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<p>Research has demonstrated that the majority of antihistamines (H1 antagonists) have sedative effects and can impair psychomotor performance; however, it is claimed that astemizole (hismanal) does not possess central nervous system side effects. A two-factor, repeated measures, double-blind design was used to compare the effects of three treatments (two antihistamines and one placebo) on cognitive information processing, mood, selected physiological measures, subjective feelings of drowsiness, and subjective performance ratings in 28 healthy men. Evaluations were given at 1,3,5,7,9,11,13, and 15 hours post ingestion. Time-of-day effects were evident in following directions, unstable tracking, code substitution, serial addition/subtraction, logical reasoning, manikin, and pattern comparison tasks. A general trend of improved scores through the day was observed and a temporal pattern of a low performance was suggested in the afternoon (2:00 pm and 4:00 pm). Temporal effects were noted for physiological measures.</p>					
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SUMMARY

Benadryl produced performance decrements at one hour post ingestion on the following directions task, at one and a half hours on the unstable tracking task, and at three hours on the serial addition/subtraction task. No decrements in performance were found post ingestion of hismanal and, in fact, the hismanal group performed the serial addition/subtraction task more quickly than either the placebo or benadryl groups at five hours post ingestion. At three and a half hours post ingestion, the performance of the benadryl group remained poorer than the hismanal group on unstable tracking, but was not different from the placebo group.

A higher level of tension, greater fatigue, and lower level of activity was experienced post benadryl. Lower vigor-activity and higher confusion-bewilderment post hismanal and benadryl were noted one hour post ingestion; however, confusion was lower and activity was higher for hismanal than benadryl. Low vigor-activity, high confusion, increased sleepiness, and low perceived performance post benadryl persisted for three hours, while fatigue-inertia persisted for seven hours. Subjects were able to determine receipt of a placebo versus an antihistamine following ingestion of either a placebo or benadryl. Results suggest that hismanal is superior to benadryl for avoidance of subjective effects and performance of information processing tasks.

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PI Signature

H. Snyder

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INTRODUCTION

Problem Statement

The classic antihistamines (H1-receptor antagonists) are lipid soluble and cross the blood-brain barrier easily, resulting in central nervous system effects such as sedation, drowsiness, and altered psychomotor performance (Hindmarch and Easton, 1986; Nicholson, Smith, and Spencer, 1982; Roth, 1987; White and Rumbold, 1988). The presence of these central nervous system effects has led to the assumption that tasks such as operation of heavy machinery, vehicle manipulation, and performance of complex cognitive tasks may be impaired. One item which interferes with the generalized acceptance of this supposition is the conflicting results of psychomotor performance tests following ingestion of antihistamines (White and Rumbold, 1988). The World Health Organization (1983) noted that apparent contradictions among studies with various drugs may be the result of the differing experimental tasks. Also of interest is the availability of three new antihistamines--astemizole (hismanal), terfenadine (seldane), and loratadine--which cross the blood-brain barrier with difficulty. Research indicates hismanal (Chapman and Rawlins, 1982; Gier, Kuijpers, and Nelemans, 1985; Hindmarch and Easton, 1986; Nicholson, Smith and Spencer, 1982; Nicholson and Stone, 1982; Richards, Brogden, Heel, Speight, and Avery, 1984), seldane (Clarke and Nicholson, 1978; Kulshrestha, Gupta, Turner and Wadsworth, 1978; Moser, Huther, Kock-Weser, and Lundt, 1978; Nicholson, Smith and Spencer, 1982, Nicholson and Stone, 1982; Sorkin and Heel, 1985), and loratadine (Kreutner, 1987; Roth, 1987) have few, if any, sedative effects. Psychomotor performance evaluations following ingestion of seldane are extensive; however, similar evaluations of hismanal and loratadine are few (see Tables 1 and 2).

The selection of hismanal for performance evaluation in this study is a result of both the number of studies which have been reported with seldane and the possible therapeutic advantage of hismanal. (Loratadine was not considered as it had not been approved for use in the United States at the time this study was introduced.) The potential benefits of using hismanal rather than seldane are the high and specific histamine H1 antagonism of hismanal (Bateman and Rawlins, 1984; Vanden Bussche, 1984), the long duration of action (Krstenansky and Cluxton, 1987; Vanden Bussche, 1984), and the effectiveness of therapeutic response in patients treated for up to a year (Wihl, Petersen,

TABLE 1

Effects of H1 Antagonists (benadryl, hismanal and seldane) on Psychomotor Performance

	Benadryl (25-50)		Hismanal (10)		Seldane (60)	
Critical flicker fusion	50:	-[18]	10:	-[13,22]	60-240:	-[1,2,3]
	100:	-[2]			60:	-[13,18,19]
					120:	-[19]
Digit-symbol substitution test	50:	+[5*,25]	10-20:	-[4]	60:	-[1,4,13,19]
	75:	-[6,7]	10:	-[13]	120:	-[19]
Arithmetic	25:	+[16]	10-20:	-[4]	60:	-[4,9,16]
	50:	-[8]				
	75:	-[7]				
	75:	+[6]				
Finger tapping	50:	-[10]				
Reaction time	25:	+[15]	10:	-[21]	60-240:	-[3,2]
	25-100:	-[11]	10:	+[22]		
	50:	+[15,20**]				
	50:	-[17]				
	100:	-[2]				
	100:	+[15]				
Tracking	25:	+[15]	10-20:	-[4,23]	60:	-[1,3,4,14,19]
	25-100:	-[8,11]	30:	-[24]	120:	-[19]
	50:	+[14,15, 17]				
	55-75:	+[6,12]				
	100:	+[15]				

*Significant effect for males only, **driving simulator

For each drug, the recommended therapeutic dose (mg PO) is indicated. Each entry shows the dose administered (mg PO), whether a significant effect was observed (+) or not (-), and the study from which the results were obtained.

1. Nicholson and Stone (1983); 2. Moser et al., (1978); 3. Luscombe et al., (1983); 4. Nicholson and Stone (1982); 5. Jaatela et al., (1971); 6. Baugh and Calvert (1977); 7. Baugh and Calvert (1976); 8. Hughes and Forney (1964); 9. Reinberg et al., (1978); 10. Carruthers et al., (1978); 11. Linnoili (1973); 12. Burns and Moskowitz (1980); 13. Nicholson, Smith and Spencer (1982); 14. Moskowitz and Burns (1988); 15. Cohen, Posner, Ashby, Smith, and Peck (1984); 16. Unchern, Unchern, Chumsawat, Sriwatanakul, and Limsuwan (1986); 17. Cohen, Hamilton, and Peck (1987); 18. Fink and Irwin (1979); 19. Nicholson and Stone (1986); 20. Gengo and Gabos (1987); 21. Dhorrantintra, Limsuwan, and Bunnag (1986); 22. Hindmarch and Easton, 1986; 23. Gier, Kuijpers, and Nelemans, 1985; 24. Hindmarch and Bhatti, 1987; 25. Gengo, Gabos, and Miller, 1989. (An adaptation of Table 1, White and Rumbold, 1988, p. 5)

TABLE 2

Effects of H1 Antagonists (triprolidine, hismanal, and seldane) on Visual Performance

	Triprolidine (10)	Hismanal (60)	Seldane (10)
Dynamic Visual Acuity	10: +[1,2,]	10: -[1,2]	60: -[1,2]
Pupil Size	10: -[1]	10: -[1]	60: -[1]

For each drug, the recommended therapeutic dose (mg PO) is indicated. Each entry shows the dose administered (mg PO), whether a significant effect was observed (+) or not (-). The results are from [1] Nicholson, Smith and Spencer (1982); [2] Nicholson and Stone (1986).

Petersen, Gundersen, Bresson, and Mygind, 1985). Studies demonstrated a decrease in effectiveness with seldane after two to four weeks (Cainelli, Seidenari, Valsecchi, and Mosca, 1986; Howarth and Holgate, 1984, as cited by Krstenansky and Cluxton, 1987). Therapeutic dosage of hismanal is 10 mg administered once a day. This dosage can significantly increase compliance as individuals do not have to remember how much time has passed in order to calculate their next dose. The half life of hismanal is calculated to be 24 hours (Heykants, 1984), which means that if one day of administration were missed, therapeutic benefits would be maintained. Validation of a test system with drugs of known sedative potential is essential before assessment of new drugs is performed (Cohen, Posner, Ashby, Smith, and Peck, 1984). Therefore, diphenhydramine (benadryl) was selected to serve as a positive control. A positive control implies the use of a drug which has been shown to have specific effects while testing a "new" drug. In this case, benadryl is known to have central nervous system effects. The positive control provides assurance that any effect or lack of effect shown by subjects that have ingested the new drug (hismanal) is due to the action of that drug.

Individuals suffering from allergic rhinitis, perennial or seasonal (hay fever), with its associated symptoms (rhinorrhea-runny nose, pruritus-itching, and lacrimation-tearing) may be reluctant to seek medical attention for numerous reasons (for example, pilots may be reluctant to be taken off flight status and truck drivers or assembly line employees may resist being taken off of a job). Instead they may choose to self medicate with available over-the-counter medications. These drugs, many of which are antihistamines (such as benadryl) or contain antihistamines (cold medications) can cause sedation and result in performance deficits. For pilots, Whitehurst (1980) cautions against the use of drugs which may potentially affect pilot judgement, vision, or fine motor coordination, or which may reduce tolerance to hypoxia. Antihistamines are included in this list. Identification of a medication that does not cause sedation would allow physicians to prescribe medications which would permit missions to proceed unhampered by either the symptoms of the illness or the side effects of the drug.

In addition, an assessment battery that is sensitive to therapeutic doses of antihistamines could be used as an assessment tool to determine an individual's ability to perform certain activities (given that the activities require skills which are similar to those tested in the assessment battery). The assessments may also be applicable to other drugs, such as other antihistamines, drugs essential during chemical warfare (antidotes), or drugs used to treat other medical conditions. The methods of evaluation currently used in

antihistamine/psychomotor research and the evaluations themselves are not comparable across studies. The exact manner in which the tasks are developed, administered, and scored are often not reported in the literature or differ from one study to another. For example, Fink and Irwin (1979) did not pre-train subjects, Moskowitz and Burns (1988) gave two training sessions, while Unchern, Unchern, Chumsawat, Sriwatanakul, and Limsuwan (1986) trained subjects for one full day so that they reached "optimal performance level." In addition, there are many types of tracking tasks and many forms of digit symbol substitution and arithmetic tasks. The standardization of performance evaluations and the methodology used is of utmost importance for comparison of research findings.

Assessments used in this research included portions of the Unified Tri-Service Assessment Battery (UTC-PAB) and the Complex Cognitive Assessment Battery (CCAB). These computerized assessment batteries were developed for use in assessment of the effects of pre-treatment drugs (medications which are used as counter agents in chemical warfare) on the complex cognitive abilities required to perform critical U. S. Army tasks (Analytical Assessments Corporation, 1988; Perez, Masline, Ramsey, and Urban, 1987). The purpose of this research was to determine whether selected cognitive tasks are sensitive to therapeutic doses of benadryl and hismanal, to identify the subjective effects of the two antihistamines, and to determine whether subjects were able to detect their own performance decay.

REVIEW OF THE LITERATURE AND TEST METHODOLOGY

Histamine/Antihistamine

Histamine occurs naturally in the body. An organic compound, $C_5H_9N_3$, it is widely distributed in the tissues, organs, body fluids (blood, plasma, gastric juice, urine, sputum, etc.) and formed elements (platelets, leukocytes, basophils) of mammals (Bergersen, 1979; Di Palma, 1971). Concentrations are especially high in the lungs, skin, and stomach (Bergersen, 1979). Histamine release can be caused by a variety of sources, such as allergens, various drugs, and tissue irritants, and can result in symptoms such as itching of the skin, a fall in blood pressure, urticaria, edema of mucous membranes, peripheral circulatory failure, bronchospasm, and increased gastric acid secretion (Di Palma, 1971). The cardiovascular effects of histamine production include relaxation or constriction of arterioles and alteration in venous tone, capillary dilation with an increase in permeability, cardiac muscle effects (diminished amplitude of the T wave, decreased conduction time, premature systoles and tachycardia), release of adrenergic mediators (Bergersen, 1979; Di Palma, 1971), and a fall of both systemic blood pressure and cerebral circulation (Bergersen, 1979; Kee-Chang-Huang, 1974). Histamine stimulates smooth muscle in man and causes marked bronchoconstriction when administered to asthmatic subjects (Bergersen, 1979; Di Palma, 1971). Histamine also stimulates lacrimal, gastric, salivary, and pancreatic glands (Bergersen, 1979; Di Palma, 1971). Histamine is considered the predominant mediator of symptoms of clinical allergy and experimental anaphylaxis through abnormal release of histamine from storage sites (Bergersen, 1979).

Antihistamines are considered to act specifically as histamine antagonists; but may also possess other properties such as anticholinergic or local anesthetic actions (Di Palma, 1971). Antihistamine drugs are considered specific because they block the actions of histamines without inducing opposite pharmacologic activities of their own. Antihistamines block the action of histamine by binding with receptors that are activated by histamine, an action known as "competitive inhibition" (Bergersen, 1979; Di Palma, 1971). Thus, antihistamines are thought to act by preventing the physiologic action of histamine. Oral dose antihistamines are used to treat allergies, urticaria (skin itching, also known as hives), upper respiratory edema, atopic dermatitis or eczema, seasonal rhinitis (hay fever), bronchial asthma (especially those with an allergic component), motion

sickness, emesis, and parkinsonian symptoms (Di Palma, 1971; Kee-Chang-Huang, 1974). Benefits of antihistamines are palliative and of brief duration. It is estimated that approximately 10 percent of the population suffers from allergies.

Antihistamines are associated with sedation in adults and can vary from decreased alertness and impaired ability to concentrate to muscular weakness and intense drowsiness (Bergersen, 1979; Di Palma, 1971). Reported side effects include loss of appetite, nausea, vomiting, epigastric distress, constipation, diarrhea, dryness of mouth, frequent urination, hypertension or hypotension, headache, faintness, tightness of the chest, and visual disturbances. High therapeutic indices (toxic dose/therapeutic dose) exist and serious toxicity from the use of antihistamines is rare (Di Palma, 1971). Minor side effects are generally alleviated by dose alteration. According to Di Palma (1971, p. 1014), "perhaps the most serious potential hazard of the injudicious use of these drugs is accident-proneness (while driving vehicles or operating machinery, for instance) as a result of experiencing characteristic drowsiness." Sedation may disappear after two or three days of treatment (Bergersen, 1979) or tolerance to the central effects (such as sedation) may develop so that sedation is no longer troublesome (Nicholson, 1983, as reported by Brandon, 1985). Brandon (1985) adds that some persons adapt well to the sedative effects and use the medications for their calming effect in daytime and insomnia at night, reporting improved performance, increased attention span, less muscle tremor, reduced tachycardia, and less restlessness. It is unclear whether sedative effects are eliminated or are merely tolerated. No specific research was cited by Brandon (1985) to substantiate assertions of improved performance following "adaptation".

Pharmacokinetics

Hismanal (Astemizole). Hismanal is produced by Janssen Pharmaceutical Company. Therapeutic dosage of hismanal is 10 mg administered once a day on an empty stomach, one hour before or two hours after a meal (Heykants, 1984). Up to 30 mg is given once daily for up to seven days, followed by 10 mg daily, when symptoms are severe. The half life of a single dose of hismanal is reported to be 20 hours (Paton and Webster, 1985) to 24 hours (Heykants, 1984), and terminal half life ranges from 9.2 to 13 days (Meuldermans, Hendricks, Lauwers, Hurkmans, Swysen, and Heykants, 1986, as reported by Krstenansky and Cluxton, 1987). Others have reported the half life of hismanal to be approximately 100 hours (Van Wauwe, Awouters, Janssen, Niemegeers,

Janssens, and Van Nueten, 1981, as reported by Seppala and Savolainen, 1982). The half life of 20 to 24 hours is for a single dose, while the half life of 100 hours is after prolonged administration and long term administration of two weeks to five months increases the half life to 18 to 20 days (Paton and Webster, 1985). Maximum plasma concentrations have been reported to occur one to four hours after single oral doses of 10 to 40 mg (Richards, Brogden, Heel, Speight and Avery, 1984). Administration with food significantly decreases bioavailability (Krstenansky and Cluxton, 1987; Richards et al., 1984).

Hismanal does not cross the blood-brain barrier easily and has a higher affinity for lung histamine-receptors than for cerebellar histamine-receptors, which may explain the lower incidence of central nervous system effects (Krstenansky and Cluxton, 1987). Hismanal is rapidly and completely absorbed in the gastrointestinal tract (Meuldermans et al., 1986, as reported by Krstenansky and Cluxton, 1987; Rombaut, Heykants, and Vanden Bussche, 1986). It is extensively metabolised and excretion is slow (mainly in the feces, within 10 to 14 days). Plasma levels of hismanal are so low, however, that terminal phase half life is reported as the combination of hismanal and active desmethylishmanal (Krstenansky and Cluxton, 1987).

Hismanal has a delayed onset of action and is therefore of limited use for treatment of acute symptoms, with effectiveness increased through initial loading above the normal maintenance dosage. Comparison of hismanal with seldane reveals no significant difference in sedation in seven trials (Howarth and Holgate, 1984; Gendreal-Reid, Simons, and Simons, 1986, as cited by Krstenansky and Cluxton, 1987). The incidence of sedation was reported to be 24 percent for seldane and 21.5 percent for hismanal in a combined report of five other studies (Cainelli, Seidenari, Valsecchi, and Mosca, 1986; Girard, Sommacol-Schopf, Bigliardi, and Henaler, 1985; Grillage, Harcup, Mayhew, and Huddleston, 1986; Rombaut, Van Roy, Bracke, and Vanden Bussche, 1986, as cited by Krstenansky and Cluxton, 1987; Wood, 1986). Absence of sedation after single doses of hismanal has been noted by Nicholson and Stone (1982) and Bateman and Rawlins (1984).

Hismanal side effects. The side effect data from over 20 efficacy trials of more than 700 hismanal treated patients resulted in central nervous system depression and dry mouth that were not significantly different from those reported with placebo (Vanden Bussche et al., 1984, as reported by Richards et al., 1984; Tables 3, 4, and 5). In a review of clinical laboratory studies involving over 500 hismanal treated patients, non-

TABLE 3

Reported Side Effects in Clinical Research with Hismanal at Therapeutic Dosage (10 mg)

Weight gain	+60:	4.4% [1] 0.098% [3]
Sedation (drowsiness/ sleepiness)	-60:	2.9% [1] 0.059% [2] 0.074% [3] 0.0 [4]
Insomnia	-84:	0.048% [4]

For each side effect, whether a significant effect was observed (+) or not (-), the number of days of hismanal administration, and the percentage individuals demonstrating the side effect is indicated.

Results obtained from: [1] Sussman and Kobric, 1985; [2] Fox, Lockey, Bukantz and Serbousek, 1986; [3] Bernstein and Bernstein, (1986); [4] Wood, 1984.

TABLE 4

Incidence (%) of Adverse Effects Reported in 744 Hismanal-treated and 331 Placebo-treated Patients (Vanden Bussche et al., 1984, as cited Richards, Brogden, Heel, Speight and Avery, 1984)

Adverse effect	Hismanal	Placebo
CNS depression	14.7	13.3
CNS stimulation	0.7	1.2
Headache	4.8	6.0
Dry mouth	5.0	4.5
Nausea	2.2	2.4
Abdominal pain	0.5	1.5
Flatulence	0.5	0.0
Diarrhea	0.9	2.1
Rash	1.2	0.3
Eczema	0.4	1.2
Increased appetite	0.5	0.6
Increased weight	0.4	0.3

TABLE 5

Incidence (%) of Adverse Effects reported in 978 Hismanal-treated and 870 Placebo-treated Patients (Vanden Bussche et al., 1987)

	Hismanal (n = 978)	Placebo (n = 870)
Central nervous system depression	6.9	7.2
Central nervous system stimulation	0.2	0.6
Headache	6.1	5.7
Dry mouth	4.6	3.6
Gastrointestinal complaints	6.2	5.2
Rash	0.3	----
Increased appetite	3.2	0.2
Increased weight	1.4	0.3

consistent changes were seen in the laboratory values and no differences in changes could be shown between hismanal treated patients and controls (Vanden Bussche et al., 1984, as reported by Richards et al., 1984). With prolonged use, hismanal may promote increased appetite and weight gain (Richards et al., 1984). Absence of sedation after single doses of hismanal has been noted by Nicholson and Stone (1982) and Bateman and Rawlins (1984). According to Rombaut, Heykants, and Vanden Bussche (1986, p. 323) "experimental and clinical pharmacologic studies failed to detect any evidence of interaction of astemizole on other drugs." Interaction is defined as "mutual or reciprocal action or interference" (*Webster's New Collegiate Dictionary*, 1981, as reported by Rombaut, Heykants, and Vanden Bussche, 1986); however, in drug research the interaction may be unidirectional. Specific research on hismanal and alcohol have found no interactive effects (Bateman, Chapman, and Rawlins, 1983; Mosser, Gerdes, Buckmann, and Hopmann, 1983, as cited by Hindmarch and Bhatti, 1987).

Hismanal is available in the United States. FDA approval was received December 28, 1988. (W. Kravec, Janssen Research Foundation Piscataway, N.J., personal communication, January 18, 1989).

Benadryl (Diphenhydramine hydrochloride). Benadryl is marketed by Parke-Davis Products. It is available in capsule form, containing 25 mg or 50 mg. The average dose is 25 mg to 50 mg three or four times daily. Benadryl is an antihistamine with anticholinergic (drying) and sedative effects (American Society of Hospital Pharmacists, 1988).

A single oral dose is quickly absorbed with maximum activity occurring in approximately one hour. The duration of activity following an average dose is from four to six hours. It is widely distributed throughout the body, including the central nervous system. Little, if any, is excreted unchanged in the urine; most appears as the degradation of products of metabolic transformation in the liver, which are almost completely excreted within 24 hours. The terminal half-life has not been fully elucidated, but appears to range from 0.4 to 7 hours.

The following description and guidelines exist for benadryl (American Society of Hospital Pharmacists, 1988).

Indications and Usage

1. antihistaminic: for allergic symptoms and conditions.
2. motion sickness: for active and prophylactic treatment of motion sickness.
3. antiparkinsonism: for adjunct treatment of parkinsonism.

4. nighttime sleep-aid.

Contraindications

1. use in the newborn or premature infant.
2. use in nursing mothers.
3. hypersensitivity to diphenhydramine hydrochloride and other antihistamines of similar chemical structure.

Warnings:

Antihistamines should be used with considerable caution in patients/subjects with narrow-angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, symptomatic prostatic hypertrophy, or bladder-neck obstruction. In infants and children, especially, antihistamines in overdosage may cause hallucinations, convulsions, or death. As in adults, antihistamines may diminish mental alertness in children. In the young child, they may produce excitation. Antihistamines are more likely to cause dizziness, sedation and hypotension in elderly patients.

Precautions:

1. General: Benadryl has an atropine like action and should be used with caution in patients/subjects with a history of bronchial asthma, increased intraocular pressure, hyperthyroidism, cardiovascular disease or hypertension.
2. Information for patients/subjects: Patients/subjects taking benadryl should be advised that this drug may cause drowsiness and has an additive effect with alcohol. They should be warned about engaging in activities requiring mental alertness such as driving a car or operating appliances, machinery, etc.
3. Drug interactions: Benadryl has additive effects with alcohol and other central nervous system depressants (hypnotics, sedatives, tranquilizers, etc). Monoamine oxidase inhibitors prolong and intensify the anticholinergic (drying) effects of antihistamines.
4. Carcinogenesis, mutagenesis, impairment of fertility: Long term studies in animals to determine mutagenic and carcinogenic potential have not been performed.
5. Pregnancy: Reproduction studies have been performed in rats and rabbits at doses up to 5 times the human dose and have revealed no harm to the fetus. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Adverse reactions:

1. General: urticaria (hives), rash, anaphalactic shock, photosensitivity, excessive perspiration, chills, dryness of mouth, nose, and throat.
2. Cardiovascular: hypotension, headache, palpitations, tachycardia, extrasystoles.
3. Hematologic system: hemolytic anemia, thrombocytopenia, agranulocytosis.

4. Nervous system: sedation*, sleepiness*, dizziness*, disturbed coordination*, fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paresthesia, blurred vision, diplopia, vertigo, tinnitus, acute labyrinthitis, neuritis, convulsions.
5. GI system: epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation.
6. GU system: urinary frequency, difficult urination, urinary retention, early menses.
7. Respiratory system: thickening of bronchial secretions*, tightness of the chest and wheezing, nasal stuffiness.

*the most frequently reported adverse reactions.

Antihistamine Use and Psychomotor Performance

Psychomotor performance testing with antihistamines falls into several categories: visual, visual motor, cognitive. The evaluations used most frequently in investigation of impaired performance following ingestion of antihistamines are critical flicker fusion, digit symbol substitution, arithmetic, finger tapping, reaction time, and psycho-motor tracking (see Tables 1 and 6).

Visual. Nicholson and Stone (1986) and Nicholson, Smith, and Spencer (1982) reported dynamic visual acuity to suffer significant decrements following antihistamine ingestion (Tables 2 and 7). Dynamic visual acuity is the ability of an individual to perceive detail in moving targets during ocular pursuit. Both sensory and motor components of the ocular response and their feedback systems are involved (Ludvig and Miller, 1958, as cited by Nicholson et al., 1982). Dynamic visual acuity is thought to be related to fatigue (Behar, Kimball, and Anderson, 1976) and drugs (Brown, Adams, Haegerstrom-Portnoy, Jones, and Flom, 1975). Nicholson et al. (1982) evaluated dynamic visual acuity at four target velocities and found significant effects on threshold and the percentage of correct responses with triprolidine, but none with seldane or hismanal. They stated "the present studies on triprolidine suggest that antihistamines may slow both saccadic eye movements and smooth pursuit....impaired performance of complex tasks could involve ocular mechanisms" (p. 689). They did not exclude the possibility, however, that control of eye movement and sleepiness secondary to sedation may be related. Pupil size was not found to be altered by ingestion of the antihistamine triprolidine (Nicholson et al., 1982).

TABLE 6

Effects of H1 Antagonists (triprolidine, clemastine, promethazine and azatadine) on Psychomotor Performance (An adaptation of Table 1 from White and Rumbold, 1988, p. 5)

	Triprolidine (5)		Clemastine (1)	
Critical flicker fusion	10:	+[1, 2, 10, 23]		
Digit symbol substitution	1.25-5:	+[6]	1:	- [12]
	2.5:	- [7]	1-2:	+[6]
	5:	+[8]		
	10:	+[1, 10, 23]		
	10:	- [9,2]		
Arithmetic	10-50:	- [9, 13]	3:	+[14]
Finger tapping	2.5:	- [7]	3:	+[16]
	2.5-5	+[8, 15]		
Reaction time	1.25-5:	- [6, 7]	1:	- [17]
	5:	+[8]	1-3:	+[6, 11]
Tracking	2.5-10:	+[1, 9, 18]	1:	- [19]
	10:	+[10, 23]		
	50:	- [13]**	1-3:	+[16, 20]

**0.74 mg/kg

For each drug, the recommended therapeutic dose (mg PO) is indicated. Each entry shows the dose administered (mg PO), whether a significant effect was observed (+) or not (-), and the study from which the results were obtained.

1. Nicholson and Stone (1983); 2. Nicholson, Smith and Spencer (1982); 3. Hedges, Hills, Maclay, Newman-Taylor, and Turner (1971); 4. Levin, Barbat, Hedges, and Turner (1984); 5. Luscombe, Nicholls, and Parish (1983); 6. Peck, Fowle, and Bye (1975); 7. Hamilton, Bush, Bye and Peck (1982); 8. Bye, Claridge, Peck, and Plowman (1977); 9. Nicholson and Stone (1982); 10. Nicholson and Stone (1984); 11. Jaatela, Mannisto, Paatero, and Tuomisto (1971); 12. Hindmarch (1976); 13. Hughes and Forney (1964); 14. Reinberg, Levi, Guillet, Burke, and Nicolai (1978); 15. Bye, Dewsbury, and Peck (1974); 16. Levander, Hagermark, and Stahle (1985); 17. Hindmarch and Parrot (1978); 18. Nicholson (1979); 19. Seppala, Nuotto, and Koritila (1981); 20. Clark and Nicholson (1978); 21. Luscombe, Nicholls, and Spencer (1980); 22. Biehl (1979); 23. Nicholson and Stone (1986).

TABLE 6 (continued)

Effects of H1 Antagonists (triprolidine, clemastine, promethazine and azatadine) on Psychomotor Performance

	Promethazine (25)	Azatadine (1-4)
Critical flicker fusion	25: +[3, 4]	1-2: - [5, 21]
Digit symbol substitution		
Arithmetic	25: +[3]	2-8: - [22]
Finger tapping		2-4: - [22] 3: +[16] 8: +[22]
Reaction time	25: - [17] 25: +[4]	1-4: - [5, 21, 22] 3: +[16] 8: +[22]
Tracking	10: +[20]	1-2: - [5, 21] 3: +[16]

**0.74 mg/kg

For each drug, the recommended therapeutic dose (mg PO) is indicated. Each entry shows the dose administered (mg PO), whether a significant effect was observed (+) or not (-), and the study from which the results were obtained.

1. Nicholson and Stone (1983); 2. Nicholson, Smith and Spencer (1982); 3. Hedges, Hills, Maclay, Newman-Taylor, and Turner (1971); 4. Levin, Barbat, Hedges, and Turner (1984); 5. Luscombe, Nicholls, and Parish (1983); 6. Peck, Fowle, and Bye (1975); 7. Hamilton, Bush, Bye and Peck (1982); 8. Bye, Claridge, Peck, and Plowman (1977); 9. Nicholson and Stone (1982); 10. Nicholson and Stone (1984); 11. Jaatela, Mannisto, Paatero, and Tuomisto (1971); 12. Hindmarch (1976); 13. Hughes and Forney (1964); 14. Reinberg, Levi, Guillet, Burke, and Nicolai (1978); 15. Bye, Dewsbury, and Peck (1974); 16. Levander, Hagermark, and Stahle (1985); 17. Hindmarch and Parrot (1978); 18. Nicholson (1979); 19. Seppala, Nuotto, and Koritila (1981); 20. Clark and Nicholson (1978); 21. Luscombe, Nicholls, and Spencer (1980); 22. Biehl (1979); 23. Nicholson and Stone (1986).

TABLE 7

Timing of Decrements in Performance Post Triprolidine Ingestion (Nicholson and Stone, 1986)

	Hours post ingestion
Visuo-motor coordination	(1.5-7.5)
Digit symbol test substitutions	(1.7 & 3.7)
symbols copied	(.8-5.8)
Critical flicker fusion	(.9-5.9)
Dynamic acuity low velocity	(1.0)
high velocity	(1.0-6.0)

Nicholson and Stone (1986) examined two target velocities and found the percentage of correct detections at the lower velocity was significantly reduced at one hour post-ingestion of triprolidine. At the higher velocity the percentage of correct detections was reduced from one to six hours post-ingestion of triprolidine. They also found visual-motor coordination, digit symbol substitution, and critical flicker fusion were impaired (Tables 2 and 7). As the latency to sleep was also reduced, their interpretation was that impaired performance may be a non-specific effect of sedation, rather than involvement of a specific skill or physiological system.

Lending further evidence to the visual component of performance decay is the research by Cohen, Hamilton, and Peck (1987). They found benadryl ingestion at therapeutic dose level impaired visual motor tracking performance at 2.5 hours post drug administration, increased tendency to body sway (this vestibular mechanism did not reach significance compared with a placebo), decreased peak saccade velocity at 2.5 and 7.5 hours post-ingestion, prolonged duration of saccades at 2.5 hours post-ingestion, and prolonged reaction time to saccades at 1 and 2.5 hours post-ingestion. Smooth pursuit was not found to be affected by benadryl. They conclude "the fact that several tests are affected in a similar manner suggests that the drugs either affect a higher center controlling psychomotor performance or cause a more generalized impairment of the CNS (central nervous system)" and that "both diphenhydramine, alcohol and their combination affected many variables indicating impaired mental activity."

Visual-motor skills. Visual-motor skills have been evaluated primarily with tracking tasks, which have been reported as being primarily oriented toward response execution in information processing terms (Perez, Masline, Ramsey, and Urban, 1987). Cohen, Posner, Ashby, Smith, and Peck (1984) evaluated an adaptive tracking task in which subjects were required to keep a spot inside a circle of 1.5 cm diameter moving in a pseudo random manner over an oscilloscope screen. When the spot remained in the circle, the circle moved faster, increasing task difficulty, and when the subject failed to keep the spot in the circle, the circle slowed decreasing task difficulty. Subjects were trained to their asymptotic level prior to testing and were evaluated over a 10-min test period. Performance impairments were found with 25 mg and 50 mg of benadryl at 2 hours post ingestion, with significantly increased variability following the 50 mg dose. Cohen, Hamilton, and Peck (1987) used the same tracking task with 50 mg and found performance impairment (with increased variability) at 2.5 hours post ingestion.

TABLE 8

Effects of H1 Antagonists (benadryl and seldane) on Psychomotor Performance (An adaptation of Table 1 from White and Rumbold, 1988, p. 5)

	Benadryl	Seldane
Visual Search	50: +	60: -
Vigilance	50: + [1, 2]	60: -
Divided Attention	50: +	60: -
Critical Tracking	50: +	60: -

For each drug, the recommended therapeutic dose (mg PO) is indicated. Each entry shows the dose administered (mg PO), whether a significant effect was observed (+) or not (-). Results obtained from 1. Moskowitz and Burns (1988); 2. Fink and Irwin (1979).

Moskowitz and Burns (1988) performed a double-blind study on the effects of seldane, benadryl, and placebo on visual search, critical tracking, divided attention, and vigilance tasks (Table 8). Performance on the tracking task was impaired at one hour and three hours post ingestion of 50 mg of benadryl. With their tracking task, a vertically oriented arrow moved horizontally on the display screen. The subject was required to attempt to keep the arrow at a marked center position. The task became increasingly difficult until it was impossible, at which time the trial would end and a new trial would begin. Hindmarch and Bhatti (1987) found that subjects' performance on a tracking task significantly decreased one hour post ingestion of 12 mg of chlorpheniramine; however, no significant differences from placebo were found post ingestion of hismanal.

White and Rumbold (1988), in their review of the behavioral effects of histamine and its antagonists, conclude that tracking tasks appear the most sensitive to the disruptive effects of antihistamines. However, overall research results remain contradictory and therefore confusing (White and Rumbold, 1988).

Cognitive. The concept of information processing assumes that cognitive operations occur in stages. Each stage is considered to be dependent on the previous stage. Incoming information requires time and is transformed in some manner, in each stage (Wickens, 1984). Proposed stages, according to a model by Wickens (1984), include input of stimuli, short-term sensory store, perception, decision and response selection, memory (working and/or long term memory), response execution, and response. Perception, working memory, decision and response selection, and response execution are mediated by attentional resources. Although this explanation is hypothetical, it permits a description and an approach for evaluation of cognitive performance. The results from information processing tasks following antihistamine ingestion have been contradictory (White and Rumbold, 1988).

Digit symbol substitution requires subjects to view a code of either digit or letter pairs and a list of symbols. Subjects then substitute the appropriate digit or letter for as many symbols as possible within a given time frame. Digit symbol substitution is used in some intelligence tests and is purported to measure information processing from perception through action (White and Rumbold, 1988). Impairment has been reported on digit symbol substitution among males with 50 mg of benadryl (Gengo, Gabos, and Miller, 1989; Jaatela, Mannisto, Paatero, and Tuomisto, 1971). Baugh and Calvert (1976; 1977) did not find impairment following ingestion of 75 mg of benadryl. Neither

hismanal, in therapeutic dosage (Nicholson, Smith and Spencer, 1982; Nicholson and Stone, 1982), nor seldane (Nicholson et al., 1982; Nicholson and Stone, 1982; Nicholson and Stone, 1983; Nicholson and Stone, 1986) was reported to impair performance on this task. Results with triprolidine and with clemastine have been contradictory (Table 6).

Arithmetic tasks can require subjects to count backwards by particular intervals or have them solve simple problems within a specified amount of time. This task involves information processing from initial perception through action and includes short-term memory storage, retrieval of long-term memory information, and utilization of procedural knowledge (Perez, Masline, Ramsey, and Urban, 1987). Results of arithmetic tests with antihistamines are conflicting. Within the therapeutic dose range, benadryl has been shown to impair performance with 25 mg (Unchern, Unchern, Chumsawat, Sriwatanakul, and Limsuwan, 1986) and not impair performance with 50 mg (Hughes and Forney, 1964). In 1976, Baugh and Calvert reported deficits in performance on arithmetic tasks following ingestion of 75 mg of benadryl, while in 1977 they reported no deficits with the same dosage. Again, neither hismanal (Nicholson and Stone, 1982) nor seldane (Nicholson and Stone, 1982; Reinberg, Levi, Guillet, Burke, and Nicolai, 1978; Unchern et al., 1986) have been reported to cause performance decrements.

The focus on finger tapping tasks is preparation and execution of response. These tasks were not found to be sensitive to 50 mg of benadryl (Carruthers, Shoeman, Hignite, and Azarnoff, 1978), but were reported to be sensitive to therapeutic doses of triprolidine (Bye, Claridge, Peck, and Plowman, 1977; Bye, Dewsbury, and Peck 1974). Results with azatadine are conflicting (Biehl, 1979; Levander, Hagermark, and Stahle, 1985).

Reaction time tasks generally require the subject to respond to visual or auditory stimuli as quickly as possible. Choice reaction time involves two or more stimuli with corresponding responses. Speed and accuracy of response are typically measured. Reaction time tasks have been reported to show deficits following histamine use although results are contradictory (Tables 1 and 6). Subjects ingesting benadryl at doses of 25 mg, 50 mg, and 100 mg have demonstrated decrements in performance (Cohen, Posner, Ashby, Smith, and Peck, 1984; Gengo and Gabos, 1987), yet other studies with doses ranging from 25 to 100 mg have not (Cohen, Hammilton and Peck, 1987; Linnoila, 1973; Moser, Huther, Koch-Weser, and Lundt, 1978). Three reaction time studies were noted with hismanal (Dhorranintra, Limsuwan, and Bunnag, 1986; Hindmarch and Bhatti, 1987; Hindmarch and Easton, 1986). In Hindmarch and Easton's (1986) research, subjects were female and were chosen on the basis of personal sensitivity to the sedative actions of

the antihistamine chlorpheniramine. They found that there was an increase in the total reaction time and recognition reaction time from pre-test to 3.5 hours post ingestion with both mequitazine and hismanal. The reaction time decreased again at 5.5 hours post ingestion. Research with seldane demonstrates no effect (Table 1).

As mentioned previously, Moskowitz and Burns (1988) performed a double blind study on the effects of seldane, benadryl, and placebo on visual search, critical tracking, divided attention, and vigilance tasks (Table 8). Evaluations were administered at one, three, and five hours post-ingestion. Each subject was given two training sessions on each of the tasks except for vigilance, which was composed of a simple stimulus response requirement, which was reported not to benefit from practice (Moskowitz and Burns, 1988). At one hour post-ingestion, tracking, divided attention, and vigilance were significantly affected following ingestion of benadryl. Again, at three hours post-ingestion, visual search, critical tracking, and divided attention were significantly affected and at five hours post-ingestion, no significant effects were found.

As noted in the section on vision (and as seen in Tables 1 and 6) critical flicker fusion (CFF) is often used "as a measure of overall CNS (central nervous system) activity" (Hindmarch and Easton, 1986, p. 458). It is interesting to note that CFF is reportedly impaired only with the use of triprolidine and promethazine. CFF was not affected following ingestion of azatadine, clemastine, or benadryl, which are considered to be sedating and display other performance decrements.

Other cognitive and perceptual motor tests, such as card sorting and glass bead picking/sorting, have not shown significant differences following administration of hismanal (Dhorranintra, Limsuvan, and Bunnag, 1986).

Driving. Driving, using either a simulator or a vehicle in off-road driving tasks, requires visual, visual motor, and cognitive abilities. Road traffic accidents have been associated with alcohol and drug use (Seppala, Linnoila, and Mattila, 1979, as cited by Hindmarch and Bhatti, 1987). Epidemiological evidence has also associated antihistamines which are considered to have sedative properties with motorcycle accidents Skegg, Richards, and Doll, 1979, as cited by Hindmarch and Bhatti, 1987).

Reaction time on a driving simulator has been found to be significantly prolonged following benadryl (50 mg) administration (Gengo, 1989; Gengo and Gabos, 1987). Betts, Markman, Debenham, Mortiboy, and McKevitt (1984) found significant impairment on two actual driving tests with triprolidine, but not with seldane. They found subjects were aware of their impairment, but were unable to prevent deterioration of

performance; therefore, the colloquial "take more care if you feel drowsy" would not be an effective admonition. Cohen et al. (1984) found that benadryl (25, 50, and 100 mg) did not impair driving performance, but all dose levels produced significant performance decrements on adaptive tracking, body sway, and visual reaction in laboratory evaluations. These results lead one to question whether arousal was increased during actual driving, which may have negated the performance effects. Cohen et al. (1984) concluded that off-road driving tests do not provide a sensitive method of assessing performance effects of drugs. The driving tasks of the two studies (Betts et al., 1984; Cohen et al., 1984) were dissimilar, which may account for the conflicting findings regarding driving performance.

Gier, Kuijpers, and Nelemans (1985) have criticized laboratory studies as being of insufficient duration and monotony and simulated driving or low speed vehicle handling tests as lacking the environment necessary to reflect real world complex skills such as driving an automobile. In a double-blind study, they administered either 10 mg of hismanal or a placebo three times per day for 7 consecutive days, followed by a maintenance dose of hismanal 10 mg or placebo for 3 days. Driving tests required operators to drive over a 60 kilometer course in city, rural, and highway traffic prior to and on the final day of hismanal ingestion. Driving performance was rated by a trained observer using a 110-item checklist, which had been shown to be sensitive to the effects of moderate quantities of alcohol (0.45 g/kg) and the sedative diazepam. They also administered a vigilance task and a tracking task for a total of two consecutive hours. Results showed no significant consistent effect following ingestion of repeated doses of hismanal. A learning effect was seen on the tracking task.

O'Hanlon (1988) has suggested that laboratory tests may be more sensitive to lower concentrations of drugs and may therefore not be indicative of an individual's ability to drive. According to O'Hanlon (1988), performance tests which reliably vary monotonically with blood concentrations of alcohol or other ingested medications have not been identified. He further states that laboratory tests such as digit symbol substitution, critical flicker fusion, and choice reaction time may have been selected for use based only on their sensitivity to one effect of a drug, sedation. Laboratory test performance has not been equated with actual driving performance, with or without the influence of drugs (O'Hanlon, 1988). He asserts that a battery of tests which are relevant to driving must be developed and evaluated as described above. Until such time, it is O'Hanlon's (1988) opinion that use of actual driving tests in controlled situations should be used. Other researchers (Hakkinen, 1976; Seppala and Savolainen, 1982) suggest that tests such as

standing steadiness, visual and auditory choice reaction time, visual motor tracking, critical flicker fusion frequency, digit symbol substitution (thought to measure perceptual speed), time anticipation, and tapping speed are reflective of skills required in driving and are sensitive to antihistamine use. In fact, some researchers refer to tracking tasks as "simulated car-tracking" (Hindmarch and Bhatti, 1987).

Antihistamine Use and Sedation

It has been postulated that the primary effect of antihistamines is sedation. In this scenario, it would appear that mundane, monotonous tasks would be more sensitive to the effects of antihistamines than would brief, interesting tasks. Vigilance tasks would therefore appear to be more susceptible. One cited vigilance study (Moskowitz and Burns, 1988) described the task as requiring a simple stimulus response, which leads one to deduce that the task was a sustained reaction time task, which did reveal significant effects with a therapeutic dosage of benadryl. Fink and Irwin (1979) used a continuous performance task in which subjects were required to maintain depression of a resilient button. An increased number of button releases was recorded post ingestion of benadryl when compared to seldane and a placebo. These performance decrements (and decreased alertness ratings) would seem to be indicative of sedative effects, i.e., increased sleepiness. Fink and Irwin (1979) also found increases in EEG slow wave activity and decreased alpha power with 25 and 50 mg doses of benadryl, which they reported as consistent with other studies of EEG research. They concluded that there is a direct correlation between the degree of sedation and antihistaminic activity and that antihistaminic drugs directly affect brain functions.

Few antihistamine studies have used objective measures of sleep (White and Rumbold, 1988). Subjective reports estimate that sleep duration increases with benadryl use (Teutsch, Mahler, Brown, Forrest, James, and Brown, 1975). The magnitude of the effects have been small, however, and subjective reports are inconsistent across the range of measures (White and Rumbold, 1988).

Roehrs, Tietz, Zorick, and Roth (1984), found benadryl decreased the latency to sleep onset, but did not increase sleep duration. They found seldane did not differ from placebo. Hindmarch and Easton (1986) used the Leeds sleep evaluation questionnaire to record subjects' impressions of the ease of falling asleep, sleep quality, the ease of waking, and the integrity of behaviour after waking. They found no differences among

mequitazine, hismanal, and placebo. Increased midday sleepiness has been noted with benadryl (Roth, 1987). Noon is generally considered the lowest point in alertness and it has been suggested that the exacerbation of sleepiness may have an interactive effect with other variables such as diurnal rhythms or individual susceptibility (Roth, 1987). H1 antagonists have been used as sleep aids; however, research results are not conclusive. Further research is needed to determine the objective changes and the nature of the changes.

Of special importance in performance is the potential interactive effect of antihistamines with other medications such as alcohol or tranquilizers. As depicted in Table 9, no potentiating effects between alcohol and hismanal have been noted. In addition, Moser, Plum, and Buckmann (in press) did not observe a potentiating effect of hismanal on the tranquilizer, diazepam.

Antihistamine Use and Physiological Measures

Craft, Vanden Bussche, De Cree and Griffiths (1987) administered 30 mg hismanal a day for three days and 10 mg hismanal a day for 12 days. These are considered therapeutic doses. Although they did not take measurements at the same time each day, they measured heart rate, blood pressure, ECG, and systolic blood pressure at different time intervals. Measurements were taken at the beginning of the day and at five different times during the treatment regimen. For example, on day three they took measurements two hours after hismanal ingestion; on day four, prior to ingestion; on day eight, two hours after ingestion; and on day 15, prior to and two hours following ingestion. All haemodynamic parameters were measured by the same observer. No significant changes were noted in any of the parameters measured (Craft, Vanden Bussche, De Cree and Griffiths, 1987). A second therapeutic study using 20 mg daily also reported no adverse haemodynamic effects (Powell and Stokes, data on file Janssen Pharmaceutical Ltd. as cited by Craft, Vanden Bussche, De Cree and Griffiths, 1987).

Subjective Reports

The most common form of self reports, generally administered as one portion of a battery of psychomotor tests, is the visual analog scale. Subjects are asked to indicate

TABLE 9

Double-blind Placebo-controlled Studies of Psychomotor Performance, Reactivity and Sedation in Healthy Volunteers after Administration of Astemizole (hismanal), Alone or in Combination with Central Nervous System Depressants (Data from Richards, Brogden, Heel, Speight and Avery, 1984)

Reference (duration in days)	No. of pts.	Drug and dosage	Results
Bateman et al. (1983)	7	10 mg od (7)	H = P H + alcohol = P + alcohol
Moser et al. (1983)	45 40	30 mg (1) 30 mg od (7)	H = P H = P
Moser et al. (1984)	21	10 mg (1)	H + alcohol = P + alcohol
Moser et al. (in press)**	32	10 mg (1)	H + alcohol = P + alcohol
Nicholson et al. (1982); Nicholson and Stone (1982)	6*	10-20 mg (1)	H = P
Seppata and Savolainen (1982)	6*	10 mg (1) 30 mg (1) 10 mg od (14)	H = P H = P H = P
Vanden Bussche et al. (1984)	12*	60 mg (3)	H = P

Parameters measured included several objective and subjective assessments of alertness, reactivity, concentration capacity, performance, mood and well being.

*Crossover design

**Not included in Richards et al., 1984.

Abbreviations: od = once daily; H = hismanal; P = placebo; alcohol = vodka 100 ml (Bateman et al., 1983) or 0.5 g/kg (Moser et al., 1984).

their current state or mood by marking a point along a 100 mm line with descriptors such as "alert" at one end and "sleepy" at the other. Another format is to have the subject complete a forced choice response with scores ranging from 0 (I am quite sleepy) to +3 (I am quite alert). According to a review on antihistamine research by White and Rumbold (1988), these evaluations have low test-retest reliability. As White and Rumbold (1988) assert, a given dose of an antihistamine across studies (even with the same researcher) has not produced the same effects on visual analog scales. With cognizance of the reliability issue, subjective reports (following oral administration of benadryl) have been extended to include general physical and mental sedation, i.e., sleepiness and drowsiness, lethargy, dullness, lowered ability to concentrate, feelings of incompetence, boredom, and being more self-centered (Carruthers, Shoeman, Hignite, and Azarnoff, 1978; Jaattela, Mannisto, Paatero and Tuomisto, 1971).

Seldane has been extensively studied and self reports following oral administration have not been found to differ from placebo (Betts, Markham, Denenham, Mortiboy, and McKevitt, 1984; Luscombe, Nicholls, and Parish, 1983; Moser, Huther, Kock-Weser, and Lundt, 1978). Performance research with hismanal is more limited, but indications are that subjective reports do not differ from placebo (Nicholson, Smith, and Spencer, 1982; Nicholson and Stone, 1982). One study did report significant differences using a visual analog rating scale at one and two hours following oral administration of both placebo and 10 mg of hismanal (Dhorranintra, Limsuvan, and Bunnag, 1986). They did not find similar results on an alertness rating scale. The only explanation given for this result was that it "might be due to the influence of psychic factors in the subjects" (Dhorranintra, Limsuvan, and Bunnag, 1986, pp. 288-289). Clinical studies with hismanal have shown infrequent and mild, self-reported side effects (Tables 3, 4, and 5 and Hindmarch and Easton, 1986; Krstenansky and Cluxton, 1987; Vanden Bussche, Rombaut, Schuermans, Gijpen, Dom, and Moens, 1984; Wihl, Petersen, Pertersen, Gundersen, Bresson, and Mygind, 1985). Headache and drowsiness were the most commonly reported side effects in the research by Hindmarch and Easton (1986); however, as they noted, the prevalence of adverse effects with hismanal did not significantly differ from that with placebo.

Subjective reports during research with benadryl have revealed symptoms such as sleepiness, drowsiness, mental and physical sedation, fatigue, and lowered ability to concentrate (Carruthers et al., 1978; Cohen, Hamilton, and Peck, 1987; Jaattela et al., 1988; Moskowitz and Burns, 1988). These subjective reports are expected and persons

using benadryl are cautioned that it may cause drowsiness (American Society of Hospital Pharmacists, 1988). A study by Miller, Taylor, and Tinklenberg (1988) found no mood effects following ingestion of 50 mg of benadryl on a visual analog mood scale and on the Profile of Mood States with abstinent alcoholics.

Conclusions from Antihistamine Research

The therapeutic benefits of antihistamines have prompted extensive study. Research demonstrates almost all of the H1 antagonists have sedative effects and can impair psychomotor performance. Seldane appears to be an exception. Initial research indicates hismanal may have properties similar to those of seldane; however, the majority of research with hismanal has focused on clinical trials, without extensive performance assessments. Reports of psychomotor testing have been limited to evaluations of dynamic visual acuity, pupil size, critical flicker fusion, digit symbol substitution and cancellation, tracking, and arithmetic. No performance effects have been reported with hismanal (Tables 1, 2, and 9).

Performance testing with antihistamines has not generated reliable assessments that indicate central nervous system effects at therapeutic dose levels. Subjective reports using visual analog scales have been reported to be unreliable in repeated administrations (White and Rumbold, 1988) although alternate and more extensive formats did not receive the same criticism.

Cognitive Tests

Four computerized complex cognitive tests, which are excerpts of two test batteries, the Unified Tri-service Performance Assessment Battery (UTC-PAB) and the Complex Cognitive Assessment Battery (CCAB), were used in this research. In addition, an unstable tracking task and two mood scales were administered. Both batteries were developed to measure the effects of pre-treatment drugs (medications which are used as counter agents in chemical warfare) on the complex cognitive abilities required to perform critical U. S. Army tasks (Analytical Assessments Corporation, 1988; Perez, Masline, Ramsey, and Urban, 1987). As these agents may affect soldier performance, assessment tools which are sensitive to drug ingestion are important. In addition, the tests selected address the five elements listed as essential components to be addressed in assessment of

the effects of drugs on driving (World Health Organization, 1983). The five elements are visual search and recognition, vigilance, information processing under variable demand, decision making and risk taking, and sensorimotor control.

Development of the CCAB was based on a taxonomic approach drawing from existing taxonomies of cognitive capabilities and on analysis of Army C2 and Operational tactical task and subtask requirements (Analytical Assessments Corporation/EATON Corporation, 1988). High level cognitive performance, identified as post-sensory motor processes that involve conceptually driven (top-down) operations (Norman and Bobrow, 1975), was emphasized.

Four types of cognitive or information processing were considered to be integral to complex cognitive capabilities. They are presented, with subcategories of specific capabilities, below (Analytical Assessments Corporation/EATON Corporation, 1988):

- (1) Responding to data
 - a. attention to detail - detection of details which provide meaningful cues.
 - b. perception of form - recognizing patterns which are embedded in a data field.
 - c. memory retrieval - search for and application of past factual and/or procedural knowledge.
 - d. time sharing - simultaneous execution of two or more cognitive tasks.
- (2) Going beyond data
 - a. comprehension - understanding the meaning of words, in this instance, printed in English on a computer display.
 - b. concept formation - development of a mental structure, representative of one or more attributes, often relating one instance to another.
 - c. verbal reasoning - application of general rules to specific verbal problems in order to derive logical results.
 - d. quantitative analysis - application of general mathematical constructs to specific quantitative problems in order to derive solutions.
- (3) Taking action based on data
 - a. planning - development of a cognitive strategy designed to achieve a particular goal.
 - b. situation assessment - ability to recognize and relate the status of an event.
 - c. decision making - given a set of alternatives, the ability to evaluate and select one alternative.

(4) Creating data

- a. communication - relating ideas with written or spoken words.
- b. problem solving - the process of finding a solution to a situation, which involves cognitive processes such as the application of stored knowledge and experience.
- c. creativity - application of a novel approach to a situation.

The taxonomy represented in the Complex Cognitive Assessment Battery is represented in Figure 1. The assignment of capabilities to categories was in accordance with psychological literature, but was not empirically tested (Analytical Assessments Corporation/EATON Corporation, 1988). A synopsis of the cognitive constructs measured is included in Table 10. The evaluations selected for this application addressed all four levels of the taxonomy.

The cognitive tests planned for inclusion are following directions and route planning from the CCAB. The description/focus of each of the tests is as follows (Analytical Assessments Corporation/EATON Corporation, 1988):

1. Following Directions: This test is designed to measure cognitive abilities concerned with responding to data and manipulating those data according to written instructions.
 - a. Focus
 1. primary - attention to detail (requiring a visual search for specific information).
 2. secondary - memory retrieval, time sharing, comprehension, and verbal reasoning.
 3. tertiary - quantitative reasoning and problem solving.
 - b. Background - This task is an adaptation of a pencil and paper test, originated by aviation psychologists (Guilford and Lacey, 1947, as cited by Analytical Assessments Corporation/EATON Corporation, 1988, p. 2-1). The original test was part of a battery used for screening military personnel for air crew training. Other tests of comprehension are those designed by Huttenlocher and Strauss (1968, as cited by Analytical Assessments Corporation/EATON Corporation, 1988) and Wright and Wilcox (1978, as cited by Analytical Assessments Corporation/EATON Corporation, 1988). The former instructs subjects to draw forms in relation to one another, such as drawing a circle

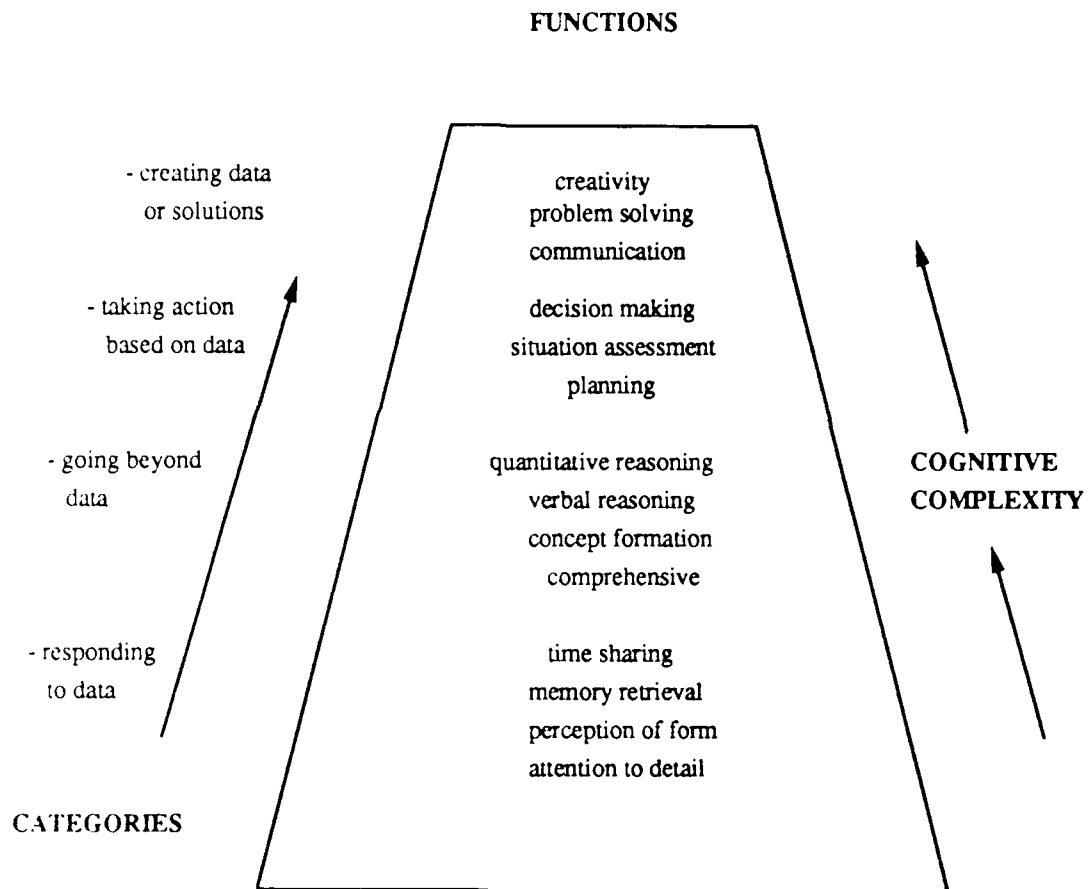


Figure 1. Complex Cognitive Assessment Battery taxonomy. Adapted from Analytical Assessments Corporation/EATON Corporation: Expanded Complex Cognitive Assessment Battery (CCAB): Test Descriptions (AAC-UM-33221), pp. 1-3.

TABLE 10

Level of Association between Complex Cognitive Assessment Battery (CCAB) Constructs and Tests (From Analytical Assessments Corporation/EATON Corporation: Expanded Complex Cognitive Assessment Battery (CCAB): Test Descriptions (AAC-UM-33221), pp. 1-8.)

	Cognitive Complexity Categories	Cognitive Construct Measured	CCAB TESTS*	
			<u>FD</u>	<u>RP</u>
I.	Responding to Data	Attention to detail Perception of form Memory retrieval Time sharing	3 2 2	1 2
II.	Going Beyond Data	Comprehension Concept formation Verbal reasoning Quantitative reasoning	2 2 1	1 1
III.	Taking Action Based on Data	Planning Situation assessment Decision making		3 2 1
IV.	Creating Data or Solutions	Communication Problem solving Creativity	1	2 2

*CCAB consists of nine tests. Codes used in the table for tests are as follows: Following Directions (FD) and Route Planning (RP). [1 = low; 2 = medium; 3 = high]

above a square, and uses total execution time as the dependent measure (Wright and Wilcox, 1978, as cited by Analytical Assessments Corporation/EATON Corporation, 1988). Huttenlocher and Strauss' (1968, as cited by Analytical Assessments Corporation/EATON Corporation, 1988) evaluation requires subjects to move objects in relation to one another, such as moving a block in front of a box. It also uses the total time from instruction presentation to task execution as the dependent measure. In the current version, the subject is required to read directions, comprehend the directions, search the text, and execute the instructions. Memory storage and memory retrieval are required simultaneous with visual search and manual task execution, thus necessitating time sharing of cognitive, perceptual, and motor response skills (Analytical Assessments Corporation/EATON Corporation, 1988).

- c. Measures of Performance - Measures are tabulated per trial and for the combined trials. They include total time, percent total hits, raw number of mark hits, percent actual mark hits, percent mark commission errors, raw number of unmark hits, percent actual unmark hits, percent unmark commission errors, mean time to mark or unmark words, standard deviation for the time to mark and unmark words, and a composite score of accuracy, speed, problem difficulty, and range constant. The time between each marked or unmarked word is recorded in seconds and is referred to as a response time vector. The point at which the subject has used half of the total allotted time is recorded as a ratio, with higher values indicating that earlier marks and unmarks took longer than later marks and unmarks and is referred to as Time Loading (Analytical Assessments Corporation/EATON Corporation, 1988).

The composite score is computed as follows:

Score = accuracy * speed * problem difficulty * range constant.

$$\text{Accuracy} = \frac{(\text{act mk hit} + \text{act unmk hit}) - (\text{mk cmt} + \text{unmk cmt})}{(\text{poss mk hit} + \text{poss unmk hit}) - (\text{mk cmt} + \text{unmk cmt})}$$

where

act mk hit = actual number of mark hits achieved by subject

act unmk hit = actual number of unmark hits achieved by subject

poss mk hit = possible number of mark hit

poss unmk hit = possible number of unmark hits
 mk cmt = number of mark commission errors
 unmk cmt = number of unmark commission errors;

Accuracy ranges from zero to one; if less than 0.1, it is set at 0.1;

Speed = the square root of $[1 - (\text{total time marking and unmarking words} / \text{maximum trial allotment time})]$.

According to the task description, the square root serves to weight the time factor so that it is less than the accuracy factor. If speed is less than 0.2, it is set at 0.2.

Problem difficulty: Easy panel = 1
 Hard panel = 1.4
 Hardest panel = 1.8

Range constant = 2000

The score is then converted to a z score and adjusted according to the following formula: $[(\text{score} - \text{mean}/\text{SD}) * 200] + 1000$. The mean is equal to 457 and the standard deviation is equal to 345.

2. Route Planning: This test is designed to measure the ability to plan and execute movement from one position to another, according to a defined set of rules.
 - a. Focus
 1. primary focus - planning
 2. secondary focus - perception of form, situation assessment, communication, and problem solving.
 3. tertiary focus - attention to detail, comprehension, quantitative reasoning, and decision making.
 - b. Background - This test uses the rules for moving a chess piece known as the knight, which moves in an "L" pattern, from one location to another. It taps both route knowledge, the navigational ability to move from one location to

another, and survey knowledge, the ability to form and utilize a cognitive map in route planning (Wickens, 1984). Survey knowledge via a visuospatial representation of the grid and the permitted moves must be retained in memory during the task. Tversky (1981) found that errors for memory/recall of maps, environments, and patterns are typically the result of the strategies employed for remembering locations. Therefore, errors on the route planning task could be the result of the encoding heuristic used (Analytical Assessments Corporation/EATON Corporation, 1988). As planning is an integral element in many tasks, research on planning has been associated with navigation and maps, the game of chess, and problem solving. Individual differences have been found for performance on map learning tasks, i.e., acquisition of survey knowledge. The techniques which distinguished good from poor learners, focusing attention and encoding of information, can be taught in order to improve performance (Thorndyke and Stasz, 1980, as cited by Analytical Assessments Corporation/EATON Corporation, 1988, p. 8-3). Subjects were given starting and ending locations, times, spatial constraints and a list of errands in a study by Goldin and Hayes-Roth (1980, as cited by Analytical Assessments Corporation/EATON Corporation, 1988, p. 8-3). Subjects verbalized their planning procedures. Goldin and Hayes-Roth reported that good planners established more criteria for planning and evaluation of planning, made more judgements concerning allocation of cognitive resources during planning, made more decisions assessing data considered relevant to planned actions, and made more decisions at higher levels of abstraction. Good planners reviewed previous decisions, compared alternatives, and used established criteria more frequently than poor planners. Research on chess has focused on chess moves and memory. DeGroot (1965) found that master chess players considered fewer moves than weaker players and had greater recall of mid-game positioning of chess pieces. Master players were found to format information in large chunks (Chase and Simon, 1973), an ability which could facilitate performance on the CCAB route planning test.

- c. Measures of Performance - Measures are tabulated per trial and for the combined trials. They include total time to solve the problem, the minimum number of moves to solve the problem, whether a solution was achieved, number of valid moves, ratio of the minimum number of moves required to

solve the problem to the actual number of moves used to solve the problem, number of illegal moves, number of reversal moves, mean time for each move, standard deviation for the respective times taken for successive moves, and a composite index of accuracy, speed, problem difficulty and range constant.

The composite score is computed as follows:

Score = Accuracy * Speed * Problem Difficulty * Range Constant;

$$\text{Accuracy} = \frac{\text{Optimal moves} - (\text{Illegal moves} + \text{Reversals})}{\text{Actual moves} - (\text{Illegal moves} + \text{Reversals})}$$

If the number of actual moves is less than the number of optimal moves, the accuracy component is computed and inverted.

Speed = the square root of $[1 - (\text{Total time to solve the problem} + \text{maximum time allowed per trial})]$.

The square root is used to reduce the effect of the time factor on the performance score in comparison with the accuracy factor. If the computed time is below 0.2, it is set at 0.2.

Problem difficulty: 3-move problem = 1.0

4-move problem = 1.4

5-move problem = 1.8

Range constant = 2000

The range constant stabilizes the range for the point score.

The score is then adjusted by converting it to a z score to permit comparison across tests. The Mean (1119) and Standard Deviation (659) used are based on data collected in a previous study with college students.

$$z = \left[((\text{score} - \text{mean}) / \text{standard deviation}) * 200 \right] + 1000.$$

The UTC-PAB is the primary assessment tool in a multiple level drug evaluation program (The Military Performance Working Group, 1983, as cited by Perez, Masline,

Ramsey, and Urban, 1987). It was developed by concentrating on information processing stages and identifying those stages considered crucial for task demands (Perez et al., 1987). In addition, tasks were identified which required divided attention . The information processing stages delineated in the UTC-PAB and the identified tasks for each stage are (Perez et al., 1987);

1. Perceptual input, detection, and identification
 - a. visual scanning task
 - b. visual probability monitoring task
 - c. pattern comparison (simultaneous)
 - d. four-choice serial reaction time
2. Central processing
 - a. auditory memory search
 - b. continuous recognition task
 - c. code substitution task
 - d. visual memory search
 - e. item order test
3. Information integration/manipulation -- Linguistic/Symbolic
 - a. linguistic processing task
 - b. two column addition
 - c. grammatical reasoning, symbolic
 - d. mathematical processing task
 - e. grammatical reasoning, traditional (referred to as the logical reasoning task)
4. Information integration/manipulation -- Spatial
 - a. spatial processing task
 - b. matching to sample
 - c. time wall
 - d. matrix rotation task (spatial processing task)
 - e. manikin test
 - f. pattern comparison (successive)
5. Output/response execution
 - a. interval production task
 - b. unstable tracking task
6. Selective/divided attention
 - a. dichotic listening task

- b. memory search/unstable tracking combination
- c. Stroop test

Subtasks from each information processing stage were used in this research. (The selective/divided attention task used was the memory search/unstable tracking combination task. Results will be reported in the masters thesis of Charlotte Waggoner. In addition, a visual search task was used, results of which will be reported in the masters thesis of Gail Whitehouse. Both masters theses are in Human Factors Engineering, Industrial Engineering and Operations Research, Virginia Polytechnic Institute and State University.) This is in accordance with the recommendation offered by the compilers of the test battery (Perez, et al., 1987). The cognitive tests utilized from the UTC-PAB are the four-choice serial reaction time, code substitution, grammatical reasoning (logical reasoning), serial addition/subtraction, time wall, manikin, pattern comparison, interval production, unstable tracking, a mood scale, and a sleepiness scale. The description/focus of each of the tests is as follows (Perez et al., 1987):

1. Four Choice Serial Reaction Time (Wilkinson Reaction Time) - This task was developed to evaluate encoding, categorization, and response selection, focusing most heavily on encoding. A red, blinking square appears in one of four quadrants on the display screen. The subject must press one of four keys on the numeric keypad corresponding to the four quadrants, as quickly and accurately as possible. The square then reappears in one of the quadrants and the procedure is repeated (Perez et al., 1987).
 - a. Focus - encoding, spatial relationships, categorization, response selection, and reaction time.
 - b. Background - Wilkinson and Houghton (1975, as cited by Perez et al., 1987) developed the four-choice reaction time task from which this computerized version was constructed by Ryman, Naitoh, and Englund (1984, as cited by Perez et al., 1987). There are three primary stages of information processing. They are perceptual input, central processing, and motor output (Wickens, 1984). Although a choice reaction time task involves all three stages, modification of the task can serve to focus on one of the stages. The UTC-PAB version has four stimuli with a 1:1 ratio of stimuli to response and a high stimulus response compatibility (Perez et al., 1987). Central processing and

motor output demands should therefore be low in comparison with encoding demands (Smith, 1968, as cited by Perez et al., 1987).

- c. Measures of performance - reaction time, incorrect responses are recorded, as well as the mean and standard deviations for correct responses and incorrect responses. The ten percent fastest/slowest, correct/incorrect responses and a percent correct response value is also recorded.
2. Interval production - The purpose of this task is to evaluate manual response timing. The subject is required to tap a key at a rate of one response per second.
 - a. Focus - time estimation and manual response.
 - b. Background - this task was originally developed to be used as a secondary task to evaluate demands placed on motor output by a primary task (Michon, 1966, as cited by Perez et al., 1987). In this situation, however, the task is used to assess the degree to which medications may disrupt response output.
 - c. Measures of performance - standard deviation of interval durations and interval production task (IPT) variability. IPT variability is computed by the following formula (Michon, 1966, as cited by Perez et al., 1987):

$$\text{IPT Variability} = \frac{N}{T} \sum_{i=1}^N |\Delta t|$$

N is the total number of intervals produced. T is the total time of data collection. Δt is the difference between successive intervals. A lower IPT variability value indicates a "more temporally regular tapping and better performance" (Perez et al., 1987, p. 237).

3. Time Wall - The ability to estimate the time at which a target will have traveled a predetermined distance, when moving at a constant rate, is evaluated by this task (Perez et al., 1987). A target appears at the top of the CRT screen and descends at a constant velocity and passes behind a opaque barrier. The subject must estimate when the target will reappear.
 - a. Focus - time estimation, integration and application of speed and distance information in determination of the time at which a target will reach a particular destination.
 - b. Background - This task was first developed and used in research which investigated the effects of noise on vigilance and time judgements (Jerison and

Arginteanu, 1958; Jerison, Crannel, and Pownall, 1957, as cited by Perez et al., 1987). The presence of noise during the time the target was behind the opaque wall (and not during the visible time period) resulted in overestimation of target reappearance time (Jerison et al., 1957, as cited by Perez et al., 1987). Subsequent evaluations with additional noise levels and target speeds revealed overestimation was less for longer intervals and noise had an effect in terms of whether the noise level was steady or changed at the time of disappearance of the target (Jerison and Arginteanu, 1958, as cited by Perez et al., 1987). This task is different from other time estimation tasks in that rate and distance information is provided, estimation occurs during the interval occurrence, and termination of the task occurs with the subject's response. Therefore, this task may be a test of time/rate projection and not strictly time estimation (Perez et al., 1987).

- c. Measures of performance - calibrated standard time value, task duration, number of trials, number of deadlines, constant error (mean estimate minus standard), proportional error (mean estimate as a percent of standard), variable error, standard deviation of the estimates in ms, and coefficient of variation.
4. Code Substitution - This task is designed to evaluate rapid encoding of information, transformation of the information, associative evaluation of stimuli, and response output. A string of nine letters and associated digits is displayed on the screen. A letter is then printed below and the subject is to indicate the corresponding digit using the numeric keypad. The pairings remain the same throughout the test.
 - a. Focus - rapid perception of form, visual search, short-term memory retrieval, transformation of information, and response execution.
 - b. Background - This task was adapted from the Wechsler Adult Intelligence Scale (Wechsler, 1958, as cited by Perez et al., 1987). Correlations between test scores on code substitution and overall IQ scores ($r = .67$ for ages 20 to 34 and $r = .70$ for ages 35 to 49) have been reported (Perez et al., 1987). As a result of such data, the code substitution task has been utilized as a metric for evaluation of the speed and efficiency of intellectual performance.
 - c. Measures of performance - Summary data include total elapsed time, number of trials completed, number and percent correct, number of extras, number of deadline occurrences, and reaction time means and standard deviations for total

responses, correct responses only, and incorrect responses only. Average reaction time for correct responses and number of errors serve as the major dependent measures.

5. Logical Reasoning - This test was designed to evaluate the ability to comprehend a pair of premises that defines a logical relationship and to measure general reasoning ability.
 - a. Focus - comprehension of logical relationships, reasoning, working memory retrieval, concept formation, and problem solving.
 - b. Background - This task was adapted from Baddeley (1968). Psycholinguistic studies have revealed that the time taken to understand a sentence is dependent on its syntactic structure; for example, positive statements, true statements, and active statements are comprehended more quickly than negative, false, or passive statements (Clark and Chase, 1974, as cited by Perez et al., 1987; Wason, 1961 and Slobin, 1966, as cited by Braddley, 1968). Further verification that positive, true, and active statements are understood more quickly has been reported by Clark and Chase (1974), Baddeley and Hitch (1974), and Hitch and Baddeley (1976, as cited by Perez et al., 1987). Using transformations of these principles, Braddley (1968) developed a short test which has been used as an indicator of comprehension and reasoning. This task involves putting items in proper order and recognizing relationships between the items.
 - c. Measures of performance - Summary statistics include number of problems responded to, number and percent correct, number and percent of errors of commission, number and percent of errors of omission, number and percent of total errors, mean and median reaction time, and standard deviation of reaction time.
6. Mathematical Processing (serial addition/subtraction) - This test is designed to evaluate information processing resources associated with working memory. Two digits are presented sequentially on the CRT, followed by either a + or - indicating the procedure required. The least significant digit is the one which is recorded (for example, 9 8 + is equal to 17 so the correct response would be 7). If the answer is negative, +10 is added to the answer and the least significant digit is recorded (for example, 4 7 - is equal to -3 and -3 added to +10 is 7 which is the correct response).

- a. Focus - visual perception, information retrieval from long-term memory, application of information from long-term memory through execution of arithmetic operations, performance of numeric comparison, response execution.
 - b. Background - Serial addition/subtraction is a variation of the task developed by Pauli and used by Wever (1979, 1981, as cited by Thorne, Genser, Sing, and Hegge, 1985) in continuous operations and sleep deprivation research. According to Thorne (D. R. Thorne, personal communication, March 21, 1989), the results of research at Walter Reed Institute of Research has indicated this task appears to "act as a vigilance task" and has been used both with medication research and sleep deprivation. Serial addition/subtraction is thought to primarily tap resources associated with central processing such as information manipulation based on implicit or memorized rules. Adults appear to rely on an organized long-term memory structure analogous to "math tables" in order to solve simple arithmetic problems (Stazyk, Ashcraft, and Haman, 1982; Battaglia, 1978, as cited by Perez et al., 1987). Subjects must maintain and update their answer to the problem which requires working memory storage and processing. Previous research (Perez, 1982, as reported by Perez et al., 1987) has shown that transitions from one operation to another (such as addition to subtraction) require more time than sequential operations of the same type (addition to addition).
 - c. Measures of performance - average and standard deviations for reaction time, number and percent correct, and number of deadline occurrences.
7. Manikin - This test evaluates spatial orientation ability, that is, the ability to perform rotations and transformations of a mental image. A human figure (manikin) holding a box of a specific shape (circle or square) and color (red or green) in each hand is displayed on the CRT screen. The manikin is enclosed in a matching circle or square. The subject must identify which hand (right or left) is holding the corresponding object, when the manikin is rotated in four orientations.
- a. Focus - mental rotation of stimulus and right/left judgement (referred to as the kinesthetic factor (Lohman, 1979, as reported by Perez et al., 1987).
 - b. Background - Lohman (1979, as reported by Perez et al., 1987) divides spatial orientation abilities into three skills: changing the observer's visual perspective, rotation of mental images, and folding or distorting a mentally imaged object.

The Manikin test is thought to be specifically related to rotation and transformation of an imaged object. Mental rotation has been reported to be a good indicator of general spatial ability (Pollock and Brown, 1982, as cited by Perez et al., 1987). Spatial ability is considered essential to piloting skills and an analysis of Army aviation accidents (helicopter) between 1967 and 1971 revealed that the majority of accidents occurred due to a loss of "orientation with respect to geographical location and height above terrain or inadvertently penetrated into instrument flight conditions" (Hart, 1988, p. 613). Although requirements to complete instrument flight training have reduced accidents attributed to inadvertent penetration into instrument conditions from 25% to 7%, the "number of accidents attributed to spatial disorientation is still high among two-person crews, and it is likely that it will increase in single-pilot operations" (Hart, 1988, p. 613).

- c. Measures of performance - mean response time, range and variance of response times, and accuracy.
8. Pattern Comparison - Short-term spatial memory and perceptual speed are evaluated in this task. A pattern of asterisks (*) is presented on the CRT screen for 1.5 seconds, the screen blanks for 3.5 seconds, and a second pattern appears. The subject must respond within 15 seconds and report the two patterns as either the same or different.
- a. Focus - perceptual speed and short-term spatial memory.
 - b. Background - Lohman (1979, as reported by Perez et al., 1987) reviewed and analyzed the literature on spatial perception. He re-analyzed the data using one procedure and interpreted the results using one theoretical framework. As mentioned previously, three spatial abilities were identified. They are visualization, spatial orientation, and spatial relations. Visualization refers to mental reorientation and is time consuming (compared to the other spatial abilities). Spatial orientation involves a mental reorientation of the observer in order to conceptualize stimuli from a different perspective. Spatial relations refers to the time dependence of spatial transformation. Mental movement and mental construction are considered to be subtypes of spatial transformation (Lohman, 1979, as reported by Perez et al., 1987). Mental movement may consist of rotation, transformation, or movement of a mental image while mental construction refers to the fabrication of a mental image from incomplete

images. The pattern comparison task is expected to utilize mental movement abilities (Perez, 1987).

- c. Measures of performance - total task time, number and percent correct, number of deadlines, and reaction time means and standard deviations.
9. Unstable Tracking - This test is directed to evaluate execution of rapid and manual response.
- a. Focus - continuous visual monitoring, central processing, and accurate manual control response to uncertainty. Demands on the operator are primarily those related to motor responses (Perez et al., 1987).
 - b. Background - The unstable tracking task was originally developed by Jex, McDonnell, and Phatak (1966, as cited by Perez et al., 1987), who attribute the origins to Ashkenas and McRuer (1959). Error is introduced into the system by the operator and is magnified (i.e., positive feedback) by the system. The subject must respond to the velocity of the cursor and to cursor position. The crossover model developed by McRuer and Krendel (1959) and McRuer and Jex (1967, as cited by Perez et al., 1987) adequately describes this system. Gain, ratio of output velocity to perceived error, and effective time delay (the subject's internal processing delay) describe the model (Wickens, 1984). Although this task is included in the description of the Unified Tri-Service Assessment Battery (Perez, 1987), the software being used in the tri-service effort was developed by Systems Research Laboratories (1987).
 - c. Measures of performance - final lambda value, root mean square which is the square root of the mean distance from the center position, and number of boundary hits.
10. Mood Scale II - This test is designed to evaluate subjective evaluation of feeling and mood.
- a. Focus - to respond to subjective ratings of emotion and psychomotor states.
 - b. Background - Mood Scale II was developed by Thorne, Genser, Sing, and Hegge (1985) as part of a computerized psychological test battery known as the Walter Reed performance assessment battery. It consists of an abbreviated three-point rating scale of 36 adjectives to which subjects respond by rating their level of agreement.

- c. Measures of performance - six subscales identified as anger, happiness, fear, depression, activity, and fatigue.
11. Profile of Mood States (POMS) - This evaluation is reported to measure dimensions of affect (McNair, Lorr, and Droppleman, 1981).
 - a. Focus - to respond to subjective ratings of emotion and psychomotor states.
 - b. Background - The Profile of Mood States was developed by McNair, Lorr, and Droppleman (1981) and is available from the Educational and Industrial Testing Service, San Diego, California. It is frequently used for evaluation of transient, fluctuating affective states of psychiatric patients and for assessing subjective reactions to various stressors. The Profile of Mood States consists of a five-point scale of 65 adjectives to which subjects respond by rating their level of agreement from a rating of 0 = not at all through 4 = extremely (McNair, Lorr, and Droppleman, 1981).
 - c. Measures of performance - six subscales identified as tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment.
 12. Stanford Sleepiness Scale - The Stanford Sleepiness Scale is included in the Walter Reed Performance Assessment Battery (Thorne, Genser, Sing, and Hegge, 1985).
 - a. Focus - to record subjective ratings of sleepiness.
 - b. Background - The Stanford Sleepiness Scale consists of a seven-point scale to which subjects respond by rating their level of agreement with ratings of 1 = "Feeling active and vital; alert; wide awake" through 7 = "almost in reverie; sleep onset soon, lost in struggle to remain awake") is required (Hoddes et al. as cited by Herscovitch and Broughton, 1981).
 - c. Measures of performance - measures recorded include the sleepiness rating, response latency, start latency, task duration in seconds, number of extra keys hit, and number of times that the reaction time is greater than the maximum timer value.
 13. Two additional questions were included. The first required subjects to evaluate their performance on a scale of one to five. The second required subjects to identify the treatment as active drug (antihistamine) or placebo.
 14. A combined memory search-tracking task developed by Systems Research Laboratory (1987) and a visual search task developed by Dr. John D'Andrea,

U. S. Naval Air Station, Pensacola, Florida were also administered. A full description of the task and results of the combined memory search-tracking task can be found in the master's thesis of Charlotte Waggoner (1990). The description and research results of the visual search task can be seen in the master's thesis of Gail Whitehouse (1990). Both theses were conducted in the Department of Industrial Engineering and Operations Research at Virginia Polytechnic Institute and State University, Blacksburg, Virginia.

Research Objectives

The objectives of this research were (1) to determine whether selected cognitive tasks show performance deterioration under the influence of two antihistamines (benadryl and hismanal) and (2) to determine the subjective effect of the antihistamines and whether research subjects could detect their own performance decay.

Based on the literature review, central nervous system effects such as sedation, drowsiness, and altered psychomotor performance are expected following ingestion of benadryl (Nicholson et al., 1982; White and Rumbold, 1988). Previous research (with therapeutic doses of benadryl) has yielded conflicting results on arithmetic (simple addition/subtraction) and reaction time tasks (Table 1). Visual-motor tracking, digit-symbol substitution, visual search, vigilance, and divided attention tasks have yielded significant effects, that is, performance decrements (Tables 1 and 8). In accordance with the literature, it was expected that decrements would be evident during test sessions one (one hour post ingestion) and two (three hours post ingestion) on the unstable tracking, code substitution, and divided attention (Following Directions) task with benadryl. No significant effects were expected following hismanal ingestion on any of the subtasks and performance was not expected to differ from performance following ingestion of a placebo.

It was expected that subjective reports of mood would differ following ingestion of benadryl, again during the first and second test sessions (one and three hours post ingestion) and that symptoms such as sleepiness, drowsiness, mental and physical sedation, fatigue, and lowered ability to concentrate would be identified (Carruthers et al., 1978; Cohen et al., 1987; Jaattela et al., 1971; Moskowitz and Burns, 1988). Moskowitz and Burns (1988) did not find significant differences in subjective reports five hours post ingestion of benadryl. As no research was identified in the literature review which

continued for the time length (16 hours) to be used in this study, it was unknown whether subjective reports would differ beyond five hours post ingestion. A fatigue effect was expected post benadryl ingestion in comparisons with placebo ingestion. No significant differences in subjective reports were anticipated following hismanal ingestion (Tables 3, 4, and 5; Krstenansky and Cluxton, 1987; Wihl et al., 1985; Vanden Bussche et al., 1984). Subjective ratings of mood following hismanal ingestion were not expected to differ from ratings following ingestion of a placebo.

Research has indicated that subjects are able to identify their own performance decay during a driving task (Betts et al., 1984) as well as during psycho-motor performance tasks (Moskowitz and Burns, 1988). It was expected that subjects' ratings of their performance would accurately reflect their performance deterioration.

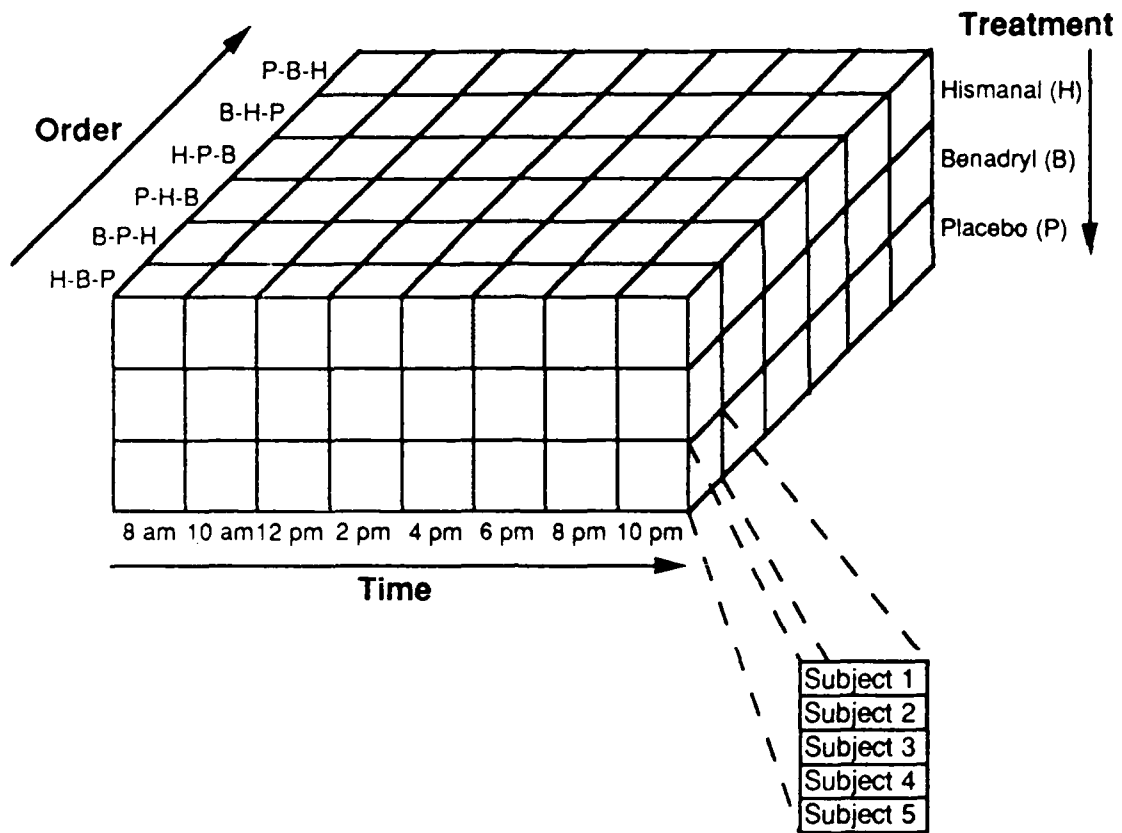
METHOD

Experimental Design

To achieve the research objectives a three factor (3 x 8 x 6) repeated measures, double-blind design focusing on subjects, sessions, order, and treatment was used (Figure 2). Double blind refers to the situation in which neither the investigators nor the subjects have knowledge of which condition the subject is receiving until all testing has been completed. Each of the subjects received each of the three treatments, with a different group of five subjects receiving each of the six orders of drug presentation. Treatments were administered on three different days. Order effect of the drug administration was completely counter-balanced, as shown in Figure 2. On each treatment day, eight test sessions were scheduled for each subject (Figure 3). The order of the individual tests was identical for each test session.

Subjects

Thirty male subjects ranging in age from 20 to 36 participated in the study. Subjects were recruited from the student body at Virginia Polytechnic Institute and State University, via advertisements posted throughout the campus. Subjects were screened for health issues and for use of illicit and prescription drugs via a telephonic screening, medical questionnaire, interview, and medical health record screening. The questionnaire and interview were developed in conjunction with Phillip L. Barkley, M.D., Chief Medical Officer and Director of Health Services, Virginia Polytechnic Institute and State University (Appendix D). All questionnaires and the students' health records were reviewed by Dr. Barkley. The individual interview included an explanation of the experiment, subject requirements, method of payment, explanation of medical terms, explanation of potential risks, and answers to questions posed by subjects. Approximately 90 potential subjects filled out questionnaires and were interviewed. The final 30 subjects were chosen on the basis of their medical history, availability for scheduled test days, and according to their date of response. Two weeks prior to the initiation of the experiment, subjects met with the members of the research team and with subjects scheduled for the same day. This group interview/explanation included an introduction to the research team, an explanation of the experiment and its purpose, an



H = hismanal
B = benadryl
P = placebo

Figure 2. Experimental design.

Hismanal	**	*		*		*		*		*		*		*		*	
Benadryl	**	*		*		*		*		*		*		*		*	
Placebo	**	*		*		*		*		*		*		*		*	
Hours	7am	8	9	10	11	12	1pm	2	3	4	5	6	7	8	9	10	11

*test session

**drug administration

Figure 3. Schedule of the eight evaluation times for each test day.

emphasis on the time commitment for participation, procedural requirements, and constraints. Subjects read and signed the informed consent forms during this meeting.

Of the 30 subjects selected for participation, two subjects did not complete the study, one voluntarily and one due to illness. One of the subjects was replaced. Data for one subject on one day were lost due to software difficulty. Average age, height, and weight, as well as a frequency count for racial background, are recorded in Table 11. Subjects were paid \$4 per hour for hours spent if they did not complete the study and \$5 per hour if they did complete the study. Subjects were paid for time spent in training, completing baseline testing, and three test days. Payment was in cash following the final session of the last test day.

Inclusion criteria for participation were:

- male
- 21- 40 years of age
- non-smokers
- willing to abstain from alcohol use for 24 hours prior to and following all test sessions. Participants must also agree to abstain from psychoactive drug use for two weeks prior to and throughout the study.
- willing to refrain from caffeine consumption throughout the test sessions.
- willing to sign an Informed Consent form (Appendix I).
- by self report, to have used antihistamines on a prior occasion, without adverse reaction.

Exclusion criteria prohibited participants who:

- have experienced adverse reactions to antihistamines.
- are currently taking prescribed or over-the-counter medications.
- have evidence of adverse medical conditions as judged by a physician.
- who do not conform to the cited inclusion criteria.

The use of male subjects was due to (1) the requirement for pregnancy testing for females immediately prior to antihistamine ingestion (each morning of the three test days) as stated by the Human Use Review Board and the lack of such testing facilities at Virginia Polytechnic Institute and State University, (2) altered psychomotor performance of

TABLE 11

Personal Data of Subjects

	Mean	Standard Deviation	Range
Height	70.33	2.84	60-75 (inches)
Weight	160.31	20.7	125-220 (lbs.)
Age	23.54	4.18	20-36 (years)

females for several days prior to, during, and immediately following menstruation, and (3) the possible performance effects due to use of birth control pills.

Equipment

All tasks were computerized and subject response was on an alphanumeric keyboard. Each response value, error status, and reaction time was temporarily stored and recorded at task conclusion. A Zenith 248 computer system with 384K of memory, a hard disk drive, a color display monitor, and a graphics card to accommodate the 40 column display characteristics was used. A description of the computer requirements was provided by Lt. Dennis Reeves, Naval Aeromedical Research Laboratory, Pensacola, Florida (personal communication, October, 1988). Further information on hardware and software design and specifications can be obtained from Hegge, Reeves, Poole, and Thorne (1985).

Test Battery

Task description. The following tasks are part of the Complex Cognitive Assessment Battery (CCAB). A full description of each task, with its purpose, background, reliability, validity, sensitivity, technical description, trial specifications, data specification, training requirements, and instructions to subjects can be found in the Expanded Complex Cognitive Assessment Battery (CCAB): Test Descriptions (Analytical Assessments Center, 1988).

1. Following Directions - A set of directions, similar to those in Appendix B1, appears on the CRT screen. The test panels are presented in sets of three and increase in level of difficulty. One word on the instructions is highlighted, which indicates the position of the cursor. The subject carries out the directions by using the arrow keys (up, down, right, and left) on the numeric keypad to move the highlighted box to the first word specified in the directions. The subject then presses the space bar which underlines and marks the word. To unmark a word, the arrow keys are used to move the highlighted box to the specific word and the space bar is pressed, which removes the underline. The line numbers are identified before each line; however, the word placement must be counted by the subject. In the first example in Appendix

B1, word number three in line two is "Mark." Word five in line four is "line." As noted in this example, a single letter or number counts as a word, while punctuation marks and line numbers do not count as words. The first level of difficulty requires the subject to follow one-step directions. The second level of difficulty uses two-step or compound directions. The most difficult screens use compound directions and directions based on numerical values of X, Y, and Z, which are displayed beneath the directions. Timing of the task begins as soon as the text is presented on the CRT screen. If the subject does not complete a panel within the amount of time allowed (90 seconds), a "time's up" message is displayed and the next panel is displayed. After all directions (marking or unmarking) are completed, the subject presses the <ESC> key and the trial is ended or if the time allotted for the task is over, then the trial is automatically ended (Analytical Assessments Center, 1988).

2. Route Planning - The trial begins when the subject presses the <SPACE-BAR>. A 5 x 5 matrix of 25 squares (11 of which are shaded) and task statement is then displayed on the CRT screen (Appendix B2). The matrix is determined by a pseudo random selection process. Each of the 14 unshaded squares contains a letter of the alphabet. The subject must "move" from a designated starting square to specific ending square using "L" shaped moves of either "one out and two over" or "two out and one over" comparable to the "Knight's" move in chess. The shaded squares may be traversed over, but not landed on. A sample screen is presented in Appendix B2. The subject does not need to be familiar with chess to perform the task, although this may facilitate speed in learning task rules. As the subject enters a letter in the route to the target square, the current position is highlighted. The task is terminated when the end square is reached or when the allotted time is completed (allotted time may be preset to 60, 90, or 120 seconds). The next session begins when the subject presses the space bar (Analytical Assessments Center, 1988). Six individual test trials were used per test session (this parameter is set by the experimenter).

The following tasks are part of the Unified Tri-Service Cognitive Assessment Battery (UTC-PAB). A full description of each task, with its purpose, background, reliability, validity, sensitivity, technical description, trial specifications, data specification,

training requirements, and instructions to subjects can be found in the Unified Tri-Services Cognitive Performance Assessment Battery: Review and Methodology (Perez et al., 1987). (Two abbreviated descriptions of the tasks are also available (Englund, Reeves, Shingledecker, Thorne, Wilson, and Hegge, 1987; Thorne, Genser, Sing, and Hegge, 1985).

1. Four Choice Reaction Time (Wilkinson) - The computer screen is divided into four quadrants. Each quadrant contains a block of either red, green, blue, or yellow. One of the colored blocks blinks and the subject must respond by touching one of four corresponding keys on the numeric keypad. The random select is derived in the following way: the last two bits of the subject's reaction time is divided by four. If the remainder is zero, the cursor is sent to the upper left quadrant; if one, the quadrant selected is the upper right; if two, lower left; if three, lower right. The colored block will continue to blink until the subject presses a response key. The quadrants will blank and remain blank until the next trial presentation. No response will be recorded if the subject responds during an interstimulus interval (Perez et al., 1987). The subject is given 2.5 seconds to respond; after that time an auditory tone prompts the subject at 0.1-s intervals until a response is made. Task time is six minutes. Perez et al. (1987) reported anticipated proficiency following two 6-min practice blocks. The Wilkinson reaction time task was run for 20 trials or 240 seconds (whichever occurred first).
2. Interval Production - A circle, which is representative of a clock, appears on the CRT screen. The subject is to tap a specified key with the index finger of his preferred hand at 1-s intervals. Each test period lasts for 60 taps or approximately one minute (Perez et al., 1987). Subjects were instructed not to count and were not permitted to wear watches during test sessions. The Interval Production task ran for 60 trials or 240 seconds (whichever occurred first).
3. Time Wall (time anticipation) - A small red square (target) appears at the top of the CRT screen and begins to descend at a constant velocity. The square appears to pass behind a large red rectangle or wall. The wall has a missing brick or notch in the bottom of it, which is the same size as the descending square. The subject is to estimate the time at which the target should fill the

notch at the bottom of the wall. Ten trials are included per session (Perez et al., 1987). This task ran for 6 trials or 240 seconds (whichever occurred first).

4. Pattern Comparison (successive) - For this task, a pattern of asterisks was presented on the CRT screen for 1.5 seconds, followed by a blank screen which remained for 3.5 seconds, and finally a second pattern was presented for 15 seconds. The subject must indicate whether the second pattern is the same or different from the first pattern. The second pattern (otherwise known as the test pattern) remains for the entire 15 seconds or until the subject responds (Perez et al., 1987). Ten trials are included in each test battery. The patterns are generated on a four-by-four grid. If the test pattern is to be classified as different (random generation) the noticeable difference algorithm developed by Irons (1984, as cited by Perez et al., 1987) is used to displace three dots in the first pattern, thus creating the second or test pattern. The Pattern Comparison Task ran for 10 trials or 180 seconds (whichever occurred first).
5. Logical Reasoning - One of two possible letter pairs, either AB or BA, is presented on the CRT screen. All characters are upper case. Directly under the letter pair, a statement regarding the sequential pattern of the pair is presented. The subject must indicate whether the statement accurately describes the letter pair by pressing one of two keys, which correspond to TRUE or FALSE. The time allotment for response is 15 s. Thirty-two letter pairs are presented per task battery (Perez et al., 1987). The Logical Reasoning task ran for 32 trials or 180 seconds, whichever occurred first.
6. Manikin - A human figure appeared on the CRT screen in one of four positions; (1) head at the top of the screen and facing the subject, (2) head at the top of the screen and facing away from the subject, (3) head at the bottom of the screen and facing the subject, and (4) head at the bottom of the screen and facing away from the subject. The figure remains on the screen for two seconds. The manikin is enclosed in either a square or a circle and is holding either a square or a circle in each hand. The subject is to indicate which hand (right or left) holds the object which is similar to the object in which the manikin is enclosed (Perez et al., 1987). This task ran for 16 trials or 240 seconds (whichever occurred first).

7. **Serial Addition/Subtraction** - Two single-digit numbers are presented sequentially on the center of the CRT screen followed by either a plus or minus sign and a prompt symbol. The subject is required to complete the arithmetic task indicated. If the answer is positive, the subject must report the least significant digit. For example, the correct response to the following sequence, (5) (8) (+) (=) is 3. If the answer is negative, the subject must add +10 and the result of this operation is the correct response. For example, the correct response for the following sequence, (5) (8) (-) (=) is 7. Responses are by pressing the correct response on the numeric keypad. Subjects have 1.5 s to respond. The screen blanks for 500 ms between problems. The test session lasts for three minutes (Perez et al., 1987). The Serial Addition/Subtraction task ran for 20 repetitions or 240 seconds, whichever occurred first.
8. **Code Substitution** - A string of nine letters is centered on the CRT display with a corresponding string of nine digits 1.25 cm below them. The letters and digits remain on the screen for the first 15 presentations and the letters are removed for the second 15 presentations. The pairing remains the same for each trial and pairs are randomly assigned (Perez et al., 1987). A test letter (probe) is then presented at the bottom center of the screen, 6 cm below the coding string. The subject is to indicate the digit which corresponds to that letter by pressing the corresponding key on the numeric keypad. The probe remains on the screen until the subject responds. During the second half of the test, the subject can press a specified key to display the code on the screen. The letter-digit pairings remain the same throughout each test session. Letters and digits are randomly paired for each session. There are 30 trials per session with an inter-stimulus interval of 500 ms between the response and presentation of the next probe. The screen will blank for five seconds if the subject responds during the inter-stimulus interval. The letters and digits are 2.0 cm in height and letters are capitalized (Perez et al., 1987). This task ran for 54 trials or 360 seconds, whichever occurred first.

Although the Unstable Tracking task was described by Perez et al. (1987), it is not yet part of the WR-PAB (UTC-PAB) software package. The version used by other members of the Unified Tri-Service Working Group was developed by System Research Laboratories (1987). This was also the version used in this study.

9. Unstable Tracking - A horizontal line appears across the center of the screen. An stationary cursor shaped like an isosceles triangle (arrow) is centered under the horizontal line. An identical cursor, which is controlled by the subject, is centered above the horizontal line. The low force multiplier (λ_2) was set at 1.0 and the high multiplier at 3.0, with the initial error equal to zero. The force multiplier takes degrees off center of the cursor position, multiplies it, and adds that amount to the position. In this manner the amount of error is increased. The low value is the lowest numerical value of the multiplier at initiation of the task. The high forcing multiplier defines the highest value that will be reached. The task is initiated at the low level and continues at equal increments to the highest level defined (Systems Research Laboratories, 1987). The percentage of the last λ value for reset was at 20 percent with a time delay of zero. Time samples occur in 1-s segments. Task time was set to match that chosen for the combined memory search-tracking combination task; therefore, task duration was 3 min, 48 s. The subject used a joystick, with his preferred hand, to control movement of the upper cursor (Perez et al., 1987; Systems Research Laboratories, 1987).

All physiological measurements were taken prior to each test battery. Blood pressure was taken using an automatic blood pressure cuff during the first two days of testing; however, adjustments required according to arm size were tedious and time consuming. A comparison of results obtained with the automatic blood pressure cuff and a sphygmomanometer and stethoscope revealed a difference of approximately 0.5 percent. Instructions on the use of the sphygmomanometer and stethoscope were provided by Phillip Barkley, M.D., Medical Director, VPI&SU Health Services. The remaining measures of blood pressure were taken using the sphygmomanometer and stethoscope at the brachial artery, non-dominant arm. Systolic pressure, generated during ventricle contraction, and diastolic pressure, maintained by the recoil of the arterial walls during ventricular relaxation, were recorded. Pulse was taken for one full minute at the radial artery. Temperature was taken by mouth using digital thermometers with disposable thermometer covers.

The following subjective questionnaires were used as part of the test battery, Mood Scale II and the Profile of Mood States. Mood Scale II is part of the Walter Reed Performance Assessment Battery (WR-PAB), which was written as part of the Unified

Tri-Service project to develop a performance assessment battery. The two performance assessment batteries (UTC-PAB and the WR-PAB) are used synonymously in the text of this research; however, the software used for the UTC-PAB tasks was actually written by individuals employed at the Walter Reed Army Institute of Research, Washington D.C., while the description of each task, with its purpose, background, reliability, validity, sensitivity, technical description, trial specifications, data specification, training requirements, and instructions to subjects can be found in the Unified Tri-Services Cognitive Performance Assessment Battery: Review and Methodology (Perez et al., 1987). As mentioned above, two abbreviated descriptions are also available (Englund, Reeves, Shingledecker, Thorne, Wilson, and Hegge, 1987 and Thorne, Genser, Sing, and Hegge, 1985). A description of Mood Scale II can be found in the articles by Thorne, et al. (1985) and by Ryman et al. (1974). The Profile of Mood States (POMS) was developed by Douglas McNair (Boston University School of Medicine), Maurice Lorr (Catholic University of America), and Leo Droppleman (University of Tennessee) and is available from the Educational and Industrial Testing Service (1989).

1. Mood Scale II - The subject is presented with 36 adjectives, one at a time, on the computer screen. The subject responds on a three-point scale with the extent to which the adjectives describe his current feelings (1 = not at all, 2 = somewhat or slightly, and 3 = mostly or generally). The adjectives represent six factors identified as anger, happiness, fear, depression, activity, and fatigue (Ryman et al. 1974; Thorne et al. 1985).
2. Profile of Mood States (POMS) - The Profile of Mood States consists of 65 adjectives which describe feelings and moods. The subject responds on a five-point Likert scale according to the level to which the adjectives describe his current feelings (1 = not at all and 5 = extremely). The six subscales included are tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment.

Subjects responded to three forms of self rating during each test session. They included; (1) the Stanford Sleepiness Scale, which is included in the Walter Reed Performance Assessment Battery (Thorne et al., 1985), (2) a self assessment indicating the subject's belief of having received an antihistamine or a placebo, and (3) a self evaluation of perceived performance. The Stanford Sleepiness Scale required one response on a six point Likert scale (1 = "feeling active and vital: alert: wide awake" to 7 =

"almost in reverie; sleep onset soon, lost in struggle to remain awake") (Hoddes et al., 1973 as cited by Herscovitch and Broughton, 1981). For the medication evaluation, subjects were asked whether they believed they received an antihistamine or a placebo and were instructed to respond with either 1 = antihistamine or 2 = placebo. For the perceived performance rating, subjects were asked to rate their performance on the immediately preceding tasks. Subjects were required to respond on a five-point Likert scale (1 = very poor and 5 = very good). All questions were displayed on the computer screen. All responses were made on the numeric keypad.

Dependent Measures

All dependent measures collected for each task were analyzed using an analysis of variance procedure. After viewing the results, it was apparent that some dependent measures were subcomponents of others and that some measures were of less interest than others. The dependent measures chosen for evaluation with post hoc tests and for inclusion in this report were those considered representative of task performance and most meaningful in an operational application. This procedure is discussed in detail for each task in the following sections. In only one case was there a significant finding for a non-selected dependent measure without a corresponding significant finding on the selected dependent measure. That single case was for the Interval Production task. No significant findings were identified for mean reaction time; however, maximum reaction time was significant for the time x drug interaction and total task duration was found to be significant for the main effect of time. Neither of these two measures was considered representative of overall task performance; therefore these measures are not reported.

Following Directions. The dependent measures collected for this task are score, total task time, percent total hits, percent mark hits, percent mark commission errors, percent unmark hits, percent unmark commission errors, mean time to mark or unmark words, and the standard deviation for marking and unmarking words (Analytical Assessments Corporation/EATON Corporation, 1988). The dependent measures chosen for analysis are score, total task time, percent total hits, and mean time to mark or unmark words. Score is equal to accuracy * speed * problem difficulty + range constant. Total task time is equal to the total amount of time taken to complete one trial of the Following Directions task. The maximum allotted time (90 seconds) is recorded if the problem is not solved correctly. A mark hit represents the number of words that were correctly

underlined (marked) and an unmark hit represents the number of words for which the underline was correctly removed (unmarked). Percent total hits is equal to the number of actual hits (both mark and unmark hits) divided by the number of possible hits and expressed as a percentage. A mark commission error represents the number of words that were incorrectly marked or unmarked. Percent mark hits, percent mark commission errors, percent unmark hits and percent unmark commission errors are subcomponents of percent total hits. In addition, percent mark hits and percent unmark hits are actually representative of the same principle; that is, they represent a correct response. Percent mark commission errors and percent unmark commission errors are also representative of the same principle; that is, they represent either underlining a non-target word or removing an underline from a non-target word. Therefore, percent mark hits, percent mark commission errors, percent unmark hits, and percent unmark commission errors were not selected as dependent measures for analysis. Mean time to mark or unmark words represents the mean time to underline or remove an underline from a target word. The standard deviation for marking or unmarking words represents the standard deviation for underlining or removing an underline from a target word. This measure was not chosen for analysis.

Each test session included three levels of difficulty. Results for each individual difficulty level are employed rather than combining the three difficulty levels in order to critique the task for usefulness in evaluating the effect of drugs on performance. For example, if one difficulty level of the test reveals a sensitivity to antihistamine ingestion more often than the other two difficulty levels, then perhaps the more sensitive level should be used exclusively in performance assessment.

Route Planning. The dependent measures collected for this task are score, total task time, solution achievement, valid moves, minimum valid moves, number of errors, number of reversals, mean time per move, and the standard deviation per move (Analytical Assessments Corporation/EATON Corporation, 1988). The dependent measures selected as dependent measures were score, total task time, minimum valid moves, number of errors, number of reversals, and mean time per move. Score is equal to accuracy * speed * problem difficulty * range constant. Total task time is equal to the total amount of time taken to complete one trial of the route planning task. If the problem is not solved, then the maximum time of 90 seconds is recorded. Solution achievement records a one if the correct solution is attained and a zero if the correct solution is not attained. Valid moves represents the number of actual moves made by the subject prior to problem completion or

until the allotted time (90 seconds) expires. Minimum valid moves represents the ratio of the number of moves required to solve the problem to the actual number of moves used. According to the CCAB manual, a perfect score would be equal to one (Analytical Assessments Corporation/EATON Corporation, 1988). The smaller the ratio, the worse the score. This ratio is not recorded if the problem is not solved. The number of valid moves is considered a subcomponent of the minimum valid moves; therefore, only the latter measure was analyzed. The number of errors represents the number of illegal moves; that is, moves to a blocked square or a square which cannot be reached according to the stated rules. The number of reversals represents the number of times that the subject reversed a move. Mean time per move represents the time used for each L-shaped move. The standard deviation per move represents the standard deviation of the mean time for each move. The standard deviation per move was not included in the dependent measures.

Each test session included three levels of difficulty. Results are collected for each individual difficulty level. As for the Following Directions task, the individual difficulty levels were analyzed rather than combining the three difficulty levels to critique the task for usefulness in evaluating the effect of drugs on performance.

Unified Tri-Services Cognitive Performance Assessment Battery (UTC-PAB).

The same dependent measures are collected for the following tasks: Four-Choice Serial Reaction Time, Pattern Comparison, Logical Reasoning, Manikin, Code Substitution, and Serial Addition/Subtraction. The available dependent measures are number of errors, mean reaction time, correct reaction time, minimum reaction time, maximum reaction time, start latency, total task duration, and overflows (Perez et al., 1987). As there tends to be a speed-accuracy tradeoff in tasks which emphasize speed of response, both mean reaction time and number of errors were selected as dependent measures for evaluation. Mean reaction time is equal to the time from the initial presentation of the test probe until the subject presses a response key. Mean reaction time for correct responses, minimum reaction time, maximum reaction time, start latency, and total task duration can be considered sub-components of the mean reaction time and the number of errors, it was determined that these variables would not be included in the analysis. Overflows pertain to the number of occasions that the maximum allotted time was reached without the subject responding. During pilot testing, fewer than ten overflows were recorded; therefore, these data were not included in the analysis. For the Code Substitution Task the number times that the subject elected to re-look at the code is also recorded; however, this response should also be reflected in the the mean reaction time.

Dependent measures which were collected for the Interval Production and Time Wall tasks are mean reaction time, minimum reaction time, maximum reaction time, total task duration, and overflows. The dependent measure selected for these tasks was mean reaction time.

The dependent measures recorded for the unstable tracking task were lambda value, root-mean-square error, and number of boundary hits (System Research Laboratories, 1987). The dependent measures chosen for analysis were root-mean-square error and number of boundary hits. Root-mean-square error is the rms offset from the center position. The number of boundary hits refer to the number of times that the cursor hit the boundary at either edge of the screen. The lambda value refers to the highest value the forcing multiplier reached before the task was completed. As the lambda value was set by the experimenter and was to be decreased by 20 percent each time a boundary was hit, this final lambda value is not a reliable indicator of performance and was therefore not selected for inclusion in the research analysis.

Physiological Measures. The dependent measures recorded were systolic blood pressure, diastolic blood pressure, pulse, and temperature. Initially physiological measures were to be taken solely for the purpose of medical monitoring. However, as literature on the effects of hismanal reported no haemodynamic effects (Craft, Vanden Bussche, De Cree, and Griffiths, 1987), it was determined to evaluate the data collected in order to examine possible drug or time effects. The mean and standard deviation of the four variables are included in Table 12.

Mood Scale II. The dependent measures collected for this task included number of items completed, six mood subscales (activity, happiness, depression, anger, fatigue, and fear), mean reaction time, start time, task duration, number of extra keys hit, and number of occasions that the allotted time ran out prior to the subject making a response (D. R. Thorne, personal communication, December, 1989; Walter Reed Performance Assessment Battery AUTOPAB and MAKEPAB instructions). The dependent measures chosen for analysis were the six mood subscales and mean reaction time. Absolute values were used for the mood subscales. Mean reaction time is equal to the time from the initial presentation of the descriptive adjective until the subject presses a response key. The rationale for not using the other variables in the analysis is described below.

TABLE 12

Means and Standard Deviations for Physiological Measurements

Variable	Mean	Standard Deviation
Systolic blood pressure	113.91	10.92
Diastolic blood pressure	69.40	11.60
Pulse	66.86	10.79
Temperature	97.16	0.76

The number of items completed was fixed; however, this value was provided as a check to insure that all items were completed in each test battery. Start time, in this case, reflects the time the subject started the test battery and the speed with which the subject completed the tasks prior to the mood scales. This was not considered relevant to the effect of either drug or time of day. Task duration can be considered a sub-component of the mean reaction time; therefore, it was determined to be a redundant measure. The number of extra keys hit and overflows were minimal (fewer than five) during pilot studies; therefore, these variables were not included in the analysis.

Profile of Mood States (POMS). The dependent measures collected for this task included six mood subscales, which are tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. All subscales were selected for inclusion in this study.

Self Ratings. Three forms of self rating were used. They are (1) the Stanford Sleepiness Scale, which is included in the Walter Reed Performance Assessment Battery (Thorne et al., 1985), (2) a self assessment of whether they believed they had received an antihistamine or a placebo, and (3) a self evaluation of how they felt they had performed during each session. For the Stanford Sleepiness Scale, one response on a seven-point Likert scale is required. For the medication evaluation, subjects were asked whether they believed they received an antihistamine or a placebo and were instructed to respond with either 1 = antihistamine or 2 = placebo. For the perceived performance rating, subjects were asked to rate their performance on the immediately preceding tasks. Subjects were required to respond on a five-point Likert scale. For each of these ratings, the absolute values reported were chosen as the dependent measures.

Instructions to Subjects

Subjects read the informed consent, which includes an introduction to the research project (Appendix A). In addition, the research project was described orally. Emphasis was given to the importance of the subjects giving their best effort, answering all questions sincerely, and carefully evaluating their schedules to ensure their ability to complete all phases of the research, in view of the possible future use of the research effort. For example, questions which assess the subject's perception of his performance are important in light of the fact that people have to judge their own working and/or driving performance in daily life (often after ingestion of medications) and determine when

their performance has become dangerous for themselves or others. It is therefore helpful to know whether subjects are capable of recognizing their own performance impairments. In addition, the researcher wished to decrease subjects' perception of the tasks as being similar to video games. O'Hanlon (1988) warned that performance tests which look like pub games will not be treated with the same motivation. Although the tasks possess face validity, the researchers wished to emphasize the seriousness of the research.

The following instructions were provided per task:

1. Following Directions - The instructions were printed on the CRT display, with the rate of presentation being determined by the subject (Appendix B1). The instructions were followed by a simulation of the task, two to four practice trials, and a 10 question true/false quiz (Appendix B1). Instructions emphasized accuracy and speed.
2. Route Planning - The instructions were printed on the CRT display, with the rate of presentation being determined by the subject (Appendix B2). The instructions were followed by a simulation of the task, two practice trials, and a 10 question true/false quiz (Appendix B2). Instructions emphasized accuracy, speed, and selection of a route with the fewest moves possible. The subject was informed that invalid moves will not be entered on the display (i.e., end moves on a shaded square).

The instructions for the tasks from the UTC-PAB were presented on the CRT screen and are provided as part of the UTC-PAB software package. Instructions included in this research are either direct quotes or paraphrased from the Unified Tri-Service Assessment Battery described by Perez et al. (1987). Instructions appeared on the computer screen during training only.

1. Four-Choice Serial Reaction Time

"The object of the four-choice reaction time task is to press the key on the numeric keypad that corresponds to the quadrant with the blinking colored block. The corresponding keys have colored tape on them to assist you with learning this task. The colored block will continue to blink until you press one of the four keys. Immediately following your response, another block (chosen at random) will begin to blink. This process will continue for approximately six minutes. You should respond as quickly and accurately as possible. If you do not respond within 2.5 seconds, a beep will sound every 0.1 second until you

respond. Reaction times of all correct and incorrect responses will be recorded. You may press any of the four keys to begin the sequence" (Perez et al., 1987). A replication of the screen display can be seen in Appendix C1.

2. Interval Production

"The purpose of the Interval Production Task is to test your timing ability. To do this, we will have you tap a key at a constant rate of one tap per second. By repeatedly tapping the key you are producing time intervals between the taps. The more consistently you tap the key, the more consistent the time intervals will be. You may start tapping whenever you are ready" (Perez et al., 1987). A replication of the screen display can be seen in Appendix C2.

3. Time Wall

"This task is to see how well you can estimate the speed of a moving square target. The target will always start at the top of the screen and descend at a constant rate toward the bottom of the screen. After the target is two thirds of the way down the screen, it will pass behind a wall and become invisible. Notice that the wall has a square notch at the bottom of it. Your task is to press the specified key at the exact moment the moving target would pass through the notch at the bottom of the wall. In making this judgement, you are not to count, instead, follow the target with your eyes and imagine it continuing straight down behind the wall to the notch. The task will continue for ten trials" (Perez et al., 1987). A replication of the screen display can be seen in Appendix C3.

4. Pattern Comparison (successive)

"This test examines your ability to compare two patterns, presented one after the other. The computer will present two patterns of dots to you. You should try hard to remember the first pattern. After a short time on the screen, it will be erased, and a second pattern will be displayed. You must decide if the second pattern is the same as or different from the first. If you think the second pattern is different from the first, press the D key for "different." If you think the two patterns are the same, press the key labeled S key for "same." It is very important to give you answer as quickly as you can without making mistakes. As soon as you give your answer, the screen will clear and a new pair of patterns will be presented. Before we begin, you will be given some practice runs (training only). If you have any questions, please ask the experimenter

now" (Perez et al., 1987). A replication of the screen display can be seen in Appendix C4.

5. Logical Reasoning

"In this task you will be presented with a letter pair AB or BA. A statement about the relationship between two letters appears below the letter pair. Your task is to determine whether the statement correctly describes the order of the letters. For example, if you were to see the statement "A is followed by B" with the letter pair AB, you should respond "same" by pressing the S key on the keyboard. If you were to see the statement "A is not preceded by B" with the letter pair BA, you should respond "different" by pressing the D key on the keyboard. For this task it is important that you make your decisions as quickly and accurately as you can. If you take more than 15 seconds to make a response, the trial will be terminated and the next trial will begin" (Perez et al., 1987). A replication of the screen display can be seen in Appendix C5.

6. Manikin

"This test examines your spatial ability. The computer will present you with a figure (manikin) holding either a square or a circle in each hand. The figure will be enclosed in either a circle or a square. The manikin may be facing toward you, away from you, standing upright, or standing on his head. Your task is to indicate, by pressing the corresponding button, which hand he is holding the matching object in by pressing the corresponding key on the keyboard. To indicate "left" press V with your left index finger. To indicate "right" press M with your right index finger. You will have two seconds to respond, so you must work as quickly and accurately as you can. If you have any questions, please ask the experimenter now" (Perez et al., 1987). A replication of the screen display can be seen in Appendix C6.

7. Serial Addition/Subtraction

"In this task, you must solve a number of simple addition and subtraction problems. If the answer is greater than ten, then you should subtract the answer from ten and the result will be the correct response. For example, the answer to the following problem $(5) (8) (+) (=)$ is 3. You may want to rest your index, middle, and ring fingers on the numeric keys 4, 5, and 6, while resting your thumb on the 0. You start the task when you are ready by pressing any of the response keys. Each test period lasts for three minutes. As soon as

you finish one problem, a new problem will appear. Try to perform the task as quickly and accurately as possible. At the end of the three minute test period, the task will automatically stop and the screen will go blank" (Perez et al., 1987). A replication of the screen display can be seen in Appendix C7.

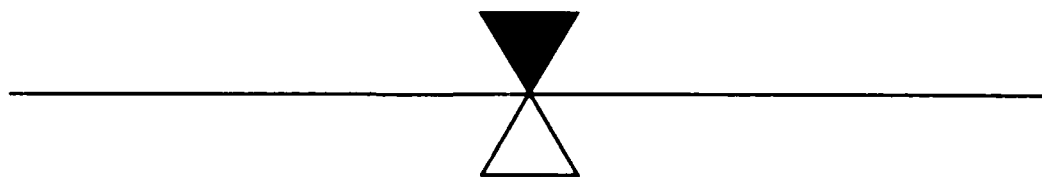
8. Code Substitution

"A row of letters will appear on the screen. There will be a row of numbers directly below the row of letters. Each number will be located directly below a corresponding letter and is called the 'code' for that letter. Your task is to learn the codes for each letter. A series of test letters will be presented, one at a time, at the bottom of the screen. Your job is to enter the digit on the keypad that is the 'code' for that letter. For example, if the letter 'J' is above the digit '7', then '7' is the code for 'J.' When the letter 'J' appears at the bottom of the screen, you should press the '7' on the keypad. Try to respond as quickly upon the presentation of the test letter as possible without making errors. The code will remain on the screen for the first half of the trials. The code will be removed for the second half of the trials and you will have to remember the code. You may press letter x to see the code again, if you need to. The number of times that you re-look at the code will also be recorded, so try and perform the task from memory" (Perez et al., 1987). A replication of the screen display can be seen in Appendix C8.

9. Unstable Tracking

As the instructions on the computer screen were brief and not comprehensive, they were supplemented by a written set of instructions and verbal reinforcement, both of which were given prior to beginning training. The written instructions included a drawing of the screen and were as follows.

"The following task is a tracking task. During this task a line will appear on the computer screen will appear as follows:



The goal of this task is to keep the top arrow (cursor) centered over the bottom arrow (target). As the cursor moves away from the center, you should try to keep it over the target by moving the tracking stick (joy stick) to the right or to the left. The tracking stick is located in front of you in the black box. You should try to keep the cursor centered over the target at all times. If the cursor reaches the edge of the screen, it will disappear, then reappear over the target and begin moving away from the center again. This is called a control error or boundary hit and should be avoided, as it lowers your accuracy score. You will be required to perform ten trials of this task during training. Each trial lasts for approximately three minutes. In order for you to keep track of how many trials you have finished, mark off each task, as you finish it, on the sheet provided for you. After you finish the first task, the results will appear on the screen with a message which reads, 'push any button except the black button to continue.' You should push the red button. Please contact the monitor now."

The experimenter supplemented the written instructions as follows.

"The object of the Tracking Task is to keep a cursor centered over a target in the center of the screen. You control the movement of the cursor by using the joystick on the control box in front of you. If you move the joystick to the right, the cursor moves to the right. If you move the joystick to the left, the joystick moves to the left. The cursor will begin to move away from the center when you press the green button on the control box. Try to keep the cursor centered over the target at all times. If the cursor reaches the edge of the screen, it will reappear over the center target and begin moving away again. Try to keep the cursor centered and to avoid having the cursor go off the edge of the screen. The tracking task will last approximately three and a half minutes. The task will become more difficult with time" (Perez et al., 1987; Systems Research Laboratories, 1987).

Instructions for the subjective questionnaires were presented on the CRT screen. Mood Scale II was provided as part of the UTC-PAB software package. Instructions included are direct quotes when appropriate or are paraphrased if the Walter Reed Performance Assessment Battery differed from that described by Perez et al. (1987).

1. Mood Scale II

"You will be presented with a list of words that describe moods and feelings. The words will appear, one at a time, on the computer screen. Indicate how each word applies to how you feel at that time by pressing the corresponding key (1, 2, or 3) on the numeric keyboard" (Ryman et al., 1974; Thorne et al., 1985).

2. Profile of Mood States

"You will be presented with a list of words that describe moods and feelings. Indicate how closely each word describes how you feel right now by responding on the corresponding scale."

Procedure

Training. Five pilot subjects were run using the training procedure and program and two pilot subjects were run using the testing procedure and program. All pilot subjects were run during a one-week session. Subsequently, subjects were trained within a two-week time frame. Time anticipated to reach plateau (10 to 15 training sessions per task) and definition of plateau performance is based on results obtained from research conducted at Walter Reed Institute of Research (D. R. Thorne, personal communication, March 21, 1989); however, training time and definition of asymptotic level were refined following the pilot study.

Subjects were scheduled for six hours of training in either two 3-hour sessions or one 6-hour session. Time was available for more training according to the need of the individual subject. The tasks were separated into four main groups: (1) unstable tracking, Sternberg memory search - and the memory search/tracking combination, (2) UTC-PAB, (3) CCAB, and (4) visual search. Although the four groups could be presented in any order (dictated by time constraints), the majority of subjects completed training in the order described above. Written instructions, a verbal explanation, time for subject questions, and a brief demonstration were given prior to the subject beginning his training for the tracking, memory search, and memory search/tracking combination tasks. Other instructions were given on the computer screen immediately preceding the corresponding task as described in the section entitled "instructions to subjects." Prior to beginning training, subjects completed a personal information questionnaire, which included a self rating of experience in several areas. As the computerized tasks bore a resemblance to

video games, all tasks involved use of a computer screen and keyboard, two tasks required simple mathematical calculations, and one task used a move from the game of chess, self ratings for experience levels in these areas were included (Table 13).

Subjects were trained to their asymptotic level on tests from the UTC-PAB. This was done in an effort to minimize learning effects. Other studies have used familiarization and/or training regimens (Hindmarch and Easton, 1986, Moskowitz and Burns, 1988; Seppala and Savolainen, 1982) in a similar attempt to decrease learning effects; however, none described training to an asymptotic level. Asymptotic level is defined, for the purpose of this experiment, as not exceeding $\pm 5\%$ of the mean score and mean time of the previous two sessions, or 16 trials had been completed. No subject required 16 trials.

Subjects were trained on the CCAB in accordance with the recommended training requirements (Analytical Assessments Center, 1988). In addition, they were required to train to their asymptotic level. The recommended requirements include subject instructions on the CRT screen (previous studies indicate that this takes approximately six minutes), an instructional task simulation, four practice trials, and a quiz of 10 True/False questions. The True/False questions focus on task comprehension and are designed to reinforce procedures; therefore, 70% are true and 30% are false. If subjects had not reached asymptotic level by the fourth hour of training on this task, training ceased. No subject required four hours of training on the CCAB tasks.

The visual-motor tracking task was practiced a total of 15 times (approximately one hour). According to Shingledecker (1984) the majority of training occurs with 6 trials at each loading level, while 10 to 12 are suggested to encourage stable performance.

Total training time ranged from five to nine hours per subject. Two subjects dropped from the study during training, one due to illness and one a voluntary withdrawal.

Testing. Subjects were divided into five groups of six subjects each. Each of the five groups was tested one day per week for three consecutive weeks, for example three Fridays in a row. Test days were Tuesday, Thursday, Friday, Saturday, and Sunday.

Subjects were required to complete a baseline session the day preceding each test day. This session consisted of a brief review of the tasks and one test session identical to the sessions completed during testing. This baseline session took approximately one hour to complete. During this time, subjects were given written copies of any final instructions and/or reminders that pertained to the next day test session.

TABLE 13

Ratings of Subjects' Personal Experience

Personal Experience	Mean	Standard Deviation	Range
Years post high school education	4.7	2.22	1-10
Hours spent on computer per week	8.11	9.66	0-40
Post high school math classes	5.07	2.73	2-12

Personal Experience	Frequency	Percent
Video game experience		
none	5	17.9
some	16	57.1
a lot	7	25
Programming experience		
none	6	21.4
some	9	32.1
a lot	13	46.4
Word processing experience		
none	3	10.7
some	4	14.3
a lot	21	75
Chess experience		
none	6	21.4
poor	4	14.3
average	12	42.9
good	6	21.4

Wake-up calls were given to all subjects at 6:30 am on the day they were tested, unless they specifically requested otherwise. Subjects reported to the test area at 7:00 am and received either hismanal (10 mg), benadryl (50 mg), or a placebo at that time. Subjects were instructed not to eat or drink anything prior to their arrival as the medication was to be taken on an empty stomach. Subjects were permitted to eat a light breakfast 30 minutes post medication ingestion, in accordance with antihistamine research reported in the literature (Gier, Kuijpers, and Nelemans, 1985).

Each participant received all three treatments (hismanal, benadryl, and placebo). For each test day, two subjects received hismanal, two subjects received benadryl, and two subjects received a placebo. Seven days later, on Test Day 2, the same six subjects were tested, but each received a different drug than in test session 1. Test Day 3 occurred one week later, with each subject will receiving the final of the three conditions.

Test batteries were administered one hour post medication ingestion (8:00 am) and every two hours thereafter, as shown in Figure 3, for a total of 16 hours. Thus, test sessions occurred at 8:00 am, 10:00 am, 12:00 pm, 2:00 pm, 4:00 pm, 6:00 pm, 8:00 pm, and 10:00 pm. Prior to each test session, the subject's heart rate, blood pressure, and temperature were recorded. Tasks were presented in the following order: UTC-PAB, visual search, CCAB, unstable tracking, and memory search/tracking combination. Subjects were permitted to read, study, talk, watch movies (from a VCR), watch television, or or sleep during the intervals between testing sessions. Subjects were not permitted to leave the laboratory vicinity and were within the purview of a member of the research team at all times. Subjects brought their own breakfast. Lunch was eaten following the 12:00 p.m. test battery and dinner after the 6:00 p.m. test battery. Subjects were able to bring their own meals and store them in the refrigerator provided, meals could be brought in by friends, and/or a member of the research team took orders and purchased food from local establishments.

Subjects were required to remain in the laboratory for a total of 16 hours due to the long half life of hismanal. A member of the research team remained with the subjects throughout each test day and a licensed physician was on call (via a beeper) throughout testing. Subjects were instructed to report adverse side effects, should they experience any, to the investigators that were present, and a written symptom checklist was completed twice a day. Subjects were permitted to leave upon completion of their final test battery. Subjects filled out a final questionnaire during their last test day. This questionnaire addressed the subjects perception of their typical response to antihistamines ingestion, a

listing on the performance tests with a space for comments on each, and an area for open comments.

Medication doses were in the therapeutic range and administered by mouth. The placebo did not contain active ingredients. The placebo consisted of lactose, corn starch, micro-crystalline cellulose, pre-gelatinized starch, providone K-90, magnesium stearate, colloidal silicone dioxide, and sodium lauryl sulfate. Medications were in capsule form and identical in appearance. All medication preparations were individually packaged for each subject by Janssen Pharmaceutical Company. Sixty envelopes were prepared (three for each subject) and labeled by subject number and day. The drug envelopes were kept in a locked vault within a locked room. Only the medications required for the particular test day were removed. In the case of an emergency, a seal could be removed to identify the medication a subject received on a particular test day. (A seal was broken for one subject who became ill consequent to his test day. It was revealed that he had received a placebo on his test day. He was consequently dropped from the study.) All unused medication was returned to Janssen Pharmaceutical Company. A master list of the contents was supplied to the researchers post testing to ensure the double blind research constraints. The drugs were administered by the research personnel.

RESULTS

Analysis of variance (ANOVA) procedures were performed on dependent variables for each task. Post-hoc simple-effect F-tests were performed to evaluate significant interactions. The Newman-Keuls test was performed to compare means. For all ANOVA procedures and the Newman-Keuls tests an alpha level of 0.05 was adopted. The Statistical Analysis System (SAS, version 5.18) was used for all analyses with the exception of the simple-effect F-tests.

To determine the subjective effect of antihistamines an ANOVA was performed on the two mood scales, Mood Scale II from the Uniformed Tri-service Performance Assessment Battery and the Profile of Mood States, on the Stanford Sleepiness Scale, and on the self rating of perceived performance. To assess the ability of subjects to detect their own performance decay, the Spearman Rank Correlation was performed which examined subjects' self ratings of their performance to their actual scores for accuracy and speed on the Uniformed Tri-service Performance Assessment Battery subtests.

The basic experimental design was a Latin square (drug x order x time), which was used to counterbalance order of presentation. To assess the drug effect, independent of the order of drug presentation, it was desirable to collapse the data across order, assuming order to be nonsignificant. Therefore, in order to determine if the order of drug administration had an effect, an analysis of variance procedure was used on the dependent variables mean reaction time and number of errors for the Uniformed Tri-service Performance Assessment Battery tasks, the root-mean-square error for the unstable tracking task, and score for the Complex Cognitive Assessment Battery tasks. There were six orders of the three drug conditions. The following equation was applied:

$$\begin{aligned}P_I &= 1 - (1 - \alpha)^N, \\ .01 &= 1 - (1 - \alpha)^{16}, \\ \alpha &= .0006279,\end{aligned}$$

where

P_I = the experimentwise probability of a Type I error existing among all comparisons, set at 0.01,

α = the significance level used per comparison, and

N = the number of dependent-variable comparisons made, which was 16.

Using this analysis, one order effect was significant, no pattern or trend was evident, and no interactive effects of drug x order were found. Therefore, the order

variable was disregarded in all subsequent analyses (resulting in a 3 x 8 experimental design).

Complex Cognitive Assessment Battery (CCAB) - Following Directions

For this task, the dependent measures analyzed were score, total task time, percent total hits, and mean time to mark or unmark words. Results were analyzed separately for each difficulty level and those that are significant are noted in Table E1.

The Spearman Rho correlation was used to compare performance with self ratings of experience on video games, computer programming, word processing, hours spent using a computer per week, chess experience, and the number of post high school math classes. The correlations compared performance under the placebo condition only, for two reasons: (1) the drug conditions could be expected to influence performance, and (2) the interactive effects of drug and experience are not the area of interest for this research. Instead, the correlation is of interest in the evaluation of the assessment technique (following directions task).

Score. For both the easy and the hard level task, the score achieved by the subjects generally improved over time. The results of the analysis of variance and the Newman-Keuls test for the easy level can be seen in Table E2 and Table E3, respectively. The results of the somewhat conservative Newman-Keuls procedure (Table E3) reveal that the score-easy means do not differ significantly by time of day, even though the ANOVA showed the effect to be significant at $p = 0.048$. Subjects' performance appears to improve over the course of the day, with a decrease in performance occurring at 2:00 pm and 4:00 pm (Figure 4). The suggestion of a fall in performance during the 2:00 pm and 4:00 pm sessions may be due to a circadian pattern in which alertness is decreased in the afternoon hours.

The medium level task did not vary with time (Table E4).

The time of day effect can be observed clearly in the hard level task with a monotonically increasing score over the eight times (Figure 5). On all figures where curves are fit, the x-axis was encoded as 0 = 7 am and 1 = 8 am followed by increments of one hour thereafter. Results of the analysis of variance for the hard level task can be found in Table E5 while the Newman-Keuls comparison of means results can be seen in Table E6. There was no significant difference by drug or drug x time for the dependent variable score for any of the three levels of difficulty.

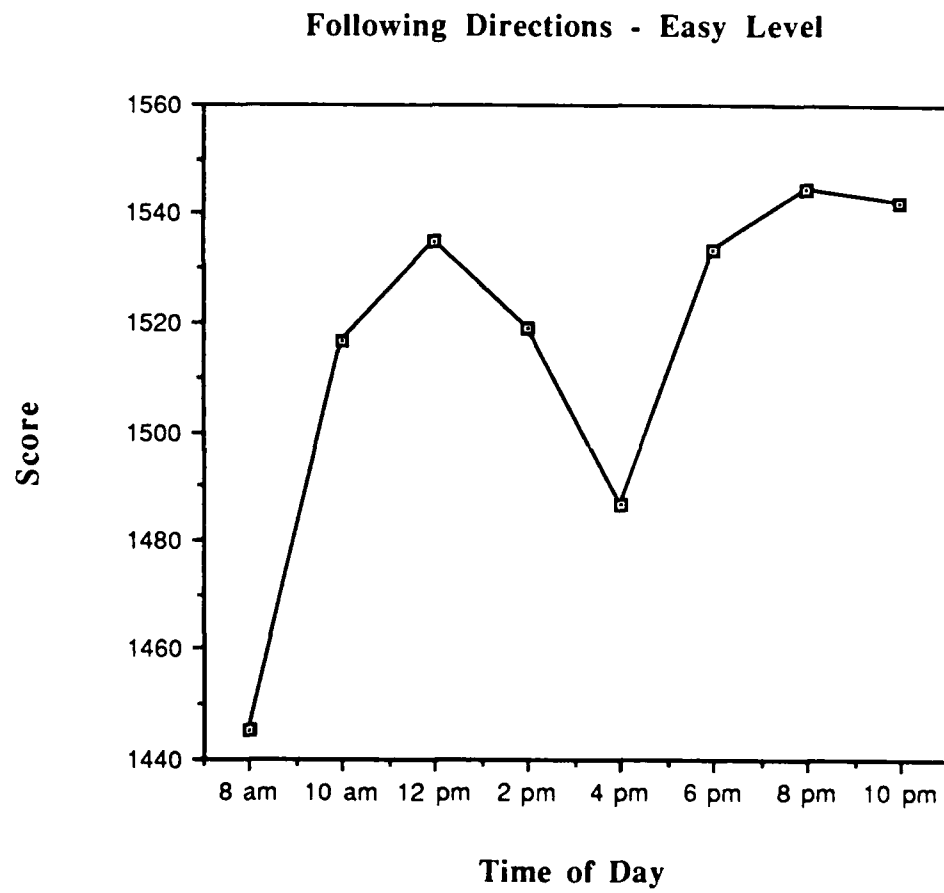


Figure 4. Time effect for Score on Following Directions - Easy level task .

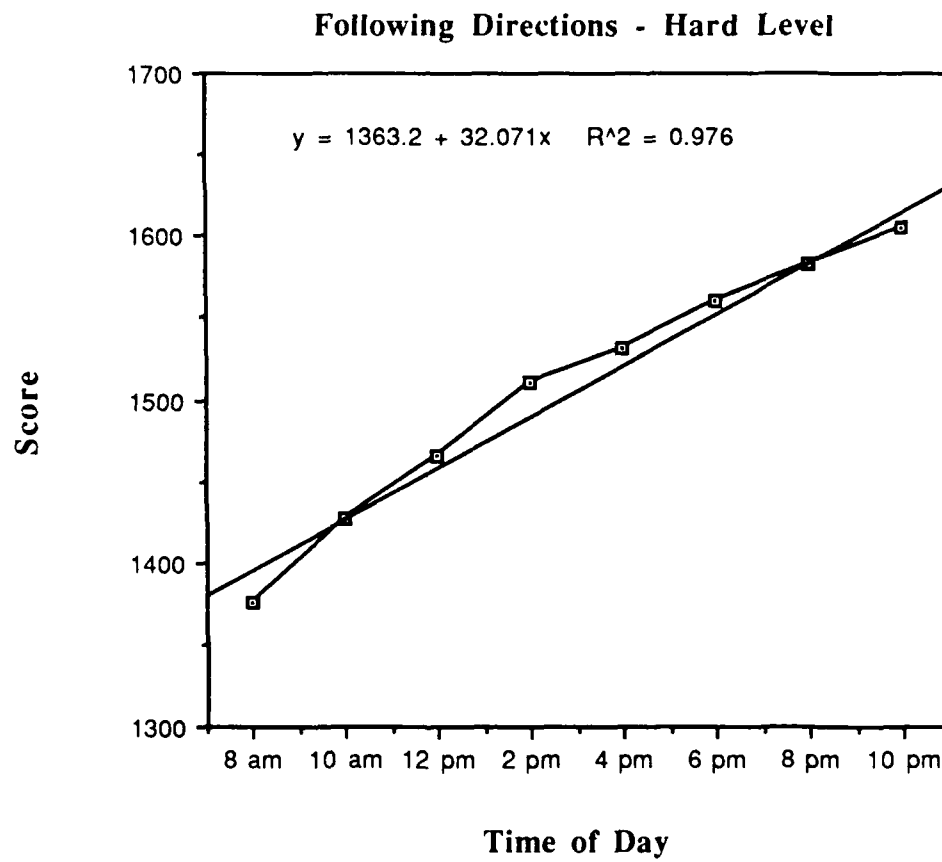


Figure 5. Time effect for Score on Following Directions - Hard level task .

Total Time. The results of the analysis of variance for the total time taken for the easy level following directions task are listed in Table E7. The total time taken for the task decreased slightly over the course of the day with the longest time occurring during the 8:00 am session and the shortest times occurring during the 8:00 pm and 10:00 pm test sessions (Figure 6). The results of the Newman-Keuls comparison of means for the easy difficulty level task can be seen in Table E8. Graphically, there is a suggestion of a decrease in total task time for the easy level task from 8:00 am through noon, an increase at 2:00 pm and 4:00 pm, and then a decrease once again. This reflects the suggested decrease in performance score at 2:00 pm and 4:00 pm seen above (Figure 4).

The analysis of variance results for the medium difficulty level revealed no time effect and are listed in Table E9.

Total task time for the hard level decreased consistently over time. The analysis of variance results are summarized in Table E10 and results of the Newman-Keuls can be seen in Table E11. The slowest mean total task time occurred at 8:00 am and decreased progressively throughout the day, described in Figure 7 by a linear function. Again, this result may be indicative of a learning effect in which subjects were able to complete the task in a briefer period of time, while continuing to improve their scores (Figure 4) as the day progressed. There was no significant difference by drug or drug x time for any of the three difficulty levels for the total task time.

Percent Total Hits. The results of the analysis of variance procedure for the easy level percent total hits are listed in Table E12. The percent total hits varied with time from a low at 8:00 am to a high at 8:00 pm (Figure 8 and Table E13). These results suggest a learning effect, although not a uniform one.

The analysis of variance results for the medium level percent total hits are listed in Table E14. A time of day x drug effect is noted. Results of the simple-effects F-test can be seen in Table E15 and the Newman-Keuls results for the significant 4:00 pm session are in Table E16. These results reveal that the subjects who had ingested a placebo achieved a lower percentage of total hits during the 4:00 pm session than did the groups receiving hismanal or benadryl (Figure 9). It is unlikely that this was due to the effects of the drugs administered. A review of stem leaf and box plots of the data reveal that two subjects from the placebo group received exceptionally low scores during this time. One achieved 14.3 percent unmark hits, while the other achieved 16.7 percent unmark hits. The highest and lowest scores for the two subjects are located in Table E17. A record was

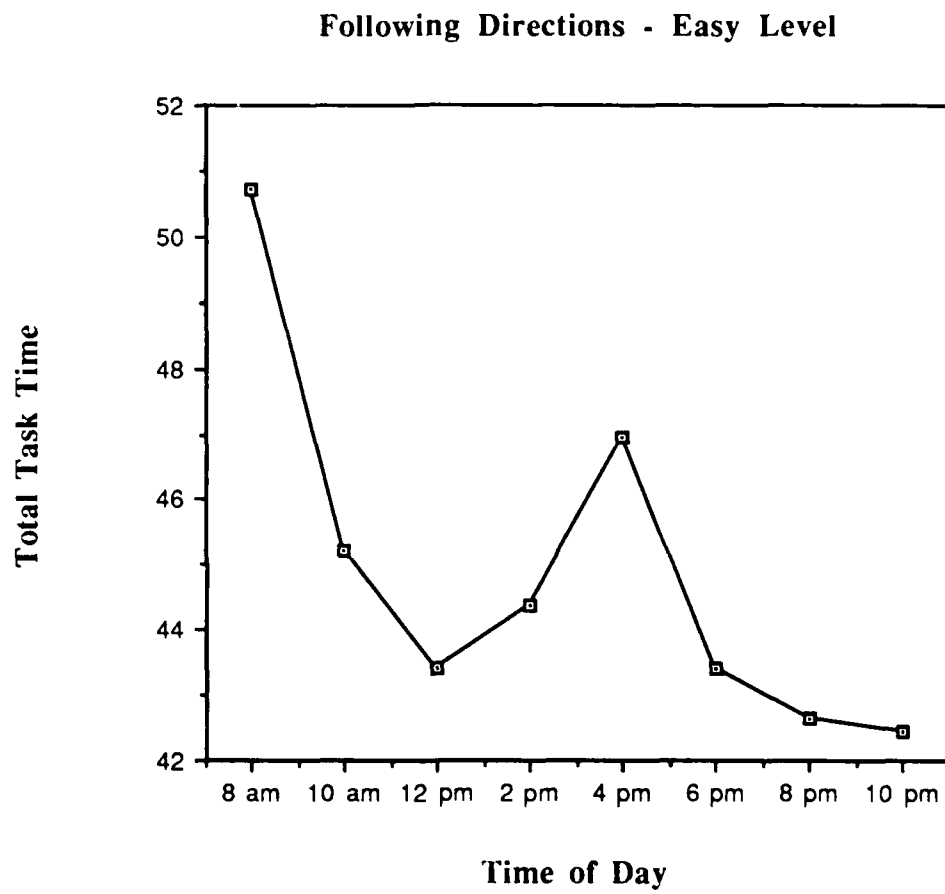


Figure 6. Time effect for Total Time on Following Directions - Easy level task.

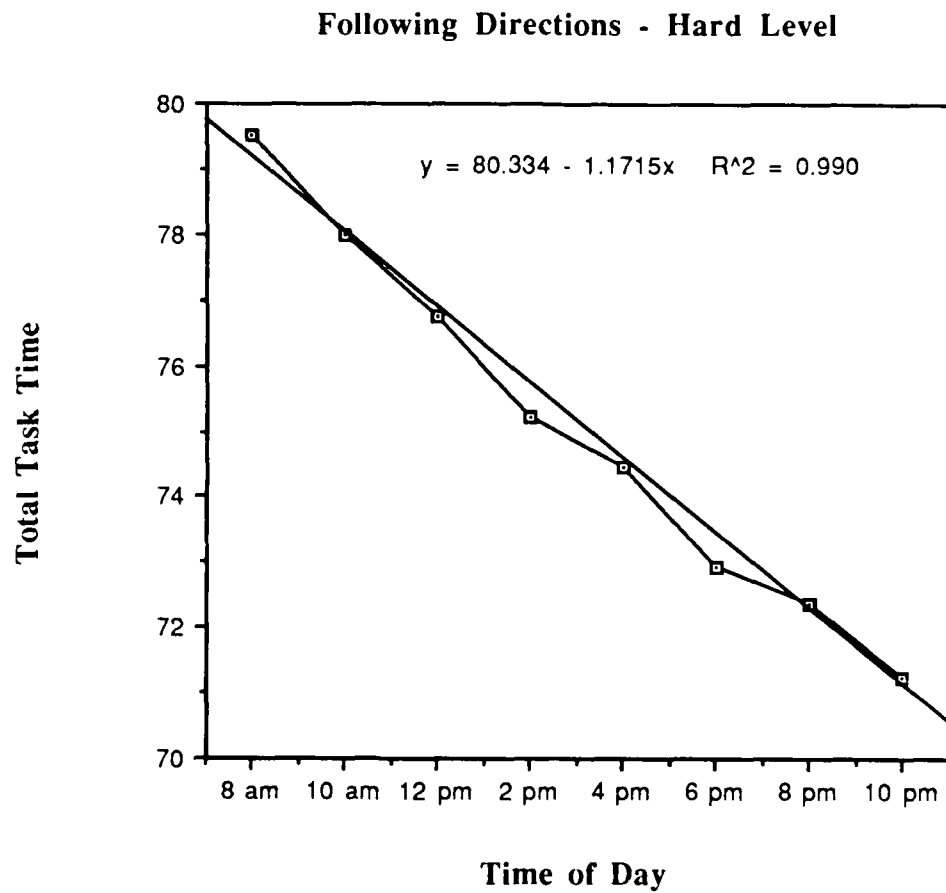


Figure 7. Time effect for Total Time on Following Directions - Hard level task .

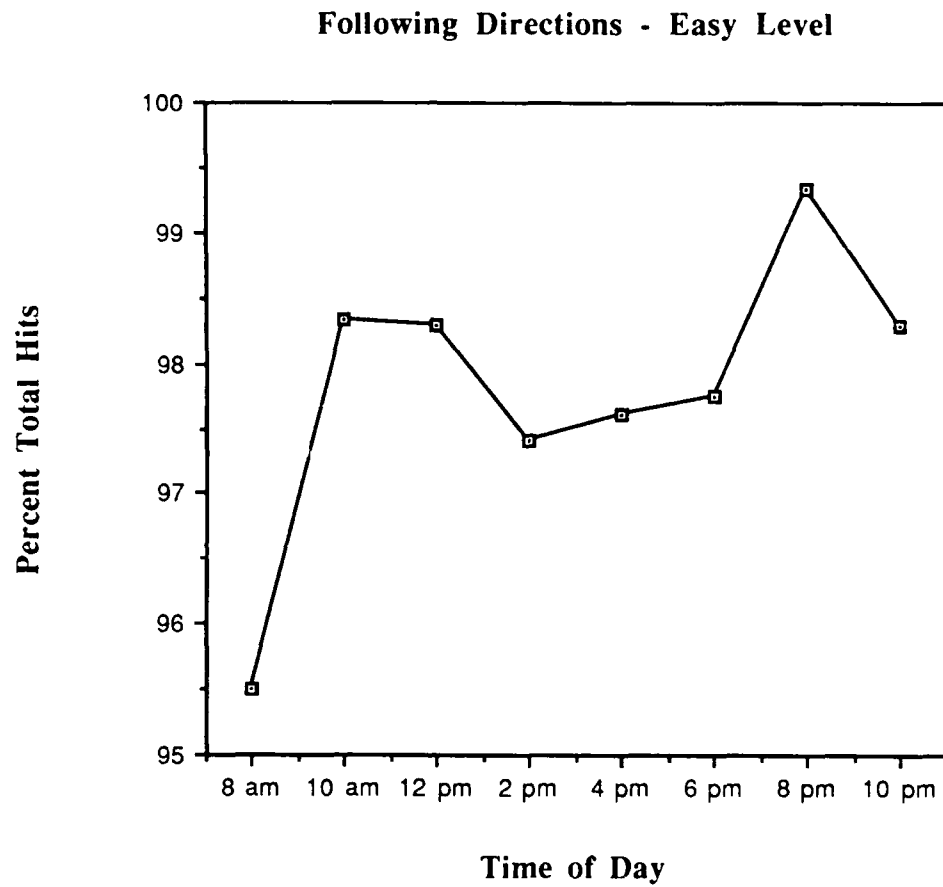


Figure 8. Time effect for Percent Total Hits on Following Directions - Easy level task .

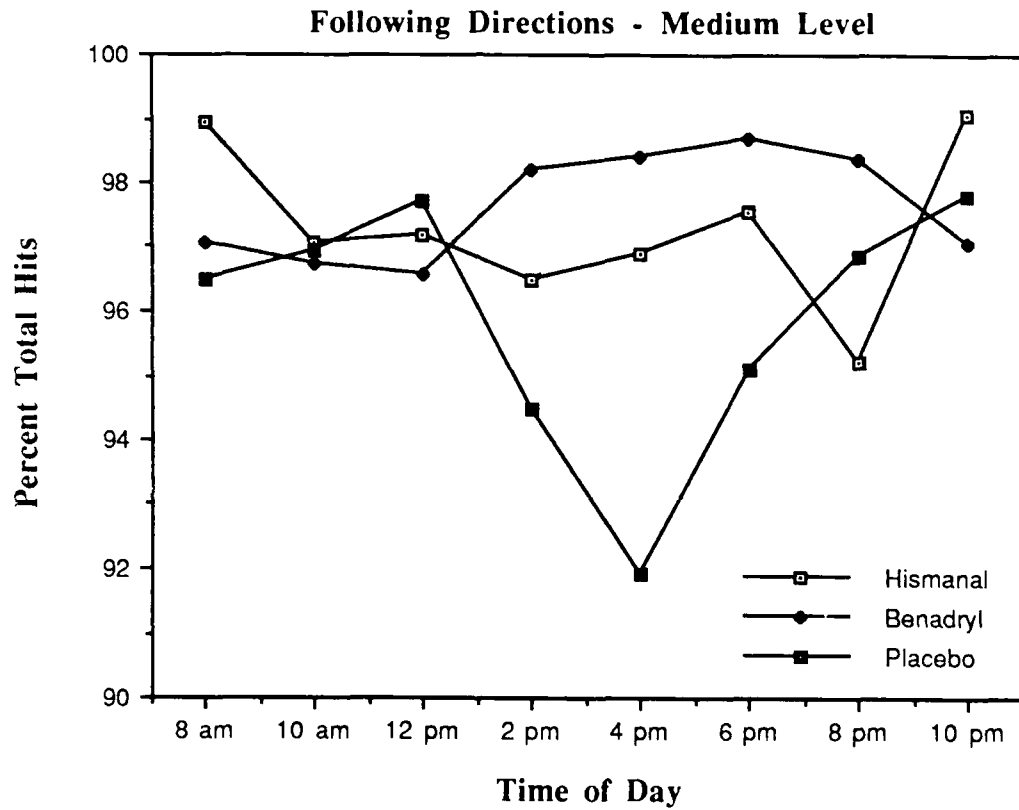


Figure 9. Time x drug interaction for Percent Total Hits on Following Directions - Medium level task.

kept of the subjects activity prior to each test session. A review of these records revealed that nothing extraordinary occurred prior to this test session. Although there is no explanation for these scores, these two subjects probably account for the low scores for the placebo group.

The percent total hits on the hard level task improved with time. The results of the analysis of variance procedure can be seen in Table E18. The Newman-Keuls results for percent total hits-hard across the time of day can be seen in Table E19. During the first session of the day, the percent total hits was lower than for any other session of the day (Figure 10). This result could be due to the subjects' experience of drowsiness after arriving at the testing laboratory at 7:00 am. There is also a suggestion of a leveling off/decrease in percentage in the afternoon, a decrease in percent total hits at 6:00 pm (just prior to dinner), an increase at 8:00 pm, and a decrease at 10:00 pm. A second order polynomial describes the secular trend with seasonal variations. Possible explanations for the suggested variations are circadian rhythms and decreased energy levels, fatigue at the end of the 16-hour test day, and trying to perform the task quicker during the final session and thus making more mistakes.

There was also a drug x time of day interaction effect for the hard level task. The results of the simple-effects F-tests are located in Table E20 and the Newman-Keuls results are in Table E21. At 8:00 am the mean percent total hits was lower for the benadryl group than for either the placebo or the hismanal group, but at 10:00 am and later, the performance of the benadryl group had improved so that there were no differences. This effect was expected according to the hypothesis that benadryl has a sedative effect and supports findings of performance impairment for two hours post ingestion (Gengo et al., 1989) (Figure 11).

Mean Time. The results of the analysis of variance procedure for the dependent variable mean time to mark and unmark words for the easy level task are located in Table E22. A temporal effect was found for the mean time to mark and unmark words for the easy level task. Mean time decreased after the first session of the day and remained relatively stable, with a non-significant difference as the day progressed. This can be seen graphically in Figure 12 and is also evident in the Newman-Keuls results located in Table E23.

The analysis of variance results for the the medium level task are located in Table E24. The mean time for the medium level task varied with time. The mean time was

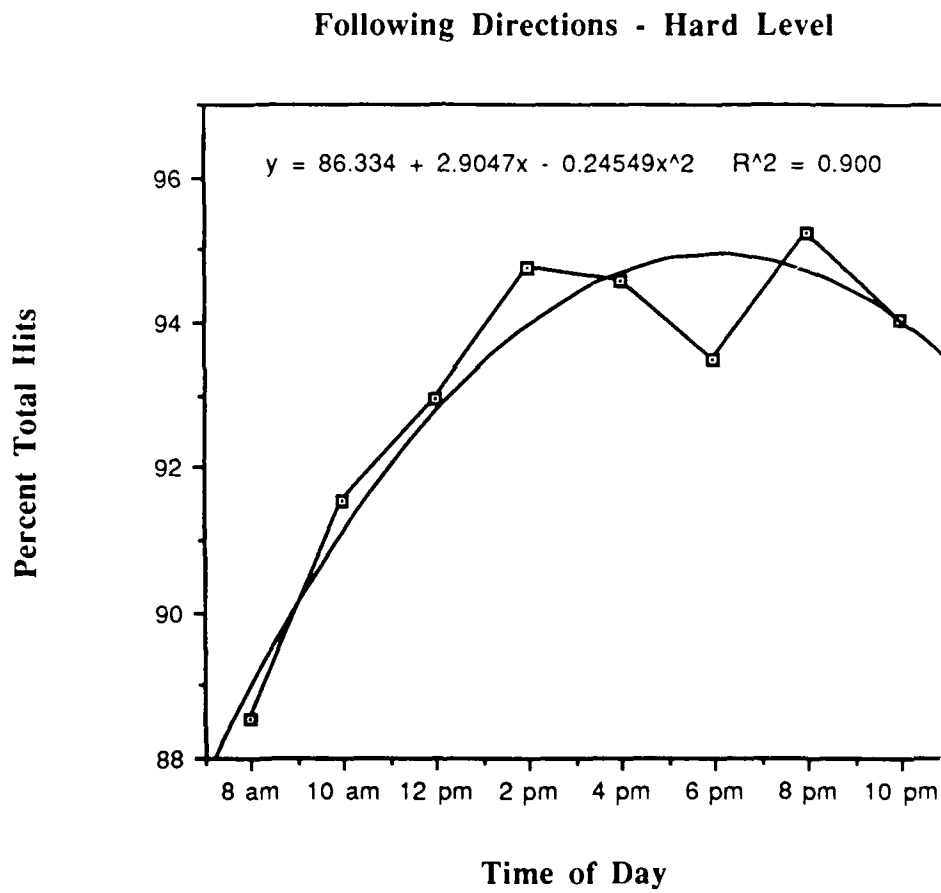


Figure 10. Time effect for Percent Total Hits on Following Directions - Hard level task.

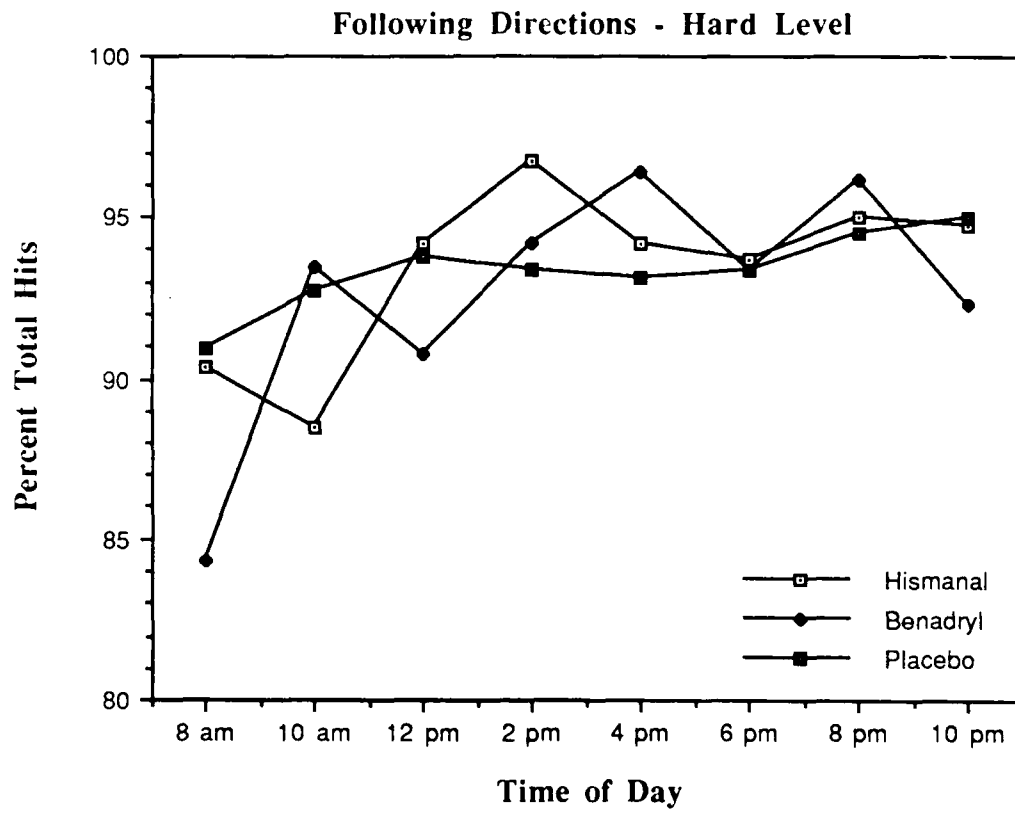


Figure 11. Time x drug effect for Percent Total Hits on Following Directions - Hard level task.

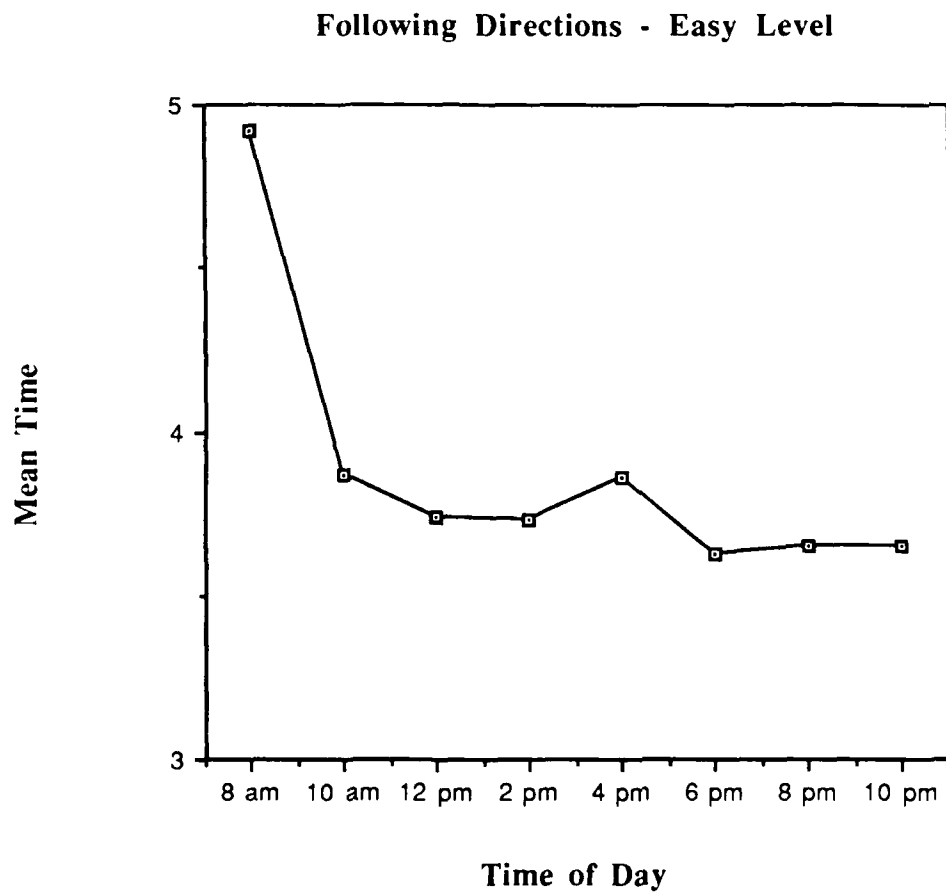


Figure 12. Time effect for Mean Time on Following Directions - Easy level task.

longest during the 8:00 am session, with a suggested increase at 4:00 pm and at 6:00 pm (Figure 13). The Newman Keuls results can be seen in Table E25.

The results of the hard level task analysis of variance are located in Table E26. The mean time to mark and unmark words was found to vary with time and was longest during the 8:00 am session and decreased over the remainder of the day (described by a second order polynomial in Figure 14). The shortest mean times were seen in the last four sessions of the day. These results may be indicative of a learning effect, with subjects responding quicker as the day progresses, while also improving the percent total hits they achieved (Figure 11). The results of the Newman-Keuls for the hard level are listed in Table E27. It is interesting to note that although the mean time for the hard level task was longer than for the easy and medium level tasks, the level of sensitivity to time, drug, or the time x drug effect was similar for the three levels. Although there were no significant drug or drug x time effects for the dependent variable mean time, the mean time for the benadryl group on the easy and hard level tasks was longer than for the other groups at the 8:00 am session; however, by 10:00 am the mean times for all three drug conditions were similar.

Subjective Experience Ratings. A positive correlation was noted between self reports of computer programming experience and score on the Following Directions task (Table E28). The Following Directions task is reported to measure the ability to attend to detail, perform a visual search task, store and retrieve information, time share, comprehend and respond to verbal instructions, and respond motorically (Analytical Assessments Corporation/EATON Corporation, 1988). Computer programming may require similar abilities.

Complex Cognitive Assessment Battery (CCAB) - Route Planning

For this task, the dependent measures were score, total task time, minimum valid moves, number of errors, number of reversals, and mean time per move.

Again each test session included three levels of difficulty. Results were analyzed separately for each individual difficulty level. Those dependent variables that were found to be significant are noted in Table E29. In addition, as DeGroot (1965) found that master chess players considered fewer moves than weaker players and had greater recall of mid-game positioning of chess pieces and Chase and Simon (1973) found master chess players format information in large chunks, the Spearman Rho Correlation was used to compare

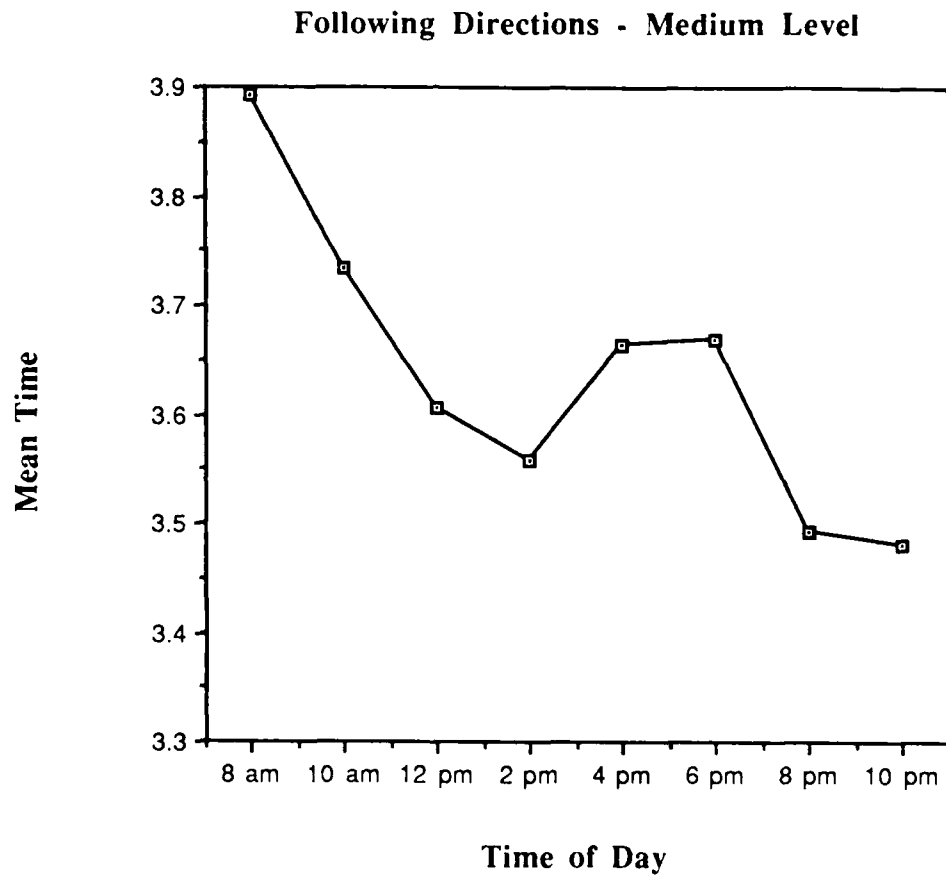


Figure 13. Time effect for Mean Time on Following Directions - Medium level task.

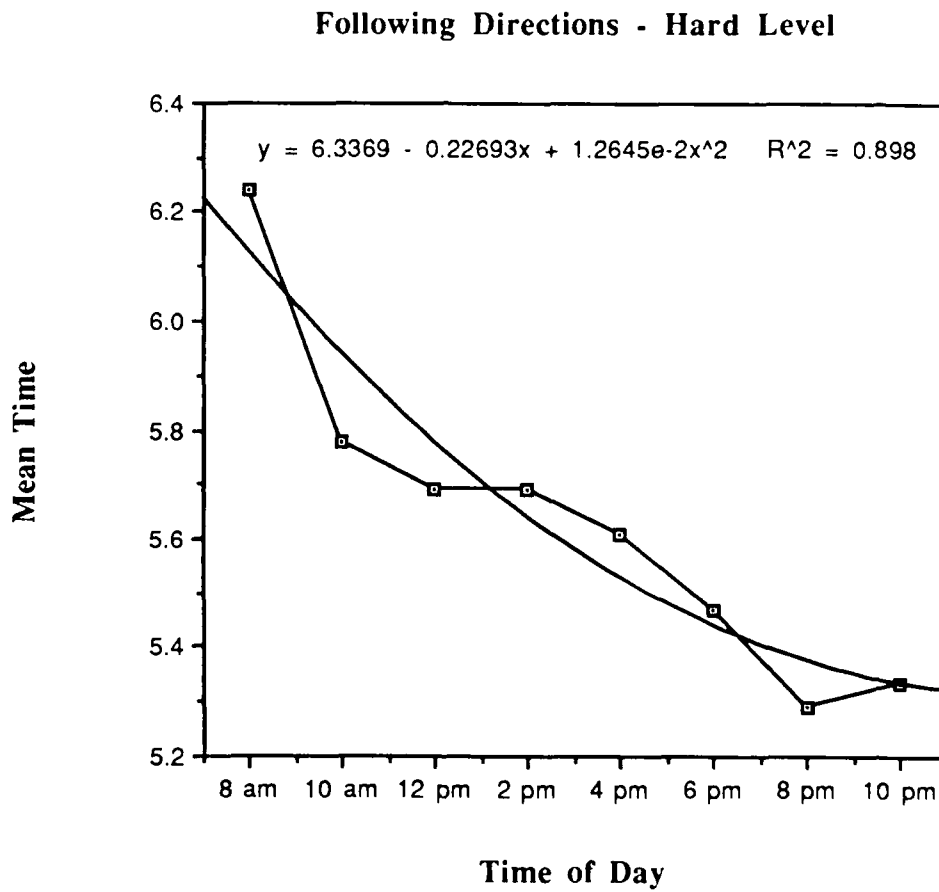


Figure 14. Time effect for Mean Time on Following Directions - Hard level task.

performance with self ratings on chess abilities. Correlations were also evaluated comparing performance with self ratings of experience on video games, computer programming, word processing, hours spent using a computer per week, and number of post high school math classes. The correlations were done comparing performance under the placebo condition only, for two reasons, (1) the drug conditions could be expected to influence performance and (2) the interactive effects of drug and experience are not the area of interest for this research. Instead, the correlation is of interest in the evaluation of the assessment technique (route planning task).

Score. Only the most difficult level dependent measure score varied with time. The results of the analysis of variance test for the easy and medium level tasks can be seen in Table E30 and Table E31, respectively. Although the analysis of variance for the hard level task (Table E32) revealed a significant time effect, the Newman-Kuels (Table E33) did not disclose a difference in the means. Graphically (Figure 15), the time of day effect shows the three lowest scores were attained at 10:00 pm, 10:00 am, and 8:00 am, respectively, with increases in scores just prior to lunch (12:00) and dinner (6:00 pm). There was no significant difference by drug or drug x time for the dependent variable score for any of the three levels of difficulty.

Total Task Time. There were no significant effects noted for total task time. The results of the analysis of variance for the easy level task are shown in Table E34, for the medium level in Table E35, and for the hard level in Table E36. This dependent measure does not appear to be sensitive to either the medication doses used in this study nor to temporal effects.

Minimum Valid Moves. The results of the analysis of variance for minimum valid moves on the easy level task are displayed in Table E37. The minimum valid moves were found to vary significantly over time. As the minimum valid moves represent the ratio of the number of moves required to solve the problem to the actual number of moves used with a perfect score being equal to one (Analytical Assessments Corporation/EATON Corporation, 1988), the results here are confusing. First, ratios greater than one were seen (Figure 16). As is apparent both by the data and by observation, solutions that could be achieved with fewer moves than the software recognized were possible. The software program should have inverted the accuracy component if the actual number of moves was less than the optimal number of moves required to solve the problem; however, this correction does not appear to have been implemented (Analytical Assessments

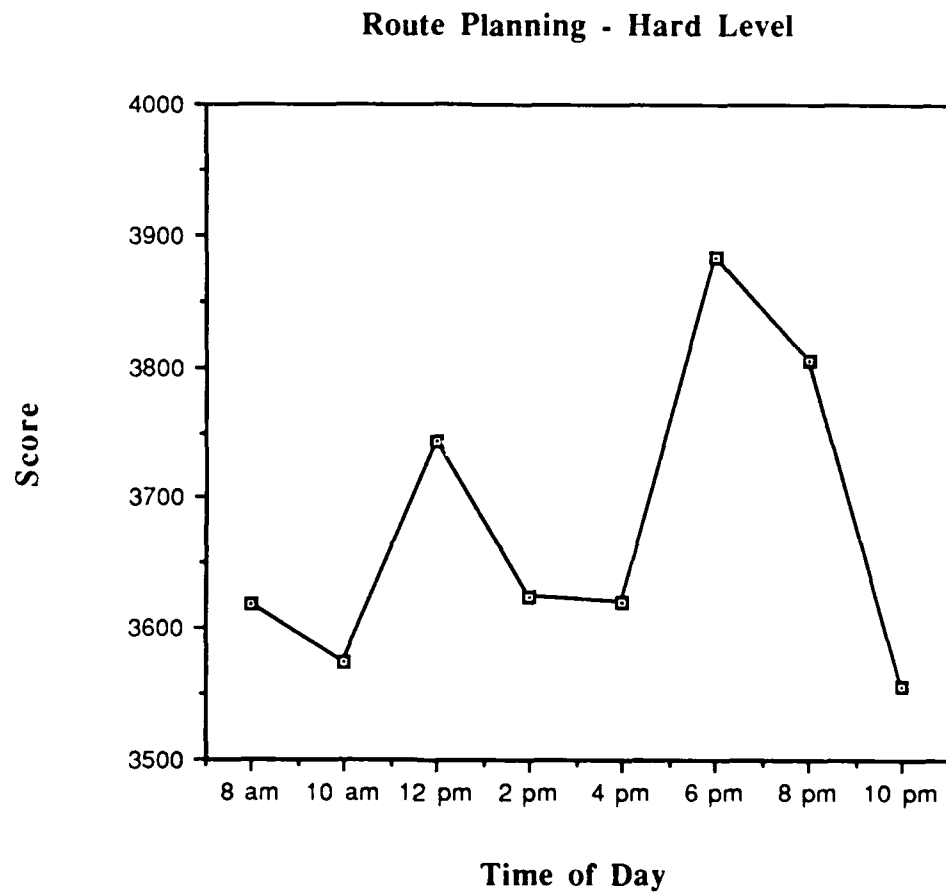


Figure 15. Time effect for Score on Route Planning - Hard level task.

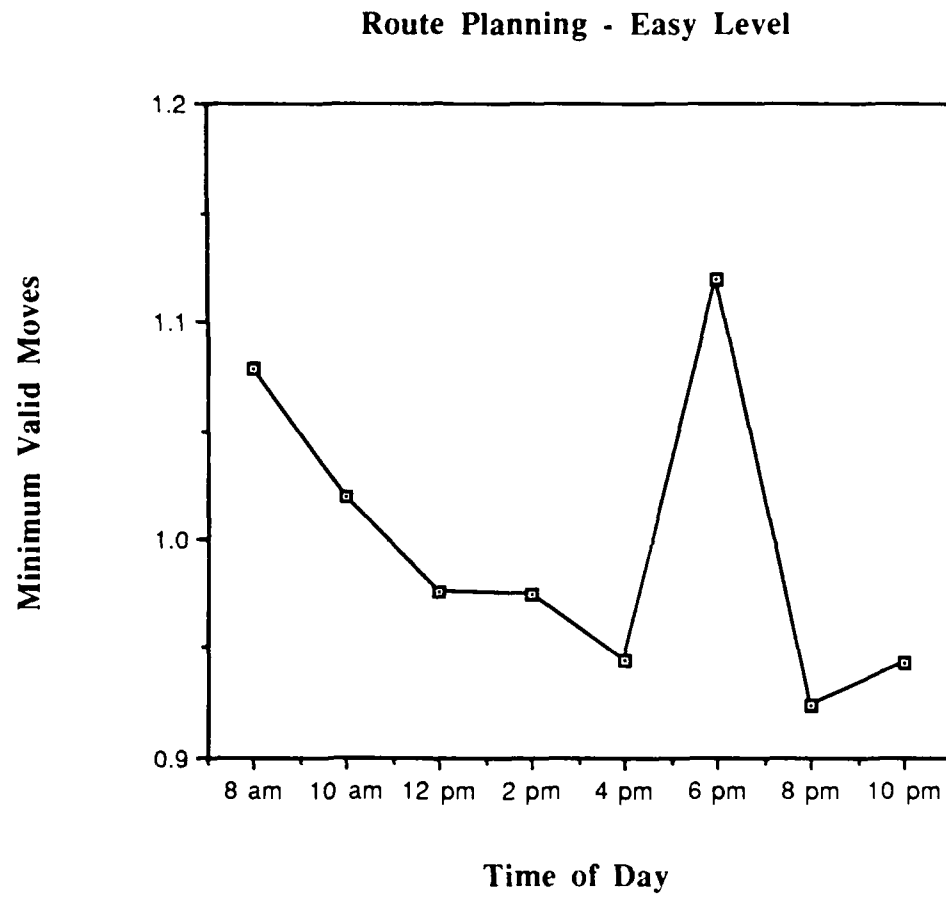


Figure 16. Time effect for Minimum Valid Moves on Route Planning - Easy level task.

Corporation/EATON Corporation, 1988). Second, if the data for minimum valid moves are correct, it would appear that performance deteriorated with time, as a smaller ratio is indicative of a lower score. Ratios achieved were smaller over the course of the day with the exception of an increase at 6:00 pm. This result is difficult to explain, unless subjects found the task so difficult or discouraging that they did not exhibit their best effort. The results of the Newman-Kuels test for the easy level task can be seen in Table E38. Results reveal no differences in the means for minimum valid move values.

Neither the medium (Table E39) nor hard level (Table E40) tasks showed main effects for time or drug, nor did they show an interactive effect for time x drug. These results suggest that the dependent measure minimum valid moves is not a sensitive indicator of the effects of time or dose levels of medication used.

Number of Errors. The results of the analysis of variance for number of errors for the three task levels can be seen in Table E41, Table E42, and Table E43. None of the task levels displayed a significant effect for time, drug, or time x drug.

Number of Reversals. The number of reversals varied with time for both the easy and hard level tasks. The results of the analysis of variance for the easy level task can be viewed in Table E44. The results of the Newman-Keuls comparison of means are located in Table E45. Although it is suggested graphically (Figure 17) that there are differences in the number of reversals, there are no significant differences among the means (Table E45).

The analysis of variance for the medium level task can be seen in Table E46. No significant differences were found for the medium level task.

Results of the analysis of variance for the hard level task can be seen in Table E47. The hard level task did vary with time of day for number of reversals. The largest number of reversals for the hard level task occurred at 10:00 pm and 4:00 pm, while the fewest reversals occurred at 6:00 pm (Table E48). This pattern is similar to that of the easy level task (Figure 17), which may be indicative of a circadian pattern, with lower performance in the late afternoon and late evening.

None of the three task levels revealed significant differences for drug or drug x time, suggesting that number of reversals may not be sensitive to the effects of time or dose levels of the antihistamines used in this study.

Mean Time. The mean time for each move did not vary with time, drug, or time x drug. The analysis of variance results are located in Tables E49, E50, and E51.

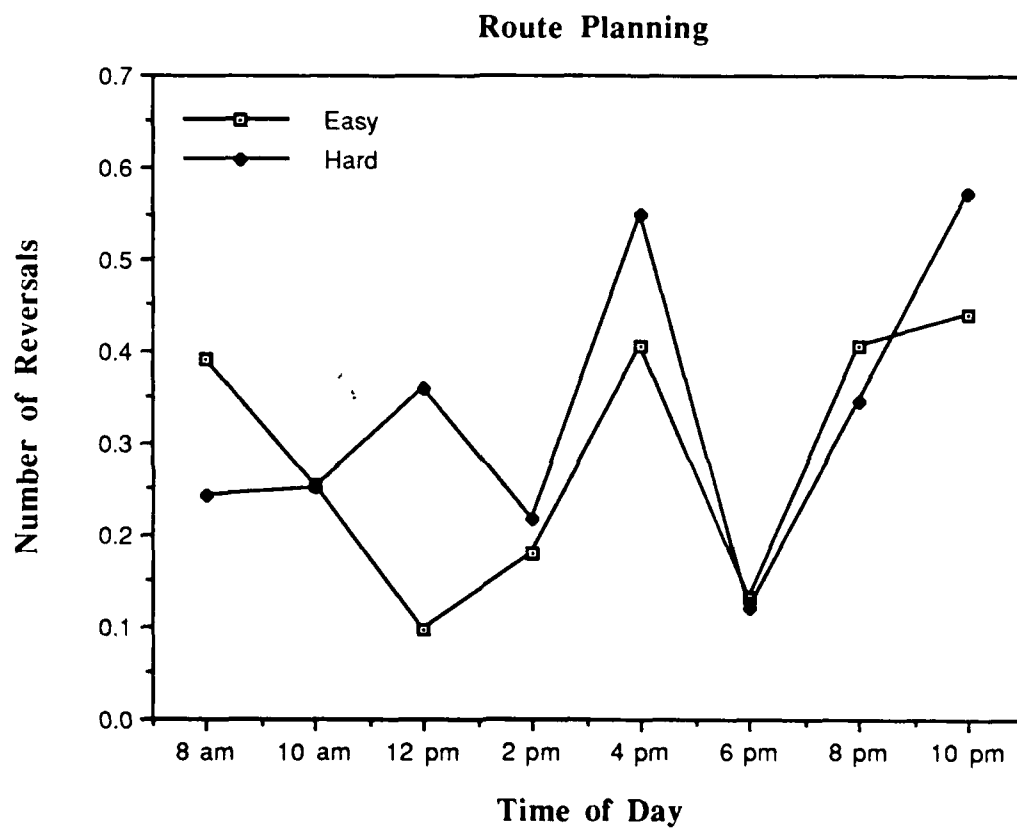


Figure 17. Time effect for Number of Reversals on Route Planning - Easy and Hard level tasks.

Subjective Experience Ratings. Significant correlations were found for video game experience, programming experience, and chess, but not for word processing, hours of computer use per week, or number of post high school math classes (Table 52). Video game experience could relate to spatial abilities which have been considered linked to route planning performance (Thorndyke and Stasz, 1980, as cited by Analytical Assessments Corporation/EATON Corporation, 1988, p. 8-4). A high level chess player may be able to perceive, remember, and recall correct moves more quickly and accurately. Computer programming experience may also relate to spatial abilities, but should especially be indicative of the ability to focus attention and establish criteria for the planning process and assessment, which are considered characteristic of good planners (Goldin and Hayes-Roth, 1980, as cited by Analytical Assessments Corporation/EATON Corporation, 1988, p. 8-3).

As a final evaluation of the Route Planning assessment, solution achievement was viewed. The problem was not solved 86.81 % of the time (Figure 18). Of the 13.19 % of the time that the correct solution was achieved, 4.46 % were achieved with hismanal, 4.81% were achieved with benadryl, and 3.92 % were achieved following placebo ingestion (Figure 19). Results of the Sutcliffe (1957) Chi-square test were nonsignificant by drug; however, these results indicate that subjects were unable to solve the problems in the allotted time regardless of the drug condition (Table E53). In addition, the difficulty level of the problem did not alter the ability of subjects to solve the problem (Figure 20). The difficulty in achieving the correct solution may have contributed to the observed lack of main and interactive effects.

Summary. The Following Directions task was subject to temporal effects which may be indicative of learning throughout the day. This result, in turn, could suggest that the level of training was insufficient. Although the benadryl group's performance was lower than the other groups during the 8:00 am session, the sole dependent measure which ascertained the effect of benadryl was the percent total hits on the hard level task. There also appears to be a circadian effect in which performance decreases during the 2:00 pm and 4:00 pm sessions, which is indicated most frequently in the easy level task. The lowest performance was typically observed during the first session and the highest performance was seen during the last sessions of the day.

The software for the Route Planning task is not programmed appropriately. Solutions which are correct can be achieved in fewer moves than the program recognizes.

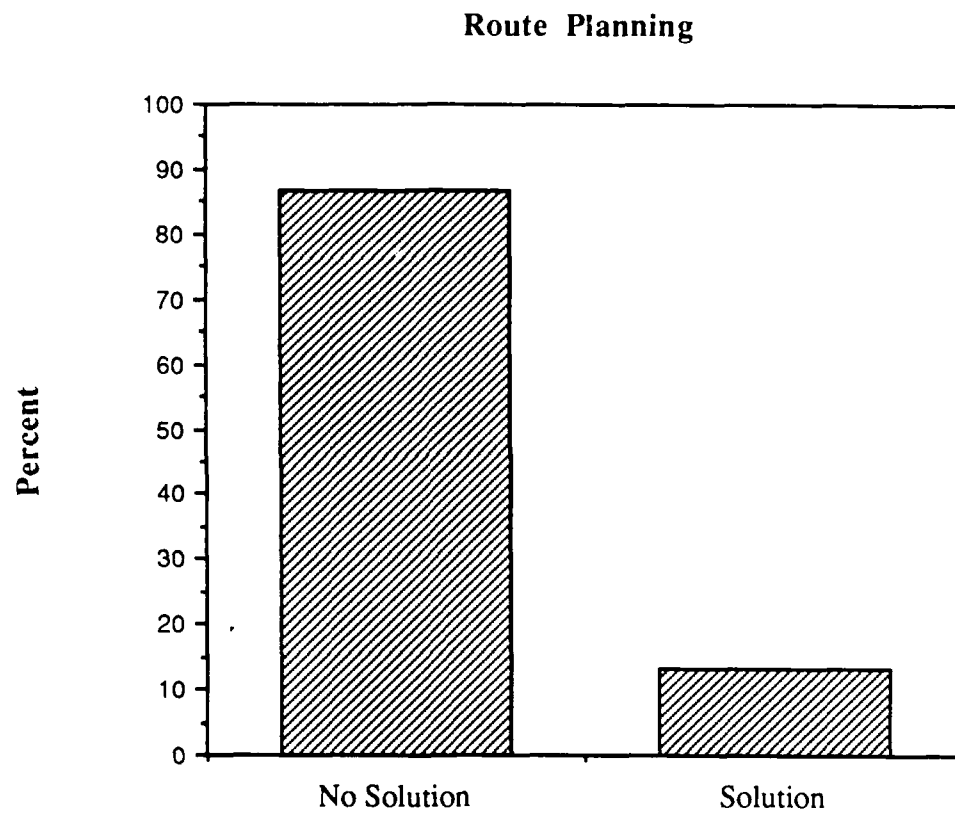


Figure 18. Solutions achieved for Route Planning - all difficulty levels.

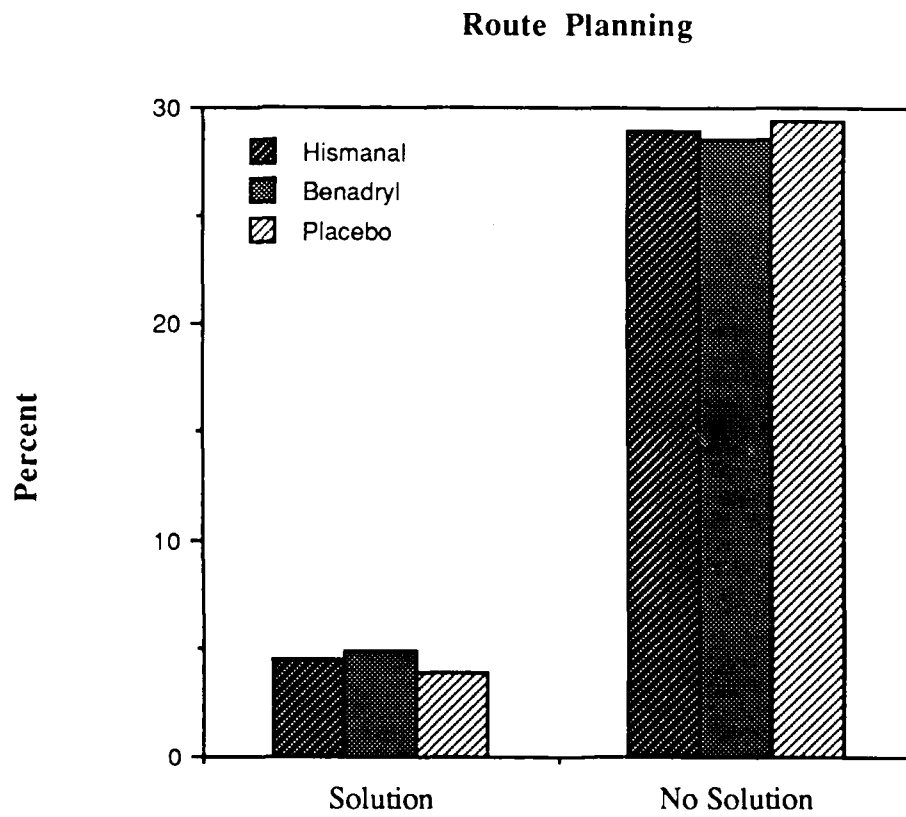


Figure 19. Solutions achieved for Route Planning - all difficulty levels by drug.

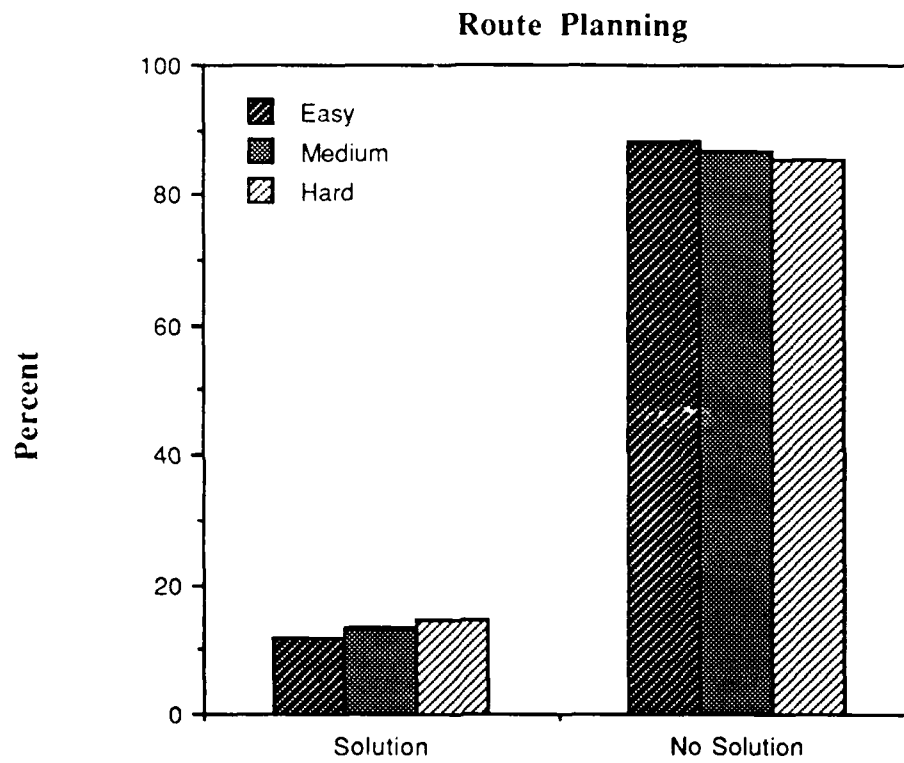


Figure 20. Solutions achieved for Route Planning - by difficulty level.

This should not affect the score, however, as score is equal to accuracy * speed * problem difficulty * range constant. None of the dependent measures was found to be of sufficient sensitivity to detect the effects of the antihistamines used. Temporal fluctuations suggest that subjects performed best at noon and in the early evening and worst at 8:00 am, 10:00 am, 4:00 pm, and 10:00 pm. A collective improvement of scores over time was not observed for this task. Both tasks generally showed low performance during the early sessions, in the late afternoon, and during the last session of the day.

UTC-PAB - Four-Choice Serial Reaction Time (Wilkinson)

The dependent measures for this task are number of errors and mean reaction time. Mean reaction time is equal to the time from the initial presentation of the test probe until the subject presses a response key.

Number of Errors. Analysis of variance results for number of errors are located in Table E54. There were no significant effects. The dependent measure of number of errors for the task four-choice reaction may not be sensitive to the dose levels of medication used in this study and may not be of sufficient sensitivity to distinguish performance changes due to circadian patterns. As this task has a high-stimulus response compatibility, task demands are primarily associated with encoding rather than stimulus categorization or motor response (Smith, 1968, as cited by Perez, 1987). Therefore, the critical variables for this test are more likely to be related to reaction times. That is, fewer errors are expected and thus the number of errors may be a less reliable index of performance.

Mean Reaction Time. The results of the analysis of variance for the Wilkinson Four-Choice Reaction Time task can be seen in Table E55. There were no time, drug, or time x drug effects for the dependent variable mean reaction time.

Subjective Experience Ratings. A correlation was found between self report of video game experience and both errors and mean reaction time on the Wilkinson four-choice reaction time task and between word processing experience and number of errors (Table E56). No association was found between self ratings of experience with computer programming, hours of computer use per week, chess experience, or number of college level math classes with performance as measured by mean reaction time. The primary demand of the Wilkinson reaction time task is thought to be on the encoding process (as

compared with central processing and response). The relationship between four-choice reaction time and video game experience may be due to the similar requirements for quick stimulus perception and response. The relationship between word processing and the four-choice reaction time task is less easily explained by the encoding demands. Familiarity with computer use may have influenced subjects' performance in terms of accuracy, however.

UTC-PAB - Interval Production

The dependent measure for the Interval Production task was mean reaction time. Mean reaction time is equal to the mean time interval between response key presses.

Mean Reaction Time. Analysis of variance results for the Interval Production task can be seen in Table E57. There were no significant effects for the dependent variable mean reaction time.

Subjective Experience Ratings. No significant correlations were found between self ratings of experience on video games, computer programming, word processing, hours of computer use per week, chess experience, or number of college level math classes with performance as measured by mean reaction time (Table E58).

UTC-PAB - Time Wall

The dependent measure for the this task was mean reaction time.

Mean Reaction Time. Analysis of variance results for the Time Wall task can be seen in Table E59. Mean reaction time generally decreased through the course of the day as illustrated in Figure 21, although a plateau exists during the middle of the day. The slowest mean reaction time occurred during the first session of the day and was significantly different from all other sessions except for the 10:00 am session. The quickest mean reaction time occurred during the last session of the day. The results of the Newman-Keuls comparison of means are located in Table E60. The slight but nonsignificant increase in reaction times during the 2:00 pm and 4:00 pm sessions reflect the trend seen in the CCAB tasks and may be indicative of altered performance due to a sluggishness after lunch or a circadian pattern of diminished afternoon performance; however, these changes are not of great magnitude. The general temporal trend and afternoon periodicity are well described by a third order polynomial in Figure 21. The

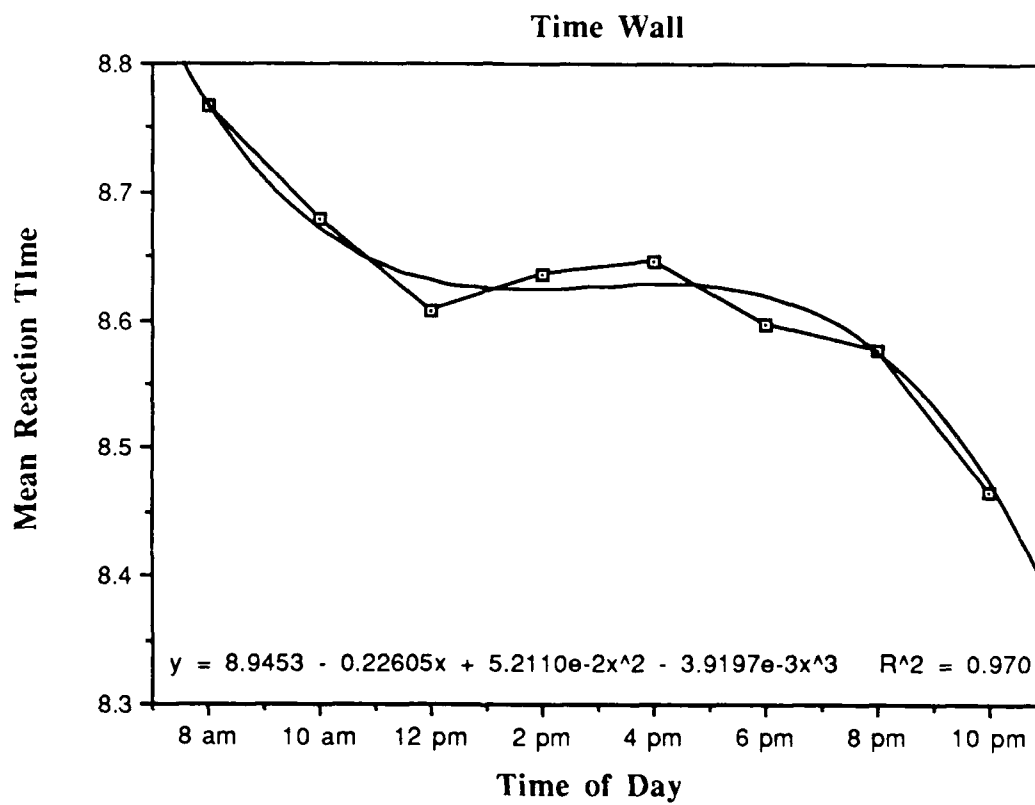


Figure 21. Time effect for Mean Reaction Time on Time Wall.

results suggest that judged time decreased over the course of the day, which is opposite to that found by Jerison and Arginteanu (1958, as cited by Perez et al. 1987). Jerison and Arginteanu found that subjects increased their time estimation over repeated trials.

There were no significant effects for either drug or time x drug for the dependent variable mean reaction time.

Subjective Experience Ratings. None of the subjective ratings of experience levels with video games, word processing, word processing, hours spent using a computer per week, level chess experience, or number of math classes post high school were found to be related to time estimation performance on the Time Wall task (Table E61).

UTC-PAB - Pattern Comparison (Successive)

Dependent measures for the Pattern Comparison task were number of errors and mean reaction time.

Number of Errors. The number of errors did not vary significantly in this test. Analysis of variance results for number of errors for the Pattern Recognition Task can be seen in Table E62.

Mean Reaction Time. The mean reaction time for the Pattern Comparison task varied over time. The results of the analysis of variance are located in Table E63 and the results of the Newman-Keuls Test are located in Table E64. The 8:00 am session was significantly slower than the noon and 4:00 pm through 10:00 pm sessions, but did not differ from the 10:00 am or 2:00 pm sessions. Mean reaction time was slowest during the 8:00 am and 10:00 am sessions and quickest during the 10:00 pm session. Depicted graphically (Figure 22), the mean reaction time is seen to have generally decreased from 8:00 am through 12:00 pm. Following lunch, the mean reaction time increased (but not to the level of the 8:00 am or 10:00 am sessions) and then decreased continuously over the remainder of the day (Figure 22). This result may suggest a learning effect as the subjects reacted more quickly as the day progressed. The decrease in mean reaction time appears to have occurred without a parallel increase in errors.

Mean reaction time did not vary with the drug; however, it did vary with the drug x time interaction. Results of the simple-effects F-tests can be seen in Table E65. Four were significant, 4:00 pm, 6:00 pm, 8:00 pm, and 10:00 pm. The results of the Newman-

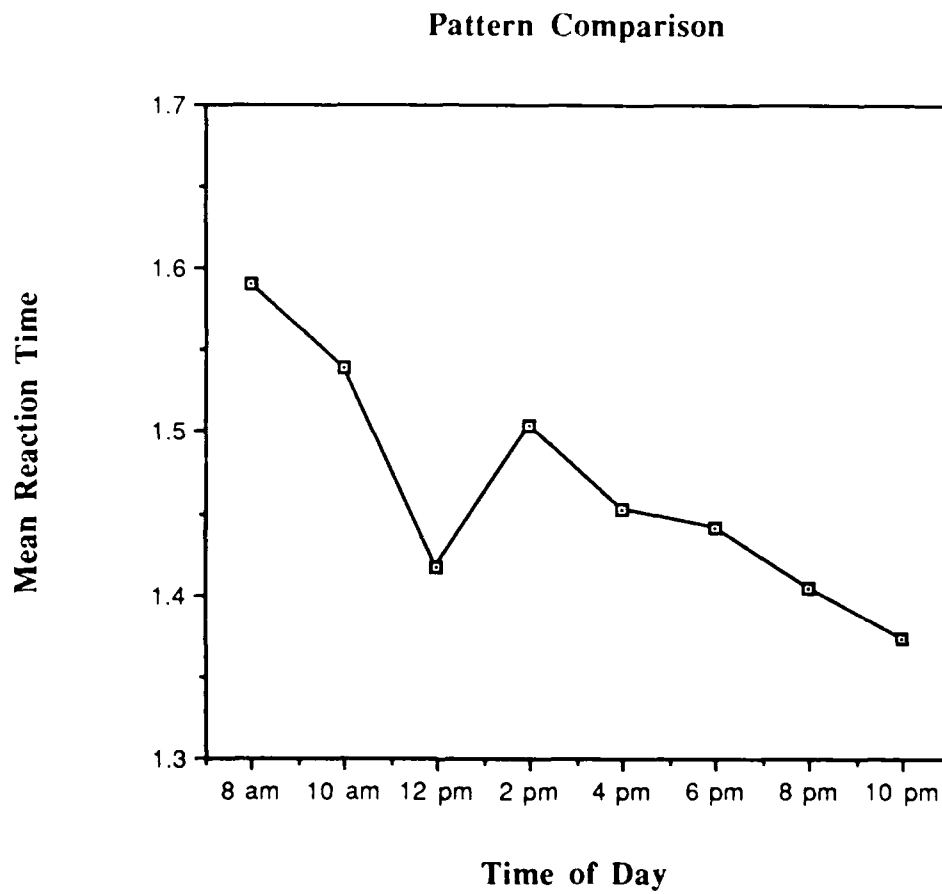


Figure 22. Time effect for Mean Reaction Time on Pattern Comparison.

Keuls comparison of means can be viewed in Table E66. A graphic representation can be seen in Figure 23.

At 4:00 pm and 6:00 pm the mean reaction time post placebo ingestion is slower than for the benadryl group. At 8:00 pm the mean reaction time for the placebo group is significantly slower than for the hismanal group and at 10:00 pm the mean reaction time for the placebo group is slower than for both the benadryl and hismanal groups. An explanation for these findings is difficult. Although some studies have found that performance following hismanal ingestion has actually been superior to performance following placebo ingestion, this does not explain the placebo group performing more slowly than benadryl group at 4:00 pm and 6:00 pm and more slowly than both the benadryl and hismanal groups at 10:00 pm.

Subjective Experience Ratings. None of the personal ratings of experience levels were found to be related to performance on the pattern recognition task (Table E67).

UTC-PAB - Logical Reasoning

The dependent measures for this task are number of errors and mean reaction time.

Number of Errors. Results of the analysis of variance shown in Table E68, revealed no significant main or second order effects.

Mean Reaction Time. The mean reaction time for the logical reasoning task was found to be significant for the main effect of time. The results of the analysis of variance are located in Table E69. A Newman-Keuls comparison of means test was performed and the results are listed in Table E70. Mean reaction time was slowest at 10:00 am and was significantly quicker during the three evening sessions. This relationship is displayed in Figure 24. No significant effects were found for drug or the second order effect of time x drug.

Subjective Experience Ratings. The subjective report on hours spent using a computer per week was correlated with the number of errors on the logical reasoning task. The reported level of experience with computer programing was found to be associated with the mean reaction time on the logical reasoning task (Table E71). Hours spent using a computer per week was not precisely defined as to the type of tasks performed; therefore, no conclusions can be drawn from this information. The logical reasoning task is thought to measure general reasoning ability, as well as information integration and

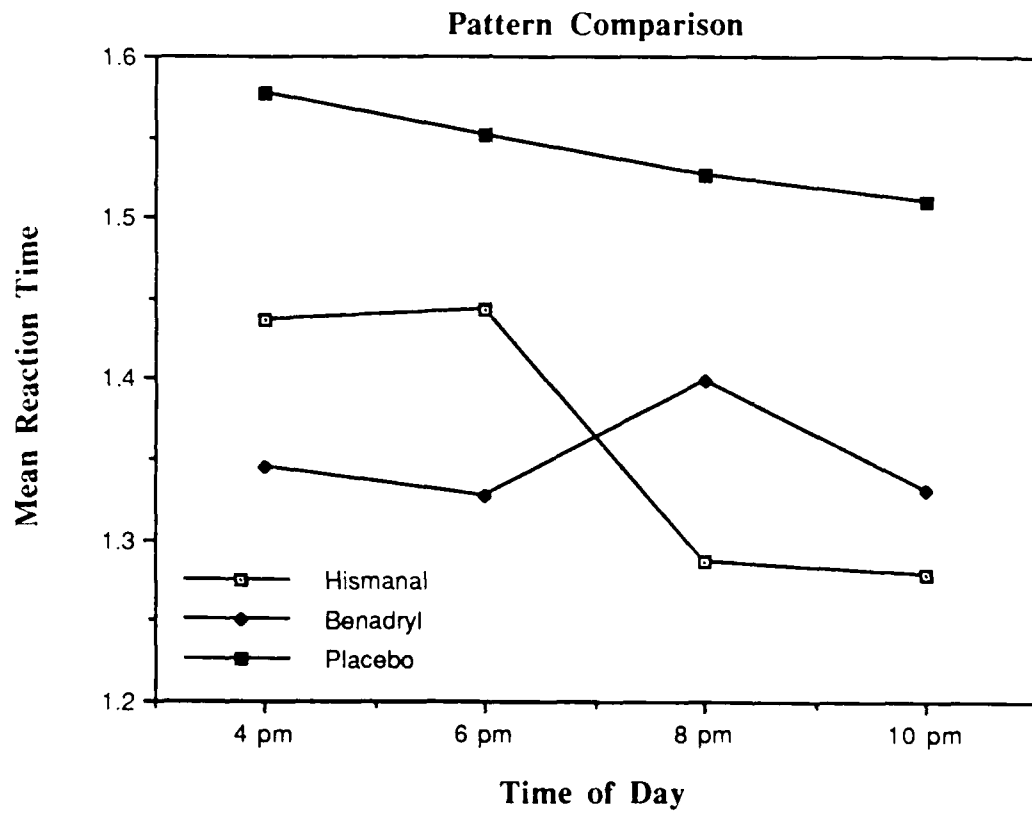


Figure 23. Time x drug interaction for Mean Reaction Time on Pattern Comparison.

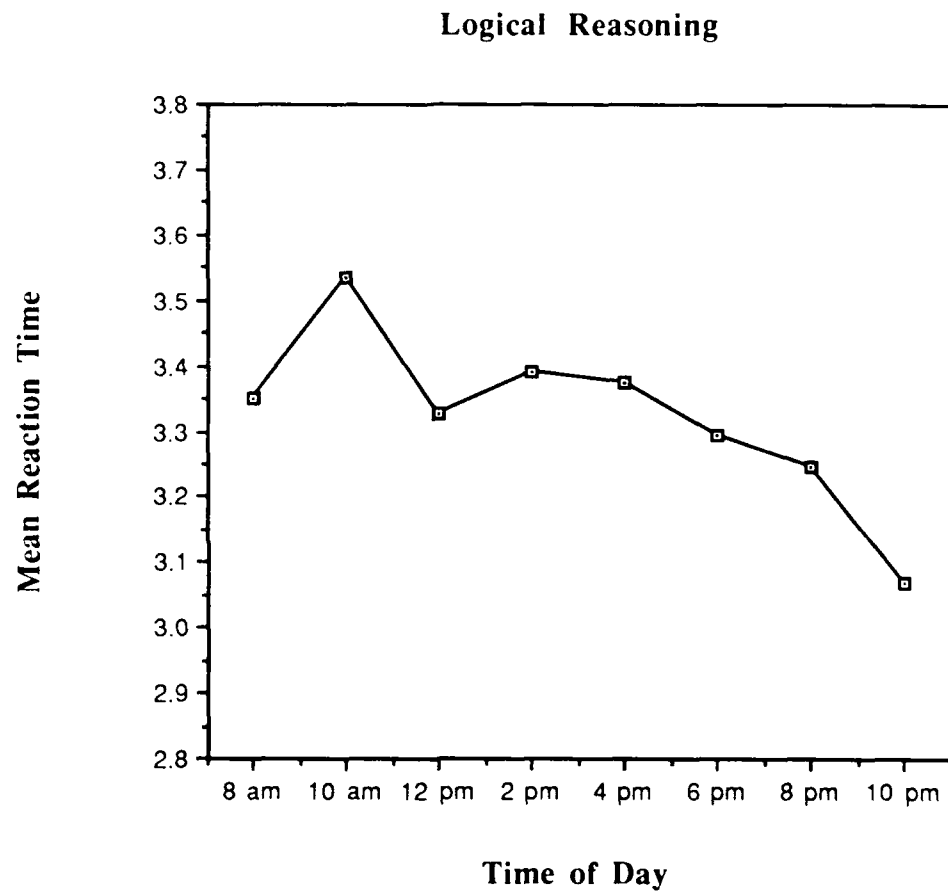


Figure 24. Time effect for Mean Reaction Time on Logical Reasoning.

manipulation (Perez et al. 1987). Computer programming may require similar skills of reasoning and manipulation of information in working memory.

UTC-PAB - Manikin

The dependent measures for the manikin task are number of errors and mean reaction time.

Number of Errors. Results of the analysis of variance for the manikin task dependent measure number of errors are shown in Table E72. Results revealed no significant effects.

Mean Reaction Time. The mean reaction time for the manikin (spatial rotation) task was found to be significant for the main effect of time, as illustrated in Figure 25. The results of the analysis of variance are located in Table E73. A Newman-Keuls comparison of means test was performed and the results are listed in Table E74. Mean reaction time for the Manikin task generally decreased over the course of the day (Figure 25). Mean reaction time was slowest at 8:00 am. The quickest reaction times occurred during the 8:00 pm, 10:00 pm, and 6:00 pm sessions. Subjects improved their speed of response over time without a synchronous increase in the number of errors. The suggested increase in reaction time at the 2:00 pm session could be the result of either ingestion of lunch and a consequent sluggish motor response or a circadian effect, with a low performance period occurring in the early afternoon. The general trend and suggested afternoon variation are described by a third order polynomial in Figure 25. There were no effects for drug or time x drug.

Subjective Experience Ratings. No relationship was identified between the experience levels and dependent measures on the manikin task (Table E75).

UTC-PAB - Serial Addition/Subtraction

The dependent measures for the serial addition/subtraction task were number of errors and mean reaction time.

Number of Errors. The analysis of variance results for number of errors on the serial addition/subtraction tasks are located in Table E76. This analysis revealed a main effect of time, shown graphically in Figure 26. Although there were no significant

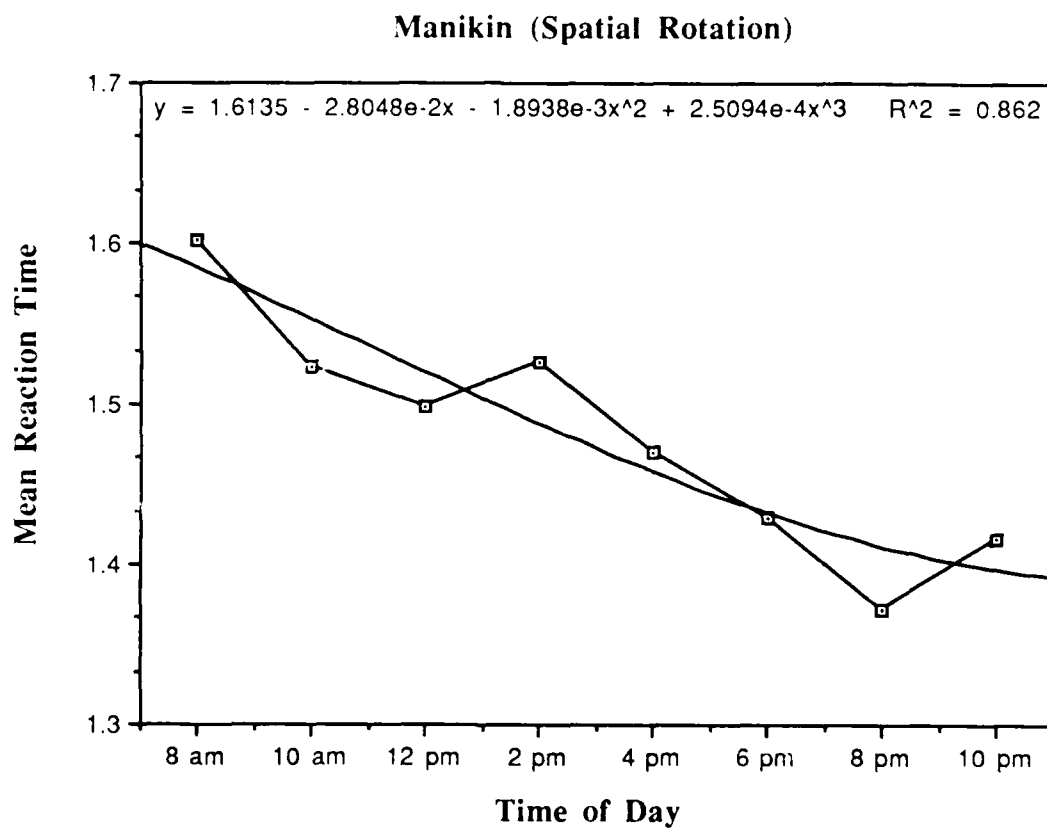


Figure 25. Time effect for Mean Reaction Time on Manikin (spatial rotation).

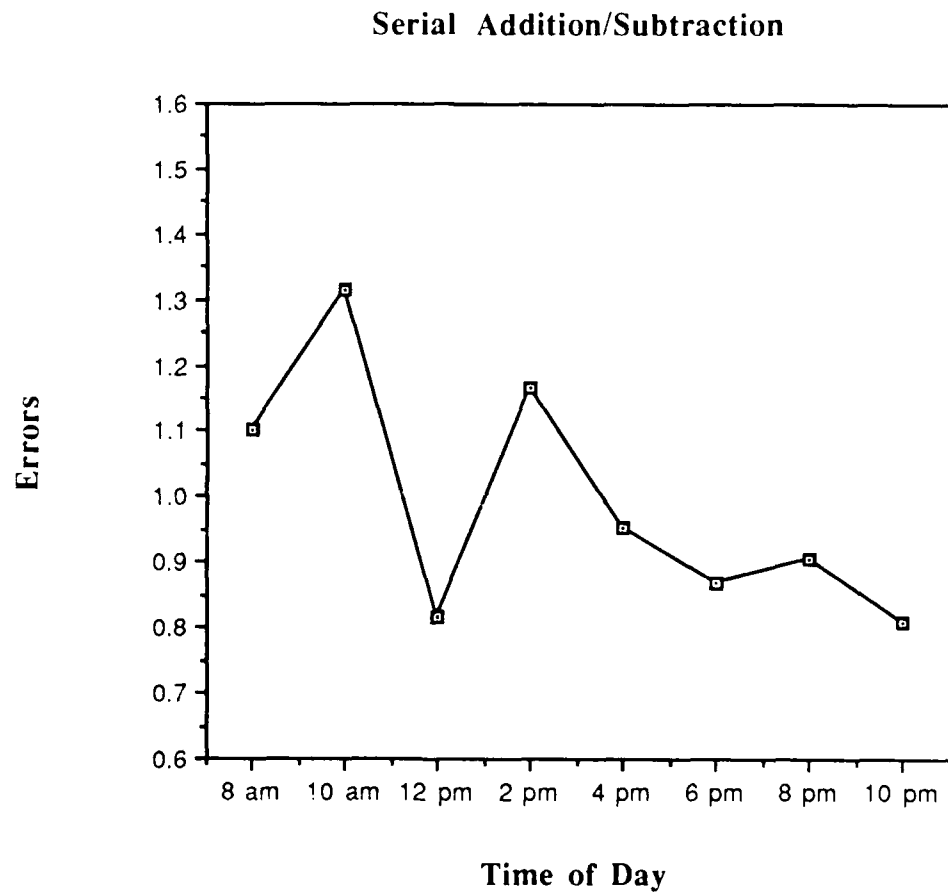


Figure 26. Time effect for Number of Errors on Serial Addition/Subtraction.

differences in the mean values, the overall trend of the data appears to indicate a learning effect as the number of errors obtained were lowest in the 10:00 pm, 12:00 pm, 6:00 pm, and 8:00 pm sessions, respectively (Table E77). There was no significant effect for drug or the time x drug interaction.

Mean Reaction Time. The mean reaction time for the addition/subtraction task was found to vary with time of day. Results of the analysis of variance are located in Table E78 and results of the Newman-Keuls comparison of means are located in Table E79. Mean reaction time generally decreased with time, and may be indicative of a learning effect. Mean reaction times at 8:00 am, 10:00 am, and 2:00 pm were significantly different than at 6:00 pm, 8:00 pm, and 10:00 pm. The trend of decreased performance (longer reaction time) over the day is well described by a linear function in Figure 27.

There was no significant effect for the dependent variable drug; however, there was a significant effect for the interaction of time x drug. A simple-effect F-test was performed and the results are located in Table E80. Significant differences were found for the 10:00 am and 12:00 pm sessions. Newman-Keuls results can be seen in Table E81. A graphic depiction of the results can be viewed in Figure 28. At 10:00 am, the mean reaction time of the benadryl group was slower than either the placebo or hismanal groups. At 12:00 noon, the mean reaction time of the hismanal group was faster than the reaction time of both the placebo and benadryl groups. The slower reaction of the benadryl group at 10:00 am (three hours post ingestion) could be anticipated due to the central effects of the medication; however, this effect should have also been seen during the 8:00 am session (one hour post ingestion). Gengo et al. (1989) found that performance decrements continued for only two hours post ingestion of benadryl on a digit symbol substitution task and in a driving simulator. Although speculative, one explanation may be that subjects were eager to perform well during the first session of the day and therefore put an extra effort into the first test session. The quicker reaction time at 12:00 pm for the hismanal group is difficult to explain.

Subjective Experience Ratings. The number of math classes taken post high school and number of hours spent using a computer per week were found to be related to the number of errors on the addition/subtraction task (Table E82). The self reported level of experience with computer programing was found to be associated with the mean reaction time on the addition/subtraction task (Table E82). As this task required the subject to perform simple math problems, it could be expected that subjects who felt comfortable working with numbers might perform with higher accuracy. The task

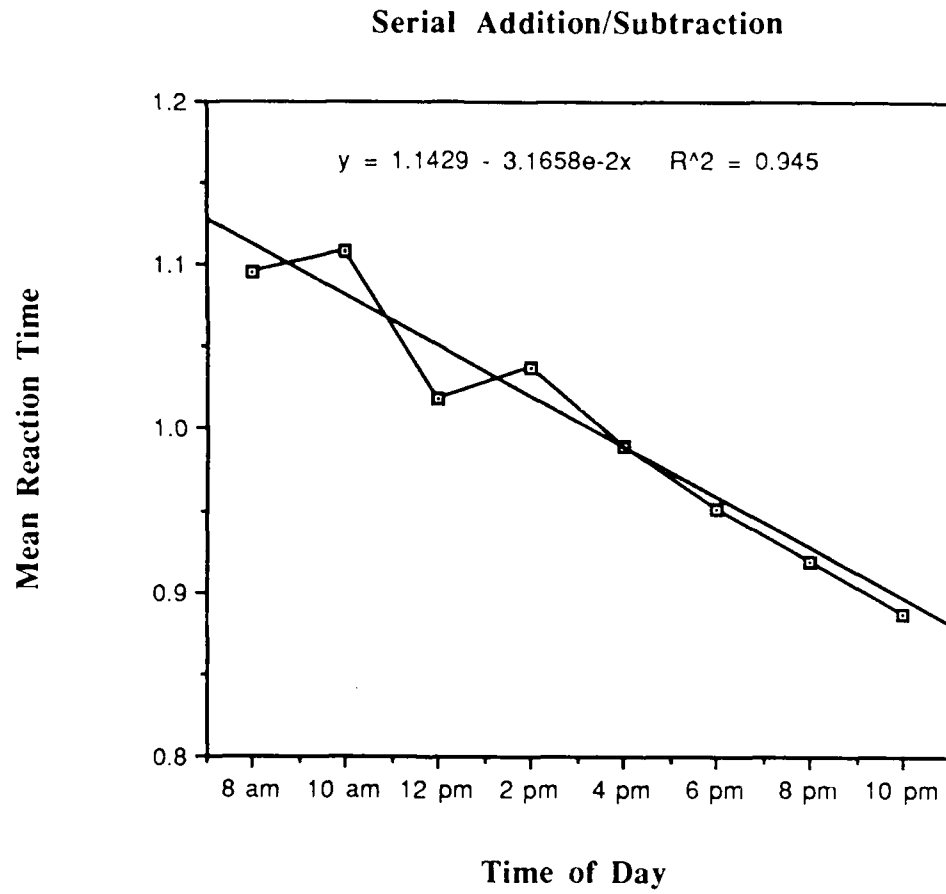


Figure 27. Time effect for Mean Reaction Time on Serial Addition/Subtraction.

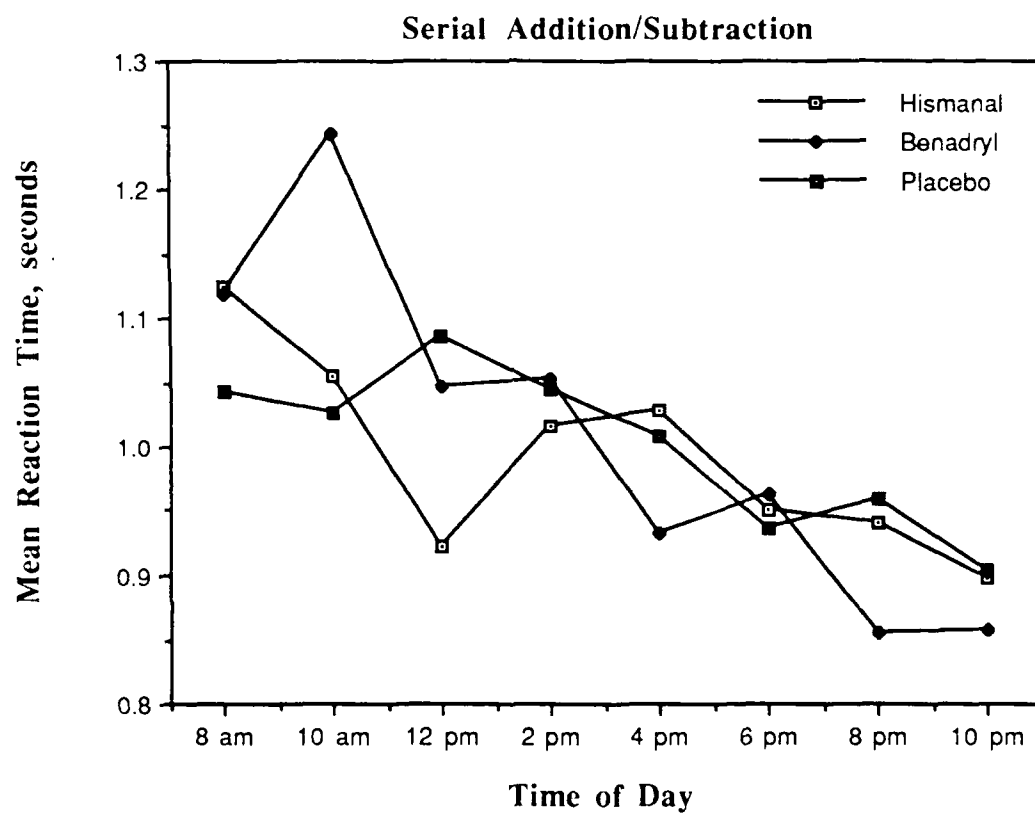


Figure 28. Time x drug interaction for Mean Reaction time on Serial Addition/Subtraction.

required very basic level calculation; however, the task is considered to measure numerical information integration and manipulation, which may be related to higher level mathematics skills developed in post high school mathematics classes.

The relevance of hours spent using a computer per week is more difficult to evaluate. Since we did not incorporate information regarding subjects' major fields of study, it is difficult to determine whether hours spent using a computer equates to using a computer for word processing, statistical analysis, or to solve engineering problems. Therefore, this relationship becomes meaningless in this context and merely encourages further research. The addition/subtraction task is stated to measure the ability to retrieve information from long term memory, apply this information to information in working memory, perform an arithmetic calculation, examine the result, and possibly perform a second calculation (Perez et al., 1987). The association between computer programming skills and mean reaction time on the addition/subtraction task may be due to the common information processing skills required in the two tasks, such as retrieval of information from long-term memory and manipulation of new information based on rules stored in long term memory.

UTC-PAB - Code Substitution

The dependent measures for the Code Substitution task are number of errors and mean reaction time.

Number of Errors. Analysis of variance results for number of errors on the Code Substitution task are located in Table E83. This analysis revealed a main effect of time, shown graphically in Figure 29. Results of the Newman-Keuls comparison of means are located in Table E84. The greatest number of errors, at 10:00 am, differed significantly from those at 8:00 pm and 10:00 pm (Table E84 and Figure 29).

There were no significant effects for drug or the interaction of time x drug.

Mean Reaction Time. A temporal effect was noted for the Code Substitution task. Results of the analysis of variance can be seen in Table E85. The slowest reaction times were recorded at 4:00 pm and 10:00 am and the fastest reaction times occurred at 10:00 pm and 8:00 pm (Table E86 and Figure 29). Both mean reaction time and number of errors reflected poorer performance at 10:00 am compared with 8:00 pm and 10:00 pm on this task (Figure 29). The suggested slower reaction time at 4:00 pm may reflect a circadian pattern of fatigue/decreased performance in the afternoon.

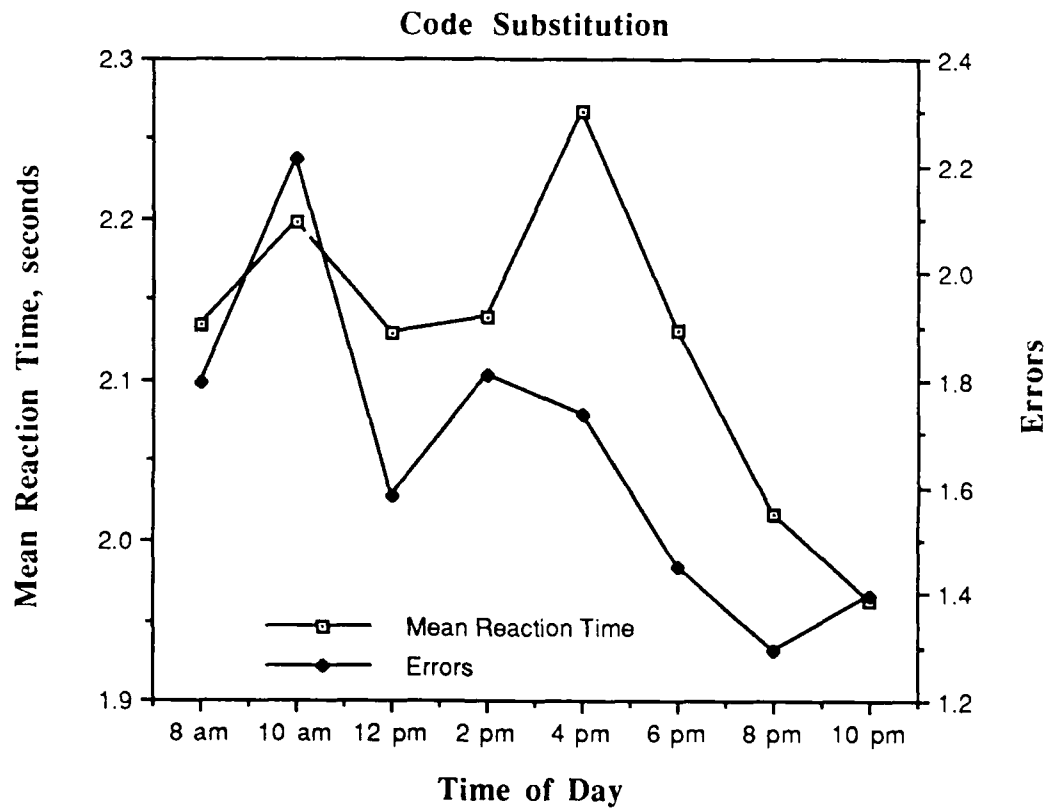


Figure 29. Time effect for Number of Errors and Mean Reaction Time on Code Substitution.

No significant effects were found for drug or the time x drug interaction.

Subjective Experience Ratings. The number of math classes taken post high school was found to approach a level of significance in the relationship to the number of errors obtained on the Code Substitution task (Table E87). The self reported levels of experience with computer programing and the game of chess were found to be associated with the mean reaction time on the Code Substitution task (Table E87). As expected, negative correlations were noted, that is, the greater the number of math classes taken, the lower the number of errors. As this task required the subject to memorize numbers which were related to specific letters, it could be expected that subjects who felt comfortable working with numbers might encode and recall a letter/number code with higher accuracy. The code substitution task is thought to measure rapid encoding of information, associative learning, and recall and it may be expected that computer programming and chess utilize the same skills. Chase and Simon (1973) found master chess players formatted information in large chunks and this skill would be of assistance in memorizing a coded string such as that used for this task.

UTC-PAB - Unstable Tracking

The dependent measures for the unstable tracking task are root-mean-square error and number of boundary hits. The number of subjects included in the analysis for this task is greater (29 subjects) than for other tasks (28 subjects). This difference is due to the data for this task being recorded manually at the completion of each test battery. Therefore, no data were lost via software problems.

Root-Mean-Square Error. The results of the analysis of variance can be seen in Table E88. Root-Mean-Square Error values were found to vary by time of day. The results of the Newman-Keuls comparison of means test are located in Table E89. The results may be indicative of a learning effect, as tracking performance improved considerably over the course of the day (Figure 30). Subjects were best able to keep the cursor centered (lowest root-mean-square error) in the evening sessions (10:00 pm, 6:00 pm, and 8:00 pm) and least able to maintain center control (highest root-mean-square error) in the morning sessions (10:00 am and 8:00 am).

Root-mean-square error did not vary with the effect of drug; however, it did vary with the time x drug interaction. A simple-effect F-test was performed and the results can be seen in Table E90. Significant effects were seen at 8:00 am, 10:00 am, and 6:00 pm.

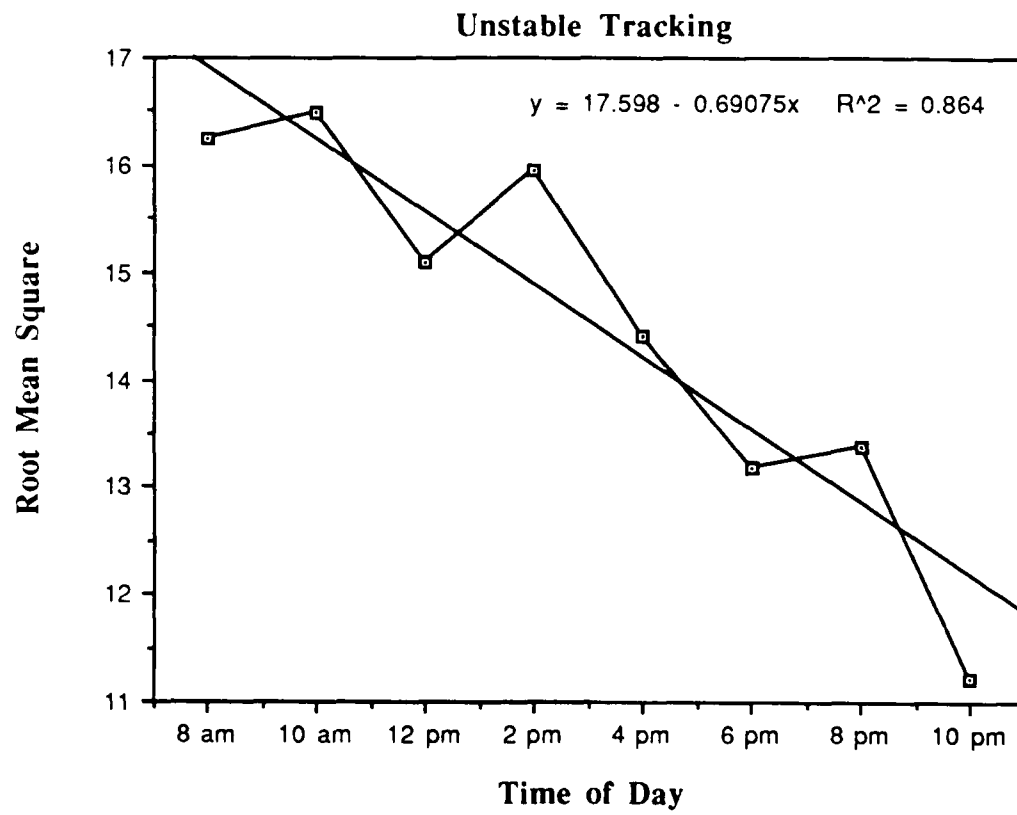


Figure 30. Time effect for Root-Mean-Square Error on Unstable Tracking.

A closer look at the results of the interaction reveal that at 8:00 am, the performance of the benadryl group was significantly poorer than either the hismanal or placebo groups (Table E91, Figure 31). At 10:00 am, the performance of the benadryl group was lower than that of the hismanal group (Table 91, Figure 31). These results reflect the expected poorer performance with benadryl at one hour post ingestion and are consistent with results found by Moskowitz and Burns (1988), Cohen et al. (1984), and Cohen et al. (1987). These results also support findings that performance decrements on a driving and a code substitution task persist for only two hours post ingestion of benadryl (compared with placebo). At three hours post ingestion, the difference between performance with benadryl and hismanal remains significant. This occurs even as the effect of benadryl begins to decrease, apparently due to the superior performance of the hismanal group. At 6:00 pm, the performance of the placebo group is significantly poorer than that of either the hismanal or the benadryl groups (Figure 31). One possible explanation is that the group receiving benadryl felt so much better as the day progressed that their performance increased substantially in accordance with their subjective state. (One subject stated that it took him until late afternoon to "wake up.") As the hismanal group was not expected to have an increased number of physiological symptoms, an explanation for the superior performance in comparison with the placebo is more difficult to explain. On several occasions, the tracking cursor was uncontrolled by the subject. This did not occur during the running of pilot subjects, but did occur during training. Although the cause of this disruption was not determined, replacing the floppy disk with a new version created on that particular hard drive alleviated the problem. Subjects were alerted and instructed to contact one of the experimenters so that the task could be restarted with a different copy of the task software. The occasions when difficulty occurred were recorded, so that the data could be re-examined following completion of data collection. No difficulties of this nature were noted during the 6:00 pm sessions. The results obtained for the 6:00 pm time frame warranted a closer examination of the data to see if extreme values were obtained. An examination of the data was performed using a stem leaf plot, box plot, extremes, and a normal probability plot. This examination revealed no further explanation of the phenomenon.

Boundary Hits. A temporal effect was found for the number of boundary hits. Results of the analysis of variance are located in Table E92, while Newman-Keuls results are located in Table E93. As can be seen in Figure 32, the number of boundary hits was highest at 8:00 am and 2:00 pm and lowest at 10:00 pm. The

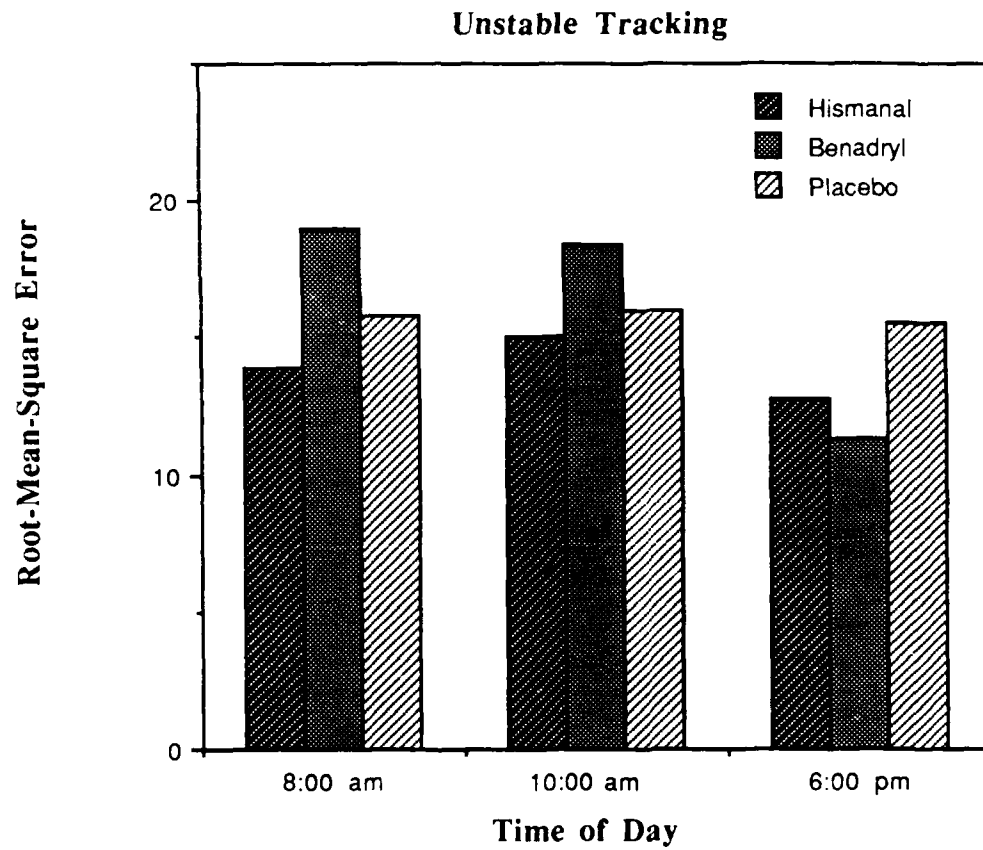


Figure 31. Time x Drug effect at 8:00 am, 10:00 am, and 6:00 pm for Root-Mean-Square on Unstable Tracking.

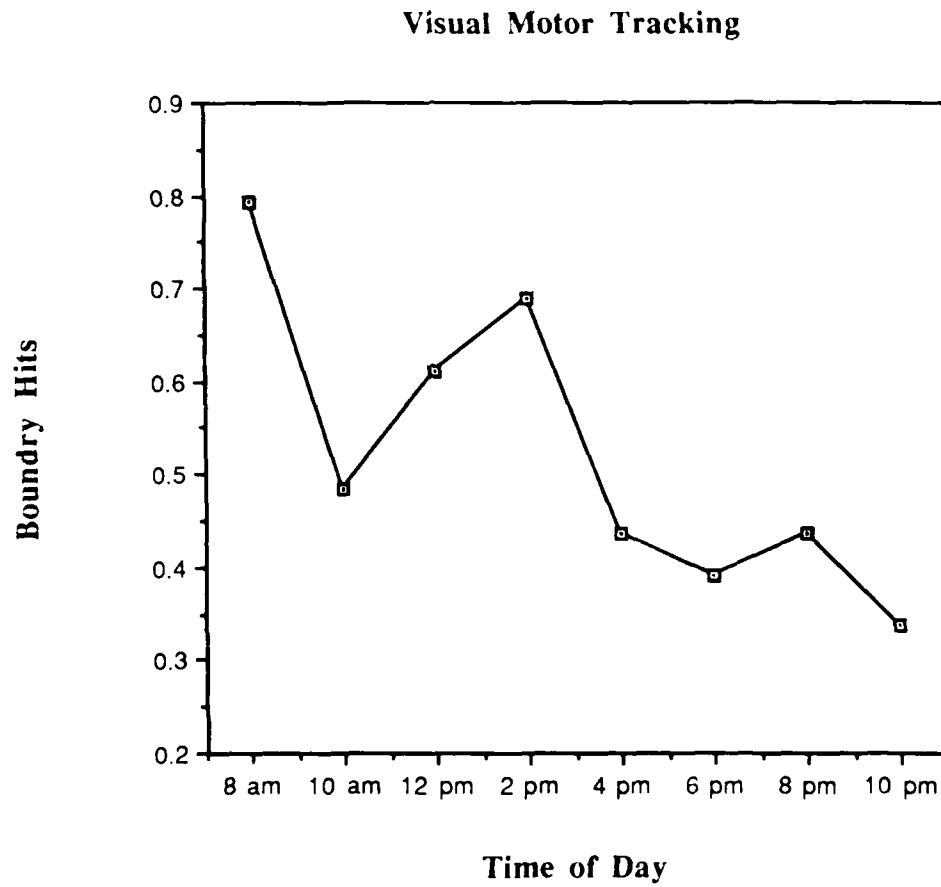


Figure 32. Time effect for Boundary Hits on Unstable Tracking.

number of boundary hits during the 8:00 am session was significantly different than the number of boundary hits seen at 10:00 am, 4:00 pm, 6:00 pm, and 10:00 pm. Although the range of boundary hits was small, the overall trend may be indicative of a learning effect, as the least number of boundary hits was seen in the evening at 10:00 pm and the largest number of boundary hits was seen at 8:00 am.

Neither the main effect of drug nor the time x drug interaction were significant for unstable tracking boundary hits.

Subjective Experience Ratings. No significant correlations were found between self ratings of experience on video games, word processing, hours of computer use per week, chess experience, or number of college level math classes with performance as measured by root-mean-square error (Table E94). Computer programming experience was found to be negatively correlated with tracking error (Table E94). Both computer programming and tracking require accurate manual responses to visual stimuli and high spatial ability, which could contribute to this relationship; however, video game experience would also be expected to be related to tracking performance on this same basis.

Summary. Temporal effects were noted for eight of the nine tasks. Although subjects trained for one and a half hours to two hours on the UTC-PAB tasks and one hour on the tracking task, an apparent learning effect was evident in all cases (except for Time Wall and Interval Production). A performance decrement was suggested in the afternoon on six of the tasks, which may implicate a circadian pattern of a low performance period occurring in the afternoon. For the Time Wall task it was found that judged time decreased over the course of the day, which is opposite to that found by Jerison and Arginteanu (1958, as cited by Perez et al., 1987), who found that subjects increased their time estimation over repeated trials.

Performance decrements due to the antihistamine ingested were found on the Serial Addition/Subtraction task and the tracking task. Mean reaction time was slower at 10:00 am post benadryl ingestion as compared to hismanal or placebo on the Serial Addition/Subtraction task. Mean reaction time at 12:00 pm was faster post hismanal ingestion than for the other two conditions on the same task. Subjects were less able to maintain center control of the cursor on the Unstable Tracking task post ingestion of benadryl at 8:00 am than for the other two conditions. At 10:00 am, performance following benadryl ingestion remained poorer than following hismanal ingestion, but was not different from the placebo.

In order to evaluate further each of the tasks, performance scores were correlated with self reports of levels of experience with video games, computer programming, word processing, hours spent using a computer per week, chess experience, and number of post high school math classes. Word processing experience was not found to be related to any of the task scores. Although a relationship was found between hours spent using a computer per week and errors on logical reasoning and serial addition/subtraction tasks, no interpretation was possible due to poor definition of the work done when using the computer. A correlation was found between experience with the game of chess and reaction time on the code substitution task, in which large chunks of information had to be memorized, and scores on the route planning task, which used the knight's move from chess. The number of post high school math classes taken was found to be correlated with the serial addition/subtraction task. A relationship was found between experience with video games and reaction times on the four choice reaction time task and scores on the route planning task. Finally, computer processing experience was found to be correlated with reaction time on the code substitution, logical reasoning, and serial addition/subtraction tasks and with accuracy scores on unstable tracking, following directions, and route planning tasks. This information does not intimate that performance scores on identified tasks were the result of high levels of experience in the associated areas. In addition, although correlations were significant, they were not great in magnitude (all less than 0.60). These results signal the need for further research as underlying skills for associated experience and tasks may be similar. In addition, research with individuals who have high levels of experience in an area such as computer programming may tend to influence the results. For example, if the level of chess experience is associated with performance scores on the route planning task, this association may interfere with the effects of the independent variable under investigation.

Physiological Measures

The dependent measures recorded were systolic blood pressure, diastolic blood pressure, pulse rate, and temperature.

Systolic Blood Pressure. Systolic blood pressure was found to vary with time. The results of the analysis of variance are located in Table E95 and the results of the Newman-Keuls comparison of means are located in Table E96. Systolic Blood Pressure was lowest during the morning sessions (between 8:00 am and 12:00 pm) and highest at

10:00 pm and 2:00 pm (Figure 33). Systolic blood pressure was not found to vary significantly with drug or the interaction of time x drug. This result suggests that systolic blood pressure is not sensitive to the dose levels of the antihistamines used in this study.

Diastolic Blood Pressure. Diastolic blood pressure was not found to vary significantly during the study (Table E97).

Pulse Rate. Pulse rate was found to vary with time. The results of the analysis of variance are located in Table E98. A Newman-Keuls comparison of means was performed, the results of which are located in Table E99. The quickest pulse rate was obtained at 2:00 pm while the slowest pulse rate was obtained at 12:00 pm. The fastest heart rate (2:00 pm) differed significantly from those taken at 10:00 am, 12:00 pm, 6:00 pm, and 10:00 pm (Figure 34). The change in pulse could be related to noon and dinner meals, with a slowing of pulse rate just before eating and a quicker post prandial rate. These results match those found by Christie and McBrearty (1977), in which they recorded pulse rates at 11:00 am, 12:00 pm, 1:00 pm, 2:00 pm, 3:00 pm, and 4:00 pm. Subjects ate lunch at 1:00 pm and a significant post prandial increase in pulse (10 beats per minute) was identified at 2:00 pm, which they attributed to metabolic origin.

Temperature. A temporal effect was noted for temperature. The results of the analysis of variance are located in Table E100. Temperature increased as the day progressed, as can be noted from results on the Newman-Keuls comparison of means in Table E101. Temperature was lowest at 10:00 am and highest at 6:00 pm, 8:00 pm, and 10:00 pm (Figure 35). Prior research results evaluating post lunch changes in temperature did not find oral or deep body temperature changes as a result of time (Christie and McBrearty, 1977). In a follow-up study in which a standard meal was provided, deep body temperature was found to vary with time and dropped slightly post lunch (Christie and McBrearty, 1979), a finding that was not repeated in this research.

Summary. Temporal effects were noted for systolic blood pressure, pulse, and temperature. Systolic blood pressure was lowest during the morning sessions and noon session and highest at 2:00 pm and 10:00 pm. The fastest pulse rate was obtained at 2:00 pm while the slowest pulse rate was obtained at 12:00 pm. Temperature was lowest in the morning and increased throughout the day.

Subjective Measures - Mood Scale II

The dependent measures for Mood Scale II were the six mood subscales and mean

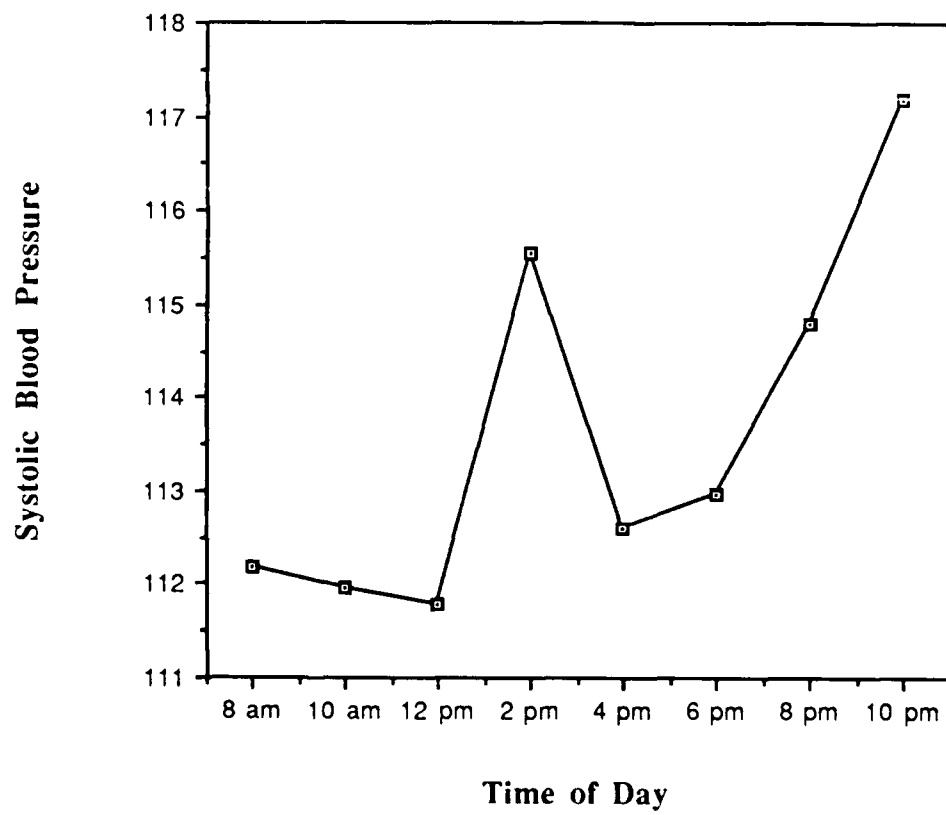


Figure 33. Time effect for systolic blood pressure.

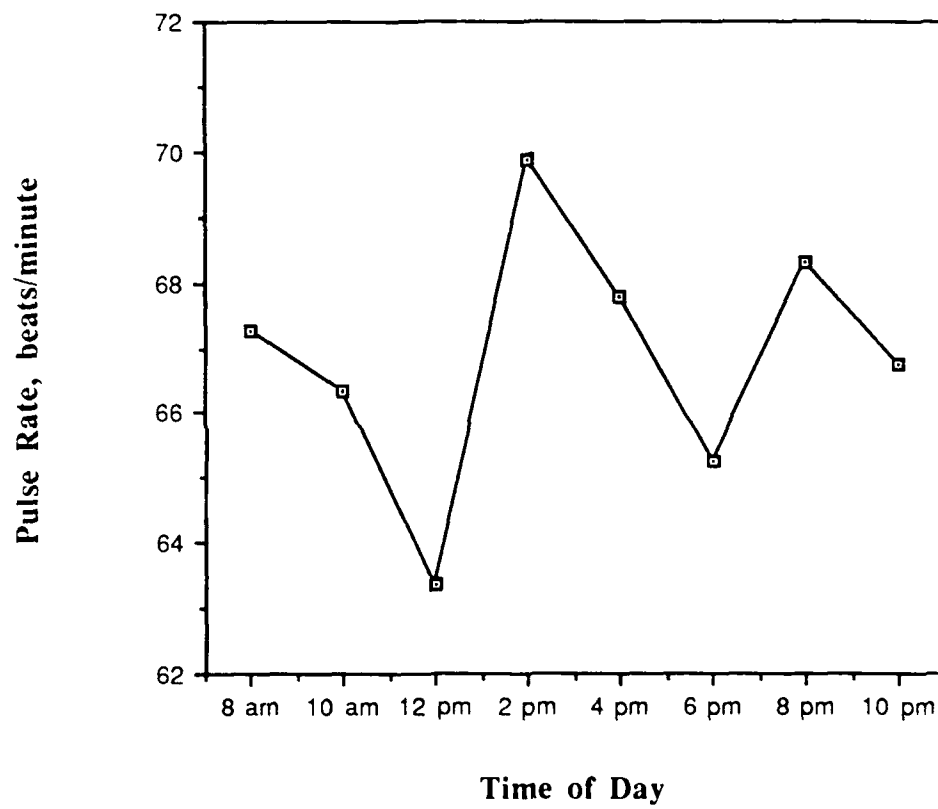


Figure 34. Time effect for pulse rate.

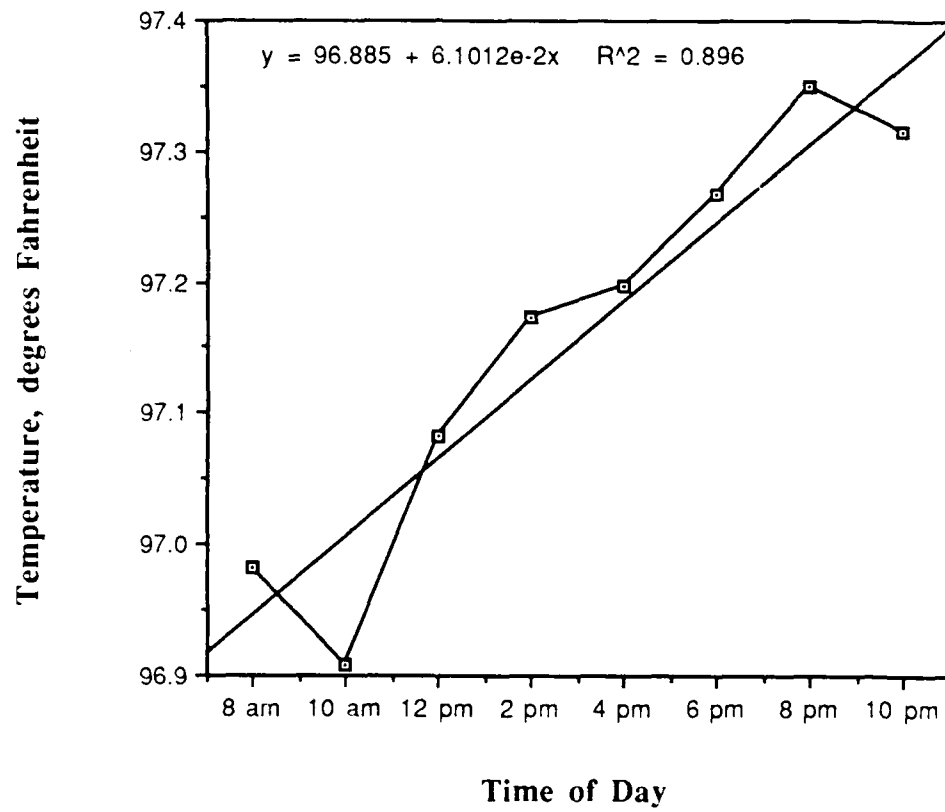


Figure 35. Time effect for temperature.

reaction time. The number of subjects included in these data (21) is less than were included in the other tasks (28) due to difficulties in loading the software onto one of the computers. One computer was located in the laboratory office and was used solely for review and baseline testing. The procedure for review and baseline testing was different than for other testing. One of the computers used for test purposes required repair and the office computer was consequently used for both review/baseline and testing. The appropriate alteration in the test program did not occur; therefore, test data gathered during that time frame on this scale could not be used.

Activity. Analysis of variance results for the activity scale are located in Table E102. While not quite significant at the 0.05 level, reported activity seems lowest early in the day, with the lowest value reported during the 10:00 session (Figure 36). For purposes of greater understanding of the data, the scale in Figure 36 is from 2.0 to 2.2 rather than from 1 to 3. Reported activity levels continued to generally increase throughout the day, with a slight decrease occurring during the 10:00 pm session, as is described by the linear fit in Figure 36. As the activity level of students may be greatest during the evening (study) hours, this general trend is not unexpected. There were no significant findings for drug. Reported activity did differ with the interaction of time x drug. A simple-effect F-test was performed, the results of which are located in Table E103. The 8:00 am session and the 10:00 am session showed significant effects. Results of the Newman-Keuls comparison of means can be seen in Table E104. A closer look at the interaction reveals that the activity level reported by the placebo group is higher at 8:00 am than is the activity level reported by either the hismanal or benadryl groups (Figure 37). For purposes of greater understanding of the data, the scale in Figure 37 is from 1.8 to 2.3 rather than from 1 to 3. The difference between the placebo and benadryl groups was expected and supports previous research results (Carruthers et al., 1978; Cohen et al., 1987; Jaattela et al., 1971; Moskowitz and Burns, 1988). The difference between the placebo and hismanal groups was not expected as hismanal is reported to be void of central nervous system effects such as drowsiness (Chapman and Rawlins, 1982; Nicholson, Smith, and Spencer, 1982; Nicholson and Stone, 1982; Richards, Brogden, Heel, Speight, and Avery, 1984) and research has indicated that subjective reports do not differ from placebo (Nicholson et al., 1972; Nicholson and Stone, 1982). During the 10:00 am session, the activity levels reported by both the placebo and hismanal groups were higher than activity levels reported by the benadryl group. Again, the difference between the placebo and benadryl groups was expected.

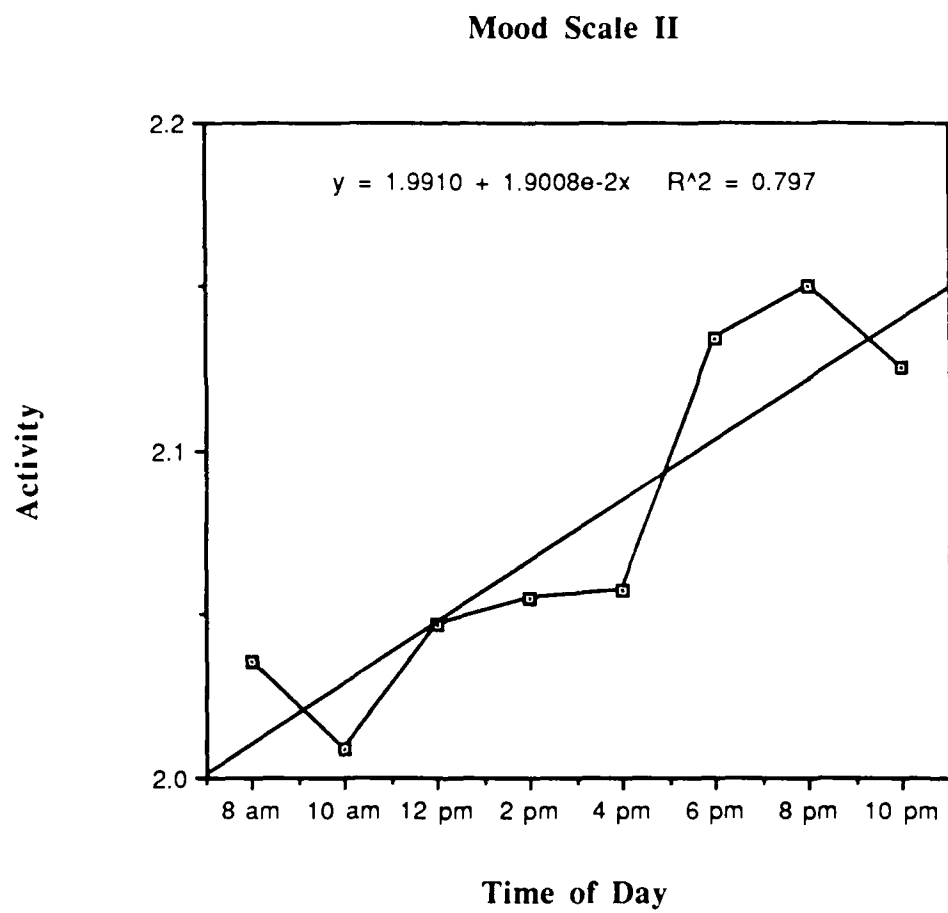


Figure 36. Time effect for activity on Mood Scale II.

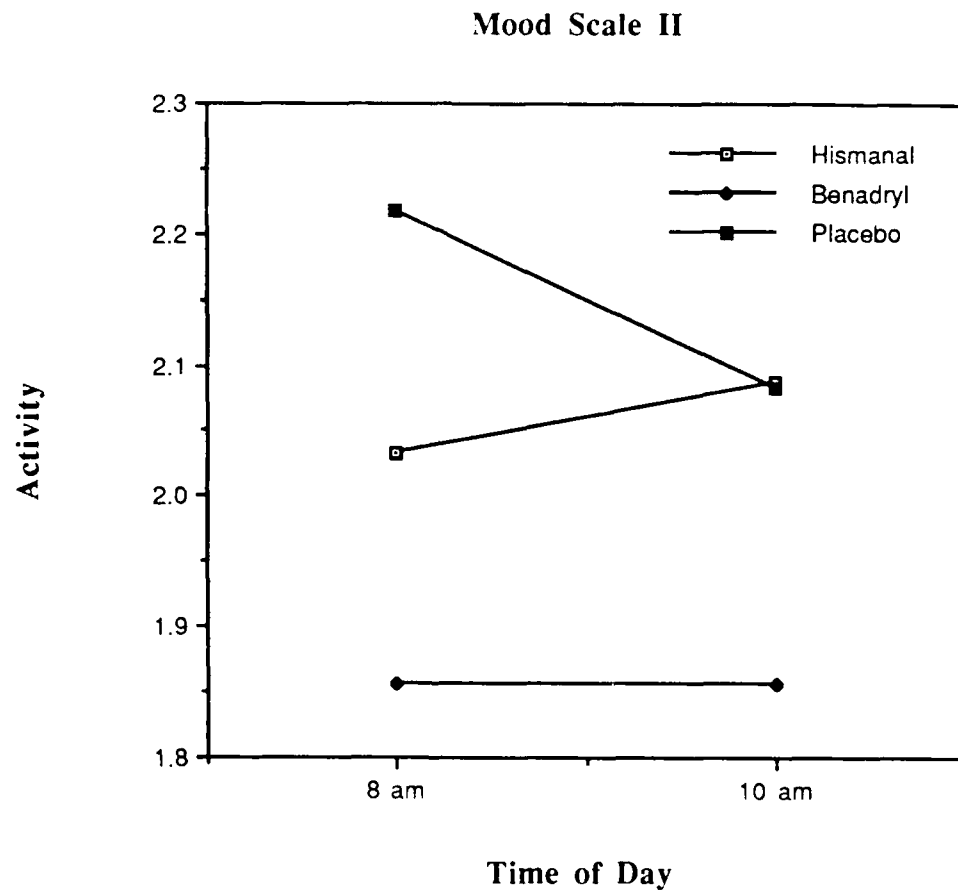


Figure 37. Time x drug interaction at 8:00 and 10:00 am for activity on Mood Scale II.

The difference between the hismanal and benadryl groups was also expected as stated above.

Happiness. An analysis of variance was conducted on the mood subscale happiness. Results of this analysis are listed in Table E105. This analysis revealed no significant effects for time, drug, or the time x drug interaction.

Depression. Results of the analysis of variance are shown in Table E106. Results indicated a significant interaction (time x drug) for the mood subscale depression, but no main effects (time or drug). A simple-effect F-test was performed; however, no significant effects were noted for the eight daily test sessions (Table E107). Thus, while the interaction is significant (Figure 38), no consistent pattern or specific drug effect at a given time of day is sufficient to permit an understanding of the interaction. For purposes of greater understanding of the data, the scale in Figure 38 is from 1.0 to 1.3 rather than from 1 to 3.

Anger. The results of the analysis of variance for the mood subscale anger can be seen in Table E108. The results indicate a significant effect for the time x drug interaction. A simple-effect F-test was performed, the results of which are shown in Table E109. None of the individual drug effects were found to be significant. As noted in Figure 39, there is little pattern to the interaction. For purposes of greater understanding of the data, the scale in Figure 39 is from 1.0 to 1.3 rather than from 1 to 3.

Fatigue. The mood subscale fatigue was found to vary with the interaction time x drug. Results of the analysis of variance are found in Table E110. A closer analysis of the data was completed using the simple-effect F-test, results of which are located in Table E111, and the Newman-Keuls comparison of means (Table E112). A graphic depiction can be seen in Figure 40. For purposes of greater understanding of the data, the scale in Figure 40 is from 1.2 to 1.8 rather than from 1 to 3. During both the 8:00 am and 10:00 am sessions, the benadryl group reported a higher level of feelings of fatigue than did either the hismanal or placebo groups, which supports previous findings of sleepiness, drowsiness, mental and physical sedation, fatigue, and decreased concentration following ingestion of benadryl (Carruthers et al., 1978; Cohen et al., 1987; Jaattela et al., 1971; Moskowitz and Burns, 1988). During the 12:00 pm and 2:00 pm sessions the benadryl group reported a higher level of fatigue than did the placebo group. In addition, this result supports findings in which drowsiness was self-assessed for up to 6 hours post benadryl ingestion (Gengo et al., 1989). The reported level of fatigue for the hismanal group did not differ significantly from either the placebo or benadryl groups.

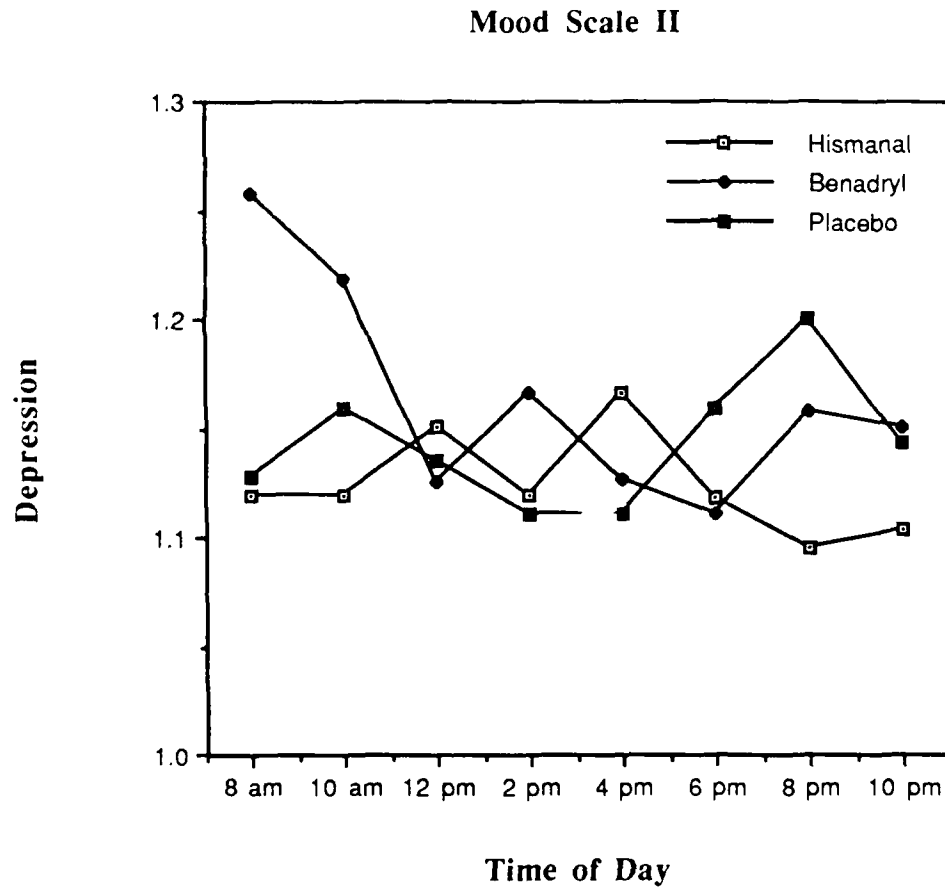


Figure 38. Time x drug interaction for depression on Mood Scale II.

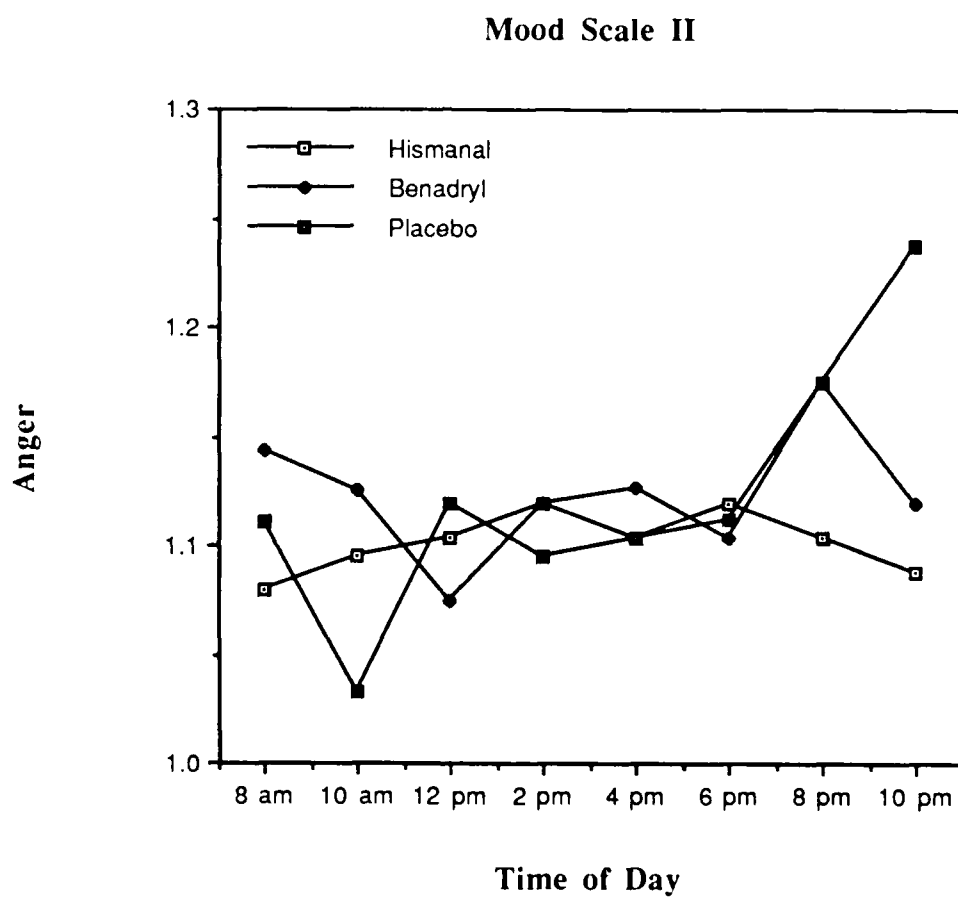


Figure 39. Time x drug interaction for anger on Mood Scale II.

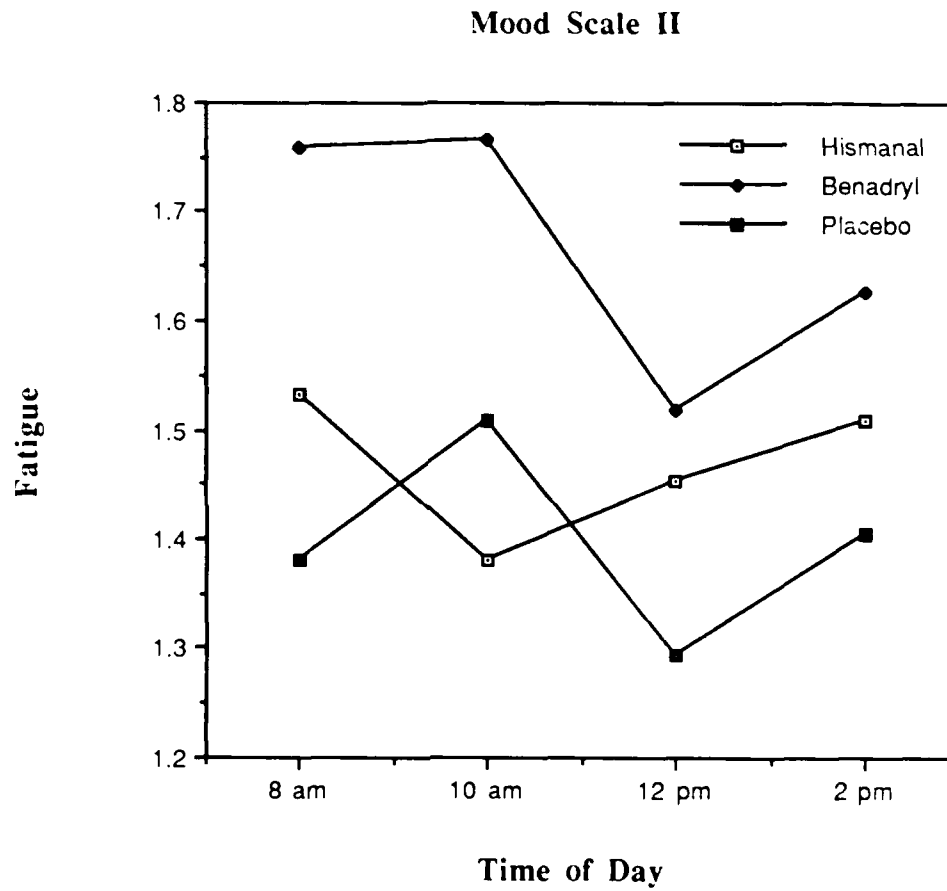


Figure 40. Time x drug interaction at 8:00 am, 10:00 am, 12:00 pm, and 2:00 pm for fatigue on Mood Scale II.

during the 12:00 pm or 2:00 pm sessions.

Fear. Reported levels of feelings of fear did not differ by time, drug, or time x drug (Table E113).

Mean Reaction Time. Mean reaction time of the Mood Scale II items was found to vary with time of day and the time of day x drug interaction. Results of the analysis of variance are located in Table E104 and the results of the Newman-Keuls comparison of means for time of day can be seen in Table E115. Mean reaction time became generally quicker as the day progressed, as is described by the logarithmic fit in Figure 41. This might be expected as subjects became familiar with the adjectives and the procedure for their response.

Subjective Measures - Profile of Mood States (POMS)

In scoring the Profile of Mood States, the raw scores were converted to an equivalent percentage rating. The response scale of 1 to 5 therefore assumes a possible response scale range based on subject scores and the number of questions which pertain to the specific subscale.

Tension-Anxiety. Analysis of variance results for the tension subscale are located in Table E116. Tension subscale values were found to vary with drug and the results of the Newman-Keuls comparison revealed that the benadryl group reported heightened feelings of tension (Table E117 and Figure 42). Although reports of drowsiness have been observed for up to six hours post ingestion of benadryl (Gengo et al., 1988), an overall drug effect was not expected.

Depression-Dejection. Analysis of variance results for the depression subscale are located in Table E118. Depression subscale values were not found to vary significantly.

Anger-Hostility. The results of the analysis of variance for the mood subscale anger are located in Table E119. Anger subscale values were not found to be affected significantly.

Vigor-Activity. The mood subscale vigor-activity was found to vary with time, drug, and the time x drug interaction. Results of the analysis of variance are located in Table E120. The level of vigor generally increased throughout the course of the day (Figure 43). The lowest level was reported at 8:00 am and the highest level was

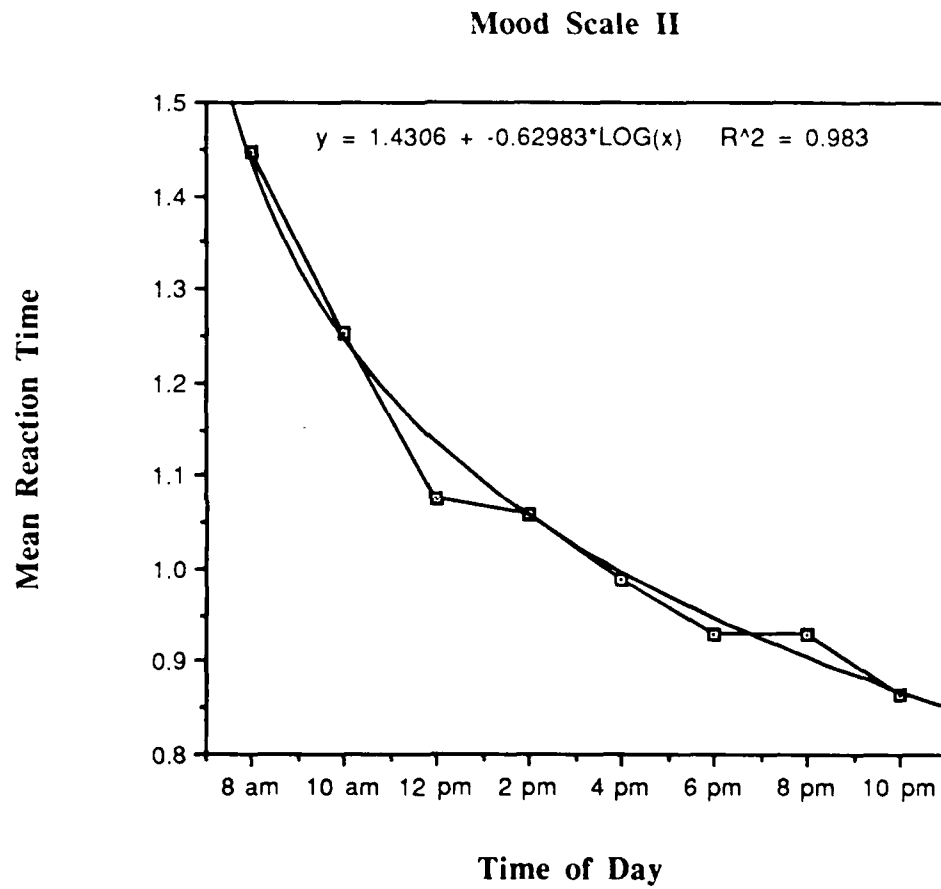


Figure 41. Time effect for Mean Reaction Time on Mood Scale II.

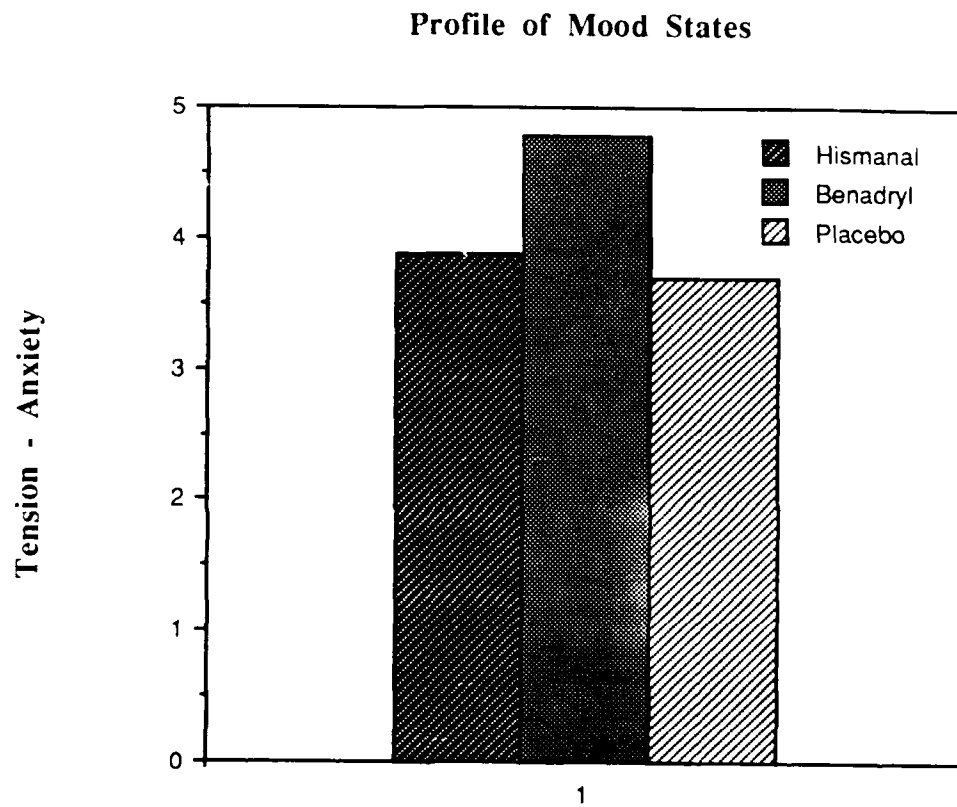


Figure 42. Drug effect for Tension-Anxiety on Profile of Mood States.

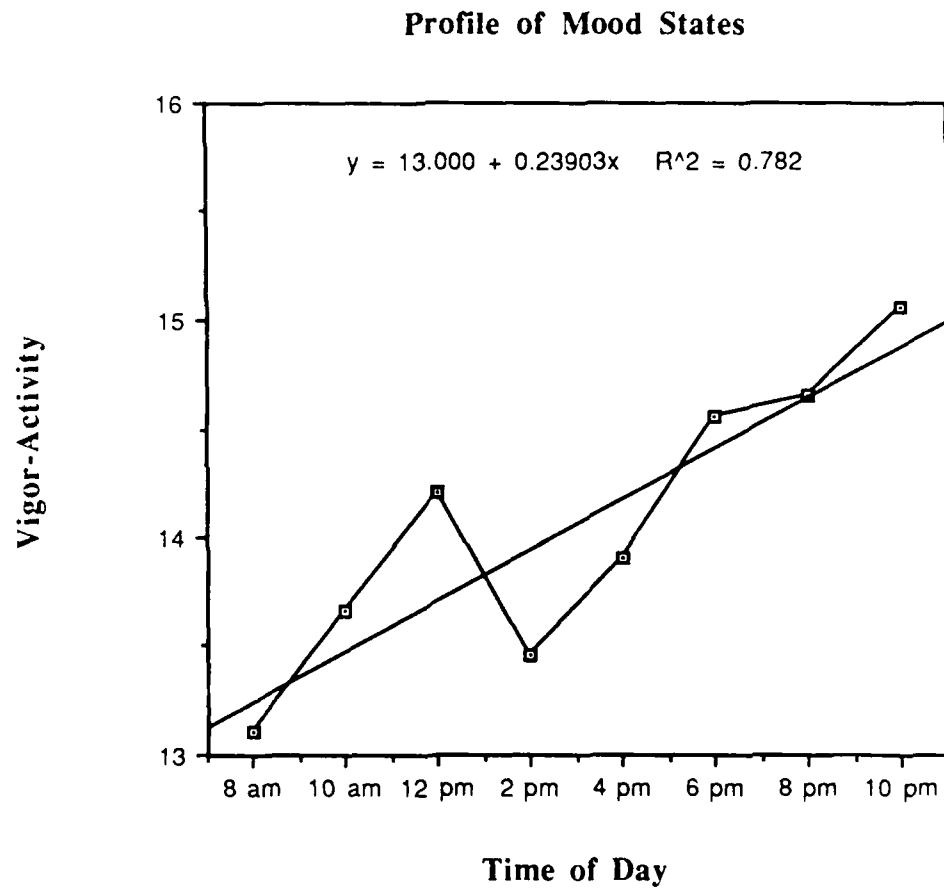


Figure 43. Time effect for Vigor-Activity on Profile of Mood States (note conversion of response scale of 1 to 5 to a scale of 13 to 16).

reported at 10:00 pm (Table E121). These results are similar to those found on the activity scale on Mood Scale II, although the lowest reported activity level in Mood Scale II occurred during the 10:00 am session (Figure 36). As previously stated, one plausible explanation for the increased activity level over the course of the day is that the typical activity level of students may be greatest during evening hours.

The results of the Newman-Keuls comparison of means for the main effect of drug can be viewed in Table E122. Again, the benadryl group reported a lower level of vigor-activity than either the placebo or hismanal groups (Figure 44). This trend continued throughout the day with the reported level of activity for the benadryl group becoming equal to that of the placebo and hismanal groups only at the end of the day, although the differences are not statistically significant after 10:00 am (Table E123). Both the 8:00 am and 10:00 am sessions displayed significant drug effects (Table E123). The placebo group reported a higher level of vigor than did either the hismanal or benadryl groups during the 8:00 am session and the hismanal group reported a higher level of vigor than did the benadryl group (Figure 44 and Table E124). During the 10:00 am session, both the placebo group and the hismanal group reported a higher level of vigor than did the benadryl group. These findings reflect the trends seen with the activity scale from Mood Scale II, although the hismanal group did not report a significantly higher level of activity than the benadryl group at 8:00 am with the Mood Scale II. Again, the difference between the placebo and benadryl groups was expected and supports previous research results (Carruthers et al., 1978; Cohen et al. 1987; Jaattela et al., 1971; Moskowitz and Burns, 1988). The results from Mood Scale II and the Profile of Mood States were similar during both the 8:00 am and 10:00 am sessions. The activity levels reported by both the placebo and hismanal groups were higher than activity levels reported by the benadryl group during the 10:00 am sessions.

Fatigue-Inertia. As can be noted in Table E125, the subscale for fatigue-inertia was found to vary both by drug and the time x drug interaction. Results of the Newman-Keuls comparison of drug means are located in Table E126. Although there was a significant overall difference by drug, the Newman-Keuls test found no pairwise differences (Table 126). A closer look at the interactive effect using a simple-effect F-test (Table E127) and Newman-Keuls comparisons (Table E128) reveals that at 8:00 am and 10:00 am the benadryl group reported higher fatigue than did either the placebo or hismanal groups (Figure 45). At 12:00 pm and 2:00 pm, the benadryl group reported greater fatigue than did the placebo group. This result suggests that subjective feelings of

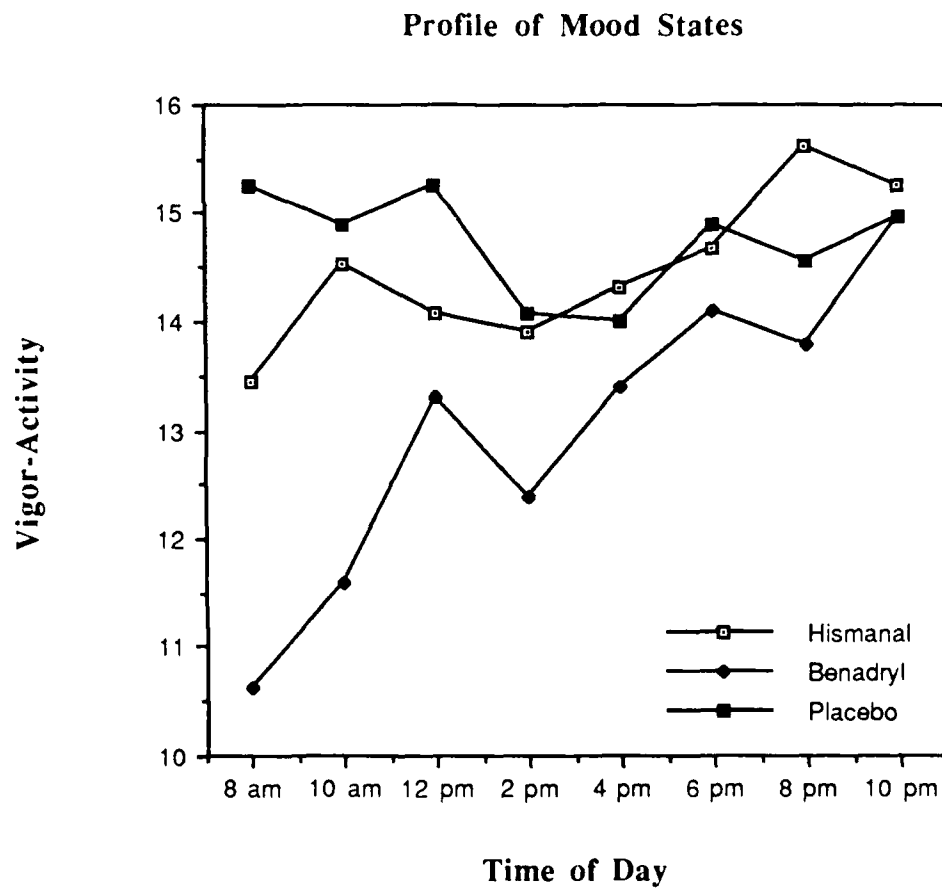


Figure 44. Time x drug interaction for Vigor-Activity on Profile of Mood States (note conversion of the response scale of 1 to 5 to a scale of 10 to 16).

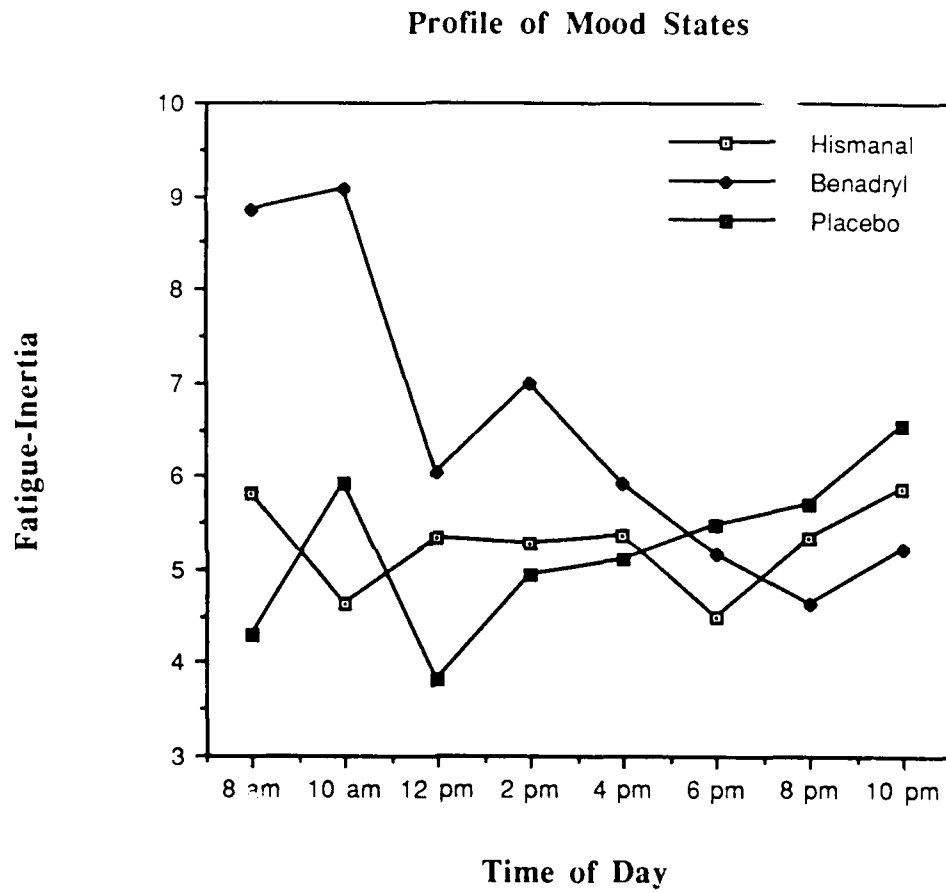


Figure 45. Time x drug interaction for Fatigue-Inertia on Profile of Mood States (note conversion of the response scale of 1 to 5 to a scale of 3 to 10).

fatigue following ingestion of 50 mg of benadryl may last up to seven hours and lends support to the research by Gengo et al. (1989) which found that subjective feelings of drowsiness lasted for up to six hours post ingestion of 50 mg of benadryl.

Mood Scale II findings for the subscale fatigue also found the benadryl group reported a higher level of agreement with feelings of fatigue than did the hismanal and placebo groups at 8:00 am and 10:00 am and that during the 12:00 pm and 2:00 pm sessions the benadryl group reported a higher level of fatigue than did the placebo group. The results from both subjective questionnaires support findings of sleepiness, drowsiness, mental and physical sedation, fatigue, and decreased concentration following ingestion of benadryl (Carruthers et al., 1978; Cohen et al., 1987; Jaattela et al., 1971; Moskowitz and Burns, 1988). These findings also agree with research that found that subjective reports post hismanal ingestion does not differ from placebo (Nicholson, Smith, and Spencer, 1982; Nicholson and Stone, 1982).

Confusion-Bewilderment. The subscale for confusion-bewilderment was found to be significant for the interaction of time x drug. Results of the analysis of variance are located in Table E129. On closer analysis using a simple-effect F-test and Newman-Keuls comparison of means, it can be seen that a higher level of confusion was reported by the benadryl group than by both the placebo and hismanal groups during the 8:00 am session and a higher level of confusion was reported by the benadryl group than either the placebo or hismanal groups at 10:00 am (Tables E130 and E131). Also, at 8:00 am the hismanal group reported a higher level of confusion than did the placebo group. This can be seen graphically in Figure 46. The adjectives used for the confusion subscale relate to feelings of unclear thinking and disorganization. The high level of agreement with these adjectives may be similar in origin to reported feelings of fatigue. Again, these findings support previous research which noted increased mental sedation and decreased concentration post ingestion of benadryl. The difference between hismanal and placebo suggests that hismanal is not totally devoid of side effects.

Summary. Temporal effects were found for the activity subscale of Mood Scale II and the vigor-activity subscale of the Profile of Mood States (POMS). The level of vigor was lowest during the first two sessions and increased throughout the day. As previously stated, one plausible explanation for the increased activity level over the course of the day is the activity level of students may be greatest during the evening (study or social) hours.

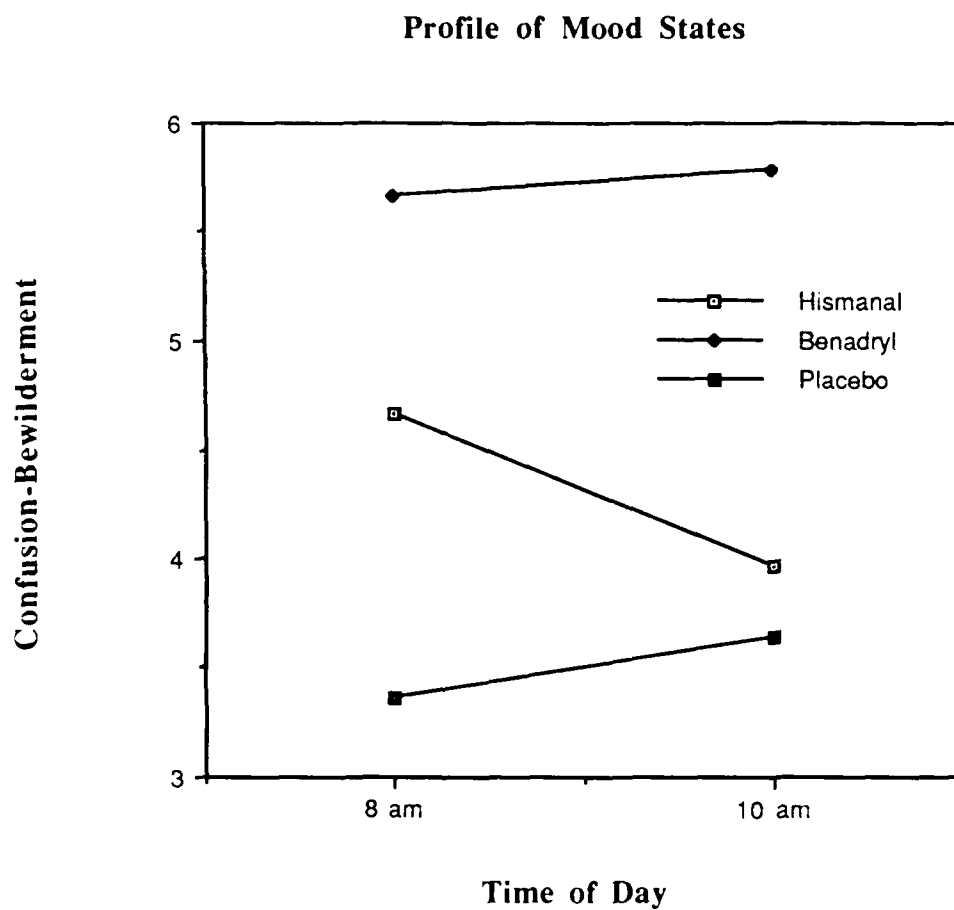


Figure 46. Time x drug interaction at 8:00 am and 10:00 am for Fatigue-Inertia on Profile of Mood States (note conversion of response scale of 1 to 5 to a scale of 3 to 6).

Drug effects were seen on the tension-anxiety, vigor-activity, and fatigue-inertia subscales for POMS. The overall trend was that a higher levels of tension-anxiety and fatigue-inertia and a lower level of vigor-activity was experienced by the benadryl group. As noted by Gengo et al. (1989), subjective reports of fatigue following benadryl ingestion lasted for up to six hours.

Time x drug interaction effects were noted for the activity, depression, anger, and fatigue subscales on Mood Scale II. Interaction effects were also found for the vigor-activity, fatigue-inertia, and confusion-bewilderment subscales of POMS. On both Mood Scale II and the POMS, the placebo group reported a higher level of vigor than did either the hismanal or benadryl groups during the 8:00 am session. Additionally, the hismanal group reported a higher level of vigor than did the benadryl group on the POMS. During the 10:00 am session, both the placebo group and the hismanal group reported a higher level of vigor than did the benadryl group on both mood scales. The difference between the placebo and benadryl groups was expected and supports previous research results (Carruthers et al., 1978; Cohen et al., 1987; Jaattela et al., 1971; Moskowitz and Burns, 1988). The difference between the placebo and hismanal groups was not expected as hismanal is reported to be void of central nervous system effects such as drowsiness (Chapman and Rawlins, 1982; Nicholson, Smith, and Spencer, 1982; Nicholson and Stone, 1982; Richards, Brogden, Heel, Speight, and Avery, 1984) and research has indicated that subjective reports do not differ from placebo (Nicholson et al., 1972; Nicholson and Stone, 1982).

For both the fatigue subscale from Mood Scale II and the fatigue-inertia subscale on the POMS, the benadryl group reported higher levels of fatigue than did either the placebo or hismanal groups for the first two sessions of the day. At 12:00 pm and 2:00 pm, the benadryl group reported higher levels of fatigue than did the placebo group for both subscales. These results support findings of sleepiness, drowsiness, mental and physical sedation, fatigue, and decreased concentration following ingestion of benadryl (Carruthers et al., 1978; Cohen et al., 1987; Jaattela et al., 1971; Moskowitz and Burns, 1988). These findings also agree with research that found that subjective reports post hismanal ingestion do not differ from placebo (Nicholson, Smith, and Spencer, 1982; Nicholson and Stone, 1982).

A higher level of confusion was reported by the benadryl group than by both the placebo and hismanal groups during the 8:00 am session. Also at 8:00 am, the hismanal group reported a higher level of confusion than did the placebo group. A higher level of

confusion was reported by the benadryl group than both the placebo or hismanal groups at 10:00 am. The adjectives used for the confusion subscale relate to feelings of unclear thinking and disorganization. Previous research has noted increased mental sedation and decreased concentration post ingestion of benadryl which would support these findings (Carruthers et al., 1978; Cohen et al., 1987; Jaattela et al., 1971; Moskowitz and Burns, 1988). The difference between the hismanal and placebo group is more difficult to explain as hismanal is reported to be devoid of central nervous system side effects such as sedation and fatigue.

Self Ratings

Three forms of self rating were used. They included: (1) the Stanford Sleepiness Scale, which is included in the Walter Reed Performance Assessment Battery (Thorne et al., 1985), (2) a self assessment of whether subjects believed they had received an antihistamine or a placebo, and (3) a self evaluation of how subjects felt they had performed (on the UTC-PAB tasks) during each session. The Stanford Sleepiness Scale and perceived performance ratings were composed of Likert-scale response data. The self assessment of medication is composed of nominal data.

Stanford Sleepiness Scale. Self reports of sleepiness, using the Stanford Sleepiness Scale, revealed that the level of sleepiness varied both by time of day and the time of day x drug interaction. Analysis of variance results can be seen in Table E132. The level of reported sleepiness decreased throughout the day, with a suggestion of a dip at 12:00 pm (Figure 47). For purposes of greater understanding of the data, the scale in Figure 47 is from 2.4 to 3.6 rather than from 1 to 7. The highest levels of sleepiness were reported at 8:00 am and 10:00 am, while the lowest levels were reported at 10:00 pm, 8:00 pm, 6:00 pm, and noon (see Newman-Keuls results in Table E133). The increase in sleepiness during the afternoon reflects the decreased performance trends seen in unstable tracking, code substitution, logical reasoning, pattern recognition, manikin, and serial addition/subtraction, and may be indicative of circadian patterns and/or sleepiness following ingestion of lunch. The temporal decrease in sleepiness is inversely related to the profile of mood state subscale for vigor-activity.

A closer look at the interaction effect (see simple-effect F-test in Table E134 and

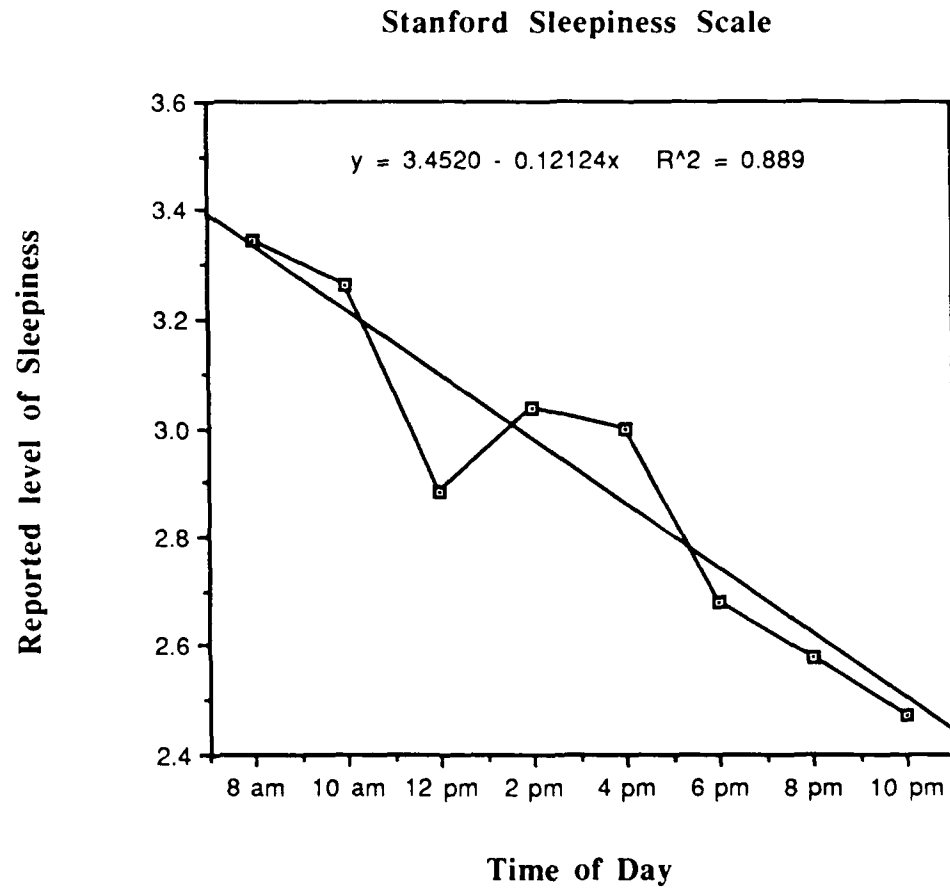


Figure 47. Time effect for Stanford Sleepiness Scale.

Newman-Keuls on Table E135) reveals that reported sleepiness was higher post benadryl than post placebo or hismanal at 8:00 am and 10:00 am . A graphic depiction can be seen in Figure 48. For purposes of greater understanding of the data, the scale in Figure 48 is from 2.0 to 5.0 rather than from 1 to 7. It is interesting to note that the level of increased sleepiness was significant for only the first two sessions on the Stanford Sleepiness Scale, while high levels of fatigue were reported through the 2:00 pm session for both Mood Scale II and the Profile of Mood States.

Self Rating of Medication Received. There was a difference in rating according to which drug/medication the subject received. Results of the Sutcliffe (1957) Chi-square analysis, which allows frequency data to be analyzed for interactions as well as main effects, are located in Table E136. All responses were evaluated to view how they were distributed according to personal responses; therefore, there is no drug effect evident. The results reveal that there was an effect for self rating and that the self rating was different for different drugs (Table E136 and Figure 49). To further examine the interaction, ratings were assessed separately for each drug using a 1-way Chi-square for each (Table E137). Significant differences were seen for the placebo and benadryl groups. Subjects responded that they had received a placebo more often when actually receiving a placebo and as having received an antihistamine after receiving benadryl (Figure 49 and Table E137). No difference was found for the hismanal group.

Symptoms. The frequency of reported symptoms for each drug is located in Table E138. The results of the Sutcliffe Chi-square analysis for number of symptoms x drug x time can be seen in Table E139. There were three symptom categories which were (1) no symptoms, (2) 1 to three symptoms, and (3) four or more symptoms. All responses were evaluated; therefore, there is no main effect of drug, symptoms, or time that is possible. The results reveal that there was an effect for the drug x symptom interaction.

In order to further examine this effect, 1 x 3 Chi-square tests were performed on each of the symptom categories (Table E140). A significant difference was seen only for the third symptom category (four or more). Subjects that received benadryl reported a much higher number of symptoms in the third category, while the placebo group reported a much lower number of symptoms. This effect is also reflected in the total number of

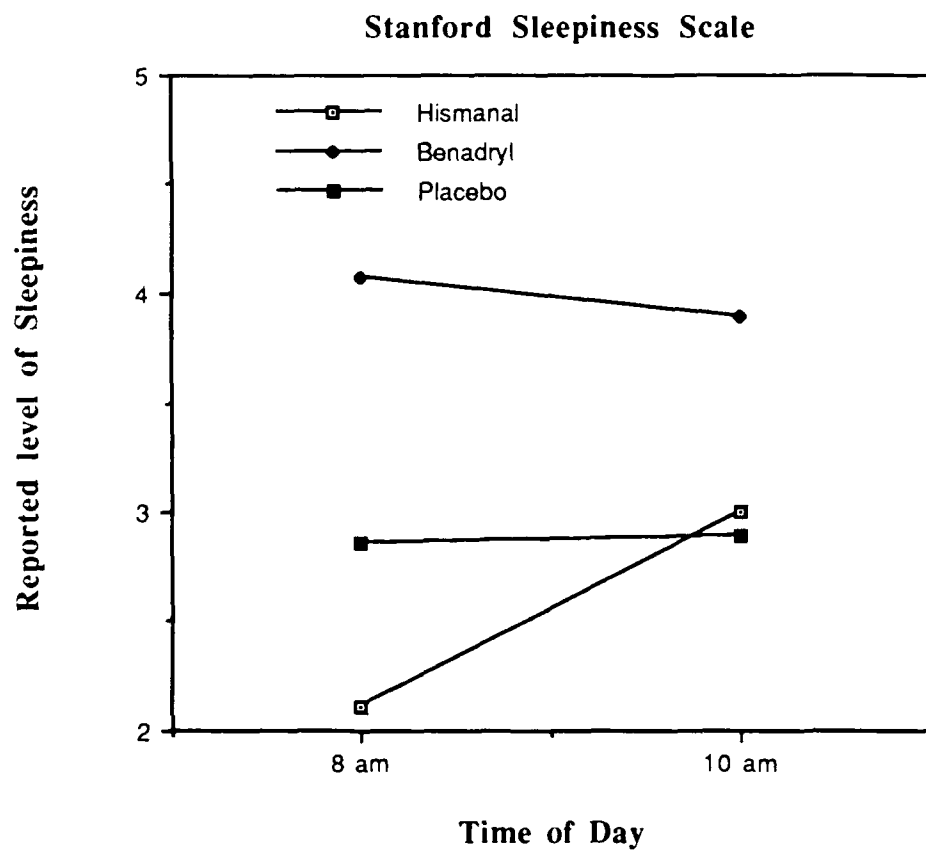


Figure 48. Time x drug interaction at 8:00 am and 10:00 am for Stanford Sleepiness Scale.

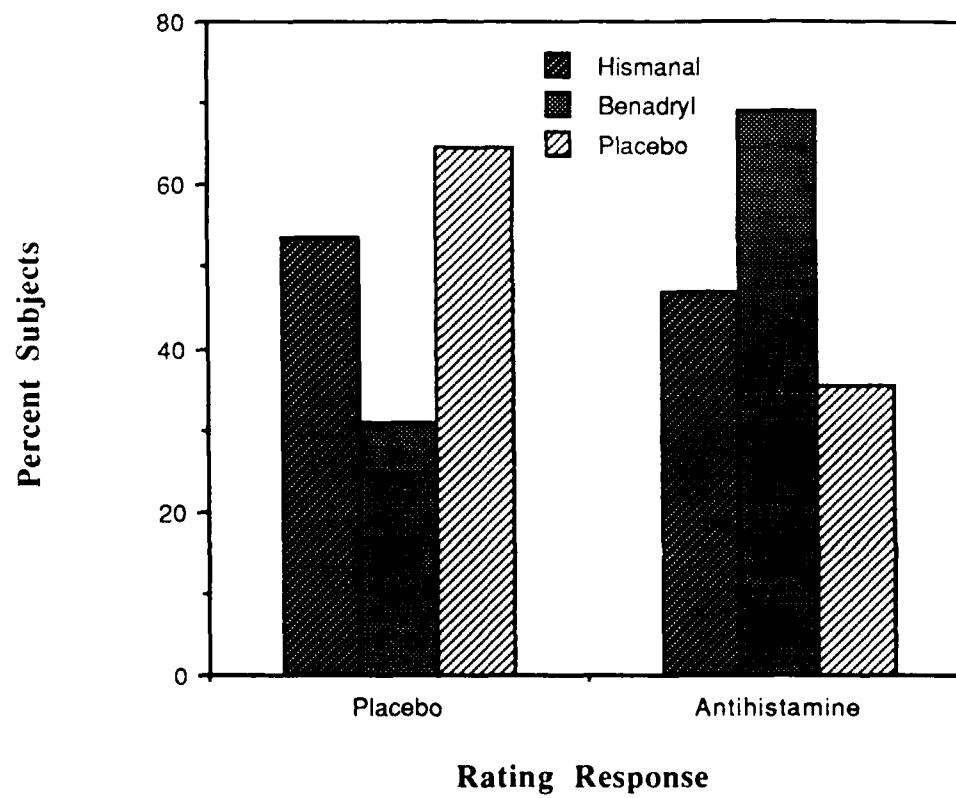


Figure 49. Medication rating.

symptoms per drug (Table E138). These results support literature which cites antihistamines as producing side effects such as loss of appetite, nausea, vomiting, epigastric distress, constipation, diarrhea, dryness of mouth, frequent urination, hypertension or hypotension, headache, faintness, tightness of the chest, and visual disturbances (Bergersen, 1979; Di Palma, 1971).

Self Rating of Perceived Performance. An ANOVA was performed on the five performance categories (Table E141). Findings were significant for time of day, drug, and the time x drug interaction. Subjects rated their performance lowest at 10:00 am and highest at 10:00 pm (Table E142 and Figure 50). For purposes of greater understanding of the data, the scale in Figure 50 is from 3.4 to 3.8 rather than from 1 to 5. Perceived performance was higher post placebo than post benadryl (Table E143). The drug effect was significant during the 8:00 am and 10:00 am sessions (Table E144 and Figure 51). Subjects perceived their performance as higher post placebo or hismanal as compared with benadryl during the two morning sessions (Table E145).

These findings are more applicable to work settings if perceived performance is indicative of actual performance. The Pearson product-moment correlation was used to compare the scores achieved on UTC-PAB performance tests with the five categories of perceived performance. Results suggest that subjects were somewhat able to evaluate their own performance on more complex tasks as indicated by both errors and mean reaction time scores (Figures 52 - 53), although the correlations are quite low (Table E146). Subjects were not able to significantly assess their performance on four-choice reaction time, time estimation, and interval production tasks (Table E146).

Learning Effect

In order to further examine the question of whether the improvement seen on several of the performance tests during the day were indeed due to a learning effect and to discover whether this effect continued over days, a comparison was made across the three test days for the placebo condition only. The dependent variable mean reaction time was used for the Pattern Recognition, Logical Reasoning, Manikin, Serial Addition/Subtraction, and Time Wall tasks. Both errors and mean reaction time were used for the Code Substitution task. Root-mean-square error and boundry hits were used for the Unstable Tracking task. On the Following Directions task, total time, percent total hits, and mean time were used for the easy difficulty level. Mean time was used for the

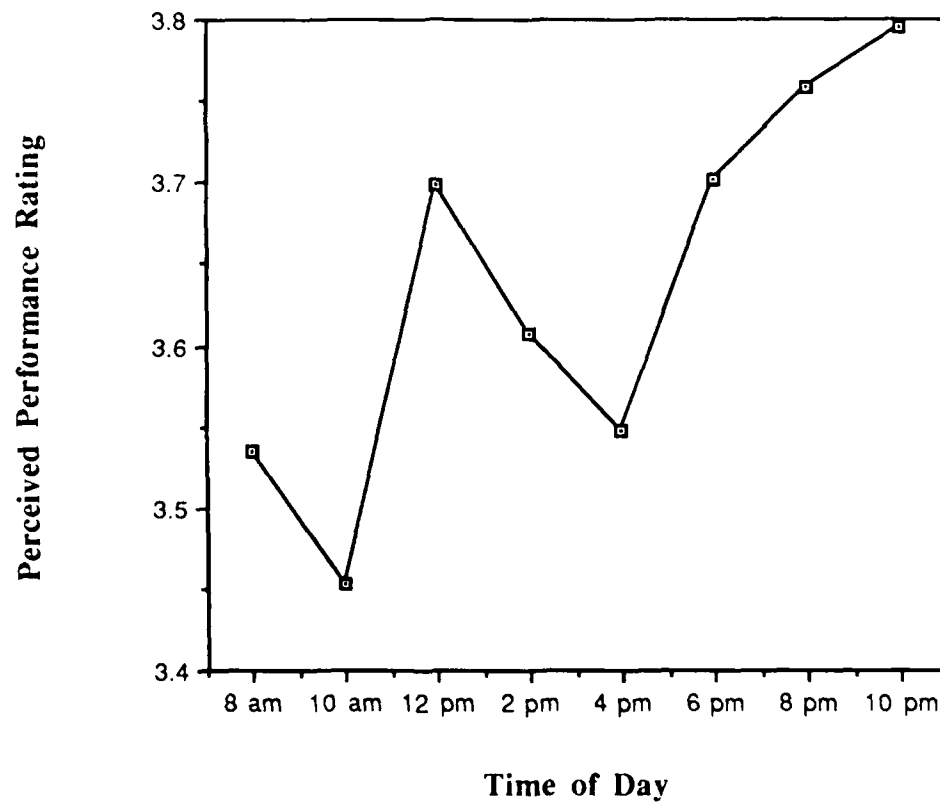


Figure 50. Time effect for Perceived Performance.

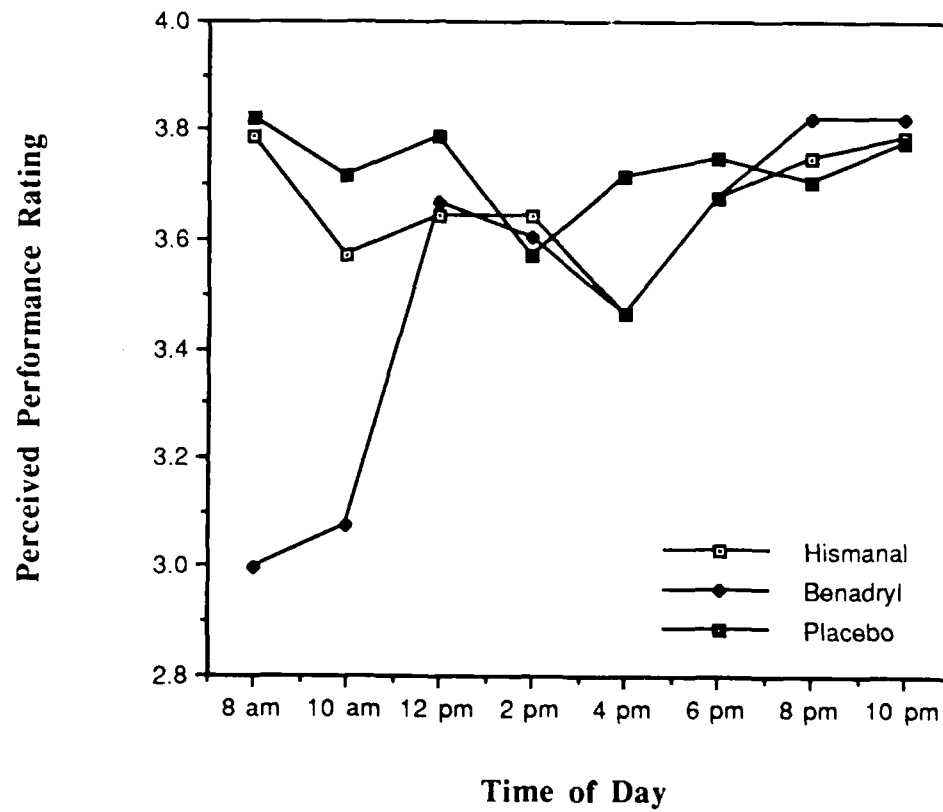


Figure 51. Time x drug interaction for Perceived Performance.

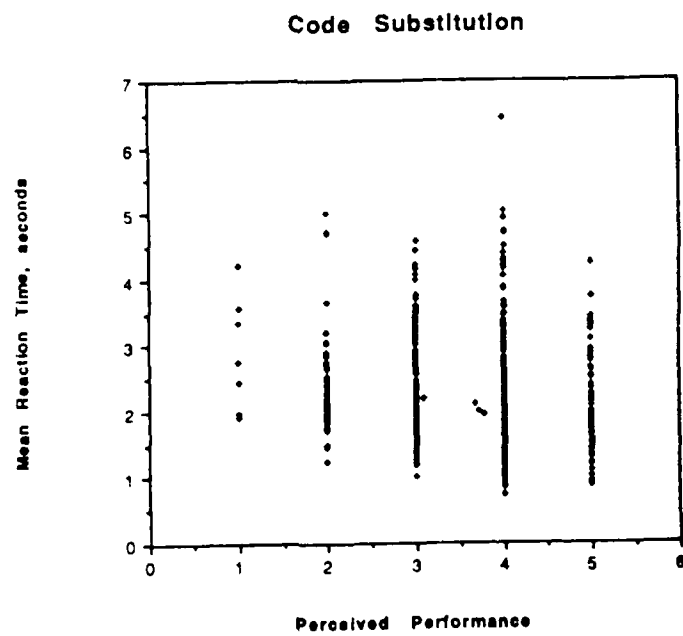
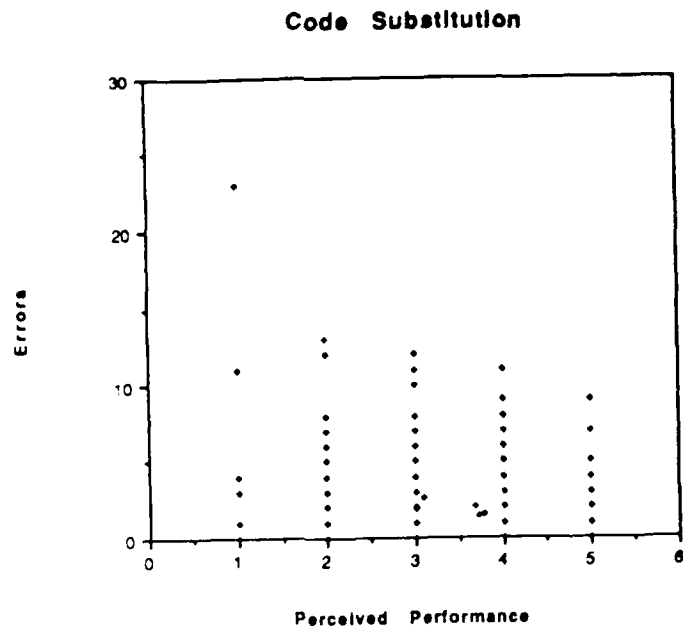


Figure 52. Correlation of Perceived Performance with Code Substitution.

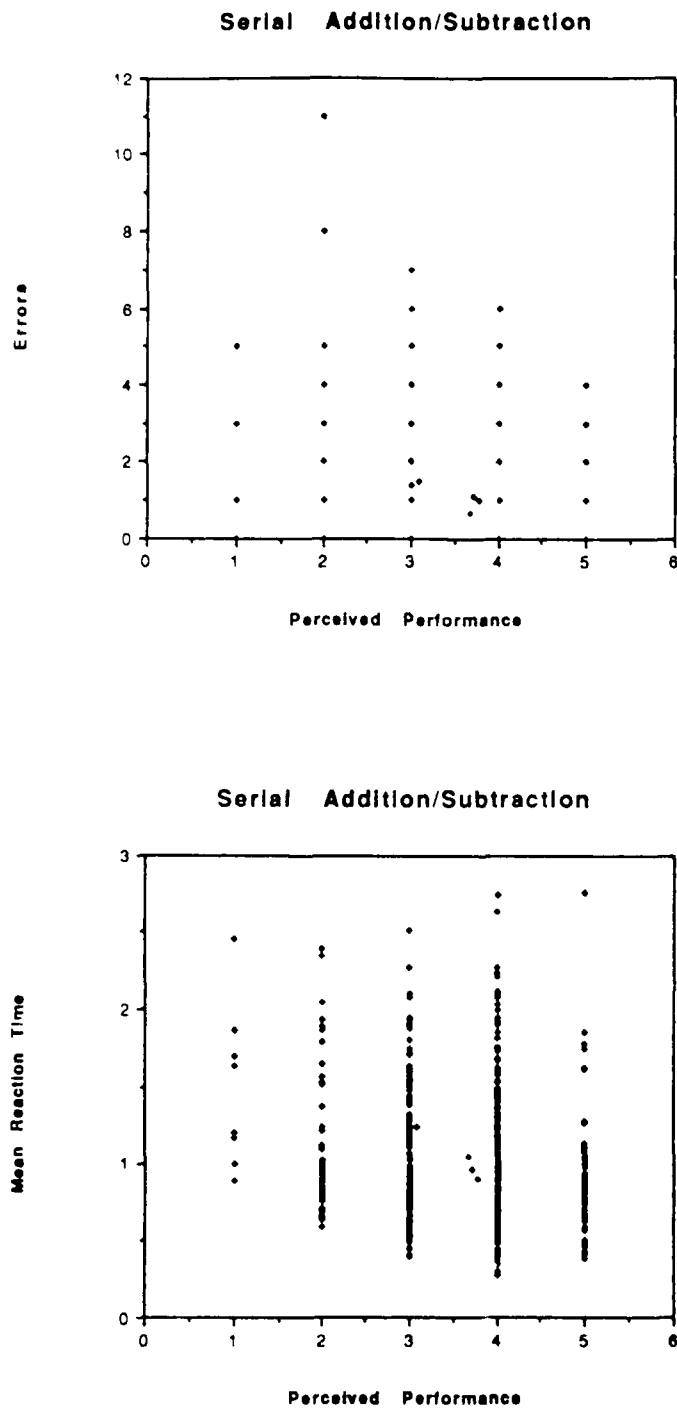


Figure 53. Correlation of Perceived Performance with Serial Addition/Subtraction.

medium difficulty level. Score, total time, percent total hits, and mean time were used for the hard level. On the Route Planning task, number of reversals were used for the hard difficulty level. These dependent variables were noted to improve over time in the original analysis.

There was a difference across the three days for the Manikin task, boundary hits and root-mean-square error on the Unstable Tracking Task, and percent total hits for both the easy and hard difficulty levels on the Following Directions Task. In the Manikin Task, the mean time for Day 1 was much slower than for the following two days (Figure 54 and Tables E147 and E148). On the Unstable Tracking task, there were fewer boundary hits on Day 3 as compared with Day 1 (Figure 55 and Tables E149 and E150) and the root-mean-square error was lower on Day 3, compared with Day 2 (Figure 56 and Tables E151 and E152). On the Following Directions Task - both easy and hard levels, the percent total hits was higher on day 3 as compared with Day 1 (Figures 57 and 58 and Tables E153 through E156). Improvement over the three test days was seen on the Following Directions percent total hits - easy and hard levels, boundary hits and root-mean-square error on Unstable Tracking, and mean reaction time on the Manikin task. Performance appears to continue with practice on these three tasks.

The temporal effects seen on the overall analysis were not present with the same level of consistency for the placebo data only. Time effects within days were seen on only 5 of the 19 dependent variables. The significant dependent variables are Serial Addition/Subtraction mean reaction time, Unstable Tracking boundary hits, and three Following Directions variables. The results of the analysis of variance for the Serial Addition/Subtraction task can be seen in Table E157. As seen graphically, the mean reaction time generally decreased throughout the day (Figure 59). The longest mean reaction time occurred at 12:00 pm and the shortest mean reaction time occurred at 10:00 pm and the absolute differences were small (Figure 59 and Table E158). Although the number of boundary hits on the Unstable Tracking Task was found to vary by time of day (Table E159), there was no difference in the means as indicated by the Newman-Keuls test (Table E160) and less than one boundary hit occurred at each time of day (Figure 60). The Following Directions significant dependent variables are score - hard level task, total time - hard level task, and mean time - medium level task. The score - hard level task generally improved throughout the day, with the two lowest scores occurring at 8:00 am and 10:00 am and the highest score at 10:00 pm (Figure 61 and Tables E161 and E162). The total time - hard difficulty level decreased over the day with the longest times

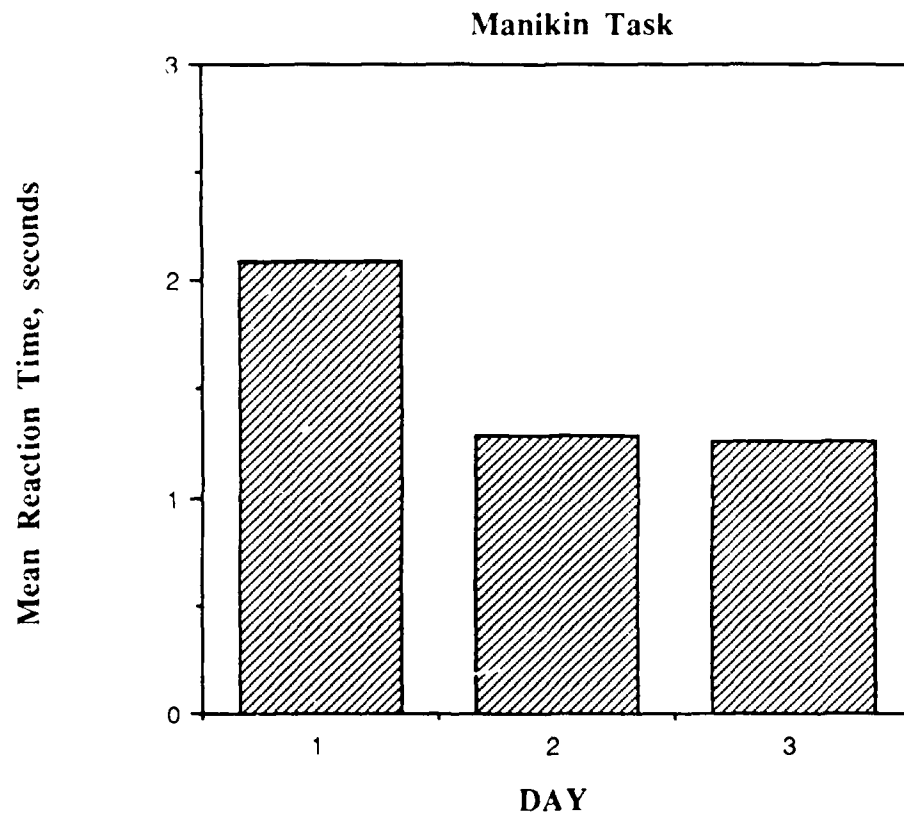


Figure 54. Day effect for Manikin task.

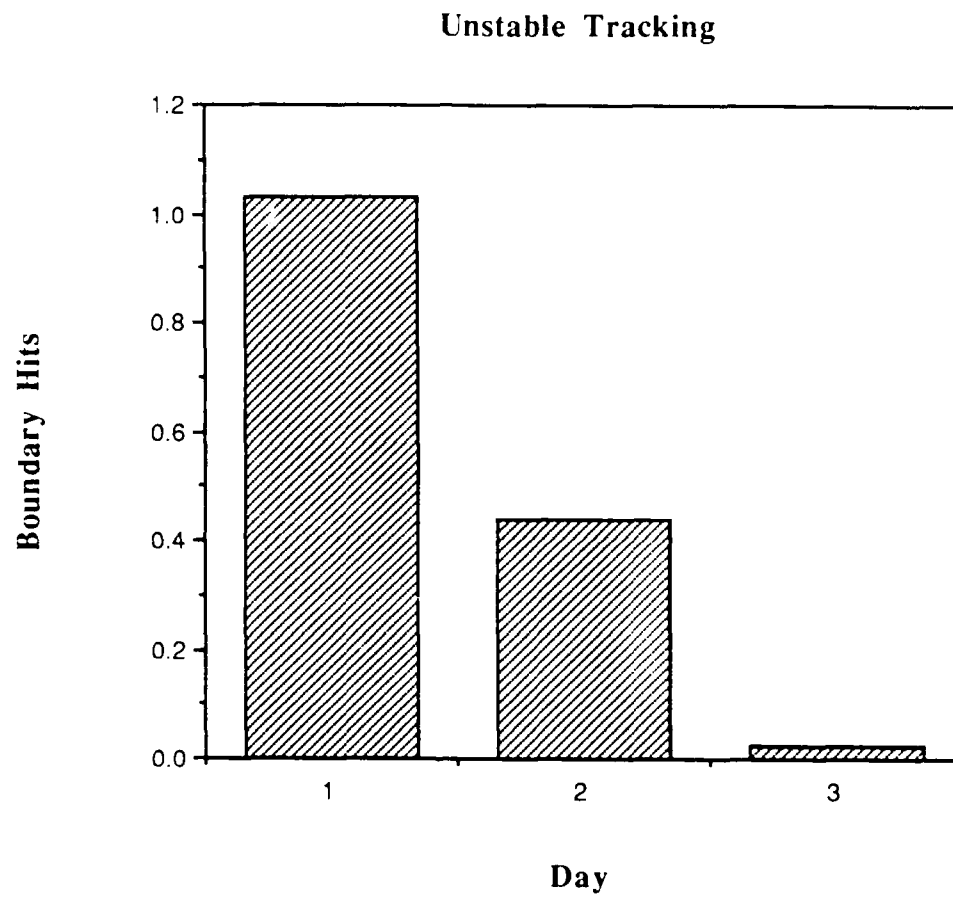


Figure 55. Day effect for Boundary Hits on Unstable Tracking task.

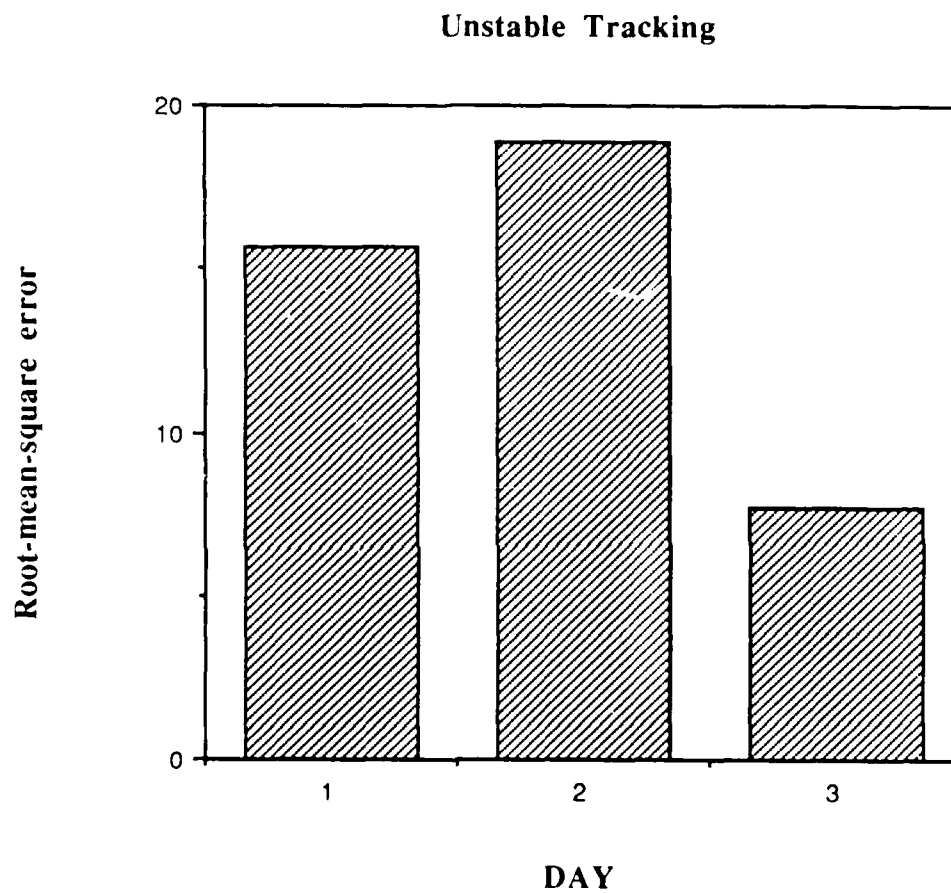


Figure 56. Day effect for Root-Mean-Square Error on Unstable Tracking task.

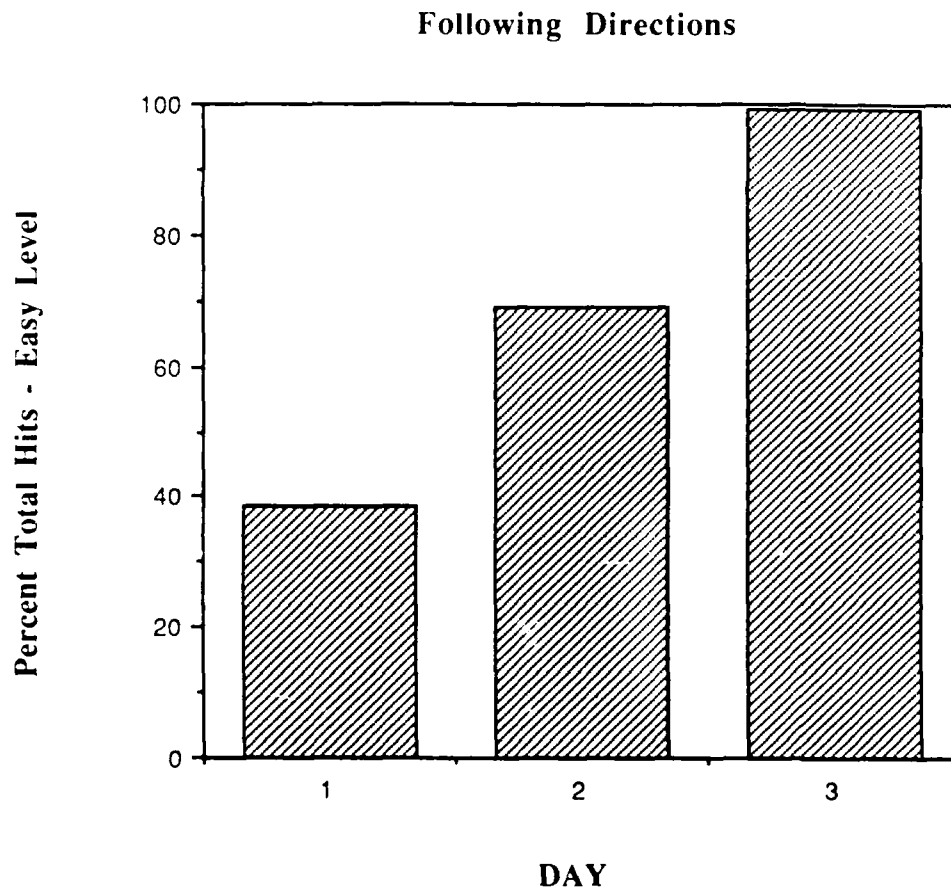


Figure 57. Day effect for Percent Total Hits on Following Directions - Easy Level task.

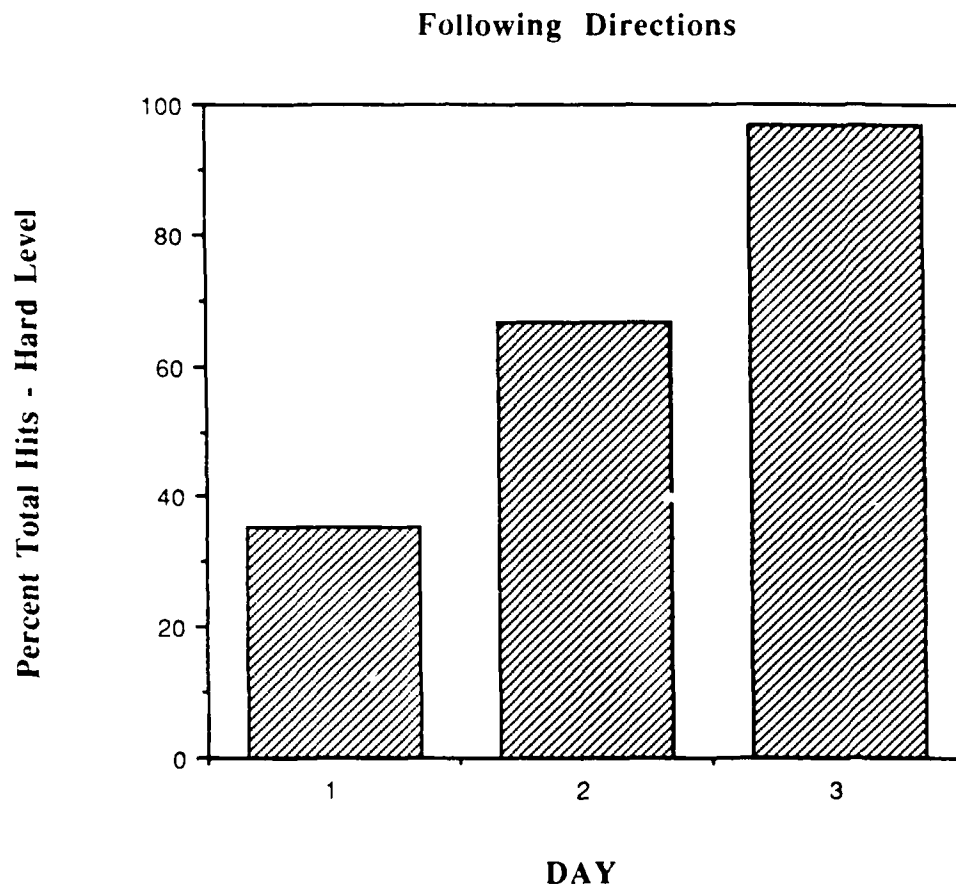


Figure 58. Day effect for Percent Total Hits on Following Directions - Hard Level task.

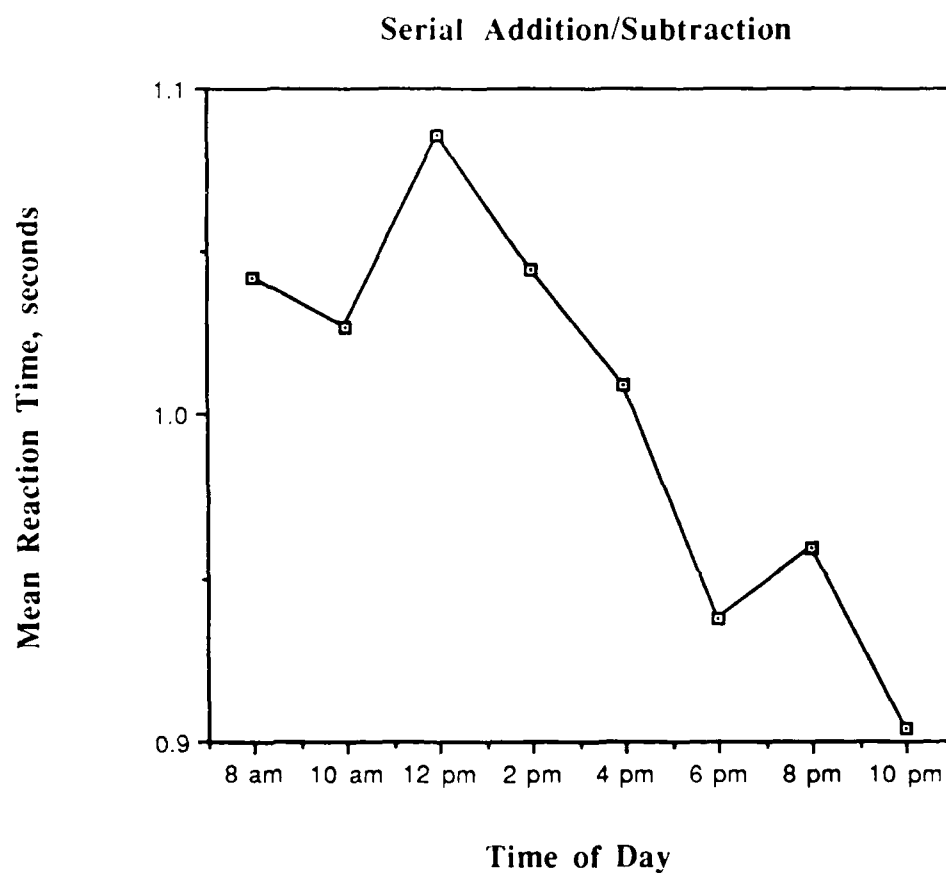


Figure 59. Time effect for Serial Addition/Subtraction task, placebo group only.

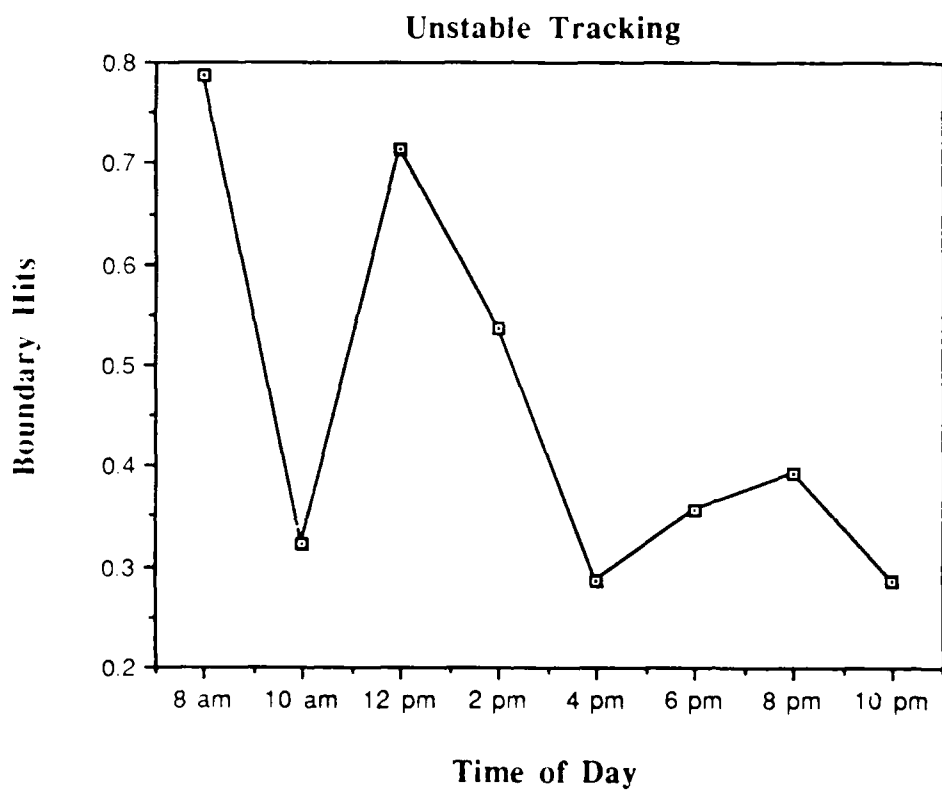


Figure 60. Time effect for Boundary Hits on Unstable Tracking task, placebo group only.

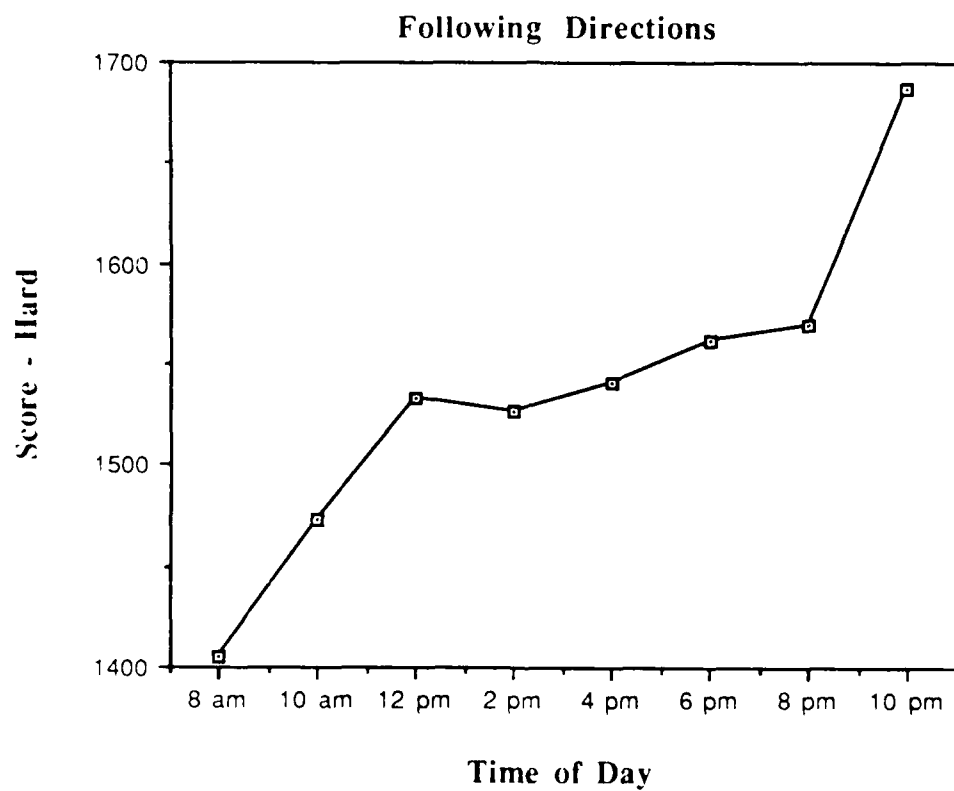


Figure 61. Time effect for Score on Following Directions - Hard Level task, placebo group only.

occurring during the two morning sessions and the shortest time at 10:00 pm (Figure 62 and Tables E163 and E164). The mean time - medium level was slowest at 4:00 pm and fastest at 8:00 pm and 10:00 pm (Figure 63 and Tables E160 and E161). These results indicate that improvement within days transpired on only two dependent variables, Following Directions score - hard difficulty level and Following Directions total time - hard difficulty level.

The difference between the time of day results on the overall analysis and the placebo data appears to be the result of the drug effect having amplified the time of day effect when using the three treatment days in the analysis.

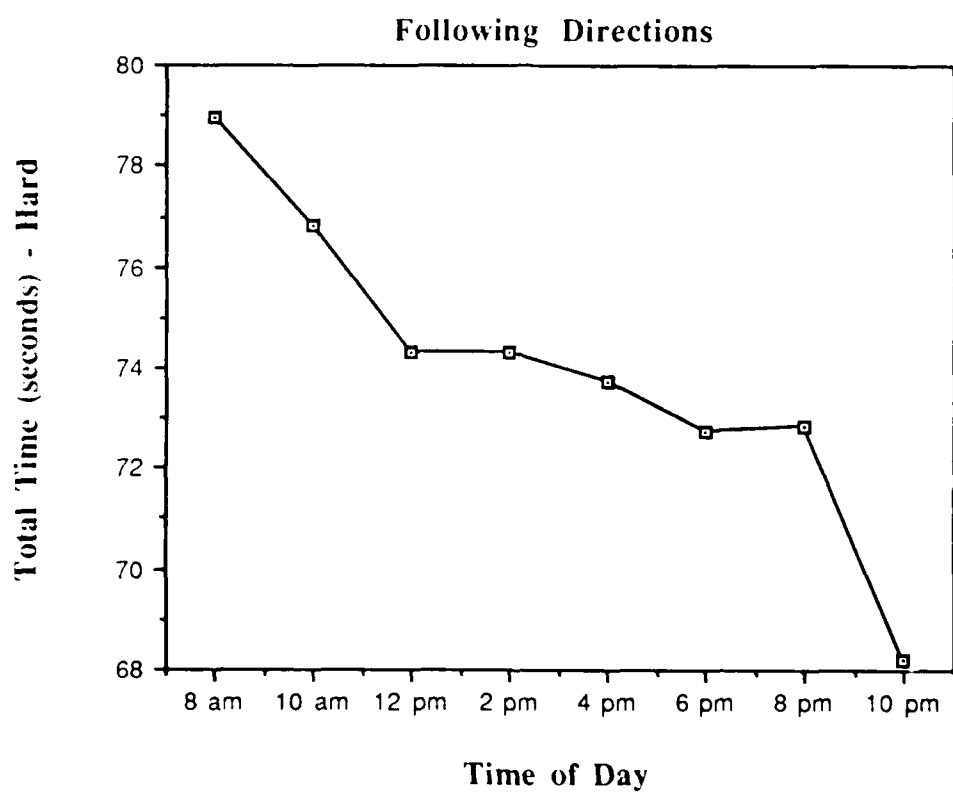


Figure 62. Time effect for Total Time on Following Directions - Hard Level task, placebo group only.

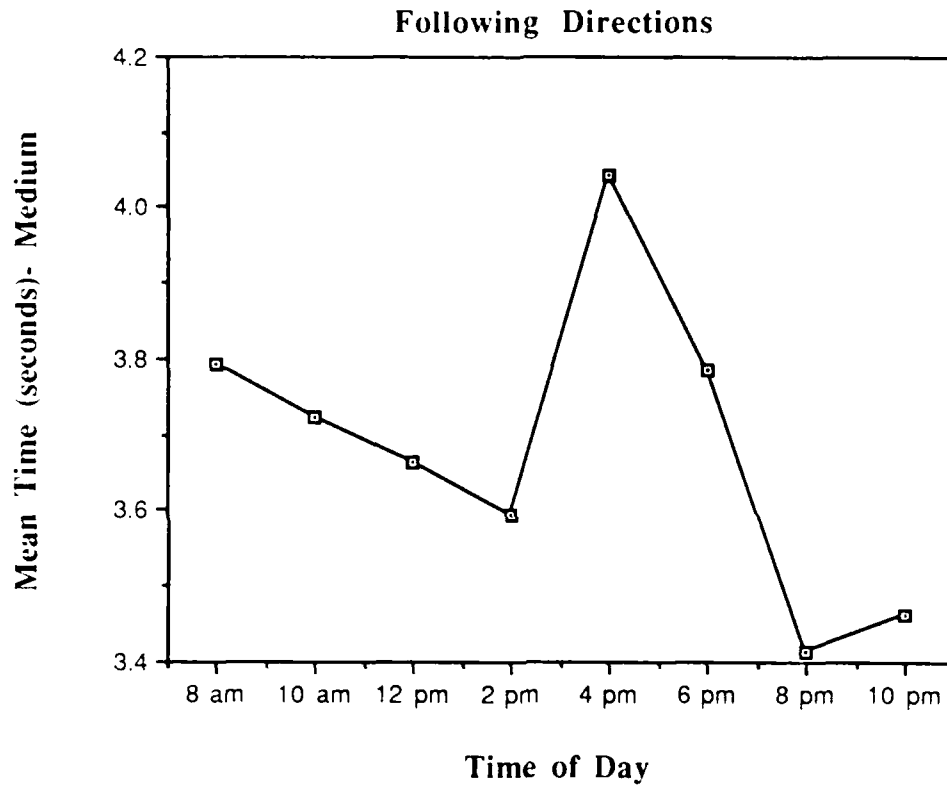


Figure 63. Time effect for Mean Time on Following Directions - Medium Level task, placebo group only.

CONCLUSIONS

Performance Tests

Complex Cognitive Assessment Battery. Time of day effects were noted on the Following Directions easy and hard level tasks. Performance was observed to be lowest during the morning sessions and to improve throughout the day, with suggested performance decrements during the 2:00 pm and 4:00 pm sessions indicated most frequently in the easy level task. This trend suggests a circadian pattern. No significant effects were noted for dependent variables on the medium level task with the exception of mean time. Although performance following ingestion of benadryl was lower than for hismanal or placebo during the 8:00 am session on several measures of both the easy and hard level tasks, the sole dependent measure which ascertained the effect of benadryl was the percent total hits on the hard level task. At 8:00 am, the benadryl group achieved fewer total hits than did either the hismanal or placebo groups. Although, no similar tasks were noted in antihistamine research literature, this task requires divided attention similar to that of a combined memory search and tracking task.

The Following Directions task requires memory storage and memory retrieval simultaneous with visual search and manual task execution, thus necessitating time sharing of cognitive, perceptual, and motor response skills (Analytical Assessments Corporation/EATON Corporation, 1988). The results of this research support findings by Moskowitz and Burns (1988) in which tracking, divided attention, and vigilance were significantly affected at one hour post ingestion of 50 mg of benadryl. However, Moskowitz and Burns (1988) also found performance decrements at three hours post ingestion on visual search, tracking, and divided attention. Gengo et al. (1989) found that performance decrements on a driving simulator and digit symbol substitution task lasted for only two hours.

The research results from this battery indicate the following conclusions.

(1) Further research is desired with an increased diversity of subjects to eliminate the possible arousal effect of a student population, which may typically be more alert in the afternoon and evening hours.

(2) The easy level Following Directions task does not appear sensitive to the antihistamines used in this research at therapeutic dose level effects. More research should

be conducted to determine the sensitivity of this task to other medications and other dose levels.

(3) The medium level task does not appear to be a reliable performance indicator as the dependent measures were insensitive to both time and drug effects. It is not recommended for further use in performance or drug testing until an evaluation of its sensitivity has been completed.

(4) The hard level task demonstrated the clearest temporal effect and the only performance decrement (8:00 am) due to antihistamine ingestion. This task possesses the greatest promise for future use in medication evaluations. More research is needed to assess possible learning effects.

(5) A pattern of decreased performance was suggested during afternoon sessions (2:00 pm and 4:00 pm). In order to interpret these results, future research should attempt to control for sleep levels, diet, and activity between test sessions.

In Route Planning, score on the hard level task and number of reversals on both the hard and easy levels were found to vary with time. However, there was no difference in the means on the Newman-Keuls test for score and easy level reversals. Temporal effects for the hard level task suggest that subjects performed best at 6:00 pm and worst at 4:00 pm and 10:00 pm, which is a pattern not seen for other tasks.

As correct solutions can be achieved in fewer moves than the program for the Route Planning task recognizes (or corrects for), values for the variable minimum valid moves cannot be interpreted and therefore should not be utilized as a dependent measure until the software is corrected. None of the dependent measures was found to be of sufficient sensitivity to detect the effects of the antihistamines used. A solution was achieved only 86.81 % of the time. The inability to achieve a correct solution occurred regardless of the drug condition. The difficulty in achieving the correct solution may have contributed to the lack of main and interactive effects observed. In addition, noting that correct solutions can be achieved in fewer moves than the software program recognizes does not encourage confidence in the software program or the recording of whether a correct solution was achieved. As this task required the use of the knight's move in the game of chess, it is interesting to note that subjects' self ratings of their ability levels at chess was correlated significantly with their scores ($\rho = 0.4004$, $p = 0.0347$). Further training could possibly alleviate this influence; however, it is important to keep this issue in mind when using a portion of a learned skill (such as chess) to evaluate the effects of an

independent variable such as medication. Experts may be better able to override the effects of the medication. If the results obtained from this task are reliable, then the following conclusions are warranted.

(1) Neither the easy nor the hard level Route Planning tasks appear sensitive to the antihistamines used in this research at therapeutic dose levels. More research should be conducted to determine the sensitivity of this task to other medications and other dose levels.

(2) The medium level task does not appear to be a reliable performance indicator as it was insensitive to both time and drug effects. It is not recommended for further use in performance or drug testing until an evaluation of its effectiveness has been completed.

(3) In order to interpret temporal effects, future research should attempt to control for sleep levels, diet, and activity between test sessions.

(4) Further research should address the issue of personal background and experience levels at related tasks (such as chess). Until completion of such research, caution on interpretation of results is advised.

In view of the low frequency of solutions achieved, the software problems in recognition of correct solutions, and the lack of sensitivity to the effects of the antihistamine levels used in this study, this task is not recommended for evaluation of pharmaceuticals. It is recommended that the software for this task be examined and corrected as necessary. Consequent to this, the task may be re-evaluated for usefulness in performance and pharmaceutical research.

Unified Tri-Service Assessment Battery. Temporal effects were evident in Unstable Tracking, Code Substitution, Serial Addition/Subtraction, Logical Reasoning, Manikin, and Pattern Comparison tasks. Mean reaction time decreased without a decrease in accuracy, which suggests that the level of training may have been insufficient. A suggestion of low performance was observed in the early afternoon (2:00 pm and 4:00 pm), which may be the result of diurnal rhythms or post-prandial effects. Post-prandial effects have been noted to decrease performance (Christie and McBrearty, 1979; Taylor and Rachman, 1988, as cited by Mindell, 1990; Wurtman, 1986). For the Time Wall task it was found that judged time decreased over the course of the day, which is opposite to that found by Jerison and Arginteanu (1958, as cited by Perez et al., 1987), who found that subjects increased their time estimation over repeated trials. The time of day effects do

not appear to be the result of overall learning, as subjects did not continue to improve over consequent days.

Performance decrements due to the antihistamine ingested were found on the Serial Addition/Subtraction task and the Unstable Tracking task. Mean reaction time was slower at 10:00 am for the benadryl group than for the other two groups on the Serial Addition/Subtraction task. Performance at 12:00 pm was quicker for the hismanal group than for the other two groups on the same task. Previous research with therapeutic doses of benadryl yielded conflicting results on arithmetic tasks. The tasks utilized in other research involved simple addition and subtraction and therefore appear to differ from the serial addition/subtraction task used in this study. The task used in this research was machine- rather than self-paced, required sustained attention, and required a secondary process of either entering the least significant digit if the answer was positive or adding 10 to the answer if it was negative. On the tracking task, subjects were less able to maintain center control of the cursor post ingestion of benadryl at 8:00 am than for the other two groups. As the tracking task was one of the two last tasks in the battery, actual performance of the task (for the 8:00 am session) occurred at one and a half hours post ingestion of benadryl (8:30). At 10:00 am, the performance of the benadryl group remained poorer than the hismanal group, but was not different from the placebo group. These results lend support to findings of tracking effects found at one and a half (Moskowitz and Burns, 1988) and two hours (Cohen, Posner, Ashby, Smith, and Peck, 1984) post ingestion of benadryl (50 mg).

The research results suggest the following conclusions.

- (1) Further research with a greater subject diversity is needed to investigate the time of day effects as students may be more alert in the afternoon and evening hours.
- (2) Future research to accurately interpret temporal effects for possible post-prandial effects is necessary. Research should control for activity and diet during testing. Research should also control for sleep prior to data collection.
- (3) Performance decrements due to antihistamine ingestion were noted at 10:00 am on the serial addition/subtraction task mean reaction time and at 8:00 am for the root-mean-square error for unstable tracking. These two tasks appear to have potential in evaluation of performance effects secondary to antihistamine use.

Experience Ratings. The correlations indicate the need for caution in application of skill-based performance evaluations. Individual differences based on past experience or

skill levels on similar tasks could influence research results. Further research is necessary to determine whether such influence interferes with the effects of the independent variables, such as medications.

Summary. Temporal effects were evident in Following Directions, Unstable Tracking, Code Substitution, Serial Addition/Subtraction, Logical Reasoning, Manikin, and Pattern Comparison tasks. These results suggest that subjects' performance improved over the day, possibly due to circadian patterns. A pattern of a low performance was suggested in the afternoon (2:00 pm and 4:00 pm), which may be the result of diurnal rhythms or post-prandial effects.

Performance deterioration was expected post ingestion of benadryl on the subtasks which were considered to be of higher complexity and to place higher cognitive demands on subjects at one and three hours post ingestion of benadryl. Decrements in performance were therefore expected on the Route Planning and Following Directions tasks. In accordance with the literature review, performance changes were also anticipated on unstable tracking and code substitution tasks. The logical reasoning task was not noted in the literature as being used in antihistamine research; however, as it was expected to tap higher cognitive functioning it was also expected to yield to the negative effects of benadryl. The UTC-PAB version of the serial addition/subtraction task demanded a higher level of information processing than did addition/subtraction tasks described in other antihistamine research; therefore, this task was also expected to display performance deficits due to benadryl ingestion. No change in performance was anticipated with either the hismanal or placebo groups.

Decreased performance was found at one hour post ingestion of benadryl (50 mg) on the Following Directions task, at one and a half hours post ingestion on the Unstable Tracking task, and at three hours post ingestion on the Serial Addition/Subtraction task. Gengo et al. (1989) found performance effects lasted only two hours post ingestion on driving simulation and digit symbol substitution tasks. These results for the Serial Addition/Subtraction task extend that time limit. In addition, results suggest that the type of skill affected by ingestion of benadryl may vary by time post ingestion. No decrements in performance were found post ingestion of hismanal and, in fact, the hismanal group performed the serial addition/subtraction task quicker than either the placebo or benadryl groups at five hours post ingestion. At three and a half hours post ingestion, the performance of the benadryl group remained poorer than the hismanal group on unstable

tracking, but was not different from the placebo group. Performance impairment was not observed on tasks thought to emphasize perceptual input, detection, and identification (four-choice reaction time), central processing (code substitution), linguistic information integration and manipulation (logical reasoning), spatial information integration/manipulation (time wall, manikin, and pattern comparison), or output without a sustained visual component (interval production). As low doses used in this study impaired the three tasks which required sustained attention and the two tasks which required the highest levels of manual task execution in this battery, cognitive impairment of these drugs may be missed if tasks which do not require similar skills are not used. Moskowitz (1984) asserts that tasks requiring concentrated attention and divided attention are differentially affected by various drugs and that both performance dimensions must be included in medication evaluations.

Physiological Tests

Temporal effects were noted for systolic blood pressure, pulse, and temperature. These changes may be the result of either circadian patterns or meal ingestion. Pulse rate was found to be quickest after meals (2:00 pm and 8:00 pm) and slowest prior to meals (12:00 pm and 6:00 pm). Recorded temperature was lowest in the morning and increased throughout the day. No main effects of drug were noted for physiological measurements. These results support findings by Craft et al. (1987) in which no changes were observed in heart rate or blood pressure post ingestion of hismanal.

Subjective Measures

Mood Scales. Temporal effects were found for the activity subscales for both Mood Scale II and Profile of Mood States (POMS). Reported activity level was lowest during the two morning sessions and increased throughout the course of the day, although no difference in means was found for Mood Scale II. A significant time of day effect was also noted for mean reaction time on Mood Scale II; as the day progressed, mean reaction time decreased. These results reflect the temporal effects found on performance tasks. As noted previously, one plausible explanation for the increased activity level over the course of the day is that university students may be more active during evening hours. The

suggested afternoon effects could also be due to post-prandial effects. Christie and McBrearty (1979) assessed mood using the Nowlis Mood Adjective Check List a half hour before lunch and one and a half hours and three hours post lunch. They found that activity decreased and deactivation increased in the session immediately following lunch and returned to post lunch levels during the final session. They regarded these results as a reflection of a "post prandial lassitude" in the 1-2 hours post lunch period (Richards, 1971, as cited by Christie and McBrearty, 1979).

Drug effects were seen on the tension-anxiety, vigor-activity, and fatigue-inertia subscales for POMS. The overall effect was that a higher level of tension-anxiety and a lower level of vigor-activity was experienced by the benadryl group throughout the day. On the fatigue-inertia subscale, the benadryl group reported a higher level of fatigue primarily during the two morning sessions. These results support findings in which symptoms of sleepiness, drowsiness, mental and physical sedation, fatigue, and lowered ability to concentrate post benadryl ingestion have been reported (Carruthers et al., 1978; Cohen, Hamilton, and Peck, 1987; Jaattela et al., 1988; Moskowitz and Burns, 1988) and refute the finding of no mood effect found by Miller et al. (1988).

Time x drug interaction effects were noted for the activity, depression, anger, and fatigue subscales on Mood Scale II, as well as a marginally significant finding for mean reaction time ($F = 1.72, p = 0.0507$). Interaction effects were also found for the vigor-activity, fatigue-inertia, and confusion-bewilderment subscales of POMS. The placebo group reported a higher level of activity than did either the hismanal or benadryl groups during the 8:00 am session on both mood scales, while the hismanal group reported a higher level of activity than did the benadryl group on the POMS. At 10:00 am, both the placebo and the hismanal groups reported a higher level of activity than did the benadryl group on both mood scales. The difference between the placebo and benadryl groups was expected and supports previous research results (Carruthers et al., 1978; Cohen et al., 1987; Jaattela et al., 1971; Moskowitz and Burns, 1988). The difference between the placebo and hismanal groups was not expected as hismanal is reported to be void of central nervous system effects such as drowsiness (Chapman and Rawlins, 1982; Nicholson et al., 1982; Nicholson and Stone, 1982; Richards et al., 1984) and research has indicated that subjective reports do not differ from placebo (Nicholson et al., 1972; Nicholson and Stone, 1982).

For both mood scales, higher levels of fatigue were reported for the benadryl group than for either the placebo or hismanal groups for the first two sessions. At 12:00 pm and 2:00 pm, the benadryl group reported higher levels of fatigue than did the placebo group for both subscales. These results support findings of sleepiness, drowsiness, mental and physical sedation, fatigue, and decreased concentration following ingestion of benadryl (Carruthers et al., 1978; Cohen et al., 1987; Jaattela et al., 1971; Moskowitz and Burns, 1988). These findings also agree with research that found that subjective reports post hismanal ingestion do not differ from placebo (Nicholson et al., 1982; Nicholson and Stone, 1982). This is an hour longer than subjective reports of fatigue following benadryl ingestion as reported by Gengo et al. (1989).

A higher level of confusion (POMS) was reported by the benadryl group compared with both the placebo and hismanal groups during the 8:00 am session and greater confusion was reported for the hismanal group compared with the placebo. A higher level of confusion was reported by the benadryl group than both the placebo or hismanal groups at 10:00 am. As previously stated, the adjectives used for the confusion subscale relate to feelings of unclear thinking and disorganization. Previous research has noted increased mental sedation and decreased concentration post ingestion of benadryl which would support these findings (Carruthers et al., 1978; Cohen et al., 1987; Jaattela et al., 1971; Moskowitz and Burns, 1988).

Although the anger and depression subscales on Mood Scale II were found significant for the interaction of time x drug, none of the individual sessions reached a level of significance. The benadryl group did report higher levels of anger and depression during the first two sessions of the day, but inexplicably the placebo group was also noted to report high levels of anger and depression during the final sessions of the day. There was no interactive effect for the subscale anger-hostility on the POMS. These findings lead one to conclude that the anger subscale may not be of sufficient sensitivity to reliably register antihistamine effects in this study.

The research results suggest the following conclusions.

(1) Further research with populations other than university students is necessary to evaluate temporal effects on subjective vigor-activity levels. Research should control for sleep levels prior to testing. Diet and activity should be controlled on test days.

(2) Both Mood Scale II and the POMS are of sufficient sensitivity to register variation in mood post antihistamine ingestion. This sensitivity was evident in the overall

drug effect (tension-anxiety, vigor-activity, and fatigue-inertia scales on the POMS) and the drug x time interactions (activity and fatigue scales on Mood Scale II and vigor-activity, fatigue-inertia, and confusion-bewilderment scales on the POMS).

(3) The POMS appears to have greater sensitivity to the effects of the antihistamines than does Mood Scale II. Further research is needed with an increased number of subjects using both the abbreviated mood scale (Mood Scale II) and the longer version (Thorne et al., 1985). Prior to the conclusion of the suggested research, the POMS is recommended for antihistamine research.

(4) Subjective differences due to antihistamine ingestion (benadryl) were found for three hours post ingestion for vigor-activity and confusion-bewilderment scales and seven hours for the fatigue and fatigue-inertia scales. Post benadryl ingestion, the subjective feeling of fatigue persists beyond the time when performance effects are evident.

(5) Activity was reduced and confusion-bewilderment was increased at one hour post ingestion for hismanal as compared with placebo. These unexpected results suggest the need for further study on the subjective effects of hismanal.

Self Ratings. Self reports of sleepiness, using the Stanford Sleepiness Scale decreased throughout the day, with a suggested increase at 2:00 pm which remained at the 4:00 pm session. The increase in sleepiness during the afternoon corresponds to the decreased performance trends seen in Unstable Tracking, Code Substitution, Logical Reasoning, Pattern Comparison, Manikin, and Serial Addition/Subtraction, and to the physiological measurement of systolic blood pressure. These results may be indicative of circadian patterns and/or sleepiness following ingestion of lunch. The temporal decrease in sleepiness is inversely related to the mood subscales for vigor-activity. Reported levels of sleepiness were higher for the benadryl group than for both placebo and hismanal groups during the two morning sessions, while high levels of fatigue were reported through the 2:00 pm session for both Mood Scale II and the Profile of Mood States. These results serve to underscore findings on the two mood scales and substantiate prior research which identified sleepiness, drowsiness, and fatigue as occurring for one to five hours post ingestion of benadryl (Carruthers et al., 1978; Cohen et al., 1987; Jaattela et al., 1971; Moskowitz and Burns, 1988). No differences were expected or identified for the hismanal group on sleepiness levels.

There was a difference in self rating of medication according to which drug/medication the subject received. Subjects responded that they had received a placebo more often when actually receiving a placebo. Subjects also responded as having received an antihistamine post benadryl, but did not respond as having received an antihistamine post hismanal. These results are expected as few side effects have been reported with hismanal ingestion (Vanden Bussche et al., 1984, as reported by Richards et al., 1984).

Subjects perceived their performance as poorer post ingestion of benadryl versus placebo and hismanal for three hours post ingestion. It appears that subjects were able to evaluate their own performance on more complex tasks as indicated by both errors and mean reaction time scores and were unable to correctly assess their performance on four-choice reaction time, time estimation, and interval production tasks. Although the correlations were low, these results tend to support research in which subjects were able to recognize their performance decay on a driving task (Betts et al., 1984) and on psychomotor performance tasks (Moskowitz and Burns, 1988), but were unable to correct it.

The research results suggest the following conclusions:

- (1) The Stanford Sleepiness Scale is sensitive to the drug effects of the antihistamines used in this study for three hours post ingestion. This rating scale is recommended for further use in antihistamine research.
- (2) As stated above, further research is needed for elucidation of temporal effects.
- (3) The correlations for actual versus perceived performance, while low, suggest the need for further research.

Summary. Clearly the mood scales used in this study were able to register both time of day and drug effects. Activity levels were lowest during the two morning sessions and increased throughout the course of the day. The Stanford Sleepiness Scale was inversely related to reported activity levels. Results of both the activity scales and the sleepiness scale reflect suggested temporal effects noted on performance tasks of lower performance during the afternoon sessions (2:00 pm and 4:00 pm).

A higher level of tension, greater fatigue, and a lower level of activity was experienced by the benadryl group. These results support findings in which symptoms of sleepiness, drowsiness, mental and physical sedation, fatigue, and lowered ability to concentrate post benadryl ingestion have been reported (Carruthers et al., 1978; Cohen, Hamilton, and Peck, 1987; Jaattela et al., 1988; Moskowitz and Burns, 1988) and refute the finding of no mood effect found by Miller et al. (1988).

The results of the two mood scales are in marked agreement on the activity and fatigue scales. Although the activity level reported for the hismanal group was higher than that of the benadryl group on the POMS, greater activity was noted for the placebo group than for both the hismanal and benadryl groups at one hour post ingestion of benadryl on both mood scales. At three hours post ingestion, both the placebo and the hismanal group reported higher levels of activity than the benadryl group. The benadryl group reported higher levels of fatigue than did either the placebo or hismanal groups at one hour and three hours post ingestion. Higher levels of fatigue continued to be reported for the benadryl group than for the placebo group at five and seven hours post ingestion. Self reports of sleepiness on the Stanford Sleepiness Scale substantiate the findings of low activity and high fatigue for the benadryl group at one and three hours post ingestion. The Profile of Mood States also includes a subscale for confusion. The benadryl group reported higher levels of confusion than did the placebo group at one hour post ingestion and higher than either the placebo or hismanal groups at three hours post ingestion. The hismanal group reported higher confusion than the placebo group at one hour post ingestion, but remained lower than the benadryl group. These results tend to extend the time that subjective changes are noted due to the disruptive effects of benadryl (Gengo et al., 1989) by one hour.

Subjects responded that they had received a placebo more often when actually receiving a placebo. Subjects also responded as having received an antihistamine post benadryl, but did not respond as having received an antihistamine post hismanal. Subjects perceived their performance as poorer post benadryl versus placebo and hismanal during the first two hours post ingestion. Perceived performance and actual performance were found to be significantly correlated on all tasks except the time based tasks of four-choice reaction time, time estimation, and interval production.

Hismanal versus Benadryl - Conclusions

Performance decrements were found on the Following Directions task at one hour post benadryl ingestion. At one and a half hours post benadryl ingestion, diminished performance was seen on the unstable tracking task and at three hours post, diminished performance was noted on the serial addition/subtraction task. All three findings were different than those comparing hismanal and placebo. These results extend the finding of

performance effects lasting for two hours post benadryl ingestion on driving performance and digit symbol substitution tasks (Gengo et al., 1989). The research results also suggest that the type of skill affected by ingestion of benadryl may vary by time post ingestion.

No performance decrements were found post hismanal ingestion. At five hours post ingestion, the hismanal group performed faster on the Serial Addition/Subtraction task. Three hours post ingestion, root-mean-square error for the benadryl group was higher than for the hismanal group, but not different from placebo. Not only were there no performance decrements noted post hismanal ingestion, on two occasions the hismanal group performed better than did the placebo group. On the basis of this research, hismanal appears superior to benadryl when high level performance is required (Table E167).

Drug effects were found which indicated higher levels of tension-anxiety and fatigue-inertia and lower levels of vigor-activity post ingestion of benadryl. At one and three hours post ingestion of benadryl, vigor-activity was lower on both mood scales (compared with placebo). Confusion was greater at one and three hours post benadryl ingestion compared with both placebo and hismanal, and at three hours compared with hismanal. Fatigue was greater at one, three, five, and seven hours post ingestion of benadryl versus placebo and greater at one and three hours post ingestion compared with hismanal. Both at one and three hours post ingestion of benadryl, sleepiness was greater than for hismanal and placebo. At one hour post ingestion of hismanal, vigor-activity was lower than with a placebo for both mood scales. Although vigor-activity was lower for the hismanal group compared with placebo, vigor-activity was still higher when compared with benadryl on the POMS. At three hours post ingestion, vigor-activity post hismanal was no different from placebo and higher than post benadryl. Confusion was greater for the hismanal group at one hour post ingestion compared with placebo; however, confusion was still lower than that seen with benadryl. Hismanal ingestion did not increase fatigue. Thus, on two occasions hismanal was rated lower than placebo (at one hour post ingestion on vigor-activity and on confusion-bewilderment) and on these occasions, hismanal remained superior to benadryl. On the basis of the single therapeutic doses administered in this research, hismanal ingestion is clearly preferable to benadryl ingestion for avoidance of subjective symptomatology (Tables E168 - E171).

There were no differences in physiological measures with either medication. Subjects were able to determine when they received a placebo and when they received benadryl; but were not able to identify hismanal receipt as an antihistamine. Subjects perceived their performance as lower post benadryl ingestion at one and three hours post ingestion as compared with both placebo and hismanal (Table E171).

Hismanal offers distinct advantages over the use of benadryl. Performance was not disrupted post hismanal ingestion; in fact, performance exceeded that of the placebo group on two occasions. On the two occasions that a subjective rating was lower for hismanal versus placebo, the rating was still higher for hismanal compared with benadryl. Based on this research, it is concluded that the use of hismanal is superior to benadryl when a high level of performance is required and when an individual desires to avoid negative subjective side effects. Hismanal appears to have excellent potential as a nonsedating antihistamine.

Identification of a medication that does not cause central nervous system deficits would allow military (or civilian) physicians to prescribe medications which would permit individuals to perform unhampered by either the symptoms of the illness or the side effects of the drug. For example, according to Whitehurst (1980) pilots will often ignore symptoms in order to be able to continue flying. Whitehurst (1980) also cautions against self medicating with over-the-counter pharmaceuticals and offers the guideline of restricting a pilot from flying when taking antihistamines and for 24 hours post final dosage or until all side effects have ceased, preferring to choose the longer of the two. If the risk of being "grounded" were lessened via use of an antihistamine which would not restrict flying, pilots (and other professionals) may be more inclined to seek the medical assistance they need.

Future Research Needs

In addition to the research needs mentioned above, for greater generalization of results, research needs to include women and subjects drawn from a more diverse population than healthy, young, college males. Individual differences in susceptibility may be of research interest. As tolerance to the central effects such as sedation may develop so that sedation is no longer troublesome (Nicholson, 1983, as reported by Brandon, 1985, and the therapeutic effects of hismanal require either a loading dose or several days for

symptom alleviation, research over an extended period of time is necessary. Drug concentration levels from blood samples that are drawn throughout the day should be included in the analysis. This research should also include therapeutic trials, performance data, and subjective ratings.

The addition of a control group which does not receive antihistamines but instead receives a placebo on all treatment days would serve to guard against subjects responding as if they had received an antihistamine. For example, as subjects are aware that they are going to receive all possible drug conditions, they may respond to symptom questionnaires as if they had received an antihistamine based on this knowledge rather than on their true perceptions/symptoms. The inclusion of a placebo-only control group would also permit a straight-forward analysis of possible learning effects. Coupled with the afore mentioned control for meals, a truer indication of circadian patterns would be revealed.

Performance tests which are used should be sensitive to the effects of drugs and should be validated. For example, although the Following Directions task was shown to be sensitive to the effects of benadryl, this was the first occasion of its use in a performance assessment of antihistamines. The Route Planning task did not show performance effects following antihistamine use, but it is unclear if this was due to the task requirements or to the software difficulties in recording data. Although laboratory techniques may be sensitive to the impairment effect of sedative drugs, validation of a laboratory test system with functional performance using drugs of known sedative potential is essential. As sustained attention and dual performance tasks appear to be more sensitive to the effects of drugs (as well as differentially affected by drugs), these tasks should be used and compared with simulations and/or actual performance.

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APPENDIX A

HUMAN USE

Complex Cognitive Performance and Antihistamine Use Consent Form Information Page

Virginia Polytechnic Institute and State University (VPI&SU)
Industrial Engineering and Operations Research Department
Human Factors Engineering Center
Whittemore Hall

The purpose of this research is to examine the effects of antihistamines on cognitive performance, visual-motor skills, and mood. Antihistamines can be purchased at drug stores and are typically used for relief of cold or allergy symptoms. This research is important to discern what types of jobs can be done safely and effectively while taking antihistamines. In this experiment you will be trained on computerized tests until your performance is at an even level. Training will take approximately 10 to 15 hours. The actual amount of time will vary for each individual. Four training sessions will be scheduled, each one for 3 hours. The tests will record your ability to do things such as visual rotation, time estimation, simple math, logical reasoning, planning, problem solving, making decisions, visual-motor tracking, and identify objects. You will also be asked to answer questions about how you feel, how you think you did on the tests, and whether you think you were given an antihistamine or a placebo. The data collected will be treated with anonymity.

After reaching an even level of performance, you will be scheduled for three testing sessions one week apart. Each session will start at 7:00 am and will last until 11:00 pm. At 7:00 am, you will be given either a placebo or an antihistamine tablet. The placebo has no active ingredients. You will be tested, using the tests described above at 8:00 am, 10:00 am, 12:00 pm, 2:00 pm, 4:00 pm, 6:00 pm, 8:00 pm, and 10:00 pm. You will be permitted to read, study, talk, or watch television between testing. Test sessions will be in the Human Factors Engineering Center, 5th floor, Whittemore Hall, VPI&SU.

Your medical records and a questionnaire will be reviewed by a licensed physician prior to being accepted for participation. You will not be allowed to participate if you have experienced adverse reactions to antihistamines, if you are currently taking prescribed or over-the-counter medications, if evidence of adverse medical conditions as judged by a physician are found, if you smoke, if you do not agree to refrain from caffeine consumption during test sessions, or if you have less than 20-20 corrected vision.

The antihistamines are being given to you at the same level that you would normally take them if you had a cold or had hay fever. They should not be harmful, but may make you feel drowsy or sluggish. Should difficulties occur during the experiment, a licensed physician will be on call at all times. You will not be allowed to participate if you have never used an antihistamine previously.

The research team includes:

1. Dr. H. L. Snyder, Faculty Member, IEOR Dept.
2. Valerie J. Berg Rice, Graduate Student, IEOR Dept.
3. Phillip Barkley, M. D., Medical Director, VPI&SU Health Services
4. Two graduate research assistants:
Gail Whitehouse, Graduate Student, IEOR Dept.
Charlotte Wagoner, Graduate Student, IEOR Dept.

INFORMED CONSENT

1. You are being asked to volunteer to be a subject in a research project whose purpose and description are contained in the document "Complex Cognitive Performance and Antihistamine Use," which you have already read.
2. There are some risks and discomforts to which you expose yourself in volunteering for this research.

The risks are:

- a. Adverse side effects may be experienced as a result of antihistamine use. The most common side effects that are reported include sedation, sleepiness, dizziness, disturbed coordination, and drying effects such as dry mouth. If you do experience side effects, they should all be gone by the end of the testing session.
- b. Other side effects which are reported less often, but which are noted on a typical "over-the-counter" preparation of an antihistamine are listed below. (Indications for use, contraindications, warnings, and precautions which are noted on over-the-counter preparations will be provided on request.) Please inform the investigators if you experience any of the side effects noted below.
 1. General: urticaria (hives), rash, anaphylactic shock (ineffective circulation due to hypersensitivity to specific substances), sensitivity to light (photosensitivity), excessive perspiration, chills, dryness of mouth, nose, and throat.
 2. Cardiovascular system: hypotension, headache, palpitations, fast heart beat (tachycardia), irregular heart beat (extrasystoles).
 3. Hematologic system: hemolytic anemia (reduction of the number of red corpuscles), thrombocytopenia (persistent decrease in the number of blood platelets), agranulocytosis (absence of granulocytes from the circulating blood).
 4. Nervous system: sedation, sleepiness, dizziness, disturbed coordination, fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paresthesia (a sensation of pricking, tingling, or creeping on the skin with no objective cause), blurred vision, diplopia (double vision), vertigo, tinnitus (a sensation of "ringing" in the

- ears), acute labyrinthitis (inflammation of the inner ear), neuritis, convulsions.
- 5. GI system: stomach discomfort (epigastric distress), lack of appetite (anorexia), nausea, vomiting, diarrhea, constipation.
- 6. GU system: urinary frequency, difficult urination, urinary retention, early menses.
- 7. Respiratory system: thickening of bronchial secretions, tightness of the chest and wheezing, nasal stuffiness.
- c. A member of the research team will ask you if you understand the above terms and explain any of them to you, should you not understand them.
- d. Both antihistamines that will be used have Federal Drug Administration (FDA) approval.

The following precautions will be taken:

- a. Your medical records and a questionnaire that you will fill out will be screened by a licensed physician.
- b. You will not be allowed to participate if you have experienced adverse reactions to antihistamines, if you are currently taking prescribed or over-the-counter medications, if evidence of adverse medical conditions as judged by a physician are found, if you smoke, if you do not agree to abstain from caffeine consumption during the study, or if you have less than 20-20 corrected vision.
- c. You will not be allowed to participate if you have never used an antihistamine previously.
- d. Should difficulties occur during the experiment, a physician will be on call at all times.
- e. A member of the research team will be present and available throughout the experimental sessions.
- f. Your heart rate will be monitored during the test sessions.
- g. The principal investigator should be contacted regarding any research related injuries. The principal investigator is Dr. H. L. Snyder. His office is in room 547 Whittemore Hall, VPISU, 231-7527.

The potential discomforts in this experiment are;

- a. The total length of the training sessions until you reach a level performance. Each training session will be scheduled for three hours. It is expected that the

total amount of time for training will take from 10 to 15 hours. The total amount of time may vary for each individual.

- b. The length of the three experimental sessions, each of which will last 16 hours. Testing will occur every two hours and you will be permitted to sleep, study and rest in between testing.
- c. The total estimated time requirement for participation in this study is 60 hours (10-15 hours of training and 3 testing sessions of 16 hours each). It is extremely important that you seriously consider your professional and/or academic requirements prior to agreeing to the time commitment required in this study.

3. The data gathered in this experiment will be treated with anonymity. Shortly after you have participated, your name will be separated from your data.

4. While there are no direct benefits to you from this research (other than payment), you may find the tasks interesting.

Your participation, along with that of the other volunteers, should make it possible to discover what types of mental and physical skills are affected by antihistamine use. It will also help to determine when or if antihistamines can be safely used by military and civilian pilots (or other persons operating critical machinery).

5. You should not volunteer for participation in this research if you are under 18 years old, if you are not in good health, if you are not male, if you smoke or use tobacco products, or if you have taken any drug, alcoholic beverage, or medication for 24 hours prior to and following test sessions. It is your responsibility to inform the experimenters of any additional condition which might interfere with your abilities. Such conditions would include inadequate sleep, hunger, hangover, headache, cold symptoms, depression, allergies, emotional upsets, visual impairment, seizures (fits), nerve or muscle disease, or other similar conditions.

6. You will be required to refrain from caffeine consumption throughout each day of the study.

7. The principal investigator, Dr. H. L. Snyder, of the research project and his associates will answer any questions that you may have about this project. You should not sign this consent form until you are satisfied that you understand all of the previous descriptions and conditions.

8. You should further be aware that you may contact Dr. Stout, Chairman of the University's Institutional Review Board, 339 Burruss Hall, VPISU, if you have questions or concerns about this experiment. His phone number is (703) 231-5281.

9. You should know that at any time you are free to withdraw from participation in this research program without penalty. If you should decide to withdraw while an experimental session is being run, you will be required to stay until the end of that session. This is for your protection, should you experience negative effects from the antihistamine.

If you decide to participate, you will be paid \$4.00 per hour for the time that you actually spend. If you complete the entire experiment, you will be paid \$5.00 per hour. Payment will be made shortly after you have finished your participation. You will not receive or become entitled to any compensation other than that mentioned.

10. You will receive a copy of this consent form.

11. The possibility exists that representatives of the United States Army Medical Research and Development Command may inspect the records of this research study, although your name will not be contained in those records.

12. Signature of the volunteer and date:

I have read and understand the scope of this research project and I have no other questions. I hereby give my consent to participate. I understand that I may stop participation if I choose to do so, however; I realize that once a testing session has begun, I will be required to remain for the entire testing session.

Signature (printed) _____

Signature (written) _____

Date _____

Subject's permanent address _____

13. Signature of a member of the research team and date:

Signature (printed) _____

Signature (written) _____

Date _____

14. Signature of witness, not a member of research team and date:

Signature (printed)_____

Signature (written)_____

Date_____

Additional Information (furnished on request)

Indications and Usage

1. antihistaminic: for allergic symptoms and conditions.
2. motion sickness: for active and prophylactic treatment of motion sickness.
3. antiparkinsonism: for adjunct treatment of parkinsonism.
4. nighttime sleep-aid.

Contraindications

1. use in the newborn or premature infant.
2. use in nursing mothers.
3. hypersensitivity to antihistamines of similar chemical structure.

Warnings:

Antihistamines should be used with considerable caution in patients/subjects with narrow-angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, symptomatic prostatic hypertrophy, or bladder-neck obstruction. In infants and children, especially, antihistamines in overdosage may cause hallucinations, convulsions, or death. As in adults, antihistamines may diminish mental alertness in children. In the young child, they may produce excitation. Antihistamines are more likely to cause dizziness, sedation and hypotension in elderly patients.

Precautions:

1. General: atropine like action and should be used with caution in patients/subjects with a history of bronchial asthma, increased intraocular pressure, hyperthyroidism, cardiovascular disease or hypertension.
2. Information for patients/subjects: this drug may cause drowsiness and has an additive effect with alcohol. They should be warned about engaging in activities requiring mental alertness such as driving a car or operating appliances, machinery, etc.
3. Drug interactions: has additive effects with alcohol and other central nervous system depressants (hypnotics, sedatives, tranquilizers, etc). Monoamine oxidase inhibitors prolong and intensify the anticholinergic (drying) effects of antihistamines.

4. Carcinogenesis, mutagenesis, impairment of fertility: Long term studies in animals to determine mutagenic and carcinogenic potential have not been performed. 5. Pregnancy: Reproduction studies have been performed in rats and rabbits at doses up to 5 times the human dose and have revealed no harm to the fetus. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Adverse reactions:

1. General: urticaria (hives), rash, anaphalactic shock, photosensitivity, excessive perspiration, chills, dryness of mouth, nose, and throat.
2. Cardiovascular: hypotension, headache, palpitations, tachycardia, extrasystoles.
3. Hematologic system: hemolytic anemia, thrombocytopenia, agranulocytosis.
4. Nervous system: sedation*, sleepiness*, dizziness*, disturbed coordination*, fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paresthesia, blurred vision, diplopia, vertigo, tinnitus, acute labyrinthitis, neuritis, convulsions.
5. GI system: epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation.
6. GU system: urinary frequency, difficult urination, urinary retention, early menses.
7. Respiratory system: thickening of bronchial secretions*, tightness of the chest and wheezing, nasal stuffiness.

*the most frequently reported adverse reactions.

APPENDIX B

INSTRUCTIONS

FOR

COMPLEX COGNITIVE ASSESSMENT BATTERY

(Analytical Assessments Center, 1988)

Welcome to this computer-administered test session.

You will be asked to perform a sequence of specially designed tasks. For each task, you will be given specific instructions and practice trials when appropriate. After reading the instructions and performing the practice trials, you may take a quiz on the task to be sure you understand how it is performed.

SPACE-BAR to continue; Esc to back up.

All of the tasks you will perform are timed. You should try to work as quickly as you can, but not so quickly that you make unnecessary mistakes. Accuracy, as well as speed, is very important for your overall score on the tasks. The points you receive should motivate you to do your best, but do not be too concerned about your scores. Your main objective is simply to perform the tasks accurately and quickly.

SPACE-BAR to continue; Esc to back up.

To perform the required tasks, you will need to press various keys on the keyboard. You do not have to know how to type, so typing speed will not affect your performance. On the next screen, a keyboard is displayed containing the keys you will need to press. These keys are displayed in the same general position as they appear on your keyboard.

SPACE-BAR to continue; Esc to back up.

	Esc	1	2	3									—	
		A		D	F	G	H	J	K	L		—		
				C		B	N							
F9				SPACE BAR										

To become familiar with the keys, press any of the keys on your keyboard that match the keys displayed. Be sure you know where the SPACE-BAR and Esc key are since these keys are used frequently. The —| key is called the "RETURN" or "ENTER" key on some keyboards. The key at the top right of the keyboard is called the "BACKSPACE" key.

APPENDIX B1

FOLLOWING DIRECTIONS INSTRUCTIONS

(Analytical Assessments Center, 1988)

- (1) Mark word 2 in line 3. Mark word 4
- (2) in line 1. Now unmark word 2 in
- (3) line 3.

Task. A trial begins with directions presented on the screen that identify specific words for you to mark and unmark. Your task is to follow the directions accurately and quickly when marking and unmarking the words identified in the directions. Each word to be marked or unmarked will be identified by a line and a word number. You should follow the directions in the order presented.

Press SPACE BAR to continue; ESC to back up.

- (1) Mark word 2 in line 3. Mark word 4
- (2) in line 1. Now unmark word 2 in
- (3) line 3.

Procedure. When you are told to mark or unmark a specific word, first use the UP, DOWN, LEFT, or RIGHT arrow keys to move the highlighted box to the specific word. Then press the SPACE-BAR to mark the word, which will underline the word. The SPACE-BAR is also used to unmark a marked word. To unmark a marked word, move the highlighted box to the specific word, and press the SPACE-BAR, which will remove the underline.

Press SPACE-BAR to continue; Esc to back up.

- (1) Mark word 2 in line 3. Mark word 4
- (2) in line 1. Now unmark word 2 in
- (3) line 3.

Procedure. Each word you are to mark or unmark will be identified by a line and word number. To find a given word, first locate the line and then count the words within the line. For example, word number 4 in line 2 of this screen is the word 'Now.' A single letter or number, e.g., 'X' or '6,' also counts as a word. Punctuation marks and line numbers within the parentheses do not count as words.

Press SPACE BAR to continue; Esc to back up

- (1) Mark word 2 in line 5. Mark word 4
- (2) in line 6. Now unmark word 2 in
- (3) line 5.

Example. In this example, you will be able to see how words are marked or unmarked. When you press the SPACE-BAR, the specified words will be marked or unmarked automatically according to the directions above. Press the SPACE-BAR now to see the example.

Press SPACE-BAR to continue; Esc to back up.

- (1) Mark word 6 in line X. Mark word Y
- (2) in line 3. Mark word X in
- (3) line Z. Now unmark word 6 of line X.

X = 2 Y = 3 Z = 1

Procedure. Some screens display number values like those at the bottom of this screen. Each value is identified by the letter X, Y, or Z. The number value may be either a 1, 2, 3, 4, or 5. For example, as shown below, the value of X is 3. You will need to refer to these values for marking or unmarking words.

Press SPACE-BAR to continue; Esc to back up.

- (1) Mark word 3 in line X.
- (2) Now mark word Y in line 5.
- (3) Now mark word 2 in line Z.
- (4) Now unmark word 6 of line X.

X = 2 Y = 4 Z = 1

Example. In this example, words will be marked or unmarked based on the values displayed at the bottom of the screen. When you press the SPACE-BAR, the specified words will be marked or unmarked automatically according to the directions above. Press the SPACE-BAR now to see the example.

Press SPACE-BAR to continue; Esc to back up.

- (1) Mark word 6 in line X. Mark word Y
- (2) in line 3. Mark word X in
- (3) line Z. Now unmark word 6 in line X.

X=2 Y=3 Z=1

Scoring. The more accurately you follow the directions, and the faster you complete them within the time limit, the more points you will receive. If you do not complete the directions before the trial ends, you will receive a partial score. If you complete the directions before the trial ends, simply wait until the displayed time reaches zero, which mean the trial is over. Your score will be displayed after each trial.

Press SPACE-BAR to continue; Esc to back up.

- (1) Mark word 6 in line X. Mark word Y
- (2) in line 3. Mark word X in
- (3) line Z. Now unmark word 6 of line X.

X=2 Y=3 Z=1









Practice. You now will be presented with x practice trials. Your performance in practice is not counted in the test score. As you practice, make sure you understand how the task is performed. Remember your objective is to follow the directions accurately and quickly in marking and unmarking the words identified in the directions.

Press SPACE-BAR to continue; Esc to back up.

APPENDIX B2









**ROUTE PLANNING
INSTRUCTIONS**

(Analytical Assessments Center, 1988)

A	B	C		E
	G	H	I	J
K		M	N	
	Q			T
U	V	W	X	









Task. A trial starts with a grid of squares displayed on the screen like the one above. Each square contains either a letter or a shaded block. When the trial begins, one letter is surrounded by a block. This letter is the starting position for the route you will plan. Another letter will be highlighted as the ending position. Your task is to plan and enter a route from the starting position to ending position.

SPACE-BAR to continue; Esc to back up.

A	B	C		E
	G	H	I	J
K		M	N	
	Q			T
U	V	W	X	









Task. Each move is made up of three squares; two are in the same direction and one square is in another direction. The path of each completed move looks like a capitol L. The two squares in the same direction make up the long bar of the L; the single square in the other direction makes up the shorter bar. You can start a move in any direction, but you must end on a letter. You may pass over a shaded block during a move, but cannot end a move on a shaded block.

SPACE-BAR to continue; Esc to back up.

A	B	C		E
	G	H	I	J
K		M	N	
	Q			T
U	V	W	X	









Procedure. When a trial begins, you enter a move by typing the letter you want to move to. Be sure the letter can be reached by the L-shaped move. For example, if the starting position is the letter **Q** and the first letter you want to move to in your route is **X**, you would type the letter **X**. Then type the next letter in your route, etc. When you have entered all the necessary letters for the complete route from the starting to the ending position, the trial will end.

SPACE-BAR to continue; Esc to back up.

A	B	C		E
	G	H	I	J
K		M	N	
	Q			T
U	V	W	X	










Procedure. When you begin a trial, the starting and ending positions are displayed. With each valid move, the letter of your new position is shown in a box. A 'beep' will sound if you try to move to a letter that cannot be reached in one move from your current position. You can move to a previous letter, one move at a time, by entering the previous letter. If you make a mistake when you enter a move, you may use the BACKSPACE key to erase the mistaken letter.

SPACE-BAR to continue; Esc to back up.

A	B	C		E
	G	H	I	J
K		M	N	
	Q			T
U	V	W	X	









Example. In this sample trial, you will be able to see how a number of moves are entered to form a route from the starting position (blocked letter) to the ending position (highlighted letter). Errors are purposely made during this example so that you can see how incorrect responses are noted and corrected.

Press SPACE-BAR to see sample trial.

A	B	C		E
	G	H	I	J
K		M	N	
				T
U	V	W	X	

Scoring. The fewer moves you make to reach the ending position, and the less time it takes you within the time limit, the more points you receive. If you do not reach the ending position before the trial ends, you will receive a partial score. Your score will be displayed at the end of each trial, along with one of the correct routes to the ending position.

SPACE-BAR to continue; Esc to back up.

A	B	C		E
	G	H	I	J
K		M	N	
	Q			T
U	V	W	X	

Practice. You now will be presented with 3 practice trials. Your performance in practice is not counted in the test score. As you practice, make sure you understand how the task is performed. Remember your objective is to plan and enter a route that will take you from the starting position to the ending position in the fewest possible moves.

SPACE-BAR to continue; Esc to back up.

ROUTE PLANNING QUIZ

(Analytical Assessments Center, 1988)

A quiz of 10 true or false questions will now be presented to test your understanding of how this task is performed. Read the first question and then press T for True or F for False. Your response will be displayed and a moment later the correct response will be presented. You may then press the SPACE-BAR to display the next question. Continue in this way until you have answered all 10 questions.

- 1) A trial begins with one letter surrounded by a block, and another letter highlighted.
- 2) The ending position is shown as a letter that is highlighted.
- 3) Each move travels through four squares of the grid.
- 4) The path of each completed move looks like a capital L.
- 5) You may end a move on a shaded block.
- 6) You may pass through a shaded block during a move.
- 7) You can return to a previous square, one move at a time, by entering the letter of the square.
- 8) You score less points for making the fewest moves in the shortest amount of time to reach the ending position.
- 9) You enter a move by typing in the letter of the square you want to move to.
- 10) If you enter a letter by mistake, you can press the BACKSPACE key to erase the letter.

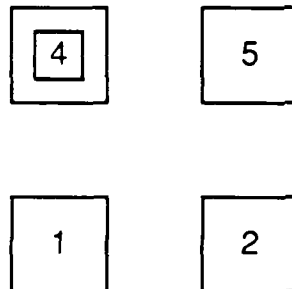
Scoring Key: 1) T 2) T 3) F 4) T 5) F
6) T 7) T 8) F 9) T 10) T

APPENDIX C

**INSTRUCTIONS FOR
THE
WALTER REED PERFORMANCE ASSESSMENT BATTERY**

APPENDIX C1**INSTRUCTIONS FOR
WILKINSON FOUR CHOICE REACTION TIME**

A red dot will appear in one of four boxes near the center of the screen. Each box corresponds to one of the 4 keys on the keypad labeled 1, 2, 4, or 5 as shown:

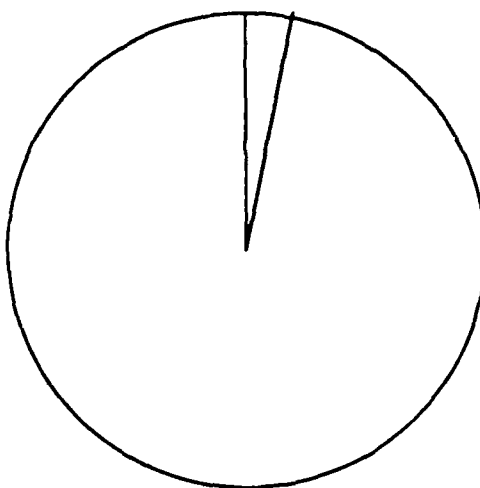


When the red dot appears you are to press the corresponding key as quickly as possible. The dot will then jump to a different (or the same) box and you are to press again, continuing to follow the dot as rapidly as you can.

Press space bar to continue.

APPENDIX C2

INSTRUCTIONS
FOR
INTERVAL PRODUCTION

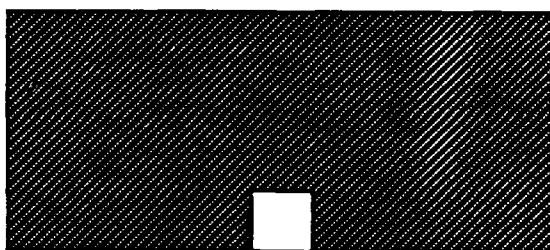


This task requires you to tap a key at regular one-second intervals. You are not to use a watch or clock, but to **ESTIMATE** each one-second period as accurately and as consistently as you can. If you are right handed, place your fingers comfortably on the lower row of keys labeled 'M' through '?' with your thumb against the front of the spacebar. If you are left handed, use the keys 'Z' through 'V'.

Tap only with your index finger, using a single brief 'down-up' movement. If you hold the key too long it will beep and you may have to repeat the test. Try a few practice taps now so you can get a feel for the correct force and duration to use. When done practicing, press the space bar, then tap once a second, as accurately and consistently as you can.

APPENDIX C3

INSTRUCTIONS
FOR
TIME WALL



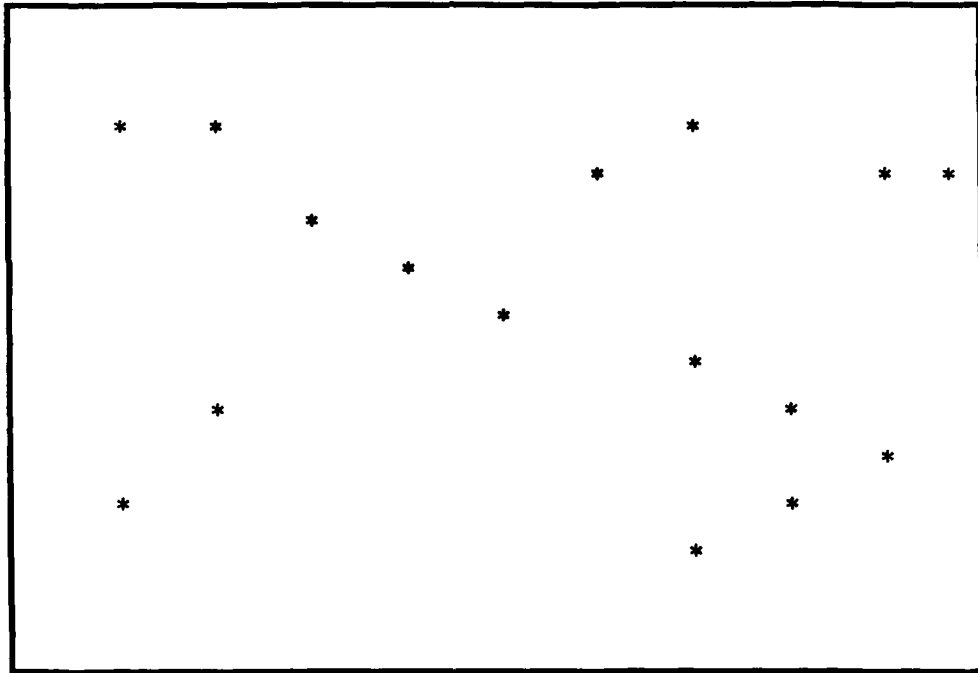
A small square will appear at the top of the screen and will move downward at a constant velocity toward a shielding barrier. When it reaches the barrier you will no longer see it. Your job is to estimate how long it will take the square to reach the small notch at the other side of the barrier.

Indicate the instant you think the square has reached the notch by pressing the 'M' key if you are right handed, or the 'V' key if you are left handed. When you do so the notch will briefly close, then the next trial will begin.

Press space bar to continue

APPENDIX C4

INSTRUCTIONS
FOR
PATTERN RECOGNITION



This task tests your ability to remember spatial relationships. A random pattern of *'s will be displayed on the screen for a very short time and the screen will go blank for several seconds. Then a second 'test' pattern will be displayed which will either be different or the same as the first pattern.

You must decide as quickly as possible which is true and enter 'S' if it is the same or 'D' if it is different. The first pattern will only be present for a very short time so look at it closely and try to remember it during the subsequent retention interval. As soon as you enter your answer another pattern will begin almost immediately.

Press space bar to continue

APPENDIX C5

INSTRUCTIONS
FOR
LOGICAL REASONING

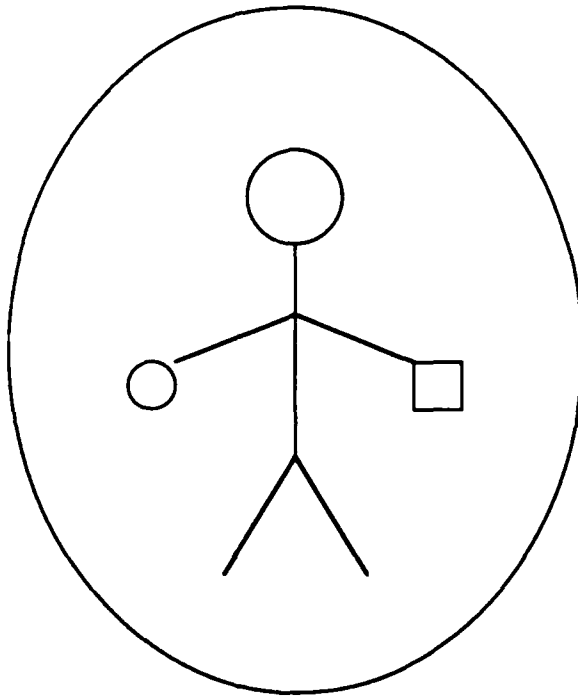
B precedes A

AB

This task will present a series of statements about the relationship between two letters. Each statement will then be followed by the two letters AB or BA. The first letter (left letter) is said to 'precede' the second letter (right letter), while the second letter is said to 'follow' the first.

You are to decide whether the statement correctly describes the order of the two letters or not. If it does, press the 'S' key for Same; If it does not, press the 'D' key for Different. Many people have difficulty at first with some of the relationships. It is extremely important that you understand all of them before the training sessions are complete.

Press the space bar to continue.

APPENDIX C6**INSTRUCTIONS
FOR
MANIKIN**

You will see a man inside either a circle or a square holding a circle in one hand, and a square in the other. You must decide as quickly as you can whether the matching shape is in his left or right hand and then press the left or right key accordingly.

Place your fingers on the bottom row of keys with your left index finger on 'V' and your right index finger on 'M'. Press only with one index finger (try now).

Press space bar to continue

APPENDIX C7

INSTRUCTIONS

FOR

SERIAL ADDITION/SUBTRACTION

In this task 2 digits will flash briefly on the screen in succession followed by either a plus or a minus sign. You are to add or subtract them accordingly and enter the last single digit of your answer. Thus 9, 8, +, would require you to add 9 and 8 and then enter 7 for 17, while 7, 4, -, would require you to subtract 4 from 7 and enter 3.

If subtraction yields a **NEGATIVE** number, you must automatically add 10 to it and enter the single positive digit that remains. Thus 3, 9, -, would require you to subtract 9 from 3 to get -6 and then add 10 to get the answer 4.

Use the numeric keypad, not the top row of keys. Place your thumb on zero and rest your first three fingers on the keys 4, 5, and 6. This requires minimum movement and will improve your speed. Return to this 'home row' after each response. Try not to look at your hand and back at the screen or you will miss some of the numbers and then make errors. Try to memorize the keys instead.

The numbers flash by very quickly so you will have to be attentive.

Press space bar to continue.

APPENDIX C8

INSTRUCTIONS

FOR

CODE SUBSTITUTION

You will see a code table of 9 letters/number pairs. Your job is to learn the code number for each letter, and to enter it from the keypad as soon as each probe letter appears.

A	S	D	F	G	H	J	K	L
1	2	3	4	5	6	7	8	9

probe letter: →

After a while the code table will disappear. Try to enter the correct code for each probe letter from memory. If you can't remember the code, press the 'H' key to see the table and then enter the code.

Correct 'memory' responses earn 2 points, 'lookup' responses earn 1 point. Errors cost 2 points. The maximum possible score is 81 points.

Press space bar to continue.

APPENDIX D

MEDICAL SCREENING

TELEPHONIC SCREENING:

Because of the nature of this research, I must ask you some medical questions before I can schedule you for a screening.

Yes No

- | | | |
|--------------------------|--------------------------|--|
| <input type="checkbox"/> | <input type="checkbox"/> | Participant is male, 18-40 years of age. |
| <input type="checkbox"/> | <input type="checkbox"/> | Do you have 20-20 corrected vision? |
| <input type="checkbox"/> | <input type="checkbox"/> | Are you currently using an over-the-counter medication (purchased at the drug store) or prescribed medication on a regular basis? |
| <input type="checkbox"/> | <input type="checkbox"/> | Do you think you will need to use an over-the-counter (purchased at the drug store) or prescribed medication during this study? You <u>could</u> be involved for up to two months. |
| <input type="checkbox"/> | <input type="checkbox"/> | Do you agree not to use alcohol for 24 hours prior to laboratory test sessions? |
| <input type="checkbox"/> | <input type="checkbox"/> | Do you use tobacco (smoke cigarettes, chew tobacco, use snuff, etc.)? |
| <input type="checkbox"/> | <input type="checkbox"/> | Do you agree to not use caffeine during test sessions (caffeinated beverages, chocolate). |
| <input type="checkbox"/> | <input type="checkbox"/> | Do you agree not to use any psychoactive drug (such as marijuana) for 2 weeks prior to and throughout the study? |
| <input type="checkbox"/> | <input type="checkbox"/> | Have you ever used an antihistamine? |
| <input type="checkbox"/> | <input type="checkbox"/> | Have you ever experienced an adverse reaction to an antihistamine (such as hives, skin rash, asthmatic reaction)? |
| <input type="checkbox"/> | <input type="checkbox"/> | To the best of your knowledge, do you have any allergies to antihistamines? |
| <input type="checkbox"/> | <input type="checkbox"/> | Have you ever had: |
| | | <input type="checkbox"/> glaucoma |
| | | <input type="checkbox"/> asthma |
| | | <input type="checkbox"/> seizure disorder |
| | | <input type="checkbox"/> urinary or prostrate problems |
| | | <input type="checkbox"/> cardiovascular disease (including arhythmias) |
| | | <input type="checkbox"/> hypertension |
| | | <input type="checkbox"/> thyroid disease |

_____ stomach problems (colitis, ulcers)
 _____ cancer
 _____ nervous or psychiatric problems
 _____ recent infectious illness (colds, flu,
 mononucleosis)

MEDICAL QUESTIONNAIRE

Subject: _____
 age: _____
 height: _____
 weight: _____
 heart rate: _____

- | | | | |
|-------|-------|-----|--|
| _____ | _____ | 1. | In the past year has there been any change in your vision? |
| _____ | _____ | 2. | Has a doctor said you have glaucoma? |
| _____ | _____ | 3. | Do you have pain within the eyes? |
| _____ | _____ | 4. | Do you have frequent, severe, or sick (migraine) headaches? |
| _____ | _____ | 5. | Have you had a hearing loss in the last six months that is still present? |
| _____ | _____ | 6. | Do you have buzzing or ringing in the ears? |
| _____ | _____ | 7. | Have you ever had epilepsy, seizures, or convulsions? |
| _____ | _____ | 8. | Is your nose stuffy or running almost every day? |
| _____ | _____ | 9. | Do you have hay fever? |
| _____ | _____ | 10. | Have you ever taken allergy shots? |
| _____ | _____ | 11. | Do you have a cough or raise phlegm? |
| _____ | _____ | 12. | Have you had sinusitis, asthma, bronchitis, emphysema, or pneumonia? |
| _____ | _____ | 13. | Do you become short of breath after climbing one flight of stairs? |
| _____ | _____ | 14. | Has a doctor said that you had high blood pressure? |
| _____ | _____ | 15. | Have you ever been told that you have hypertension? |
| _____ | _____ | 16. | Has a doctor said that you had a heart murmur? |
| _____ | _____ | 17. | Have you ever had a heart attack or rheumatic fever? |
| _____ | _____ | 18. | Have you had racing or thumping of the heart? |
| _____ | _____ | 19. | Have you had any form of heart disease? |
| _____ | _____ | 20. | Do you have heartburn, indigestion, or pain in your stomach? |
| _____ | _____ | 21. | Has a doctor told you that you had a stomach or duodenal ulcer? |
| _____ | _____ | 22. | Has a doctor told you that you had colon or bowel disease (such as colitis)? |
| _____ | _____ | 23. | Have you ever had chronic diarrhea? |
| _____ | _____ | 24. | Has a doctor told you that you had liver disease (such as hepatitis or cirrhosis)? |
| _____ | _____ | 25. | Do you have to get up from sleep to urinate (pass your water)? |
| _____ | _____ | 26. | Do you have any burning or pain when urinating (passing water)? |
| _____ | _____ | 27. | Have you ever had a kidney or bladder infection? |
| _____ | _____ | 28. | Do you have a slow or small stream when urinating (passing water)? |
| _____ | _____ | 29. | Have you ever had prostatitis? |
| _____ | _____ | 30. | Has a doctor told you that you had gout? |
| _____ | _____ | 31. | Have you had any arthritis or rheumatism of the joints? |

- ____ 32. Have you had any stiffness in your joints that lasted more than thirty minutes?
 ____ 33. Has a doctor told you that you have diabetes (sugar)?
 ____ 34. Has a doctor told you that you have thyroid disease or a goiter?
 ____ 35. Have you ever been told you have elevated or high blood cholesterol or blood lipids?
 ____ 36. Have you ever been told that you have anemia, hepatitis, or a blood disease?
 ____ 37. Has the doctor ever said you had cancer or a tumor?
 ____ 38. Have you ever been told that you have a nervous or mental disease?
 ____ 39. Have you had problems with depression?
 ____ 40. Have you ever had mononucleosis or Epstein Barr disease?
 ____ 41. Have you ever smoked cigarettes? If yes, how many packs per day?
 ____ How many years did you smoke? ____
 ____ 42. Have you sometimes, in the past year, gotten drunk on working days?
 ____ 43. Is anyone close to you concerned about your drinking?
 ____ 44. Have you had problems with insomnia?
 ____ 45. Have you had problems with dizziness or fainting?
 ____ 46. Have been sick (such as an infection like the flu or a cold) within the last month?

List all the medications that you regularly take. Please include aspirin, hormones, and decongestants.

What medications are you allergic to (cannot take)?

APPENDIX E

**ANALYSIS OF VARIANCE, NEWMAN-KEULS,
PEARSON PRODUCT-MOMENT CORRELATION,
SPEARMAN RANK CORRELATION
AND CHI-SQUARE TABLES**

TABLE E1

Following Directions Task Significant Results

Dependent Measure	Difficulty Level	p	Effect
Score	Easy	0.0480	Time
	Medium	---	---
	Hard	0.0001	Time
Total time per task	Easy	0.0349	Time
	Medium	---	---
	Hard	0.0001	Time
Percent total hits	Easy	0.0228	Time
	Medium	0.0345	Time x drug
	Hard	0.0001	Time
		0.0490	Time x drug
Mean time to mark words	Easy	0.0011	Time
	Medium	0.0003	Time
	Hard	0.0001	Time

TABLE E2

Analysis of Variance Summary Table for Following Directions Task - Score - Easy

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	403285.1413		
<u>Within Subjects</u>				
Time (T)	7	96333.5134	2.08	0.0480
S x T	189	46406.5560		
Drug (D)	2	105427.7059	0.94	0.3968
S x D	54	112133.6581		
T x D	14	18280.7344	0.35	0.9870
S x T x D	374*	52587.8684		

* four degrees of freedom lost due to missing data

TABLE E3

Newman-Keuls Results for Following Directions Task - Score Easy - Time of Day

Time	Mean	Group
8:00 am	1544.38	A
10:00 pm	1542.32	A
12:00 pm	1534.92	A
6:00 pm	1533.37	A
2:00 pm	1519.07	A
10:00 am	1516.81	A
4:00 pm	1486.79	A
8:00 am	1445.22	A

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E4

Analysis of Variance Summary Table for Following Directions Task - Score - Medium

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	1069731.6911		
<u>Within Subjects</u>				
Time (T)	7	58321.7748	0.88	0.5253
S x T	189	66463.0816		
Drug (D)	2	8161.6233	0.06	0.9391
S x D	54	129738.4198		
T x D	14	68964.1817	0.98	0.4768
S x T x D	374*	70626.4342		

* four degrees of freedom lost due to missing data

TABLE E5

Analysis of Variance Summary Table for Following Directions Task - Score - Hard

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	2013904.9238		
<u>Within Subjects</u>				
Time (T)	7	531235.6338	7.57	0.0001
S x T	189	70135.2246		
Drug (D)	2	256853.3221	0.71	0.4971
S x D	54	362774.9736		
T x D	14	66127.9450	0.95	0.5092
S x T x D	374*	69908.7675		

* four degrees of freedom lost due to missing data

TABLE E6

Newman-Keuls Results for Following Directions Task - Score - Hard - Time of Day

Time	Mean	Group
10:00 pm	1605.93	A
8:00 pm	1582.95	A
6:00 pm	1560.76	A B
4:00 pm	1530.63	A B C
2:00 pm	1510.58	A B C
12:00 pm	1466.17	B C D
10:00 am	1426.85	C D
8:00 am	1375.99	D

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E7

Analysis of Variance Summary Table for Following Directions Task - Total Time - Easy

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	3013.2746		
<u>Within Subjects</u>				
Time (T)	7	648.1849	2.21	0.0349
S x T	189	292.7577		
Drug (D)	2	690.0587	0.94	0.3961
S x D	54	732.4653		
T x D	14	117.9786	0.35	0.9870
S x T x D	374*	340.1278		

* four degrees of freedom lost due to missing data

TABLE E8

Newman-Keuls Results for Following Directions Task - Total Time Easy - Time of Day

Time	Mean, Seconds	Group
8:00 am	50.727	A
4:00 pm	46.957	A B
10:00 am	45.197	A B
2:00 pm	44.368	A B
12:00 pm	43.410	A B
6:00 pm	43.401	A B
8:00 pm	42.652	B
10:00 pm	42.462	B

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E9

Analysis of Variance Summary Table for Following Directions Task - Total Time - Medium

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	3147.8803		
<u>Within Subjects</u>				
Time (T)	7	169.6496	1.02	0.4218
S x T	189	167.0828		
Drug (D)	2	4.7234	0.01	0.9866
S x D	54	348.7666		
T x D	14	161.0111	0.88	0.5796
S x T x D	374*	182.6872		

* four degrees of freedom lost due to missing data

TABLE E10

Analysis of Variance Summary Table for Following Directions Task - Total Time - Hard

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	2955.4797		
<u>Within Subjects</u>				
Time (T)	7	698.3674	6.77	0.0001
S x T	189	103.1529		
Drug (D)	2	361.0767	0.72	0.4927
S x D	54	503.5139		
T x D	14	75.5900	0.84	0.6205
S x T x D	378*	89.5274		

* four degrees of freedom lost due to missing data

TABLE E11

Newman-Keuls Results for Following Directions Task - Total Time Hard - Time of Day

Time	Mean	Group
8:00 am	79.511	A
10:00 am	78.010	A B
12:00 pm	76.755	A B C
2:00 pm	75.233	B C D
4:00 pm	74.468	B C D
6:00 pm	72.914	C D
8:00 pm	72.371	D
10:00 pm	71.239	D

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E12

Analysis of Variance Summary Table for Following Directions Task - Percent Total Hits - Easy

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (s)	27	196.3803		
<u>Within Subjects</u>				
Time (T)	7	103.8613	2.39	0.0228
S x T	189	43.3885		
Drug (D)	2	40.4559	0.53	0.5944
S x D	54	77.0101		
T x D	14	27.1925	0.66	0.8097
S x T x D	374*	40.9664		

* four degrees of freedom lost due to missing data

TABLE E13

Newman-Keuls Results for Following Directions Task - Percent Total Hits Easy - Time of Day

Time	Mean	Group
8:00 pm	99.338	A
10:00 am	98.342	A B
12:00 pm	98.297	A B
10:00 pm	98.294	A B
6:00 pm	97.761	A B
4:00 pm	97.612	A B
2:00 pm	97.406	A B
8:00 am	95.495	B

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E14

Analysis of Variance Summary Table for Following Directions - Percent Total Hits - Medium

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	319.0594		
<u>Within Subjects</u>				
Time (T)	7	38.8280	1.13	0.3451
S x T	189	34.3181		
Drug (D)	2	189.4578	1.60	0.2121
S x D	54	118.6991		
T x D	14	68.8220	1.82	0.0345
S x T x D	374*	37.8703		

* four degrees of freedom lost due to missing data

TABLE E15

Simple-Effect F-Tests for Drug at Each Time of Day: Following Directions Task - Percent Total Hits Medium

	df	MS	F	p
S x T x D	374*	73.1697		
8:00 am	2	45.6429	0.6238	0.536455
10:00 am	2	0.8550	0.0117	0.998311
12:00 pm	2	9.1081	0.2612	0.770304
2:00 pm	2	96.5467	1.3195	0.268497
4:00 pm	2	325.4757	4.4482	0.012321
6:00 pm	2	94.0000	1.2847	0.277939
8:00 pm	2	70.2758	0.9605	0.383653
10:00 pm	2	28.9301	0.3954	0.673702

* four degrees of freedom lost due to missing data

TABLE E16

Studentized Newman-Keuls Results for Following Directions Task - Percent Total Hits -
Medium - Drug at 4:00 pm

Drug	Grouping	Mean	N
Benadryl	A	98.4214	28
Hismanal	A B	96.8857	28
Placebo	B	91.9000	28

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E17

Extreme Scores Affecting Following Directions Task - Percent Total Hits - Medium

	Extremes	
	Lowest	Highest
Subject 27	16.7*	100
	100	100
	100	100
	100	100
	100	100
Subject 23	14.3*	60.0
	50.0	66.7
	50.0	100
	60.0	100
	66.7	100

*mean score achieved post ingestion of placebo, 4:00 pm session.

TABLE E18

Analysis of Variance Summary Table for Following Directions - Percent Total Hits - Hard

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	1213.4258		
<u>Within Subjects</u>				
Time (T)	7	405.6983	5.38	0.0001
S x T	189	75.3822		
Drug (D)	2	45.7481	0.17	0.8426
S x D	54	266.3063		
T x D	14	126.1139	1.72	0.0490
S x T x D	374*	73.1697		

* four degrees of freedom lost due to missing data

TABLE E19

Newman-Keuls Results for Following Directions Task - Percent Total Hits - Hard - Time of Day

Time	Mean	Group
8:00 pm	95.233	A
2:00 pm	94.773	A
4:00 pm	94.593	A
10:00 pm	94.042	A
6:00 pm	93.493	A
12:00 pm	92.934	A
10:00 am	91.550	A
8:00 am	88.542	B

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E20

Simple-Effect F-Tests for Drugs at the Eight Times of Day: Following Directions Task -
Percent Total Hits - Hard

	DF	MS	F	p
S x T x D	374*	73.1697		
8:00 am	2	376.0793	5.1398	.006275
10:00 am	2	204.2481	2.7914	.062625
12:00 pm	2	101.9980	1.3940	.249350
2:00 pm	2	82.6948	1.1288	.324500
4:00 pm	2	78.9068	1.0784	.341300
6:00 pm	2	0.7243	0.0099	.999000
8:00 pm	2	0.5402	0.2701	.763450
10:00 pm	2	1.7557	0.8778	.416500

* four degrees of freedom lost due to missing data

TABLE E21

Newman-Keuls Following Directions Task Percent Total Hits - Hard - Drug Effect
at 8:00 am

Drug	Grouping	Mean	N
Placebo	A	90.9286	28
Hismanal	A	90.3750	28
Benadryl	B	84.3221	28

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E22

Analysis of Variance Summary Table for Following Directions Task - Mean Time - Easy

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	16.6502		
<u>Within Subjects</u>				
Time (T)	7	15.4759	3.61	0.0011
S x T	189	4.2862		
Drug (D)	2	10.1712	1.21	0.3061
S x D	54	8.4053		
T x D	14	5.7379	1.19	0.2819
S x T x D	374*	4.8300		

* four degrees of freedom lost due to missing data

TABLE E23

Newman-Keuls Results for Following Directions Task - Mean Time Easy - Time of Day

Time	Mean	Group
8:00 am	4.5171	A
10:00 am	3.8671	B
4:00 pm	3.8580	B
12:00 pm	3.7429	B
2:00 pm	3.7287	B
8:00 pm	3.6518	B
10:00 pm	3.6488	B
6:00 pm	3.6229	B

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E24

Analysis of Variance Summary Table for Following Directions Task - Mean Time -
Medium

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject	27	9.7287		
<u>Within Subjects</u>				
Time	7	1.5462	4.08	0.0003
S x T	189	0.3788		
Drug	2	0.3808	0.31	0.7347
S x D	54	1.2284		
T x D	14	0.5940	1.58	0.0830
S x T x D	374*	0.3767		

* four degrees of freedom lost due to missing data

TABLE E25

Newman-Keuls Results for Following Directions Task - Mean Time Medium -
Time of Day

Time	Mean	Group
8:00 am	3.8929	A
10:00 am	3.7341	A B
6:00 pm	3.6677	A B
4:00 pm	3.6629	A B
12:00 pm	3.6057	B
2:00 pm	3.5586	B
8:00 pm	3.4926	B
10:00 pm	3.4808	B

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E26

Analysis of Variance Summary Table for Following Directions Task - Mean Time - Hard

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	33.5298		
<u>Within Subjects</u>				
Time (T)	7	7.5342	10.48	0.0001
S x T	189	0.7192		
Drug (D)	2	1.0227	0.23	0.7961
S x D	54	4.4664		
T x D	14	0.8222	1.05	0.4013
S x T x D	374*	0.7820		

* four degrees of freedom lost due to missing data

TABLE E27

Newman-Keuls Results for Following Directions Task - Mean Time Hard - Time of Day

Time	Mean	Group
8:00 am	6.2406	A
10:00 am	5.7729	B
2:00 pm	5.6915	B C
12:00 pm	5.6902	B C
4:00 pm	5.6096	B C D
6:00 pm	5.4682	B C D
10:00 pm	5.3364	C D
8:00 pm	5.2911	D

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E28

Spearman Correlation Coefficients between Following Directions Score and Subjects Experience

	Rho	p
Video Games Score	0.3451	0.0721
Computer Programming Score	0.5070	0.0059
Word Processing Score	0.2090	0.2858
Hours/week Computer Time Score	0.1474	0.4540
Chess Experience Score	0.2839	0.1432
Post High School Math Classes Score	-0.0294	0.8821

TABLE E29

Route Planning Significant Results

	Level	p	Source
Score	Easy	---	---
	Medium	---	---
	Hard	0.0359	Time
Total time per task	Easy	---	---
	Medium	---	---
	Hard	---	---
Minimum valid moves	Easy	0.0296	Time
	Medium	---	---
	Hard	---	---
Number of errors	Easy	0.0197	Time
	Medium	---	---
	Hard	---	---
Number of reversals	Easy	---	---
	Medium	---	---
	Hard	0.0193	Time
Mean time per move	Easy	---	---
	Medium	---	---
	Hard	---	---

TABLE E30

Analysis of Variance Summary Table for Route Planning Task - Score - Easy

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	314814.9362		
<u>Within Subjects</u>				
Time (T)	7	76379.4471	1.43	0.1936
S x T	189	53242.3858		
Drug (D)	2	27588.3748	0.41	0.6673
S x D	54	67689.7375		
T x D	14	67179.3597	1.06	0.3916
S x T x D	374*	63292.2104		

* four degrees of freedom lost due to missing data

TABLE E31

Analysis of Variance Summary Table for Route Planning Task - Score - Medium

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	286404.7111		
<u>Within Subjects</u>				
Time (T)	7	90917.1841	1.76	0.0982
S x T	189	51742.6289		
Drug (D)	2	63013.3171	1.30	0.2808
S x D	54	48455.7784		
T x D	14	31604.7467	0.55	0.9026
S x T x D	374*	586616.2946		

* four degrees of freedom lost due to missing data

TABLE E32

Analysis of Variance Summary Table for Route Planning Task - Score - Hard

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	304345.9675		
<u>Within Subjects</u>				
Time (T)	7	131373.6481	2.20	0.0359
S x T	189	59685.8313		
Drug (D)	2	33076.7162	0.45	0.6403
S x D	54	73574.4698		
T x D	14	49257.8037	0.76	0.7106
S x T x D	374*	64651.6629		

* four degrees of freedom lost due to missing data

TABLE E33

Newman-Keuls Results for Route Planning - Score Hard - Time of Day

Time	Root Mean Square	Group
6:00 pm	1294.75	A
8:00 pm	1268.54	A
12:00 pm	1247.36	A
2:00 pm	1208.19	A
4:00 pm	1206.65	A
8:00 am	1206.04	A
10:00 am	1191.33	A
10:00 pm	1185.21	A

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE 34

Analysis of Variance Summary Table for Route Planning Task - Total Time - Easy

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject	27	1478.3168		
<u>Within Subjects</u>				
Time (T)	7	320.6170	1.34	0.2333
S x T	189	239.1768		
Drug (D)	2	83.6496	0.36	0.6993
S x D	54	232.2039		
T x D	14	157.4727	0.57	0.8849
S x T x D	374*	274.1120		

* four degrees of freedom lost due to missing data

TABLE E35

Analysis of Variance Summary Table for Route Planning Task - Total Time - Medium

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	1658.1877		
<u>Within Subjects</u>				
Time (T)	7	364.8981	1.24	0.2818
S x T	189	293.8324		
Drug (D)	2	350.2185	1.30	0.2800
S x D	54	268.6741		
T x D	14	303.5676	1.14	0.3209
S x T x D	374*	266.3012		

* four degrees of freedom lost due to missing data

TABLE E36

Analysis of Variance Summary Table for Route Planning Task - Total Time - Hard

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	1499.9728		
<u>Within Subjects</u>				
Time (T)	7	367.3490	1.14	0.3385
S x T	189	321.6349		
Drug (D)	2	109.1277	0.32	0.7249
S x D	54	337.2350		
T x D	14	91.7884	0.32	0.9917
S x T x D	374*	288.8519		

* four degrees of freedom lost due to missing data

TABLE E37

Analysis of Variance Summary Table for Route Planning Task - Minimum Valid Moves - Easy

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	0.3704		
<u>Within Subjects</u>				
Time (T)	7	0.3912	2.28	0.0296
S x T	189	0.1713		
Drug (D)	2	0.0276	0.28	0.7563
S x D	54	0.0983		
T x D	14	0.1186	0.87	0.5930
S x T x D	374*	0.1365		

* four degrees of freedom lost due to missing data

TABLE E38

Newman Keuls Results for Route Planning - Minimum Valid Moves Easy - Time of Day

Time	Mean	Group
6:00 pm	1.1199	A
8:00 am	1.0781	A
10:00 am	1.0192	A
12:00 pm	0.9758	A
2:00 pm	0.9746	A
4:00 pm	0.9449	A
10:00 pm	0.9436	A
8:00 pm	0.9343	A

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E39

Analysis of Variance Summary Table for Route Planning Task - Minimum Valid Moves - Medium

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	0.4014		
<u>Within Subjects</u>				
Time (T)	7	0.2373	1.13	0.3433
S x T	189	0.2092		
Drug (D)	2	0.0287	0.92	0.4066
S x D	54	0.3139		
T x D	14	0.2628	1.22	0.2554
S x T x D	374*	0.2149		

* four degrees of freedom lost due to missing data

TABLE E40

Analysis of Variance Summary Table for Route Planning Task - Minimum Valid Moves - Hard

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	0.1827		
<u>Within Subjects</u>				
Time (T)	7	0.1872	1.33	0.2399
S x T	189	0.1412		
Drug (D)	2	0.0759	0.45	0.6404
S x D	54	0.1690		
T x D	14	0.0687	0.44	0.9615
S x T x D	374*	0.1567		

* four degrees of freedom lost due to missing data

TABLE E41

Analysis of Variance Summary Table for Route Planning Task - Number of Errors - Easy

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	3.4384		
<u>Within Subjects</u>				
Time (T)	7	0.0897	0.36	0.9260
S x T	189	0.2512		
Drug (D)	2	0.1325	0.17	0.8474
S x D	54	0.7977		
T x D	14	0.3852	1.10	0.3591
S x T x D	374*	0.3514		

* four degrees of freedom lost due to missing data

TABLE E42

Analysis of Variance Summary Table for Route Planning Task - Number Errors - Medium

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	1.8410		
<u>Within Subjects</u>				
Time (T)	7	0.2245	0.73	0.6417
S x T	189	0.3091		
Drug (D)	2	0.0430	0.01	0.9892
S x D	54	0.3950		
T x D	14	0.1603	0.59	0.8764
S x T x D	374*	0.2737		

* four degrees of freedom lost due to missing data

TABLE E43

Analysis of Variance Summary Table for Route Planning Task - Number Errors - Hard

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	2.9445		
<u>Within Subjects</u>				
Time (T)	7	0.3771	0.93	0.4847
S x T	189	0.4056		
Drug (D)	2	0.0556	0.09	0.9124
S x D	54	0.6049		
T x D	14	0.2356	0.58	0.8844
S x T x D	374*	0.4097		

* four degrees of freedom lost due to missing data

TABLE E44

Analysis of Variance Summary Table for Route Planning Task - Number of Reversals - Easy

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	3.5309		
<u>Within Subjects</u>				
Time (T)	7	1.6189	2.46	0.0197
S x T	189	0.6593		
Drug (D)	2	0.8605	2.00	0.1457
S x D	54	0.4311		
T x D	14	1.1628	1.42	0.1427
S x T x D	378	0.8217		

* four degrees of freedom lost due to missing data

TABLE E45

Newman-Keuls Results for Route Planning - Number of Reversals Easy - Time of Day

Time	Mean	Group
10:00 pm	0.4405	A
4:00 pm	0.4048	A
8:00 pm	0.4048	A
8:00 am	0.3907	A
10:00 am	0.2535	A
2:00 pm	0.1799	A
6:00 pm	0.1310	A
12:00 pm	0.0974	A

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E46

Analysis of Variance Summary Table for Route Planning Task - Number Reversals -
Medium

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	4.9290		
<u>Within Subjects</u>				
Time (S)	7	0.1461	0.24	0.9744
S x T	189	0.6054		
Drug (D)	2	1.3590	1.63	0.2059
S x D	54	0.8350		
T x D	14	0.8832	1.05	0.4040
S x T x D	374*	0.8423		

* four degrees of freedom lost due to missing data

TABLE E47

Analysis of Variance Summary Table for Route Planning Task - Number Reversals - Hard

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	5.5332		
<u>Within Subjects</u>				
Time (T)	7	2.1344	2.46	0.0193
S x T	189	0.8662		
Drug (D)	2	0.9196	1.15	0.3236
S x D	54	0.7981		
T x D	14	0.7480	0.90	0.5610
S x T x D	374*	0.8329		

* four degrees of freedom lost due to missing data

TABLE E48

Newman Keuls Results for Route Planning - Number of Reversals Hard - Time of Day

Time	Mean	Group
10:00 pm	0.5714	A
4:00 pm	0.5476	A
12:00 pm	0.3611	A B
8:00 pm	0.3452	A B
10:00 am	0.2526	A B
8:00 am	0.2429	A B
2:00 pm	0.2160	A B
6:00 pm	0.1190	B

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E49

Analysis of Variance Summary Table for Route Planning Task - Mean Time - Easy

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	135.8872		
<u>Within Subjects</u>				
Time (T)	7	41.5278	1.33	0.2361
S x T	189	31.1215		
Drug (D)	2	8.5134	0.37	0.6895
S x D	54	22.7419		
T x D	14	27.3494	1.01	0.4413
S x T x D	374*	27.0548		

* four degrees of freedom lost due to missing data

TABLE E50

Analysis of Variance Summary Table for Route Planning Task - Mean Time - Medium

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	168.6698		
<u>Within Subjects</u>				
Time (T)	7	67.0505	1.63	0.1278
S x T	189	41.0135		
Drug (D)	2	44.3057	0.85	0.4351
S x D	54	52.4248		
T x D	14	37.0183	1.10	0.3551
S x T x D	374*	33.6277		

* four degrees of freedom lost due to missing data

TABLE E51

Analysis of Variance Summary Table for Route Planning Task - Mean Time - Hard

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	113.0185		
<u>Within Subjects</u>				
Time (T)	7	27.7585	1.07	0.3840
S x T	189	25.9275		
Drug (D)	2	32.3304	1.37	0.2637
S x D	54	23.6624		
T x D	14	16.9538	0.69	0.7876
S x T x D	374*	24.6004		

* four degrees of freedom lost due to missing data

TABLE E52

Spearman Correlation Coefficients between Route Planning Score and Subjects Experience

	Rho	p
Video Games Score	0.3955	0.0372
Computer Programming Score	0.5569	0.0021
Word Processing Score	0.2971	0.1247
Hours/week Computer Time Score	0.1726	0.3799
Chess Experience Score	0.4004	0.0347
Post High School Math Classes Score	-0.0196	0.9212

TABLE E53

Sutcliffe Chi-Square Results for Route Planning Task, Solution Achieved: Drug x Difficulty Level

Source	Chi-Square	df	p
Drug	1.8571	2	> .05
Difficulty Level	0	0	N/A
Drug x Difficulty level	<u>0.2846</u>	<u>4</u>	>.05
Total	2.1417	6	> .05

TABLE E54

Analysis of Variance Summary Table for Wilkinson Reaction Time - Number of Errors

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	3.3022		
<u>Within Subjects</u>				
Time (T)	7	0.6037	1.09	0.3720
S x T	189	0.5544		
Drug (D)	2	0.5045	0.79	0.4577
S x D	54	0.6362		
T x D	14	0.2298	0.58	0.8807
S x T x D	373*	0.3961		

* Five degrees of freedom lost due to missing data

TABLE E55

Analysis of Variance Summary Table for Wilkinson Reaction Time - Mean Reaction Time

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	0.0945		
<u>Within Subjects</u>				
Time (T)	7	0.0001	1.35	0.2306
S x T	189	0.0022		
Drug (D)	2	0.0020	0.18	0.8320
S x D	54	0.0109		
T x D	14	0.0011	0.62	0.8469
S x T x D	373*	0.0017		

* Five degrees of freedom lost due to missing data

TABLE E56

Spearman Correlation Coefficients between Wilkinson Reaction Time and Subjects Experience

	Rho	p
Video Games		
Mean Reaction Time	-0.5203	0.0045
Errors	0.5551	0.0022
Computer Programming		
Mean Reaction Time	-0.3173	0.0999
Errors	0.1722	0.3810
Word Processing		
Mean Reaction Time	-0.2004	0.3067
Errors	0.4159	0.0277
Hours/week Computer Time		
Mean Reaction Time	0.2391	0.2204
Errors	-0.2184	0.2642
Chess Experience		
Mean Reaction Time	-0.1633	0.4064
Errors	0.2395	0.2197
Post High School Math Classes		
Mean Reaction Time	0.2506	0.1983
Errors	0.0023	0.9908

TABLE E57

Analysis of Variance Summary Table for Interval Production - Mean Reaction Time

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	3.3045		
<u>Within Subjects</u>				
Time (T)	7	0.3402	0.80	0.5890
S x T	189	0.4258		
Drug (D)	2	0.4912	0.28	0.7594
S x D	54	1.7754		
T x D	14	0.4187	1.00	0.4572
S x T x D	373*	0.4207		

* Five degrees of freedom lost due to missing data

TABLE E58

Spearman Correlation Coefficients between Interval Production and Subjects Experience

	Rho	p
Video Games Mean Reaction Time	0.1709	0.3847
Computer Programming Mean Reaction Time	0.0112	0.9548
Word Processing Mean Reaction Time	-0.0704	0.7219
Hours/week Computer Time Mean Reaction Time	0.0641	0.7461
Chess Experience Mean Reaction Time	0.0242	0.9026
Post High School Math Classes Mean Reaction Time	0.1516	0.4412

TABLE E59

Analysis of Variance Summary Table for Timewall - Mean Reaction Time

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	14.6715		
<u>Within Subjects</u>				
Time (T)	7	0.6282	6.29	0.0001
S x T	189	0.0999		
Drug (D)	2	0.2970	0.21	0.810
S x D	54	1.4057		
T x D	14	0.0777	0.73	0.7467
S x T x D	373*	0.1068		

* Five degrees of freedom lost due to missing data

TABLE E60

Newman-Keuls Results for Time Wall Mean Reaction Time - Time of Day

Time	Mean	Group
8:00 am	8.7671	A
10:00 am	8.6790	A B
4:00 pm	8.6469	B
2:00 pm	8.6354	B
12:00 pm	8.6074	B
6:00 pm	8.5965	B
8:00 pm	8.5764	B
10:00 pm	8.4661	C

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E61

Spearman Correlation Coefficients between Time Wall (Time Estimation) and Subjects Experience

	Rho	p
Video Games Mean Reaction Time	0.2323	0.2342
Computer Programming Mean Reaction Time	0.1126	0.5685
Word Processing Mean Reaction Time	-0.0477	0.8097
Hours/week Computer Time Mean Reaction Time	-0.0336	0.8619
Chess Experience Mean Reaction Time	0.0594	0.7639
Post High School Math Classes Mean Reaction Time	0.2806	0.1482

TABLE E62

Analysis of Variance Summary Table for Pattern Comparison - Number of Errors

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	4.8982		
<u>Within Subjects</u>				
Time (T)	7	0.3077	0.19	0.9866
S x T	189	1.5902		
Drug (D)	2	2.5715	1.33	0.2730
S x D	54	1.9333		
T x D	14	2.1245	1.54	0.0942
S x T x D	373*	1.3795		

* Five degrees of freedom lost due to missing data

TABLE E63

Analysis of Variance Summary Table for Pattern Comparison - Mean Reaction Time

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	5.3309		
<u>Within Subjects</u>				
Time (T)	7	0.4530	4.13	0.0003
S x T	189	0.1098		
Drug (D)	2	0.5492	1.60	0.2105
S x D	54	0.3423		
T x D	14	0.1732	1.72	0.0502
S x T x D	373*	0.1009		

* Five degrees of freedom lost due to missing data

TABLE E64

Newman-Keuls Results for Pattern Comparison - Mean Reaction Time - Time of Day

Time	Mean	Group
8:00 am	1.5906	A
10:00 am	1.5393	A B
2:00 pm	1.5040	A B C
4:00 pm	1.4527	B C
6:00 pm	1.4408	B C
12:00 pm	1.4178	B C
8:00 pm	1.4042	B C
10:00 pm	1.3740	C

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E65

Simple-Effect F-Tests for Pattern Recognition - Mean Reaction Time - Drug Effects at each Time of Day

Source of Variance	df	MS	F	p
8:00 am	2	0.4334	0.4296	0.6511
10:00 am	2	0.4191	0.4155	0.6604
12:00 pm	2	0.1021	1.0124	0.3643
2:00 pm	2	0.0245	0.2431	0.7844
4:00 pm	2	0.3816	3.7823	0.0236
6:00 pm	2	0.3518	3.4868	0.0316
8:00 pm	2	0.4019	3.9841	0.0194
10:00 pm	2	0.4145	4.1084	0.017

TABLE E66

Newman-Keuls Results for Pattern Comparison - Mean Reaction Time - Drug at 4:00 pm, 6:00 pm, 8:00 pm, and 10:00 pm

	Grouping	Mean	Drug
4:00 pm	A	1.5766	Placebo
	AB	1.4369	Hismanal
	B	1.3447	Benadryl
6:00 pm	A	1.5514	Placebo
	AB	1.4439	Hismanal
	B	1.3273	Benadryl
8:00 pm	A	1.5265	Placebo
	AB	1.3991	Benadryl
	B	1.2870	Hismanal
10:00 pm	A	1.5113	Placebo
	B	1.3312	Benadryl
	B	1.2795	Hismanal

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E67

Spearman Correlation Coefficients between Pattern Recognition and Subjects Experience

	Rho	p
Video Games		
Mean Reaction Time	-0.1730	0.3786
Errors	0.0499	0.8009
Computer Programming		
Mean Reaction Time	-0.2683	0.1675
Errors	-0.3449	0.0723
Word Processing		
Mean Reaction Time	-0.3325	0.0839
Errors	-0.0671	0.7343
Hours/week Computer Time		
Mean Reaction Time	0.0041	0.9833
Errors	0.0158	0.9365
Chess Experience		
Mean Reaction Time	0.1471	0.4550
Errors	0.1226	0.5342
Post High School Math Classes		
Mean Reaction Time	-0.3228	0.0939
Errors	-0.1849	0.3462

TABLE E68

Analysis of Variance Summary Table for Logical Reasoning - Number of Errors

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	31.8670		
<u>Within Subjects</u>				
Time (T)	7	0.6396	0.34	0.9351
S x T	189	1.8855		
Drug (D)	2	7.4269	2.69	0.0770
S x D	54	2.7651		
T x D	14	1.6946	0.87	0.5952
S x T x D	373*	1.9545		

* Five degrees of freedom lost due to missing data

TABLE E69

Analysis of Variance Summary Table for Logical Reasoning - Mean Reaction Time

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	0.0370		
<u>Within Subjects</u>				
Time (T)	7	1.4899	5.75	0.0001
S x T	189	0.2590		
Drug (D)	2	0.7244	0.41	0.6647
S x D	54	1.7602		
T x D	14	0.3240	0.90	0.5631
S x T x D	373*	0.3615		

Five degrees of freedom lost due to missing data

TABLE E70

Newman-Keuls Results for Logical Reasoning - Mean Reaction Time - Time of Day

Time	Mean	Group
10:00 am	3.5361	A
2:00 pm	3.3920	A B
4:00 pm	3.3734	A B
8:00 am	3.3519	A B
12:00 pm	3.3277	A B
6:00 pm	3.2935	B
8:00 pm	3.2453	B
10:00 pm	3.0706	C

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E71

Spearman Correlation Coefficients between Logical Reasoning and Subject Experience

	Rho	p
Video Games		
Mean Reaction Time	-0.2664	0.1705
Errors	0.0932	0.6371
Computer Programming		
Mean Reaction Time	-0.5936	0.0009
Errors	-0.3390	0.0776
Word Processing		
Mean Reaction Time	-0.0368	0.8524
Errors	0.0557	0.7782
Hours/week Computer Time		
Mean Reaction Time	0.0268	0.8924
Errors	-0.4698	0.0117
Chess Experience		
Mean Reaction Time	-0.1298	0.5102
Errors	0.0894	0.6511
Post High School Math Classes		
Mean Reaction Time	0.0375	0.8498
Errors	-0.1841	0.3483

TABLE E72

Analysis of Variance Summary Table for Manikin (Spatial Rotation) - Number of Errors

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	38.8101		
<u>Within Subjects</u>				
Time (T)	7	1.0955	1.16	0.3298
S x T	189	0.9472		
Drug (D)	2	0.3213	0.09	0.9166
S x D	54	3.6821		
T x D	14	0.7385	0.81	0.6631
S x T x D	373*	0.9166		

* Five degrees of freedom lost due to missing data

TABLE E73

Analysis of Variance Summary Table for Manikin (Spatial Rotation) - Mean Reaction Time

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	5.3356		
<u>Within Subjects</u>				
Time (T)	7	0.4489	7.79	0.0001
S x T	189	0.0576		
Drug (D)	2	0.1609	0.18	0.8374
S x D	54	0.9039		
T x D	14	0.0356	0.66	0.8157
S x T x D	373*	0.0541		

* Five degrees of freedom lost due to missing data

TABLE E74

Newman-Keuls Results for Manikin (Spatial Rotation) - Mean Reaction Time - Time of Day

Time	Mean	Group
8:00 am	1.60163	A
2:00 pm	1.52599	A B
10:00 am	1.52238	A B
12:00 pm	1.49842	B C
4:00 pm	1.47043	B C
6:00 pm	1.42993	B C D
10:00 pm	1.41605	C D
8:00 pm	1.37195	D

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E75

Spearman Correlation Coefficients between Manikin Task and Subjects Experience

	Rho	p
Video Games		
Mean Reaction Time	-0.2308	0.2374
Errors	0.3013	0.1192
Computer Programming		
Mean Reaction Time	-0.3670	0.0547
Errors	-0.0172	0.9308
Word Processing		
Mean Reaction Time	-0.0545	0.7829
Errors	0.2698	0.1650
Hours/week Computer Time		
Mean Reaction Time	0.0737	0.7093
Errors	-0.0843	0.6694
Chess Experience		
Mean Reaction Time	-0.2862	0.1398
Errors	0.0663	0.7376
Post High School Math Classes		
Mean Reaction Time	0.2157	0.2704
Errors	-0.2038	0.2982

TABLE E76

Analysis of Variance Summary Table for Serial Addition/Subtraction - Number of Errors

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	10.0334		
<u>Within Subjects</u>				
Time (T)	7	2.8142	2.30	0.0285
S x T	189	1.2233		
Drug (D)	2	0.0262	0.01	0.9916
S x D	54	3.1103		
T x D	14	1.3276	0.97	0.4810
S x T x D	373*	1.3653		

* Five degrees of freedom lost due to missing data

TABLE E77

Newman-Keuls Results for Serial Addition/Subtraction - Number of Errors - Time of Day

Time	Mean	Group
10:00 am	1.3153	A
2:00 pm	1.1667	A
8:00 am	1.1001	A
4:00 pm	0.9524	A
8:00 pm	0.9061	A
6:00 pm	0.8690	A
12:00 pm	0.8175	A
10:00 pm	0.8095	A

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E78

Analysis of Variance Summary Table for Serial Addition/Subtraction - Mean Reaction Time

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	2.8874		
<u>Within Subjects</u>				
Time (T)	7	0.5346	11.87	0.0001
S x T	189	0.0450		
Drug (D)	2	0.0161	0.12	0.8868
S x D	54	0.1338		
T x D	14	0.1186	3.26	0.0001
S x T x D	373*	0.3634		

* Five degrees of freedom lost due to missing data

TABLE E79

Newman-Keuls Results for Serial Addition/Subtraction - Mean Reaction Time - Time of Day

Time	Mean	Group
10:00 am	1.10782	A
8:00 am	1.09520	A B
2:00 pm	1.03750	A B C
12:00 pm	1.01792	B C D
4:00 pm	0.98986	C D E
6:00 pm	0.95082	D E F
8:00 pm	0.91839	E F
10:00 pm	0.88619	F

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E80

Simple-Effect F-Tests for Drugs at the Eight Times of Day: Serial Addition/Subtraction - Mean Reaction Time

Source of Variance	df	MS	F	p
S x T x D	373*	0.0363		
8:00 am	2	0.0597	1.6423	0.194912
10:00 am	2	0.3876	10.6650	0.000031
12:00 pm	2	0.2062	5.6733	0.003736
2:00 pm	2	0.0104	0.2855	0.751800
4:00 pm	2	0.0717	1.9727	0.140510
6:00 pm	2	0.0050	0.1364	0.872536
8:00 pm	2	0.0585	1.6106	0.201136
10:00 pm	2	0.0176	0.4843	0.616510

* Five degrees of freedom lost due to missing data

TABLE E81

Newman-Keuls Results for Drug Effects on Serial Addition/Subtraction Task - Mean Reaction Time

	Grouping	Mean	Drug
10:00 am	A	1.2427	Benadryl
	B	1.0541	Hismanal
	B	1.0266	Placebo
12:00 pm	A	1.08589	Placebo
	A	1.04637	Benadryl
	B	0.92150	Hismanal

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E82

Spearman Correlation Coefficients between Serial Addition/Subtraction and Subjects Experience

	Rho	p
Video Games		
Mean Reaction Time	-0.2944	0.1283
Errors	0.2802	0.1487
Computer Programming		
Mean Reaction Time	-0.4435	0.0181
Errors	-0.1279	0.4435
Word Processing		
Mean Reaction Time	-0.0307	0.8768
Errors	0.0920	0.6416
Hours/week Computer Time		
Mean Reaction Time	-0.1977	0.3133
Errors	-0.4581	0.0142
Chess Experience		
Mean Reaction Time	-0.2031	0.2999
Errors	0.1623	0.4092
Post High School Math Classes		
Mean Reaction Time	-0.3085	0.1102
Errors	-0.4645	0.0128

TABLE E83

Analysis of Variance Summary Table for Code Substitution - Number of Errors

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	32.6315		
<u>Within Subjects</u>				
Time (T)	7	7.2446	2.43	0.0210
S x T	189	2.8399		
Drug (D)	2	10.9069	1.84	0.1690
S x D	54	5.9402		
T x D	14	2.2321	0.61	0.8560
S x T x D	373*	3.6512		

* Five degrees of freedom lost due to missing data

TABLE E84

Newman-Keuls Results for Code Substitution Number of Errors - Time of Day

Time	Mean	Group
10 a.m.	2.2108	A
2 p.m.	1.8095	A B
8 a.m.	1.7972	A B
4 p.m.	1.7381	A B
12 p.m.	1.5842	A B
6 p.m.	1.4524	A B
10 p.m.	1.3990	B
8 p.m.	1.2910	B

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E85

Analysis of Variance Summary Table for Code Substitution - Mean Reaction Time

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	10.2858		
<u>Within Subjects</u>				
Time (T)	7	0.7724	4.85	0.0001
S x T	189	0.1592		
Drug (D)	2	0.8221	1.40	0.2550
S x D	54	0.5866		
T x D	14	0.1535	1.13	0.3263
S x T x D	373*	0.1354		

* Five degrees of freedom lost due to missing data

TABLE E86

Newman-Keuls Results for Code Substitution Mean Reaction Time - Time of Day

Time	Mean	Group
4:00 pm	2.26779	A
10:00 am	2.19896	A
2:00 pm	2.13990	A B
8:00 am	2.13466	A B
6:00 pm	2.13131	A B
12:00 pm	2.12999	A B
8:00 pm	2.01574	B
10:00 pm	1.96302	B

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E87

Spearman Correlation Coefficients between Code Substitution and Subjects Experience

	Rho	p
Video Games		
Mean Reaction Time	-0.3325	0.0838
Errors	0.2245	0.2509
Computer Programming		
Mean Reaction Time	-0.5262	0.0040
Errors	-0.1859	0.3435
Word Processing		
Mean Reaction Time	-0.1394	0.4794
Errors	0.2507	0.1982
Hours/week Computer Time		
Mean Reaction Time	-0.1709	0.3845
Errors	-0.0587	0.7665
Chess Experience		
Mean Reaction Time	-0.4131	0.0289
Errors	0.0428	0.8190
Post High School Math Classes		
Mean Reaction Time	-0.0747	0.7057
Errors	-0.3603	0.0596

TABLE E88

Analysis of Variance Summary Table for Unstable Tracking Root-Mean-Square Error

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	29	2075.6551		
<u>Within Subjects</u>				
Time (T)	7	288.2592	6.59	0.0001
S x T	196	43.7241		
Drug (D)	2	195.7825	1.17	0.3172
S x D	56	167.0204		
T x D	14	53.0042	1.88	0.0262
S x T x D	391*	28.1800		

* One degree of freedom lost due to missing data

TABLE E89

Newman-Keuls Results for Unstable Tracking Root-Mean-Square Error - Time of Day

Time	Mean	Group
10:00 am	16.484	A
8:00 am	16.240	A
2:00 pm	15.938	A B
12:00 pm	15.098	A B C
4:00 pm	14.392	A B C
8:00 pm	13.372	B C D
6:00 pm	13.170	C D
10:00 pm	11.221	D

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E9C

Simple-Effect F-Tests for Drugs at the Eight Times of Day: Unstable Tracking - Root Mean Square

Source of Variance	df	MS	F	p
S x T x D	291*	11046.5712	28.1800	
8:00 am	2	186.8974	6.6323	0.0015
10:00 am	2	90.0974	3.1972	0.0419
12:00 pm	2	13.1670	0.4672	0.6271
2:00 pm	2	18.0904	0.6420	0.5268
4:00 pm	2	6.5765	0.2334	0.7920
6:00 pm	2	138.0008	4.8971	0.0079
8:00 pm	2	66.8491	2.3722	0.0946
10:00 pm	2	47.4246	1.6829	0.1872

* One degree of freedom lost due to missing data

TABLE E91

Newman-Keuls Results for Drug Effect: Unstable Tracking - Root-Mean-Square Error

	Grouping	Mean	Drug
8:00 am	A	18.9586	Benadryl
	B	15.8310	Placebo
	B	13.9310	Hismanal
10:00 am	A	18.4379	Benadryl
	AB	16.0	Placebo
	B	15.0138	Hismanal
6:00 pm	A	11.2621	Benadryl
	B	15.5483	Placebo
	A	12.7	Hismanal

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E92

Analysis of Variance Summary Table for Unstable Tracking Boundry Hits

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	28	8.5411		
<u>Within Subjects</u>				
Time (T)	7	2.1915	3.99	0.0004
S x T	196	0.5498		
Drug (D)	2	0.6758	0.27	0.7669
S x D	56	2.5159		
T x D	14	0.4713	0.86	0.6054
S x T x D	391*	0.5493		

* One degree of freedom lost due to missing data

TABLE E93

Newman-Keuls Results for Unstable Tracking Boundary Hits - Time of Day

Time	Mean	Group
8:00 am	0.7931	A
2:00 pm	0.6897	A B
12:00 pm	0.6092	A B C
10:00 am	0.4828	B C
4:00 pm	0.4368	B C
8:00 pm	0.4368	B C
6:00 pm	0.3908	B C
10:00 pm	0.3380	C

Note: Means with the same letters are not significantly different, $p > 0.05$.

Table E94

Spearman Correlation Coefficients between Unstable Tracking and Subjects Experience

	Rho	p
Video Games Root-Mean-Square Error	-0.3513	0.0668
Computer Programming Root-Mean-Square Error	-0.4721	0.0112
Word Processing Root-Mean-Square Error	-0.2116	0.2799
Hours/week Computer Time Root-Mean-Square Error	0.1309	0.5068
Chess Experience Root-Mean-Square Error	-0.0427	0.8292
Post High School Math Classes Root-Mean-Square Error	-0.03636	0.8543

TABLE E95

Analysis of Variance Summary Table for Physiological Data - Systolic Blood Pressure

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	28	1295.6271		
<u>Within Subjects</u>				
Time (T)	7	340.9899	5.47	0.0001
S x T	196	62.3382		
Drug (D)	2	174.0618	0.90	0.4144
S x D	56	194.4785		
T x D	14	69.4789	1.40	0.1480
S x T x D	392	49.5044		

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E96

Newman-Keuls Results for Physiological Data - Systolic Blood Pressure - Time of Day

Time	Mean	Group
10:00 pm	117.172	A
2:00 pm	115.563	A B
8:00 pm	114.805	A B C
6:00 pm	112.977	B C
4:00 pm	112.598	B C
8:00 am	112.184	C
10:00 am	111.966	C
12:00 pm	111.782	C

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E97

Analysis of Variance Summary Table for Physiological Data - Diastolic Blood Pressure

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	28	801.4480		
<u>Within Subjects</u>				
Time (T)	7	115.0567	1.44	0.192
S x T	196	80.0936		
Drug (D)	2	31.5690	0.07	0.9297
S x D	56	432.6672		
T x D	14	63.2488	0.89	0.5692
S x T x D	392	71.0102		

TABLE E98

Analysis of Variance Summary Table for Physiological Data - Pulse Rate

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	28	1443.9926		
<u>Within Subjects</u>				
Time (T)	7	339.5860	6.04	0.0001
S x T	196	56.2620		
Drug (D)	2	97.8793	0.65	0.5267
S x D	56	150.9463		
T x D	14	25.6938	0.59	0.8697
S x T x D	392	43.2250		

TABLE E99

Newman-Keuls Results for Physiological Data - Pulse Rate - Time of Day

Time	Mean	Group
2:00 pm	69.885	A
8:00 pm	68.287	A B
4:00 pm	67.770	A B
8:00 am	67.241	A B
10:00 pm	66.747	B
10:00 am	66.322	B
6:00 pm	65.253	B
12:00 pm	63.356	C

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E100

Analysis of Variance Summary Table for Physiological Data - Temperature

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	28	4.6092		
<u>Within Subjects</u>				
Time (T)	7	2.1684	5.63	0.0001
S x T	196	0.3854		
Drug (D)	2	0.0897	0.14	0.8676
S x D	56	0.6302		
T x D	14	0.4582	1.31	0.2003
S x T x D	392	0.3508		

TABLE E101

Newman-Keuls Results for Physiological Data - Temperature - Time of Day

Time	Mean	Group
8:00 pm	97.34943	A
10:00 pm	97.31609	A
6:00 pm	97.26667	A
4:00 pm	97.19770	A B
2:00 pm	97.17241	A B
12:00 pm	97.08276	A B C
8:00 am	96.98161	B C
10:00 am	96.90805	C

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E102

Analysis of Variance Summary Table for Mood Scale II - Activity

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	20	5.34004		
<u>Within Subjects</u>				
Time (T)	7	0.17147	2.02	0.0573
S x T	140	0.08510		
Drug (D)	2	0.63600	2.05	0.1418
S x D	40	0.30992		
T x D	14	0.12672	1.86	0.0310
S x T x D	274*	0.06826		

* Six degrees of freedom lost due to missing data

TABLE E103

Simple-Effect F-Tests for Drugs at the Eight Times of Day: Mood Scale II - Activity Scale

Time of Day	df	MS	F	p
S x T x D	274*	19.11900		
8:00 am	2	0.68467	10.03080	0.00006
10:00 am	2	0.39032	5.71843	0.00368
12:00 pm	2	0.15617	2.29096	0.10306
2:00 pm	2	0.15172	2.22270	0.11022
4:00 pm	2	0.02396	0.35095	0.70433
6:00 pm	2	0.03970	0.58163	0.55966
8:00 pm	2	0.04168	0.61060	0.54375
10:00 pm	2	0.06095	0.89288	0.41064

* Six degrees of freedom lost due to missing data

TABLE E104

Newman-Keuls Results for Drug Effect: Mood Scale II - Activity

	Grouping	Mean	Drug
8:00 am	A	2.2176	Placebo
	B	2.0329	Hismanal
	B	1.8565	Benadryl
10:00 am	A	2.0876	Placebo
	A	2.0824	Hismanal
	B	1.8570	Benadryl

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E105

Analysis of Variance Summary Table for Mood Scale II - Happiness

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	20	7.95110		
<u>Within Subjects</u>				
Time (T)	7	0.113986	1.53	0.1631
S x T	140	0.074695		
Drug (D)	2	0.954950	1.78	0.1822
S x D	40	0.537428		
T x D	14	0.104979	1.57	0.0856
S x T x D	274*	0.066667		

* Six degrees of freedom lost due to missing data

TABLE E106

Analysis of Variance Summary Table for Mood Scale II - Depression

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	20	1.28020		
<u>Within Subjects</u>				
Time (T)	7	0.015274	0.67	0.6962
S x T	140	0.022776		
Drug (D)	2	0.068050	0.83	0.4439
S x D	40	0.082125		
T x D	14	0.033679	1.86	0.0303
S x T x D	274*	0.018089		

* Six degrees of freedom lost due to missing data

TABLE E107

Simple-Effect F-tests for Drugs at the Eight Times of Day: Mood Scale II - Depression

Time of Day	df	MS	F	p
S x T x D	274*	0.01809		
8:00 am	2	0.12733	1.86548	0.156741
10:00 am	2	0.05155	0.75519	0.470877
12:00 pm	2	0.00349	0.05106	0.950231
2:00 pm	2	0.01848	0.27071	0.763045
4:00 pm	2	0.02396	0.35095	0.704328
6:00 pm	2	0.01374	0.20130	0.817786
8:00 pm	2	0.05895	0.86362	0.422761
10:00 pm	2	0.01332	0.19518	0.822782

* Six degrees of freedom lost due to missing data

TABLE E108

Analysis of Variance Summary Table for Mood Scale II - Anger

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	20	1.97181		
<u>Within Subjects</u>				
Time (T)	7	0.02349	1.20	0.3040
S x T	140	0.01950		
Drug (D)	2	0.04135	1.93	0.1578
S x D	40	0.02140		
T x D	14	0.02443	1.87	0.0294
S x T x D	274*	0.01306		

* Six degrees of freedom lost due to missing data

TABLE E109

Simple-Effect F-Tests for Drugs at the Eight Times of Day: Mood Scale II - Anger

Time of Day	df	MS	F	p
S x T x D	274*	.0131		
8:00 am	2	.0209	0.3062	0.7365
10:00 am	2	.0050	0.0737	0.9290
12:00 pm	2	.0107	0.1569	0.8549
2:00 pm	2	.0041	0.0601	0.9417
4:00 pm	2	.0038	0.0558	0.9457
6:00 pm	2	.0014	0.0202	0.9800
8:00 pm	2	.0361	0.5285	0.5901
10:00 pm	2	.1304	1.9099	0.1500

* Six degrees of freedom lost due to missing data

TABLE E110

Analysis of Variance Summary Table for Mood Scale II - Fatigue

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	20	3.12801		
<u>Within Subjects</u>				
Time (T)	7	0.19203	1.43	0.1984
S x T	140	0.13441		
Drug (D)	2	0.56190	2.10	0.1352
S x D	40	0.26702		
T x D	14	0.27974	3.47	0.0001
S x T x D	274*	0.08056		

* Six degrees of freedom lost due to missing data

TABLE E111

Simple-Effects F-Test for Drugs at the Eight Times of Day: Mood Scale II - Fatigue

Time of Day	df	MS	F	p
S x T x D	274*	0.0806		
8:00 am	2	0.7587	11.1156	< 0.0001
10:00 am	2	0.8107	11.8767	< 0.0001
12:00 pm	2	0.2779	4.0718	0.0181
2:00 pm	2	0.2589	3.7927	0.0237
4:00 pm	2	0.1001	1.4667	0.2325
6:00 pm	2	0.0398	0.5832	0.5588
8:00 pm	2	0.1340	1.9626	0.1424
10:00 pm	2	0.1401	2.0522	0.1304

* Six degrees of freedom lost due to missing data

TABLE E112

Newman-Keuls Results for Drug Effects: Mood Scale II - Fatigue

	Grouping	Mean	Drug
8:00 am	A	1.7590	Benadryl
	B	1.5319	Hismanal
	B	1.3814	Placebo
10:00 am	A	1.7665	Benadryl
	B	1.38095	Hismanal
	B	1.50809	Placebo
12:00 pm	A	1.5170	Benadryl
	A B	1.4519	Hismanal
	B	1.2933	Placebo
2:00 pm	A	1.6267	Benadryl
	A B	1.5086	Hismanal
	B	1.4048	Placebo

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E113

Analysis of Variance Summary Table for Mood Scale II - Fear

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	20	0.79484		
<u>Within Subjects</u>				
Time (T)	7	0.01431	1.20	0.3086
S x T	140	0.01197		
Drug (S)	2	0.04590	2.90	0.0668
S x D	40	0.01586		
T x D	14	0.01209	0.98	0.4695
S x T x D	274*	0.01229		

* Six degrees of freedom lost due to missing data

TABLE E114

Analysis of Variance Summary Table for Mood Scale II - Mean Reaction Time

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	20	2.52818		
<u>Within Subjects</u>				
Time (T)	7	2.37196	21.81	0.0001
S x T	140	7.61240		
Drug (D)	2	0.00375	0.01	0.9920
S x D	40	0.47223		
T x D	14	0.07575	1.72	0.0507
S x T x D	274*	0.04396		

* Six degrees of freedom lost due to missing data

TABLE E115

Newman-Keuls Results for Mood Scale II - Mean Reaction Time - Time of Day

Time	Mean	Group
8:00 am	1.44670	A
10:00 am	1.25202	B
12:00 pm	1.07558	C
2:00 pm	1.05860	C
4:00 pm	0.98729	C D
6:00 pm	0.92995	C D
8:00 pm	0.92824	C D
10:00 pm	0.86545	D

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E116

Analysis of Variance Summary Table for Profile of Mood States - Tension/Anxiety

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	354.0471		
<u>Within Subjects</u>				
Time (T)	7	9.8086	1.57	0.1462
S x T	189	6.2430		
Drug (D)	2	75.5426	6.23	0.0037
S x D	54	12.1349		
T x D	14	3.6660	0.72	0.7562
S x T x D	373*	5.1035		

* Five degrees of freedom lost due to missing data

TABLE E117

Newman-Keuls Results for Profile of Mood States - Tension-Anxiety - Drug

Drug	Grouping	Mean
Benadryl	A	4.7796
Hismanal	B	3.8799
Placebo	B	3.6938

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E118

Analysis of Variance Summary Table for Profile Mood States - Depression-Dejection

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	527.3646		
<u>Within Subjects</u>				
Time (T)	7	2.1818	0.29	0.9580
S x T	189	7.5975		
Drug (D)	2	0.5986	0.02	0.9826
S x D	54	34.0799		
T x D	14	6.5064	1.15	0.3163
S x T x D	373*	5.6808		

* Five degrees of freedom lost due to missing data

TABLE E119

Analysis of Variance Summary Table for Profile of Mood States - Anger-Hostility

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	753.2552		
<u>Within Subject</u>				
Time (T)	7	2.2475	0.47	0.8545
S x T	189	4.7677		
Drug (D)	2	19.6707	1.55	0.2213
S x D	54	12.6802		
T x D	14	5.1878	1.32	0.190
S x T x D	373*	3.9221		

* Five degrees of freedom lost due to missing data

TABLE E120

Analysis of Variance Summary Table for Profile of Mood States - Vigor-Activity

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	956.41626		
<u>Within Subjects</u>				
Time (T)	7	36.81321	2.64	0.0127
S x T	189	13.96012		
Drug (D)	2	191.07025	4.21	0.0201
S x D	54	45.43611		
T x D	14	19.72725	1.81	0.0357
S x T x D	373*	10.91094		

* Five degrees of freedom lost due to missing data

TABLE E121

Newman-Keuls Results for Profile Mood States - Vigor-Activity - Time of Day

Time	Mean	Group
10:00 pm	15.0591	A
8:00 pm	14.6495	A B
6:00 pm	14.5595	A B
12:00 pm	14.2059	A B
4:00 pm	13.9048	A B
10:00 am	13.6680	A B
2:00 pm	13.4524	A B
8:00 am	13.1080	B

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E122

Newman-Keuls Results for Profile of Mood States - Vigor-Activity x Drug

Drug	Grouping	Mean
Placebo	A	14.7345
Hismanal	A	14.4730
Benadryl	B	13.0202

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E123

Simple-Effect F-Tests for Drug at the Eight Times of Day: Profile of Mood States Vigor-Activity

Time of Day	df	MS	F	p
S x T x D	373*	10.9110		
8:00 am	2	151.8115	13.9136	<0.0001
10:00 am	2	91.4340	8.3799	0.0003
12:00 pm	2	27.0998	2.4836	0.0848
2:00 pm	2	23.7976	2.1811	0.1143
4:00 pm	2	6.2262	0.5706	0.5657
6:00 pm	2	4.6191	0.4233	0.6552
8:00 pm	2	23.3084	2.1362	0.1195
10:00 pm	2	0.7654	0.0702	0.9323

* Five degrees of freedom lost due to missing data

TABLE E124

Newman-Keuls Results for Drug Effect: Profile of Mood States - Vigor-Activity

	Grouping	Mean	Drug
8:00 am	A	15.2500	Placebo
	B	4.8057	Hismanal
	C	1.8056	Benadryl
10:00 am	A	14.8929	Placebo
	A	14.5186	Hismanal
	B	11.5926	Benadryl

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E125

Analysis of Variance Summary Table for Profile of Mood States - Fatigue-Inertia

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	534.0266		
<u>Within Subjects</u>				
Time (T)	7	26.7722	1.42	0.1999
S x T	189	18.8716		
Drug (D)	2	116.4191	3.49	0.0376
S x D	54	33.3650		
T x D	14	40.5302	3.78	0.0001
S x T x D	373*	10.7164		

* Five degrees of freedom lost due to missing data

TABLE E126

Newman-Keuls Results for Profile of Mood States - Fatigue-Inertia x Drug

Drug	Grouping	Mean
Benadryl	A	6.4909
Hismanal	A	5.2609
Placebo	A	5.2244

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E127

Simple-Effect F-Tests for Drugs at the Eight Times of Day: Profile of Mood States
Fatigue-Inertia

Source of Variance	df	MS	F	p
S x T x D	373*	10.7164		
8:00 am	2	151.2558	13.8627	< 0.0001
10:00 am	2	146.2269	13.4018	< 0.0001
12:00 pm	2	35.7980	3.2809	0.0387
2:00 pm	2	34.3333	3.1467	0.0441
4:00 pm	2	4.9643	0.4550	0.6348
6:00 pm	2	6.8690	0.6296	0.5334
8:00 pm	2	8.0828	0.7408	0.4774
10:00 pm	2	12.6005	1.1549	0.3162

* Five degrees of freedom lost due to missing data

TABLE E128

Newman-Keuls Results for Drug Effect: Profile of Mood States Fatigue-Inertia

	Grouping	Mean	Drug
8:30 am	A	8.8519	Benadryl
	B	5.8146	Hismanal
	B	4.2857	Placebo
10:00 am	A	9.0741	Benadryl
	B	5.9286	Placebo
	B	4.6296	Hismanal
12:00 pm	A	6.0370	Benadryl
	A B	5.3214	Hismanal
	B	3.8214	Placebo
2:00 pm	A	7.000	Benadryl
	A B	5.2857	Hismanal
	B	4.9286	Placebo

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E129

Analysis of Variance Summary Table for Profile of Mood States-Confusion-Bewilderment

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	278.5495		
<u>Within Subjects</u>				
Time (T)	7	7.3110	1.60	0.1383
S x T	189	4.5761		
Drug (D)	2	48.7176	2.77	0.0713
S x D	54	17.5633		
T x D	14	6.1991	2.32	0.0046
S x T x D	373*	2.6755		

* Five degrees of freedom lost due to missing data

TABLE E130

Simple-Effect F-Tests for Drugs at the Eight Times of Day: Profile of Mood States -
Confusion-Bewilderment

Time of Day	df	MS	F	p
S x T x D	373*	2.6755		
8:00 am	2	37.5606	3.4425	0.0330
10:00 am	2	37.1200	3.4021	0.0343
12:00 pm	2	2.6151	0.2397	0.7870
2:00 pm	2	4.3333	0.3972	0.6725
4:00 pm	2	1.6548	0.1517	0.8593
6:00 pm	2	4.0833	0.3742	0.6881
8:00 pm	2	2.3902	0.2191	0.8034
10:00 pm	2	2.3528	0.2156	0.8062

* Five degrees of freedom lost due to missing data

TABLE E131

Newman-Keuls Results for Drug Effects: Profile of Mood States - Confusion-Bewilderment

	Grouping	Mean	Drug
8:00 am	A	5.6667	Benadryl
	B	4.6668	Hismanal
	C	3.3571	Placebo
10:00 am	A	5.7778	Benadryl
	B	3.9629	Hismanal
	B	3.6429	Placebo

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E132

Analysis of Variance Summary Table for Stanford Sleepiness Scale

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	13.7334		
<u>Within Subjects</u>				
Time (T)	7	8.3301	7.43	0.0001
S x T	189	1.1219		
Drug (D)	2	6.1019	1.94	0.1536
S x D	54	3.1449		
T x D	14	2.5461	3.60	0.0001
S x T x D	373*	0.7080		

* Five degrees of freedom lost due to missing data

TABLE E133

Newman-Keuls Results for Stanford Sleepiness Scale - Time of Day

Time	Mean	Group
8:00 am	3.3461	A
10:00 am	3.2606	AB
2:00 pm	3.0357	ABC
4:00 pm	3.0000	ABCD
12:00 pm	2.8818	BCDE
6:00 pm	2.6786	CDE
8:00 pm	2.5776	DE
10:00 pm	2.4713	E

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E134

Simple-Effect F-Tests for Drugs at the Eight Times of Day: Stanford Sleepiness Scale

Source of Variance	df	MS	F	p
S x T x D	373*	0.7080		
8:00 am	2	11.5670	16.3360	<0.000001
10:00 am	2	8.3706	11.8221	0.00001
12:00 pm	2	1.0975	1.5500	0.2136
2:00 pm	2	1.0000	1.4123	0.2449
4:00 pm	2	0.4643	0.6557	0.5197
6:00 pm	2	0	0	1.0000
8:00 pm	2	0.3948	0.5575	0.5731
10:00 pm	2	1.0320	1.4575	0.2341

* Five degrees of freedom lost due to missing data

TABLE E135

Newman-Keuls Results for Drug Effect: Stanford Sleepiness Scale

	Grouping	Mean	Drug
8:00 am	A	4.0741	Benadryl
	B	3.1071	Hismanal
	B	2.8571	Placebo
10:00 am	A	3.8889	Benadryl
	B	3.0000	Hismanal
	B	2.8929	Placebo

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E136

Summary of Sutcliffe Chi-Square Test for Self Rating of Medication Received x
Medication Received

Source	Chi-Square	df	p
Drug (D)	0	0	N/A
Self Rating (R)	0.05	1	>.05
D x R	53.29	2	<.001
Total	<u>53.34</u>	<u>3</u>	<.001

TABLE E137

Chi-Square Summary Tests for Self Rating of Medication Received: Hismanal, Benadryl, and Placebo

Source	Chi-Square	df	p
Hismanal	0.8750	1	>.05
Benadryl	33.0179	1	<.001
Placebo	19.4464	1	<.001

TABLE E138

Number of Symptoms per Drug, N = 58

Symptom	Hismanal	Benadryl	Placebo
Lack of concentration	13	25	7
Excessive sweating	0	0	0
Dryness of mouth	9	14	8
Chills	2	4	1
Dryness of throat	8	13	5
Dryness of nose	7	9	7
Sedation	9	20	7
Disturbed coordination	5	12	2
Blurred vision	5	9	2
Dizziness	4	4	5
Frequent urination	0	2	1
Difficulty in urinating	1	0	0
Nausea	0	0	0
Ringling of ears	0	1	1
Stuffy nose	7	6	4
Euphoria	3	2	1
Headache	4	8	8
Fast heart beat	2	4	2
Eyes sensitive to light	7	6	6
Tightness of chest	1	0	0
Light-headed	5	10	3
Sleepy	31	36	26
Nervous	0	1	1
Irritable	0	4	3
Jittery	0	0	2
Tingling sensations of skin	<u>0</u>	<u>2</u>	<u>0</u>
	123	192	102

TABLE E139

Summary of Sutcliffe Chi-Square Test for Number of Symptoms Reported x Drug x Time

Source	Chi-Square	df	p
Drug (D)	0	0	N/A
Symptom (S)	0	0	N/A
Time (T)	0	0	N/A
T x D	0	0	N/A
T x S	3.0610	2	not significant
D x S	16.1391	4	< .01
T x D x S	<u>0.6976</u>	<u>4</u>	not significant
Total	20.1428	10	< .05

TABLE E140

Summary of Sutcliffe Chi-Square Tests for Drug Effects at Each Symptom Category

Source	Chi-Square	df	p
No symptoms	1.1429	2	not significant
1 to 3 symptoms	4.0572	2	not significant
4 or more symptoms	10.9390	2	< .01

TABLE E141

Analysis of Variance Summary Table for Perceived Performance

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Subject (S)	27	6.8449		
<u>Within Subjects</u>				
Time (T)	7	1.2076	2.60	0.0137
S x T	189	0.4637		
Drug (D)	2	2.6749	3.37	0.0419
S x D	54	0.7945		
T x D	14	1.0668	2.83	0.0005
S x T x D	373*	0.3772		

* Five degrees of freedom lost due to missing data

TABLE E142

Newman-Keuls Results for Perceived Performance - Time of Day

Time	Mean	Group
10:00 pm	3.7950	A
8:00 pm	3.7584	AB
6:00 pm	3.7024	AB
12:00 pm	3.6984	AB
2:00 pm	3.6071	AB
4:00 pm	3.5476	AB
8:00 am	3.5357	AB
10:00 am	3.3	B

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E143

Newman-Keuls Results for Perceived Performance - Drug

Drug	Mean	Group
Placebo	3.7298	A
Hismanal	3.6652	AB
Benadryl	3.5167	B

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E144

Simple-Effect F-Tests for Drugs at the Eight Times of Day: Perceived Performance

Source of Variance	df	MS	F	p
S x T x D	373*	0.3772		
8:00 am	2	6.1357	15.7892	< 0.0001
10:00 am	2	3.1624	8.2726	0.0003
12:00 pm	2	0.1640	0.4290	0.6515
2:00 pm	2	0.0357	0.0934	0.9109
4:00 pm	2	0.5834	1.5260	0.2188
6:00 pm	2	0.0476	0.1245	0.8830
8:00 pm	2	0.9850	0.2576	0.7730
10:00 pm	2	0.0152	0.0396	0.9611

* Five degrees of freedom lost due to missing data

TABLE E145

Newman-Keuls Results Table for Drug Effect - Perceived Performance

	Grouping	Mean	Drug
8:00 am	B	3.8214	Placebo
	B	3.7857	Hismanal
	A	3.0000	Benadryl
10:00 am	B	3.7143	Placebo
	B	3.5714	Hismanal
	A	3.0741	Benadryl

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E146

Pearson Product-Moment Correlations between Perceived Performance and UTC-PAB Tasks

	Correlation Coefficient	df	p
Wilkinson Reaction Time			
Mean Reaction Time	0.0700	664	0.0403
Time Wall			
Mean Reaction Time	0.2526	664	0.0001
Interval Production			
Mean Reaction Time	-0.0233	664	0.5462
Code Substitution			
Mean Reaction Time	-0.1592	664	0.0001
Errors	-0.2530	664	0.0001
Serial Addition/Subtraction			
Mean Reaction Time	-0.1807	664	0.0001
Errors	-0.2574	664	0.0001
Logical Reasoning			
Mean Reaction Time	-0.2564	664	0.0001
Errors	-0.1974	664	0.0001
Pattern Comparison			
Mean Reaction Time	-0.0878	664	0.0228
Errors	-0.2536	664	0.0001
Manikin			
Mean Reaction Time	-0.0245	664	0.5265
Errors	-0.0982	664	0.0109

TABLE E147

Analysis of Variance Summary Table for Manikin - Mean Reaction Time (Placebo group)

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Day (D)	2	14.9271	5.84	0.0083
Subject (S/D)	25	2.5545		
<u>Within Subjects</u>				
Time (T)	7	0.1031	1.64	0.1259
T x D	14	0.0935	1.49	0.1183
T x S/D	170*	0.0627		

* Five degrees of freedom lost due to missing data

TABLE E148

Newman-Keuls Results for Day Effect: Manikin (Placebo group)

Day	Grouping	Mean
1	A	2.0855
2	B	1.2887
3	B	1.2666

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E149

Analysis of Variance Summary Table for Unstable Tracking Boundary Hits (Placebo group)

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Day (D)	2	18.0317	5.05	0.0143
Subject (S/D)	25	3.5680		
<u>Within Subjects</u>				
Time (T)	7	1.0861	2.23	0.0234
T x D	14	0.5159	1.13	0.3307
T x S/D	175	0.4546		

TABLE E150

Newman-Keuls Results for Day Effect: Unstable Tracking Boundary Hits (Placebo group)

Day	Grouping	Mean
1	A	1.0313
2	AB	0.4375
3	B	0.0250

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E151

Analysis of Variance Summary Table for Unstable Tracking Root-Mean-Square Error
(Placebo group)

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Day (D)	2	2648.4527	4.32	0.0245
Subject (S/D)	25	613.6137		
<u>Within Subjects</u>				
Time (T)	7	44.9433	1.35	0.2274
T x D	14	52.9628	1.60	0.0840
T x S/D	175	33.1703		

TABLE E152

Newman-Keuls Results for Day Effect: Unstable Tracking Root-Mean-Square Error
(Placebo group)

Day	Grouping	Mean
2	A	18.902
1	AB	15.655
3	B	7.676

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E153

Analysis of Variance Summary Table for Following Directions - Percent Total Hits - Easy
(Placebo group)

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Day (D)	2	65859.5111	5.31	0.0119
Subject (S/D)	25	12391.7799		
<u>Within Subjects</u>				
Time (T)	7	9.0445	0.27	0.9649
T x D	14	107.9769	1.61	0.0804
T x S/D	175	33.1703		

* Four degrees of freedom lost due to missing data

TABLE E154

Newman-Keuls Results for Day Effect: Following Directions - Percent Total Hits - Easy (Placebo group)

Day	Grouping	Mean
3	A	99.24
2	AB	69.11
1	B	38.49

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E155

Analysis of Variance Summary Table for Following Directions - Percent Total Hits - Hard
(Placebo group)

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Day (D)	2	67186.0529	6.06	0.0071
Subject (S/D)	25	11081.2684		
<u>Within Subjects</u>				
Time (T)	7	27.7559	0.38	0.9141
T x D	14	83.7313	1.14	0.3255
T x S/D	175	73.3763		

* Four degrees of freedom lost due to missing data

TABLE E156

Newman-Keuls Results for Day Effect: Following Directions - Percent Total Hits - Easy (Placebo group)

Day	Grouping	Mean
3	A	96.73
2	AB	66.82
1	B	35.33

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E157

Analysis of Variance Summary Table for Serial Addition/Subtraction - Mean Reaction Time (Placebo group)

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Day (D)	2	1.8228	1.61	0.2194
Subject (S/D)	25	27.4883		
<u>Within Subjects</u>				
Time (T)	7	9.3771	2.85	0.0078
T x D	14	0.0371	0.99	0.4650
T x S/D	170*	0.0375		

* Five degrees of freedom lost due to missing data

TABLE E158

Newman-Keuls Results for Serial Addition/Subtraction Mean Reaction Time - Time of Day (Placebo group)

Time	Mean	Group
12:00 pm	1.0859	A
2:00 pm	1.0448	AB
8:00 am	1.0420	AB
10:00 am	1.0266	AB
4:00 pm	1.0089	AB
8:00 pm	0.9596	AB
6:00 pm	0.9375	AB
10:00 pm	0.9041	B

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E159

Analysis of Variance Summary Table for Unstable Tracking Boundary Hits (Placebo group)

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Day (D)	2	18.0317	5.05	0.0143
Subject (S/D)	25	3.5680		
<u>Within Subjects</u>				
Time (T)	7	1.0861	2.23	0.0234
T x D	14	0.5159	1.13	0.3307
T x S/D	175	0.4546		

TABLE E160

Newman-Keuls Results for Unstable Tracking Boundary Hits - Time of Day (Placebo group)

Time	Mean	Group
8:00 am	0.7857	A
12:00 pm	0.7143	A
2:00 pm	0.5357	A
8:00 pm	0.3929	A
6:00 pm	0.3571	A
10:00 am	0.3214	A
4:00 pm	0.2857	A
10:00 pm	0.2857	A

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E161

Analysis of Variance Summary Table for Following Directions Score - Hard (Placebo group)

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Day (D)	2	867517.45	0.92	0.4117
Subject (S/D)	25	23582132.90		
<u>Within Subjects</u>				
Time (T)	7	184592.09	2.65	0.0120
T x D	14	90194.88	1.26	0.2135
T x S/D	171*	69566.96		

* Four degrees of freedom lost due to missing data

TABLE E162

Newman-Keuls Results for Following Directions Score - Hard - Time of Day (Placebo group)

Time	Mean	Group
8:00 am	1687.43	A
10:00 am	1569.64	AB
4:00 pm	1562.25	AB
2:00 pm	1540.79	AB
12:00 pm	1533.32	AB
6:00 pm	1526.11	AB
8:00 pm	1472.64	B
10:00 pm	1404.61	B

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E163

Analysis of Variance Summary Table for Following Directions Total Time - Hard (Placebo group)

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Day (D)	2	843.2640	0.58	0.5669
Subject (S/D)	25	1452.1792		
<u>Within Subjects</u>				
Time (T)	7	276.3777	3.02	0.0042
T x D	14	113.4501	1.27	0.2288
T x S/D	171*	89.1775		

* Four degrees of freedom lost due to missing data

TABLE E164

Newman-Keuls Results for Following Directions Total Time - Hard - Time of Day
(Placebo group)

Time	Mean	Group
8:00 am	78.936	A
10:00 am	76.800	A
4:00 pm	74.318	AB
2:00 pm	74.289	AB
12:00 pm	73.718	AB
6:00 pm	72.861	AB
8:00 pm	72.764	AB
10:00 pm	68.186	B

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E165

Analysis of Variance Summary Table for Following Directions - Mean Time - Medium
(Placebo group)

Source of Variance	df	MS	F	p
<u>Between Subjects</u>				
Day (D)	2	18.6580	1.83	0.1811
Subject (S/D)	25	4.7280		
<u>Within Subjects</u>				
Time (T)	7	1.1331	2.87	0.0073
T x D	14	0.9798	2.48	0.0031
T x S/D	171*	0.3945		

* Four degrees of freedom lost due to missing data

TABLE E166

Newman-Keuls Results for Following Directions Mean Time - Medium - Time of Day
(Placebo group)

Time	Mean	Group
8:00 am	4.0421	A
10:00 am	3.7925	AB
4:00 pm	3.7850	AB
2:00 pm	3.7218	AB
12:00 pm	3.6654	AB
6:00 pm	3.5936	AB
8:00 pm	3.4618	B
10:00 pm	3.4125	B

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E167

Summary Table of Significant Performance Measures

Dependent Variable	Hours Post Ingestion	Grouping	Mean	Drug
<u>Following Directions</u>				
Percent total hits	1	A	90.9286	Placebo
		A	90.3750	Hismanal
		B	84.3221	Benadryl
<u>Serial Addition/subtraction</u>				
Mean reaction time	3	A	1.2427	Benadryl
		B	1.0541	Hismanal
		B	1.0266	Placebo
	5	A	1.08589	Placebo
		A	1.04637	Benadryl
		B	0.92150	Hismanal
<u>Unstable Tracking</u>				
RMS error	1	A	18.9586	Benadryl
		B	15.8310	Placebo
		B	13.9310	Hismanal
	3	A	18.4379	Benadryl
		AB	16.0	Placebo
		B	15.0138	Hismanal

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E168

Summary Table of Significant Subjective Measures

Dependent Variable	Grouping	Mean	Drug
POMS			
Tension - anxiety	A	4.7796	Benadryl
	B	3.8799	Hismanal
	B	3.6938	Placebo
Vigor - activity	A	14.7345	Placebo
	A	14.4730	Hismanal
	B	13.0202	Benadryl
Fatigue - inertia	A	6.4909	Benadryl
	A	5.2609	Hismanal
	A	5.2244	Placebo

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E169

Summary Table for Vigor-Activity scale on Mood Scale II and the POMS

Dependent Variable	Grouping	Mean	Drug
Vigor - activity			
<u>8:00 am</u>			
Mood Scale II	A	2.2176	Placebo
	B	2.0329	Hismanal
	B	1.8565	Benadryl
POMS	A	15.2500	Placebo
	B	4.8057	Hismanal
	C	1.8056	Benadryl
<u>10:00 am</u>			
Mood Scale II	A	2.0876	Placebo
	A	2.0824	Hismanal
	B	1.8570	Benadryl
POMS	A	14.8929	Placebo
	A	14.5186	Hismanal
	B	11.5926	Benadryl

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E170

Summary Table for Fatigue-Inertia scale on Mood Scale II and the POMS

Dependent Variable	Grouping	Mean	Drug
<u>8:00 am</u>			
Mood Scale II	A	1.7590	Benadryl
	B	1.5319	Hismanal
	B	1.3814	Placebo
POMS	A	8.8519	Benadryl
	B	5.8146	Hismanal
	B	4.2857	Placebo
<u>10:00 am</u>			
Mood Scale II	A	1.7665	Benadryl
	B	1.5081	Placebo
	B	1.3810	Hismanal
POMS	A	9.0741	Benadryl
	B	5.9286	Placebo
	B	4.6296	Hismanal
<u>12:00 pm</u>			
Mood Scale II	A	1.5170	Benadryl
	A B	1.4519	Hismanal
	B	1.2933	Placebo
POMS	A	6.0370	Benadryl
	A B	5.3214	Hismanal
	B	3.8214	Placebo
<u>2:00 pm</u>			
Mood Scale II	A	1.6267	Benadryl
	A B	1.5086	Hismanal
	B	1.4048	Placebo
POMS	A	7.0000	Benadryl
	A B	5.2857	Hismanal
	B	4.9286	Placebo

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE E171

Summary Table for Confusion, Sleepiness, and Performance Scales

Dependent Variable	Grouping	Mean	Drug
<u>Confusion - Bewilderment</u>			
8:00 am	A	5.6667	Benadryl
	B	4.6668	Hismanal
	C	3.3571	Placebo
10:00 am	A	5.7778	Benadryl
	B	3.9629	Hismanal
	B	3.6429	Placebo
<u>Sleepiness</u>			
8:00 am	A	4.0741	Benadryl
	B	3.1071	Hismanal
	B	2.8571	Placebo
10:00 am	A	3.8889	Benadryl
	B	3.0000	Hismanal
	B	2.8929	Placebo
<u>Performance</u>			
8:00 am	B	3.8214	Placebo
	B	3.7857	Hismanal
	A	3.0000	Benadryl
10:00 am	B	3.7143	Placebo
	B	3.5714	Hismanal
	A	3.0741	Benadryl

Note: Means with the same letters are not significantly different, $p > 0.05$.