizing radiation after the Chernobyl nuclear accident. *Archives of Clinical Neuropsychology*, *20*(1), 81–93.

Gastaldo, E., Reeves, D., Levinson, D., & Wenger, B. (2001). ANAM USMC normative data: Effects of heat stress on neurocognitive performance. *Archives of Clinical Neuropsychology*, *16*(8), 725.

French, J., Neville, K. J., Eddy, D., Storm, W., & Flynn, C. (1999). *Sensitivity of SCAT to Sleep Deprivation: NASA Technical Report*. Limited Distribution.

Harris, W. C. (2004). Stress effects on soldier performance. In *Proceedings of the human factors and ergonomics society 48th annual meeting*.

Harris, W. C., & Hancock, P. A. (2003). Field assessment of cognitive performance under stress. In *Proceedings of the human factors and ergonomics society 47th annual meeting*.

Harris, W. C., Hancock, P. A., & Harris, S. C. (2005). Information processing changes following extended stress. *Military Psychology*, *17*(2), 115–128.

Harris, W. C., Hancock, P. A., & Morgan, C. A., III. (2005). Cognitive change following Special Forces training. In *Proceedings of the human factors and ergonomics society, Vol. 49* (pp. 1776–1779).

Jacobson, N. S., & Truax, P. (1991). Clinical significance: A statistical approach to defining meaningful change in psychotherapy research. *Journal of Consulting and Clinical Psychology*, *59*(1), 12–19.

Kane, R. L., Short, P., Sipes, W., & Flynn, C. F. (2005). Development and validation of the Space-flight Cognitive Assessment Tool for Windows (WinSCAT). *Aviation, Space, and Environmental Medicine*, *76*(Suppl. 6), B183–B189.

Law, W. A., Kane, R. L., Ashburn, J. R., Kim, S. J., & Deuster, P. A. (2003). Cognitive inefficiency after exercise-stress: Resistance to tyrosine enhancement. *Journal International Neuropsychological Society*.

Levinson, D. M., & Reeves, D. L. (1996). Monitoring recovery from traumatic brain injury using the automated neuropsychological assessment metrics. *Archives of Clinical Neuropsychology*, *11*(5), 419.

Lowe, M. A., & Reeves, D. L. (1999). At depth evaluation of a computerized neuro-pyschological assessment tool: Deep dive 98. *Undersea and Hyperbaric Medicine*, *26*(Suppl.), 18.

Lowe, M. A., & Reeves, D. L. (2000). Accelerated decompression from Nitrox saturation diving: Neuropsychological findings. *Undersea and Hyperbaric Medicine*, *27*(Suppl.), 15.

Lowe, M. A. & Reeves, D. L. (2001). *Deep dive 1998: Neuropsychological findings* (NEDU TR 13-01). Panama City, FL: Navy Experimental Diving Unit.

Lowe, M. A. & Reeves D. L. (2002). *Automated neuropsychological assessment metrics: Norms for U.S. Navy divers* (NEDU TR 02-05). Panama City, FL: Navy Experimental Diving Unit.

Lowe, M. A. & Reeves, D. L. (in press). *Accelerated decompression from Nitrox saturation using 100% oxygen: Neuropsychological findings* (NEDU Technical Report). Panama City, FL: Navy Experimental Diving Unit.

Lowe, M. A., Southerland, D. G., & Reeves, D. (1999). Computer-based neuropsychological findings in a patient with dcs following accelerated decompression from a saturation dive: A case study. *Undersea and Hyperbaric Medicine*, *26*(Suppl.), 17.

Lowe, M. A., Reeves, D. L., & Kane, R. (2000). At depth computerized assessment of neurocognitive changes in divers. *Archives of Clinical Neuropsychology*, *15*(8), 699.

Lowe, M. A., Reeves, D. L., & Long, E. (2002). *Warm water diving 1999: Neuropsychological findings* (NEDU-TR-02-11). Panama City, FL: Navy Experimental Diving Unit.

Lowe, M. A., Reeves, D. L., & Kane, R. (in press). *Construct validity of the automated neuropsychological assessment metrics (ANAM) Battery used in U.S. Navy Diving Research*. Camp Pendleton, CA: Naval Hospital Technical Report.

McDiarmid, M. A., Keogh, J. P., Hooper, F. J., McPhaul, K., Squibb, K., Kane, R., et al. (2000). Health effects of depleted uranium on exposed Gulf War Veterans. *Environmental Research: Section A*, *82*, 168–180.

McDiarmid, M. A., Squibb, K., Engelhardt, S., Oliver, M., Gucer, P., Wilson, D., et al. (2001). Surveillance of depleted uranium exposed Gulf War veterans: health effects observed in an enlarged "friendly fire" cohort. *Journal of Occupational and Environmental Medicine*, *43*(12), 991–1000.

Muza, S. R., Kaminsky, D., Fulco, C. S., Banderet, L. E., & Cymerman, A. (2004). Cysteinyl leukotriene blockade does not prevent acute mountain sickness. *Aviation, Space, and Environmental Medicine*, *75*, 413–419.

Muza, S. R., Kaminsky, D., Fulco, C. S., Sonna, L. A., Banderet, L. E., Kane, et al. (2001). *Effect of cysteinyl leukotriene blockade on development of acute mountain sickness* (Technical Report T-01/12). Natick, MA: US Army Research Institute of Environmental Medicine.

Rahill, A., Weiss, B., et al. (1996). Human performance during exposure to toluene. *Aviation, Space, and Environmental Medicine*, *67*(7), 640–647.

Reeves, D., Lowe, M., & Levinson, D. (2001). Comparative results of traditional and computerized tests in a case of decompression sickness following a saturation dive. *Archives of Clinical Neuropsychology*, *16*(8), 733.