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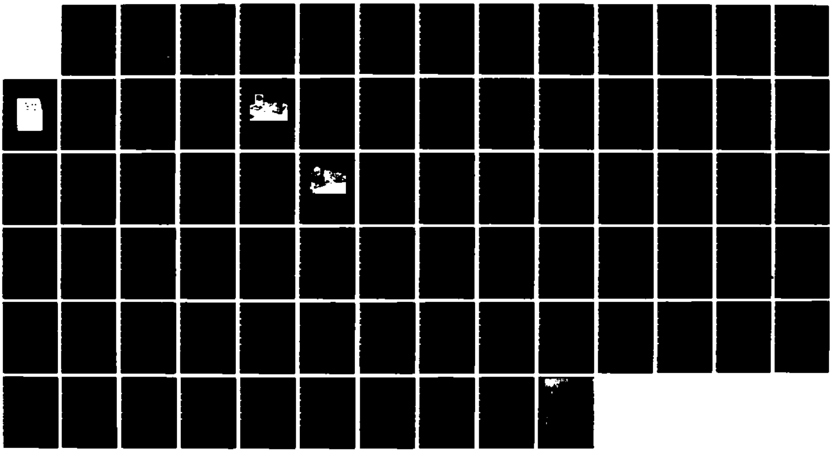

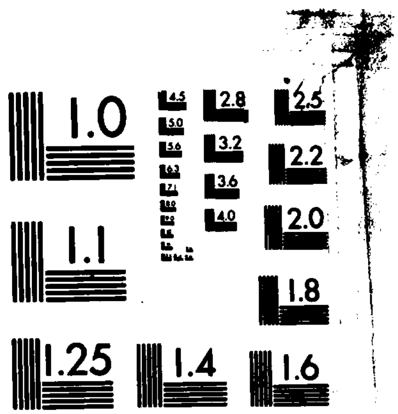

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THE ACUTE EFFECTS OF THYROTROPIN RELEASING HORMONE ON REACTION TIMES

THESIS

Norman E. Michel
Captain, USAF

AFIT/GSO/OS/83D-8

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THESIS

Presented to the Faculty of the School of Engineering

of the Air Force Institute of Technology

Air University

In Partial Fulfillment of the

Requirements for the Degree of

Master of Science in Space Operations

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Preface

It was indeed a rare privilege to work on an experiment that is designated for a Space Shuttle flight and, in the process, combine my background in Life Sciences with my present studies in Space Operations. In order for me to understand the implications of this study it was important to have experience on my side. Much of that experience came from my advisors. Therefore, I would like to thank Dr. Matthew Kabrisky and Major Joseph W. Coleman for their help in the design and analysis of this work.

I am also grateful to the staff of AFAMRL for sharing their know-how with me. Specifically, I want to thank Dr. (Capt) Tom Jennings and Sgt. Laura Howell for their work during the early mornings and occasional tedium that this long-running experiment produced. In addition, I wish to thank Dr. (Lt Col) Jim Jacobsen of WPAFB Hospital for his experience, enthusiasm, and encouragement. His knowledge of the "human machine" is matched only by his knowledge of the human psyche. For the extensive computer and statistical labors, I wish to thank the nameless statistician of AFAMRL. Regardless of his name, he remained tireless. And, for the completion of the report, (through all those changes) the typing of Ladeena Massey is greatly appreciated. The quality of the experiment depended on the inputs and performance of these exceptional people.

Most importantly, I wish to thank my sponsor, Dr. Daniel Repperger of AFAMRL. His extensive sacrifices of time in coordinating, scheduling, and monitoring this work were the backbone of its accomplishment. His sponsorship, expertise, and many valuable inputs gained my highest respect and thanks.

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List of Abbreviations

AFAMRL	Air Force Aerospace Medical Research Laboratories
CNS	Central Nervous System
CRT	choice reaction time
msec	millisecond
PT	information processing time
SRT	simple reaction time
TRH	Thyrotropin Releasing Hormone

Abstract

The effects of Thyrotropin Releasing Hormone (TRH) on simple and choice reaction times and information processing time was studied using an electronic reaction time tester. The Air Force Aerospace Medical Research Laboratory (AFAMRL) originally designed the tester for use by NASA astronauts, but AFAMRL decided to also apply it to TRH studies.

To develop a test procedure applicable to NASA use and the TRH study, a pilot study was performed with sixteen subjects. Each subject performed sixteen modes of operation with the tester. From the analysis of results, four tester modes were deemed applicable for later use: simple reaction time (SRT) and choice reaction time (CRT) each performed with the left hand and right hand.

To analyze the effects of TRH, ten subjects were tested during two sessions each in a double-blind study. One session involved an injection of TRH (500 micrograms) and another involved an injection of saline (1 normal) as a control. RTs were tested during seven time periods from injection-minus-20 minutes (baseline) to injection-plus-120 minutes. Results showed large differences (13 msec or more) between TRH and saline SRT and CRT baselines. Therefore, the means for time periods 2 through 7 were subtracted from baselines and analyzed. ANOVA's showed significantly slower ($p < .05$) SRT for TRH immediately after injection (+ 5 min). TRH did show significantly improved CRT at +90 and +120 minutes and improved information processing times at +65, +90, and +120 minutes. None of these improvements was significantly better than those during saline sessions.

It is concluded that (1) the experimental procedure is sound and applicable to NASA and other scientific use, (2) TRH, in the dose administered, does not significantly improve reaction and information processing times in the acute time frame (+120 minutes) and (3) the improved RTs during later stages of TRH sessions could lead to later research on the neurological effects of TRH in humans.

THE ACUTE EFFECTS OF THYROTROPIN RELEASING
HORMONE ON REACTION TIMES

I. INTRODUCTION

Background

Experiments performed on the Space Shuttle (STS) have provided data on many areas of manned space flight. Often evaluated have been the areas relating medicine and biomedical engineering to crew workload. It has been noted that during times of G-stress scheduled workload may be high and decisions must often be made at a rapid rate. The STS astronauts experience this most acutely during reentry from orbit. The return from a weightless environment to the earth's one G environment requires an approximate two G transition as well as an increased workload for the members. The astronauts have related that at that time they experience drowsiness or a fatigue-like syndrome which degrades on-time decision making capabilities. The reasons for this syndrome may be changes in blood chemistry, changes in vestibular or proprioceptor inputs, boredom, cumulative fatigue, or any number of physiological or mental effects. Though the syndrome is common among STS astronauts, no measurements have been taken on their basic mental capabilities for processing information during that phase of flight.

The Air Force Aerospace Medical Research Laboratory (AFAMRL) at Wright-Patterson AFB, Ohio was notified of the syndrome by one of the physicians attending the astronauts, Dr. James Logan. His desire is to provide basic research on any changes in astronauts' reaction times during STS missions. This would be done through reaction time measurements while the astronauts are on the ground, in zero-G, and in the re-entry phase.

At Dr. Logan's request, AFAMRL developed a hand-held machine that could be carried by STS crew members on upcoming missions. The machine will test a subjects' simple reaction time (SRT) or choice reaction time (CRT) to visual stimuli (Fig 1). SRT deals with a response to a single stimulus always presented in light B. CRT is measured after the subjects' correct response to either light 3 or light C. That is, depending on which light is illuminated, the subject must respond by moving the response switch, S3, in the direction of that light. CRT minus SRT provides a basic measure of subject information processing time (PT). Whether SRT or CRT is tested is dependent upon the mode switch, S1, being in MODE 1 or MODE 2, respectively. Ready light, A, indicates that the tester is ready to be reset between each trial and switch S2 is used for the reset. Dr. Daniel Repperger and Mr. Donald McCollar of AFAMRL were responsible for designing the tester.

In addition to these basic measurements, AFAMRL desired to test the effects of thyrotropin releasing hormone (TRH) to see if it will improve human reaction and processing times. TRH is normally released by the hypothalmus of the brain. It causes the pituitary gland to release thyroid stimulating hormone (TSH), which, in turn, effects the release of hormones by the thyroid gland (2:88). Because of this chain of events, TRH is often used on patients with suspected thyroid disease to determine their abilities to secrete TSH. The effects of injected TRH on human performance have not been thoroughly studied. That is, TRH's effects on basic reaction and processing times have not been measured.

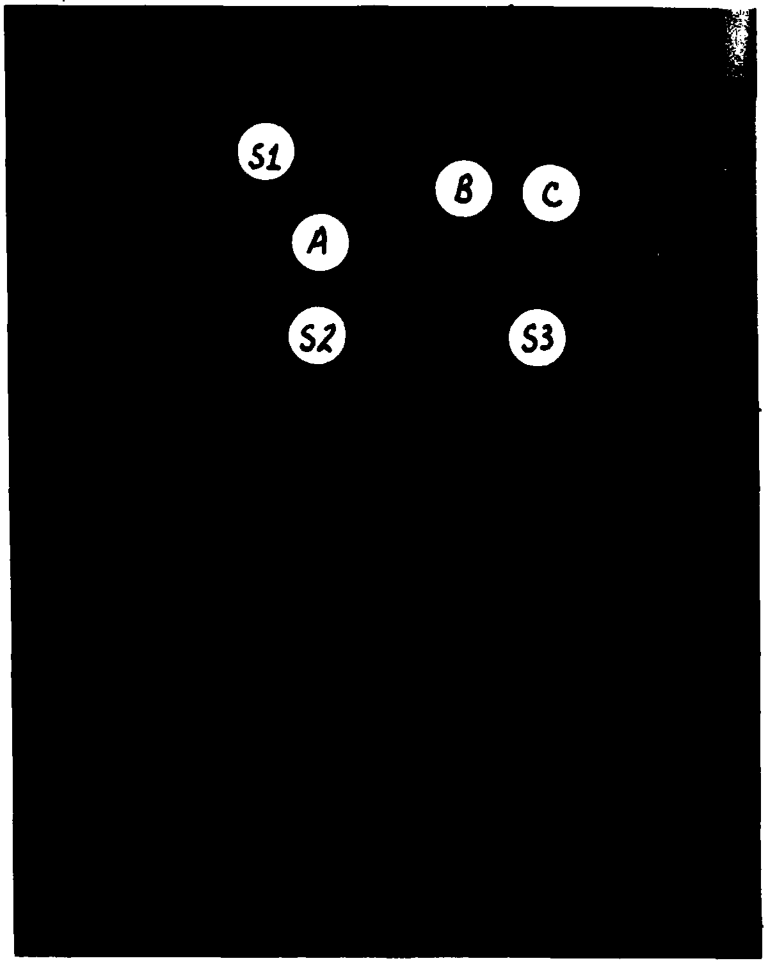

Figure 1. Reaction Time Tester

Because a hypodermic injection is required to introduce a bolus of TRH into subjects, the necessary experimental protocol was submitted and approved by medical councils for "Human Use in Research" at Wright-Patterson AFB and Headquarters Aerospace Medical Division, Brooks AFB, Texas.

Significance of Research

The importance of these studies is found in the desires of NASA and the Air Force to improve the decision making capabilities of astronauts and pilots during high workloads and/or stress. The measurements of SRT, CRT and PT during shuttle re-entry or following the introduction of TRH may provide insight into the causes and possible alleviation of the discussed difficulties.

Statement of Problem

Astronauts' physicians desire a reliable means of measuring PT during various phases of STS flight, particularly re-entry. The basic reaction time measurements have never been taken during STS missions and a device and experiment must be developed to do that.

Similarly, the effects of TRH on reaction times have never been measured at the level of one bit of information for stimulus, ie. CRT dependent on a choice between only two possibilities. The Air Force desires an investigation into TRH phenomena for insight into improving pilots' responses during high task, high stress phases of flight.

The significant questions to be answered in the research are:

- whether reaction times and processing time are affected by TRH.

- whether the experimental procedure for the tester is transferable to STS operations and, thus

- whether an adequate data base can be provided to NASA and the Air Force for later use.

Scope

The effects of TRH on human reaction and processing times is the major thrust of the research. Times were expected to improve, ie. become shorter, with the introduction of TRH. The ANOVA for reaction time tests were used to either verify this hypothesis or show cause to reject it.

Another important aspect of the work was tailoring the experiment to fit the STS environment and astronaut workloads. That is, with or without TRH, the experiment should provide a baseline of data for NASA to study and an experimental procedure that is readily adaptable to astronaut use. For this reason a pilot study using sixteen reaction time modes was performed. It is discussed in Chapter III.

Methodology

Subjects for the TRH study were briefed on the experiment and asked to sign a consent form which explained the experiment and possible TRH side effects (Appendix A). The Visual Evoked Reponse (VER), "oddball paradigm", and tracking tasks mentioned on the form were not included in the experiment. The subjects were asked to refrain from ingesting caffeine products or eating breakfast on the day of the experiment. Because peoples' diets vary, this was felt to be the best way to reduce variability and witness the effects of TRH. The experiment session involved the following schedule of events:

MINUTES	ACTIVITY
- 20	Perform baseline SRT & CRT tests; blood drawn
0	TRH/Saline injection
5	SRT/CRT Tests
20	Blood drawn
25	SRT/CRT Tests
40	Blood drawn
45	SRT/CRT Tests
60	Blood drawn
65,90,120	SRT/CRT Tests

This was a double-blind experiment in that none of the parties involved, physician, subject, or investigator, knew if the injection was one saline solution or TRH. Injections and blood drawings were performed by medical personnel.

The reaction tester was bolted to a desk for stability. The subjects were seated and manipulated the response switch with either their dominant or non-dominant hand. The hand used and SRT or CRT mode were randomly assigned. SRT and CRT were measured in groups of 15 trials per mode with five practice trials allowed at the beginning of each mode. (Appendix B)

Stimuli were pr[illegible] after the subject reset the device. From reset, the tester circuitry provided a random time delay of between one and 6.12 seconds for the presentations. Subjects reaction times were displayed by a computer monitor and recorded by the investigator. (See Figure 2).

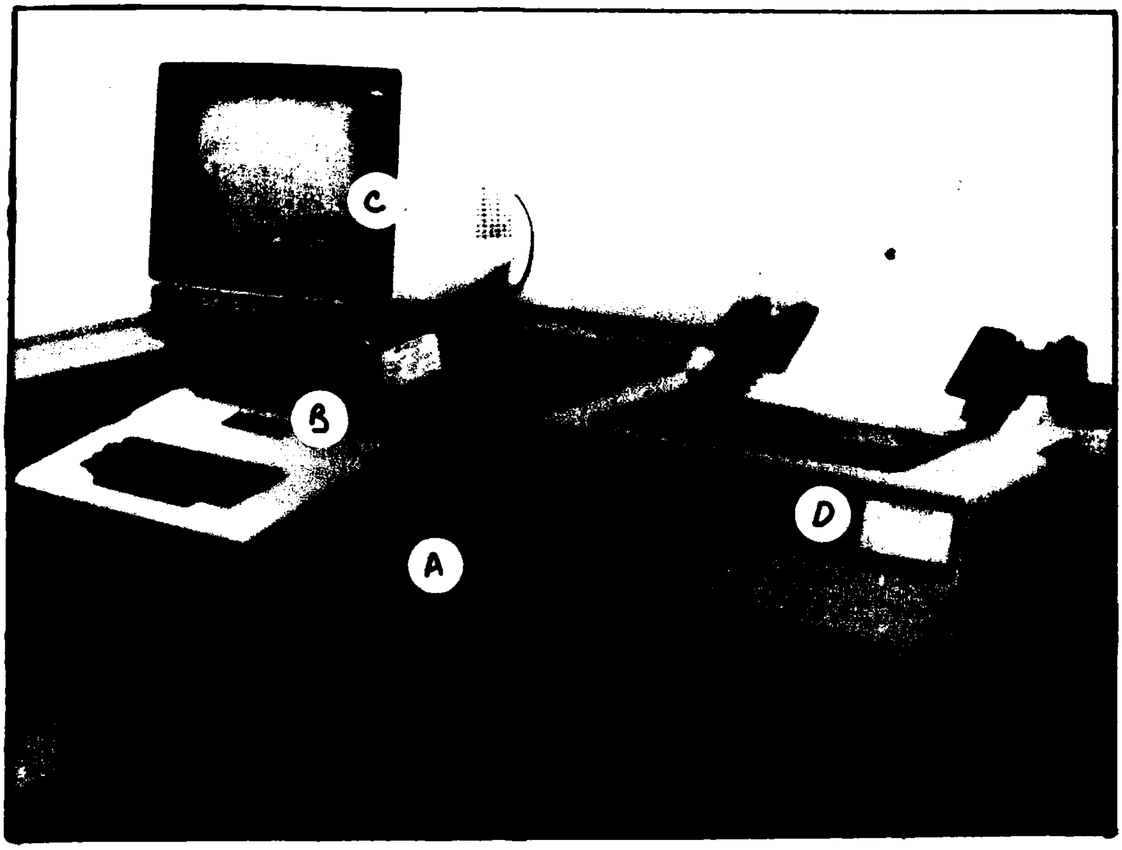

Figure 2. Reaction Time Tester and Associated Computer Hardware

The Reaction time tester (A) is connected to the computer (B) which has an internal clock to measure reaction times. The reaction times are displayed on the monitor (C). The optional printer (D) was not used during the experiment in order to reduce noise and distractions.

A more indepth description of the tester circuitry is found in Appendix C and is taken from a description by Repperger (29).

Sequence of Presentation

Chapter II gives a brief review of the literature applicable to this study. One section of that chapter includes a review of various reaction time studies and another cites research dealing with the effects of TRH.

Chapter III explains the pilot study performed prior to the TRH experiment. The pilot study design, methodology, and results are described. Chapter IV provides a description of the TRH study, from subject selection to the results obtained in the experiment. The discussion of those results, the conclusions drawn, and recommendations for further study are found in Chapter V.

II. LITERATURE REVIEW

Literature abounds on reaction time studies as well as experiments involving Thyrotropin Releasing Hormone (TRH). However, it is necessary to discuss each separately as no works were found combining the two areas of research. Therefore, a discussion of general reaction time research and the influences of drugs on reaction times should reveal a precedence for the present study. Additionally, current knowledge on TRH, its neurological, physiological and psychological effects, will relate this study to previous work with TRH.

General Reaction Time Research

Reaction time (RT) experiments have been used in the study of human information processing for over a century. Donders' classical work in 1868 established standards for choice reaction time experiments (7:430). He felt that CRT and SRT were related by the formula CRT = SRT + b + c, with SRT a constant, b being the time necessary for stimulus catagorization and c being the time for response selection. Merkel added to the work by showing a linear relationship between CRT and the number of possible choices to which a subject is exposed (21). Studies by Hyman and Hick conclude that RT increased with the stimulus information transmitted, specifically when the presentation was between 0 and 3 bits (11;13).

Klemmer found that by varying the time periods between trials RTs changed (16). Periods between 1.25 and 4.25 seconds resulted in the fastest RTs while shorter or much longer periods (8 seconds) increased RTs. The time periods between trials for the present study were comparable to Klemmer's. The tester provides from 1 to 6.12 second delays after reset (see Appendix C). Related to Klemmer's work is a study by Wagenaar and Stakenburg dealing with the pace of stimulus presentation (35). This experiment involved speed vs accuracy tradeoffs with reactions to either subject-paced or investigator-paced stimulus presentations. It was found that when investigators paced the presentations accuracy declined. It was also found that RTs generally improved as the pace increased to a pre-determined maximum frequency. That is, subjects' speed improved without a significant loss of accuracy. The relationship of the Wagenaar and Stakenburg study to the present study will be discussed in Chapter III.

Though studies show reaction times to visual stimuli are slower than those to auditory or tactile stimuli, historically the most reliable studies have used visual stimuli (27:380; 34:79). The light-key experiments, in which subjects respond to a light stimulus by pressing or releasing a telegraph key, constitute the majority of recognized RT work. (34:82).

The analysis of information processing time (PT) by means of reaction time tests has been used many times, most notably by Fitts, Hick and Pachella (9;11;27). The difference between a subjects SRT and CRT has been used to provide PT for various information rates and experimental paradigms. (13;27).

Practice, of course, has its effects or reaction time tests. Mowbray and Rhodes found that a learning process continued to lower CRT through 45,000 trials in two-choice and four-choice tests. (23).

Reaction Time Tests Using Drugs

Various drug-produced stresses have been tested for reaction time effects. Carpenter found that caffeine had a short-lived effect of decreasing RTs (3:494). Amphetamines also improved RTs in studies by Frowein (10). Frowein tested the effects of barbiturates as well, and both SRT and CRT were lengthened. Alcohol, a known depressant, was shown to increase reaction times in studies by Carpenter (3) and Chiles and Jennings (4). Several other drugs have been introduced in reaction time studies, however, at this writing no works involving TRH in these studies were found.

Classic TRH Effects

As mentioned before, injections of TRH are frequently used to evaluate suspected thyroid patients. This polypeptide is primarily found in the hypothalmus and, when released, causes the subsequent release of TSH (also called thyrotropin) from the pituitary gland. TSH causes the secretion of thyronine (T_4) and tri iodothyronine (T_3) from the thyroid gland. The system works in the manner of a classical feedback loop with T_3, in particular, inhibiting the response to TRH at the pituitary. This chain of events is reviewed in detail by Burger and Patel (2). Also, Snyder and Utiger discuss the effects of TRH injections on normal subjects, especially with regard to TSH levels in the blood. (30:384). They found that TSH response was clearly dependent upon the dosage of TRH.

TRH Locations and Neurologic Effects

Hokfelt, et al found that TRH was contained not only in the hypothalmic and pituitary regions but also in the spinal cord (12:390). The study concluded that TRH may act as a neurotransmitter or neuromodulator within the central nervous system (CNS). In 1979, Mailman, et al., found increased TRH in all areas of rat brain tissue after a peripheral injection. (20:520). The studies led to the conclusion that even peripheral administration of TRH could have effects on the CNS. Since 1972, Breese, et al., have done research on neurological effects of TRH following direct injection (1:112). It was found that TRH had profound effects on the neurological responses to the depressants pentobarbital and ethanol. TRH caused rats to recover more quickly from sleep and hypothermia induced by the drugs. Experimentally it was determined that the effects were not due to increased metabolism, re-distribution of the drug throughout the body or varied endocrine actions.

Nicoll, et al., showed that TRH had an excitatory effect on spinal motoneurons of laboratory animals (25:243). Their later work emphasized the fact that the time course for this effect was slow and the depolarization of neurons was at a sub-threshold level (26:144). It was concluded that TRH may only set the level of excitability in these neurons and, therefore, be a modulator rather than transmitter in CNS processes. Stanton, et al., discovered that arousal state changed TRH effects on the CNS of ground squirrels (31:680). When awake TRH decreased body temperature, metabolic rate and electromyographic activity. When asleep, body temperature and electromyographic activity increased.

Related to these CNS responses is a study of Koss, et al., (17:103). In this work, TRH improved the tone of the irises in anesthesized cats, independent of the excitatory light reflex. It was proposed that TRH may also be a neurotransmitter or modulator with respect to parasympathetic functions in the eye.

Psychological and Physiological Effects

Morley, et al., have shown that TRH increases arterial blood pressure and plasma levels of norepinephrine in man (22:20). Such "fight or flight" symptoms have been backed-up by studies showing an increase in motor activity in laboratory animals following TRH injections (28;33). Recent studies were done involving the use of TRH to stem degredation of neural transmission and attending muscle atrophy in humans affected by Amyotrophic Lateral Sclerosis (5). Slight improvements in muscular activity and temporary cessation of nerve degradation have been noted when using large doses of TRH.

Research in the psychological effects of TRH are less conclusive. Specific tests using TRH to treat mental depression have shown mixed results. Itil, et al., found that TRH increased interest and drive for work, food and sex in depressed subjects. (14:533). Winokur, et al., recorded a decrease in tension in healthy menopausal women following TRH injection (36:242). These findings differ from those of Kiely, et al. (15:239). When TRH was administered to depressed patients, no clinical benefits were found. In fact, the placebo used showed more improvements in subject well-being.

The present study adds to the work involving TRH effects on humans. By combining a reaction time test with a bolus injection of TRH, the psychomotor effects may be seen more clearly.

III. PILOT STUDY

A pilot study was performed prior to implementing research on TRH. The purpose of the pilot study was to refine the experiment, not only for TRH testing but also for NASA/STS use. It was naturally assumed that limited time frames would be allotted for the experiment on the STS. In a ten to fifteen minute span, the experiment was to provide the most important and useful information of astronaut RT's* (19). For this reason, it was necessary to carefully design the pilot study for later analysis. The tester itself was analyzed to find modes that would provide the most information, and a proven test design incorporated each of those modes into the study. Also, the test procedures and environment were the same for each subject. These areas as well as the results of the pilot study are discussed in this chapter.

Test Design

The RT tester was analyzed for the various modes of testing it provided and four, paired areas of interest were recognized.

Aside from SRT and CRT differences, it was important to find whether RT's differed with reset mode, ie. either the tester is reset by the subject or by the investigator. Also important were dominant and non-dominant hand reaction times and whether outward (abductive) movement or inward (adductive) movement of the switch produced faster SRT or CRT.

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* This 10 to 15 minute timeframe was confirmed by Dr. (Lt Col) Ralph Luciani, Chief of Aerospace Medinine, AMD/RD, Brooks AFB, Texas. Dr. Luciani is one of the primary mediators between NASA and the USAF for biomedical research in space.

This last condition was met by either leaving the tester as shown in Figure 1 or turning it "upside down". That is the mode and reset switches would be on the right side, as viewed by the subject. SRT would then be measured with abductive movement. By nature of the tester, CRT was measured during both types of movement, regardless of the tester orientation. These four, paired areas of interest resulted in 2^4, or sixteen, possible modes for the study. To randomize the modes, a cross-over design, as explained by Neter and Wasserman, was used (24:792). With this design, subjects were assigned the sixteen modes in different orders. An explanation of the modes and the experimental order are given in Appendix D.

Methodology

Sixteen subjects were tested in a room adjoining a clinic at WPAFB Hospital. The room was situated so that little or no noise from the clinic was heard. Distractions were, therefore, at a minimum during the testing. Eight of the subjects were right-hand dominant and eight were left-hand dominant, with four males and four females in each category. Their ages ranged from twenty-one to thirty-nine years.

Each subject was allowed as many practice trials as they believed necessary to become familiar with the tester. Usually this was accomplished with twenty trials, ten SRT and ten CRT performed left and right handed with the tester "upright." Often subjects performed fewer trials before they expressed that they were familiar with the tester.

Before each mode, a coin was flipped to determine if the subject would perform the mode right-handed (heads) or left-handed (tails). Five practice trials were given prior to data collection in each mode.

The practice trials were to familiarize subjects with the particular mode they were about to perform. Subjects were aware that the five trials were merely practice and verbal feedback of the times was provided by the investigator, just as it was for data trials.

Twenty data trials were performed in each mode, and a particular subject would perform all sixteen modes in one "sitting." Of course, breaks were allowed whenever desired. Standing to re-orient the tester, a one-to-two minute walk, and/or stretching were most often used to overcome stated effects of fatigue. The time for each trial was recorded by the investigator as was the direction of movement for CRT trials. Subjects were allowed to eliminate a trial (prior to the next trial) if for some reason they felt they gave less than optimum performance. The times were transferred to punch cards, entered into a file on the CDC 6600 computer, and analyzed in a ANOVA using the available Statistical Analysis System (SAS) package on the computer (32). The factors included were reaction type, box orientation, hand used, and reset mode, with a randomized block for subjects.

Results

The mean SRT for all subjects and all eight SRT modes was 207.089 milliseconds. The CRT modes resulted in a mean of 268.064 milliseconds. This 60.975 millisecond difference was significant ($p = .0001$) at the $p = .05$ level and was expected.

A significant difference was also found when comparing reset modes. When subjects reset the tester between trials the mean over all RT's was 235.26 msec while investigator reset produced a mean of 239.89 msec. ($p = .028$). The reset was also significant in CRT where subject-reset mean was 265.48 and investigator-reset mean was 270.65 ($p = .038$).

However, the SRT means, subject-reset of 205.04 and investigator-reset of 209.14, were not significantly different (p = .065).

No significant differences were found for any mode with different tester orientation, upside down or right-side up. More surprisingly, no significant differences were found between dominant hand and non-dominant hand RT's. The means and p-values for these are listed in Appendix E.

Statistical analysis, therefore, showed that only two of the four areas considered for final experimental design yielded significant differences. One difference, SRT-vs-CRT, was expected, while the other, Subject-vs-Investigator reset, called for closer scrutiny.

Discussion

The expected significant difference in SRT and CRT was a basic premise of the study. However, the difference found in Subject-vs-Investigator reset presented a slight problem for the final design. To retain the two modes needed to accommodate the difference, the present experiment would be increased by five or more minutes and, therefore, extend beyond the allotted time frame. Eliminating reset interactions from the statistical model did indeed increase mean squared error (MSE) from 851.406 to 856.245.

It should be noted, though, that mean RT's were faster with subject-reset in all cases, and only SRT showed no significant difference with respect to reset mode. Also, the desire throughout the study was for subjects to produce the fastest times that they could. This reset method was also in agreement with the findings of Wagenaar and Stakenburg which showed that subject-pacing improved RT's and accuracy (35).

For the above reasons, plus the fact that it may be impractical to involve two STS crew members in each experimental session, final design included only subject reset modes.

Though dominant-vs-non-dominant hand RT's were not significantly different, this area of investigation was of interest to AMRL. These modes were retained for possible later research. Conversely, the removal of separate tester-orientation modes was decided upon due to the insignificance between ab/adductive movement RT's.

These seemingly fickle choices required proof that the statistical analysis would not be degraded by changing the various interactions in the statistical model. As stated above, the model showed a MSE of 856.245 without the RESET factor. Without RESET or TESTER ORIENTATION factors the model improved slightly with a MSE of 856.193. Therefore, different reset modes were eliminated from the design for the practical problems of a limited time frame while different tester-orientation modes were eliminated on a statistical basis. (See Appendix E)

The final test design included four modes: SRT and CRT, tested left-handed and right-handed. The tester remained in the "upright" position and the subject always accomplished the reset. It was also determined to include 5 practice trials and 15 data trials per mode, rather than 5 practice and 20 data trials as 5 fewer trials did improve the speed of testing without hindering data validity. In this form, the experiment took approximately three minutes per mode and a very manageable twelve minutes per set of trials.

IV. Effects of TRH on Reaction Time: Part I

This chapter explains the implementation of a proven reaction time test following a bolus injection of thyrotropin releasing hormone (TRH). It is the first such experiment known to the author and his sponsors at AFAMRL. In this part, the subject selection and training and the test methods and results are discussed.

Subject Selection and Training

Subjects were originally requested from the AFAMRL Dynamic Environment Simulator (Centrifuge) panel. However, scheduling those individuals was difficult due to their centrifuge and other Air Force duties. As an alternative, advertisements were made in WPAFB daily bulletins (see Appendix F). Over thirty people responded, and each was briefed on the test procedure and what would be required of them for the experiment as outlined in Appendix E. None of the respondents were involved in the pilot study and twelve of them were chosen, ten of which completed the experiment. All subjects were right-handed males between 23 and 34 years old, and all were active duty Air Force members stationed at WPAFB. Female subjects were not used because the possible hormonal effects of TRH during different phases of the menstrual cycle would add greater variability to the test. Of the subjects which completed the experiment, two were Air Force pilots, and another was an aircrew member involved in airborne scientific research projects. Seven were officers and three were enlisted men.

Training sessions were held in an AFAMRL laboratory where the experiment was also conducted. Each subject was given 80 practice trials with the tester. Twenty trials were given in each of the four nodes used for the experiment; SRT and CRT performed left-handed and right-handed. The subjects were then scheduled for the first of two test sessions, one involving an injection of TRH, the other an injection of a saline solution (control).

Methodology

Though this study only reports the acute effects of TRH on SRT, CRT and PT (up to injection + 120 minutes), each session involved tests up to injection + 54 hrs. (see Table 1).

Table 1. Session Test Sequence

Time Period	Time From Injection	Activity
1 (baseline)	- 20 min	Baseline blood Draw and RT Tests
2	+ 5 min	RT Test
3	+ 25 min	Blood draw and RT Tests
4	+ 45 min	Blood draw and RT Tests
5	+ 65 min	Heparin Lock Removed
6	+ 90 min	RT Test
7	+120 min	RT Test
8	+ 6 hr	Blood draw and RT Tests
9	+ 30 hr	Blood draw and RT Tests
10	+ 54 hr	Blood draw and RT tests

Because it was desirable to use only weekdays for testing, the 54 hour time frame required that a session start on a Monday, Tuesday or Wednesday. Hence, with each subject acting as his own control, he was involved in two separate weeks of testing. Subjects fasted for ten hours prior to starting a session and also refrained from ingesting products containing caffeine. This was done so the effects of TRH could be better observed. Following the tests at time period 7, subjects could break the fast.

They also returned to their regular duties at that time and only returned to the laboratory for subsequent blood draws and RT tests at the six, thirty, and fifty-four hour marks.

Normally, one subject was tested per day (Monday - Wednesday), with the procedure beginning at 7:15 am. When subjects' and physicians' schedules allowed, two subjects were tested, with the second one starting at 10:15.

Physician's inserted a catheter and heparin lock into either the cephalic or accessory cephalic vein on the dorsal side of a subjects forearm. This allowed for easier injections and blood draws but was removed after the blood draw at time period 5. Five subjects had the lock in their left arm and five in their right. Baseline blood draws and reaction time tests were made with the heparin lock in place.

After baseline tests, a one milliliter (1 cc) injection of either TRH (500 micrograms) or saline solution (1 normal) was administered by the physician. The subject, physician, and investigator were unaware of which compound would be injected. This choice was made by an independent fourth party. Because of the immediate effects of TRH (see Appendix A), the subjects often knew when they had received TRH.

During the testing, the tester was bolted to a desk for stability, and the subjects were seated at the desk. (See figure 3). For each trial, the investigator read the reaction time from the computer monitor to provide feedback. If inattention or improper movement for CRT hampered reaction times, subjects were allowed to eliminate a trial before the time was read to them. Also, reaction times under 100 msec were not

Figure 3. Subject and Tester Setup

This figure shows a subject seated for right-handed tracking. The tester (A) is bolted to the desk. For left-handed tracking a chair was placed to the right of the desk and the subject sat in it to perform trials. The monitor (B) displayed reaction times and the investigator announced and recorded the times as they appeared on the screen.

allowed. It was determinied that that was the minimum time in which a person could react to the stimulus without guessing or pre-loading the switch (8:44,45).

For motivation, subjects were paid a small fee for participation and were awarded a bonus amount for scoring the fastest times during a week of testing. In addition, the fastest times for SRT and CRT were posted in the laboratory for subject perusal.

Throughout the sessions, subjects were allowed to take rest breaks between tests. Changes from right to left-hand modes required changes in seating and allowed for frequent, though brief, periods of stretching or relaxation. These breaks alleviated any stated effects of fatigue.

Results

The ten subjects provided 8400 data points (trials) or 210 SRT and 210 CRT trials per session for each subject. The same hardware and statistics package used in the pilot study was used for the analysis. The questions to be answered by the analysis were:

- As compared to the saline (control) sessions, was there a significant difference in SRT, CRT or PT during TRH sessions?

- Were there significant differences between the two within time periods?

The following model was proposed for analysis:

$$y = \mu + \alpha_i + B_j + \Delta_k + \epsilon_{ijk}$$

The dependent variable (y) is expected value of the reaction time. On the independent side of the equation, μ is the overall mean for the

RT or PT in questions, α_i is a randomized block for subject with $i = 1, 2...10$, B_j is the injection type either TRH ($j = 1$), or saline ($j = 2$), Δ_k is the time period, and ε_{ijk} is the random error term.

At one time in the experimentation, there was a shortage of the TRH supply and, as a result, seven of the ten subjects received saline for their first session and TRH for their second session. When the mean baseline times (time period 1) were compared for TRH sessions and saline sessions, it was noted that baselines for TRH sessions were usually lower. This was true in all cases for baseline SRT's and in eight of ten cases for baseline CRT's. The baselines for SRT were significantly different ($p < .05$), though the CRT baselines were not, probably due to the large standard deviations. Likewise, PT baselines were not significantly differently. The baseline data are listed in Table 2.

Table 2. Baseline Data

Session	μ_{SRT}	σ_{SRT}	μ_{CRT}	σ_{CRT}	μ_{PT}	σ_{PT}
Saline	209.95	9.5	270.81	27.03	60.86	29.27
TRH	197.26	11.6	258.60	16.51	61.31	18.53

Because of significantly different SRT baselines and the relatively large numerical difference in CRT baselines it was decided that entire saline sessions would not be used as controls for TRH sessions. For this reason, the analysis of each injection type was performed by two methods. First, the means for each time period were subtracted from the baseline mean, and, second, the means for each time period were compared to its preceeding time period. An ANOVA was run for each time period and the linear model described above consistently showed a poor linear relationship ($p \geq .05$) between time period and injection type, and the chosen dependent variable.

There was concern that because seven of ten subjects received saline first and TRH second, there might be a bias in the data. Therefore, the same methods of analyses were applied using only those seven subjects and ANOVA's run as before. Again, the model showed poor linear relationships and it was decided to use the analysis of all ten subjects.

Because of the poor relationships within the model, each method was analyzed by a paired t-test and verified by the Wilcoxen signed-rank test. The results of each analysis are found in tables in Appendix G as are plots of the means and computer printouts of the data.

V. Effects of TRH on Reaction Times: Part II

This chapter discusses the findings of the analysis outlined in Chapter IV, the conclusions drawn from that analysis and the recommendations for future work in the area. As mentioned in Chapter IV, the analysis using only the subjects who received TRH in the second session revealed the same basic outcome as the analysis using all ten subjects. For this reason the more rigorous ten-subject data is discussed.

Discussion

Over all the time periods a practice or learning effect is noticable for SRT and CRT. This is best noticed in the plots of those RT's (Figures 6-8). The learning effect is expected in such experiments. The work by Mowbray and Rhodes is a classic case of continued learning effects for reaction time studies (23:22). For simple reaction time, saline showed a more consistent downward trend over two hour sessions than did TRH. A sharp rise at time period 2 interrupted the TRH curves. This will be discussed in more depth later in this section. Choice reaction times revealed a more consistent learning curve for both saline and TRH.

By analyzing RT differences from baseline and between time periods, the effects of an injection over time could be more easily seen. Then, t-tests comparing the differences for TRH and saline would give an analysis of the TRH (vs control) effects within a given time period.

The analysis of SRT in Table G-1 revealed very few significant differences ($p \leq .05$) from baseline values. For TRH, the only significant change from baseline was a sharp rise at time period 2 (+7.52 msec).

This was probably due to the neurological effects of TRH which cause nausea and other physiological responses as mentioned in Appendix A. TRH showed only one decrease from baseline in period 4. Differences in baseline for saline SRT were significant in time periods 3 and 7, and the differences were due to decreasing reaction times. Because TRH RT's generally stayed above baseline values, the saline changes were significantly different from those of TRH in periods 3 and 7.

The means for choice reaction time were significantly lower than baseline for time periods 6 (-8.37) and 7 (-10.24) with TRH and time periods 3 (-7.96), 6(-9.52), and 7 (-9.60) for saline (See Table G-2). There were no significant differences between TRH and saline choice reaction times for any time period.

For TRH the downward trend in CRT's and the greater than baseline values for SRT's resulted in significant changes from baseline processing time at time periods 5 (-8.64), 6 (-8.96), and 7 (-14.10). These differences are found in Table G-3. Saline sessions showed no significant differences in processing time, and there were no significant differences between saline ahd TRH processing times for any period.

For the analysis of differences in successive times (Table G-4), TRH revealed only the significant SRT rise between times 1 and 2. Saline sessions again showed significant declines in simple RT between times 5 and 6 and in choice RT between times 2 and 3. There were no significant differences in processing time.

One other aspect of the study should be discussed though it is not easily charted or quantified. That is the factor of subject motivation. For our purposes, subject motivation could be simply defined as the personal desire to do better when challenged. The subjects may have viewed TRH as a challenge to his ability to react. Therefore, subject attentiveness or alertness would be increased, and, with that, faster RT's would result. The converse might be true for saline sessions. Believing that the challenge was not confronting them subject RT's would be higher. Because of the physiological events caused by TRH, the experiment was not perfectly double-blind. That is, subjects knew that they had received TRH in the first session or would receive it in session two because of the presence or absence of the known and readily perciev-able events following the injection. Overall, this subject motivation appeared to be a contributing factor as TRH reaction times, even with the sharp rise at time period 2, were faster than saline RT's. As mentioned before, the differences between TRH and saline RT's at time 1 necessitated the analysis used for this study. There was no way to include this intangible aspect of motiviation by other than subjective analysis.

Nevertheless, such analysis are well recorded in other studies. For example, Leibowitz, et al., studied the effects of heat stress on reaction times using volunteers from the general public (18:157). Surveys to record subject motivation were used. It was concluded that experience and motivation to excel were most important in keeping RT's from degrading with increasing heat. The subject motivation can play a vital role in human experiments, and though not addressed quantitatively may have been important in the results of this study.

Conclusions

The purpose of the study was to determine the following:

- whether reaction times and processing time are affected by TRH.

- whether the experimental procedure for the tester is transferable to Space Shuttle operations.

- whether an adequate data base can be provided to NASA and the A.F. for later use.

In addressing the second and third points, it is concluded that the experimental design for the reaction time tester is, indeed, applicable to STS operations and is supported by the data. The pilot study, which involved 16 subjects, highlighted the significance of the four modes used for the TRH study. The pilot study showed no statistical significance ($p \geq .05$) between dominant and non-dominant RT's. Though both modes were used in the TRH study, the data would justify the use of either one mode or the other if time was of the essence in the STS environment. Also subject-reset modes were significantly different from investigator-reset modes but they always produced faster RT's, which was desirable. Because subject-reset modes required only one person to participate in a test session, any one STS crew-member could perform the experiment in any phase of flight.

With respect to the TRH experiment, the data base is probably too small for Air Force or NASA use. This is further discussed in the Recommendations section.

For the effects of TRH on reaction and processing times several conclusions can be made. In general, it is concluded that TRH showed no benefits over saline for SRT or CRT. The results of this study seem to parallel those of Kiely, et al., (15:239). They found that subjects suffering from mental depression were as effectively treated by a placebo as they were by TRH. In both SRT and CRT analyses of the present study, saline provided as much or more improvement as TRH did. Also, the significant processing time improvements seen within the TRH sessions (periods 5,6, and 7) were not significantly better than the improvements in saline sessions.

It is concluded that learning or practice effects had a greater effect on improving RT's or PT than did TRH. The neurological effects of TRH which cause adverse physiological events soon after injection may even hinder subject learning.

From this study using healthy male subjects, it is concluded that TRH, in the dose administered, will not enhance the performance of Air Force pilots under increased workload or stress, in acute time frames.

Of scientific interest, however, are the significant improvements of CRT and PT in the later time periods of TRH sessions. Nicoll, et. at., concluded that TRH may modulate or set the level of excitability in the motoneurons of laboratory animals (26:146). This activity was noted to evolve on a slow time course, ie., greater than 30 minutes. From the present study it is concluded that the significant CRT and PT improvements in later time periods under TRH may denote similar modulating effects in humans. However, much more research must be accomplished if this is to be verified. The present study outlines one objective means of analyzing the modulating effect of TRH, that is, through the measurements of basic reaction and information processing times.

Recommendations

It is recommended that data gathered but not used for this study be analyzed for possible effects of TRH on reaction times. One such analysis would involve the blood samples taken during the course of the study. The blood levels of thyroid stimulating hormone (TSH), thyronine (T_4) and tri-iodothyronine (T_3) will change due to the TRH injection. These endocrinologic effects should be correlated to RT's in all time periods, including periods 8 through 10. The indirect (ie, endocrinologic rather than neurological) effects of TRH on RT's and PT might be found. In the process, one of the other hormones mentioned above may prove of interest for further studies on enhancing reaction and processing times.

Another recommendation is that more subjects be included in future studies. This is self-explanatory and is the desire of all experimenters. It is not unrealistic to think that ten subjects may be too few to properly study the effects of TRH.

A recommendation that might influence the Air Force use of TRH is to involve the subjects in a stressful environment, preferably G-stress, during the reaction time tests. In the rather sterile environment of the present study, the benefit of TRH in high workload or stress was not adequately tested.

Also recommended are future studies that include other than a saline injection to oppose TRH. As mentioned, the study was not perfectly double-blind in that the subject was able to differentiate between saline and TRH injections. A drug which produces nausea after injection may be best to test against TRH. Certainly, this drug would not be a control, per se, and its effects on RT would have to be closely analyzed against the effects of TRH. A different test design may be needed. However, it is hoped that the subject motivation factors discussed previously would be more consistent for each session. It is also hoped that the initial finding from such an experiment would be baseline RT's that are closer together and not significantly different.

In all possible future studies mentioned above, it is also recommended that some means of measuring subject motivation be included. This would improve those studies by adding an important though hard-to-observe factor to the analysis of data.

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APPENDIX A: Consent Form

You are invited to participate in a study that will determine if a polypeptide called Thyrotropin Releasing Factor (TRF) will affect a person's tracking performance, reaction and processing time and visual evoked responses. TRH is released from a portion of the brain called the hypothlamus and stimulates the pituitary gland to secrete a protein called thyroid stimulating hormone (TSH). TSH stimulated the thyroid gland and causes the gland to release thyroid hormone. Previous studies have shown that TRH increases the performance of animals in various psychomotor tests such as solving mazes, etc.

In this study, a small needle will be placed in your vein and through it TRF will be injected and blood for laboratory tests withdrawn. Blood will be drawn immediately pre-injection, at 20 mins, 40 mins, 60 mins, 6 hrs, 30 hrs, and 54 hrs. Since this will be a double blind control study, neither you nor the monitoring physician will know whether you will receive a TRF or saline injection on a particular day.

Immediately before and then at various intervals (-20 min, 5 min, 25 min, 45 min, 65 min, 90 min, 120 min, 6 hr, 30 hr, and 54 hr) after receiving the injection, you will be asked to perform various tasks such as a tracking task, a reaction and processing time task, visual evoked response (VER) and "oddball paradigm". One series of psychomotor tests will last approximately 10-15 mins. With the tracking task, you must try to keep the hashmark's center over the center point of a circle on the screen. The reaction/processing time task is performed by pressing the appropriate direction with a switch on a reset time tester in response to a small light." Also we will measure a part of the brain wave due to stimulation of the visual system (VER). After cutting a small patch of hair at the electrode sites, the skin will be mildly abraded with an alcohol soaked gauze pad and electrodes will be applied so that your brain waves can be recorded. You will be asked to view a white screen on which light will be flickered at frequencies between 40 and 60 times per second. The brightness of the light will be about the same as a brightly lit room. Another parameter to be measured in the experiment is known as the "oddball paradigm". This is an indicator of cognitive function. Out of a series of one hundred tones, you will be asked to count the number of specific tones. The electrical signal the brain generated during this process will be provided by scalp electrodes. The scalp electrodes are placed on

TRF is routinely and safely given to patients to assess their pituitary gland's ability to secrete TSH. About half the patients who receive TRF develop the following transitory (lasting 1-2 min) symptoms: nausea without vomiting, flushing, sweating, palpitations and/or an urge (only an urge) to urinate or defecate. After 2 minutes, these symptoms disappear. No adverse medical affects are anticipated or have ever been reported.

There are no medical risks associated with the tracking task, reaction/processing time task, oddball paradigm or visual evoked response. There are, however, two considerations you should be aware of concerning the visual evoked response. A small percent of the general population are prone to seizures (approximately 9%). Two to four percent of this seizure population may have seizures as a result of exposure to low frequency flickering lights. Therefore, for your own safety if you have ever had a seizure, we ask that you not participate in this study. If you experience any subjective discomfort, or if for any other reason, you desire to withdraw from this experiment, you are free to terminate your participation without prejudice.

No alternative means exist to obtain the required information. Your decision to participate will not prejudice your future relations with the medical staff, Wright-Patterson Medical Center, or the Air Force Aerospace Medical Research Laboratory. If you decide to participate, you are free to withdraw your consent and to discontinue participation at any time without prejudice. If you have any questions, we expect you to ask us. If you have additional questions later, please call LtCol James Jacobsen (74288) or Capt Tom Jennings (55742).

(Signature)	(Date/Time)
(Signature of Witness)	(Signature of Investigator)

APPENDIX B: Performance Task Record and Data Collection Sheet

This appendix contains an example of a Performance Task Record used in the TRH study. Also included is an example of the data collection sheets used in the pilot study as well as the TRH study.

APPENDIX B: Performance Task Record (Example)

Subject__________________________ Date___________________________

Time				
- 20 minutes to Injection	A1	B1	A2	B2
5 minutes	B2	A1	A2	B1
25 minutes	A2	A1	B2	B1
45 minutes	B1	B2	A1	A2
65 minutes	B2	B1	A1	A2
90 minutes	A2	B1	B2	A1
120 minutes	A1	A2	B2	B1
6 hours	B1	A2	B2	A1
30 hours	B2	B1	A2	A1
54 hours	A1	B2	B1	A2

A1 = Right Hand, Simple

A2 = Right Hand, Choice

B1 = Left Hand, Simple

B2 = Left Hand, Choice

Box is always upright

Subject always resets

Simple/Choice Reaction Time Data Mode = ________

Subject:____________ Box Upright________? Upside Down________?

Date:____________ Simple________? Choice________?

Time:____________ Subject Sets Reset____? PI Sets Reset____?

Scores - Comments

Training	Data Runs	Comments, Other Trials
1.________	1.________	
2.________	2.________	
3.________	3.________	
4.________	4.________	
5.________	5.________	
Other Trials?	6.________	
________	7.________	
________	8.________	
________	9.________	
________	10.________	
________	11.________	
________	12.________	
________	13.________	
________	14.________	
________	15.________	

APPENDIX C: Tester Circuitry

The tester dimensions are 5 1/4" width x 6 3/4" length x 2 1/2" depth. Within it are microcircuits which randomize the stimulus presentation times and the light (B or C) that will illuminate during CRT tasks.

Stimulus presentation times are randomized by a circuit logic like that diagramed in figure 4. The reset switch, S3, initiates the signal. After a built in one second delay, the signal starts as internal clock which is a chip that generates a square wave pulse train of 50 pulses per second (50 Hz). The pulses go to an 8 bit binary counter which is in an arbitrary setting dependent on the duration of the previous trial and time between trials. The counter's output goes to a NAND circuit only when the 8 bits are in the positions 11111111. The maximum number of pulses required for the counter output is $2^8 = 256$. At the clock rate of 50 Hz, the maximum time is $256/50 = 5.12 + 1$ second time delay, or 6.12 seconds. Thus, depending on the initial counter setting, the time for a pulse to be sent to the light circuit is $1 \leq + \leq 6.12$ seconds.

Circuit logic to randomize which light (B or C) will illuminate during CRT tasks is illustrated in figure 5. The pulse from the light circuit in figure 4 initiates the top flip-flop circuit which affects both NAND circuits for B and C. The clock pulse changes the state of the bottom flip-flop 25 times a second. Since its initial state is unknown and the arrival of the pulse from the light circuit is random, the selection of light B or C is random. The reset switch, S2, and response switch, S3, in figure 1 are toggle-type switches which provide an inhibit property. That is, both switch positions cannot be activated simultaneously.

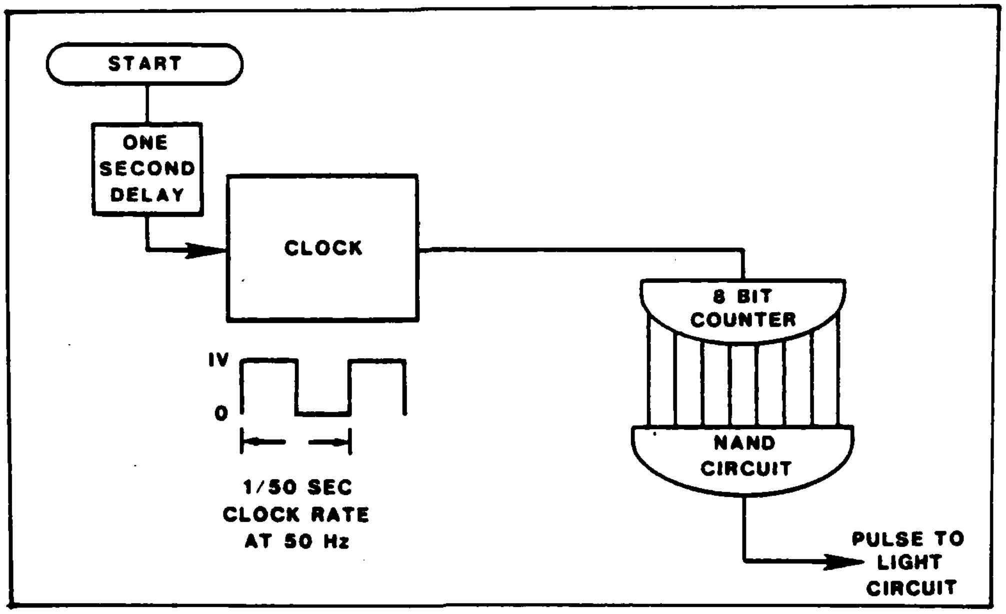

Figure 4. Tester Circuit Logic for Stimulus Randomization

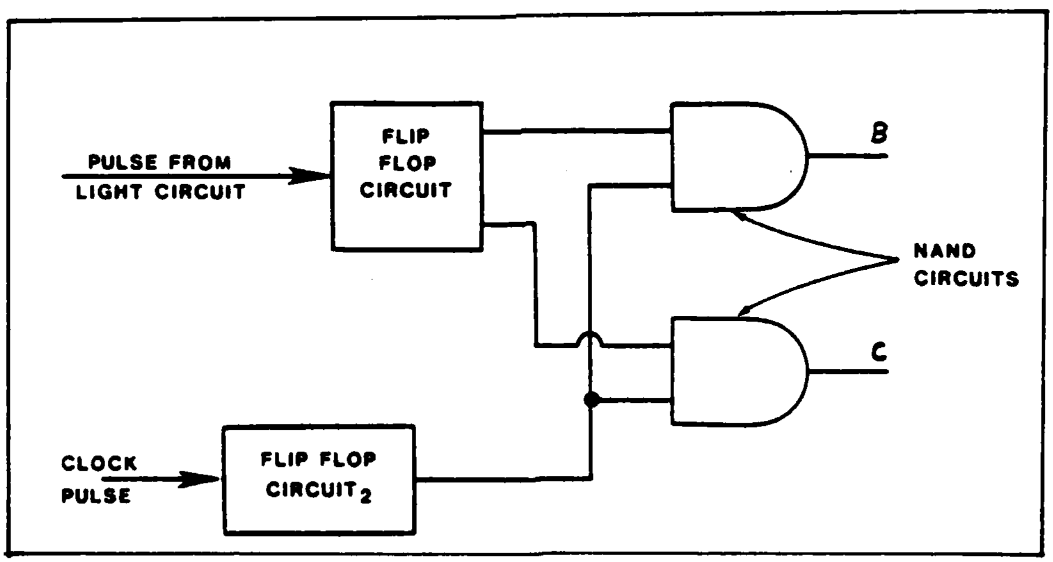

Figure 5. Tester Circuit Logic for Choice Reaction Time Tasks

In the electrical circuits the time delay between closing the switch and termination of the pulse is in microseconds. (Typical subject responses are around 0.2 second). The reaction time is measured by an Apple II computer which samples the pulse and switch changes. The computer has an internal clock of 1 MHz, and is an 8 bit machine. The construction of the clock board allows time measurements of 1 msec apart. The investigator reads the duration of the time pulse from the computer monitor to provide feedback to the subject.

APPENDIX D: Pilot Experiment Design and Modes

This appendix shows the Experiment Design for the Pilot Study and a tabular explanation of each mode. If a person was right-handed they were assigned a subject number from 1 to 8, and, if left-handed, they were assigned a subject number from 9 to 16. The subject would then follow the mode sequence across from their number in both the Right-handed Tracking and Left-handed Tracking columns. the modes were performed at random, with the flip of a coin. Heads indicated that the mode would be performed right-handed and tails indicated left-hand performance.

APPENDIX D: Pilot Experiment Design and Modes

Subject #'s — Right hand dominant subjects are #'s 1-8
Left hand dominant subjects are #'s 9-16

Right Hand Tracking	Left Hand Tracking	Modes Performed							
1	6	A	B	H	C	G	D	F	E
2	4	B	C	A	D	H	E	G	F
3	7	C	D	B	C	A	F	H	E
4	5	D	E	C	F	B	G	A	H
5	1	E	F	D	G	C	H	B	A
6	2	F	G	E	H	D	A	C	B
7	8	G	H	F	A	E	B	D	C
8	3	H	A	G	B	F	C	E	D
9	14	A	B	H	C	G	D	F	E
10	12	B	C	A	D	H	E	G	F
11	15	C	D	B	E	A	F	H	G
12	13	D	E	C	F	B	G	A	H
13	9	E	F	D	G	C	H	B	A
14	10	F	G	E	H	D	A	C	B
15	16	G	H	F	A	E	B	D	C
16	11	H	A	G	B	F	C	E	D

Mode	Box Upright	Box Upside Down	Simple	Choice	Subject Sets Reset	PI Sets Reset
A	X		X		X	
B	X		X			X
C		X	X		X	
D		X	X			X
E	X			X	X	
F	X			X		X
G		X		X	X	
H		X		X		X

APPENDIX E: Pilot Study Results

This appendix shows the results of the Pilot Study. A table showing the means and p-values of the areas of interest outline the results. Computer printouts of the ANOVA's performed verify the significance of modes to be used in later studies. For the ANOVA's the factors of interest are designated as follows:

- Tester orientation is designated "BOX"
- Reaction type (SRT or CRT) is designated "Reaction"
- Reset method (Subject or Investigator) is designated "Reset"
- Dominant-vs-Non Dominant hand is designated "Hand"

As can be seen the factors were eliminated as the analysis proceeded to determine the validity of the modes to be used in the TRH study.

APPENDIX E: Pilot Study Areas of Interest - Means and p-values (p = .05 level)

Area	μcrt	pcrt	μort	pcrt	μoverall	poverall
RESET						
Subject	205.04	.065	265.48	.038	235.26	.028
Investigator	209.14		270.65		239.89	
HAND						
Dominant	207.20	.950	265.95	.175	236.57	.368
Non-Dominant	206.97		270.18		238.58	
MOVEMENT						
Inward	207.33	.935	268.30	.614	237.82	.674
Outward	207.07		267.50		237.29	
REACTION TYPE	207.09		268.06			.0001

DEPENDENT VARIABLE: R_TIME

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PR > F
MODEL	25	5867213.46953125	234688.53878125	275.65	0.0001
ERROR	5094	4337062.82343750	851.40612945		STD DEV
CORRECTED TOTAL	5119	10204276.29296875			29.17886443

SOURCE	DF	TYPE III SS	F VALUE	PR > F
BOX	1	82.51953125	0.10	0.7556
REACTION	1	4758976.10000000	5589.55	0.0001
RESET	1	27500.30283125	32.30	0.0001
SUBJECT	15	1066336.25546875	83.50	0.0001
HAND	1	5141.31953125	6.04	0.0140
BOX*REACTION	1	427.81250000	0.50	0.4784
BOX*RESET	1	151.56328125	0.18	0.6741
BOX*HAND	1	1793.14453125	2.11	0.1468
REACTION*RESET	1	365.51250000	0.43	0.5124
REACTION*HAND	1	6381.37812500	7.50	0.0062
RESET*HAND	1	53.10203125	0.07	0.7922

DEPENDENT VARIABLE: R_TIME

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PR > F
MODEL	21	5864759.42968750	279274.25855655	328.09	0.0001
ERROR	5098	4339516.86328125	851.21947102		STD DEV
CORRECTED TOTAL	5119	10204276.29296875			29.17566573

SOURCE	DF	TYPE III SS	F VALUE	PR > F
REACTION	1	4758376.30000000	5590.78	0.0001
RESET	1	27500.30283125	32.31	0.0001
SUBJECT	15	1066336.25546875	83.51	0.0001
HAND	1	5143.01953125	6.04	0.0140
REACTION*RESET	1	365.51250000	0.43	0.5123
REACTION*HAND	1	6381.37812500	7.50	0.0062
RESET*HAND	1	53.08203125	0.07	0.7922

DEPENDENT VARIABLE: R_TIME

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PR > F
MODEL	21	5839137.92363750	278054.18712790	324.74	0.0001
ERROR	5098	4365138.36328125	856.24526545		STD DEV
CORRECTED TOTAL	5119	10204276.29296875			29.26166800

SOURCE	DF	TYPE III SS	F VALUE	PR > F
REACTION	1	4758876.00000000	5557.96	0.0001
BOX	1	82.51953125	0.10	0.7662
HAND	1	5140.01953125	6.00	0.0143
SUBJECT	15	1066336.25546875	83.02	0.0001
REACTION*BOX	1	427.01250000	0.50	0.4797
REACTION*HAND	1	6381.37812500	7.45	0.0064
BOX*HAND	1	1793.14453125	2.09	0.1478

DEPENDENT VARIABLE: R_TIME

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PR > F
MODEL	18	5836834.45312500	324268.58072917	378.73	0.0001
ERROR	5101	4367441.83984375	856.19326464		STD DEV
CORRECTED TOTAL	5119	10204276.29296875			29.26178838

SOURCE	DF	TYPE III SS	F VALUE	PR > F
REACTION	1	4758876.00000000	5556.30	0.0001
HAND	1	5140.01953125	6.00	0.0143
SUBJECT	15	1066335.25586875	83.13	0.0001
REACTION*HAND	1	6381.37812500	7.45	0.0064

APPENDIX F: Subject Advertisement and Briefing

This appendix shows (1) the advertisement placed in the Wright-Patterson AFB bulletins to attract subjects for the TRH study, and (2) the briefing outline for briefings given to prospective subjects.

APPENDIX F: Subject Advertisement and Briefing

Space Shuttle Experiment

Active duty AF members between the ages of 23 and 35 are need to participate in an experiment destined for STS-11. Chosen subjects will provide important baseline data for a reaction time test for AFAMRL (WPAFB) is developing for NASA astronauts. For further information contact Dr. Dan Repperger, AFAMRL, ext. 55742 or Capt Norm Michel, AFIT/EN, ext 55533 (Box 4465). Subjects will be paid for their participation.

TRF Briefing

1. 2 x 3 days --- Off arm study (no centrifuge)
2. Day 1 training (20 minutes of your time)
3. Last two days you are here 2½ hr + 20 min, 1st day
   2nd day 20 min - 3rd day 20 min
4. You get an injection by a medical doctor either saline solution salt water) or TRH
5. TRF has a ½ life of 5 minutes. TRF is a stimulent, routinely given to thyroid patients. It has no long term side effects. It has been known to improve concentration, comprehension, self-confidence and energy level. Possible short term effects: 40 - 50% of subjects - Transient symptoms of nausea without vomiting, flushing, sweating, palpatatims and an urge to go to the bathroom (1-2 minutes, this is gone) Must abstain from food that morning (10 hr fast) and refrain from ingesting caffeine products on the day of the test.
6. This is a double blind study, neither the physician or you will know which injection is given.
7. Recently 50 subjects at WPAFB Hospital underwent TRH test without difficulties.
8. TRF is more innocuas than valium or cold remedies.
9. Blood draws at 20 min, 40 min, 60 min, 6 hr, 30 hr, 54 hr.
10. This study will not involve flickering lights. The consent form talks about seizures with respect to this stimulus.

APPENDIX G: TRH Study Results

The following appendix contains tables showing the results from the analysis of the TRH-study data. Separate tables are provided for difference-from-Baseline data for simple reaction, choice reaction, and processing times. Also included is a table showing the succesive-time period analysis. The plots of mean times for SRT, CRT and PT follow the tabulated results and computer print-outs of data for differences-from-baseline complete the appendix. It should be noted that computer print-outs designate PT as "Decision Time."

Table G-1: Simple Reaction Time Results

TIme = 1
Baseline -20 minutes

	Mean	Standard Deviation
Saline	209.95	9.50
TRH	197.29	11.66

H_o: Change from baseline for saline = change from baseline for TRF

	Saline			TRF				
Time Period	Mean	Standard Deviation	Change from baseline from Significance	Mean	Standard Deviation	Change from baseline and Significance	Difference in change from baseline (TRF-Saline)	Test statistic and p-value
2	210.66	15.69	.71 $p \geq .05$	204.81	13.87	7.52 $p \leq .05$	6.81	t=1.26 p=.240
3	205.34	12.68	-4.61 $p \leq .05$	200.82	13.99	3.53 $p \geq .05$	8.14	t=2.50 p=.034
4	297.43	13.42	-2.52 $p \geq .05$	195.58	10.98	-1.71 $p \geq .05$	.81	t=.24 p=.815
5	208.11	8.67	-1.84 $p \geq .05$	198.00	15.86	.71 $p \geq .05$	2.55	t=.66 p=.526
6	204.77	8.12	-5.18 $p \geq .05$	197.73	14.62	.64 $p \geq .05$	5.82	t=1.56 p=.153
7	201.91	10.19	-8.04 $p \leq .05$	201.15	15.31	3.86 $p \geq .05$	11.90	t=2.83 p=.020

Note: All t-tests were verified by the Wilcoxan Signed Rank Test

Table G-2: Choice Reaction Time Results

Time = 1
Baseline -20 minutes

	Mean	Standard Deviation
Saline	270.71	27.03
TRF	258.60	16.51

H_o: Change from baseline for saline = change from baseline for TRF

	Saline			TRF				
Time Period	Mean	Standard Deviation	Change from baseline and Significance	Mean	Standard Deviation	Change from baseline and Significance	Difference in change from baseline (TRF-Saline)	Test statistic and p-value
2	269.44	18.40	-1.37 $p \geq .05$	258.67	18.02	.07 $p \geq .05$	1.44	t=.22 p=.829
3	265.85	22.58	-7.96 $p \leq .05$	254.37	18.94	-4.23 $p \geq .05$	3.73	t=.62 p=.550
4	264.27	18.92	-6.54 $p \geq .05$	254.99	17.77	-3.61 $p \geq .05$	2.93	t=.50 p=.550
5	264.55	20.72	-6.26 $p \geq .05$	250.67	12.99	-7.93 $p \geq .05$	-1.67	t=-.25 p=.808
6	261.29	20.15	-9.52 $p \geq .05$	250.18	16.92	-.832 $p \leq .05$	1.2	t=.18 p=.858
7	261.21	20.87	-9.60 $p \leq .05$	248.36	11.72	-10.24 $p \leq .05$	-.64	t=1.83 p=.927

Note: All t-tests were verified by the Wilcoxan Signed Rank Test

Table G-3: Processing Time Results

Time = 1
Baseline -20 minutes

	Mean	Standard Deviation
Saline	60.86	29.27
TRF	61.31	18.53

H_o: Change from baseline for saline = change from baseline for TRF

	Saline			TRF				
Time Period	Mean	Standard Deviation	Change from baseline and Significance	Mean	Standard Deviation	Change from baseline and Significance	Difference in change from baseline (TRF-Saline)	Test statistic and p-value
2	58.78	26.12	-2.08 $p \geq .05$	53.86	20.75	-7.45 $p \geq .05$	-5.37	t=-.68 p=.515
3	57.50	28.79	-3.36 $p \geq .05$	53.55	23.85	-7.76 $p \geq .05$	-4.40	t=-.74 p=.478
4	56.84	26.59	-4.02 $p \geq .05$	59.41	19.24	-1.90 $p \geq .05$	2.12	t=.34 p=.738
5	56.45	22.06	-4.41 $p \geq .05$	52.67	18.84	-8.64 $p \leq .05$	-4.23	t=.58 p=.573
6	56.52	21.61	-4.34 $p \geq .05$	52.35	19.41	-8.96 $p \leq .05$	-4.62	t=-66 p=.525
7	59.29	24.57	-1.57 $p \geq .05$	47.21	16.43	-14.10 $p \leq .05$	-12.53	t=-1.89 p=.091

Note: All t-tests were verified by the Wilcoxan Signed Rank Test

Table G-4: Differences in Successive Times

Differences between successive times were taken. The chart below contains the mean differences and p-values for Ho: Difference = 0.

	Simple		Choice		Processing	
Difference	Saline	TRF	Saline	TRF	Saline	TRF
2-1	.71 p=.856	7.52 p=.027	-1.37 p=.776	.07 p=.983	-2.08 p=.701	-7.45 p=.174
3-2	-5.31 p=.023	-3.98 p=.104	-6.59 p=.023	-4.29 p=.115	-1.28 p=.655	-.31 p=.925
4-3	2.08 p=.146	-5.24 p=.127	1.42 p=.580	.62 p=.800	-.66 p=.795	5.86 p=.152
5-4	.68 p=.831	2.42 p=.381	.28 p=.859	-4.32 .368	-.40 p=.890	-6.74 p=.185
6-5	-3.33 p=.035	-.07 p=.974	-3.26 p=.180	-.39 p=.907	.07 p=.973	-.32 p=.931
7-6	-2.86 p=.322	3.22 p=.02	-.08 p=.970	-1.92 p=.645	2.78 p=.206	-5.14 p=.320

Note: All t-tests were verified by the Wilcoxan Signed Rank Test

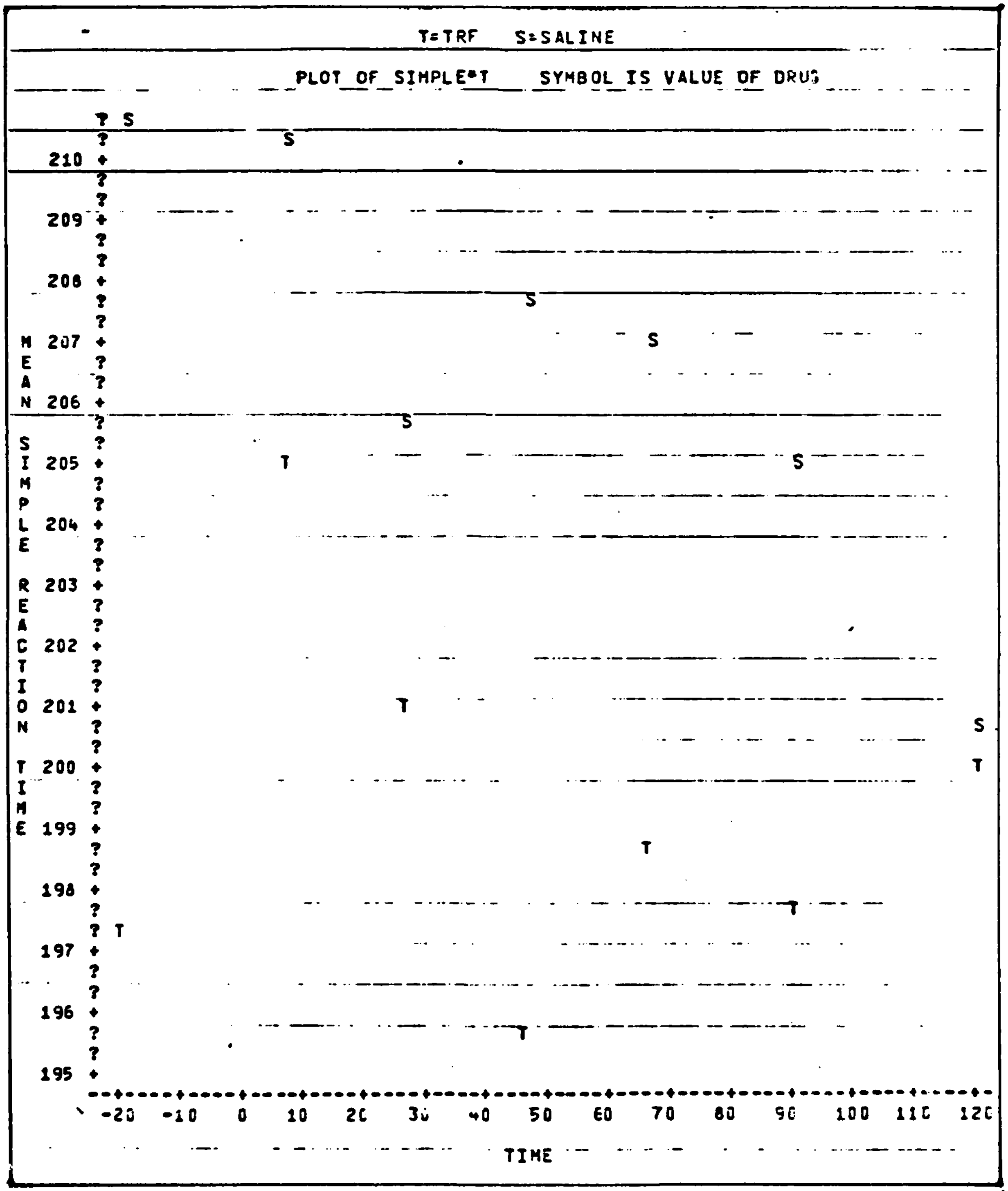

Figure 6. Plot of Simple Reaction Time Means

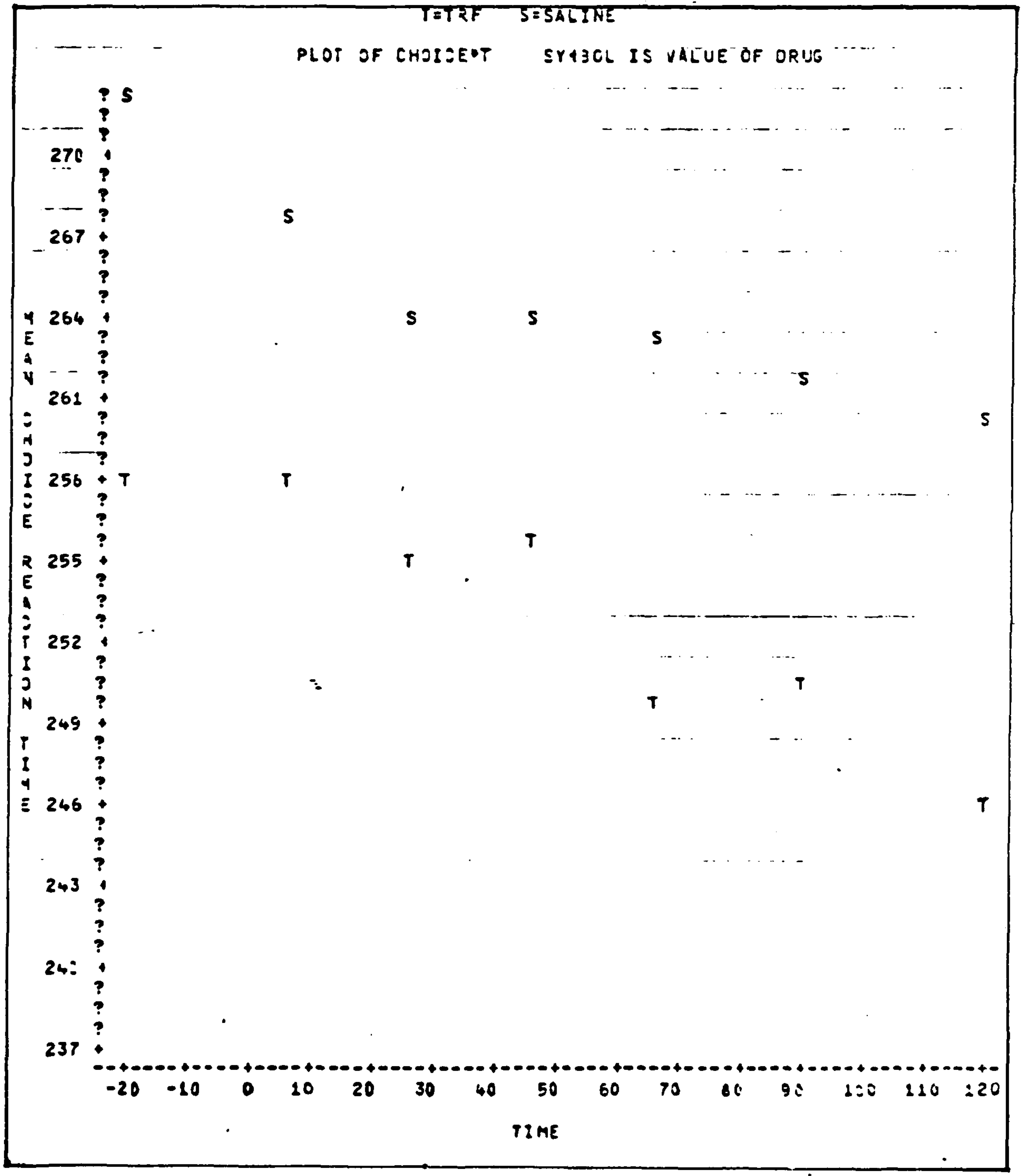

Figure 7. Plot of Choice Reaction Time Means

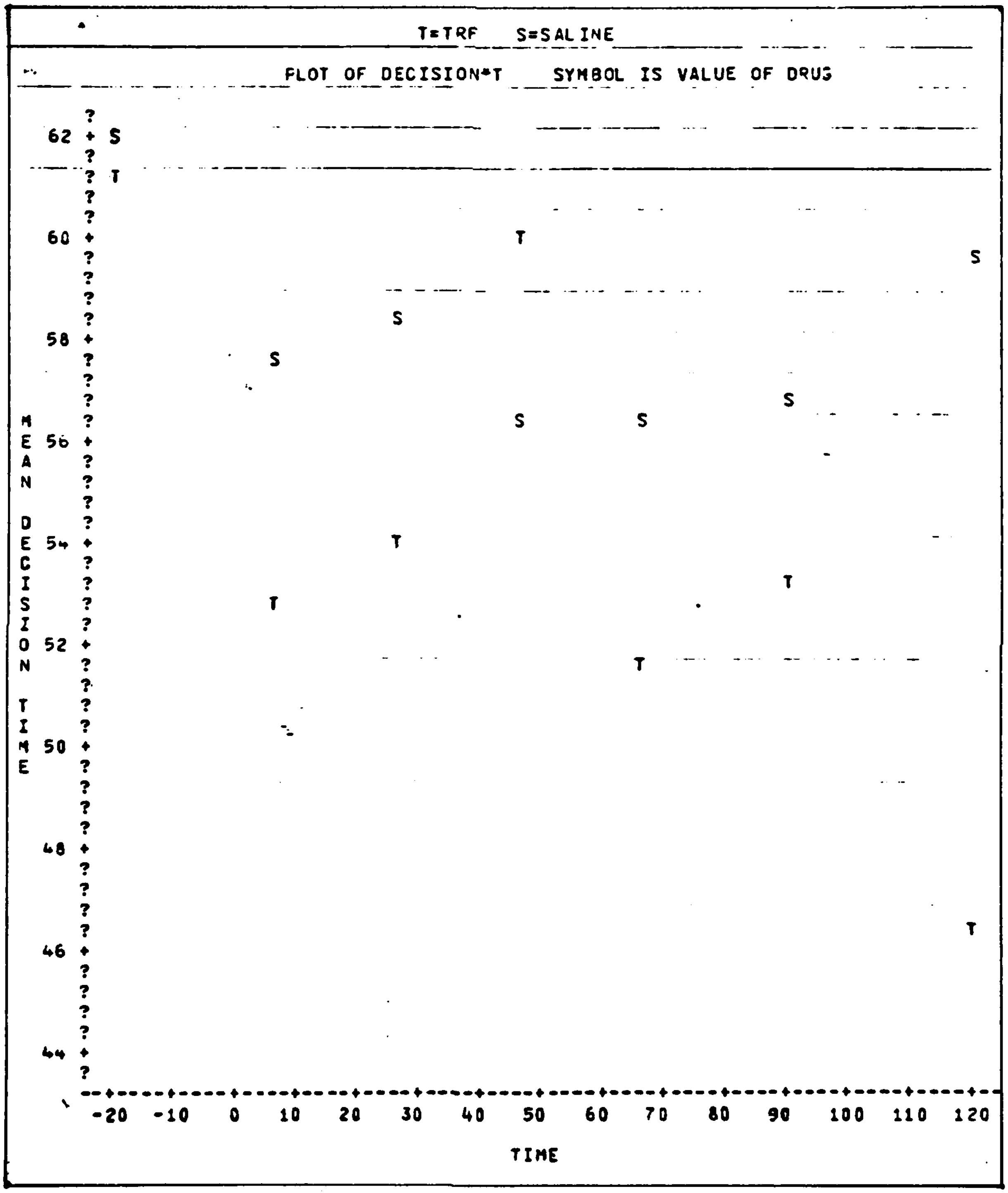

Figure 8. Plot of Processing Time Means

MEAN REACTION TIMES AND THE STANDARD DEVIATIONS
OF SUBJECTS AROUND THOSE MEANS

-- REACTION=CHOICE --

OBS	TIME	OVERALL MEAN FOR SALINE	STANDARD DEVIATION FOR SALINE	OVERALL MEAN FOR TRH	STANDARD DEVIATION FOR TRH
1	1	270.910	27.0265	250.500	16.5127
2	2	269.443	18.3965	258.670	16.0236
3	3	262.347	22.5777	254.377	18.5309
4	4	264.278	14.9152	254.393	17.7637
5	5	264.533	20.7232	250.676	12.9928
6	6	261.230	20.1517	252.203	16.9153
7	7	261.237	20.8674	246.363	11.7217
8	8	252.823	16.2118	242.577	14.3837
9	9	247.819	21.4265	236.353	15.4014
10	10	245.157	20.8553	235.284	17.0215

-- REACTION=SIMPLE --

OBS	TIME	OVERALL MEAN FOR SALINE	STANDARD DEVIATION FOR SALINE	OVERALL MEAN FOR TRH	STANDARD DEVIATION FOR TRH
11	1	203.967	9.5911	197.290	11.6650
12	2	210.657	15.6923	204.007	13.0675
13	3	205.343	12.6892	201.923	13.9857
14	4	237.427	13.4244	195.563	10.9779
15	5	203.107	8.6720	198.900	15.8585
16	6	204.773	8.1200	197.433	14.6233
17	7	231.313	10.1963	201.153	15.3690
18	8	197.237	9.6944	195.427	14.2316
19	9	193.333	13.9907	187.000	12.1962
20	10	193.337	11.9960	190.133	12.1945

MEAN DECISION TIMES AND THE STANDARD DEVIATIONS
OF SUBJECTS AROUND THOSE MEANS

OBS	TIME	OVERALL MEAN FOR SALINE	STANDARD DEVIATION FOR SALINE	OVERALL MEAN FOR TRF	STANDARD DEVIATION FOR TRF
1	1	60.8633	23.2723	61.3100	18.5237
2	2	59.7433	26.1169	53.8633	20.7445
3	3	57.5033	29.7871	53.5533	23.8493
4	4	56.8433	26.5800	59.4100	19.2419
5	5	56.4467	22.0609	52.6700	19.8439
6	6	56.5167	21.6123	52.3467	19.4119
7	7	59.2333	24.5747	47.2100	16.4396
8	8	54.7267	15.3732	52.1500	17.3152
9	9	57.4259	14.9766	49.3533	17.9095
10	10	51.9100	20.6306	45.0704	19.9841

T TESTS FOR DIFFERENCE FROM BASELINE
BETWEEN TRH AND SALINE FOR REACTION TIME

NOTE: A NEGATIVE MEAN IMPLIES A GREATER DROP FOR TRH

REACTION=CHOICE

OBS	TIME	MEAN	STANDARD ERROR OF MEAN	T	PR>|T|
1	2	1.4400	6.46520	0.22273	[illegible]
2	3	3.7400	6.01920	0.62145	0.549719
3	4	2.9333	5.88819	0.49917	0.636303
4	5	-1.6733	6.67862	-0.25[illegible]55	0.807769
5	6	1.2000	6.52626	0.18347	[illegible]
6	7	-0.6333	6.74970	-0.[illegible]9363	0.927299

REACTION=SIMPLE

OBS	TIME	MEAN	STANDARD ERROR OF MEAN	T	PR>|T|
7	2	6.8067	5.40439	1.25954	0.234518
8	3	8.1367	3.25974	2.49611	[illegible]
9	4	0.8133	3.38312	0.24036	0.815437
10	5	2.5500	3.86148	0.66037	0.525557
11	6	5.8167	3.72554	1.56129	0.152898
12	7	11.8967	4.28553	2.82082	0.[illegible]13761

T TESTS FOR DIFFERENCES IN CHANGE FROM BASELINE
BETWEEN TRF AND SALINE FOR DECISION TIME

NOTE: A NEGATIVE MEAN IMPLIES A GREATER CHANGE FOR TRF

OBS	TIME	MEAN	STANDARD ERROR OF MEAN	T	PR>|T|
1	2	-5.367	7.92439	-0.6772	0.515206
2	3	-4.397	5.94063	-0.7401	0.478109
3	4	2.120	6.15186	0.3446	0.738302
4	5	-4.223	7.22654	-0.5844	0.573293
5	6	-4.617	6.98431	-0.6610	0.525166
6	7	-12.530	6.62593	-1.8911	0.091179

MEAN DIFFERENCES FROM SUCCESSIVE TIMES

EXAMPLE: D21=MEAN(TIME2) - MEAN(TIME 1)

T TESTS FOR HO: DIFFERENCES=0

VARIABLE	MEAN	STD ERROR OF MEAN	T	PR>|T|
DRUG=SALINE REACTION=CHOICE				
D21	-1.37000000	4.67183167	-0.29	0.7760
D32	-6.59333333	2.38286394	-2.77	0.0219
D43	1.42333333	2.47988475	0.57	0.5801
D54	0.28333333	1.54701026	0.18	0.8587
D65	-3.26333333	2.24719551	-1.45	0.1804
D76	-0.08333333	2.13369355	-0.04	0.9697
DRUG=SALINE REACTION=SIMPLE				
D21	0.71000000	3.73196372	0.19	0.8556
D32	-5.31333333	2.98493419	-1.78	0.1088
D43	2.09333333	1.30760148	1.59	0.1456
D54	0.68000000	3.10114356	0.22	0.8313
D65	-3.33333333	1.34240710	-2.48	0.0348
D76	-2.86000000	2.72618140	-1.05	0.3215
DRUG=TRF REACTION=CHOICE				
D21	0.07000000	3.23969939	0.02	0.9832
D32	-4.29333333	2.46210590	-1.74	0.1152
D43	0.61666667	2.35207421	0.26	0.7991
D54	-4.32333333	4.55971310	-0.95	0.3678
D65	-0.39000000	3.24326101	-0.12	0.9069
D76	-1.91666667	4.01553542	-0.48	0.6445
DRUG=TRF REACTION=SIMPLE				
D21	7.51666667	2.83944382	2.65	0.0266
D32	-3.98333333	2.20006313	-1.81	0.1036
D43	-5.24000000	3.11242353	-1.69	0.1266
D54	2.41666667	2.62489624	0.92	0.3812
D65	-0.05666667	1.97406643	-0.03	0.9738
D76	3.22000000	2.45538552	1.31	0.2222

Vita

Norman Ernest Michel was born in Seattle, Washington on February 25, 1952. He graduated from Monroe High School in Monroe, Washington in 1970 and attended the United States Air Force Academy. He received the degree of Bachelor of Science in Life Sciences and a regular commission in the United States Air Force from that institution in 1974. After completing undergraduate pilot training at Webb AFB, Texas in 1975 he flew C-141 transports at McGuire AFB, New Jersey. He was a Flight Examiner Pilot at that base until being accepted to the School of Engineering, Air Force Institute of Technology, in June 1982.

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Block 17: COSATI Codes:

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06	04

Block 19: Abstract: The acute effects of thyrotropin releasing hormone (TRH) on human simple reaction time (SRT), choice reaction time (CRT), and information processing time (PT) were investigated using an electronic reaction time tester. The tester presented visual stimuli, and, to determine its statistically significant ($p \leq .05$) modes of operation, a pilot study was conducted with sixteen subjects (S_s). Left and right-handed performance of SRT and CRT tasks were determined to be beneficial for the primary study.

Ten, right-handed male Ss participated in the double-blind TRH study. Ss acted as their own controls, so two sessions were required for each S, one involving an injection (I) of TRH (500 micrograms) and another a saline injection (1 normal). For acute time frame analysis, seven test periods, from I-20 minutes to I+120 minutes, were included in each session. With TRH, SRT increased significantly ($p \leq .05$) at I+5 minutes, probably due to the neurological effects of TRH. CRT decreased significantly in TRH and saline sessions at I+90 and +120 minutes, and PT decreased significantly at I+60, +90, and +120 minutes in TRH sessions. However, analysis revealed that no TRH-session times were significantly better than saline-session times.

END

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