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NAMRL TECHNICAL REPORT 09-15

EVALUATION OF SEVERAL COMMON ANTIMOTION SICKNESS MEDICATIONS AND
RECOMMENDATIONS CONCERNING THEIR POTENTIAL USEFULNESS DURING
SPECIAL OPERATIONS

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14. ABSTRACT NAMRL evaluated antimotion sickness medications to help the USSOCOM Biomedical Initiatives Steering Committee explore alternatives to meclizine. This double-blind, placebo-controlled study compared five groups (n = 30 per condition): 1) oral + transdermal placebo (control); 2) 50 mg oral meclizine + transdermal placebo; 3) 25 mg oral promethazine + transdermal placebo; 4) 0.8 mg oral scopolamine + transdermal placebo; 5) oral placebo + transdermal scopolamine (1.5 mg). Each condition included oral caffeine (200 mg). Medication efficacy was defined as the number of tilts tolerated upon reaching sustained moderate nausea during a Coriolis, cross-coupling stimulus. A past motion susceptibility rating was employed as a covariate. Performance was evaluated with cognitive and psychomotor test batteries derived from USSOCOM's Mission-Related Performance Measures. MANOVA detected no medication-related performance differences in either battery. Planned contrasts compared meclizine to promethazine and scopolamine (oral or transdermal), while controlling for past susceptibility. The only observed difference was between meclizine (M = 170 tilts, SE = 13) and oral scopolamine (M = 217, SE = 13), p = .04; however, a post-hoc comparison failed to distinguish oral scopolamine from placebo. Lack of observed medication performance differences implied that USSOCOM may consider alternatives to meclizine; however, efficacy findings were inconclusive.			
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Executive Summary

The Naval Aerospace Medical Research Laboratory (NAMRL) evaluated several antimotion sickness medications for the Biomedical Initiatives Steering Committee (BISC) of the U.S. Special Operations Command (USSOCOM). The BISC wished to explore likely alternatives to meclizine, its usual first-line defense against motion sickness. Hence, this study sought to determine whether scopolamine (oral or transdermal) or oral promethazine were more effective than oral meclizine and whether they induced unwanted performance decrements which might render them unsuitable for further evaluation by Special Operations Forces (SOF).

This double-blind, placebo-controlled, double-dummy, randomized study evaluated five independent groups ($n = 30$ per condition): 1) 50 mg oral meclizine + transdermal placebo (the comparison condition closest to the current USSOCOM regimen); 2) 25 mg oral promethazine + transdermal placebo; 3) 0.8 mg oral scopolamine + transdermal placebo; 4) oral placebo + transdermal scopolamine (1.5 mg); 5) oral + transdermal placebo (the control condition). The BISC requested that each condition also include oral caffeine (200 mg) to counteract any sedation from the treatment medications. Motion sickness was elicited via 12 roll tilts per minute during continuous yaw rotation, with yaw starting at 6 dg/s (1 rpm) and increasing by 6dg/s each minute, up to a maximum of 240 dg/s (40 rpm). The main measure of medication efficacy was the number of sickening roll head tilts tolerated upon reaching moderate nausea for 1 min. without abatement. A rating of past motion susceptibility was employed as a covariate using the Motion Sickness Susceptibility Questionnaire (MSSQ-short, Golding, 2003). Performance side-effects were evaluated with cognitive and psychomotor test batteries derived mainly from the USSOCOM's Mission-Related Performance Measures.

MANOVA detected no medication-related performance differences in the cognitive or psychomotor test battery. Planned contrasts of medication efficacy compared meclizine (the reference drug) to promethazine, oral scopolamine and transdermal scopolamine, while controlling for past susceptibility (MSSQ) via ANCOVA. Three treatment conditions (promethazine, oral scopolamine, transdermal scopolamine) were not planned for ANCOVA comparison with one another *a priori*, because they yielded similar efficacy in the literature and thus were not hypothesized to differ from one another. The planned comparisons detected a significant difference between meclizine ($M = 170$ tilts, $SE = 13$) and oral scopolamine ($M = 217$, $SE = 13$), $p = .039$, implying that significantly more sickening head movements were tolerated under oral scopolamine. Nevertheless, a *post-hoc* comparison failed to distinguish oral scopolamine from placebo, so the efficacy findings are not conclusive.

Lack of observed medication-related performance side-effects in this large battery of measures relevant to Special Operations Forces (SOF) implied that if the BISC of the USSOCOM wishes to consider further evaluation of the tested medications, they may do so without undue concern about major performance side-effects, i.e., based mainly on comparisons of relative medication efficacy. Collectively, the literature, operational and logistical concerns, and our experimental findings imply that oral scopolamine merits further evaluation under conditions where a clear distinction from placebo can be established. However, we recommend oral scopolamine should be used only if the first-line defense (meclizine) does not help the patient sufficiently; also, it should be administered with an appropriate stimulant and it should be tested before the mission, so the patient can be monitored for visual blurring or excessive drowsiness.

Introduction

Prevalence and Magnitude of the Motion Sickness Problem.

Motion sickness is common in sea, air, and land operations and represents a significant problem for the Department of Defense and NASA. Incidence estimates vary among different platforms, conditions, duties, and personnel, but the problem is very common by any estimate. Seasickness affects approximately 25% of military personnel adversely in moderate seas and 70% in rough seas (Pethybridge, 1982). Approximately 14-50% of personnel are affected by airsickness (Acromite et al., 2004); while up to 64% of military parachutists are initially afflicted (Antunano & Hernandez, 1989). Motion sickness even affects approximately 55% of Army soldiers traveling by land in a command vehicle (Cowings et al., 1999).

Since motion sickness does not require actual body motion, it is often experienced by military personnel outside the transportation setting. The vestibular brainstem is affected by stimuli other than physical acceleration; hence, whole-field visual motion triggers a type of motion sickness that afflicts roughly 30% of Navy simulator trainees and 60% of Virtual Environment users (Lawson et al., 2002). Some individuals experience lasting effects even after the cessation of the challenging visual or motion stimulus. For example, up to 8% of simulator users and 5% of sea voyagers will experience effects lasting more than six hours after cessation of the stimulus. Sometimes, such effects persist for several days (Lawson et al., 2002). Loss of normal gravity alters vestibular functioning as well. Space sickness is reported by 67% of astronauts, incurring tremendous cost (Davis et al., 1988). In fact, motion sickness medications are the most commonly-prescribed drugs in space, accounting for 47% of all medications taken (Graebe et al., 2004).

Motion sickness is costly to the government in terms of readiness, time, and money. A crew member's failure to perform required duties during rough seas is correlated with his or her past history of motion sickness susceptibility (Colwell, 2000). The experience of stomach symptoms in a moving ship simulator slows a subject's performance and makes failure to complete tasks more likely (Colwell, 2000). In fact, approximately 80% of personnel have difficulty working while seasick (Pethybridge, 1982). During North Atlantic operations aboard a 3000 ton (U.K.) Frigate, about 38% of the voyage time will be spent at Sea State 5 or above, leading to a loss of productive days at a rate of about 1 day lost per 10 at sea (or about 15 days lost over the duration of the average voyage). (Dobie, 2003.)

The distraction of nausea at sea is obvious, but a more insidious problem is motion-induced loss of alertness. During NATO Atlantic Fleet operations, the most common symptoms were fatigue and poor sleep, which were related to sea state and ship location, but not energy expenditure (Colwell, 2000). This pattern of findings tends to implicate visual-vestibular mechanisms more than simple physical fatigue due to muscular compensation for ship motion. Even aboard an aircraft carrier, the USS Kennedy (CV-67), a Senior Medical Officer (E. Hopkins III, personal communication, 2001) noted that motion-induced drowsiness indicative of sopite syndrome (Graybiel and Knepton, 1976; Lawson and Mead, 1998) was common and the need to take naps was not always traceable to sleep deprivation.

Motion sickness has operational ramifications beyond those triggered by the discomfort associated with nausea. In fact, the most commonly documented motion-related performance decrements occur in tasks that are directly relevant to situation awareness, such as tasks requiring concentration, target tracking, navigation plotting, and time estimation (Lawson et al., 2003).

Motion stimuli even affect muscular coordination and equilibrium (Lawson et al., 2003). Of special interest to USSOCOM, seasickness is known to be greatest for small vessels (Pethybridge, 1982), such as those critical to expeditionary or special operations. Naval Combat Demolition Unit 46 is a notable early example from WWII (Topics Entertainment, Markham Interview, 2002); its officer was too seasick to organize the evacuation of his men from a sinking LCT or to lead them into battle.

Countermeasures for Motion Sickness

Adaptation protocols or medications are the two most common countermeasures for motion sickness. Adaptation protocols are effective and drug-free, but implementation is time-consuming and relatively costly in terms of labor and equipment. Obviously, adaptation protocols do not provide protection until adaptation has been acquired. Finally, adaptation must be maintained via repeated exposure to motion, because much adaptation can be lost during a long layoff.

Medications are generally the cheapest and fastest-acting means to control motion sickness symptoms, but their efficacy against motion sickness is limited. Oral medications are the most common means to control motion sickness symptoms; however, their onset time is slow (compared to injectables), their efficacy varies, their absorption is disrupted by vomiting, and they may elicit unwanted side effects (Graybiel & Lackner, 1987). Transdermal delivery offers certain advantages over oral delivery (e.g., convenience, continued delivery over time, resistance to loss by vomiting), but onset time is even slower and absorption is more variable (Parrot, 1989). Perhaps the most effective administration method is injection, which has become the method of choice for astronauts in need. This method is highly effective with a relatively small dose of medication; moreover, side-effects appear to be fewer than those associated with oral or transdermal delivery (Graybiel & Lackner, 1987). However, invasive intramuscular injection could be inconvenient for military soldiers in a dynamically moving vehicle setting, because of difficulty with manual coordination, extra time required, the need for sterile handling/disposal without fluid exchange, and problems with user acceptance. Hence, oral medications are most commonly used in military operations, although faster-acting intranasal medications are being investigated for possible future use (Simmons et al., 2007; Simmons et al., 2008a,b).

Medications the USSOCOM Wished to Compare to their Current Regimen of Meclizine

According to the BISC's USSOCOM Biomedical R&D Task Statement #2005-4, several Naval Surface Warfare units requested improved treatments for motion sickness, because the currently recommended regimen of meclizine was not as effective as desired and was sometimes sedating. The USSOCOM sponsor was interested in exploring medications beyond meclizine, while still focusing on medications that were readily available on the market. Hence, the BISC of the USSOCOM requested The NAMRL to carry out a study of several common antimotion sickness medications, some of which were to be tested in combination with oral caffeine. The BISC did not wish to evaluate a stronger stimulant than caffeine, but did agree with the NAMRL's recommendation that caffeine should be administered in all conditions of the experiment in order to improve interpretation of the results concerning antimotion sickness medication efficacy. Hence, the final study the BISC sponsored entailed monitoring motion

sickness symptoms and performance side-effects among groups of participants subjected to one of five experimental conditions:

1. Current Regimen: Oral meclizine (50 mg) plus oral caffeine plus transdermal placebo.
2. Alternative Medication: Oral promethazine (25 mg) plus oral caffeine plus transdermal placebo.
3. Alternative Medication: Oral scopolamine (0.8 mg) plus oral caffeine plus transdermal placebo.
4. Alternative Medication: Oral placebo plus oral caffeine plus transdermal scopolamine patch (1.5 mg).
5. Control Condition: Oral placebo plus oral caffeine (200 mg) plus transdermal placebo (Control Condition).

A Consideration of Meclizine (the Current Regimen)

Meclizine hydrochloride (Antivert™, Bonine™), promethazine (Phenergan™), and scopolamine hydrobromide (Scopace™, Transderm-Scop™) are three well-established antimotion sickness drugs, with scopolamine or promethazine tending to offer stronger motion resistance than meclizine (Wood & Graybiel, 1968; Graybiel & Lackner, 1987; Wood et al., 1992); however, these medications have the potential for eliciting drowsiness (Wood et al., 1990). The present study administered caffeine in all conditions to minimize drowsiness and also monitored several measures of cognitive performance, subjective sleepiness, and sopite syndrome. Since meclizine is the reference medication for this study, it is described in more detail below.

According to the Biomedical Initiatives Steering Committee (BISC) of the USSOCOM, the first line of defense against motion sickness among special surface warfare units is typically meclizine hydrochloride (Antivert™, Bonine™). The recommended dosage of this over-the-counter medication is 25 to 50 mg, one hour before traveling, to be repeated every 24 hours as needed [Physicians' Desk Reference (PDR), 2000]. Meclizine is a good choice for a first-line defense against motion sickness, due to the relatively mild side-effects most users experience (PDR, 2000). However, it may not be appropriate for severe motion or for individuals of greater-than-average susceptibility. Meclizine should not be taken with alcohol. It has been noted (Kuver et al., 2004) that the depressant effects of some antimotion sickness drugs (e.g., promethazine, meclizine) will be additive if alcohol is consumed.

The most common side-effects of meclizine are drowsiness and dry mouth; rare side-effects include blurred vision (PDR, 2000). For both promethazine and meclizine, the sedating and performance effects decrease with repeated administration for three or four days; however, drowsiness may still be significant many days after starting treatment (up to seven days of significant drowsiness has been observed with meclizine, according to the U.K. Department for Transport, 2004). Meclizine can have measurable effects on evoked potentials and hand-eye coordination (Lauter et al., 1999). When more than 25mg of meclizine are administered, subjective drowsiness may occur, along with impairment of Choice Reaction Time (also called "Complex Reaction Time") and Digit Symbol Substitution. Of special concern for military missions following transportation to the theater of operations is the finding that greatest performance impairment occurs nine hours post-dose (Department of Transport, 2004).

Meclizine is slower to take effect than promethazine or scopolamine (Machen, 2004; Wood et al., 1981; Canadian Committee to Advise on Tropical Medicine and Travel, 2003), making it less

suitable than these other oral medications as a prophylactic once transportation has begun, or as a “rescue remedy” after the earliest warning symptoms of motion sickness are perceived. However, since meclizine has fewer unwanted side-effects than promethazine, it is often considered a first line of defense against weak to moderate motions (Hain, 2003). One comparison of oral scopolamine, cinnarizine, and meclizine found that meclizine conferred the most tolerance to the sickening stimulus, with no differences in the Digit-Span Test (memory) between the different countermeasures (Bashyal et al, 1998). However, the majority of research finds that promethazine and scopolamine are superior to meclizine for alleviating the symptoms of motion sickness (Dahl et al., 1984). For example, Wood, Graybiel, and Kennedy (1966) conducted a sickening test requiring the adjustment of dials arranged around the subject while he was inside a rotating room. They found the most effective drug combination was scopolamine plus amphetamine, second best was scopolamine alone, third best was amphetamine, and fourth best was meclizine. Hence, meclizine was not a top performer in this test. Wood & Graybiel (1970) compared eight drugs during the dial test in the Slow Rotation Room. They noted meclizine was not a top performer and found that increasing the dose of meclizine did not improve its effectiveness, which they asserted is a common finding with certain antimotion sickness drugs. For this reason, the NAMRL did not propose to test higher doses of meclizine in the current research, to see if greater protective benefit could be obtained while avoiding the side effects associated with stronger drugs.

Wood et al., 1985 studied the baseline side effects of motion sickness drugs, in absence of motion. Drowsiness was the side effect that appeared to have the best association with performance decrement. Combining ≥ 5 mg amphetamine with ≥ 0.8 mg doses of scopolamine or promethazine resulted in good (placebo level or better) performance on a visual pursuit tracking task. Scopolamine alone at ≥ 0.8 mg produced deficits. However, scopolamine alone at 0.6 mg or less produced no performance deficit versus placebo. Also, 50 mg of either cyclizine, meclizine, or dimenhydrinate produced no deficit versus placebo (i.e., good performance). Based on these findings, we conclude that meclizine does not always produce appreciable baseline side-effects for performance and that the dosage of stronger drugs such as scopolamine and promethazine can be controlled (or combined with other drugs) to avoid such effects. Overall, we agree with the oral medication advice of Wood et al. (1981), who recommended meclizine at 50mg for mild motions and scopolamine 0.6mg plus d-amphetamine 5mg for severe motions.

The Purpose of the Current Study

The current study sought to determine whether oral scopolamine, transdermal scopolamine, or oral promethazine would provide significantly improved resistance to sickening motion, compared to oral meclizine. Hence, our planned comparisons were of meclizine versus the three other medications. A placebo group was included to establish, *post hoc*, whether any medication which was significantly more effective than meclizine would be distinguishable from placebo as well.

Numerous measures of psychomotor and cognitive performance were evaluated to quantify any medication side-effects. In fact, one of the key operational questions was whether the BISC of the USSOCOM should consider field evaluations of antimotion sickness medication choices beyond meclizine, or if a noticeable sacrifice in performance would make such evaluations not

worthwhile. This experiment attempts to answer these questions and provides eight recommendations to the USSOCOM BISC.

Methods

Participants

The subjects consisted of 150 males ranging in age from 18 to 37 years, with the mean age of participants being 24 years ($SD = 3$). No females were recruited, because the findings of this study were meant to apply to Special Operations Forces (SOF). Based on a sample size estimate using the data of Stott et al. (1989), 30 subjects were assigned to each of the five conditions of the study. Volunteers were recruited from a pool of U.S. Naval Officer flight candidates and enlisted aviation support students waiting to begin classes at Naval Air Station Pensacola, FL. All participants were screened for past and present medical conditions, sensitivity to medications, and current physical health. Each participant gave written informed consent prior to participation. The study protocol was approved by the NAMRL Institutional Review Board, in compliance with applicable federal regulations concerning the protection of human subjects.

Apparatus and Materials

Stimulus. The most reliable and widely-employed method for eliciting motion sickness in a controlled manner was developed by Navy investigators in Pensacola, Florida (e.g., Miller & Graybiel, 1970); it consists of seated rotation in the yaw axis at constant velocity, accompanied by paced head movements out of the yaw axis. This stimulus is known as Coriolis cross-coupling. The cross-coupling test elicits at least minimal stomach symptoms in the majority of participants, usually in less than 30 mins. (Miller & Graybiel, 1970), but symptoms usually build gradually enough that test can be terminated quickly to avoid vomiting.

The current study called for yaw-axis rotation up to 240 dg/s (40 rpm) maximum while paced head movements in the roll axis were made (See Figure 1). The sickening stimulus was based loosely on the protocol of Stott et al., 1989, which calls for frequent but small changes in yaw velocity during head tilt. The rotation device is shown in Figure 2. Participants began rotating in yaw at 6 dg/s (one rpm), made 12 roll head tilts (right, up, left, up, then repeat this sequence twice more) of 40 degree-amplitude during 48 seconds of yaw rotation, then were allowed 12 seconds of rotation without head movements, during which motion sickness symptoms were reported. If, at the conclusion of the symptom assessment, the participants were not experiencing moderate nausea, they would begin rotating at 12 dg/s (two rpm), and continue the one-minute head tilt sequences, increasing yaw rotation velocity by 6 dg/s (one rpm) each minute, up to a maximum of 240 dg/s (40 rpm). The yaw velocity profile and recorded roll head tilt instructions were synchronized and controlled automatically using Labview™ software.

Head movement amplitude was controlled by padded head stops above the subject's shoulders, which were calibrated to allow for the same amount of roll head movement to each side, for each subject. The subject practiced the angle and timing of the head movements prior to rotation and was observed by a chair-mounted video camera during rotation, to ensure safety and strict compliance with the protocol. The subjects executed the head movements with their eyes open, while viewing the interior of a chair-fixed canopy which eliminated room-referenced

ambient visual cues concerning self motion (Figure 2). The interior of the canopy was lit during rotation, while the room which housed the rotating chair was dark.

Unless the subject asked to be removed from the study, this head tilt sequence was repeated at increasing dwell velocity steps of chair rotation until 1) the participant experienced moderate nausea which did not abate during one minute of cessation of head movements, 2) the participant experienced three consecutive periods of moderate nausea during roll head movements (although it abated during each one-minute rest), or 3) the participant reached 40 rpm or a total of 480 head movements without meeting endpoint criteria #1 or 2, above.

Performance Measures.

Because of the potential for the antimotion sickness drugs in this study to elicit drowsiness (Wood et al., 1990), we did *post hoc* comparisons of the relative degree of psychomotor and cognitive side-effects elicited by the medication/stimulant combinations listed above. Many of the measures were derived from Special Operations Forces Mission-Related Performance Measures (MRPM) (Thomas et al., 1994; Shurtleff et al., 1994) and are based on widely-used tests which are known to be reliable (Kane & Kay, 1992). We looked for differences in performance across medication conditions (across subjects) and from baseline (no motion) to post-motion (within subjects). We grouped the measures into those focusing on laboratory tests of psychomotor performance and those focusing on computerized tests of cognitive performance. This distinction allowed us to group similar performance tests for subsequent multivariate analysis. We also tracked several aspects of subjective response using questionnaires. The various performance tests and questionnaires are described below. The number and timing of the administration of the tests is treated in the Procedures section.

Psychomotor Tests

Maximal Handgrip Strength and Endurance. As a measure of handgrip strength, subjects performed a maximal voluntary contraction (MVC) three times with the dominant hand (Figure 3). The average of the three values was recorded. A value equal to 50% of the average MVC was calculated and displayed on a computer screen. As a measure of endurance, subjects were asked to maintain a force equal to $50 \pm 5\%$ of the average MVC for as long as possible. The average MVC, duration, and integral (force multiplied by time) were recorded.

Shooting Skills. A specially modified weapon and target system (Figure 4) was used to assess the ability of subjects to quickly acquire and hit a series of randomly presented targets. The weapon, a demilitarized M-16 rifle, operated pneumatically. When the subject pulled the trigger, a loud blast of gas was released (which mildly perturbed the sight picture) and a laser beam shot at the target. Eight target disks were mounted 18 feet from the shooting line, on computer-controlled pneumatically-activated targets. Targets were placed such that vertical and horizontal adjustments of the rifle were necessary between shots. Targets were presented one at a time and in pseudo-random order. Once a target was hit, the next target was presented. Subjects were instructed to hit as many targets as possible during a two-minute session. Number of targets hit and total number of shots taken were recorded by a laptop computer remotely connected to the weapon. The two measures of shooting performance were as follows 1) the USSCOOM MRPM (Thomas et al., 1994; Shurtleff et al., 1994) shooting score, which awarded

2 points for hitting the target in one shot, 1.4 points for hitting the target in two shots, 0.8 points for hitting the target in three shots, etc); 2) the NAMRL measure of number of hits per second, which was used because it captured speed and accuracy in one simple score and because it avoided some of the potential drawbacks of the MRPM scoring method, such as the possibility for a subject to achieve the same shooting score via different combinations of speed and accuracy (for further details, see NAMRL's evaluation of the MRPM apparatus in Appendix A).

Balance. Standing balance performance was assessed based on a portion of the Fregly Ataxia Test Battery (Fregly, 1974). Participants stood on a slightly elevated balance beam, 30 in. x 2 ¼ in., approximately 6 inches off the ground (Figure 5). Subjects were instructed to stand toe-to-heel with their legs straight and their arms crossed over their chests (known as the Sharpened Romberg stance), while wearing a set of noise dampening headphones. Subjects closed their eyes and tried to maintain balance as long as they could, for a period of up to 60 seconds. The time from eyes closed to stepping off the beam was measured with a stopwatch and recorded for three trials per assessment. The subjects were closely observed to ensure that their eyes remained closed during the task.

Visual Accommodation (VA). Near focus of Visual Accommodation was assessed using a Royal Air Force Rule (Neely, 1956), shown in Figure 6. One end of the rule was rested on the participants' cheek bones, just under the eyes. At the other end of the rule there was a small rectangular target, capable of sliding from one side of the rule to the other. Participants were instructed to read a line of text printed on the target repeatedly as the box was moved towards their eyes. Participants were instructed to say "stop" as soon as the line of text became blurred. The distance of the target from the subject's eyes was recorded (in cm).

Cognitive Tests

Five computerized tests were used to measure cognitive performance. The tests (described below) are found in the Unified Tri-Service Cognitive Performance Assessment Battery (UTC-PAB) (Englund et al., 1985) and the Walter Reed Army Institute of Research Performance Assessment Battery (WRAIR-PAB) (Thorne, Genser, Sing, & Hegge, 1985). Tests in these batteries have been used extensively (Kennedy & Bittner, 1977; Simmons & Kimball, 1982; Naitoh, 1982; Edwards et al., 1985; Reeves & Thorne, 1988; Semple, 1992). These tests show stable reliability and are generally viewed to be valid for the unique factor being measured by each test (Kennedy, Turnage, & Osteen, 1989; Cambridge Cognition Limited, 2005). Three of the tests below (Complex Reaction Time, Logical Reasoning, and Matching to Sample) were administered as they appear in USSOCOM's MRPM (Thomas et al., 1994; Shurtleff et al., 1994). Two others (Simple Reaction Time and Time Estimation) were supplied by the NAMRL due to their relevance to the detection of sedation (Simple Reaction Time) or motion side-effects (Time Estimation) (Lawson et al., 2003).

Simple Reaction Time. Simple Reaction Time consisted of the subject viewing a computer screen where the word "go" appeared on the screen (in large green font) at randomly-timed intervals. The subject was instructed to press the spacebar on the keyboard as soon as they saw the word "go" appear on the screen, at which point the word "stop" (in large red font) would

appear to confirm the button press. The amount of time (in milliseconds) from when the word “go” appeared on the screen to when the spacebar was pressed was recorded.

Complex Reaction Time. In the Complex Reaction Time test (also called Choice Reaction Time in the literature), participants were asked to use the up, down, left, or right arrows key on the keyboard to follow a black square as it rapidly moved among four boxes arrayed similarly to the arrows on the keyboard. The amount of time (in milliseconds) was recorded from the onset of movement of the black square until the correct following key was pressed. An example stimulus trial is shown in Figure 7.

Logical Reasoning. In Logical Reasoning (also called Semantic Reasoning in the literature), participants were presented with two letters: A or B in random alternating sequences (i.e. AB/BA). Statements such as: “A precedes B”, “B follows A”, “A does not follow B”, “B is not preceded by A” were presented after each pair of letters and participants indicated whether the statements were true or false by hitting the right or left arrow keys. Accuracy (percent correct) and reaction time (in milliseconds) were recorded. An example trial is shown in Figure 8.

Matching to Sample. The Matching to Sample task measured short-term spatial memory and pattern recognition skills by assessing an individual's ability to quickly and accurately identify a comparison stimulus identical to a standard stimulus presented previously. The sample stimulus (an eight-cell by eight-cell matrix) was presented on the screen for three seconds and then removed from the screen. The presentation was followed by a delay interval (either one or fifteen seconds). After the delay interval, two matrices were presented side by side on the screen. One matrix matched the original, and one differed by two cells. The subject was instructed to choose the matrix that matched the original. Twenty sample stimuli were presented, ten for each of the two delay intervals. Accuracy data and response times were recorded for each presentation. The second screen of a Matching to Sample trial is shown in Figure 9.

Time Estimation. Time Estimation was measured using a “time wall” task. The task consisted of visually tracking a square which fell at a constant rate of decent from the top of the computer screen and then disappeared behind a red “wall” about halfway down the screen. Participants were asked to hit the “Enter” key at the time they believed the square would have reached the bottom of the wall. The time estimated by the participant was recorded and used to calculate the difference between the actual and estimated times. The stimulus is shown in Figure 10.

Questionnaires

Confidential Medical Questionnaire. The NAMRL’s Confidential Medical Questionnaire (see Selected Documents and Forms, Appendix B) was a recruitment screening tool which consisted of 24 questions concerning the existence of significant medical conditions, allergies, or recent illnesses. It also asked about current level of fitness and current (last 24 hours) intake of medications and/or alcohol.

Pre-Experiment Compliance Checks. The NAMRL's Confidential Exclusionary Behavior Questionnaire and Pre-Dose Compliance Checklist (both in Appendix B) verified compliance with the behaviors required before the experiment. They consisted of questions concerning recent alcohol consumption, medicine intake, use of nicotine or herbal products, consumption of grapefruit juice, and caffeine consumption.

Motion Sickness Susceptibility Questionnaire Short-Form (MSSQ). The MSSQ-short form is an 18-item questionnaire that reliably estimates how susceptible an individual is to motion sickness based on prior exposure to motion stimuli, e.g., transportation aboard a car, boat, airplane; or amusement park ride (Golding, 2006).

Simulator Sickness Questionnaire (SSQ). The SSQ is a multi-symptom motion sickness checklist developed by Kennedy (1993) based on the Pensacola Motion Sickness Questionnaire (Hardacre & Kennedy, 1963; Kennedy & Graybiel, 1965; Kennedy, Tolhurst, and Graybiel, 1965). The scale has been through many modifications over the years; the scale used for this research was based on the expanded Kennedy list of all 26 symptoms appropriate for motion challenges (rather than sharpened for simulator challenges), rated on a 1 to 4 scale (none, slight, moderate, severe). A total score for was derived simply by summing the ratings for all 26 items.

Mild Motion Questionnaire (MMQ). The MMQ (Lawson et al., 2001; Wallace, Kass, & Lawson, 2002) is a 39-item scale intended to assess the symptoms of sopite syndrome (Graybiel & Knepton, 1976). Participants were asked to rate items on a 1 to 5 scale (not at all, a little, moderately, fairly strongly, very strongly) regarding their reactions to mild or non-sickening motions.

Stanford Sleepiness Scale (SSS). The SSS is a well established self-report measure of alertness. Participants are asked to "choose the statement that best applies to your current state". A rating of 1 indicated "feeling active and vital; alert; wide awake" and a rating of 7 indicated "almost in reverie; sleep onset soon; lost struggle to remain awake" (Hoddes et al., 1973).

NASA Task-Load Index. The NASA Task-Load Index is a semantic differential scale that asks participants to rate their current state by marking a "ruler" between the semantic opposites (Hart & Staveland, 1988). For the present study, we employed four (of six available) subscales, measuring perceived level of a) Task Difficulty, b) Performance, c) Mental/Sensory Effort, and d) Frustration associated with the computerized cognitive tests. This scale was employed because we wished to determine whether a subjective increase in effort was required in any experimental medication condition (i.e., separately from whether actual performance decrements had been detected).

Rotation Data Sheet (RDS). The RDS (Appendix B) was used to record motion sickness symptoms (based on the diagnostic symptom criteria of Miller & Graybiel, 1970) just prior to rotation, once a minute during rotation, and immediately after rotation. During each symptom assessment, participants were asked to indicate if they were experiencing any stomach awareness, stomach discomfort, or nausea. In addition to stomach/nausea symptoms, participants were asked to report on common motion sickness symptoms including: dizziness, cold sweating, increase salivation, warmth/flushing, drowsiness, and headache. Pallor was not

scored, because no direct face-to-face observations were possible during much of the experiment. Participants were asked to rate each symptom as minimal, moderate, or major, based on definitions provided prior to rotation (Lawson, 1993), with the exception of pre-nausea symptoms (stomach awareness or discomfort), which were simply noted as present or absent (Miller & Graybiel, 1970).

Procedure

Condition Randomization and Double Blinding. Study volunteers were randomly assigned to conditions using assignment without replacement. Participants in all conditions were administered both a patch and a capsule. There was no way for the participant or experimenter to identify the medication condition based on the appearance of the patch or capsule.

Participant Recruitment. During the initial recruitment sessions, potential volunteers were briefed on the purpose of the study, what the study entailed, and the risks and benefits associated with participation. Recruits who chose not to volunteer were dismissed without penalty. Recruits who decided to volunteer were asked to complete a Confidential Medical Questionnaire (Appendix B). As a screening procedure, the Confidential Medical Questionnaires were reviewed by a research assistant during recruitment sessions. Any questions pertaining to exclusionary medical criteria were referred to the medical monitor, who made the final decision concerning inclusion or exclusion. Volunteers who reported no exclusionary criteria were asked to read and sign a consent form. The protocol, consent form, and recruitment procedures were reviewed by the NAMRL Institutional Review Board. Participants were asked to refrain from, or limit, certain behaviors listed on the Confidential Exclusionary Behavior Questionnaire (Appendix B) for a specified number of days (three or seven days, depending on the behavior) prior to participation. Recruitment sessions were concluded by scheduling two consecutive participation days (one practice day, one test day) for each participant.

Practice Day (Day One). Each participant was asked to arrive at 1300 on his scheduled practice day. Upon arrival, the participant was reminded about the nature of the experiment and what he would be asked to do. The participant was asked to review, initial, and date the consent form (which he previously signed during his recruitment session). A memorandum was then placed in the participant's medical records that described the possible medications ingested by the participant during his participation in the study. This was done to enhance safety and to avoid unwarranted penalty to any military participant who might be asked to engage in a urine test during the period of his participation in the experiment. The Confidential Exclusionary Behavior Questionnaire was completed by the participant and reviewed by the experimenter.

The participant then completed two computerized questionnaires (the MSSQ and the MMQ) before beginning five performance practice sessions to become proficient at the performance tests (see Practice Sequence Checklist, Appendix B). The number of times a given test appeared in the practice sequences depended on how reliable the measure was and how quickly it became stable with practice, as indicated by past studies (e.g., Kane and Kay, 1992; McGrath, Lawson, & Kass, 2007) and by test-retest data provided by the custodians of the MRPM at Naval Experimental Dive Unit, Panama City, FL (personal communication, Dr. Dale Hyde, 2005). Additionally, logistical factors influenced the number of times a test was practiced. For

example, the maximal handgrip task is easy to learn, yet tiring to perform, so practice was limited to three sessions to avoid fatigue as a confound during practice and muscle soreness as a confound on Day 2 of testing.

During a given practice sequence, the participant performed a particular combination of physical and cognitive tasks (Appendix B Practice Sequence Checklist). The practice sequences were designed to familiarize the participant with the equipment and allow the participant to reach his performance asymptote. At the completion of each practice sequence the participant was given a ten minute break.

After all practice sequences were completed the experimenter reviewed a list of possible side effects associated with the medications being studied. The participant was escorted to the medical monitor's office at approximately 1545. The medical monitor applied a patch behind the ear of the participants' non-dominant eye (e.g., the patch was applied behind the left ear of right-eye dominant participants). The participant was instructed on how to avoid disturbing or dislodging the patch and asked to return the following morning at 0830 for his Test Day. This protocol allowed complete absorption of the transdermal scopolamine, if any was present in the patch.

Test Day (Day Two). Each participant was asked to arrive at 0830 on the day following his practice day. Upon arrival, the participant was asked to initial and date his consent form (to verify continued consent) and fill out a Pre-Dose Compliance Checklist (Appendix B). The participant was then asked if he had experienced any symptoms (since departing the laboratory the previous afternoon) which he would consider out of the ordinary or which caused him any concern. To enhance experimenter blinding concerning medication condition assignment, this symptom information (if any) was gathered and recorded in such a manner that it remained unknown to the experimenter who would be recording the subject's symptoms during rotation. The participant's response was recorded on an Adverse Event Form (Appendix B). If the participant reported experiencing any symptoms, further documentation of the symptom, duration, and severity was recorded. The participant then completed a set of computerized questionnaires which included the SSS, the MMQ, and the SSQ. At approximately 0845, the final pre-rotation assessments of performance began. The participant performed the physical and cognitive performance batteries in the following order: Visual Accommodation, Balance test, Cognitive Battery (including Simple Reaction Time, Complex Reaction Time, Logical Reasoning, and Matching to Sample), Shooting, and Handgrip. Visual Accommodation and Balance Test were performed first because they took very little time and were likely to show subtle or transient disruption. Shooting and Handgrip were assessed towards the end of the sequence because they were the most physically demanding tasks.

After completing the performance batteries the participants swallowed a capsule (medication or placebo) with 240 ml of water. The capsules were administered between 0910 and 0920 and a 60 minute break followed to allow full absorption of the oral medication, if any. At approximately 1010, the participant was reminded of the symptom definitions and was seated in the chair. The participant practice executing the roll head tilts at the prescribed amplitude and the same pace as the recorded instruction. An assessment of any symptoms or adverse events was taken before rotation commenced (again, by a person other than the experimenter assessing symptoms during rotation). At approximately 1025, the rotation test began. Hence, rotation began approximately 75 minutes after capsule administration and 18.6 hours after transdermal patch administration. Participants were rotated as described in the stimulus section above.

Following rotation, a final symptom report was recorded. The participant then began the post-rotation assessment. The performance batteries were completed in the same order as in the baseline assessment. After completing the performance tests, the participant filled out the same set of computerized questionnaires that were completed pre-rotation (i.e., SSS, MMQ, SSQ). The experimenter then removed the transdermal patch from the participant and took a final symptom/adverse event report. The participant was debriefed and confirmed as symptom-free before leaving the experiment. Any questionable cases were referred to the medical monitor.

Results

Stimulus Efficacy

The stimulus was very effective at producing motion sickness. Moderate nausea was reported by 149 of the 150 participants. One participant reached 40 rpm (the maximum chair velocity allowed in this experiment) without reporting moderate nausea, but he reported stomach discomfort that was not strong enough to be called minimal nausea.

Medication Efficacy

The meclizine group had the smallest adjusted mean ($M = 170$, the fewest sickening head movements tolerated) and the oral scopolamine group had the largest adjusted mean ($M = 217$, the most head movements tolerated). Planned contrasts examined the difference in efficacy between USSOCOM's current meclizine regimen and the three other treatment medications investigated, while partially controlling for past motion susceptibility (MSSQ score), via one-way analysis of covariance (ANCOVA). The three other medications (promethazine, oral scopolamine, transdermal scopolamine) tend to yield similar efficacy in the literature and were not hypothesized to differ from one another. Hence, the following three comparisons were planned: meclizine vs. promethazine, meclizine vs. oral scopolamine, and meclizine vs. transdermal scopolamine. The independent variable was medication condition and the dependent variable was number of sickening head movements tolerated. Results of the planned contrasts from ANCOVA were Bonferroni-adjusted to control for multiple comparisons. A significant difference was revealed between the meclizine group ($M = 170$) and the oral scopolamine group ($M = 217$), $p = .04$ (1-tailed). No other contrasts were significant (See Figure 11).

It should be noted that overall conditional differences were not significant when all five levels of the study (including three medications not hypothesized to differ from one another) were evaluated via ANCOVA (placebo, meclizine, promethazine, oral scopolamine, and transdermal scopolamine). The result of this omnibus ANCOVA fell short of significance, at $F(4, 144) = 2.09$, $p = .09$, partial $\eta^2 = 0.06$.

Following the significant meclizine versus oral scopolamine difference detected by the planned comparisons, a post-hoc comparison was conducted on oral scopolamine vs. placebo, controlling for MSSQ score. Although the oral scopolamine group ($M = 217$ head movements) was the group with the largest number of head movements tolerated and the only group that resulted in significantly more head movements than the meclizine group, a post-hoc comparison to the placebo group ($M = 181$) failed to reveal a significant difference between the oral scopolamine and placebo groups.

Performance Side Effects by Medication Condition

In general, the various performance measures were suitable for this experiment and a failure to see a performance effect would not likely be due to a lack of stability or reliability in the performance measures. More than half (6/12) of the measures were stable by the third practice trial, and 92% (11/12) of the measures were stable by the last practice trial, as revealed by the average Cohen's $d = 0.08$ when the last two practice trials were compared to one another (Turnage & Kennedy, 1992). The only measure that did not fully stabilize was Complex Reaction Time, which still showed a small (11 ms) improvement on the last practice trial. The performance measures showed good reliability as well. As in the literature and in our past research (McGrath et al., 2007, summarized in Appendix C), speed of response was more reliable than accuracy once subjects were practiced and proficient. The mean test-retest reliability of response speed in the last two practice trials was good, with a Pearson's r of 0.84. Finally, our recent assessment (McGrath et al., 2007) suggests that the measures are sensitive to environmental stressors, e.g., the first presentation of a loud, distracting noise had measurable effects on performance.

Multivariate analysis of variance (MANOVA) was conducted to determine if there were post-rotation medication condition differences detectable via the performance measures. The performance measures were grouped (for MANOVA) into those which were mainly physical/psychomotor and those which were part of the computerized cognitive test battery. Six dependent measures of post-rotation physical performance were entered into the first MANOVA. The six dependent measures of physical performance included: two measures of handgrip performance (maximum grip score and grip endurance score), two measures of shooting performance (MRPM shooting score and targets hit per second), score on the Fregly balance test, and visual accommodation score. No significant differences in physical performance were found among the five medication conditions; Pillai's Trace = .15, $F(24, 572) = .90$, $p = .61$.

In addition, a one-way MANOVA was conducted to determine if there were conditional differences (post-rotation) detected by the computerized cognitive performance measures. Five dependent measures of post-rotation cognitive performance were entered into the MANOVA. The five dependent measures of cognitive performance included; Simple Reaction Time, Complex Reaction Time, Logical Reasoning, Matching to Sample, and Time Estimation. All dependent cognitive variables were measured by reaction time (in milliseconds), which is more stable (after practice) than accuracy (Kane & Kay, 1992). No significant differences were found among the five conditions on cognitive performance measures; Pillai's Trace = .12, $F(20, 568) = .90$, $p = .60$.

Post-Rotation Questionnaire Findings by Medication Condition

Although no performance decrements were detected, it is possible that significant changes may have occurred in the participant's subjective well-being or perception of how hard he had to work to maintain his concentration or performance. A Kruskal-Wallis was conducted on all questionnaire data to determine if there were any conditional differences in subjective measures. We checked questionnaire responses for SSQ, MMQ, Stanford Sleepiness, and mental effort required to do the performance measures (NASA TLX). Of all these questionnaires, only the MMQ (Factor A) revealed a statistically significant difference among conditions, yielding $\chi^2(4,$

$N = 149$) = 11.50, $p = .02$. To determine which conditions were significantly different from one another in the MMQ, Mann-Whitney analyses were employed. These analyses revealed that subjects in the oral scopolamine condition reported significantly higher scores on MMQ Factor A after rotation, in comparison to all other conditions [p = (meclizine) .004, (placebo) .021, (transdermal) .008, (promethazine) .006]. Nevertheless, it should be noted that this statistically significant increase was not likely to be operationally significant, since the observed MMQ rating for this factor under oral scopolamine (2.3 on a scale from 1-5) was only 0.5 points higher than the condition with the lowest rating (meclizine = 1.8), and in either case, ratings near 2 would be considered “minimal.” Nevertheless, the small difference we detected in one of the five questionnaires is displayed in Figure 12.

Pre Rotation versus Post Rotation Comparisons, Regardless of Condition

We did a repeated measures assessment of performance before and after rotation, regardless of condition. This was done to determine whether the general experimental situation (medication plus rotation) was sufficiently challenging to change performance. Paired t-tests (two-tailed) detected three significant performance changes. First, Simple Reaction Time was significantly slower (by 113.79 ms) immediately after rotation plus medication ($t = -3.45$, Bonferroni-corrected $p = .009$). Second, Balance score (time on rail before stepping off) was significantly shorter (i.e., worse by 312.71 ms) immediately after rotation plus medication ($t = 7.45$, Bonferroni-corrected $p < .001$). Third, Grip Endurance was significantly longer (by 558.60 ms) immediately after rotation plus medication ($t = -3.38$, Bonferroni-corrected $p = .009$). The findings collectively imply that a failure to detect conditional performance differences in this study was not entirely due to a lack of sensitivity of all the measures to a change in state of the individual subject.

Discussion

Overall Medication Efficacy Findings and Study Limitations

This study evaluated several common antimotion sickness medications during a sickening rotation stimulus. The stimulus proved effective at producing sickness in the participants, but high variability was observed in the number of sickening head movements tolerated by individuals across the five conditions (Figure 13). Thus, the only medication found to be more effective than meclizine (the reference medication) was oral scopolamine, but this was not a conclusive finding, due to the lack of difference detected between the oral scopolamine condition and the placebo condition.

The independent design necessary for this large five-condition study contributed to the high variability that was observed. Lower variability would have been obtained with a repeated measures design. The sponsor requested five medication conditions, which we judged was too many to execute under a repeated-measures design. This decision was partly based on the observation that Benson and Bodin (1966) and Wood (2002) were not able to get more than 40-66% of their subjects to complete each rotation trial (Benson) or all experimental conditions (Wood) for their respective four-condition, repeated measures motion sickness studies.

Conversely, Denise et al. (1996) were able to successfully complete a six-condition motion sickness experiment using an independent design.

The decision to employ an independent design for this five-condition study was also based on considerations of subject recruitment and retention. A problem for any study of motion sickness is subject recruitment. Although the NAMRL has reliable access to large pools of student volunteers (e.g., Naval Aviation Schools Command, Marine Aviation Support Group, Naval Aviation Technical Training Center), recruitment is not straightforward when a study involves repeated exposures to a sickening stimulus while taking various medications. Moreover, since the study participants are aviation students, they can be called away for primary flight training before they have completed all the conditions of a repeated-measures experiment. Hence, as a result of significant subject attrition or incomplete trials, it might not be possible to collect the needed data for all five experimental conditions using a repeated measures design.

A third concern for a repeated measures design with five sickening exposures is the possibility that confounding motion adaptation would build up which would carry over from one session to the next (Graybiel & Miller, 1970; Denise et al., 1996), especially among subjects were more resistant and thus likely to ride longer. The vestibular system is very adaptable; while the confound due to adaptation can be distributed equally by balancing the order of presentation of conditions, the error is still present and can wash out the overall findings. To minimize this problem, it would be necessary to allow one week between rotation exposures if feasible, which would have required each subject to be available for five weeks for this study, further increasing the likelihood that data would be lost due to failure to complete all conditions.

For the reasons above, each subject in this study did just one baseline practice session and one experimental session over the course of two days. Our military subjects were relatively homogenous in age (most were 23-27 years old), sex (all male), education (most held a bachelor's degree), and health (all were screened for entry into a flight program), compared to many of the motion sickness studies in the literature. Nevertheless, the actual variability obtained was higher than expected, so it is possible that certain conditional differences existed that were not detectable due to a lack of statistical power; hence, we recommend that any subsequent independent design experiments of this type should employ approximately 39 subjects per condition, rather than the 30 per condition we employed (Appendix D).

Another possible reason for the failure to find more significant medication differences may have been our choice of "sickness endpoint" or stopping criteria for the experiment, i.e., moderate nausea up to three times in a row, or moderate nausea for one minute without abatement. We investigated several other criteria (minimal nausea without a pause, moderate nausea without a pause, and moderate nausea with one or two pauses allowed, instead of the original three). It was not possible to improve our findings regarding conditional differences using these other stopping criteria. In fact, the original three-pause criterion seemed to work best. Therefore, we concluded that our choice of sickness criteria was not the likely reason for failure to observe more extensive medication efficacy differences.

This study employed a single control condition consisting of caffeine plus placebo (in place of a motion sickness medication), followed by rotation. This allowed for comparison of sickening rotation conditions with or without antimotion sickness medications. However, the present study did not employ a placebo condition without any caffeine, so it is not possible to ascertain (from this study alone) the effects of rotation in the absence of any drug at all.

While the three additional control conditions described above would have assisted the interpretation of the effects of caffeine per se and rotation per se, they were not included because

the experiment requested by the sponsor already included five conditions requiring the testing of 150 subjects, with approximately eight hours of time experimenter time required to obtain data from each subject, over the course of the recruitment day, baseline/practice day, and rotation day. Hence, it was not feasible to add more conditions to the experiment with the resources available for the project.

Fortunately, since caffeine has no proven protective value against motion sickness and its effects on arousal have been very well documented for decades, limited benefit would be derived from the inclusion of a no-caffeine control condition. In fact, given the ubiquitous use of caffeine worldwide and especially during military operations, it could be argued that the caffeine-only control condition in this study allows the most realistic generalization of our findings to SOF, who have been advised to consider making limited doses of caffeine supplements available during sustained operations (Letter 6710, 12 Sep., 1997, Commander Naval Special Warfare Command).

For comparison, Table 1 shows the placebo condition results from two other recent motion sickness studies at the NAMRL (Hoyt et al., 2008; Simmons et al., 2007) which employed a placebo condition without caffeine. These experiments employed the same yaw rotation velocity profile, the same number of roll head tilts per minute, and the same diagnostic symptom criteria for obtaining ratings of motion sickness. The main difference was that the present study was the only one of which used active, voluntary roll head tilts (instead of passive roll tilts through a head-centered axis). A lesser difference is that the Simmons et al. (2007) study used somewhat different criteria for establishing the motion sickness endpoint, requiring moderate nausea to be reached even if more than three pauses were required. We conclude from the overlapping placebo results in Table 1 and from the arguments made above concerning additional control conditions that the absence of a no-caffeine placebo condition was not a serious limitation for the present study, especially when one considers that medications such as promethazine and scopolamine are generally administered by the military in combination with a stimulant of some kind.

List of Recommendations to the USSOCOM

Recommendation 1: the Biomedical Initiatives Steering Committee (BISC) of the USSOCOM should consider further evaluation of medications other than meclizine. In simple rankings of number of head movements tolerated in this study, meclizine tended to be at the bottom (fewest head movements tolerated). When the findings from this study are expressed as the mean percent improvement obtained with various medications vs. head movements tolerated under meclizine (Figure 14), it appears that a trend towards large percentage improvements may potentially be obtained with other medications, which should be evaluated further under conditions where variability and statistical power are more favorable. For example, a three-condition repeated measures comparison of just oral meclizine versus oral scopolamine versus placebo may be warranted, preferably with a gap of at least one-week between each of the three rotations tests is allowed, to reduce carry-over effects. It should be noted that Dahl, Offer-Ohlsen, Lillevold, and Sandvik (1984) found that transdermal scopolamine provided better protection than oral meclizine or placebo using a three condition repeated-measures study.

Recommendation 2: the BISC should consider further evaluation of oral scopolamine. Oral scopolamine was the only medication to show significantly improved efficacy versus meclizine,

although this finding needs to be confirmed under conditions where the placebo comparison works out favorably as well. Despite this limitation, there is much evidence from the literature (Wood & Graybiel, 1968; Graybiel & Lackner, 1987; Wood et al., 1992) that oral scopolamine is effective against motion sickness, and that it tends to be more effective than meclizine.

An interesting question is the extent to which this study is comparable to other recent NAMRL studies and to past trends from the literature. Figure 15 displays the number of head movements tolerated (head movement data lumped, regardless of experimental condition) in this experiment (Lawson et al., 2008) versus three other experiments conducted at our laboratory recently (Lawson et al., 2007; Simmons et al., 2007; Hoyt et al., 2008). All four experiments used similar participant pools, step-wise yaw rotation velocity increases of 1 rpm per minute, 12 roll head tilts per minute, and similar diagnostic criteria for motion sickness. The main difference was that the present study was the only one which used active, voluntary head movements (instead of passive roll tilts through a head-centered axis). A lesser difference is that the present study used slightly different criteria for establishing the motion sickness endpoint versus the Simmons et al. (2007) study, which allowed for more than three pauses.

When the overall findings of the four NAMRL experiments are compared in Figure 15 (regardless of condition), it can be seen that the present study (dark/blue¹ “SOCOM” histogram) is approximately in the middle of the range of head movements tolerated among the four studies. Moreover, when just the placebo groups from each study were compared with one another using a Kruskal-Wallis test, there was no significant difference detected. These two observations imply that the present USSOCOM study is not highly divergent from the other recent studies at the NAMRL in terms of the number of head tilts tolerated overall.

A gross idea of the ranking of head movements tolerated among different medications in these four NAMRL studies can be estimated in Figure 16. Medications tested in this study are shown as the dark/blue histogram bars. While the methods and stimuli were not identical in each NAMRL experiment, it is remarkable to see how closely the ranking of relative medication efficacy (by number of sickening head movements tolerated) from Figure 16 agrees with the earlier rankings established by Wood and Graybiel (1968) for comparable medications (Figure 17). In general, Figures 16 and 17 are displayed as general support for our recommendation that oral scopolamine deserves further consideration by the BISC.

Recommendation 3: the BISC should be cautious concerning the use of transdermal scopolamine. While transdermal scopolamine provides long-lasting relief from motion sickness and is convenient for the user (no pills to carry or dose schedule to remember), oral scopolamine offers greater ease of dosage adjustment than transdermal scopolamine (e.g., to body weight, motion sensitivity, motion severity, or motion duration), which is a significant advantage in the special operations setting, where dosage should be controlled carefully to achieve the best therapeutic benefit obtainable without inducing performance decrements.

There are certain practical concerns with using transdermal scopolamine during water immersion, an important aspect of Navy special operations. The Physician’s Desk Reference instructs as follows: “Keep the patch dry, if possible, to prevent it from falling off. Limited contact with water, however, as in bathing or swimming, will not affect the system.” (p. 2224: PDR 57th edition, 2003). It goes on to say: “Patients who expect to participate in underwater sports should be cautioned regarding the potentially disorienting effects of scopolamine.” (p. 2222, PDR 57th edition, 2003). The PDR also counsels on the need to avoid cutting or blistering

¹ The histogram bar will appear as darker than the others when printed in B&W and as blue when printed in color.

the patch and the need to wash one's hands after application to avoid inadvertently transferring the drug from one's fingers to one's eyes (Gahlinger, 1999).

Many of these operational disadvantages of transdermal scopolamine are not severe. The patch is not that likely to become cut unintentionally (personnel are warned not to "trim the dose" intentionally) and if the patch were worn under a wet suit, then prolonged water immersion should not be a serious problem. Nevertheless, the long delay in absorption of transdermal scopolamine (6-8 hours after application) requires precise prediction and timing of anticipated operations. Since special operations must be flexible concerning their initiation, faster-absorbing oral scopolamine may be more appropriate for such operations. Furthermore, high individual variability of absorption has been seen with transdermal scopolamine (Gil et al., 2005), possibly due to variation in the body size of the user receiving the fixed dose patch (Sherman, 2002). Finally, it appears that unwanted side-effects occur less frequently with the oral form of scopolamine (Sherman, 2002.) A final consideration against transdermal scopolamine is the recent failure of a USSOCOM-sponsored study by Estrada et al. (2007) to detect better resistance to airsickness when subjects used transdermal scopolamine instead of placebo (and better results obtained with promethazine). For these various reasons, we recommend caution when using transdermal scopolamine for special operations. Further possible drawbacks of transdermal scopolamine will become apparent in the discussion of side-effects in Recommendation 4, below.

Recommendation 4: Based on the measures, subjects, dosages and conditions employed in this experiment, performance side-effects are not likely to be the main limiting factor in similar future evaluations of medications such as oral scopolamine. Overall, no performance decrements were detected by the psychomotor or cognitive test batteries. This is particularly encouraging, since many of these tests were chosen specifically for their relevance to the basic abilities needed for special operations or for their likely sensitivity to the medications used in this experiment. Moreover, the literature (e.g., Kane & Kay, 1992) and our recent observations (e.g., McGrath et al., 2007; Appendix C) indicated that the measures were generally sensitive, stable, and reliable.

To be fully confident concerning Recommendation 4, we explored medication side-effects in more detail. Even though no significant mean performance decrements were seen for oral scopolamine nor even a subjective increase in perceived effort, it is still possible that a few people might be especially sensitive to the drug and their performance might be extremely affected by oral scopolamine, even though this change would not be reflected in the averaged group data. We explored this possibility by plotting a frequency histogram showing the number of subjects at each time interval of speed of response in Matching to Sample (see Figure 18), which was the performance measure that came closest to showing a significant difference between meclizine and oral scopolamine. For comparison, the frequency histogram for transdermal scopolamine is displayed also. Outliers were treated as evidence of possible subject sensitivity to the drug.

On the left side of Figure 18, it is clear that oral scopolamine exhibits no extreme outliers, while as right, transdermal scopolamine appears to exhibit some outliers. This implies that none of the subjects in our sample were extremely sensitive to oral scopolamine (as reflected by slowing of their speed on a Matching to Sample task), while it is possible that some of our subjects were especially sensitive to transdermal scopolamine. In fact, the outlier shown on the right side of Figure 18 was the largest observed in this study. Hence, even though no overall

performance decrements were seen in the batteries, nor even with this particular measure (Matching to Sample) in the oral scopolamine condition, we recommend that care should be taken when using transdermal scopolamine during operations, due to the possibility that certain persons are more sensitive to the transdermal form of this medication.

Similar cautions can be inferred concerning transdermal scopolamine by considering the open-ended reports of medication side-effects from the “adverse events” reporting sheets we had each subject fill out. There were no serious adverse reactions caused by the medications used in this study, but the record of clinical symptoms that were reported indicates that by far the greatest number of reports were volunteered by subjects in the transdermal scopolamine condition. Thirty reports of minimal-severity symptoms were recorded from the 30 subjects in the transdermal scopolamine condition after medication absorption and prior to rotation (i.e., across all participants during the first and second pre-rotation assessments, cumulatively), including six cases of dizziness, four of drowsiness, four of stomach symptoms, three of headache, and two of dry mouth. By contrast, only 2 – 4 minimal symptoms were reported by prior to rotation by any single group of subjects in the other four conditions (including placebo). This suggests that subjective sensitivity to transdermal scopolamine may be more prevalent than with oral scopolamine.

Recommendation 5: Special Operations Forces clinicians anticipating the use of any of the medications from this study should carry out an assessment of medication tolerance prior to recommending that the patient use the medication during mission-critical duties demanding optimal performance. Overall, no performance deficits were detected in either of the performance batteries across any of the medication conditions. Additionally, few and minimal subjective effects were detected. Nevertheless, given the sensitive and demanding nature of special operations missions, any medication that is intended for field use should be evaluated carefully on shore first, when the individual is not out on a mission. Moreover, the few non-significant performance trends in this experiment should be noted and considered as dependent measures in future studies of motion sickness countermeasures intended for use by SOF. For example, despite the fact that the MANOVA of performance speed in the computerized cognitive test battery failed to detect significant decrement overall (and hence, individual tests were not evaluated), we feel it is worth noting that one of the measures, Matching to Sample, would have shown a significant slowing of performance under transdermal scopolamine, in comparison to meclizine, had it been the only test conducted. (ANOVA n.s. at $p = 0.27$; Tukey’s post-hoc significant at $p = 0.01$). Such a finding would not typically be reported in context of our study design, but it is mentioned because the observed tendency for transdermal scopolamine to be associated with a slowing of Matching to Sample performance is large enough to be clinically worth further attention (531 ms slowing, see Figure 19). Also, the trend matches the literature and a recent clinical evaluation we made of the Matching to Sample performance of an airsick aviator (unpublished) under transdermal scopolamine. Hence, we recommend that Matching to Sample performance be evaluated in further studies of this type, and we reiterate the point that caution should be exercised in the use of transdermal scopolamine for special operations.

Recommendation 6: Evidence from this study implies that the BISC should not be concerned that large deficits in the MRPM shooting test will result from these medications; however, several improvements to the shooting test are recommended. We noted earlier that no significant decrements were observed in shooting performance across conditions. Nevertheless, since

shooting performance is such a critical aspect of special operations and will factor heavily into medication recommendations for SOF, the non-significant mean trends for shooting performance are displayed in Figure 20. We analyzed the number of targets hit per second, because this was the single best measure of accuracy and speed that we could devise, and it avoided some of the drawbacks of the scoring system inherent in the MRPM (See Appendix A). However, for ease of visual interpretation, hits per minute are displayed in Figure 20.

Note that in Figure 20, there is only a one hit per minute difference between the most different conditions (placebo versus meclizine), and no visible difference for any other condition. We conclude that this statistically insignificant result is not likely to be worth further concern operationally, either. This is particularly useful news from a logistical standpoint, because this dependent measure was the most difficult to set up of the measures employed in this study, as well as the most trouble-prone, the most expensive to maintain (due to the need for regular gas supplies), and the most susceptible to prolonged practice effects. Hence, it is useful for the BISC to know that in future studies of this type, it should be possible to obtain much valuable information concerning performance effects even in cases where the shooting measure cannot be employed easily or fails during experimentation. Elsewhere (Appendix A), we provide the BISC with specific recommendations concerning areas of suggested improvement to the existing shooting measurement apparatus, recommend an improvement to the method of scoring shooting performance, and make a suggestion concerning a new shooting system which may be a suitable replacement for the existing apparatus.

Recommendation 7: The BISC should advise personnel to increase fluid intake when caffeine is used in combination with antimotion sickness medications and advise limiting the number and size of caffeine doses. The BISC also should consider a wider range of stimulants than caffeine. Caffeine was the only stimulant requested for evaluation by the USSOCOM Task Statement of the BISC. Caffeine is very much a part of our culture and a widely accepted adjunct to our military operations. Caffeine has been shown to partially counteract the effect of scopolamine on baseline performance (Riedel et al., 1995, from U.K. Department of Transport Report No. 24, 2004). Hence, caffeine may be a cheap, accepted, and convenient way to counteract some of the drowsiness seen with common sedating antimotion sickness medicines (Canadian Committee to Advise on Tropical Medicine and Travel, 2003). However, we recommend the BISC advise the USSOCOM to have patients increase fluid intake when caffeine is taken with antimotion sickness agents, since caffeine is a diuretic. Another reason for advising increased fluid intake is that some antimotion sickness drugs cause dry mouth, and if vomiting occurs during challenging motions, a significant amount of fluid may be lost.

Caffeine has other limitations. A sizable portion of the public is already tolerant to caffeine and relatively immune to the benefits it could provide during administration of an antimotion sickness drug. Moreover, physical dependency on caffeine develops rapidly, with withdrawal causing profound headache and fatigue (Griffiths & Woodson, 1988), which could detract from readiness for the next day's duties. We recommend that the frequency and dosage of caffeine should be limited by the BISC. A report from by DeJohn et al. (1992) notes that while caffeine has been proven to enhance performance and alleviate the effects of sleep loss, the duration and magnitude of its effects are less than other stimulants and the >200mg doses likely to counteract fatigue can lead to tolerance, anxiety, tremor, and dysphoria. Along similar lines, Kaplan et al. (1997) note that a 250mg dose of caffeine produces more favorable subjective and

cognitive performance effects than a 500mg dose. Hence, higher doses of caffeine should be avoided. In general, we agree with the original USSOCOM Task Statement recommending the use of 200mg caffeine as an adjunct to antimotion sickness medications and with an earlier recommendation that caffeine supplements not exceed 200 mg per dose every 4-6 hours (Commander, Naval Special Warfare Command letter 6710, 12 Sep, 1997). We would add to this point that the total allowed number of doses should be carefully considered as well, and that a maximum number of doses should be established by the BISC, at least in routine cases where the costs of repeated dosing may outweigh the benefits.

While short-term use of caffeine should help minimize the sedative effects of certain antimotion sickness, caffeine is not likely to ameliorate sedation as much as sympathomimetics such as d-amphetamine, nor will it potentially amplify the resistance conferred by those drugs, as some limited evidence suggests d-amphetamine may do (Wood & Graybiel, 1968). While very little is known about the efficacy of coupling caffeine with antimotion sickness medications, a great deal of literature has proven the efficacy of coupling d-amphetamine with such medications. The Navy and NASA has had prolonged success coupling certain antimotion sickness medications (such as scopolamine or promethazine) with d-amphetamine. For these reasons, the BISC of the USSOCOM should consider coupling antimotion sickness medications with a wider range of stimulants than caffeine.

Recommendation 8: The BISC should consider replacing the Complex Reaction Time task in its MRPM battery with a Simple Reaction Time task. Findings from the present study and from McGrath et al. (2007) suggest that the Simple Reaction Time task takes less time to learn and perform than Complex Reaction Time and is more stable and reliable. Moreover, the Simple Reaction Time task is a widely-accepted and validated measure of cognitive arousal and medication side-effects and is available as the well-established Psychomotor Vigilance Test (Jewett et al., 1999).

Summary

It is difficult to identify the best medication countermeasure for treating motion sickness, because the drug(s) of choice will depend on the user and the situation. There are a bewildering number of factors to consider, including route of administration (pros and cons), safety of drug if used properly (e.g., percent likelihood of serious adverse reactions, risk to special groups when used outside the SoF setting (e.g., pregnant women, children), the presence of existing medical conditions that contraindicate the drug, interactions with drugs already being taken, the likelihood of misuse or abuse of certain drugs, severity of motion against which the drug is effective, duration of sickening motion anticipated (vs. duration of drug action), latency to onset of action of the drug, individual motion susceptibility of the user (high or low), the user's task demands (e.g., high alertness required or not), the predictability of onset of sickening motion (e.g., unpredictable start to many military operations, predictable start to most recreational ocean cruises), whether the symptoms have already begun by the time the medicine is taken, and whether the drug interferes with normal motion adaptation processes (Canadian Committee to Advise on Tropical Medicine and Travel, 2003). Simply selecting an anti-emetic drug that is non-sedating may not be sufficient, because certain anti-emetic drugs are ineffective against motion sickness (Reid et al., 1999; Stott et al., 1989). Moreover, some anti-emetic drugs that

prevent motion-induced emesis in animals do not do so in humans (Reid et al., 1999). The situation is complicated, indeed.

Nevertheless, consideration of the literature, operational and logistical concerns, and our experimental results collectively suggest that, of the medications tested in this experiment, oral scopolamine appears to be of potential interest for further evaluation as a therapeutic during special operations. We recommend that it be used only after a more conclusive experimental evaluation is completed, it should be tried only if the usual “first-line defense” (meclizine) does not help the patient sufficiently, and it should be tested by each patient on shore (before the mission), during which time the patient should be monitored for visual blurring, excessive drowsiness (the most common PDR side effects of relevance to special operations), and, when feasible, working memory for visual patterns (Matching to Sample performance – the most likely deficit to occur, based on our experimental findings). Finally, we recommend that oral scopolamine should always be accompanied by an appropriate stimulant (the most common choice being d-amphetamine).

In general, any antimotion sickness drug should be tried by the patient to assess tolerance before his or her mission and many such drugs should be combined with an appropriate stimulant. If the eight recommendations and related cautions in the discussion section of this report are followed by the USSOCOM, then we expect that improved motion sickness protection will become available to future SOF, without compromising mission effectiveness or safety.

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Table 1
Means and Standard Errors of Number of Head Movements Tolerated for the Control Conditions in Three Recent NAMRL Motion Sickness Studies

Study	Condition	<i>M</i>	<i>SE</i>	<i>n</i>
Present Study	Placebo + caffeine	181*	13.21	30
Simmons et al., 2008	Placebo	210*	28.13	18
Hoyt et al., 2008	Placebo	213	23.48	20

* Estimated marginal mean (adjusted for MSSQ score) is reported.

Figure 1. The sickening Coriolis, cross-coupling stimulus: yaw-axis body rotation plus roll-axis head movements.

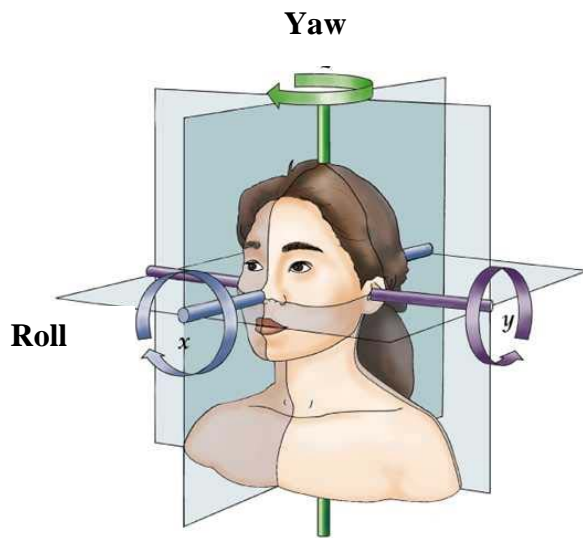


Figure 2. Rotating chair, showing adjustable head stops and visual canopy (being closed).



Figure 3. Grip strength test.



Figure 4. Shooting test, depicting the shoot and the targets. In this case, the middle-right target has just become visible and the shooter must shoot directly in the center of the disk.



Figure 5. The balance test.

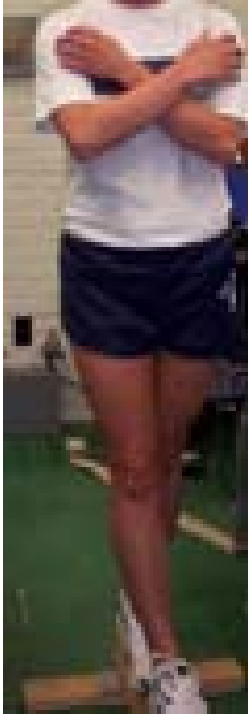


Figure 6. The Visual Accommodation task (of near focus)



Figure 7. The Complex Reaction Time task. In this case, the “up” arrow should be selected.

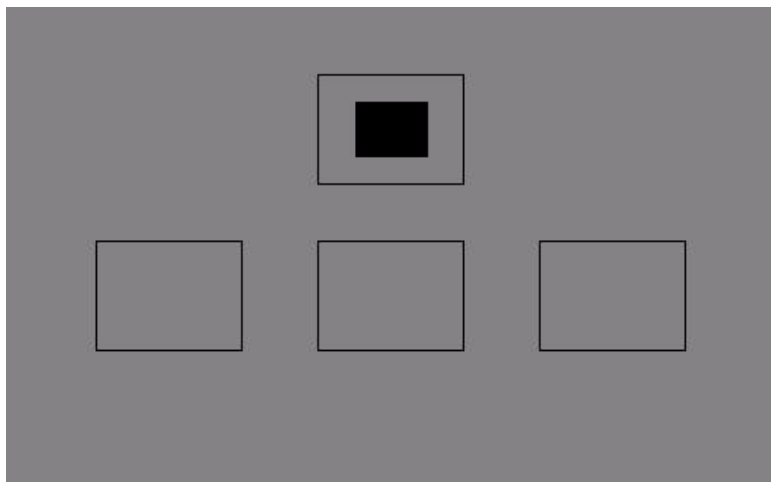


Figure 8. The Logical Reasoning task. In this case, the left-pointing arrow should be selected.

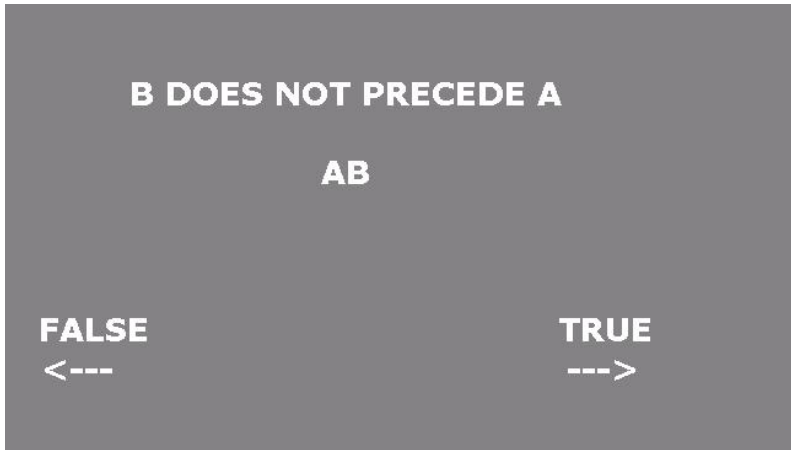


Figure 9. Matching to Sample task. If the left pattern had just been observed in the last screen, then the subject should select the left arrow in the final screen shown above.

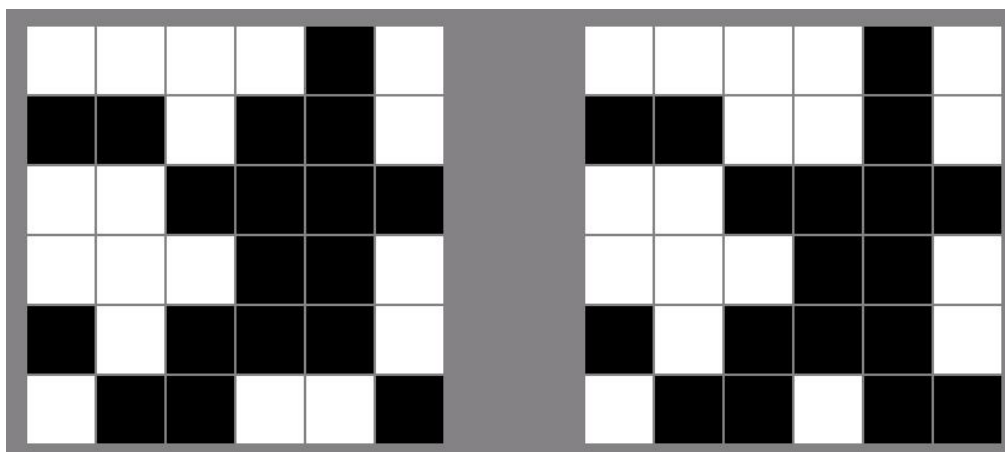


Figure 10. Time Estimation task. The falling square is shown near the bottom of the stimulus.

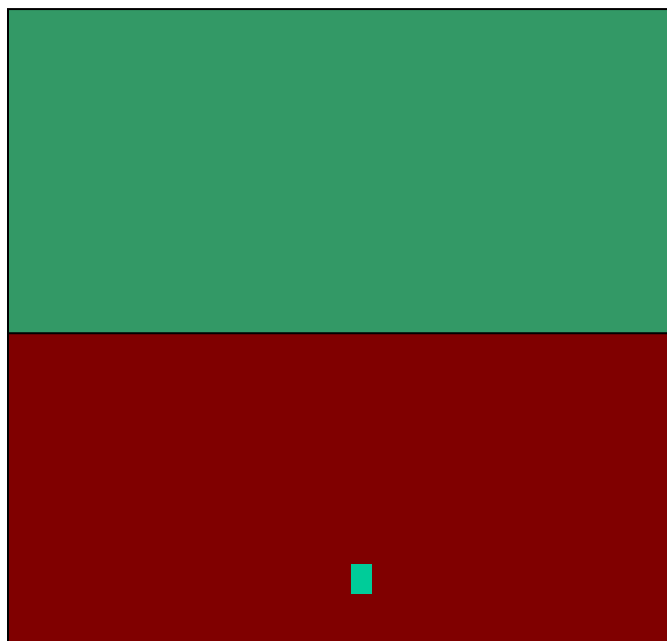


Figure 11. Mean head movements tolerated by condition

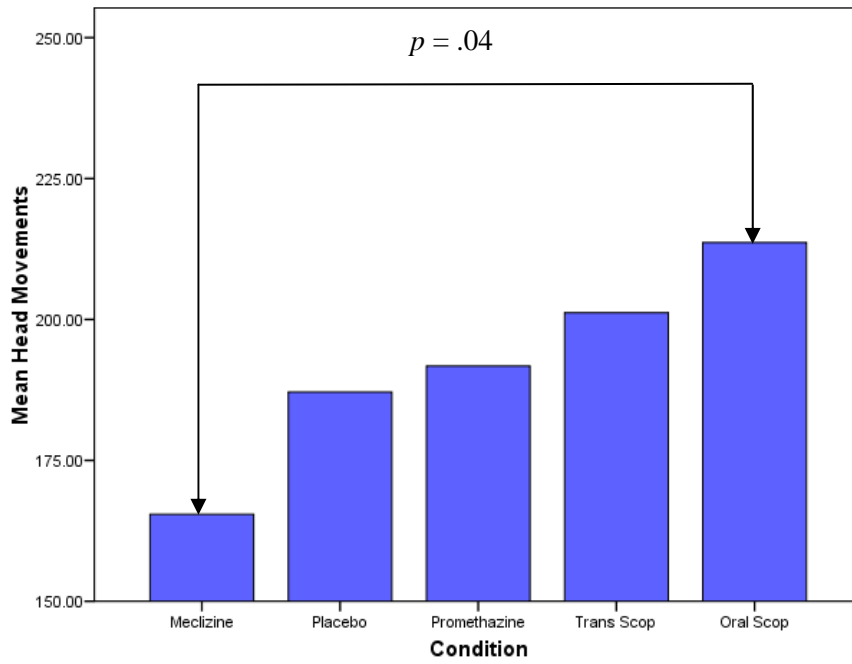


Figure 12. A significant, but small increase in subjective effect under oral scopolamine, found in one of factors from one questionnaire (MMQ). Medians and 95% confidence intervals are displayed, along with the size of the difference between oral scopolamine and meclizine.

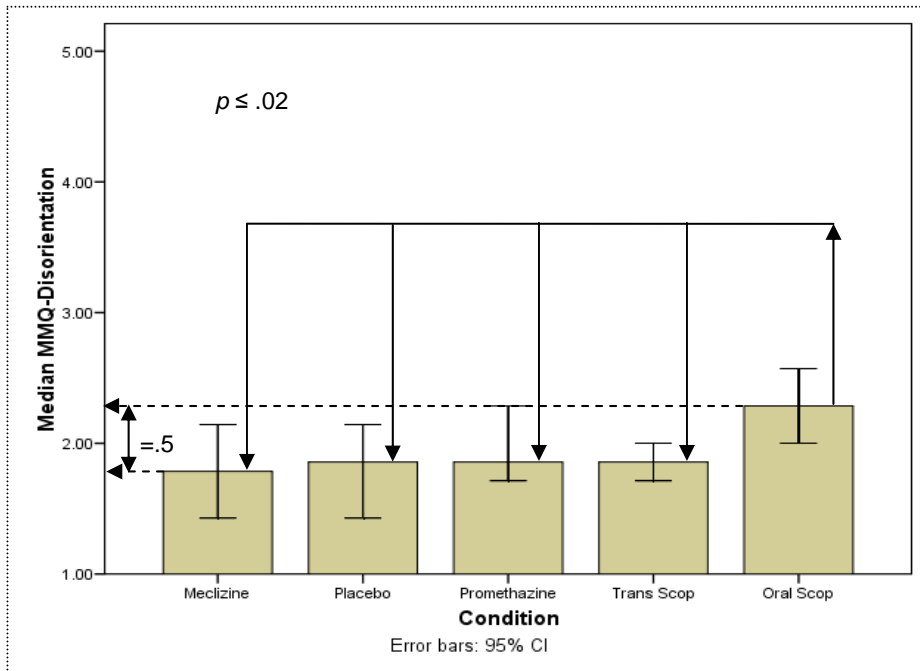


Figure 13. Mean and standard deviation of head movements tolerated by condition, showing high individual variability.

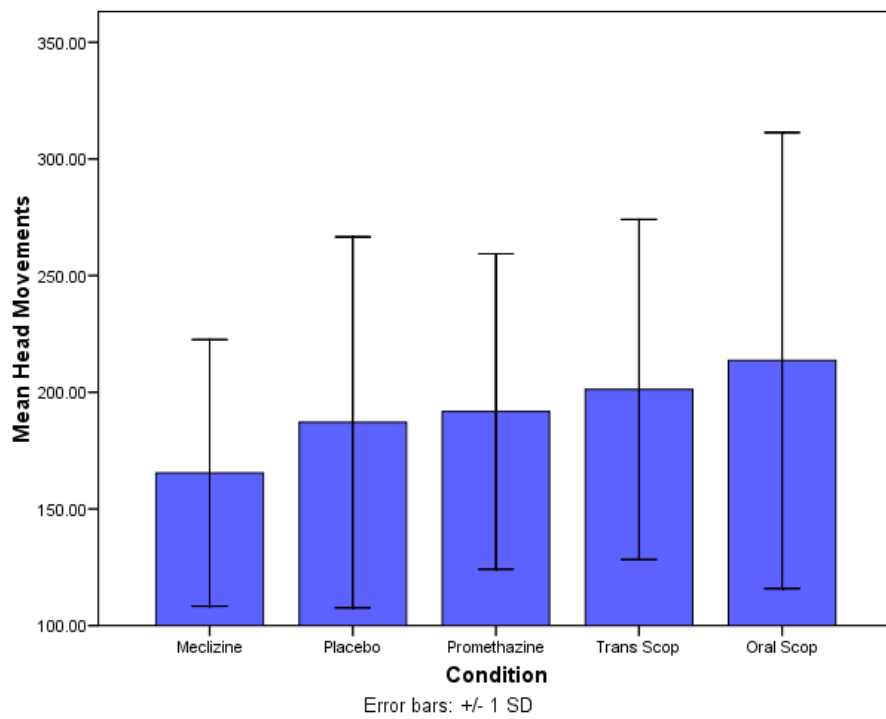


Figure 14. Percent increase in head movements tolerated under three medications, relative to meclizine (as reference).

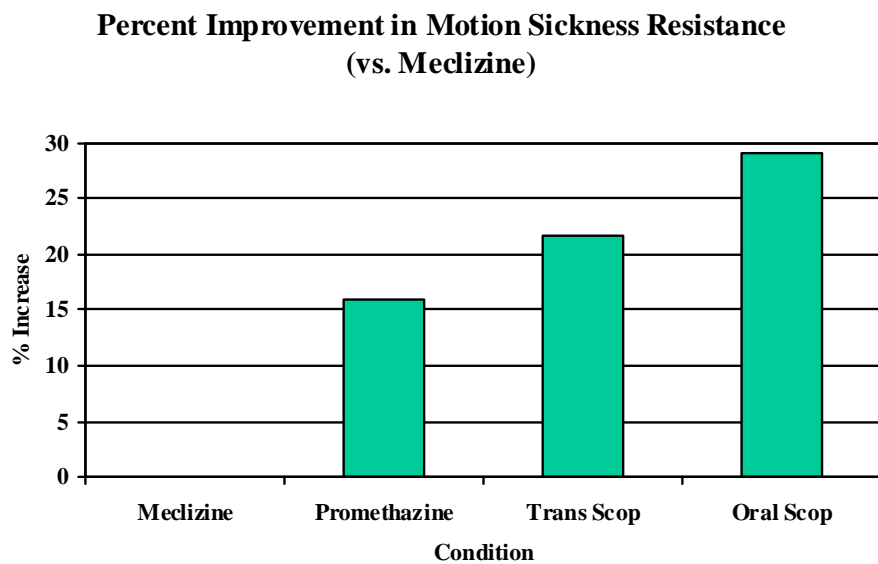


Figure 15. Comparison of the present study (dark/blue “SOCOM” histogram) to three other recent studies at the NAMRL (“Alcohol” = Lawson et al., 2007; “INScop” = Simmons et al., 2007; “Modafinil” = Hoyt et al., 2008.)

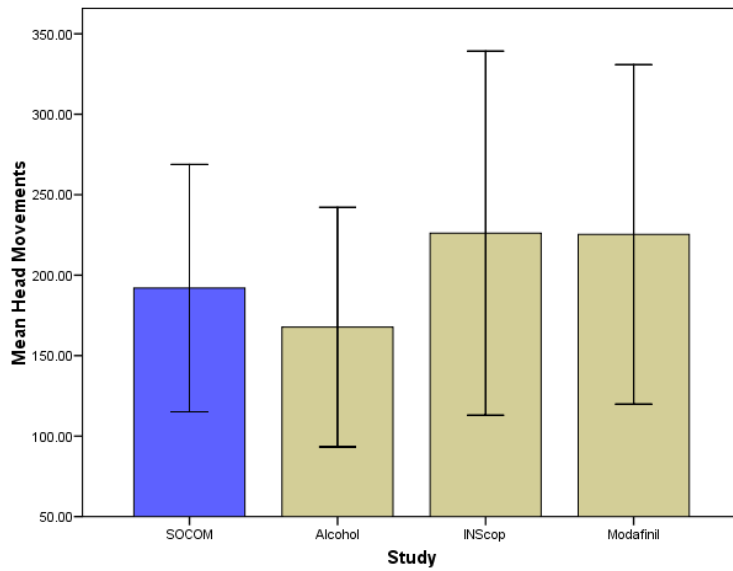


Figure 16. Simple ranking of medication efficacy in the present study (the four dark/blue histogram bars) versus other recent experiments at the NAMRL. More head movements implies a possible trend towards greater efficacy.

Head Movements by Condition

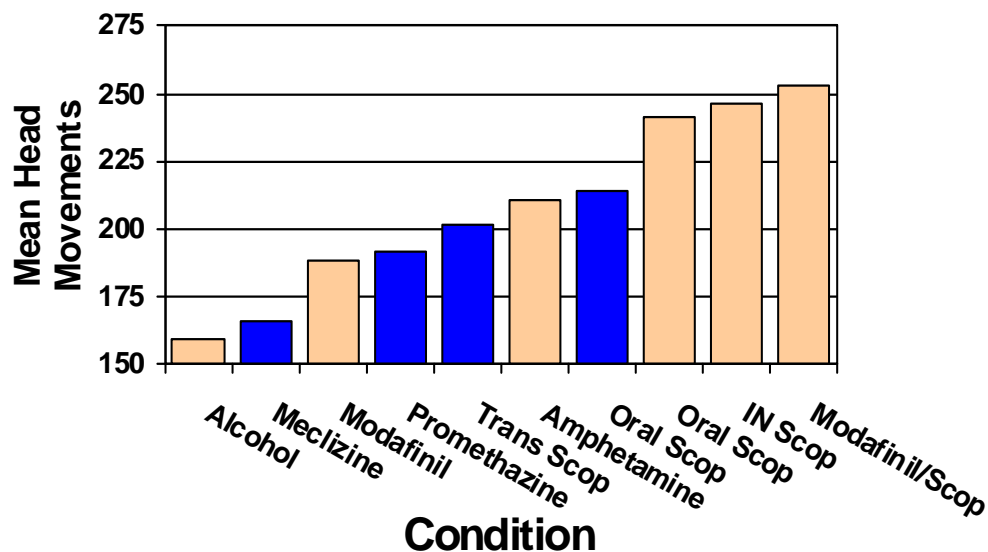


Figure 17. Simple ranking of medication efficacy in experiments summarized by Wood and Graybiel, showing a similar relative ranking of medications as in Figure 16. Note that oral scopolamine consistently ranks higher than promethazine, which consistently ranks higher than meclizine.

Wood & Graybiel (1968)

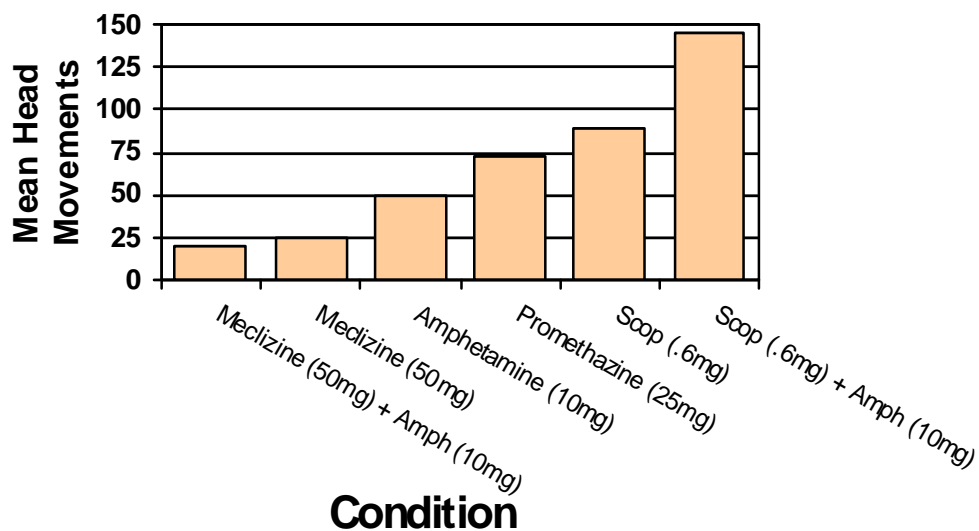


Figure 18. Evaluation of whether any subjects were extremely sensitive to scopolamine. Oral scopolamine at left, transdermal scopolamine at right.

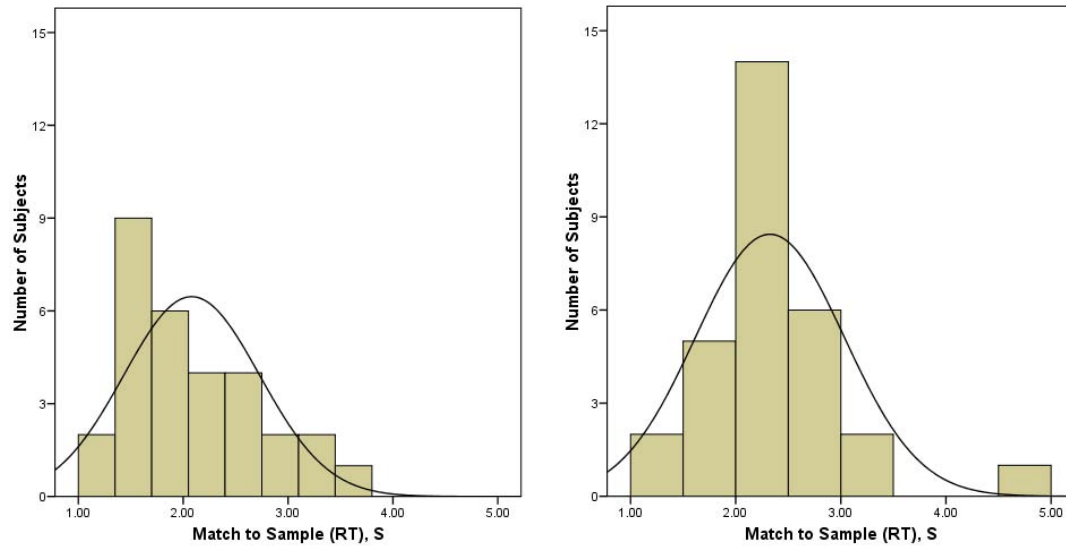


Figure 19. Limited evidence concerning a possible performance decrement in one measure (Matching to Sample); not significant in MANOVA with other measures.

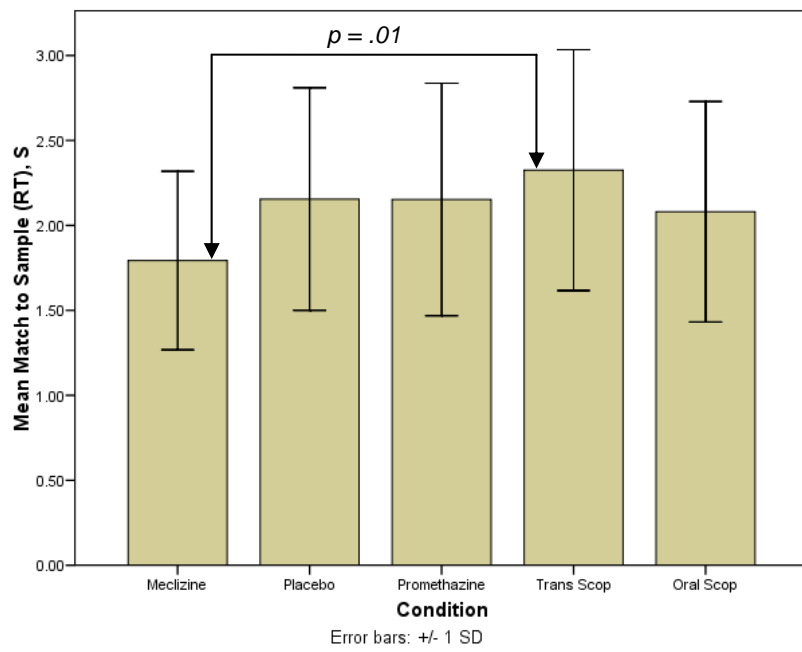
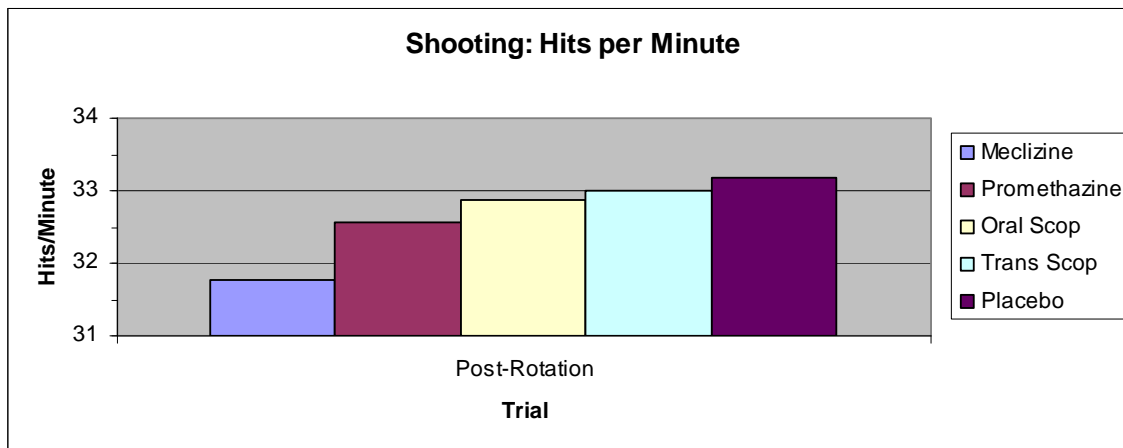


Figure 20. Shooting performance: no difference in number of hits across different medication conditions.



Appendix A

NAMRL Evaluation of USSOCOM's MRPM Apparatus

This appendix briefly summarizes the “lessons learned” after running 150 subjects with the MRPM apparatus which is maintained by the Naval Experimental Diving Unit (NEDU, Panama City, FL) and is recommended by the BISC for the assessment of human performance in USSOCOM-sponsored studies. The main problems we encountered were with the shooting system. Lesser difficulties were encountered with the handgrip system and the old laptops which ran the various measures of the MRPM. A brief summary of problems and recommendations shown below; it is derived from a 19 September 2007 PowerPoint brief distributed to the BISC and NEDU.

Lessons Learned...

Afterthoughts Regarding **Shooting, Handgrip & Laptop Performance**

Including:

Obstacles Encountered ☹️

Mitigations 😊

&

Recommendations

Shooting: The Rifle



- Trigger occasionally stuck 😊 → Problem fixed after rifle disassembly
- Trigger double fired (randomly) 😞 → Participants occasionally reported being disturbed by the double fire
- 😊 → Double shots were not counted by the scoring system

Shooting: Targets





- Occasionally targets would not flip 😞 →problem with gas flow to targets
→problem only fixed with target disassembly (time consuming)
- 1st shooting test of the day: presentation of 3rd target was delayed 😊 →after the first session the system worked fine
→experimenters completed a dry run prior to participant arrival
→the delay never occurred during a participant run








Shooting: Gas System



- Changing the tanks  → time consuming
→ heavy
→ expensive to replace empties
- Gas leaks (tank to rifle)  → leaking gas = wasting \$
 → easy to locate leak & fix
- Blocks in gas lines (tank to targets)  → targets would not flip

Shooting: Scoring

- Recording Errors  → scores occasionally reported fewer shots than target hits (*impossible : you can't more targets than you take shots*)
- Lacks specificity  → different performances result in the same score
 → alternative scoring procedures can be adopted (e.g., # hits per second)

Shooting: Common Participant Complaints

- Rifle lacks realism
 - Lack of kick
 - Feel of the trigger (little resistance)
- Random double firing

Shooting System RECOMMENDATIONS...



- Consider an electronic based shooting system

Our #1 Recommendation...



Mini-RETS Range System by MPRI-Training Technology Group
(product information available @ www.beamhit.com)

Handgrip: Calibration




- Temperature changes affected calibration  → daily calibration was necessary during winter months
- Time consuming to calibrate daily  → ≈ 15 to 20 minutes to properly calibrate

Handgrip: Data Recording

- Max grip not recorded if squeezes were too quick  → had to remind participants to squeeze for ≈ 1 second
-  → not a big problem – participants were instructed to squeeze again

Handgrip: Common Participant Complaints

- Slippery (if hands were slightly sweaty) 
- Discomfort
 - participants experienced some pain during repeated grip tests

Handgrip: RECOMMENDATIONS...

- Consider self-calibrating grip devices
 - Improve on current grip device:
 - rubber grip (less painful)

Laptops

- Slow
- Frequently froze up

RECOMMENDATIONS...

- Upgrade



Appendix B

Selected NAMRL Documents and Forms Used in this Study

This Appendix shows several NAMRL documents or forms mentioned in the body of the paper, including (in order) the **Confidential Medical Questionnaire** (for determine subject health status and safety to participate), the **Confidential Exclusionary Behavior Questionnaire** (for determining if the subject has engaged in any behaviors that would exclude him from participation until a wash-out period elapsed), the **Mild Motion Questionnaire** (for determining reactions to mild or non-sickening motion), the **Rotation Data Sheet** (for monitoring symptoms minute by minute during the study to determine when to end the experiment), the **Practice Sequence Checklist** (for determining the number and sequence of cognitive tasks during the practice session), the **Pre-Dose Compliance Checklist** (a last check before taking the study medications to ensure the subject has not engaged in any exclusionary behaviors), and the **Adverse Event Form** (for tracking any side-effects the subject experiences).

OVR - Confidential Medical Questionnaire

Subject Number: _____ **Gender:** Male / Female

Age: _____ **Hand Dominance:** Right / Left

Height: _____ **Weight:** _____

Part I-

Directions: The following is a list of medical conditions. If you currently suffer from or have ever been diagnosed with the condition, please circle **Yes**. If not, please circle **No**. If you are unsure, please discuss the question with the experimenter. The only reason we are asking these questions is to be sure that it is safe for you to be in this study.

- | | | |
|---|------------|-----------|
| 1. Have you ever been diagnosed with an inner ear disorder?
(e.g. Menier's syndrome) | Yes | No |
| 2. Do you currently or have you ever been diagnosed with asthma? | Yes | No |
| 3. Do you have a history of or currently suffer from severe allergies? | Yes | No |
| 4. Have you ever been diagnosed with sleep apnea? | Yes | No |
| 5. Have you ever been diagnosed with a seizure disorder? | Yes | No |
| 6. Do you currently or have you ever suffered from liver/kidney problems? | Yes | No |
| 7. Do you have a history of urinary retention? | Yes | No |
| 8. Have you ever been diagnosed with heart/circulatory disease? | Yes | No |
| 9. Do you currently suffer from high blood pressure? | Yes | No |

e) Are you fully recovered? YES NO

3. How much alcohol have you consumed during the past 72 hours?

_____ 12 oz. cans/bottles of beer _____ ounces wine _____ ounces hard liquor

4. How much caffeine have you consumed during the past 72 hours? (please list the beverages/ food and amounts)

4. Have you engaged in any of the following activities during the past week?

- a) Consumption of herbal products (including vitamins)
- b) Consumption of prescription or over-the-counter medications
- c) Tobacco / Nicotine use
- d) Participation in an investigational drug study
- e) Blood donation
- f) NONE OF THE ABOVE

5. a) How many hours of sleep did you get last night? _____ hours

b) Was this amount sufficient? (Circle one) YES NO

6. Please list any other comments regarding your present physical state which might affect your performance on our test battery.

Confidential Exclusionary Behavior Questionnaire

Directions: Please answer the following questions honestly, and to the best of your ability. Some of the questions relate to your past experiences. In the questions regarding a feeling or attitude you are to use a rating from 1-5 with 1 being “strongly disagree” and 5 being “strongly agree”. Please circle the number that best reflects your feeling or attitude.

Participant Number _____(last 4)

1. Have you consumed any alcoholic drinks in the last 3 days? _____
2. Have you taken any drugs or medications in the last 7 days? _____
(yes /no)
3. Have you consumed any tobacco products in the last 7 days? _____
(yes/no)
4. If you have consumed any herbal products in the last 7 days please list the products and amounts.

5. Have you drank grapefruit juice in the last 7 days? _____
(yes/no)
6. How much caffeine have you consumed in the last 3 days? (please answer in number of 8oz cups) _____
7. If you have consumed any caffeine in the past 24 hours, please list the beverages/ food and amounts.

Thank you for your participation in this research study.

Rotation Data Sheet

OVR-SOCOM DATASHEET															Baseline Fregly (in secs):			a)	b)	c)				
ID:		Condition:			Weight (lbs):			Height (in):			Post-Rotation Fregly:			a)	b)	c)								
Age:		Gender: M / F			Hand Dominance: L R			Baseline Visual Accommodation:			Post-Rotation Visual Accommodation:													
Practice Date:					Actual Run Date:																			
	Stomach		Nausea			Dizziness			Sweating			Salivation			Warmth			Drowsiness			Headache			Pallor
	Awa	Dis	Min	Mod	Maj	Min	Mod	Maj	Min	Mod	Maj	Min	Mod	Maj	Min	Mod	Maj	Min	Mod	Maj	Min	Mod	Maj	
Pre-exp	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 1	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 2	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 3	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 4	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 5	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 6	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 7	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 8	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 9	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 10	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 11	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 12	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 13	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 14	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 15	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 16	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 17	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 18	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 19	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 20	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 21	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 22	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Post-exp	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	

HEAD MOVEMENTS:

ELAPSED:

TOTAL PAUSED:

	Stomach		Nausea			Dizziness			Sweating			Salivation			Warmth			Drowsiness			Headache			Pallor
	Awa	Dis	Min	Mod	Maj	Min	Mod	Maj	Min	Mod	Maj	Min	Mod	Maj	Min	Mod	Maj	Min	Mod	Maj	Min	Mod	Maj	
Time 23	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 24	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 25	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 26	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 27	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 28	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 29	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 30	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 31	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 32	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 33	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 34	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 35	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 36	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 37	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 38	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 39	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time 40	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Post-exp	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	

HEAD MOVEMENTS:

ELAPSED:

TOTAL PAUSED:

USSOCOM Practice Sequence Checklist

The subject completes the following five practice sequences in order. The experimenter places a check in the box when each sequence is completed.

Practice Item Code:

- CB = Cognitive Battery**
- F = Fregly (balance task)**
- HG = Handgrip**
- S = Shooting System**
- VA = Visual Accommodation**

Sequence #	Practice Items		
1	VA, CB ¹ , S, HG <input type="checkbox"/>	VA:	HG:
2	VA, CB ² , S, HG <input type="checkbox"/>	VA:	HG:
3	F, VA, CB ³ , S <input type="checkbox"/>	VA	
4	F, CB ³ , S, HG <input type="checkbox"/>		HG
5	F, VA, CB ³ , S <input type="checkbox"/>	VA	

¹ CB Sequence 1 contains: Logical Reasoning

² CB Sequence 2 contains: Logical Reasoning, Match to Sample, Simple Reaction Time, Complex Reaction Time

³ CB Sequence 3, 4 and 5 contain: Logical Reasoning, Match to Sample, Simple Reaction Time, Complex Reaction Time, Time Wall

FREGLY	Time 1 (in secs)	Time 2	Time 3
Sequence 3			
Sequence 4			
Sequence 5			

PRE-DOSE COMPLIANCE CHECKLIST

SUBJECT NUMBER:

TEST DATE: / /

TRANSDERMAL TIME: :

PO DOSE TIME: :

In the past 24 hours, have you consumed any of the following products (Please all the answers which apply):

Tobacco/
Nicotine Yes No If YES, please explain: _____

Prescription Yes No

Over-the
counter (OTC) Yes No If YES, please list the drugs: _____

Herbal Yes No If YES, please list the drugs: _____

Alcohol Yes No

Caffeine Yes No If YES, please list the beverages/ food and amounts:

Grapefruit juice Yes No

ADVERSE EVENT FORM

SUBJECT NUMBER: ADMIT DATE: / /

TRANSDERMAL TIME: : PO DOSE TIME: :

NONE

<u>ADVERSE EVENT</u>	<u>SEVERITY</u> <small>1= Mild 2= Moderate 3= Severe</small>	<u>ONSET DATE</u>	<u>ONSET TIME</u> <small>(24-hour clock)</small>	<u>END DATE</u>	<u>DURATION</u> <small>(sec, min, hrs, days)</small>	<u>PATTERN</u> <small>1= Continuous 2= Intermittent</small>	<u>RELATIONSHIP TO STUDY DRUG</u> <small>1= None 2= Remote 3= Possible 4= Probable 5= Definite</small>	<u>ACTION TAKEN</u> <small>1= None 2= OTC Drug 3= Non-Drug 4= Rx Drug 5= Hospitalized 6= Other (Please specify in COMMENTS)</small>	<u>OUTCOME</u> <small>1= Resolved 2= Ongoing 3= Alive w/ sequelae 4= Death 5= Other (Please specify in COMMENTS)</small>
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3.		<input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/>					
4.		<input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/>					
5.		<input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/>					
6.		<input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/>					
7.		<input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/>					
8.		<input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/>					

COMMENTS: _____

Appendix C

NAMRL Evaluation of Some of the Key Cognitive Measures of the MRPM

This appendix briefly summarizes the result of a separate study we did (Mc Grath et al., 2007) to independently assess the sensitivity, stability, reliability, and platform sensitivity of some of the key cognitive performance measures employed by USSOCOM in the MRPM. This appendix is derived from the abstract and slide lecture delivered to the Aerospace Medical Association annual meeting in New Orleans in May, 2007. These two items are shown respectively, below.

Abstract:

EVALUATING PERFORMANCE OF TWO COGNITIVE TEST BATTERIES UNDER CONDITIONS OF DISTRACTING NOISE.

C. MCGRATH¹, B. LAWSON¹, S. KASS²,

¹Naval Aerospace Medical Research Laboratory, Pensacola, Florida; ²University of West Florida, Pensacola, Florida

INTRODUCTION. We evaluated two cognitive test batteries: a) a PDA-based battery provided by NASA and b) a laptop-based battery provided by the U.S. Special Operations Command (USSOCOM). Of four tests in each battery, three tested the same abilities. Mean reaction time and percent correct measures from each test were assessed for reliability, practice effects, and noise sensitivity. **METHODS.** Tests included reaction time (simple and complex), running memory, matching to sample, and logical reasoning. On day 1, subjects (n = 26) practiced each test six times (trials 1-6). On day 2, subjects were assigned to one of two conditions (n = 13 each): 1) A two-trial session (i.e., trials 7-8) wherein a distracting noise was introduced in the first trial; 2) a two-trial session wherein the noise was introduced in the second trial. The noise was a 95 dB random medley of noxious noises, including: cat screeching, woman screaming, glass breaking, baby crying, gun firing, air raid siren wailing, and car alarm sounding. **RESULTS.** Performance was high, averaging 91% correct. Average speed of response was more reliable than percent correct: mean reliability of response speed was .88 overall. Practice was effective: 88% of measures were stable by trial 4. Logical reasoning was the measure most sensitive to noise. Running memory and complex reaction time were not sensitive to noise, and the remaining measures produced mixed findings. **DISCUSSION.** The tests were reliable and stable after practice. Logical reasoning was the most useful test for detecting distraction due to noise. Though the NASA and USSOCOM batteries measured similar abilities, the tests were not identical. Lack of test standardization is a common concern when data comparison is desired. Currently, we are using these tests to determine whether there are performance decrements following the use of certain antimotion sickness medications during a sickening motion stimulus.

The presentation follows:



Evaluating Performance of Two Cognitive Test Batteries Under Conditions of Distracting Noise

Purpose



- Compare two cognitive test batteries for use in subsequent studies
 1. Mission-Related Performance Measures (MRPM)
 2. Automated Readiness Evaluation System (AREST™)

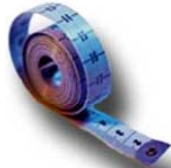
Platforms

- MRPM: Laptop
- ARES™: PDA



Test Assessments

- Stability
- Reliability
- Sensitivity



Participants

- 26 US Naval Aviation Candidates
 - 25 men, 1 woman
 - Average age 23, *SD* of 2.3



Eight Tests Evaluated

Similar tests in both platforms:

- Matching to Sample (M2S)
- Logical Reasoning (LR)
- Simple Reaction Time (SRT)

PDA ARES Only:

- Running Memory Task (RM)

Laptop MRPM Only:

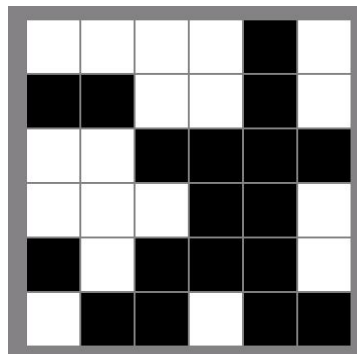
- Complex Reaction Time (CRT)



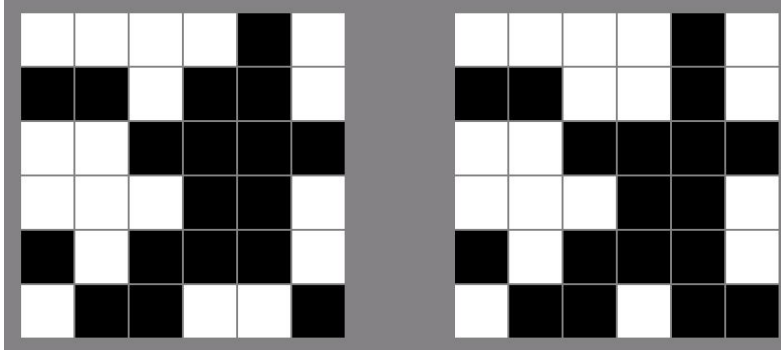
Simple Reaction Time (SRT)

STOP

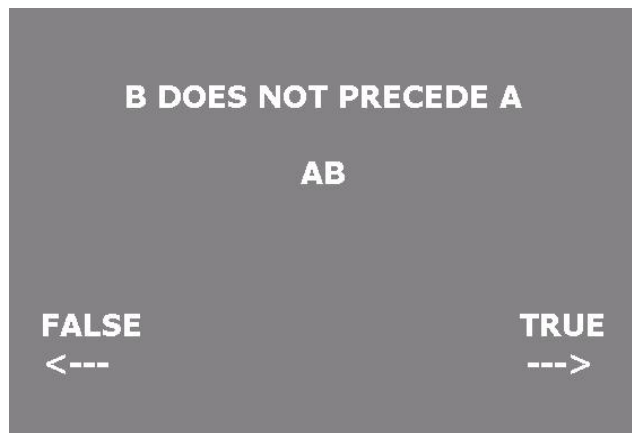
Matching to Sample (M2S)



Matching to Sample (M2S)



Logical Reasoning (LR)



Running Memory (RM) - PDA



Is next number different
or same?

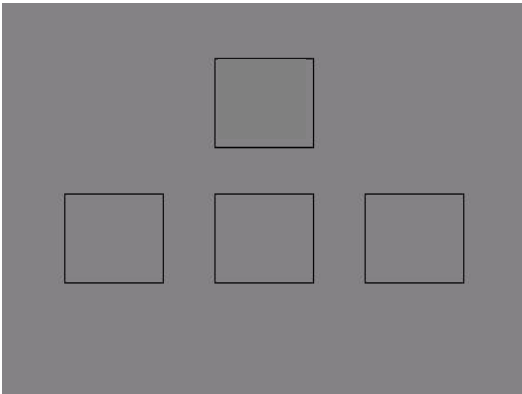
Different Same

Running Memory (RM) - PDA

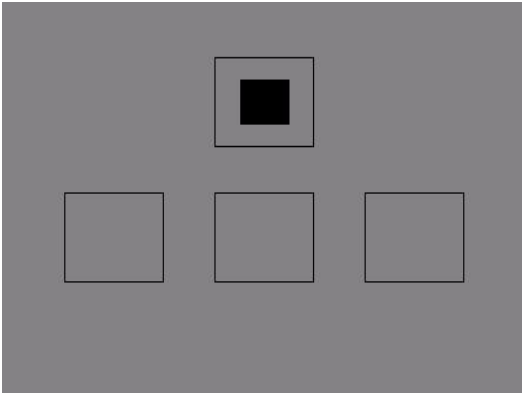


Different

Complex Reaction Time (CRT) - Laptop



Complex Reaction Time (CRT) - Laptop



Procedure – Practice (Day 1)

- One trial = Performing all 4 tests on each platform (order balanced)
 - 5 minute rest between trials
- Total of 6 trials
 - First 4 trials included performance feedback



Day 1 Results – Practice

- Across both platforms:
 - Practice was effective
 - 7/8 measures stable by trial 4
(Differential stability using Cohen's d)
 - Accuracy was high, but avg. speed more reliable (0.88) than avg. accuracy (0.76)
 - These trends agree with literature
 - Kane & Kay, 1992
 - Kennedy et al., 1992
 - Carter et al., 1986

Laptop vs. PDA Versions of Tests

- Both batteries adequate
- Test-specific observations:
 - SRT, M2S and LR faster & less variable on PDA ARES
 - M2S accuracy ceiling effect on PDA ARES

Day 2: Sensitivity

- Noise & no-noise conditions
 - Random medley of noxious noises
 - 95 decibels (well within OSHA safety limits)



Recommendations

- Give ≥ 4 practice sessions
- Measure speed of response
- Logical reasoning good performer
- Be aware that version/platform may affect performance of a given test

Appendix D

Statistical Power Estimate

A *Post hoc* power analysis was computed using the program G*Power (Erdfelder, Faul, & Buchner, 1996).² Achieved power was calculated with the following parameters:

- The analysis was conducted for a one-way fixed effects analysis of variance with five levels*
- Alpha level was set at .05 (1-tailed); .025 (2-tailed)
- Total sample size: 150 (30 per condition)
- Observed effect size f : .25 (effect size calculated from variance (i.e., partial eta squared = .06)
 - Effect Size Conventions (as given in G*Power program):
 - $f = .10$ = small
 - $f = .25$ = medium
 - $f = .40$ = large

Results:

- Power = .68 (1-tailed) ; .57 (2-tailed)

We also wished to determine what sample size would have been needed (for this study) to achieve a power of 0.80.

Results:

- Sample size needed = 39 (1-tailed); 46 (2-tailed)

Note: The analyses were conducted using all five treatment conditions; however, it should be noted that the scopolamine and promethazine conditions were not predicted to differ significantly from each other.

² Erdfelder, E., Faul, F., & Buchner, A. (1996). GPOWER: A general power analysis program. *Behavior Research Methods, Instruments, & Computers*, 28, 1-11.