THE EFFECTS OF ANTIHISTAMINE USE ON VISUAL SEARCH TASKS

by

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Thesis submitted to the Faculty of the
Virginia Polytechnic Institute and State University
in partial fulfillment of the requirements for the degree of

MASTERS OF SCIENCE
in
Industrial Engineering and Operations Research

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May, 1990

Blacksburg, Virginia

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(ABSTRACT)

Previous research has shown that most antihistamines have sedative effects and can lead to deterioration of psychomotor performance. The objective of this research was to determine if two antihistamines (diphenhydramine and astemizole) administered at a therapeutic dose level will affect a subject's visual search capabilities. The results of this research indicate that astemizole did not significantly decrement a subject's ability to visually search as compared to the performance of that same subject after ingesting a placebo. Diphenhydramine produced significantly poorer visual search results than did astemizole.

ACKNOWLEDGEMENTS

The author would like to acknowledge a number of people for their contributions and support of this thesis. I would first like to thank Dr. Harry Snyder for all his help and encouragement throughout the entire project. His leadership and guidance allowed me to set and attain challenging goals. I would also like to thank the other members of my committee, Dr. Robert Beaton and Professor Paul Kemmerling, whose advice and suggestions contributed to the success of this thesis.

I am gratefully indebted to Major Valerie Rice for including me in her dissertation research. Without her, this project would not have been successful. I would also like to thank Charlotte Waggoner, the third member of the research team, for her help. A special thanks goes to Linda Gooding; without her computer expertise and moral support the difficulty of this project would have been insurmountable.

The author wishes to thank a number of people for their emotional support. A special thanks to my immediate family (Mom, Dad, and Glenn) for their encouragement to move forward and achieve all of my goals. A sincere thanks to Wynand, whose caring and understanding kept me going. Finally, thanks to my friends, Christy, Linda, Dianne, and the fifth floor of Whittemore for not allowing me to lose my sense of humor.

Preface

This research was conducted under Contract #88337003 for the United States Army Medical Research and Development Command, Fort Detrick, MD, as an auxiliary study to Major Valerie Berg Rice's dissertation entitled "Complex Cognitive Performance and Antihistamine Use." Therefore, many parameters of this research were dictated by the procedures of Major Rice's research.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Research has shown that H1-receptor antagonists (classic antihistamines) affect the central nervous system (Nicholson, Smith, and Spencer, 1982; White and Rumbold, 1988). These central nervous system effects, such as sedation, drowsiness, and altered psychomotor performance, may reduce a person's ability to operate heavy machinery or perform complicated cognitive tasks. Classic antihistamines affect the central nervous system because they are able to cross the blood-brain barrier without difficulty. However, there are two new antihistamines, astemizole (hismanal) and terfenadine (seldane), which have difficulty crossing the blood-brain barrier and consequently do not affect the central nervous system. Previous research has shown that both hismanal (Nicholson et al., 1982; Nicholson and Stone, 1982; Richards, Brogden, Heel, Speight, and Avery, 1984) and seldane (Kulshrestha, Gupta, Turner and Wadsworth, 1978; Nicholson et al., 1982) have few sedative side effects and would therefore be beneficial in a work environment.

New drugs are most often tested by comparing a drug of known sedative level to a new drug. Therefore, the known antihistamine diphenhydramine (benadryl) was selected to serve as the control to which to compare the new drug. Benadryl has known central nervous system effects. Hismanal was selected for use in this study rather than seldane because of the possible therapeutic advantages of hismanal over seldane. Hismanal has a high and specific level of histamine H1 antagonism (Bateman and Rawlins, 1984, and Vanden Bussche, 1984, both as cited by Rice, 1990) and has produced an

effective therapeutic response in patients treated for up to one year (Wihl, Petersen, Petersen, Gundersen, Bresson, and Mygind, 1985). In contrast, seldane has shown to decrease in effectiveness after two to four weeks (Cainelle, Seidenari, Valsecchi, and Mosca, 1986, and Howarth and Holgate, 1984, both as cited by Krstenansky and Cluxton, 1987).

Many people choose to use over-the-counter drugs to relieve symptoms of allergic rhinitis. These drugs, which often contain antihistamines, can cause sedation which may affect the user's occupational performance. A drug that does not cause sedation will allow people to perform their normal daily duties without being restricted by the illness or the drug. A testing system that uses therapeutic doses of antihistamines could be used to predict a subject's ability to perform real-world tasks that resemble those modelled in the testing system.

REVIEW OF LITERATURE

Histamine/Antihistamine

Histamines are found naturally in human tissues, organs, and body fluids. The release of histamines can result in various symptoms such as itching of the skin, a drop in blood pressure, urticaria, edema of mucous membranes, peripheral circulatory failure, bronchospasm, and increased gastric secretion (Di Palma, 1971). The cardiovascular system also is affected by histamines. Histamines relax or constrict arteries and alter venous tone, dilate capillaries while increasing permeability, affect cardiac muscles, release adrenergic mediators, and decrease both systemic blood pressure and cerebral circulation (Bergersen, 1979; Di Palma, 1971). The release of histamines can be caused by allergens, various drugs, or tissue irritants. The abnormal release of these histamines from storage sites is considered to be the primary cause of the symptoms of clinical allergy (Bergersen, 1979).

Antihistamines block the action of histamines by binding with receptors and preventing the physiologic action of histamine (Di Palma, 1971). Antihistamines are used to treat allergies, hives, upper respiratory edema, atopic dermatitus, hay fever, bronchial asthma, motion sickness, and Parkinsonian symptoms (Di Palma, 1971). Since approximately 10 percent of the population suffers from allergies (Rice, 1990), the use of antihistamines to relieve allergy symptoms is common practice and affects a rather large number of people.

Antihistamines produce various side effects including sedation (from decreased alertness to muscular weakness and intense drowsiness), loss of appetite, nausea, vomiting, epigastric distress, constipation, diarrhea, dryness of mouth, frequent urination, hypertension and hypotension, headache, faintness, tightness of the chest, and visual disturbance. Minor side effects can be alleviated by altering the dosage. Serious illness from toxic doses of antihistamines is rare (Di Palma, 1971). 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." The sedation effects of most antihistamines will either disappear in two to three days or, after prolonged usage, a tolerance will be built up to the sedation effects (Bergersen, 1979).

Pharmacokinetics

Hismanal (Astemizole). Hismanal is produced by Janssen Pharmaceutical Company. The normal (therapeutic) dosage of hismanal is 10 mg taken once a day on an empty stomach (one hour before or two hours after a meal). Whenever symptoms are severe dosage is increased to 30 mg per day for seven days, followed by 10 mg daily. The half life of hismanal ranges from 20 to 24 hours (Heykant, 1984, and Paton and Webster, 1985, both as cited by Rice, 1989) and the terminal life ranges from 9.2 to 13 days (Meuldermans, Hendricks, Lauwers, Hurkmans, Swysen, and Heykants, 1986, as cited by Krstenansky and Cluxton, 1987). Maximum concentration of astemizole in the

body's plasma occurs one to four hours after oral doses of 10 to 40 mg (Richards et al., 1984).

Hismanal has difficulty crossing the blood brain barrier, which explains the lack of sedative effects. Sedation effects occurred a reported 21.5 percent of the time for hismanal (combination of five reports cited by Krstenansky and Cluxton, 1987).

Hismanal has produced no significant side effects when compared to a placebo (Richards et al., 1984). However, with prolonged use hismanal may increase appetite and promote weight gain (Tables 1 and 2).

Hismanal is FDA approved (December 28, 1988) and available in the United States.

Benadryl (diphenhydramine hydrochloride). Benadryl is marketed by Parke-Davis Products. The average dosage is 25 to 50 mg taken three or four times a day. Benadryl has been shown to produce anticholinergic (drying) and sedative effects in human subjects (American Society of Hospital Pharmacists, 1988).

The maximum activity of benadryl occurs approximately one hour after ingestion. The duration of activity is between four and six hours after ingesting an average dose. Benadryl passes the blood brain barrier easily; it therefore affects the central nervous system and results in sedation. The terminal half life of benadryl has not been researched extensively, but appears to range from 0.4 to 7 hours.

TABLE 1

Reported Side Effects of a Therapeutic Dosage of Hismanal (10 mg)

Side Effects	Number of Days	Percent Affected
Weight Gain	+ 60	4.4% (1)
		0.098% (3)
Sedation	- 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 of 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, all as cited by Rice, 1990.

TABLE 2

Occurrence (%) of Adverse Effects Reported in 978 Hismanal-Treated and 870 Placebo-Treated Patients

	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	5.2	6.2
Rash	0.3	---
Increased Appetite	3.2	0.2
Increased Weight	1.4	0.3

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

Indications and Usage

1. antihistaminic: for allergic symptoms and condition.
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 overdosages 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 on 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 interaction: Benadryl has additive effects with alcohol and other central nervous system depressants (hypnotics, sedatives, tranquilizers, etc.). Monoamine oxidase inhibitors prolong and intensify the anticholinergic effects of antihistamines.
4. Carcinogenesis, mutagenesis, impairment of fertility: Long term studies in animals to determine mutagenesic and carcinogenic potential have not been performed.

5. Pregnancy: Reproduction studies have been performed in rats and rabbits at doses 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 reaction:
1. General: uticaria (hives), rash, anaphalactic shock, photosensitivity, excessive perspiration, chills, dryness of mouth, nose and throat.
2. Cardiovascular: hypotension, headache, palpatations, 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 Effects on Visual and Visual-Motor Skills

Visual. Research has shown that dynamic visual acuity, the ability to perceive detail in moving targets during ocular pursuit, declines significantly after taking antihistamines (Nicholson, Smith, and Spencer, 1982). Nicholson et al. (1982) found significant effects on threshold and percentage of correct responses involving dynamic visual acuity while using triprolidine (a classic antihistamine), but not seldane or hismanal (Table 3). They found that pupil size was not altered by the antihistamines tested.

TABLE 3

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

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

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

Cohen, Hamilton, and Peck (1987) found that therapeutic doses of diphenhydramine impair visual motor tracking performance 2.5 hours after administering the drug. 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)."

Visual-motor. Visual-motor skills are usually tested using tracking tasks. Cohen et al. (1987) found that tracking skills were impaired 2.5 hours after ingesting 50 mg of benadryl. Another study (Moskowitz and Burns, 1988) involved seldane, benadryl, and a placebo and their effects on visual search, critical tracking, divided attention, and vigilance tasks (Table 4). The tracking task showed a performance decrement one and three hours after after ingesting benadryl (50 mg). White and Rumbold (1988) stated that tracking tasks seem to be the most sensitive to the disruptive effects of antihistamines.

Visual Search Tasks

Previous research has found that size and luminance differences between the target disk and that of the background disks have greater influence on the ability to locate the target disk than the density of background disks. Engel (1974) stated that by comparing complex-background visibility data with the simple-background results, it is easy to recognize the interfering influence of the background disks as the size of the target disk gets closer to the size of the background disks. Jenkins and Cole (1982) conclude that the task of

TABLE 4

Effects of Antihistamines (diphenhydramine and seldane) on Psychomotor Performance. (an adaptation of Table 1 from White and Rumbold, 1988, p. 5)

	Diphenhydramine (50 mg)	Seldane (60 mg)
Visual Search	+	-
Vigilance	+ (1,2)	-
Divided Attention	+	-
Critical Tracking	+	-

(+) indicates a significant effect, (-) indicates a nonsignificant effect. Results obtained from (1) Moskowitz and Burns, 1988; (2) Fink and Irwin, 1979.

discriminating a target that differs in size from the element of a complex background is no more difficult than comparing the size of two disks on an otherwise uniform background. Jenkins and Cole (1982) went on to say that differences in size between target and background disks are more effective than differences in luminance for the task of identifying the target disk.

Engel (1977) was able to relate experimentally the cumulative probability of target recognition against search time with the size of the conspicuity area concerned by assuming random distribution of fixation positions over the display area during search. Engel (1977) defined the conspicuity area as the retinal field in which a target can be recognized during a single eye pause, when the subject has no previous knowledge of the target's location. Engel confirmed Howarth and Bloomfield's (1969) findings (as cited by Engel, 1977) that the average search time is inversely proportional to the squared difference in diameter between target disk and background disk. As the diameter of the target disk approaches the diameter of the background disk, the search time increases. Engel's (1977) results differ from those obtained by Jenkins and Cole (1982); however, this difference is explained by the smaller background disk size and longer periods of exposure to the testing configuration (target disk among background disks) used by Engel (1977).

Visual search task experiments conducted in conjunction with antihistamines show a significant decrement in performance while under the influence of diphenhydramine (Moskowitz and Burns, 1988). Visual search performance was found to be poorer at all test times with diphenhydramine than seldane or a placebo; however, diphenhydramine only produced statistically significant

poorer performance three hours after ingestion, but not one or five hours after the drug was administered.

Subjective Reports

Moskowitz and Burns (1988) studied the effects of terfenadine (seldane), diphenhydramine, and a placebo on various types of skilled performance (visual search, critical tracking, divided attention, and vigilance). This experiment also required subjects to record whether they thought they received a drug treatment or a placebo for each test session. Subjects were able to recognize diphenhydramine as an active drug treatment, but their ability to recognize a placebo or terfenadine differed only slightly from a chance level.

PURPOSE OF THE PRESENT RESEARCH

The objective of this research was to determine if two antihistamines (diphenhydramine and astemizole) administered at therapeutic dose levels would affect a subject's visual search capabilities. Previous research has shown a visual search performance decrement after ingesting benadryl (Cohen, Hamilton, and Peck, 1987; Moskowitz and Burns, 1988). The results from this research are expected to show a decrease in visual search performance after ingesting benadryl. This decrement in performance is expected to be especially noticeable for those variables involving the largest target size (the most difficult to discriminate from the background squares).

METHOD

Subjects

Thirty male subjects were recruited from the student body at Virginia Polytechnic Institute and State University. The use of only males eliminated the necessity for pregnancy screenings prior to each test session. Antihistamine studies often require females not to be using birth control pills and do not allow performance testing for several days prior to, during, and for several days following menstruation. Of the 30 recruited subjects, 27 subjects successfully completed all the required screening and assessment.

The subjects were recruited with the use of advertisements posted throughout the campus of Virginia Polytechnic and State University. Potential subjects were initially screened with the use of a questionnaire presented over the telephone by a member of the research team. Subjects that passed the initial screening were required to meet with a member of the research team for an individual interview and to complete a medical questionnaire. The individual interview included an explanation of the experiment, exactly what would be required of the subjects, the amount of time required to complete the experiment, method of payment, and associated risks. Subjects were permitted to ask any questions. The medical questionnaire was developed in conjunction with Philip L. Barkley, M. D., Chief Medical Officer and Director of Health Services, Virginia Polytechnic Institute and State University. All questionnaires and the students' health records were reviewed by Dr. Barkley. Approximately

90 potential subjects filled out medical questionnaires. 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 before the subjects began the experiment, subjects met with the members of the research team and were scheduled for their test days. This group interview/explanation included an introduction to the research team, an explanation of the experiment and its purpose, an emphasis on the time commitment for participation, and procedural requirements and constraints. The subjects read and signed the informed consent forms at this group meeting. The subjects used in this experiment possessed the characteristics summarized in Table 5.

Experimental Design

To achieve the research objectives, a two-factor (3 x 8) repeated measures, double-blind design focusing on subjects, sessions, and drugs was used (Figure 1). 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 is completed. Each of the 30 subjects received each of the three drugs. Drugs were administered on three different days. The order of the drug administration was counterbalanced, as shown in Table 6. A balanced random order design was achieved by assigning applicants, as they qualified, to the next available sequence number. A group variable was employed as a between-subjects factor, with five subjects assigned to each group. Although it was preferred for the same six subjects to return on the three testing days, this was not necessary. Each subject was assigned a specific number which

TABLE 5

Personal Data of Subjects

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

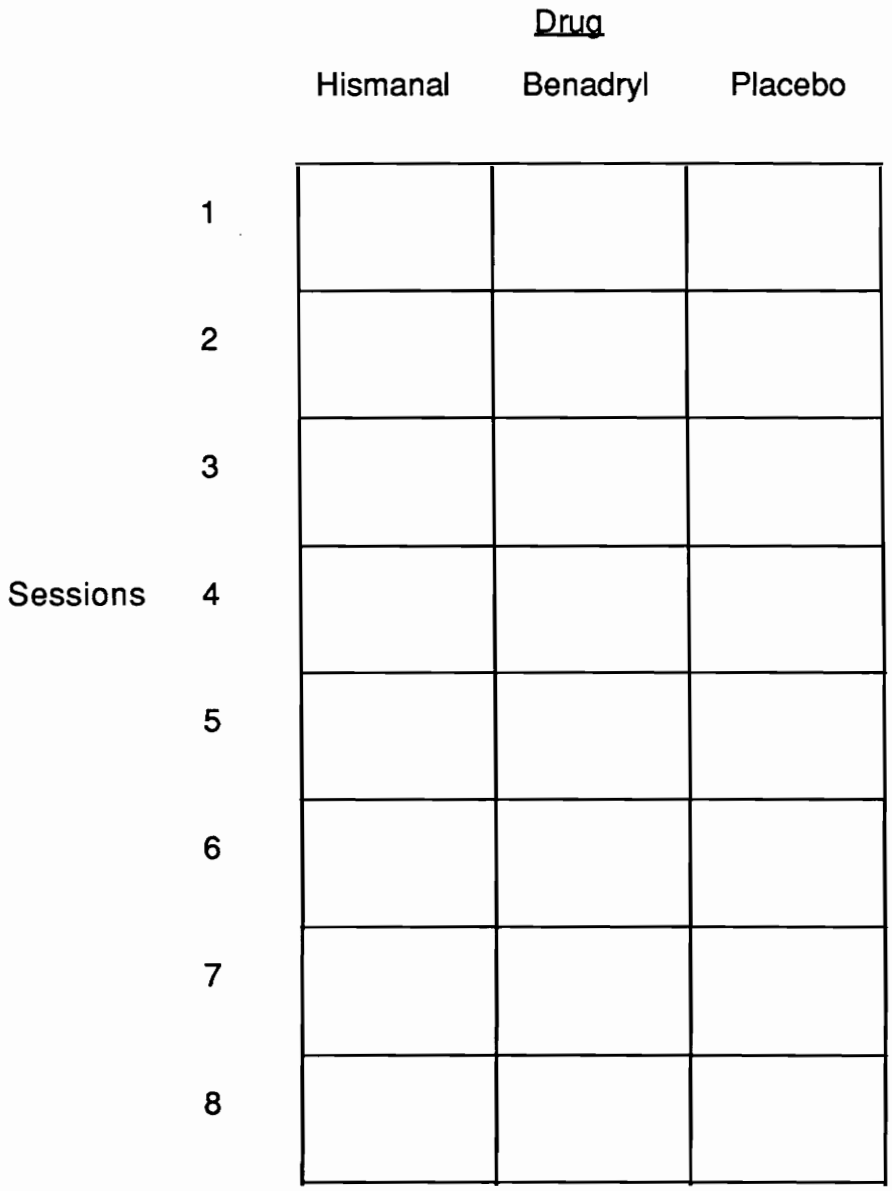

Figure 1. Two-factor, within-subjects, 3 x 8 design.

TABLE 6

Counterbalance for Treatment (drug administration)

	Test Day		
	1	2	3
Group 1	H	B	P
Group 2	B	P	H
Group 3	P	H	B
Group 4	H	P	B
Group 5	B	H	P
Group 6	P	B	H

Abbreviations: H = hismanal, B = benadryl, P = placebo

coincided with a medication packet number. The medication packet contained three sealed envelopes, labeled Test Day 1, Test Day 2, and Test Day 3 which indicated the order of administration.

On each treatment day, eight test sessions were scheduled for each subject (Table 7). The order of the individual test measurements was controlled by giving the tests in the same order for each application.

Equipment

The tests were computerized and designed to run on IBM-PC compatible (Zenith, Model K) microcomputers meeting the following minimal specifications:

1. CPU processor: a 16-bit 80286 processor with a clock speed of 8.0 MHz.
2. Math coprocessor: 80287 math coprocessor.
3. Disk storage: two soft-sectored, double-sided, double-density, 48 tracks-per-inch 360 kilobyte 5.25-inch floppy disk drives and one 20 megabyte hard disk drive.
4. Random access memory: 640k RAM memory.
5. BUS: must be IBM compatible, with 4 unused slots minimum.
6. Input/Output: two RS-232C serial ports and one parallel port.
7. MS-DOS operating system version 3.2 or above.

TABLE 7

Test Sessions Scheduled for Each Day

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

*** drug administration

* test session

The video display specifications were as follows: a 12-inch high-resolution RGB color monitor that operates in a non-interlace mode, capable of a minimum of 640 x 400 pixel resolution, with a minimum of 16 colors.

The Systems Research Laboratory PC-Labpac Multifunction Board, designed specifically for Unified Tri-Service Cognitive Assessment Battery (UTC-PAB), combined the multi-event timer and workstation interface. It is a modular "plug-in" style unit which can contain three subject response apparatus simultaneously. Modular response apparatus required were a 180-degree switching joystick (used in the tracking and the tracking/memory search tasks) and a numeric keypad (also used in the aforementioned tasks).

Although not required, an uninterruptable power supply was utilized for each individual work station. This not only provided power to continue functioning in case of an outage, but more importantly it protected the equipment from possible damage in the event of an outage.

Task Description

The visual search task to be used in this research was developed by Dr. John D'Andrea at the U. S. Naval Air Station, Pensacola, Florida. A computerized task was selected because of its compatibility with visual search tasks used in other military research.

This task consists of 80 to 120 small rectangles randomly placed on the screen with a crosshair in the center of the screen. All of the squares are a solid color (i.e., filled in). The blocks are black on a green background. The target square is smaller than the background squares (Figure 2). The subject locates

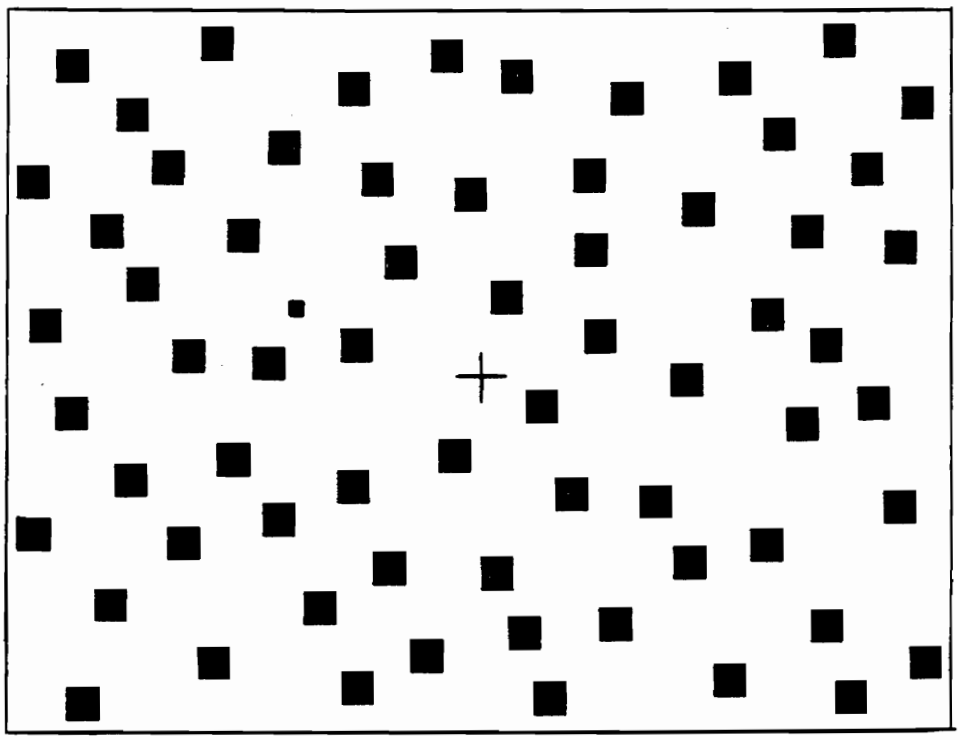

Figure 2. Sample screen from visual search task.

the one square that is smaller than the others and presses one of four keys to indicate which quadrant contains the target. There are three levels of difficulty: target square is 60%, 70%, or 80% the size of the background squares. Forty trials are run at each level. The entire test is always run in the same order with respect to difficulty level. For example, 40 trials at the 60% target size (referred to as the small target), then 40 trials at 70% (medium target), followed by 40 trials at the 80% target size (large target). However, within each difficulty level the presentations of background configurations and locations of the target disk are completely randomized. In addition, each session is separately randomized. Accuracy and time data are collected. The designer of this task was not concerned with the image quality of the equipment used to run this task (luminance, angular diameter, distance to screen, etc. were not specified but are held constant). The dependent variables which descibe all three target sizes (percent correct for all three size targets, overall mean, and overall standard deviation) and the dependent variables related to the largest size target (percent correct of large size target, mean time and standard deviation to correctly identify the large target, and number of large targets correctly identified) are believed to be the most meaningful because they will best detect the general effects of the antihistamine on visual search performance and the ability of the subject to discriminate between small differences while under the influence of antihistamines.

Procedure

Training. Subjects who were selected for this experiment were scheduled for six hours of training in either two 3-hour sessions or one 6-hour session. Total training time ranged from five to nine hours. Training time for the visual search task averaged 11.40 minutes. Two weeks were spent training all the subjects.

During the training sessions each subject was required to perform the tasks presented in the testing session a specified number of times. The subjects performed the entire visual search task (40 trails at each of three target sizes) five times. The tasks were broken up into four main groups (1) tracking, memory search, and tracking/memory search, (2) UTC-PAB, (3) Complex Cognitive Assessment Battery (CCAB), and (4) visual search. These groups could be presented in any order depending upon time constraints; however, most subjects received the four groups in the order presented above. Written instructions, verbal explanation, time for subject questions, and a brief demonstration were given prior to the subject beginning his training for the tracking/memory search tasks. Instructions for all other tasks were presented to the subjects on the computer screen immediately before the corresponding tasks were to be performed as described in the section entitled "instructions to subjects." Prior to beginning training, subjects completed a personal information questionnaire which included self ratings in several areas.

Testing. Subjects were divided into five groups of six subjects each. Each of the five groups were tested one day per week for three consecutive

weeks, for example, three Fridays in a row. The five different groups were tested on Tuesday, Thursday, Friday, Saturday, and Sunday.

Subjects were required to perform a baseline (review) session sometime during the day before they were to be tested. This baseline session consisted of a brief review (a few repetitions of the tasks conducted on the computer) of all the tasks to be performed during the testing sessions. Also during the baseline session, which took approximately one hour to complete, subjects were given any final instructions or reminders that pertained to the next days testing sessions.

Subjects were given a wake-up call at 6:30 a.m., if they so requested, on the day they were tested. Subjects were required to be at the laboratory at 7:00 a.m. Subjects were instructed not to eat or drink anything before they arrived at the laboratory because the drug needed to be taken on an empty stomach. Subjects were permitted to eat a light breakfast 30 minutes after ingesting the drug at 7:00 a.m. and before the testing batteries began.

Each subject received all three treatments (hismanal, benadryl, and placebo) over the course of the three testing sessions. For each testing session, two subjects received hismanal, two received benadryl, and two received placebo. Seven days later on the second test day, the same six subjects were tested, but each received a different drug than he did on the first test day. The third test day occurred one week later, with each subject receiving the third of the three drugs (whichever drug he did not receive on the first and second test days). This schedule was followed for all five groups.

Test batteries were administered one hour post drug ingestion and every two hours thereafter, as shown in Table 7, for a total of 16 hours. Subjects were

tested 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. Before each test battery the subjects' heart rate, blood pressure, and temperature were taken by a member of the reserach team and recorded. A stop watch, standard blood pressure cuff, and digital thermometer were used to determine the heart rate, blood pressure, and temperature of the subjects. The subjects were permitted to talk, read, study, sleep, watch video movies, or watch live television between testing batteries. Subjects were not permitted to leave the general vicinity of the laboratory. A member of the research team remained with the subjects throughout the entire day and a licensed physician was on call (via a beeper).

Subjects were required to remain in the laboratory for a total of 16 hours (even if they should decide to cease participation in the study). This was necessary due to the long half life on hismanal. (The peak effect of hismanal was expected to occur 10 to 12 hours after ingestion, while the peak effect of benadryl was expected to occur 1 to 2 hours post ingestion.)

The subjects brought their own breakfast. The subjects were permitted breakfast after ingesting the drug and before the first testing battery began. The subjects ate lunch after they completed the 12:00 pm test battery, and they ate dinner after the 6:00 pm test battery. Subjects were permitted to bring their lunch and dinner at the beginning of the day and keep it in the provided refrigerator, or someone would bring them their meals. Also, a member of the research team took orders and went to area fast food restaurants for some of the subjects' meals.

For all test sessions the specific tasks were presented in the following order: UTC-PAB, visual search, CCAB, tracking task, and tracking/memory

search task. On the third test day each subject was asked to complete a final questionnaire. (The UTC-PAB and CCAB were described by Rice, 1990.)

Doses of the drug were in the therapeutic range and administered by mouth. The placebo did not contain any active ingredients. The dosage for benadryl was 50 mg and for hismanal, 10 mg. Medications were in capsule form and all identical in appearance. All the medications were individually packaged for each subject by Janssen Pharmaceutical Company. Sixty envelopes were prepared, three for each subject. Each envelope was labeled by subject number and test day. The drug envelopes were kept in a locked vault within a locked room. Only medications required for that particular test day were removed. In the case of an emergency, a special code was provided which could be broken to determine which drug a subject had taken. One code was broken for one subject because he complained of chest pains. He was subsequently dropped from the study. A master list of the contents of each envelope was supplied to the research team after the experiment was completed.

Subjects were paid $4.00 per hour for the time actually spent participating in the study. If the subject completed the entire experiment, he was paid $5.00 per hour. No payment was made for time spent during the initial screening process. Payment was made in cash at the end of the last test day.

RESULTS

The visual search task software provides for measures on each of 26 dependent variables (Table 8). The target or box size "small" refers to the smallest of the three target sizes (60% of background box size) or, in other words, the largest difference between target size and background size. "Large" targets are those boxes that are closest in size (80%) to the background boxes. For each of these variables statistical analyses were used to test for significant differences among eight sessions, three drugs, and six groups.

An analysis of variance (ANOVA) was performed to determine if the group effect was significant and therefore should be included in the analysis of dependent variables. The group effect was not significant at the .05 level for any of the 26 dependent variables. The group and drug interaction was significant for 9 of the 26 dependent variables. However, closer examination of these seemingly significant effects yielded nothing consistent or logical; therefore, the group variable was disregarded in all subsequent analyses.

After the group effect was removed from the analysis, an ANOVA was used to examine the 26 dependent variables for significant differences among sessions (time of day, Table 9), drugs, and their interaction. Thirteen dependent variables were found to show significant differences. Post-hoc comparisons using the Newman-Keuls Sequential Range Test were made on the significant effects. Effects were considered statistically significant if the probability of a Type-1 error is less than .05. Numerical and graphical representations are contained in the following sections.

Percent Correct All Size Targets

An ANOVA of this dependent variable (Table 10) shows there are significant differences among sessions, drugs, and their interaction. A post-hoc comparison (Table 11) revealed that session 4 produced a significantly lower percentage of correct responses than session 8 (Figure 3). In addition, hismanal yielded a significantly higher percent correct than benadryl (Table 12 and Figure 4).

Further analysis was conducted on the significant interaction between drugs and sessions. A simple-effect F-test was performed on the drug variable at all eight levels of the sessions variable. Sessions 1 through 4 were significant at the .05 level (Table 13). The Newman-Keuls results for these sessions are shown in Tables 14-17. For sessions one and two, benadryl produced a lower number of correct responses than both the placebo and hismanal. However, for sessions three and four, hismanal led to better results than benadryl or the placebo (Figure 5).

Percent Correct for Large Targets

The ANOVA (Table 18) revealed a significant difference among drugs and their interaction with sessions. The subjects' performance after ingesting hismanal was significantly better than their performance after ingesting benadryl (Table 19 and Figure 6). Neither drug differed significantly from the placebo.

A simple-effect F-test was performed on the drug by session interaction. Sessions one through four were found to be significant (Table 20). Significantly fewer correct responses were achieved with benadryl than the placebo or

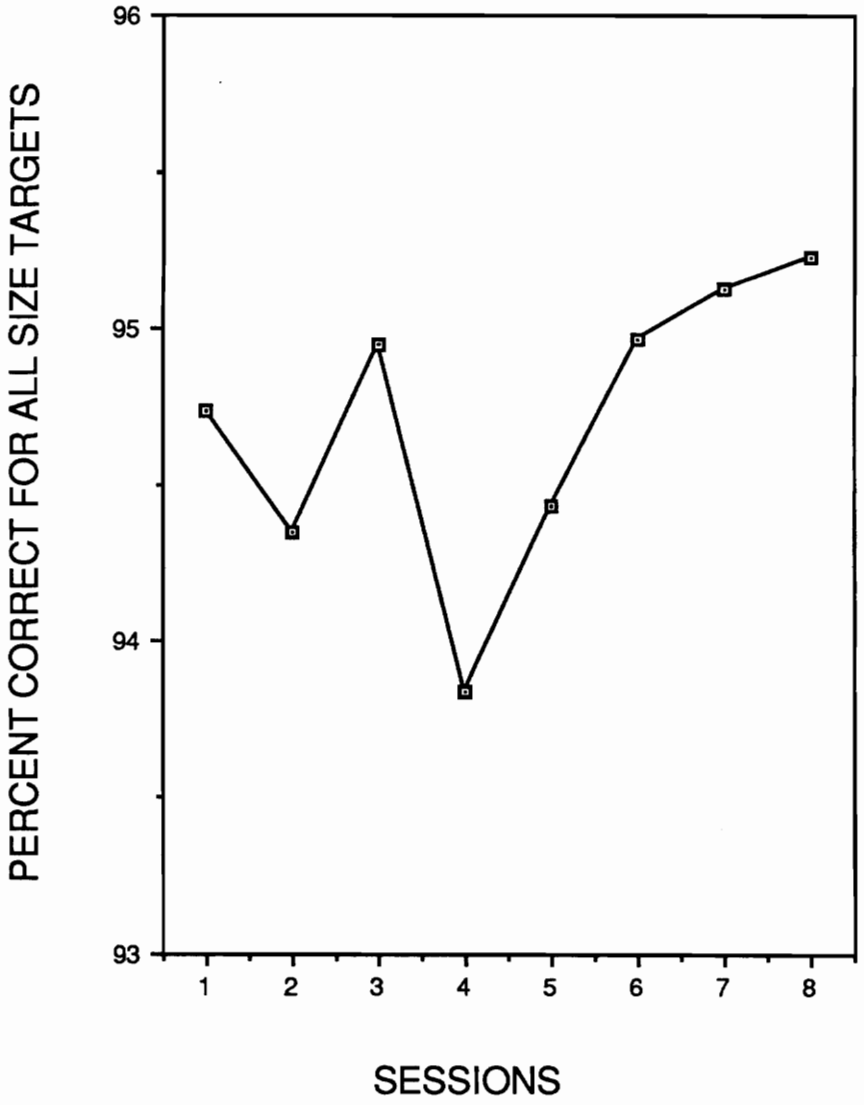

Figure 3. Sessions effect for percent correct for all size targets. The average standard deviation is 7.441.

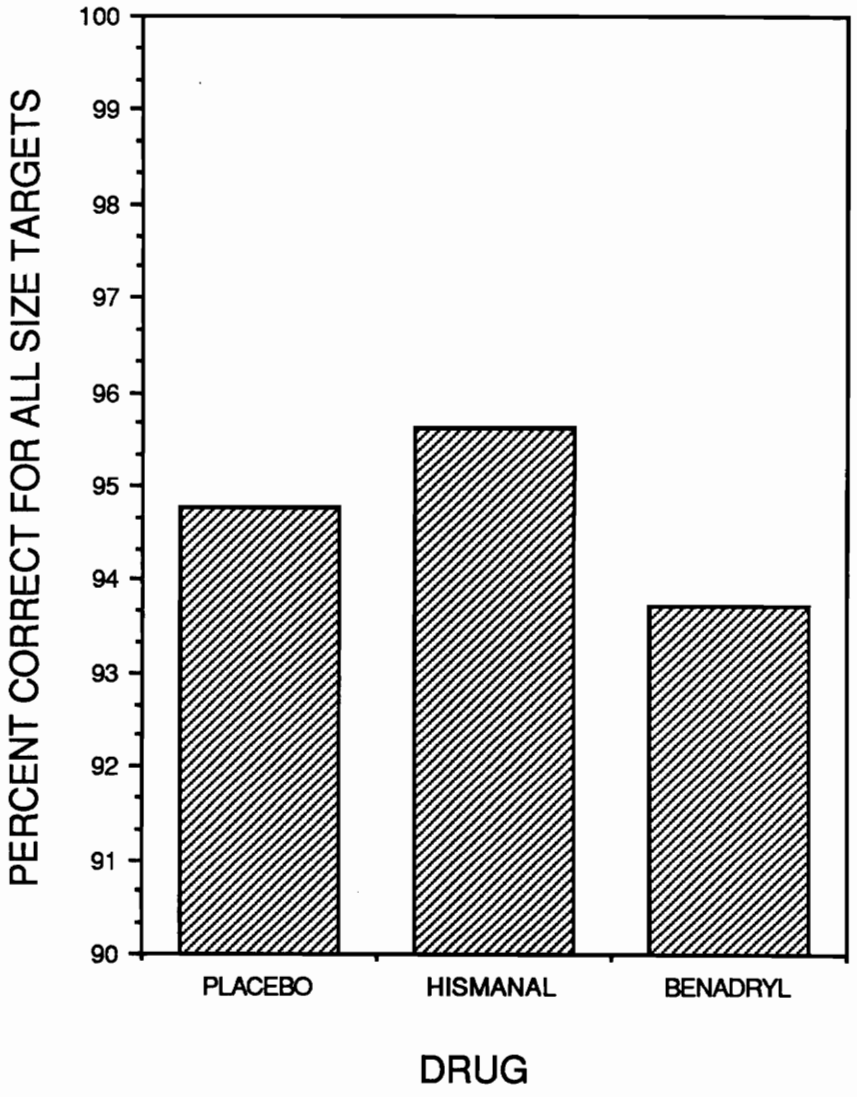

Figure 4. Drug effect for percent correct for all size targets. The average standard deviation is 7.375.

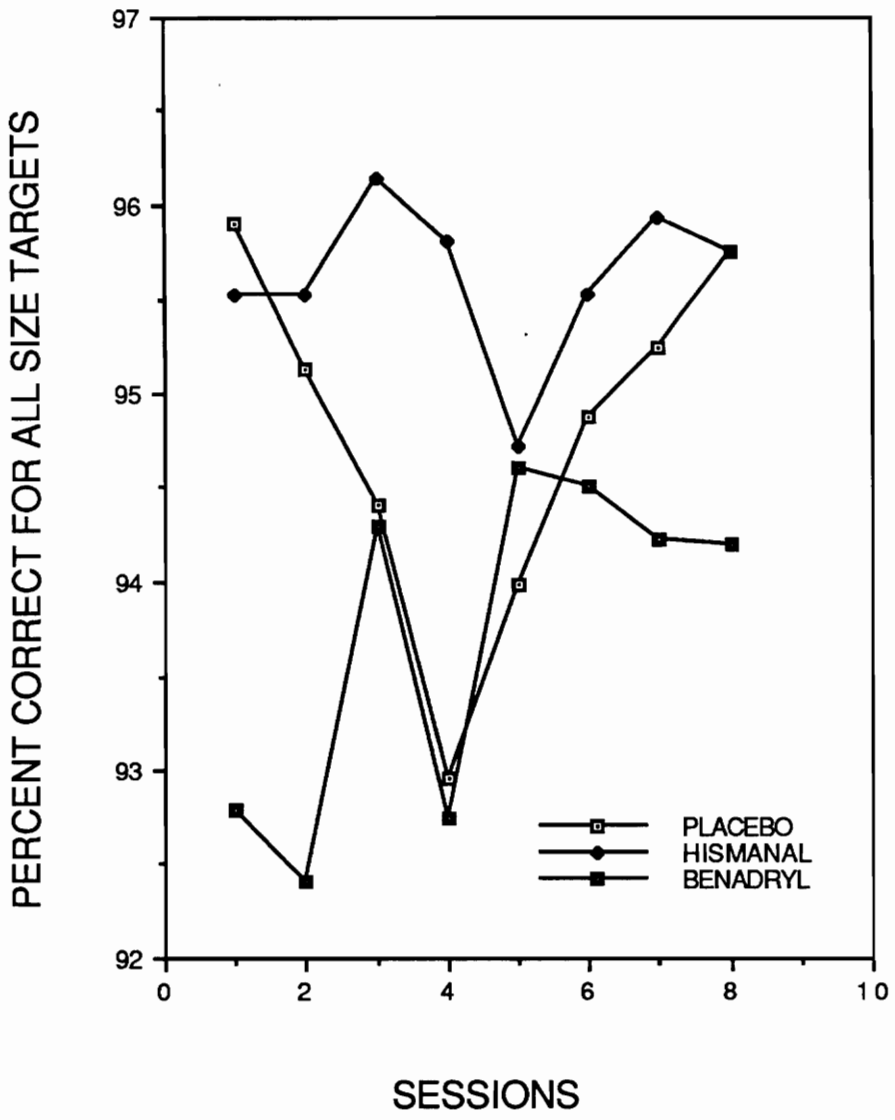

Figure 5. Sessions by drug interaction for percent correct for all size targets. The average standard deviation is 7.402.

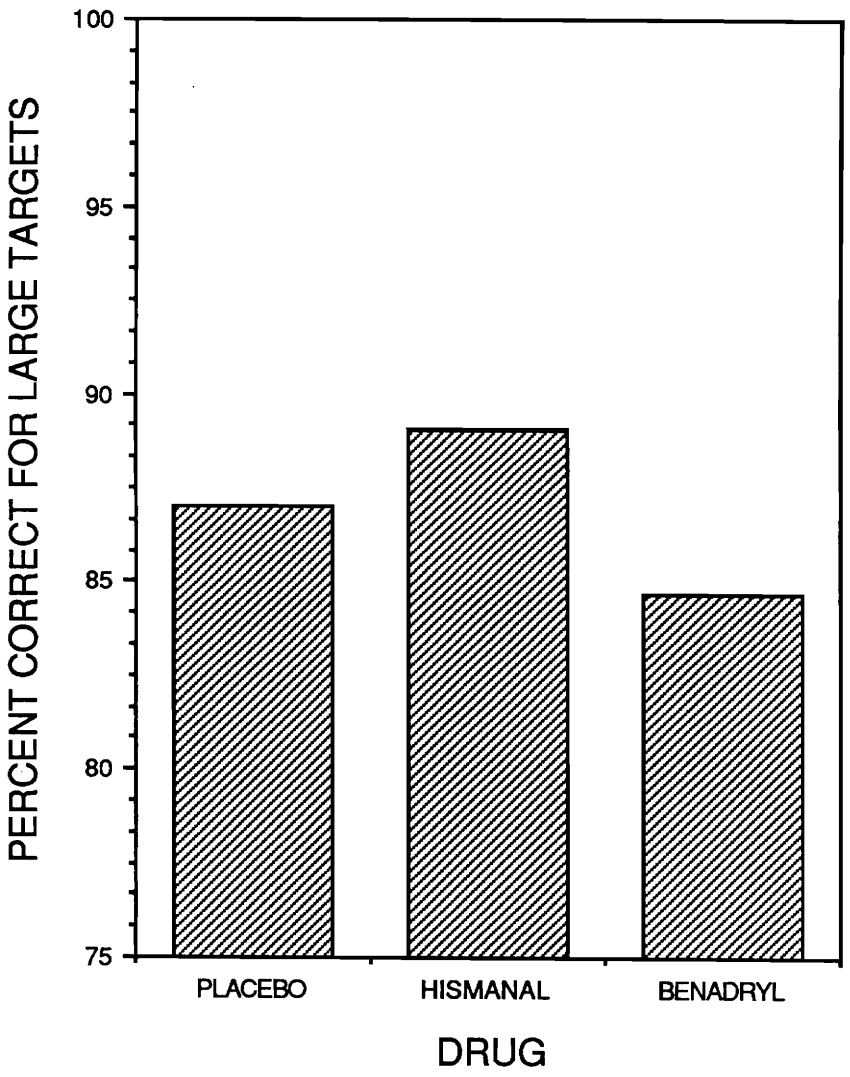

Figure 6. Drug effect for percent correct for large targets. The average standard deviation is 19.541.

hismanal for sessions one and two (Tables 21 and 22). The Newman-Keuls analyses for sessions three and four (Tables 23 and 24) show that hismanal resulted in a higher percentage of correct answers than benadryl or the placebo (Figure 7).

Mean Time to Match Small Targets

An ANOVA showed a significant difference among sessions (Table 25). During those sessions at the beginning of the day it took the subjects significantly longer to correctly match small targets than it did the last session of the day (Table 26 and Figure 8). A linear trend fits the data fairly well (R^2 = .909).

Standard Deviation to Match Small Targets

This variable's analysis of variance (Table 27) revealed a difference among sessions. There was a greater variance in response times during the first three sessions of the day than the last two sessions of the day (Table 28 and Figure 9).

Mean Time to Match Medium Targets

The ANOVA for this variable showed that sessions were significantly different (Table 29). The first two sessions had significantly slower times to match medium size targets than the other sessions throughout the day (Table 30 and Figure 10).

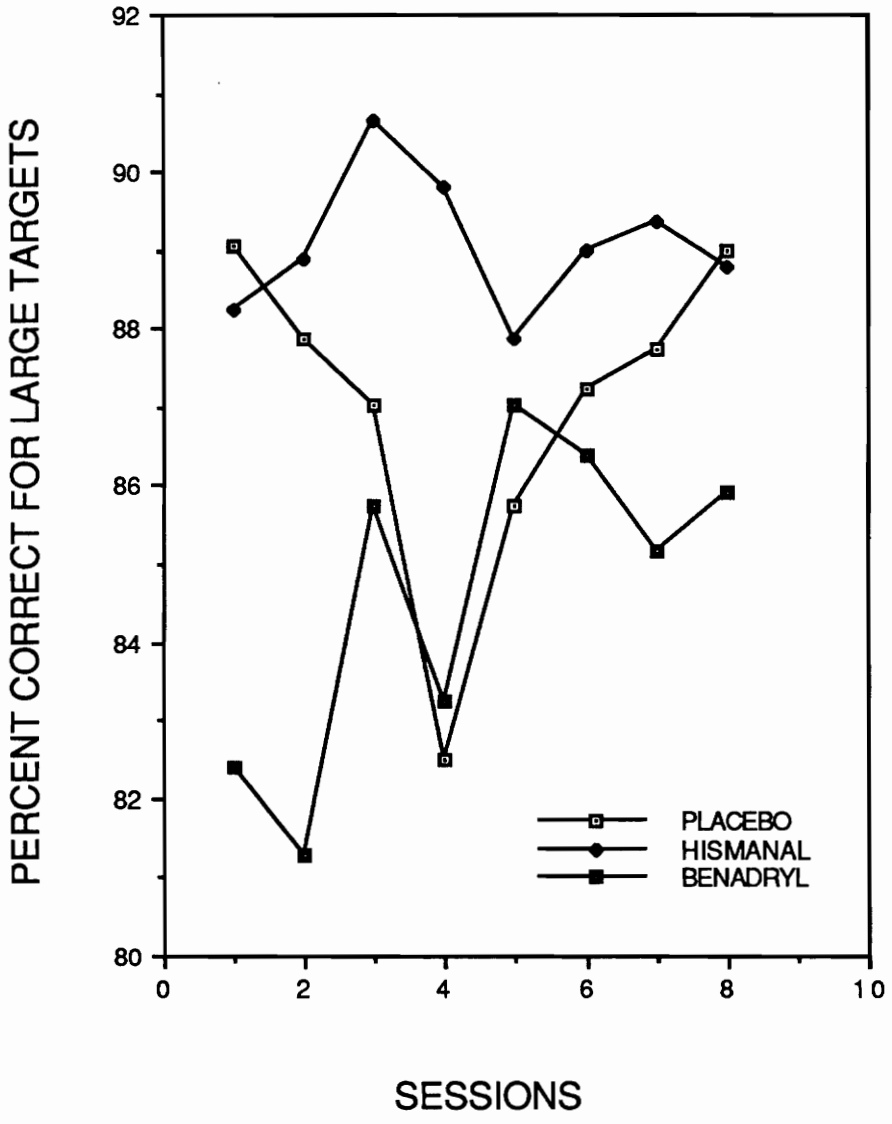

Figure 7. Session by drug interaction for percent correct for large targets. The average standard deviation is 19.741.

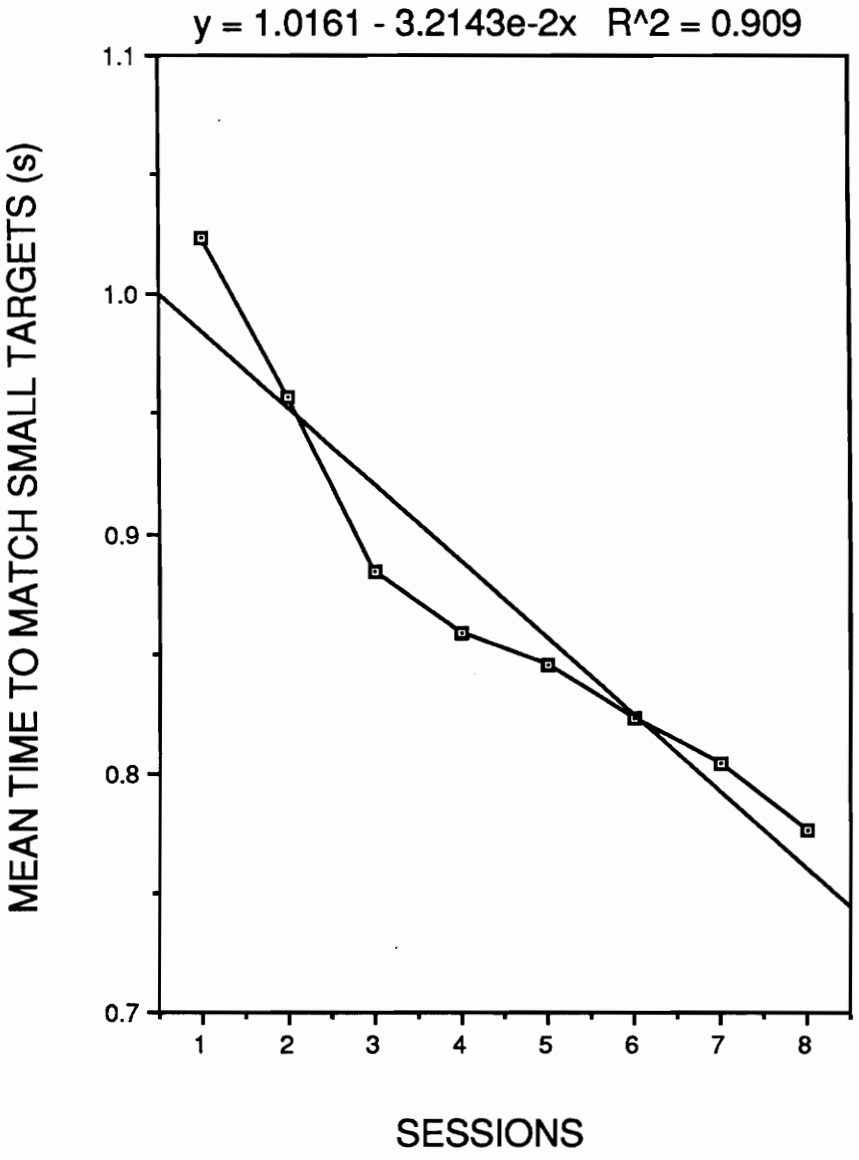

Figure 8. Sessions effect for mean time to match small targets. The average standard deviation is 0.279.

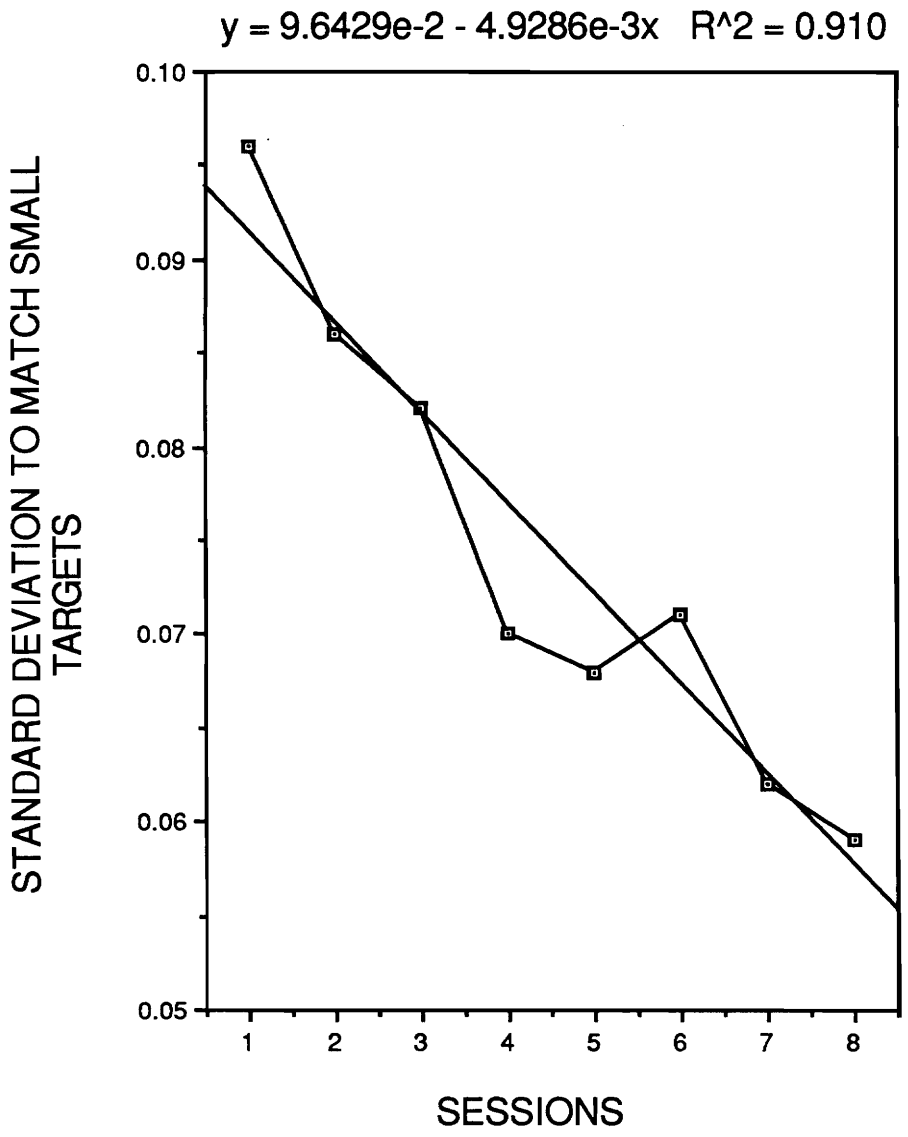

Figure 9. Session effect for standard deviation to match small targets. The average standard deviation is 0.057.

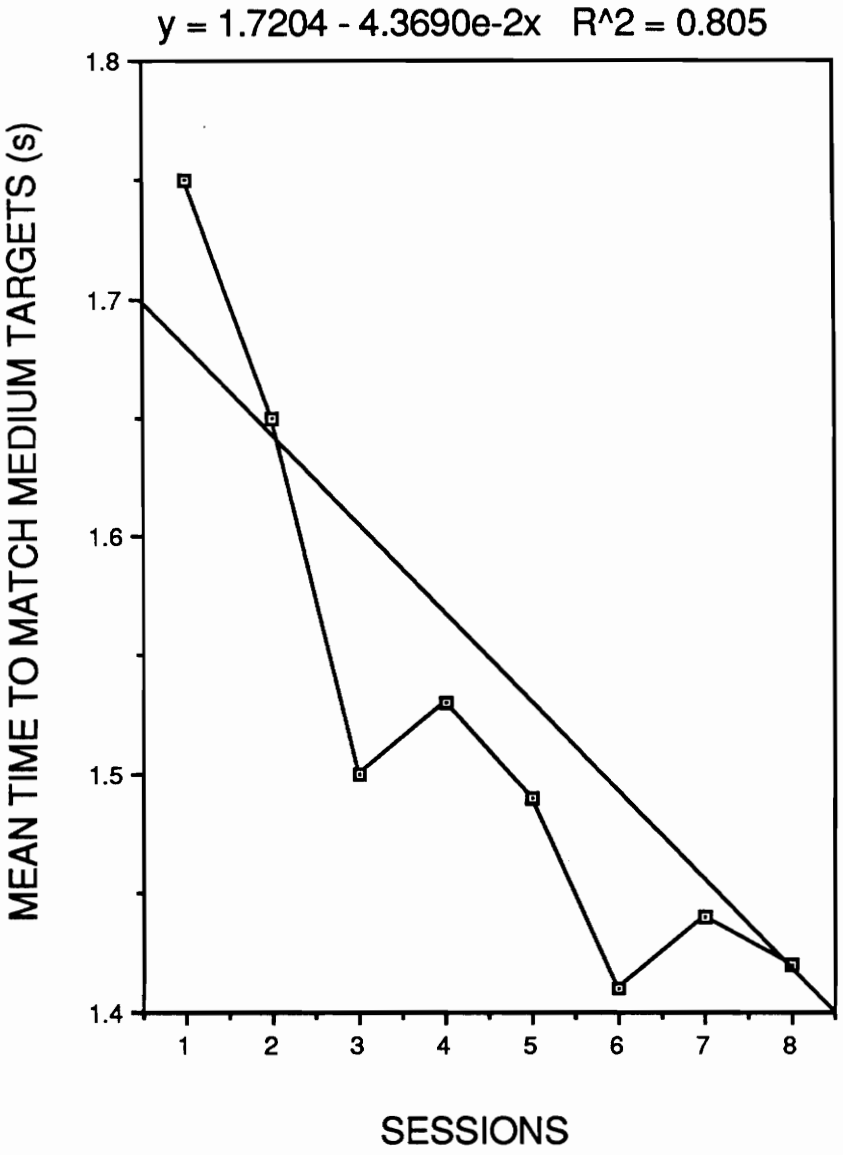

Figure 10. Sessions effect for mean time to match medium targets. The average standard deviation is 0.647.

Standard Deviation to Match Medium Targets

An ANOVA revealed a difference among sessions (Table 31). A post-hoc comparison showed that session 1 had a larger standard deviation than sessions 6, 7, and 8 (Table 32 and Figure 11), although the trend over all sessions is fairly linear (R^2 = .720).

Mean Time to Match Large Targets

The analysis of variance for this variable also showed a significant difference among sessions (Table 33). During the first three sessions of the day subjects took longer to correctly identify large targets than during the last session of the day (Table 34 and Figure 12). Again, a linear fit describes the session effect quite well (R^2 = .825).

Number of Matched Large Targets

Table 35 shows the ANOVA for this variable. The drug effect and the interaction between drug and sessions were found to be significant. Hismanal produced a significantly greater number of matched targets than benadryl (Table 36 and Figure 13). The placebo was not different from either drug.

The drug by session interaction is shown in Figure 14. A simple-effect F-test was performed on this interaction. Sessions one, two, three, and four were significant (Table 37). A Newman-Keuls comparison reveals that benadryl produced significantly fewer matched targets than the placebo and hismanal for sessions one and two (Tables 38 and 39). However, hismanal produced significantly more matched targets than the placebo and benadryl during sessions three and four (Tables 40 and 41).

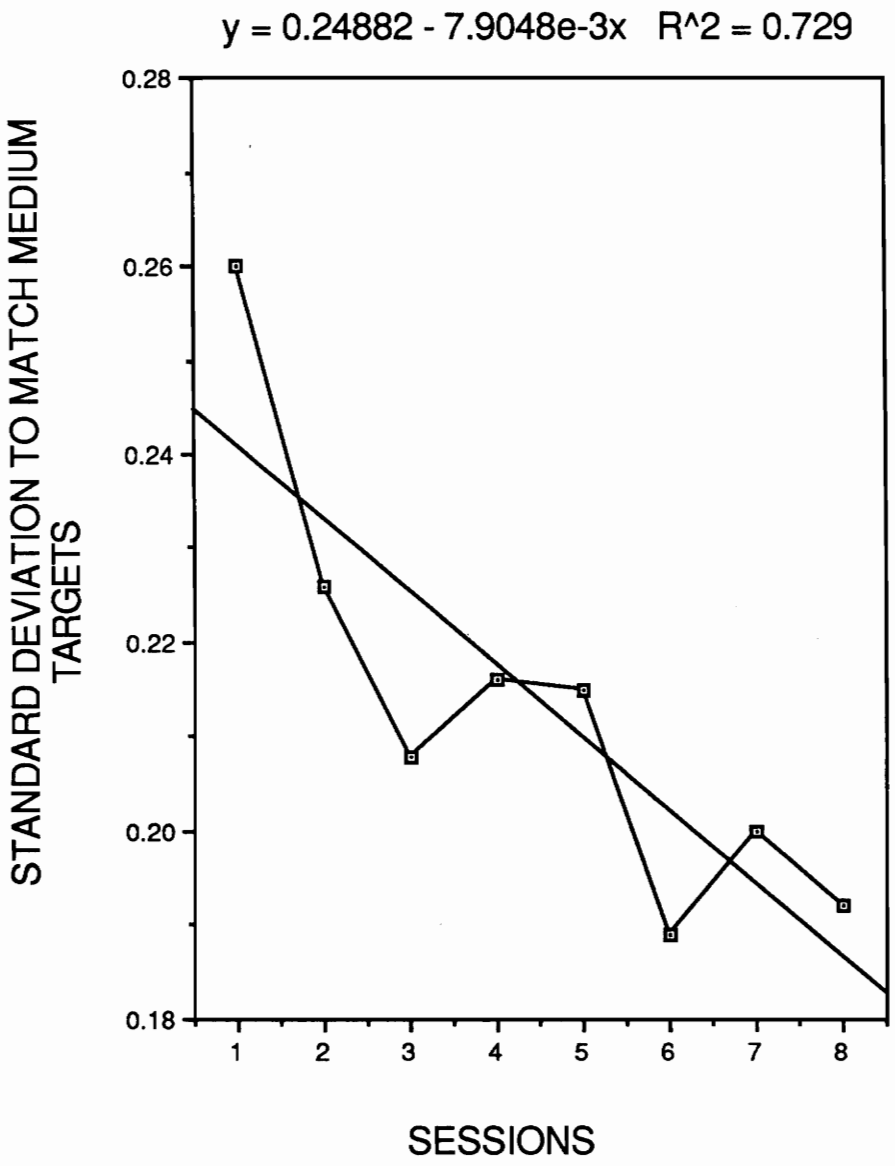

Figure 11. Sessions effect for standard deviation to match medium targets. The average standard deviation is 0.152.

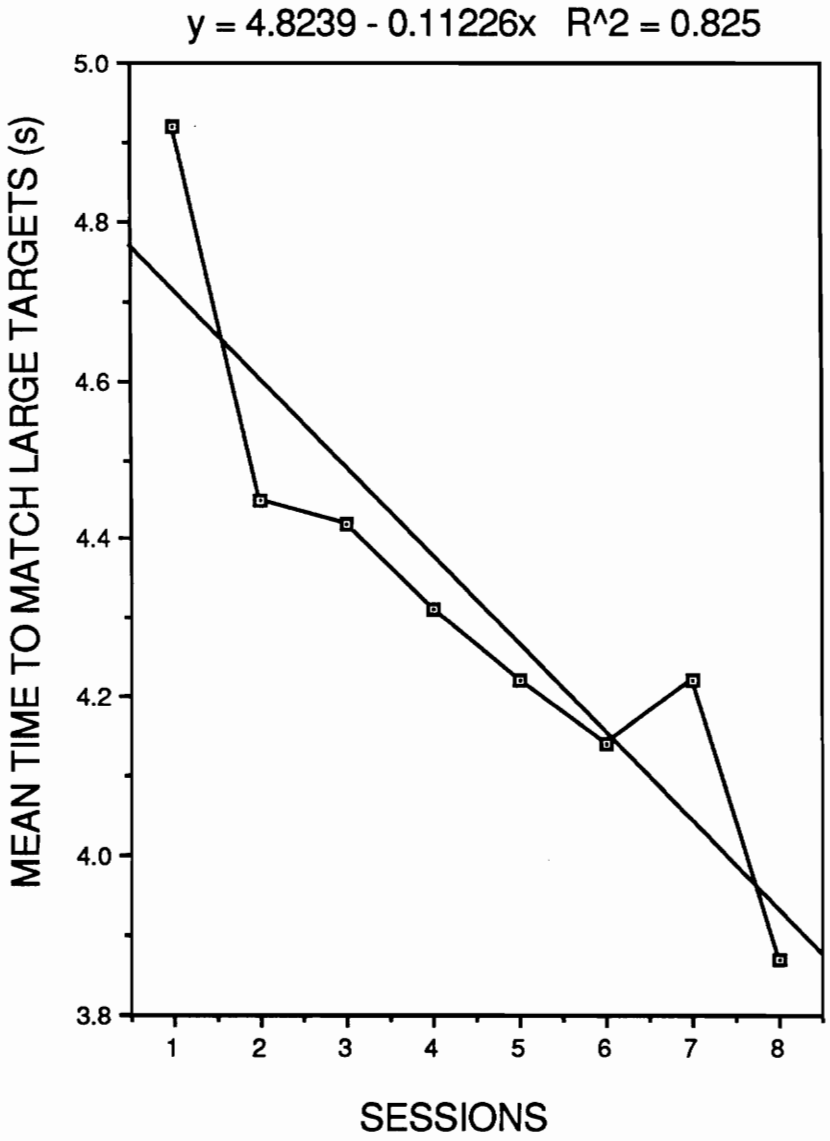

Figure 12. Sessions effect for mean time to match large targets. The average standard deviation is 1.919.

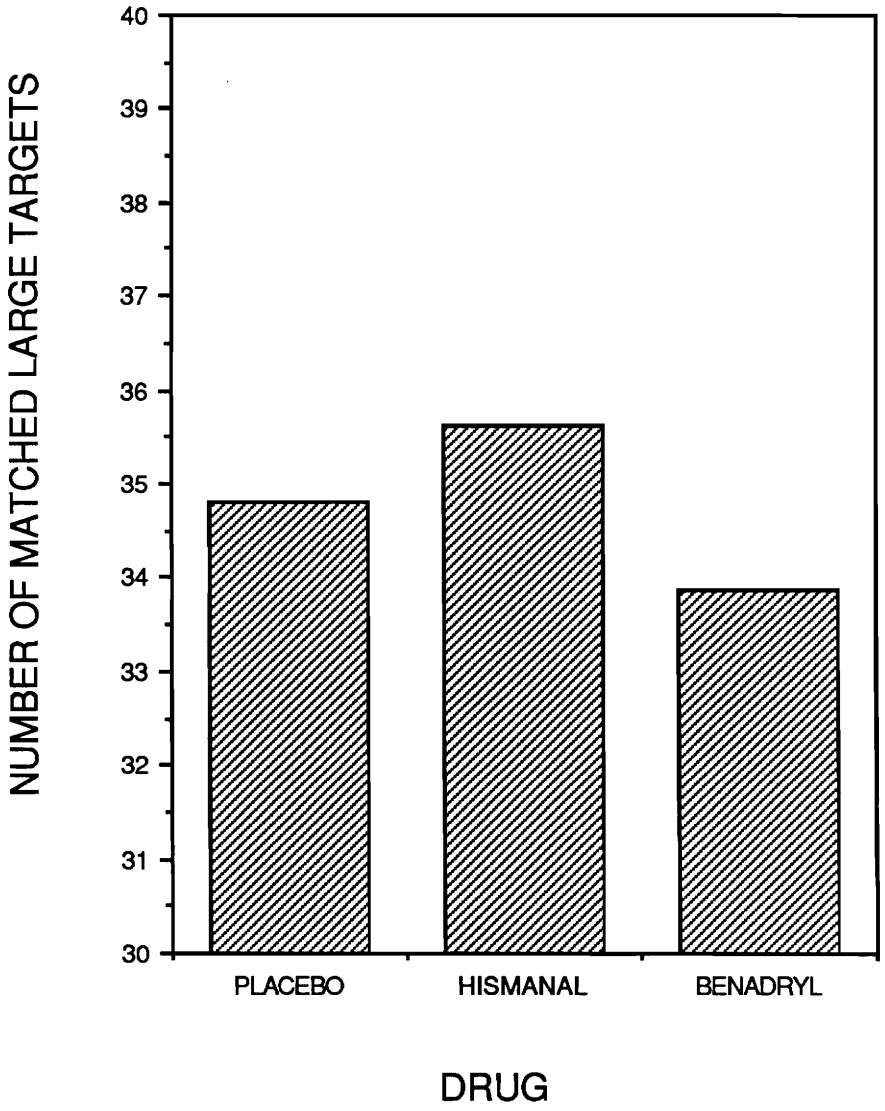

Figure 13. Drug effect for number of matched large targets. The average standard deviation is 7.816.

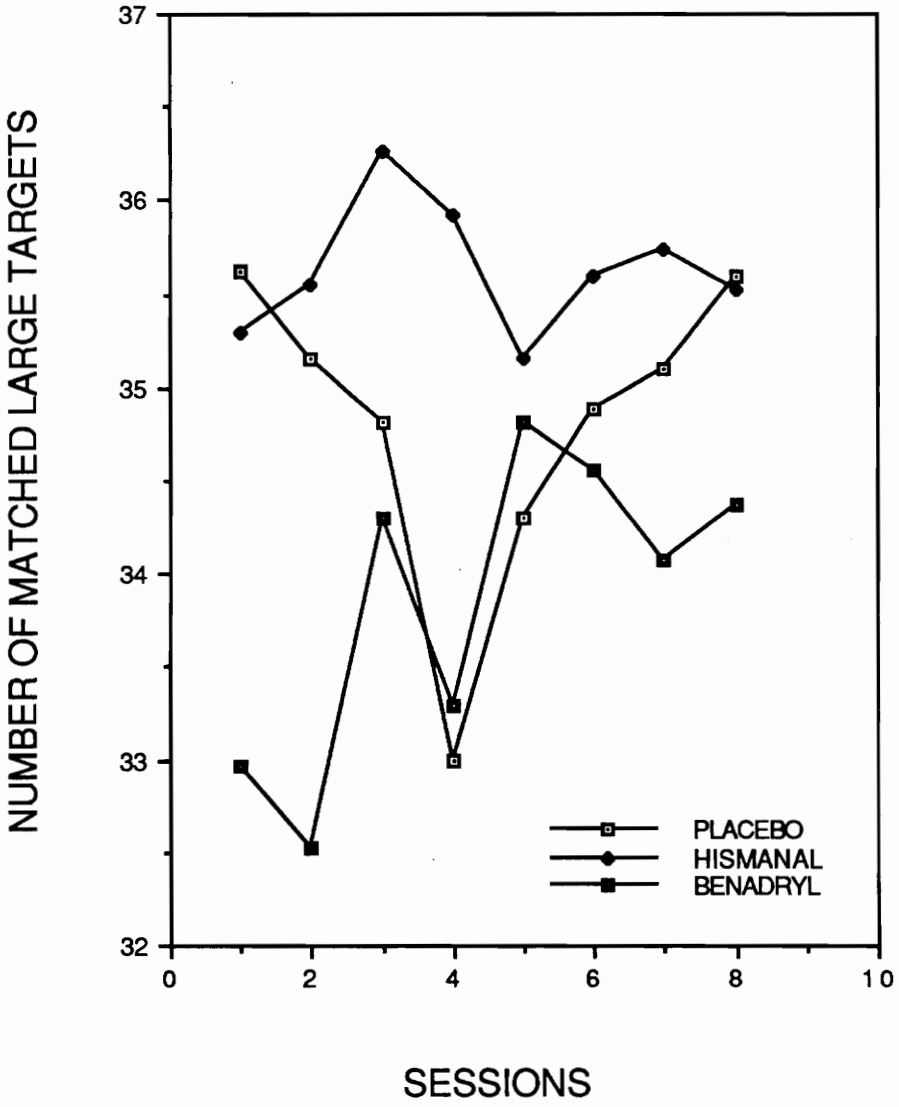

Figure 14. Session by drug interaction for number of matched large targets. The average standard deviation is 7.896.

Mean Time for Unmatched Small Targets

Only the drug effect was found to be significant using an ANOVA (Table 42). Benadryl produced the slowest responses while a placebo produced a significantly faster time (Table 43 and Figure 15).

Number of Unmatched Large Targets

The ANOVA in Table 44 shows that the drug effect and the interaction between drugs and sessions are significant for this variable. Benadryl produced the most unmatched targets, while hismanal produced a significantly smaller number of unmatched targets (Table 45 and Figure 16). A simple-effect F-test was performed, and once again sessions one through four were significant (Table 46). A Newman-Keuls comparison reveals that benadryl produces significantly more unmatched targets than either hismanal or the placebo for sessions one and two. During sessions three and four, hismanal produced fewer unmatched targets than benadryl or the placebo (Tables 47-50, and Figure 17).

Overall Mean Time

Table 51 shows the ANOVA for the overall mean time for each response. Only the sessions effect was significant (Table 52 and Figure 18). The time it took subjects to make a response, either correct or incorrect (matched or unmatched), became consistently shorter as the day went on ($R^2 = .893$).

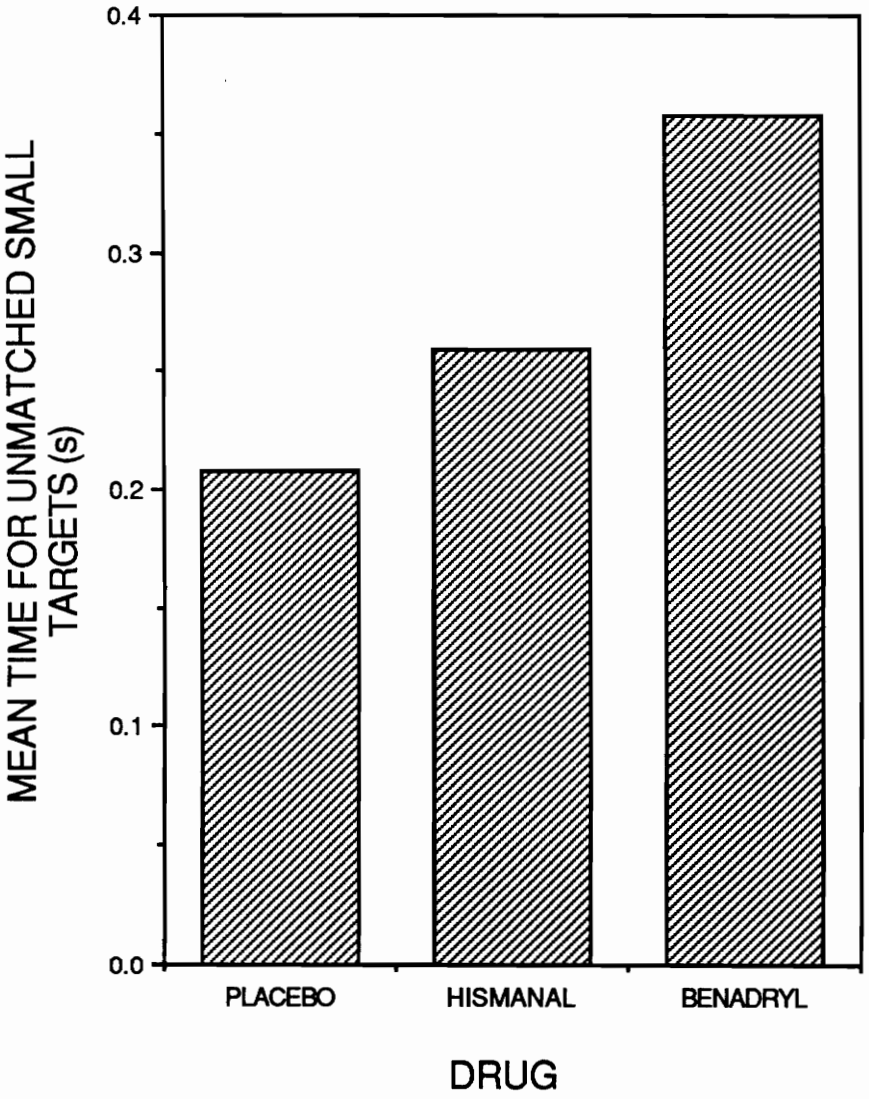

Figure 15. Drug effect for mean time for unmatched small targets. The average standard deviation is 0.753.

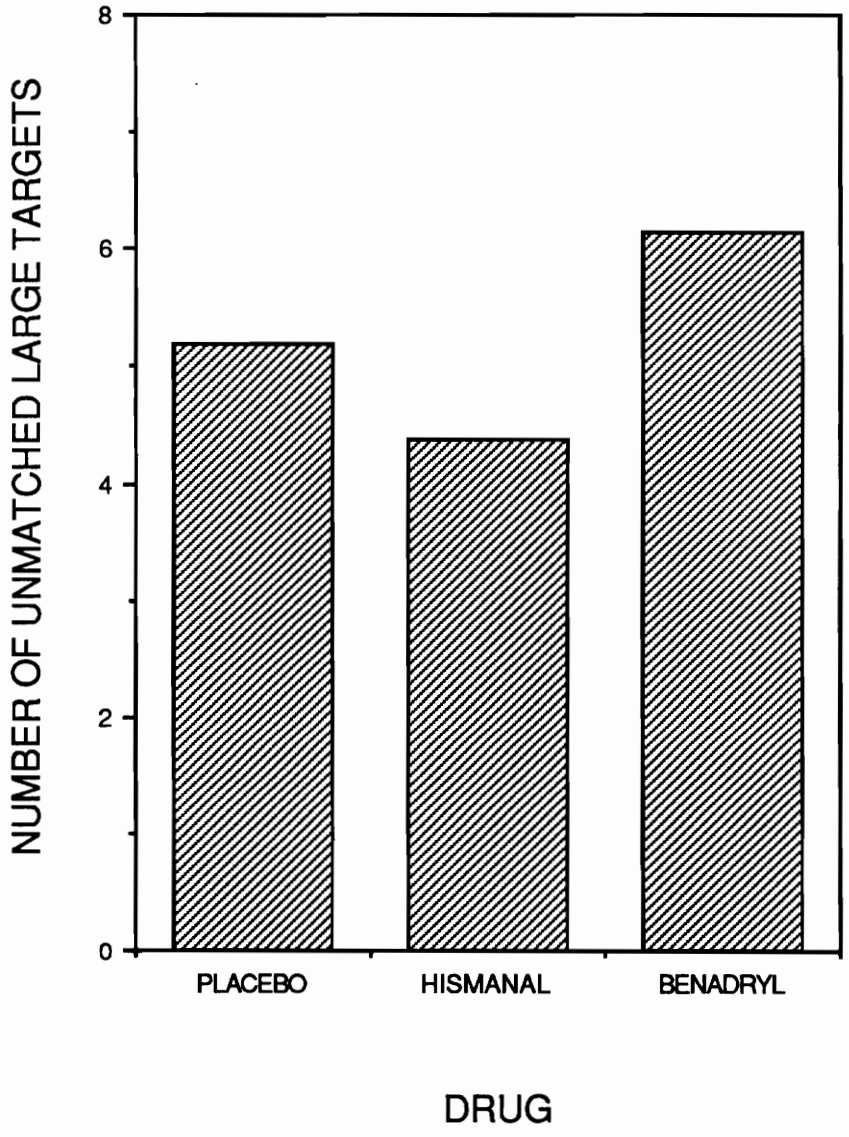

Figure 16. Drug effect for number of unmatched large targets. The average standard deviation is 7.816.

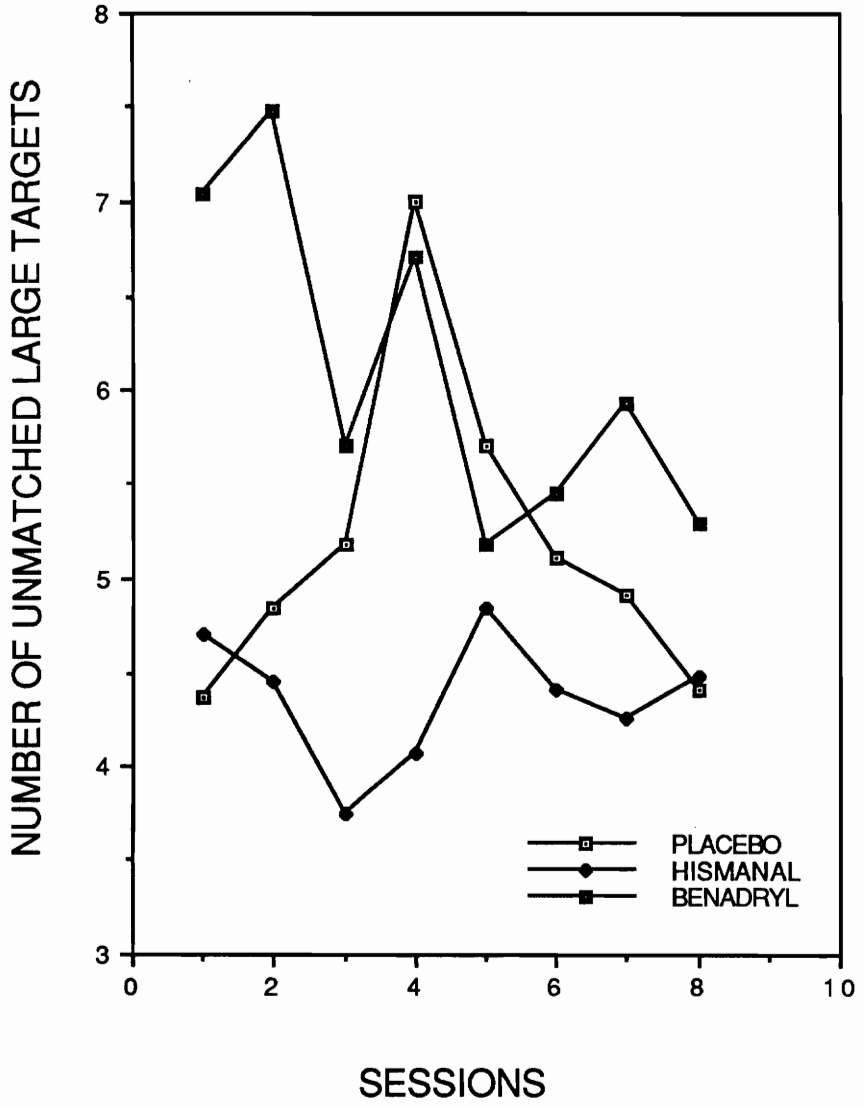

Figure 17. Session by drug interaction for number of unmatched large targets. The average standard deviation is 7.896.

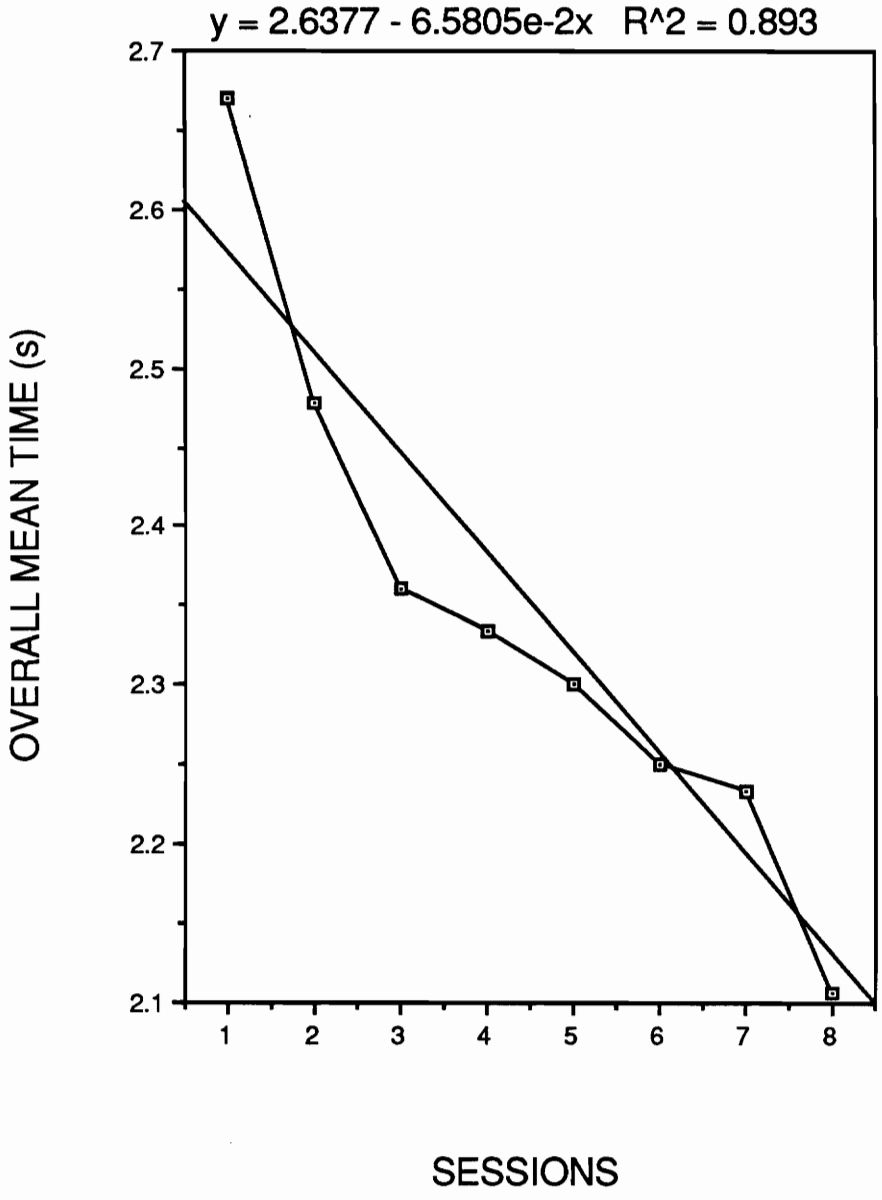

Figure 18. Session effect for overall mean time. The average standard deviation is 0.821.

Overall Standard Deviation

The analysis of variance for this variable (Table 53) shows that the sessions effect is significant. Session 1 has a significantly greater standard deviation than all other sessions throughout the day (Table 54 and Figure 19).

Duration

The duration of each testing period is significant for the sessions effect (Table 55). The subjects took a significantly longer time to complete the entire task at the beginning of the testing day as compared to the middle or end of the day (Table 56 and Figure 20).

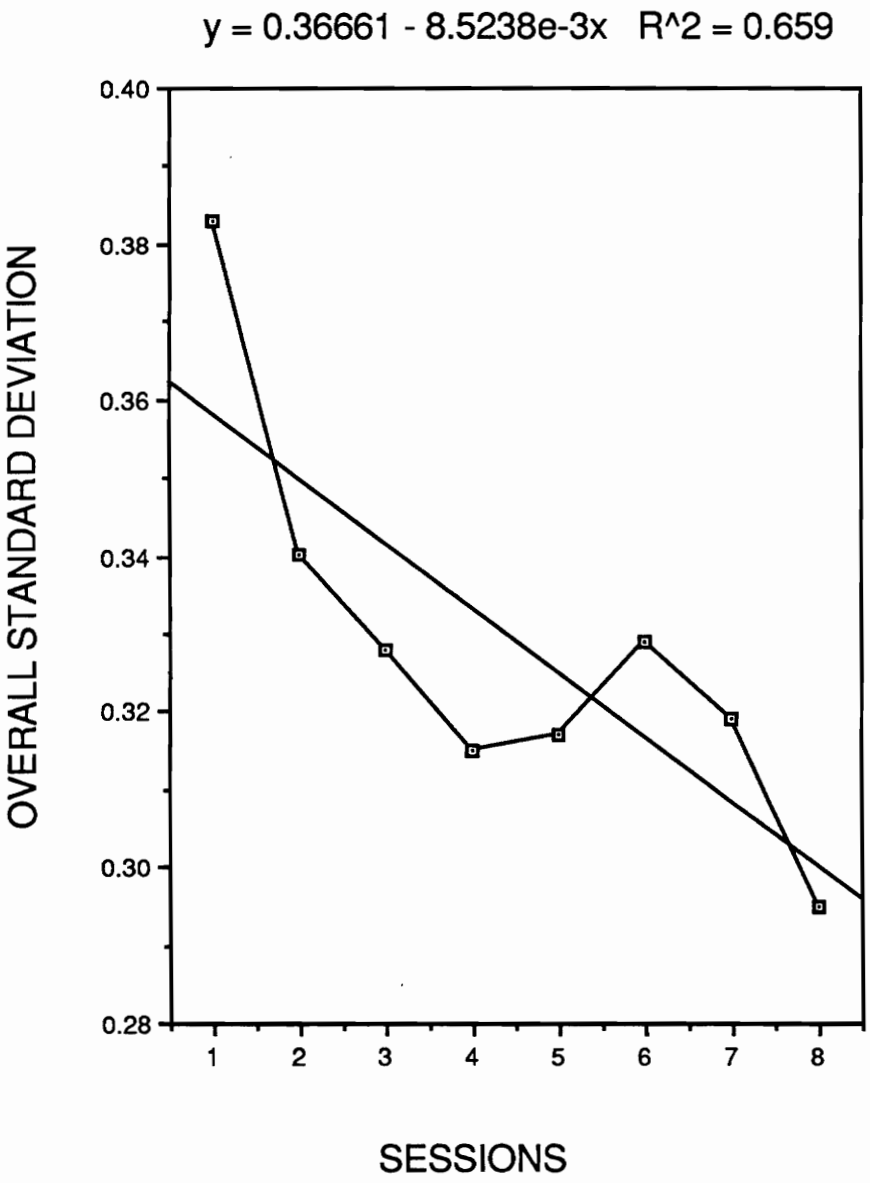

Figure 19. Session effect for overall standard deviation. The average standard deviation is 0.191.

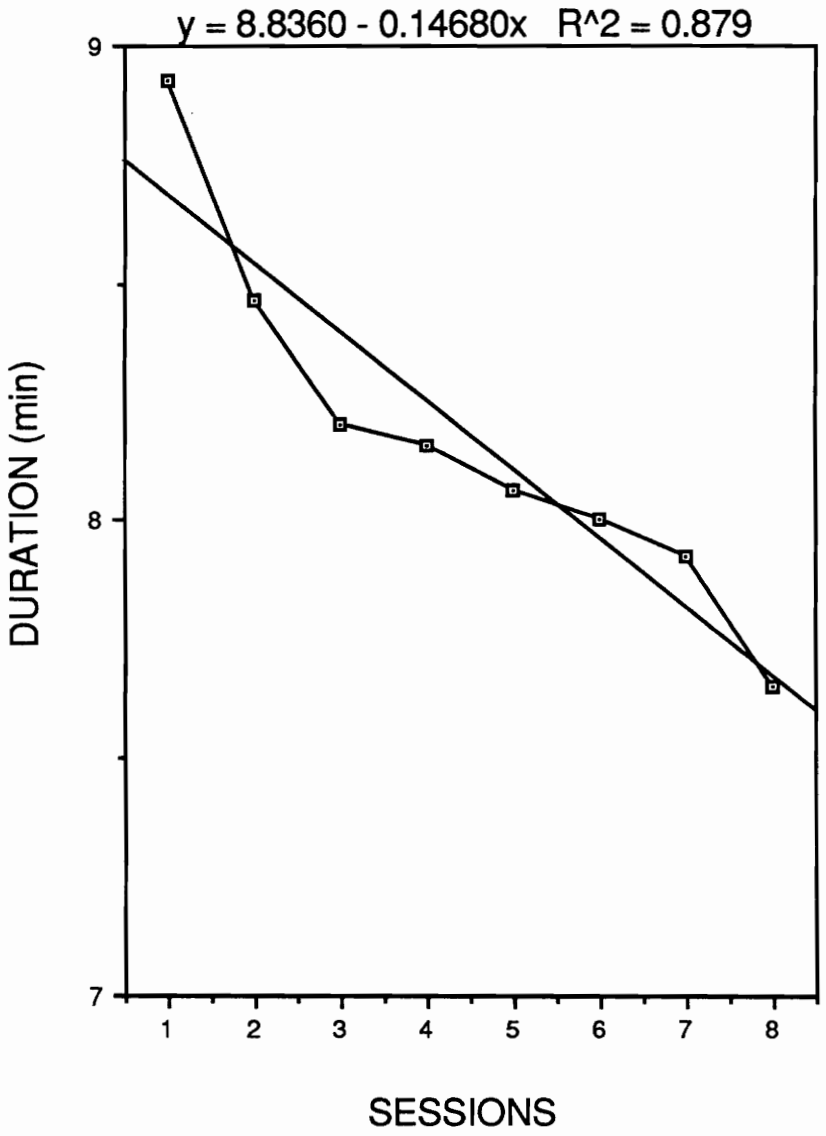

Figure 20. Session effect for duration. The average standard deviation is 1.673.

DISCUSSION

Sessions Effect

The sessions or time of day effect was significant for 9 of the 26 dependent variables (Table 57). To verify an apparent decrease in performance from session one to session eight, a line was fitted to the sessions data for all dependent variables with a significant sessions effect. Except for one dependent variable (percent correct for all size targets), the underlying trend is that performance is significantly poorer at the beginning of the day than at the end of the day. For most of the dependent variables that had a sessions effect, the first session of the day and occasionally the second and third sessions of the day contained significantly poorer performance than the last session of the day. The possibility of a learning effect is discussed in the next section.

The one exception to the above trend, percent correct for all size targets, showed that during session 4 there was a significantly lower percentage of correct matches made than during session 8. Session 4 occurred directly after the subjects ate lunch. There was a decrement in performance during session 4 for a few of the dependent variables; however, this decrement was usually not significantly different from other sessions.

Learning Effect

An ANOVA was performed on the nine dependent variables with significant sessions effects (Tables 58 - 66) to determine if there was a learning effect over each test day or over all three test days using only the days that a placebo was

administered. Of the six dependent variables with a significant sessions effect, five dependent variables showed improvement within each day (Tables 67 - 71 and Figures 21 - 25). The other four (of the original nine dependent variables with sessions effects) showed significant improvement over the entire three-day period, but not within each day (Tables 72 - 75 and Figures 26 - 29). The percent correct of all three size targets had a significant sessions effect (Figure 30). However, no learning trend was evident for this dependent variable, only a difference between sessions 1 and 8 and session 4 (Table 76). This analysis shows that a learning effect did generally occur and that the differences among sessions were due at least in part to this learning effect rather than some property of the antihistamines.

A decrement in performance, for several dependent variables, is noticeable during the session (session 4) that was administered after lunch. For the days a placebo was administered, the subjects' ability to correctly match targets significantly decreased for session 4 (Figure 30). Also, the average time taken to match small targets during session 4 was longer than session 3 or session 5 (Figure 22). This decrement in performance during session 4 was also noticeable in benadryl (Figures 5, 7, 14, and 17). A slight decrement in performance is evident after dinner too, although not as large a difference as the session after lunch. Figure 24 shows that the overall standard deviation increased during the session following dinner.

No attempt was made to control the subjects' diet during the experiment. Different subjects ate different foods throughout the day. The control of diet was not practical for this type of study. Outside the controlled research environment, antihistamine consumers will also eat a variety of foods.

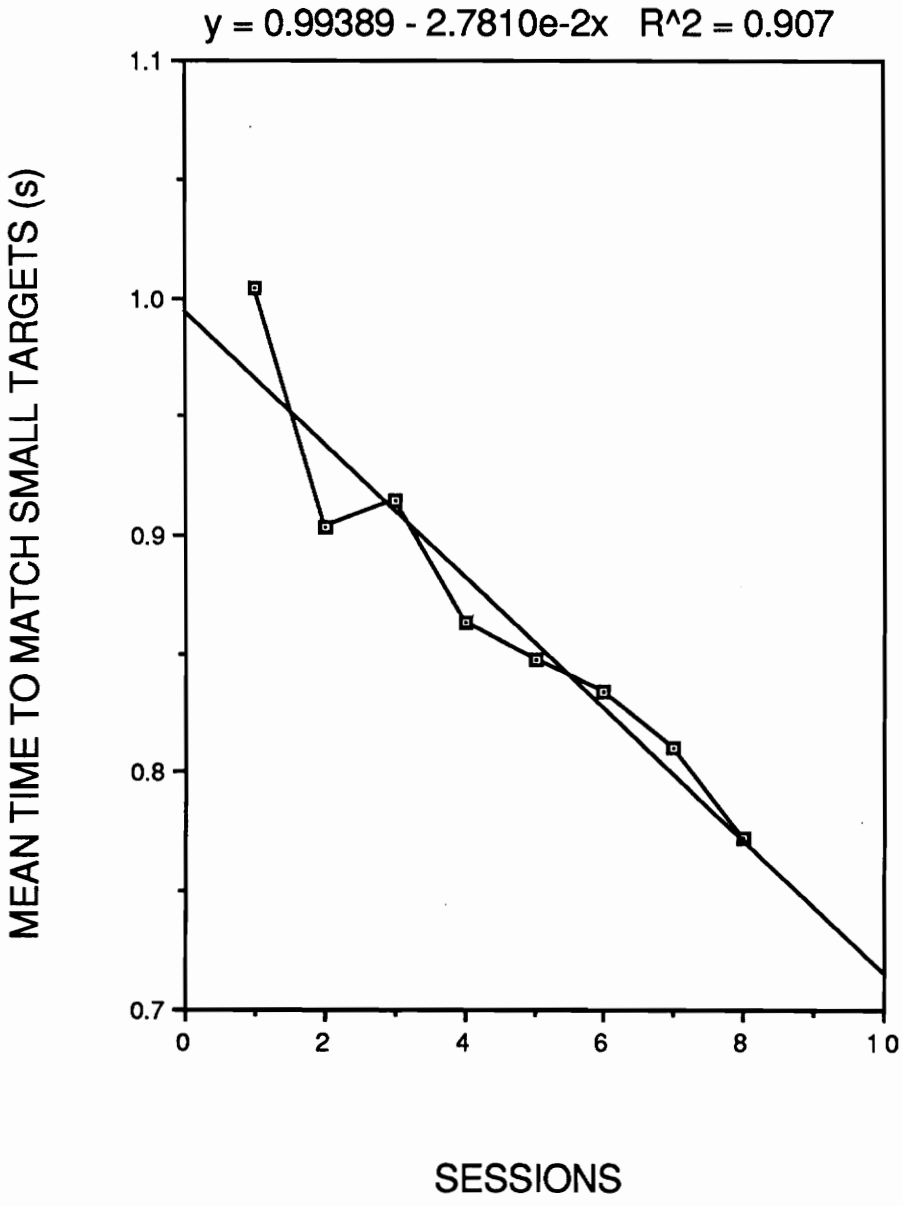

Figure 21. Session effect for mean time to match small targets, placebo days only. The average standard deviation is 0.286.

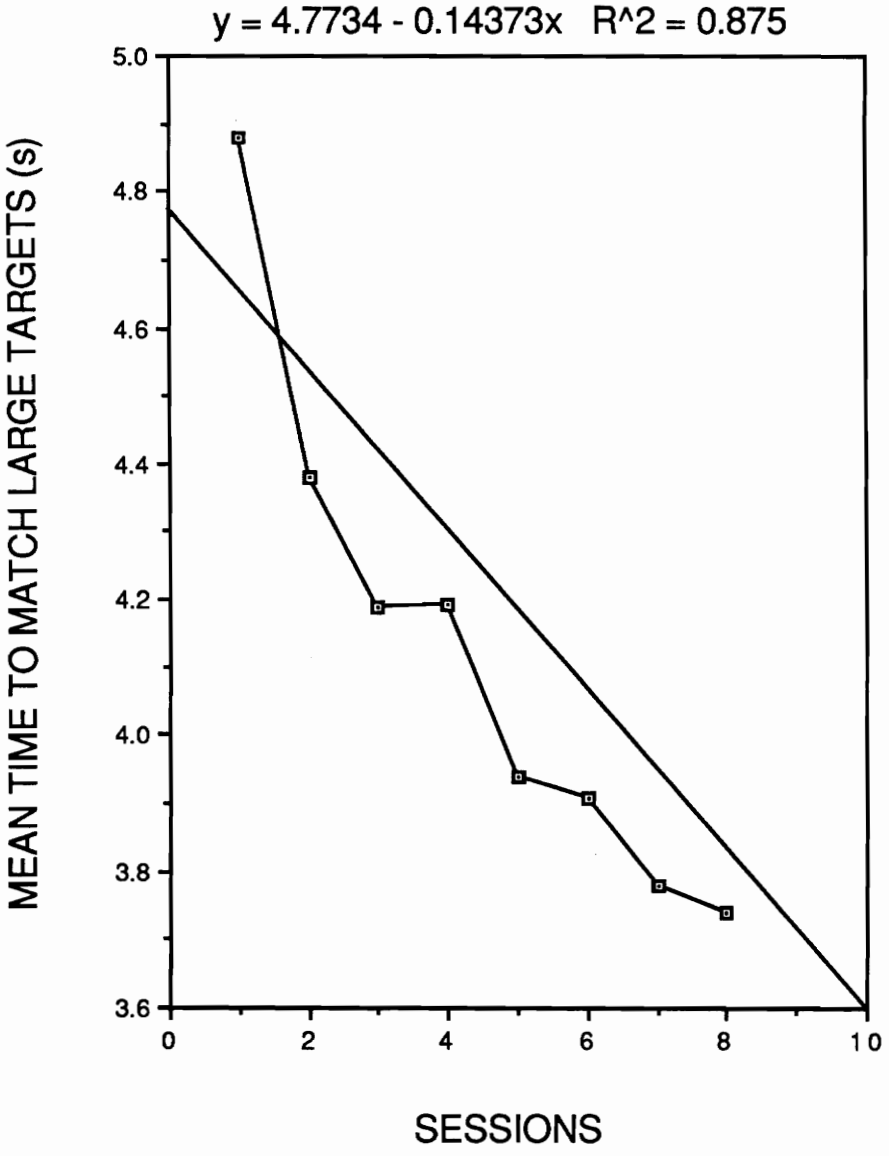

Figure 22. Session effect for mean time to match large targets, placebo days only. The average standard deviation is 1.396.

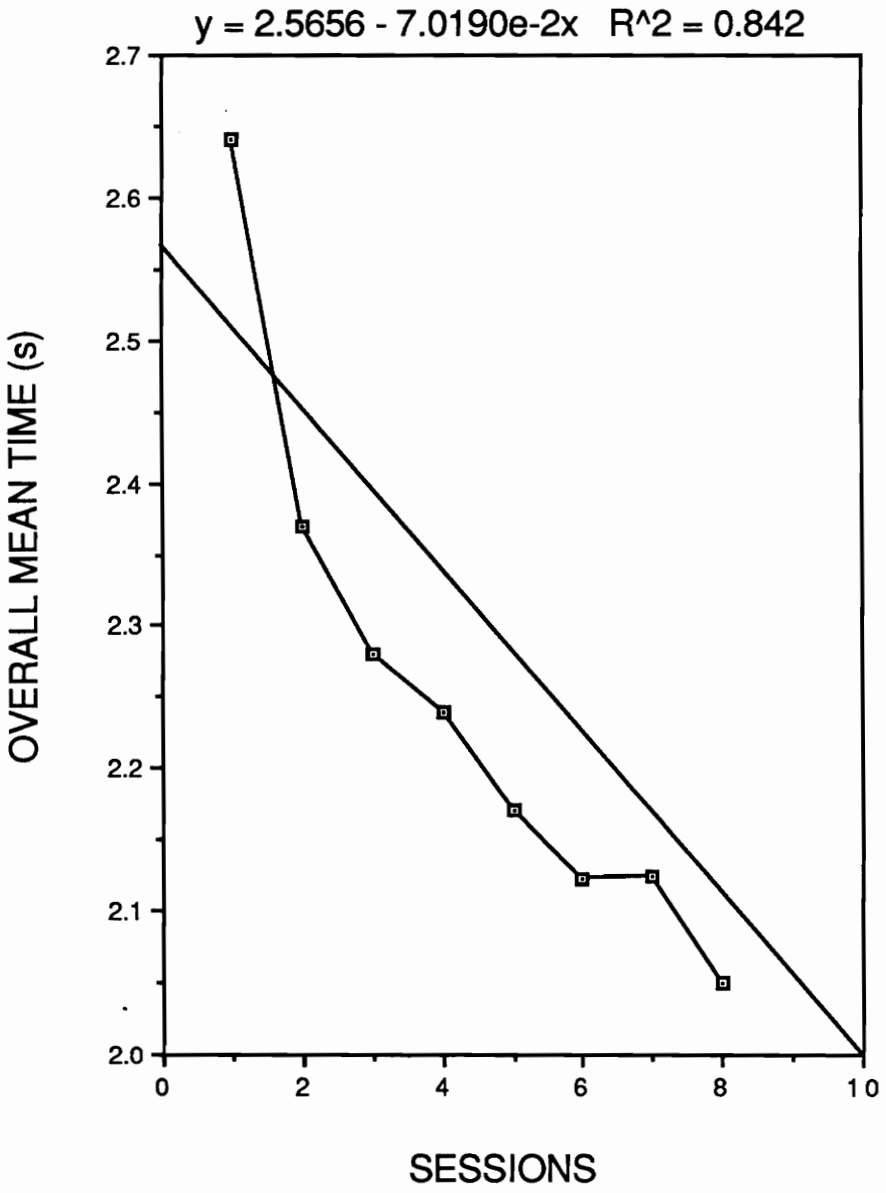

Figure 23. Session effect for overall mean time, placebo days only. The average standard deviation is 0.668.

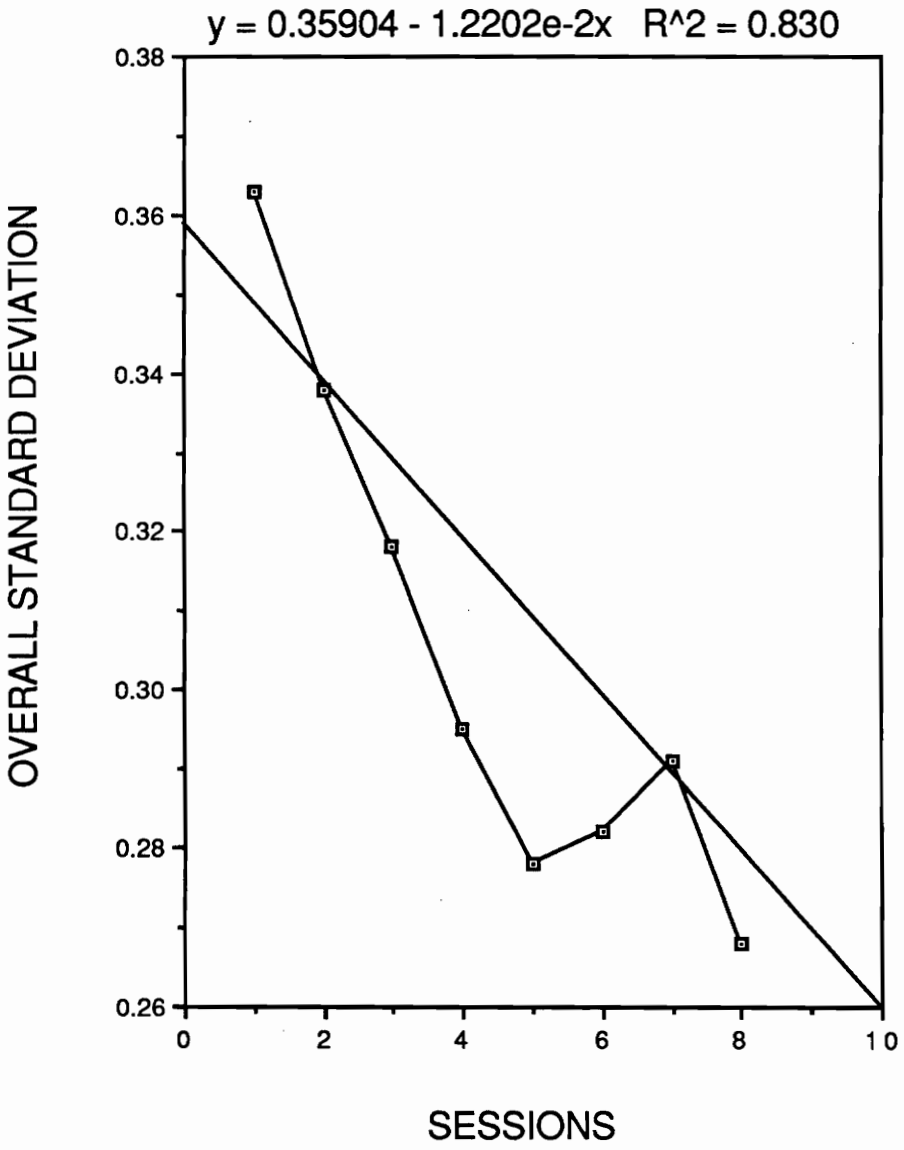

Figure 24. Session effect for overall standard deviation, placebo days only. The average standard deviation is 0.125.

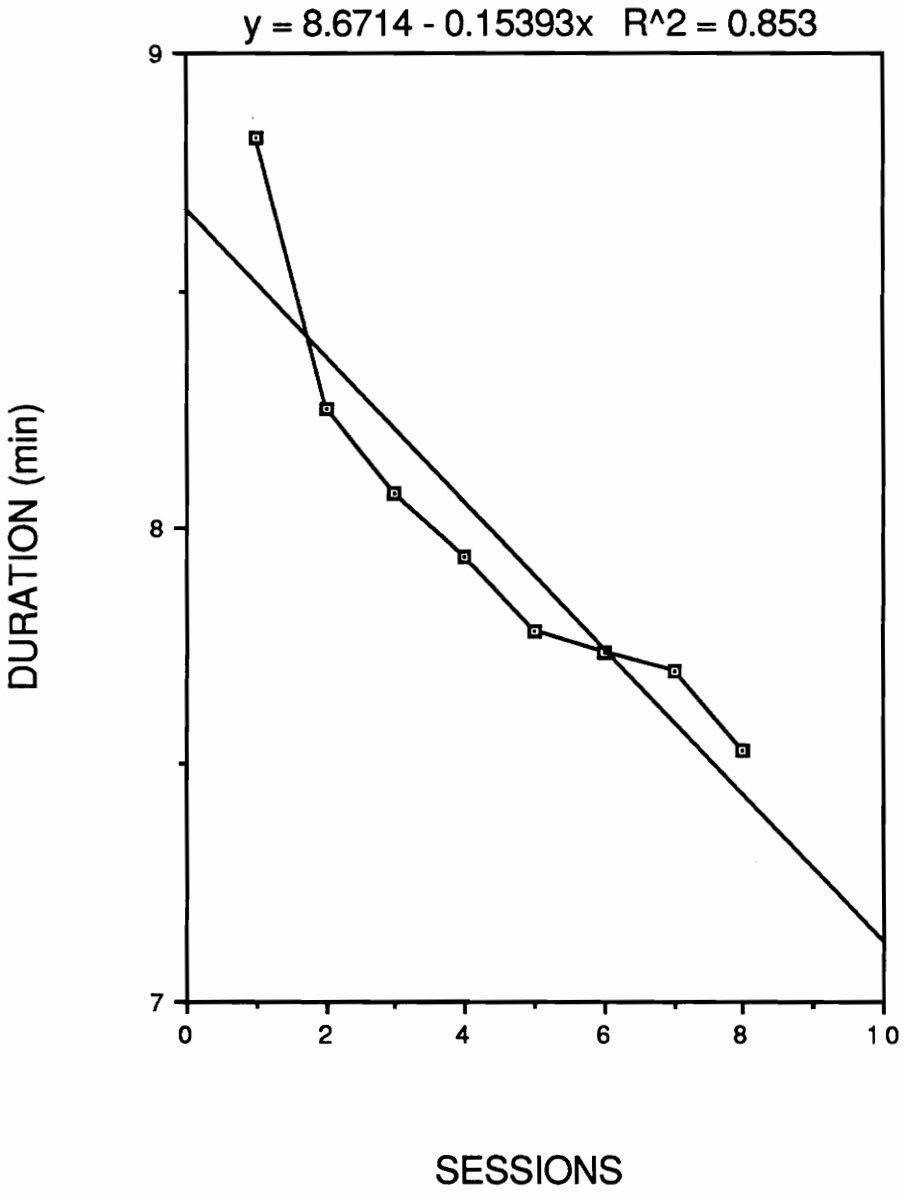

Figure 25. Session effect for duration, placebo days only. The average standard deviation is 1.372.

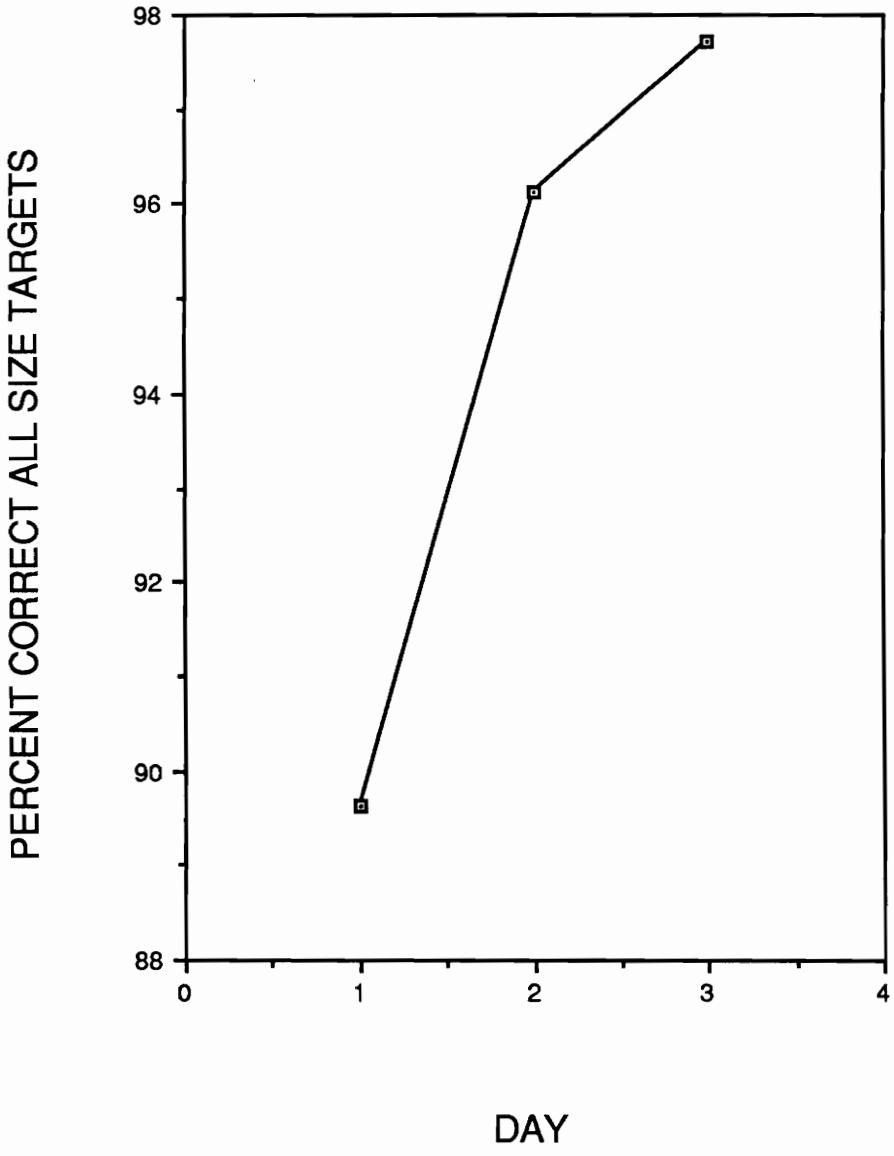

Figure 26. Day effect for percent correct for all size targets, placebo days only. The average standard deviation is 6.395.

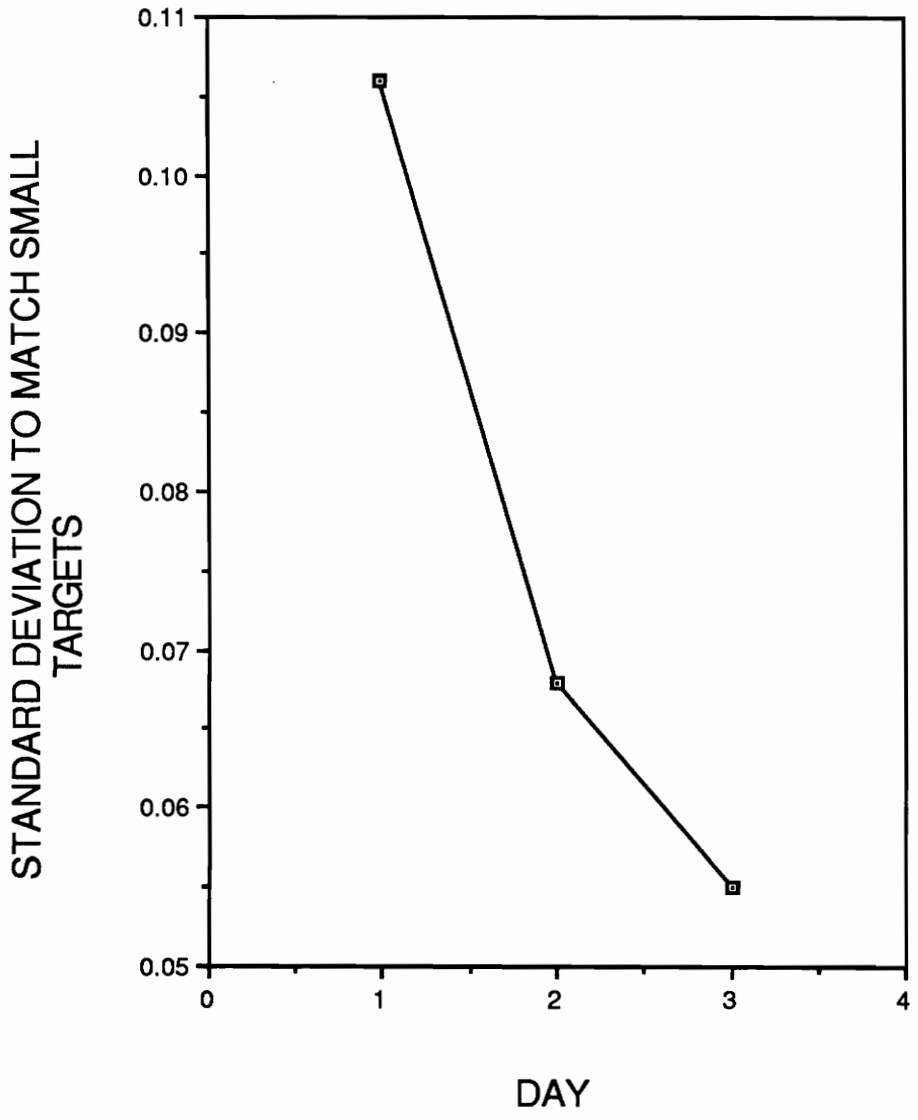

Figure 27. Day effect for standard deviation to match small targets, placebo days only. The average standard deviation is 0.060.

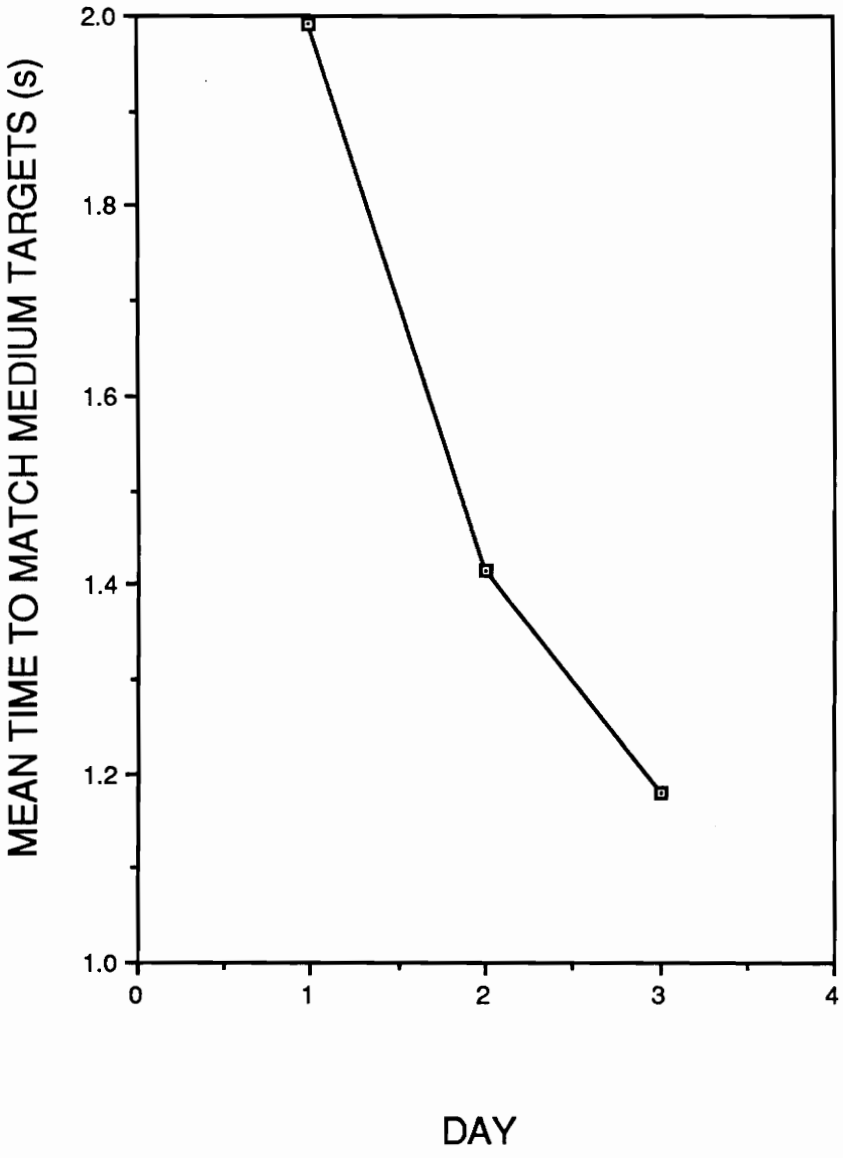

Figure 28. Day effect for mean time to match medium targets, placebo days only. The average standard deviation is 0.575.

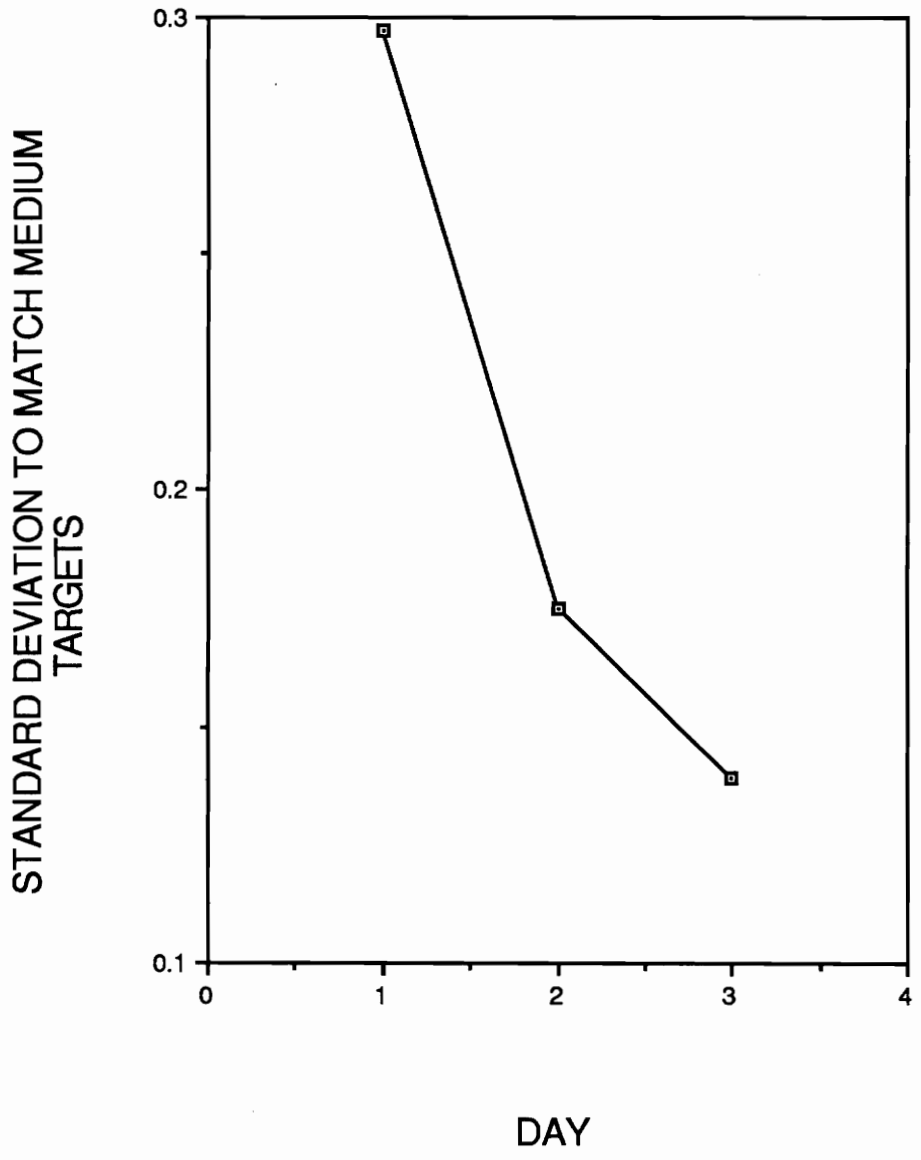

Figure 29. Day effect for standard deviation to match medium targets, placebo days only. The average standard deviation is 0.112.

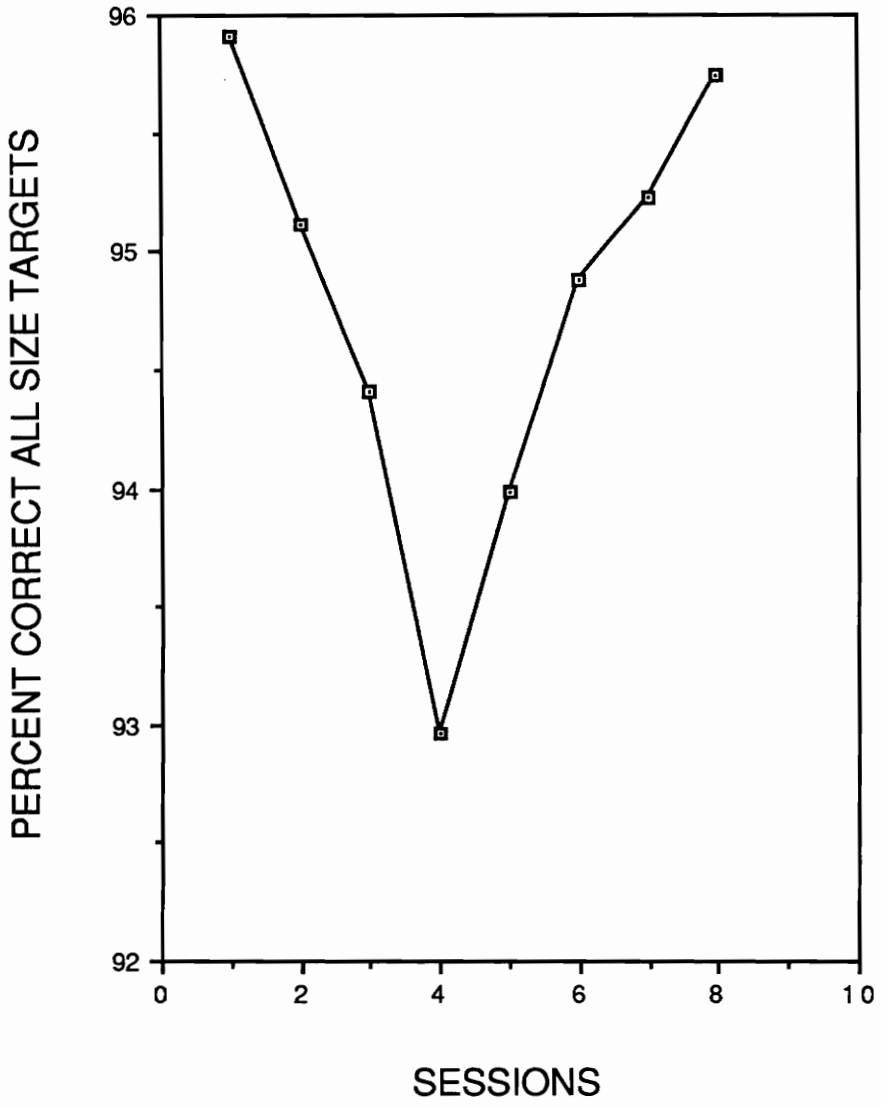

Figure 30. Session effect for percent correct for all size targets, placebo days only. The average standard deviation is 7.749.

Drug Effect

Five dependent variables had an overall drug effect (Table 57). For four of these dependent variables, hismanal produced results with significantly better performance than benadryl, but not significantly different than the placebo results. These results support the findings of Moskowitz and Burns (1988), who stated that visual search performance declined while under the influence of benadryl. The variable that did not produce the above results (mean time for unmatched small targets) showed a significantly longer time for benadryl as compared to a placebo.

Session and Drug Interaction Effect

Four dependent variables had a significant session/drug interaction effect (Table 57). All four of these dependent variables produced essentially the same results. Sessions one through four were found to be significant using a simple-effect F-test. During sessions one and two benadryl produced significantly poorer results than hismanal or the placebo (Figures 5, 7, 14, and 17). There was not a significant difference between hismanal and the placebo. All four dependent variables that had a significant drug by session interaction exhibited similar trends during sessions three and four. Hismanal produced better performance than benadryl or the placebo. There was no difference between the placebo and benadryl. These results do not completely support the findings of Moskowitz and Burns (1988). They found that benadryl produced significantly poorer performance three hours after ingestion, but not one hour after the drug was administered. The results from this research found that

benadryl produced significantly poorer performance one and three hours after ingestion.

It is not surprising the four dependent variables that showed a significant session and drug interaction all exhibited the same trends for the first four sessions of the day. These common trends could have been predicted because the four dependent variables are components of one another. For example, the number of unmatched large targets and the number of matched large targets are subsidiaries of the percent correct for large targets, which in turn is a component of percent for all size targets.

CONCLUSIONS

Two main conclusions can be drawn from the results of this research. First, benadryl (diphenhydramine hydrochloride) adversely affected visual search performance. Second, there was a learning trend evident in several of the measures of visual search. This trend occurred within each day and/or over the entire three-day period.

The effects of the antihistamines on performance were most evident in the measures relating to the large target size. The percent correct and number of large targets correctly identified showed significant decrements in performance after benadryl had been ingested. The overall percent correct (for all three target sizes) was lower after the subjects had taken benadryl. There was no significant difference in performance between tests conducted after hismanal ingestion and placebo ingestion.

In general, the subjects' performance (without having taken any antihistamines) continued to improve over the course of the research. The amount of time it took a subject to correctly identify a medium or small sized target decreased over the three days. Also, the subjects' variance from this mean time decreased between day 1 and day 3. Those measures of overall performance (percent correct for all size targets, overall mean time, overall standard deviation, and duration), as well as the average time required to correctly identify the large target, improved within the test day. Session 1 produced significantly poorer results than session 8. This learning trend indicates that the subjects were not trained to an asymptotic level. In order to

detect the true performance changes due to antihistamine use, a longer training period should be used.

Additional similar research, employing a longer training period, should be conducted to compare results with the results found in this study. Another area that should be studied further is the idea of making the visual search task longer in duration and therefore adding a vigilance element to the study. Another possibility for similar research is the inclusion of female subjects.

REFERENCES

American Society of Hospital Pharmacists. (1988). *American hospital formulary service: Drug information.* Bethesda, MD: Author.

Bergersen, B.S. (1979). *Pharmacology in nursing.* St. Louis, MO: C.V. Mosby.

Cohen, A.F., Hamilton, M.J., and Peck, A.W. (1987). The effects of acrivastine (BW825C), diphenhydramine and terfenadine in combination with alcohol on human CNS performance. *European Journal of Clinical Pharmacology, 32,* 279-288.

Di Palma, J.R. (1971). *Drills pharmacology in medicine.* New York: McGraw-Hill.

Engel, F.L. (1974). Visual conspicuity and selective background interference in eccentric vision. *Vision Research, 14,* 459-471.

Engel, F.L. (1977). Visual conspicuity, visual search and fixation tendencies of the eye. *Vision Research, 17,* 95-108.

Fink, M., and Irwin, P. (1979). CNS effects of the antihistamines diphenhydramine and terfenadine (RMI9918). *Pharmacopsychiatry, 12,* 35-44.

Jenkins, S.E., and Cole, B.L. (1982). The effect of the density of background elements on the conspicuity of objects. *Vision Research, 22,* 1241-1252.

Kulshrestha, V.K., Gupta, P.P., Turner, P., and Wadsworth, J. (1978). Some clinical pharmacological studies with terfenadine, a new antihistamine drug. *British Journal of Clinical Pharmacology, 6,* 25-30.

Krstenansky, P.M., and Cluxton, R.J. (1987). Astemizole: a long-acting, nonsedating antihistamine. *Drug Intelligence and Clinical Pharmacology, 21,* 947-953.

Moskowitz, H., and Burns, M. (1988). *A study of the effect of seldane (terfenadine) 60 mg, diphenhydramine 50 mg, and placebo on skills performance.* (Project Report R-88-01). Biostatistics, Merrell Dow Pharmaceuticals Inc., Cincinnati, Ohio.

Nicholson, A.N., Smith, P.A., and Spencer, M.B. (1982). Antihistamines and visual function: Studies on dynamic acuity and the pupillary response to light. *British Journal of Clinical Pharmacology, 14,* 683-690.

Nicholson, A.N., and Stone, B.M. (1982). Performance studies with the H1-Histamine receptor antagonists, astemizole and terfenadine. *British Journal of Clinical Pharmocology, 13,* 199-202.

Rice, V.J. (1990). Complex cognitive performance and antihistamine use (Unpublished Doctoral Dissertation). Virginia Polytechnic Institute and State University. Blacksburg, Va.

Richards, D.M., Brogden, R.N., Heel, R.C., Speight, T.M., and Avery, G.S. (1984). Astemizole: A review of its pharmacodynamic properties and therapeutic efficacy. *Drugs, 28,* 38-61.

White, J.M., and Rumbold, G.R. (1988). Behavioral effects of histamine and its antagonists: A review. *Psychopharmacology, 95,* 1-14.

Wihl, J.A., Petersen, B.N., Petersen, L.N., Gundersen, G., Bresson, K., and Mygind, N. (1985). Effect of the nonsedative H1-receptor antagonist astemizole in perennial allergic and nonallergic rhinitis. *Journal of Allergy and Clinical Immunology, 75,* 720-727.

APPENDIX I - TABLES

TABLE 8

List of Dependent Variables

Abbreviation	Description
PA	Percent correct of all sized targets
PL	Percent correct of large targets
PM	Percent correct of medium targets
PS	Percent correct of small targets
LMM	Mean time to match large targets
LMS	Standard deviation to match large targets
LMN	Number of matched large targets
MMM	Mean time to match medium targets
MMS	Standard deviation to match medium targets
MMN	Number of matched medium targets
SMM	Mean time to match small targets
SMS	Standard deviation match small targets
SMN	Number of matched small targets
LUM	Mean time for unmatched large targets
LUS	Standard deviation for unmatched large targets
LUN	Number of unmatched large targets
MUM	Mean time for unmatched medium targets

TABLE 8. (continued)

MUS	Standard deviation for unmatched medium targets
MUN	Number of unmatched medium targets
SUM	Mean time for unmatched small targets
SUS	Standard deviation for unmatched small targets
SUN	Number of unmatched small targets
OM	Overall mean time per response
OS	Overall standard deviation per response
DUR	Duration of session

TABLE 9

Time of Each Session

Session	Time of Day
1	8:00 am
2	10:00 am
3	12:00 noon
4	2:00 pm
5	4:00 pm
6	6:00 pm
7	8:00 pm
8	10:00 pm

TABLE 10

Analysis of Variance Summary Table for Percent Correct of All Size Targets

Source of Variance	df	MS	F	p
Between Subjects				
Subjects (O)	26	1094.02		
Within Subjects				
Sessions (S)	7	17.74	2.21	.0350
O X S	182	8.01		
Drug (D)	2	194.41	4.18	.0207
D X O	52	46.51		
S X D	14	17.32	2.33	<.05
S X D X O	361*	7.43		
Total	644*			

* Three degrees of freedom were subtracted for missing data

TABLE 11

Newman-Keuls Comparison of Sessions for Percent Correct of All Size Targets. Means with the same letter are not significantly different ($p > .05$).

Session	Mean	Grouping	
8	95.23	A	
7	95.13	A	B
6	94.97	A	B
3	94.95	A	B
1	94.74	A	B
5	94.43	A	B
2	94.35	A	B
4	93.84		B

TABLE 12

Newman-Keuls Comparison of Drugs for Percent Correct of All Size Targets. Means with the same letter are not significantly different ($p > .05$).

Drug	Mean	Grouping	
Hismanal	95.61	A	
Placebo	94.78	A	B
Benadryl	93.72		B

TABLE 13

Simple-Effect F-Test for Drug by Session Interaction for Percent Correct of All Size Targets

Session	MS	F	p
1	78.05	10.51	<.05
2	77.65	10.46	<.05
3	28.94	3.90	<.05
4	78.51	10.57	<.05
5	4.25	0.57	>.05
6	7.18	0.97	>.05
7	19.68	2.65	>.05
8	21.43	2.89	>.05

TABLE 14

Newman-Keuls Comparison of Drug by Session Interaction for Percent Correct All Size Targets, Session 1. Means with the same letter are not significantly different ($p > .05$).

Drug	Mean	Grouping	
Benadryl	92.79	A	
Hismanal	95.53		B
Placebo	95.91		B

TABLE 15

Newman-Keuls Comparison of Drug by Session Interaction for Percent Correct All Size Targets, Session 2. Means with the same letter are not significantly different ($p > .05$).

Drug	Mean	Grouping	
Benadryl	92.41	A	
Placebo	95.12		B
Hismanal	95.53		B

TABLE 16

Newman-Keuls Comparison of Drug by Session Interaction for Percent Correct All Size Targets, Session 3. Means with the same letter are not significantly different ($p > .05$).

Drug	Mean	Grouping	
Benadryl	94.29	A	
Placebo	94.41	A	
Hismanal	96.14		B

TABLE 17

Newman-Keuls Comparison of Drug by Session Interaction for Percent Correct All Size Targets, Session 4. Means with the same letter are not significantly different ($p > .05$).

Drug	Mean	Grouping	
Benadryl	94.29	A	
Placebo	94.41	A	
Hismanal	96.14		B

TABLE 18

Analysis of Variance Summary Table for Percent Correct of Large Targets

Source of Variance	df	MS	F	p
Between Subjects				
Subjects (O)	26	8179.41		
Within Subjects				
Sessions (S)	7	73.15	1.72	.1075
O X S	182	42.61		
Drug (D)	2	1057.52	5.33	.0078
D X O	52	198.42		
S X D	14	92.33	2.30	<.05
S X D X O	361*	40.12		
Total	644*			

* Three degrees of freedom were subtracted for missing data

TABLE 19

Newman-Keuls Comparison of Drugs for Percent Correct of Large Targets. Means with the same letter are not significantly different ($p > .05$).

Drug	Mean	Grouping	
Hismanal	89.07	A	
Placebo	87.02	A	B
Benadryl	84.65		B

TABLE 20

Simple-Effect F-Test for Drug by Session Interaction for Percent Correct for Large Targets

Session	MS	F	p
1	356.21	8.88	<.05
2	458.57	11.43	<.05
3	174.61	4.35	<.05
4	437.73	10.91	<.05
5	31.10	0.78	>.05
6	47.30	1.18	>.05
7	119.06	2.97	>.05
8	79.24	1.98	>.05

TABLE 21

Newman-Keuls Comparison of Drug by Session Interaction for Percent Correct Large Targets, Session 1. Means with the same letter are not significantly different ($p > .05$).

Drug	Mean	Grouping	
Benadryl	82.40	A	
Hismanal	88.24		B
Placebo	89.07		B

TABLE 22

Newman-Keuls Comparison of Drug by Session Interaction for Percent Correct Large Targets, Session 2. Means with the same letter are not significantly different ($p > .05$).

Drug	Mean	Grouping	
Benadryl	81.30	A	
Placebo	87.87		B
Hismanal	88.89		B

TABLE 23

Newman-Keuls Comparison of Drug by Session Interaction for Percent Correct Large Targets, Session 3. Means with the same letter are not significantly different ($p > .05$).

Drug	Mean	Grouping	
Benadryl	85.74	A	
Placebo	87.04	A	
Hismanal	90.65		B

TABLE 24

Newman-Keuls Comparison of Drug by Session Interaction for Percent Correct Large Targets, Session 4. Means with the same letter are not significantly different ($p > .05$).

Drug	Mean	Grouping
Placebo	82.50	A
Benadryl	83.24	A
Hismanal	89.82	B

TABLE 25

Analysis of Variance Summary Table for Mean Time to Match Small Targets

Source of Variance	df	MS	F	p
Between Subjects				
Subjects (O)	26	1.320		
Within Subjects				
Sessions (S)	7	0.550	23.38	.0001
O X S	182	0.024		
Drug (D)	2	0.015	0.16	.8559
D X O	52	0.097		
S X D	14	0.028	1.24	>.05
S X D X O	361*	0.023		
Total	644*			

* Three degrees of freedom were subtracted for missing data

TABLE 26

Newman-Keuls Comparison of Sessions for Mean Time to Match Small Targets. Means with the same letter are not significantly different ($p > .05$).

Session	Mean	Grouping				
1	1.02	A				
2	0.96		B			
3	0.88			C		
4	0.86			C	D	
5	0.84			C	D	
6	0.82			C	D	E
7	0.80				D	E
8	0.78					E

TABLE 27

Analysis of Variance Summary Table for Standard Deviation to Match Small Targets

Source of Variance	df	MS	F	p
Between Subjects				
Subjects (O)	26	0.033		
Within Subjects				
Sessions (S)	7	0.013	6.47	.0001
O X S	182	0.002		
Drug (D)	2	0.001	0.21	.8121
D X O	52	0.004		
S X D	14	0.003	1.25	>.05
S X D X O	361*	0.002		
Total	644*			

* Three degrees of freedom were subtracted for missing data

TABLE 28

Newman-Keuls Comparison of Sessions for Standard Deviation to Match Small Targets. Means with the same letter are not significantly different ($p > .05$).

Session	Mean	Grouping		
1	0.096	A		
2	0.086	A	B	
3	0.082	A	B	
6	0.071		B	C
4	0.070		B	C
5	0.068		B	C
7	0.062			C
8	0.059			C

TABLE 29

Analysis of Variance Summary Table for Mean Time to Match Medium Targets

Source of Variance	df	MS	F	p
Between Subjects				
Subjects (O)	26	6.80		
Within Subjects				
Sessions (S)	7	1.17	10.54	.0001
O X S	182	.11		
Drug (D)	2	.12	.18	.8364
D X O	52	.70		
S X D	14	.12	1.22	>.05
S X D X O	361*	.10		
Total	644*			

* Three degrees of freedom were subtracted for missing data

TABLE 30

Newman-Keuls Comparison of Sessions for Mean Time to Match Medium Targets. Means with the same letter are not significantly different ($p > .05$).

Session	Mean	Grouping		
1	1.75	A		
2	1.65		B	
4	1.53			C
3	1.50			C
5	1.49			C
7	1.44			C
8	1.42			C
6	1.41			C

TABLE 31

Analysis of Variance Summary Table for Standard Deviation to Match Medium Targets

Source of Variance	df	MS	F	p
Between Subjects				
Subjects (O)	26	.230		
Within Subjects				
Sessions (S)	7	.042	2.61	.0137
O X S	182	.016		
Drug (D)	2	.058	1.33	.2736
D X O	52	.044		
S X D	14	.011	1.09	>.05
S X D X O	361*	.010		
Total	644*			

* Three degrees of freedom were subtracted for missing data

TABLE 32

Newman-Keuls Comparison of Sessions for Standard Deviation to Match Medium Targets. Means with the same letter are not significantly different ($p > .05$).

Session	Mean	Grouping	
1	0.26	A	
2	0.23	A	B
4	0.22	A	B
5	0.22	A	B
3	0.21	A	B
7	0.20		B
8	0.19		B
6	0.19		B

TABLE 33

Analysis of Variance Summary Table for Mean Time to Match Large Targets

Source of Variance	df	MS	F	p
Between Subjects				
Subjects (O)	26	42.88		
Within Subjects				
Sessions (S)	7	7.48	7.04	.0001
O X S	182	1.06		
Drug (D)	2	22.19	1.78	.1791
D X O	52	12.48		
S X D	14	0.53	0.53	>.05
S X D X O	361*	1.01		
Total	644*			

* Three degrees of freedom were subtracted for missing data

TABLE 34

Newman-Keuls Comparison of Sessions for Mean Time to Match Large Targets. Means with the same letter are not significantly different ($p > .05$).

Session	Mean	Grouping		
1	4.92	A		
2	4.45		B	
3	4.42		B	
4	4.31		B	C
5	4.22		B	C
7	4.22		B	C
6	4.14		B	C
8	3.87			C

TABLE 35

Analysis of Variance Summary Table for Number of Matched Large Targets

Source of Variance	df	MS	F	p
Between Subjects				
Subjects (O)	26	1308.71		
Within Subjects				
Sessions (S)	7	11.70	1.72	.1075
O X S	182	6.82		
Drug (D)	2	169.20	5.33	.0078
D X O	52	31.75		
S X D	14	14.77	2.30	<.05
S X D X O	361*	6.42		
Total	644*			

* Three degrees of freedom were subtracted for missing data

TABLE 36

Newman-Keuls Comparison of Drugs for Number of Matched Large Targets. Means with the same letter are not significantly different ($p > .05$).

Drug	Mean	Grouping	
Hismanal	35.63	A	
Placebo	34.81	A	B
Benadryl	33.86		B

TABLE 37

Simple-Effect F-Test for Drug by Session Interaction for Number of Matched Large Targets

Session	MS	F	p
1	56.99	8.88	<.05
2	73.37	11.43	<.05
3	27.94	4.35	<.05
4	70.04	10.91	<.05
5	4.98	0.78	>.05
6	7.57	1.18	>.05
7	19.05	2.97	>.05
8	12.68	1.98	>.05

TABLE 38

Newman-Keuls Comparison of Drug by Session Interaction for Number of Matched Large Targets, Session 1. Means with the same letter are not significantly different ($p > .05$).

Drug	Mean	Grouping	
Benadryl	32.96	A	
Hismanal	35.30		B
Placebo	35.63		B

TABLE 39

Newman-Keuls Comparison of Drug by Session Interaction for Number of Matched Large Targets, Session 2. Means with the same letter are not significantly different ($p > .05$).

Drug	Mean	Grouping	
Benadryl	32.52	A	
Placebo	35.15		B
Hismanal	35.56		B

TABLE 40

Newman-Keuls Comparison of Drug by Session Interaction for Number of Matched Large Targets, Session 3. Means with the same letter are not significantly different ($p > .05$).

Drug	Mean	Grouping	
Benadryl	34.30	A	
Placebo	34.82	A	
Hismanal	36.26		B

TABLE 41

Newman-Keuls Comparison of Drug by Session Interaction for Number of Matched Large Targets, Session 4. Means with the same letter are not significantly different ($p > .05$).

Drug	Mean	Grouping	
Placebo	33.00	A	
Benadryl	33.30	A	
Hismanal	35.93		B

TABLE 42

Analysis of Variance Summary Table for Mean Time of Unmatched Small Targets

Source of Variance	df	MS	F	p
Between Subjects				
Subjects (O)	26	1.33		
Within Subjects				
Sessions (S)	7	.32	.73	.6496
O X S	182	.45		
Drug (D)	2	1.23	3.20	.0491
D X O	52	.39		
S X D	14	.38	.74	>.05
S X D X O	361*	.52		
Total	644*			

* Three degrees of freedom were subtracted for missing data

TABLE 43

Newman-Keuls Comparison of Drugs for Mean Time for Unmatched Small Targets. Means with the same letter are not significantly different ($p > .05$).

Drug	Mean	Grouping	
Benadryl	0.36	A	
Hismanal	0.26	A	B
Placebo	0.21		B

TABLE 44

Analysis of Variance Summary Table for Number of Unmatched Large Targets

Source of Variance	df	MS	F	p
Between Subjects				
Subjects (O)	26	1308.71		
Within Subjects				
Sessions (S)	7	11.70	1.72	.1075
O X S	182	6.82		
Drug (D)	2	169.20	5.33	.0078
D X O	52	31.75		
S X D	14	14.77	2.30	<.05
S X D X O	361*	6.42		
Total	644*			

* Three degrees of freedom were subtracted for missing data

TABLE 45

Newman-Keuls Comparison of Drugs for Number of Unmatched Large Targets. Means with the same letter are not significantly different ($p > .05$).

Drug	Mean	Grouping	
Hismanal	6.14	A	
Placebo	5.19	A	B
Benadryl	4.37		B

TABLE 46

Simple-Effect F-Test for Drug by Session Interaction for Number of Unmatched Large Targets

Session	MS	F	p
1	56.99	8.88	<.05
2	73.37	11.43	<.05
3	27.94	4.35	<.05
4	70.04	10.91	<.05
5	4.98	0.78	>.05
6	7.57	1.18	>.05
7	19.05	2.97	>.05
8	12.68	1.98	>.05

TABLE 47

Newman-Keuls Comparison of Drug by Session Interaction for Number of Unmatched Large Targets, Session 1. Means with the same letter are not significantly different ($p > .05$).

Drug	Mean	Grouping	
Placebo	4.37	A	
Hismanal	4.70	A	
Benadryl	7.04		B

TABLE 48

Newman-Keuls Comparison of Drug by Session Interaction for Number of Unmatched Large Targets, Session 2. Means with the same letter are not significantly different ($p > .05$).

Drug	Mean	Grouping	
Hismanal	4.44	A	
Placebo	4.85	A	
Benadryl	7.48		B

TABLE 49

Newman-Keuls Comparison of Drug by Session Interaction for Number of Unmatched Large Targets, Session 3. Means with the same letter are not significantly different ($p > .05$).

Drug	Mean	Grouping	
Hismanal	3.74	A	
Placebo	5.19		B
Benadryl	5.70		B

TABLE 50

Newman-Keuls Comparison of Drug by Session Interaction for Number of Unmatched Large Targets, Session 4. Means with the same letter are not significantly different ($p > .05$).

Drug	Mean	Grouping	
Hismanal	4.07	A	
Benadryl	6.70		B
Placebo	7.00		B

TABLE 51

Analysis of Variance Summary Table for Overall Mean Time

Source of Variance	df	MS	F	p
Between Subjects				
Subjects (O)	26	7.88		
Within Subjects				
Sessions (S)	7	2.58	16.25	.0001
O X S	182	0.16		
Drug (D)	2	2.85	1.06	.3548
D X O	52	2.69		
S X D	14	0.05	0.31	>.05
S X D X O	361*	0.15		
Total	644*			

* Three degrees of freedom were subtracted for missing data

TABLE 52

Newman-Keuls Comparison of Sessions for Overall Mean Time.

Means with the same letter are not significantly different ($p > .05$).

Session	Mean	Grouping			
1	2.70	A			
2	2.48		B		
3	2.36		B	C	
4	2.33		B	C	
5	2.30			C	
6	2.25			C	D
7	2.23			C	D
8	2.11				D

TABLE 53

Analysis of Variance Summary Table for Overall Standard Deviation

Source of Variance	df	MS	F	p
Between Subjects				
Subjects (O)	26	.297		
Within Subjects				
Sessions (S)	7	.053	3.11	.0040
O X S	182	.017		
Drug (D)	2	.264	1.96	.1506
D X O	52	.134		
S X D	14	.009	0.64	>.05
S X D X O	361*	.014		
Total	644*			

* Three degrees of freedom were subtracted for missing data

TABLE 54

Newman-Keuls Comparison of Sessions for Overall Standard Deviation.

Means with the same letter are not significantly different ($p > .05$).

Session	Mean	Grouping
1	0.38	A
2	0.34	B
6	0.33	B
3	0.33	B
7	0.32	B
5	0.32	B
4	0.32	B
8	0.29	B

TABLE 55

Analysis of Variance Summary Table for Duration

Source of Variance	df	MS	F	p
Between Subjects				
Subjects (O)	26	32.19		
Within Subjects				
Sessions (S)	7	11.91	18.46	.0001
O X S	182	0.65		
Drug (D)	2	12.33	1.08	.3467
D X O	52	11.41		
S X D	14	0.27	0.27	>.05
S X D X O	361*	0.63		
Total	644*			

* Three degrees of freedom were subtracted for missing data

TABLE 56

Newman-Keuls Comparison of Sessions for Duration. Means with the same letter are not significantly different ($p > .05$).

Session	Mean	Grouping			
1	8.93	A			
2	8.47		B		
3	8.20			C	
4	8.16			C	
5	8.07			C	
6	8.00			C	
7	7.92			C	
8	7.65				D

Table 57
Dependent Variables, Their Significant Effects, and a Brief Description

Variable	Significant effect	Description of variable
Percent correct for all size targets	S, D, I	Percent of correct matches made (target correctly identified) for all three size boxes
Percent correct for large targets	D, I	Percent of correct matches made for large target size
Mean time of matched small targets	S	Average amount of time (in sec) the subject took to correctly identify the small target
Standard deviation of matched small targets	S	Standard deviation of time the subject took to correctly identify the small target
Mean time of matched medium targets	S	Average amount of time (in sec) the subject took to correctly identify the medium target
Standard deviation of matched medium targets	S	Standard deviation of time the subject took to correctly identify the medium target
Mean time of matched large targets	S	Average amount of time (in sec) the subject took to correctly identify the large target
Number of matched large targets	D, I	Number of correctly identified large targets (out of 40)
Mean time of unmatched small targets	D	Average amount of time (in sec) the subject took to incorrectly identify the small target
Number of unmatched large targets	D, I	Number of incorrectly identified large targets (out of 40)
Overall mean time	S	Average amount of time (in sec) the subject took to respond (either correctly or incorrectly)
Overall standard deviation	S	Standard deviation of time the subject took to respond (either correctly or incorrectly)
Duration	S	Total amount of time (in min) the subject took to complete the task

Where S = Session, D = Drug, and I = Drug by Session Interaction

TABLE 58

Analysis of Variance Summary Table for Percent Correct of All Size Targets, Placebo Days Only

Source of Variance	df	MS	F	p
Between Subjects				
Day (A)	2	1256.21	3.01	.0052
Subjects/Day (O/A)	24	359.57		
Within Subject				
Sessions (S)	7	25.44	3.49	.0466
S X A	14	6.59	0.78	.6886
S X O/A	168	8.44		
Total	215			

TABLE 59

Analysis of Variance Summary Table for Mean Time to Match Small Targets, Placebo Days Only

Source of Variance	df	MS	F	p
Between Subjects				
Day (A)	2	1.47	10.06	.0001
Subjects/Day (O/A)	24	.497		
Within Subject				
Sessions (S)	7	.138	2.95	.0713
S X A	14	.012	0.90	.5641
S X O/A	168	.014		
Total	215			

TABLE 60

Analysis of Variance Summary Table for Standard Deviation to Match Small Targets, Placebo Days Only

Source of Variance	df	MS	F	p
Between Subjects				
Day (A)	2	.049	1.85	.0807
Subjects/Day (O/A)	24	.014		
Within Subject				
Sessions (S)	7	.006	3.44	.0486
S X A	14	.001	0.45	.9542
S X O/A	168	.003		
Total	215			

TABLE 61

Analysis of Variance Summary Table for Mean Time to Match Medium Targets, Placebo Days Only

Source of Variance	df	MS	F	p
Between Subjects				
Day (A)	2	12.06	1.74	.1024
Subjects/Day (O/A)	24	2.79		
Within Subject				
Sessions (S)	7	.157	4.32	.0250
S X A	14	.078	0.86	.6001
S X O/A	168	.090		
Total	215			

TABLE 62

Analysis of Variance Summary Table for Standard Deviation to Match Medium Targets, Placebo Days Only

Source of Variance	df	MS	F	p
Between Subjects				
Day (A)	2	.469	0.39	.9080
Subjects/Day (O/A)	24	.070		
Within Subject				
Sessions (S)	7	.003	6.67	.0050
S X A	14	.005	0.67	.7983
S X O/A	168	.007		
Total	215			

TABLE 63

Analysis of Variance Summary Table for Mean Time to Match Large Targets, Placebo Days Only

Source of Variance	df	MS	F	p
Between Subjects				
Day (A)	2	0.16	5.40	.0001
Subjects/Day (O/A)	24	11.19		
Within Subject				
Sessions (S)	7	3.80	0.01	.9854
S X A	14	1.61	2.28	.0070
S X O/A	168	0.70		
Total	215			

TABLE 64

Analysis of Variance Summary Table for Overall Mean Time, Placebo Days Only

Source of Variance	df	MS	F	p
Between Subjects				
Day (A)	2	3.00	10.14	.0001
Subjects/Day (O/A)	24	2.91		
Within Subject				
Sessions (S)	7	.956	1.03	.3735
S X A	14	.253	2.68	.0014
S X O/A	168	.094		
Total	215			

TABLE 65

Analysis of Variance Summary Table for Overall Standard Deviation, Placebo Days Only

Source of Variance	df	MS	F	p
Between Subjects				
Day (A)	2	.029	3.67	.0010
Subjects/Day (O/A)	24	.077		
Within Subject				
Sessions (S)	7	.029	0.38	.6862
S X A	14	.008	1.03	.4269
S X O/A	168	.008		
Total	215			

TABLE 66

Analysis of Variance Summary Table for Duration, Placebo Days Only

Source of Variance	df	MS	F	p
Between Subjects				
Day (A)	2	13.71	11.38	.0001
Subjects/Day (O/A)	24	12.18		
Within Subject				
Sessions (S)	7	4.54	1.13	.3410
S X A	14	1.17	2.92	.0005
S X O/A	168	0.40		
Total	215			

TABLE 67

Newman-Keuls Comparison of Sessions for Mean Time to Match Small Targets, Placebo Days Only. Means with the same letter are not significantly different ($p > .05$).

Session	Mean	Grouping		
1	1.00	A		
3	.915		B	
2	.903		B	
4	.863		B	C
5	.847		B	C	D
6	.834		B	C	D
7	.811			C	D
8	.773				D

TABLE 68

Newman-Keuls Comparison of Sessions for Mean Time to Match Large Targets, Placebo Days Only. Means with the same letter are not significantly different ($p > .05$).

Session	Mean	Grouping
1	4.88	A
2	4.38	B
4	4.19	B
3	4.19	B
5	3.94	B
6	3.91	B
7	3.78	B
8	3.74	B

TABLE 69

Newman-Keuls Comparison of Sessions for Overall Mean Time, Placebo Days Only. Means with the same letter are not significantly different ($p > .05$).

Session	Mean	Grouping		
1	2.64	A		
2	2.37		B	
3	2.28		B	C
4	2.24		B	C
5	2.17		B	C
7	2.12			C
6	2.12			C
8	2.05			C

TABLE 70

Newman-Keuls Comparison of Sessions for Overall Standard Deviation, Placebo Days Only. Means with the same letter are not significantly different ($p > .05$).

Session	Mean	Grouping	
1	.363	A	
2	.338	A	B
3	.318	A	B
4	.295		B
7	.291		B
6	.282		B
5	.278		B
8	.268		B

TABLE 71

Newman-Keuls Comparison of Sessions for Duration, Placebo Days Only. Means with the same letter are not significantly different ($p > .05$).

Session	Mean	Grouping			
1	8.82	A			
2	8.25		B		
3	8.07		B	C	
4	7.94		B	C	D
5	7.78			C	D
6	7.74			C	D
7	7.70			C	D
8	7.53				D

TABLE 72

Newman-Keuls Comparison of Days for Percent Correct of All Size Targets, Placebo Days Only. Means with the same letter are not significantly different ($p > .05$).

Day	Mean	Grouping	
3	97.71	A	
2	96.11	A	B
1	89.63		B

TABLE 73

Newman-Keuls Comparison of Days for Standard Deviation to Match Small Targets, Placebo Days Only. Means with the same letter are not significantly different ($p > .05$).

Day	Mean	Grouping	
1	.106	A	
2	.068	A	B
3	.055		B

TABLE 74

Newman-Keuls Comparison of Days for Mean Time to Match Medium Targets, Placebo Days Only. Means with the same letter are not significantly different ($p > .05$).

Day	Mean	Grouping	
1	1.99	A	
2	1.41	A	B
3	1.18		B

TABLE 75

Newman-Keuls Comparison of Days for Standard Deviation to Match Medium Targets, Placebo Days Only. Means with the same letter are not significantly different ($p > .05$).

Day	Mean	Grouping	
1	.297	A	
2	.175		B
3	.139		B

TABLE 76

Newman-Keuls Comparison of Sessions for Percent Correct for All Size Targets, Placebo Days Only. Means with the same letter are not significantly different
($p > .05$).

Session	Mean	Grouping	
1	95.91	A	
8	95.74	A	
7	95.23	A	B
2	95.12	A	B
6	94.88	A	B
3	94.41	A	B
5	93.98	A	B
4	92.96		B

APPENDIX II - 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 four 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 planning, problem solving, and making decisions. A fifth test will evaluate your visual-motor coordination. You will also be asked to answer questions about how you feel, how you think you did on the tests, and which antihistamine you think you were given. 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, VPISU.

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

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: uticaria (hives), rash, anaphlactic 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. An 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). <u>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.</u>

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 often 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 mutagenesic 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: uticaria (hives), rash, anaphlactic shock, photosensitivity, excessive perspiration, chills, dryness of mouth, nose, and throat.
2. Cardiovascular: hypotension, headache, palpatations, 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.

VITA

Gail Lynn Whitehouse was born in Allentown, Pennsylvania, on August 28, 1966. She received a B.S. in Industrial Engineering from North Carolina State University in May of 1988. After receiving her M.S. in Human Factors at Virginia Polytechnic Institute and State University, she plans to work toward her Doctorate in Industrial Engineering at Georgia Institute of Technology. She is a member of Phi Kappa Phi, Tau Beta Pi, Alpha Pi Mu, the Human Factors Society, and the Institute of Industrial Engineers. Her interests included music, cycling, sports, family, and friends.