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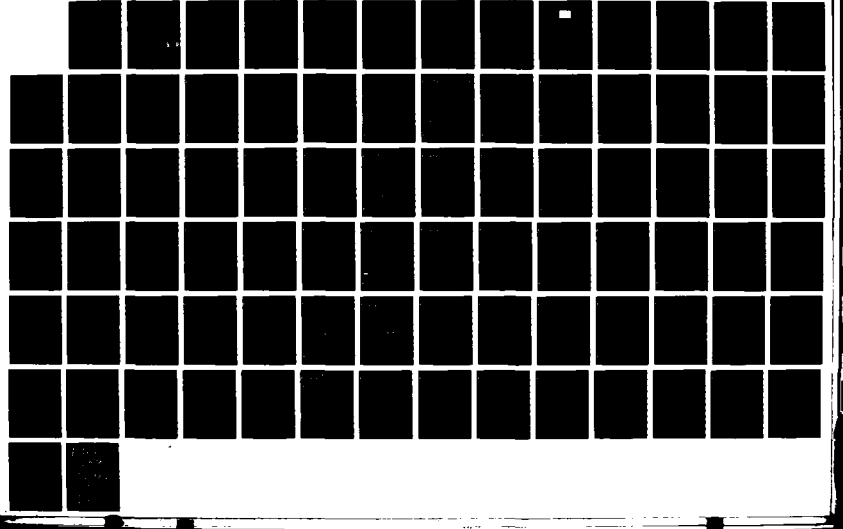

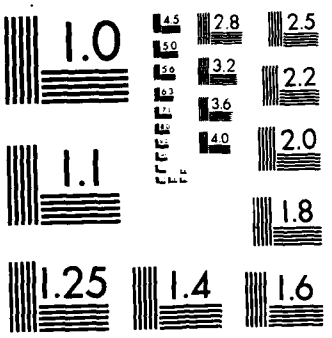

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ASSESSMENT OF NEUROLOGICAL EFFECTS OF DRUGS ON OCULOMOTOR AND VISUAL FUNCTION IN THE PRIMATE

Annual and Final Report

E. Gregory Keating, Ph.D.

October 10, 1984

Supported by

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Monkeys were given cholinergic drugs in doses considered to provide protection against organophosphate poisoning. Their eye movements were recorded while they carried out visual search and target tracking tasks. In general these agents had subtle effects. At the worst, monkeys remained capable of carrying out moderately good search and tracking performance. Pyridostigmine (7 mg/K) was the most benign, having no observable effect.

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Pralidoxime impaired behavior only at the highest dose (16 mg/K). Similarly, atropine and physostigmine degraded performance clearly and consistently only at the highest dose tested (.25 mg/K and .075 mg/K respectively). Degraded search and tracking was generally attributable to impaired oculomotor competence, rather than to altered visual, cognitive, or motivational status.

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Summary

Monkeys were given cholinergic drugs in doses considered to provide protection against organophosphate poisoning. Their eye movements were recorded while they carried out visual search and target tracking tasks. In general these agents had subtle effects. At the worst, monkeys remained capable of carrying out moderately good search and tracking performance. Pyridostigmine (7 mg/K) was the most benign, having no observable effect. Pralidoxime impaired behavior only at the highest dose(16mg/K). Similarly, atropine and physostigmine degraded performance clearly and consistently only at the highest dose tested (.25 mg/K and .075 mg/K respectively). Degraded search and tracking was generally attributable to impaired oculomotor competence, rather than to altered visual, cognitive, or motivational status.

Foreward

The experiments reported here were conducted according to The Guide for Care and Use of Laboratory Animals (1978) as prepared by the Committee on Care and Use of Laboratory Animals, National Research Council, DHEW Publication No. (NIH) 78-23, Revised 1978.

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INTRODUCTION

The experiments reported here were designed to test the neurotoxicity of various cholinergic compounds. Cholinergic agents represent the principal source of neurotoxicity in an industrial and military setting. The most potent of these agents are the group of irreversible cholinesterase inhibitors known as organophosphate poisons. By blocking acetylcholinesterase (ACHase) they produce an abnormal build-up of neurotransmitter which deranges normal transmission of signals at cholinergic synaptic junctions.

Cholinergic junctions ramify widely in the nervous system. Acetylcholine (ACH) is the principal neurotransmitter of the neuromuscular junction, and it is the putative neurotransmitter at several points in the central nervous system as well (4,6). The behavioral effects of altering cholinergic transmission are global. At high doses respiratory failure leads to death. At lesser doses sensory, motor, and cognitive systems can be affected. These include generalized muscle weakness, ataxia, loss of concentration and memory, fatigue, irritability, and visual hallucinations. Learning and performance of complex sequential operations are impaired (8).

The therapeutic reply to organophospate poisoning is to reinstate normal cholinergic transmission by a variety of strategies that protect or restore the normal balance between ACH and its inhibitor acetylcholinesterase. Atropine and related compounds can counter the build-up of ACH by blocking it directly. Physostigmine can block ACHase temporarily protecting it from more irreversible binding with the organophosphate compounds. Oximes like pralidoxime reactivate the inhibited ACHase.

Since these therapies themselves affect cholinergic transmission they are not without their own risks (5,9,10). For most, dosages which provide some cure or prophylaxis against organophospate compounds have been established. Mortality or severe neurological derangement is known to be of little risk at these levels. However, the more subtle effects of these therapies on behavior are not well known.

The studies reported here assessed the visual search and tracking ability of monkeys receiving therapeutic doses of several cholinergic compounds. The tasks were designed to be analogous to operations frequently carried out by military personnel in the field.

METHODS OF RESEARCH

Six adolescent cynomolgous monkeys (M. fascicularis) served as subjects. They were housed and cared for by the Animal Care Facility at Upstate Medical Center. On testing days the monkeys were water-deprived and kept at 90% of their normal weight (4-5.5 K), and on these days all of their liquid intake was achieved as reward in the testing apparatus.

Recording of Eye Movements. Eye movements were recorded with the magnetic search coil technique (3). The monkey sat in a primate restraining chair positioned so that its eyes were centered in a double magnetic field. The field was produced by voltages in four large coils of wire surrounding the monkey (Figure 1). A small coil of wire was surgically implanted around the

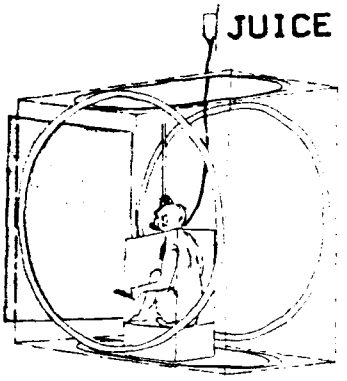


figure 1

optic globe of one eye of the animal and leads from the coil were brought up from the orbit under the scalp to an electrical connector atop the monkey's head. Rotations of the eye coil in the magnetic field induced a voltage that is a linear function of the rotation of the eye. A phase detector separated the voltages induced by horizontal and vertical eye movements. Since eye and head movements in the magnetic field are indistinguishable the head was held rigid by a holder attached with bolts and dental acrylic to the monkey's skull.

For analyzing the eye movements made during the Visual Search test the horizontal and vertical eye position signals were sampled every millisecond by a microprocessor. The computer first separated the saccadic movements of the eyes from the fixations by a duration and velocity criterion. A movement exceeding 10 deg/sec was judged to be a saccadic shift of gaze. Any slower epoch that lasted for at least 100 msec was named a fixation. Pursuit movements made during the Target Tracking task were sampled every three msec.

Behavioral Tests. For both tasks the monkey faced a 4' square projection screen. A borderless rectangular area in the center of the screen subtending 22° x 36° of visual angle was used as the viewing area. An optical bench projected stimuli onto the screen from behind. The monkey learned to first fixate a red spot centered on the viewing area. If the computer judged the spot to be accurately fixated by the monkey it enabled the target presentation to begin. A presentation consisted of presenting a small white spot of light at some position on the screen for a few seconds. The monkey was trained to fixate this target as quickly and accurately as possible. If it did fixate the target within some margin of accuracy (described below for each test) then it received a squirt of orange drink. The spot of light could be embedded in an array of visual distractors and serve as a target to be found in the Visual Search test. The spot of light could also move during the presentation and thus serve as a target to be pursued in the Target Tracking test.

Visual Search Test. Figure 2 shows the stimuli employed in the Visual Search test. When the monkey initiated a presentation, shutters in front of two projectors opened simultaneously. One presented the target which could appear at any one of the locations marked by crosses in the figure. The second projector presented the distractor elements projected from 35 mm slides. The

presentation lasted until the monkey found (fixated) the target and was rewarded or until 6 seconds had elapsed.

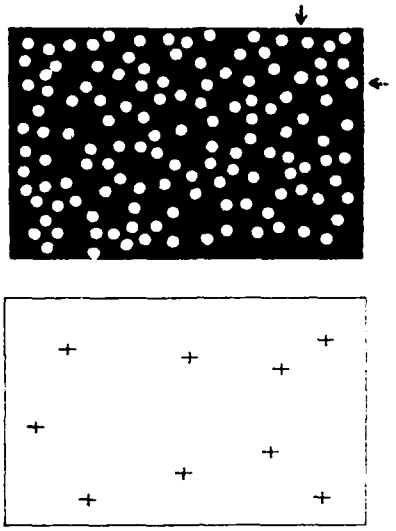
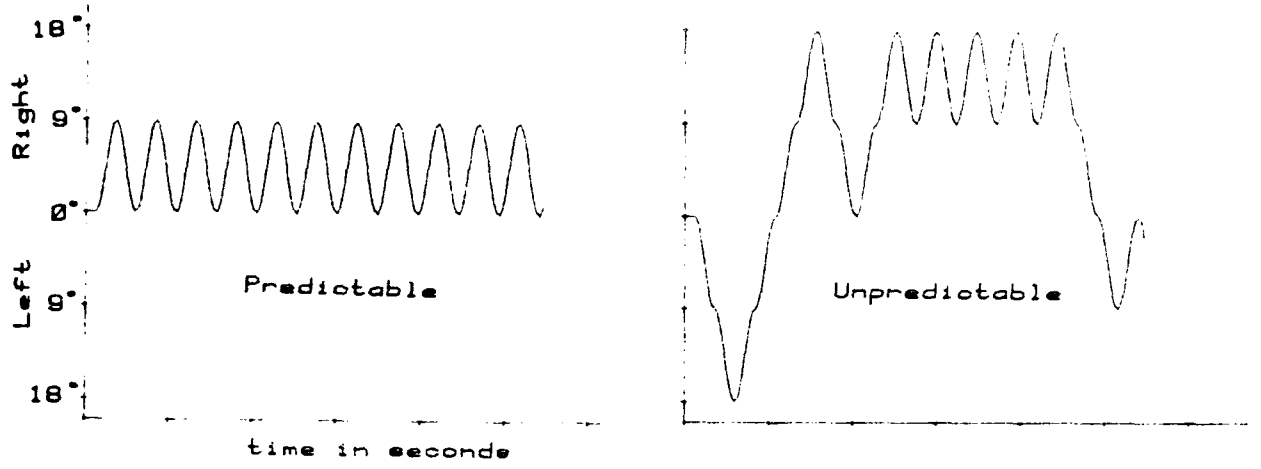


figure 2

The computer judged a target to have been acquired and the monkey was rewarded if a fixation fell within a 3° radius of the target. In plotting the position of the fixation relative to the target the entire system had a typical inaccuracy ± 0.5° with a worst case inaccuracy of 2.0°.

For the Visual Search test the target could appear under one of three conditions of varying difficulty. The NO NOISE condition was easiest; the target appeared alone on an otherwise blank screen. In the LOW NOISE and HIGH NOISE condition the target was embedded in textures of background distractors that made it harder to find. Figure 2 illustrates the stimuli as they appeared in the High Noise condition. Arrows point to the target, a spot slightly larger than the distractors. At bottom, crosses indicate the potential positions of the target. A daily testing run included 40-50 calibration trials and two sessions (Early and Late) of Visual Search testing. Each session contained one block each of the NO, LOW, and HIGH NOISE condition. A block contained 36 presentations of the target.

Target Tracking test. For this task the same white spot of light was used as a target, but it appeared during the presentation at the center of an otherwise empty screen. After 150 msec had elapsed the spot began to move along the horizontal meridian of the screen, either toward the left or toward the right. The target followed a PREDICTABLE sinusoidal trajectory or the UNPREDICTABLE trajectory shown to the right of figure 3. The target remained in motion during the 8 sec. of the presentation and the monkey was required to maintain fixation. The computer offered a reward every time the monkey's angle of gaze remained within 3° of the target for some duration (1,2, or 3 sec., variably). The speed of the target varied sinusoidally and only along the horizontal plane. Only horizontal eye position was monitored.



Drug Protocol

Each week the monkey underwent four days of such testing. Sessions on Monday, Tuesday and Wednesday were used to establish the baseline of the monkey's normal performance. Baseline performance was the average of these sessions collected over the 10-12 week period of drug trials with a particular agent. On Friday of each week the monkey was tested under the influence of a dose of the drug of interest.

When the monkey completed the sequence with one drug, it was started on a new schedule with a different agent. Drugs were administered by intramuscular injection into the lateral thigh.

On atropine trials testing began 45 minutes (t.45) after injection. Half of the data was collected from t.45-70, called the EARLY session. and was followed by a 15 minute pause. The second, LATE session, was run during the period from t.75-90. Trials for the other drugs were run in a similar pattern except that the EARLY session was run at t.15-30 and the LATE session at t.45-60.

Monkeys were tested on the doses and administration schedule of Atropine, Physostigmine, Pralidoxime, Pyridostigmine, and Atropine/Pralidoxime shown in tables 1 and 2. Performance on the Visual Search task under the schedule of drug trials shown in table 1 was completed first, then the drug trials in table 2 were conducted with the same subjects performing the Target Tracking task.

Each monkey was tested with the entire dose sequence of a single drug before beginning testing on another agent. Each dose of an agent was tested twice. The sequence of doses was randomly assigned to each subject. Also the sequence of drugs was varied with each monkey, but in this case the assignment was modified by practical decisions and cannot be considered random or counterbalanced.

Table 1. Drug Trials with Visual Search Test

Atropine (A = .014; B = .045; C = .14; D = Saline; E = .25 mg/K)

Subject 1	D C A E D E C B B A
Subject 2	C C B A E B E A D D
Subject 3	E A C D A C B E B B
Subject 6	D D C A E A B E B C

Pralidoxime (A = 1; B = 2; C = 4; D = Saline; E = 8; F = 16 mg/K)

Subject 1	B D C C C B D D A E E A* A
Subject 2	D C C E E B D A B* A B
Subject 3	A* A D B D B C E C E F F
Subject 4	C* A D B C A E B E D F F

Physostigmine (A = .025; B = .050; C = .075 mg/K)

Subject 1	D A B B A D C C
Subject 2	B D B C D A C A
Subject 3	D C B A A D C B* B
Subject 5	D D C C* A A B B

Atropine-Pralidoxime (combination of doses shown above for individual drugs)

Subject 1	A D E A B C E B C D
Subject 2	D B E C B D A E A C
Subject 3	D D C A E A* B E B C

Pyridostigmine (7 mg/K twice daily for 14 days)

Subject 1	Completed trial
Subject 2	Completed trial
Subject 3	Completed trial

Table 2. Drug trials with Target Tracking test.

Atropine (A = .014; B = .045; C = .14; D = Saline; E = .25 mg/K)

Subject 1	C E A E A B B C D D
Subject 2	E C B A A B C D D E
Subject 3**	A B D C B A D C E E*
Subject 6	D E C B C A D A E D

Pralidoxime (B = 2; C = 4; D = Saline; E = 8; F = 16 mg/K)

Subject 1	C D F C F E E B B D
Subject 2	C B C D D E B F F E
Subject 3	C D B C F F B E D E
Subject 6	B E B D F C E D F C

Physostigmine (A = 0.025; B = .050; C = 0.075 mg/K)

Subject 1	B A C D A C D B
Subject 2	A C C D B A D B
Subject 3	B D C A C
Subject 6	A B C A D B C D

Pyridostigmine (7 mg/K twice daily for 14 days)

Subject 1	Completed trial
Subject 2	Completed trial
Subject 3	Completed trial
Subject 6	Completed trial

*Technical imperfections invalidate data.

**By permission of the USAMRDC this Final Report also serves as a progress report for the contract period of 9/1/84 - 2/29/84). The drug trials underlined in Table 2 represent the drug trials tested and/or analyzed during that period.

Table 3. Sequence of drugs tested on each subject.

Visual Search Test

Subject 1	Phy	Pra	Atr	Pyr	Atr/Pra
Subject 2	Phy	Pra	Atr	Pyr	Atr/Pra
Subject 3	Pra	Phy	Atr	Pyr	Atr/Pra
Subject 4	Pra				
Subject 5	Phy				
Subject 6	Atr				

Target Tracking

Subject 1	Atr	Phy	Pra	Pyr
Subject 2	Atr	Phy	Pra	Pyr
Subject 3	Atr	Pyr	Pra	Phy
Subject 6	Atr	Phy	Pra	

Abbreviations: Atr - atropine; Phy - physostigmine; Pra - pralidoxime; Pyr - pyridostigmine.

ANALYTICAL MEASURES

Neurological Symptoms: At the start and end of the EARLY and LATE sessions we observed the monkeys for obvious neurological effects. The testing apparatus constrained the monkey's movement but pupillary diameter, vomiting, tremor, ptosis, and jaw weakness could be observed. Limb weakness evident when the monkey transferred to and from the test apparatus was recorded.

Oculomotor Competence: A polygraph provided a written record of the raw horizontal and vertical eye position signals collected during the session. In addition, the computer quantified certain parameters of eye movements:

Fixation - an epoch in which velocity of movement remained below 10°/sec for at least 100 msec.

Saccade - an epoch in which velocity of movement exceeded 10°/sec (Visual Search) or 50°/sec (Target Tracking) for at least 4 msec.

Fixation drift - failure to hold a point of gaze. Specifically, the distance traversed during the course of a fixation.

Fixation duration - average duration of all fixations made during a presentation (in msec).

On-target fixation - any fixation falling within a 3° radius of the target.

Targeting error - the radial distance from the target of the first fixation to fall within the on-target sector (in minutes of arc of visual angle).

Saccadic velocity - On the Visual Search test, the average velocity of all saccades made prior to fixating the target (in degrees of arc).

Saccadic duration - average duration of all saccades (in msec).

Reaction time - time elapsed between stimulus onset and the beginning of the first saccade.

Measures of Visual Search: Three indices were chosen to describe the monkeys' success in Visual Search:

1. Percent of trials in which the target was successfully fixated.

2. On successful trials, the time required to find the target, i.e. time elapsed between stimulus onset and the first fixation to fall within 3° of the target.

3. On successful trials, the numbers of fixations required to foveate the target.

The raw scores from the 108 presentations of a session were averaged to yield a session score for each of these measures. Thus, the performance on the No, Low and High conditions were collapsed into a single score.

Measures of Target Tracking. Eye position records plotted over time the position of the target and the monkey's gaze. An informal assessment of tracking performance can be gotten from examining the fit between eye and target position traces. In addition two formal measures were developed:

To examine the dynamics of just the pursuit epochs the eye position trace was differentiated to yield a trace of eye velocity. Saccades were removed from the record and a cross-correlation analysis of the "cleaned" eye velocity

trace was carried out, in general outline according to the method described by Cassell (2). The target velocity trace was first correlated with itself and the first positive peak of the autocorrelation function was taken as a measure of target velocity (V_T). The autocorrelated target trace was cross-correlated with the monkey's "cleaned" velocity trace. The first positive peak of the cross-correlation was considered an index of the monkey's best tracking performance (V_E) and expressed as a second measure:

1. $\underline{\text{Gain}} = \dfrac{V_E}{\overline{V_T}}$

The second index was a measure of phase or the average tendency of the monkey to lead or lag behind the target:

2. Phase (in msec) = $T_{V_E} - T_{V_T}$

T_{VE} is the time of occurrence of the monkey's best performance relative to a target time ($T_{V_T} = 0$).

Data are reported for testing under two target conditions. The Predictable condition was a regular sinusoidal function of 9° amplitude and a frequency of 1.4 Hz (figure 3). With such a function, the subject can predict that whenever the target slows to zero velocity it will reverse direction. The Unpredictable condition was a "random walk" of sinusoids. Each time the target sinusoid crossed zero velocity, a random number table was consulted to see if the next half-cycle of the target function would reverse direction and complete the sinusoidal cycle or instead continue on with a sinusoidal velocity in the same direction. This left the monkey uncertain of the exact trajectory and less able to generate a predetermined program of movement to it.

This report includes for each of the tested drugs a summary of any observed neurological effects, description of oculomotor changes as characterized by unanalyzed strip-chart recordings of the eye movement traces, and finally, graphs of performance on the Visual Search and Tracking tests. Performance on these tests is expressed as "Z scores" in which the monkeys' behavior under the influence of the drug is normalized to the mean and variation of its baseline behavior. Specifically, $Z = \dfrac{X_D - M_B}{\sigma B}$, where

X_D = average performance over the trials of Visual Search or Target Tracking on the day of the drug

M_B = mean performance over all blocks of trials on the baseline days (20-36 days of testing)

σ_B = standard deviation of the baseline blocks

Under the assumption that the "Z scores" distribute normally, performance within $Z < \pm 1.96$ is considered to represent the limits of normal behavior. In practice, our previous experience with this measure is that reliable drug decrements are signalled by Z scores falling well outside these limits.

RESULTS

Baseline Performance

Table 4 and 5 show typical baseline performance achieved by the monkeys on the Visual Search and Target Tracking task. Training of the animals on these tests required 3-6 weeks. The tables indicate that by the time they had begun the drug trials they were quite accomplished at the tasks. The small standard deviations indicate highly reliable day-to-day performance over the 20-30 baseline days during a 10-12 week course of testing several doses of the same drug.

On the Search test the targets were found on virtually all the presentations of the stimuli. The short time and small number of fixations required to foveate the target suggest the monkeys had usually detected the target before their eyes had moved from the center of the screen. Naeve human subjects first attempting the same task failed to find the target in the allotted time on about 1/3 of the presentations.

Table 4. Baseline performance on Visual Search of Subject 1 during the physostigmine trial

	Baseline Average	Std among sessions
Percent of successful trials	98.6	2.43
Reaction time to begin search (msec)	232	11
Time to find target (msec)	375	42
Number of fixations to find target	1.51	0.12

Table 5. Baseline performance of Target Tracking of Subject 1 during physostigmine trial.

	Baseline average	Std. among sessions
Gain (Eye Veloc/ Target Veloc)	.73	.02
Phase (in msec.; positive number indicates lag behind target)	38	2
Percent of time spent in saccades	9.5	.09

Figure 3 illustrates tracking performance comparable to that indicated by the formal measures in the table. Performance on the Target Tracking test was not perfect (i.e. equal to a gain of 1.0 with no saccades) but was quite good and was stable as indicated by the small variability from session to session. The figure and table 4 indicate that monkeys like humans are capable of predictive tracking. If the animal were merely following the target then its eye would lag behind it on the average 125 msec, the reaction time for the oculomotor pursuit system. That Phase is considerably less indicates that the monkey is anticipating the trajectory of the target. This point is also apparent in the eye position trace for the Unpredictable target to the right of Figure 3. The monkey is clearly expecting a sinusoidal trajectory and reverses its tracking direction at points where the target normally changes direction (arrows).

Tables 6 and 7 document that there was no decrement in baseline performance caused by repeated testing with these toxic agents. For these tables the baseline performance of four subjects undergoing the first drug trial (1) is compared with that during the last agent (L) to be tested. The change in performance is expressed as a Z score =

$$\frac{Avg._1 - Avg._L}{Std._1}$$

where $Avg._1$ = average baseline performance during the subject's first drug trial; $Avg._L$ = baseline performance during the last drug tested: $Std._1$ = standard deviation of the initial baseline performance. Z scores outside the range between +/- 1.96 would have signalled an improvement or decrement in baseline performance over the course of the study.

Table 6. Comparison of baseline performances on Visual Search during first and last agent tested.

	Z score
Percent of targets fixated	1.42
Time to find the target	0.79
Number of fixations to find target	1.31

Table 7. Comparison of baseline performances on Target Tracking during first and last agent tested.

	Z score
Gain	-0.34
Phase	0.04

Results of Drug Trials

ATROPINE

.014 mg/K

Neurological status: Slight and inconsistent pupillary mydriasis appeared; the monkeys were otherwise neurologically normal.

Oculomotor: Eye position traces during Search were mostly normal, but with excessive eye blinks (figure 4) and the suggestion of slight drift of fixations in 2 subjects.

Visual Search: Normal.

Target Tracking: Target tracking is Normal (figure 5) but for a borderline increase in phase during the Late session in one subject. Abnormal Phase in Saline trial for Subject 2 was caused by poor performance on a single day's testing, and is unexplained. Gain for the same day was normal.*

0.045 mg/K

Neurological status: Moderate mydriasis and lip movements indicative of a dry mouth occurred in all subjects, but there was no evidence of muscle weakness.

Oculomotor: The polygraph record was mostly normal, but contained excessive eye blinks and the hint of shorter and perhaps slightly drifting fixations.

Visual Search: Normal

Target Tracking: Normal, but for a borderline abnormal Phase in Subject 3.

0.14 mg/K

Neurological status: Mydriasis and dry mouth was variable and ranged from moderate to severe. Slight ptosis occurred in one monkey, but limb movement and posture did not indicate general muscle weakness.

* A technical error in the program for analyzing the data from the Unpredictable condition invalidated much of the formal measures of this testing condition. Plots of examples of target tracking under both target conditions are presented, but the graphs include only the formal measures for the Predictable condition.

Oculomotor: The position record at this dose displayed obvious drift in fixations and the saccadic traces were sloped (slowed). Fixations were shorter than normal -- interrupted more frequently by small shifts of gaze (fig. 4). There was slight dysmetria which included both over- and undershooting of the target.

Visual Search: Largely normal, but with some variability between subjects and between first and second testing of this dose. Two subjects (1,2) required slightly more fixations to find the target on the first but not the second testing. This dose did not appear to disrupt the monkey's willingness to search for targets.

Target Tracking: Decrements in the gain of pursuit movements appeared in three subjects. The decrements were borderline in two of these animals, and in general target tracking remained quite competent.

0.25 mg/K

Neurological status: Mydriasis was quite pronounced although the pupils were not dilated to their limits. Dry mouth and ptosis were seen but no obvious skeletal weakness.

Oculomotor: The oculomotor record was markedly disfigured by eye blinks, drifting and fractured fixations.

Visual Search: Testing of two subjects proceeded smoothly. The other two appeared less motivated and paused occasionally between trials. The effect on performance is reflected in fewer targets acquired and an incraese in time and number of fixations to find the target. However, these changes did not show up consistently and at their worst were not drastic decrements.

Target tracking: Decrements in this test were clear and consistent. The loss in Gain of pursuit occurred in all four subjects, and was marked in 3 of them. Abnormal increase in Phase (lag) also appeared in all subjects.

Table 8. Atropine. "Worst case" Session scores on Visual Search. Subject 1; Dose: .25 mg/K; Session: Early.

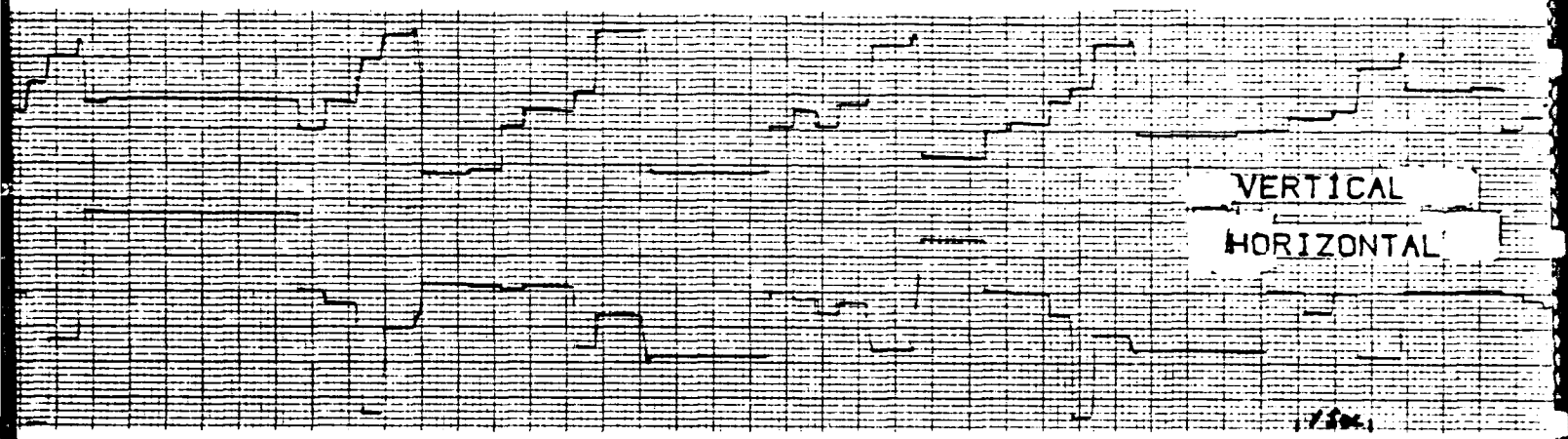
	Baseline Avg./Std		Drug Avg.
Percent of targets fixated	97.3	2.6	90.3
ON SUCCESSFUL TRIALS:			
Time required to fixate target (msec)	298	13	330
Number of fixations to find target	1.16	0.04	1.37

Table 9. Atropine. "Worst case" Session scores on Target Tracking. Subject 2. Dose: 0.25 mg/K

	Baseline Avg./Std.		Drug Avg.
Gain	0.57	0.08	0.43
Phase (Lag in msec)	29	9	65

Atropine
Eye Position During Search

Normal



.25 mg/K

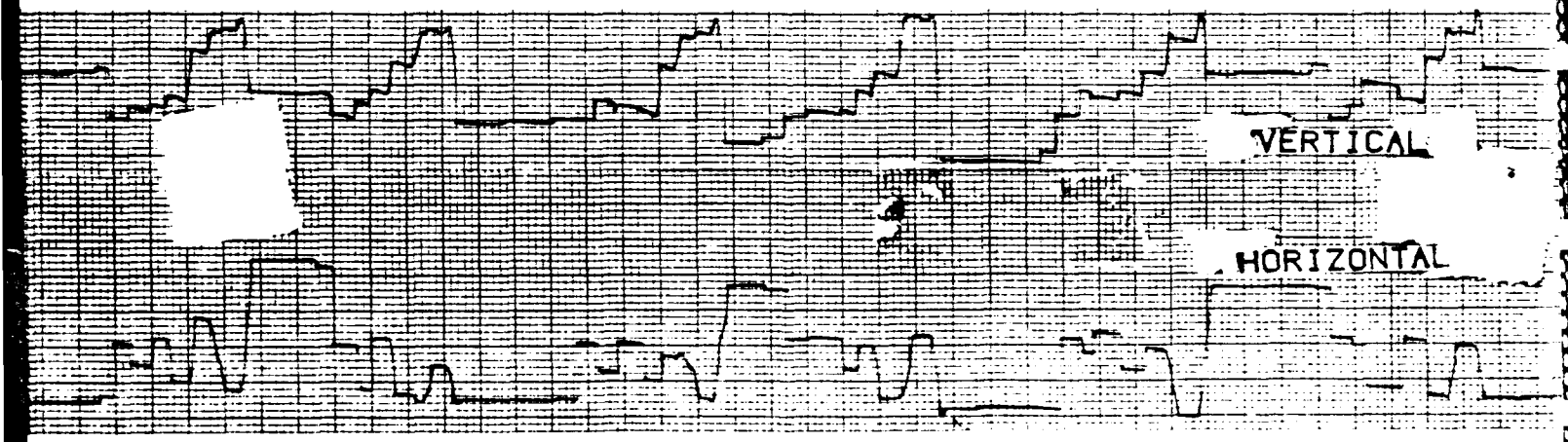
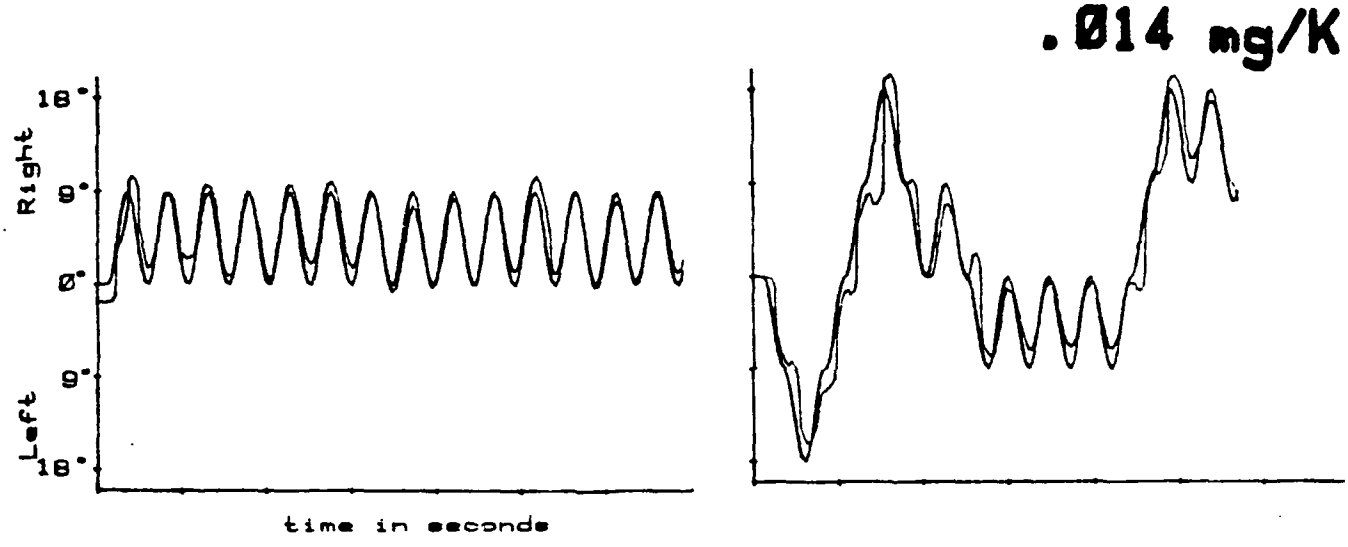


figure 4

Atropine

Eye Position During Tracking



PREDICTABLE TARGET

UNPREDICTABLE TARGET

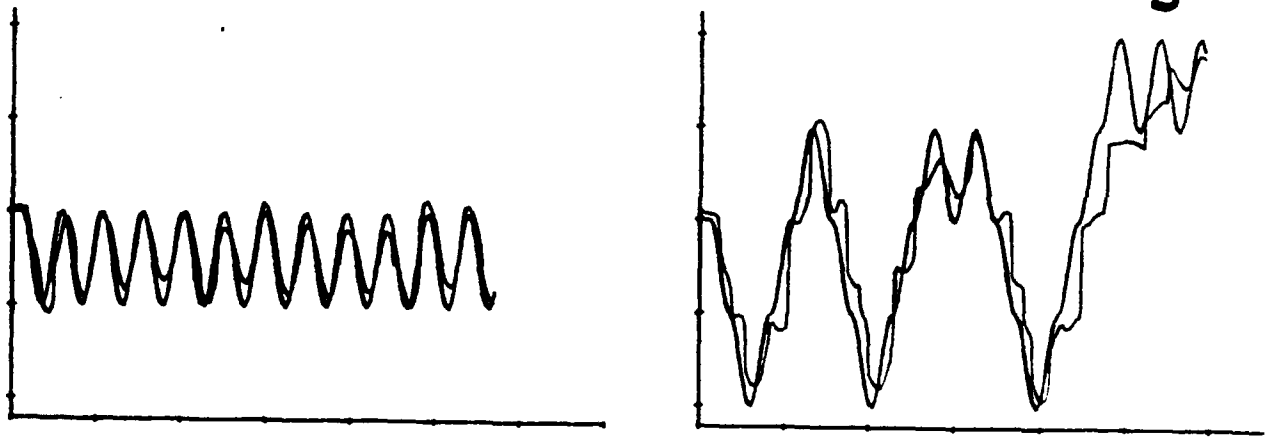


figure 5

ATROPINE
PERCENT OF TARGETS FIXATED

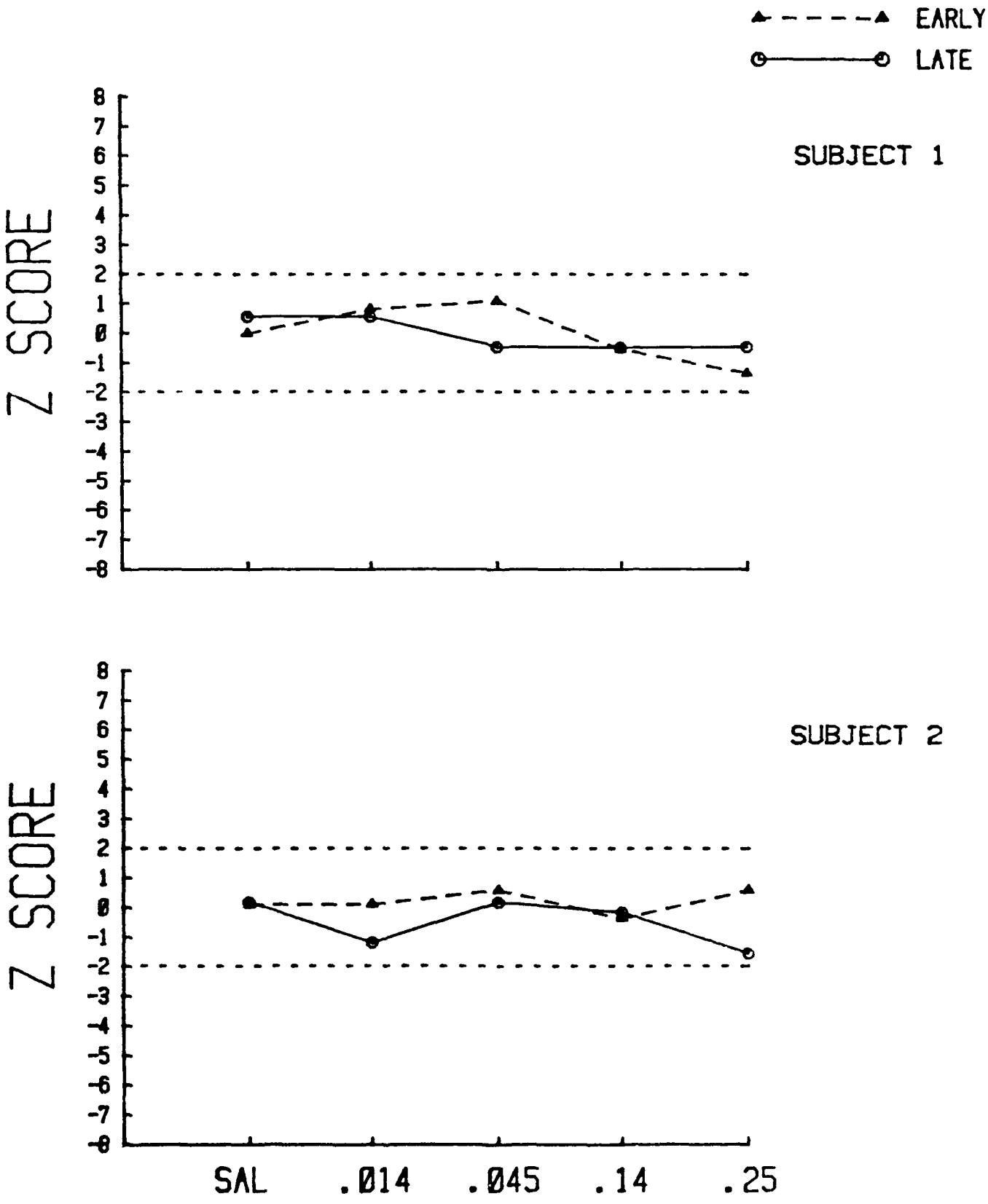


figure 6

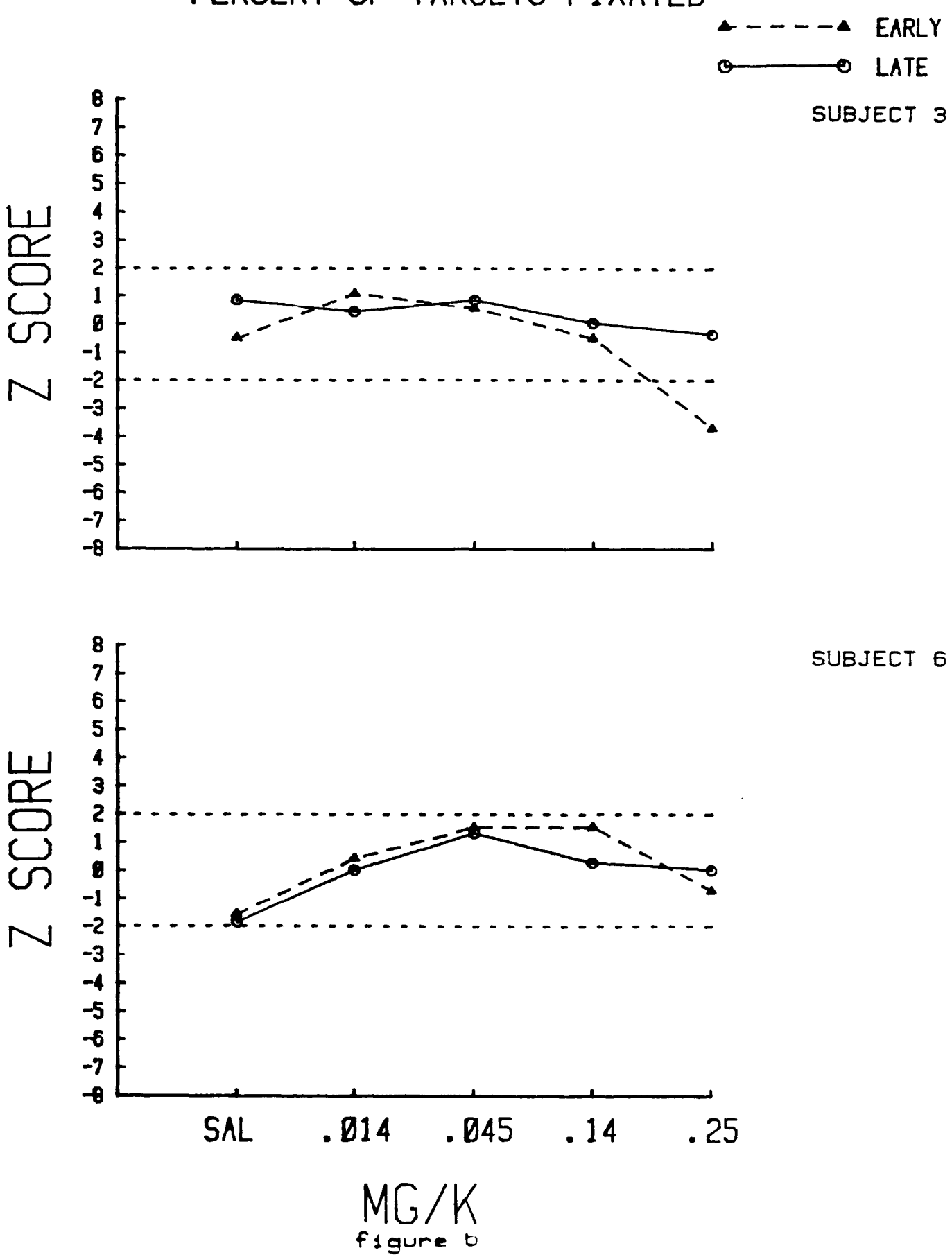

ATROPINE
PERCENT OF TARGETS FIXATED
EARLY
LATE
SUBJECT 3
SUBJECT 6
Z SCORE
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
SAL
.014
.045
.14
.25
MG/K

figure b

ATROPINE
TIME TO FIND TARGET

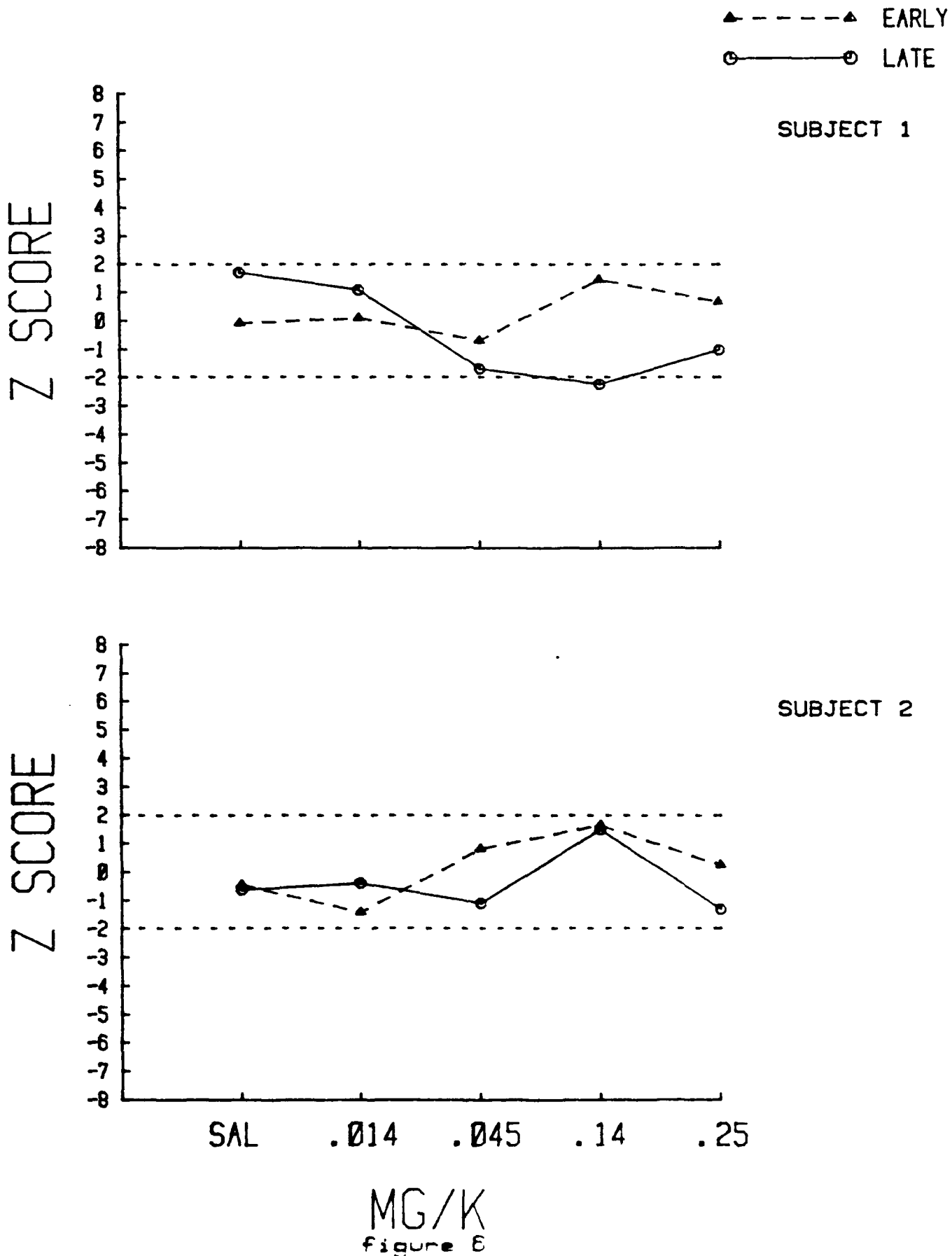


figure 8

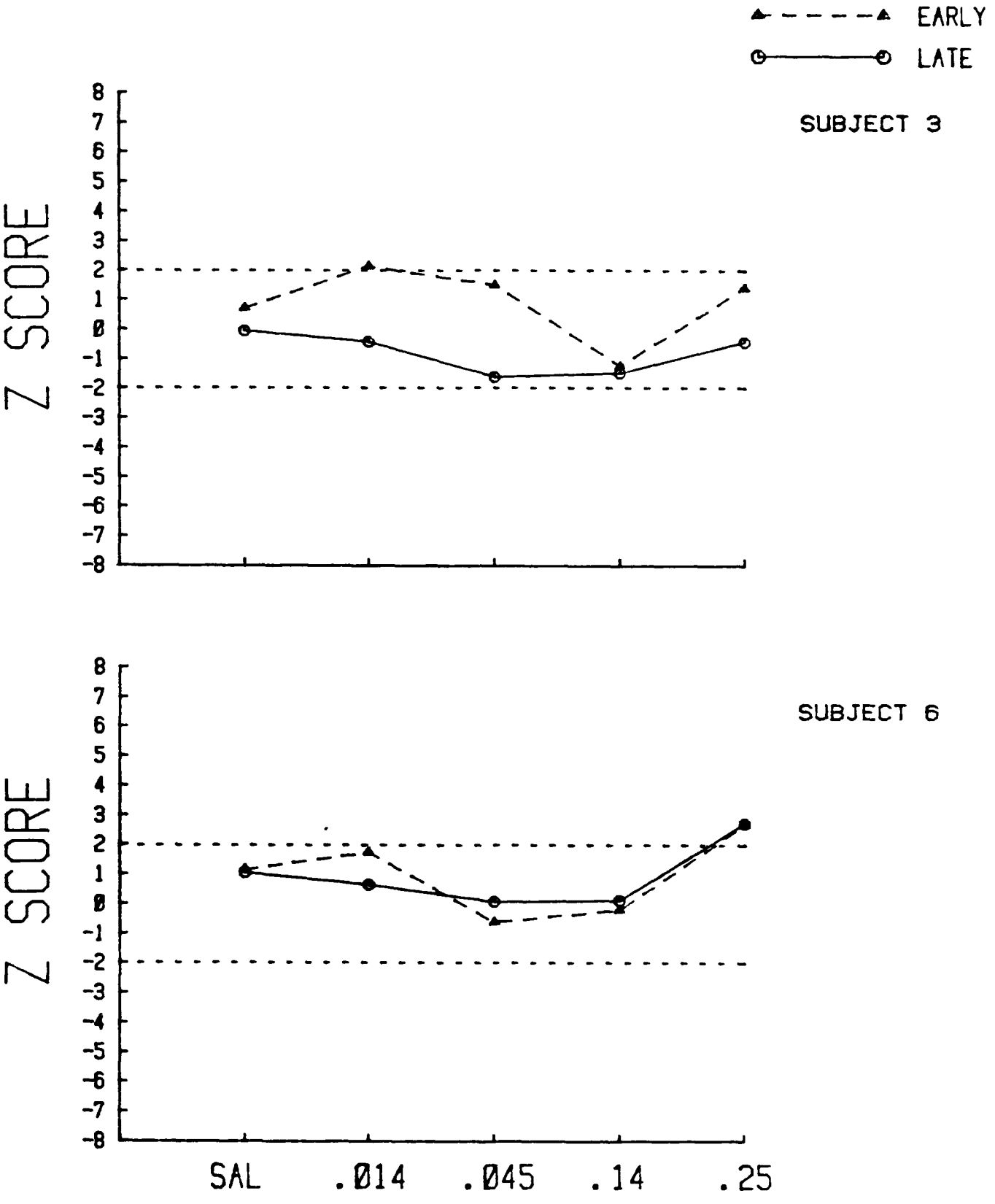

ATROPINE
TIME TO FIND TARGET
EARLY
LATE
SUBJECT 3
SUBJECT 6
Z SCORE
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
SAL
.014
.045
.14
.25
MG/K

figure 6

ATROPINE
NUMBER OF FIXATIONS TO FIND TARGET

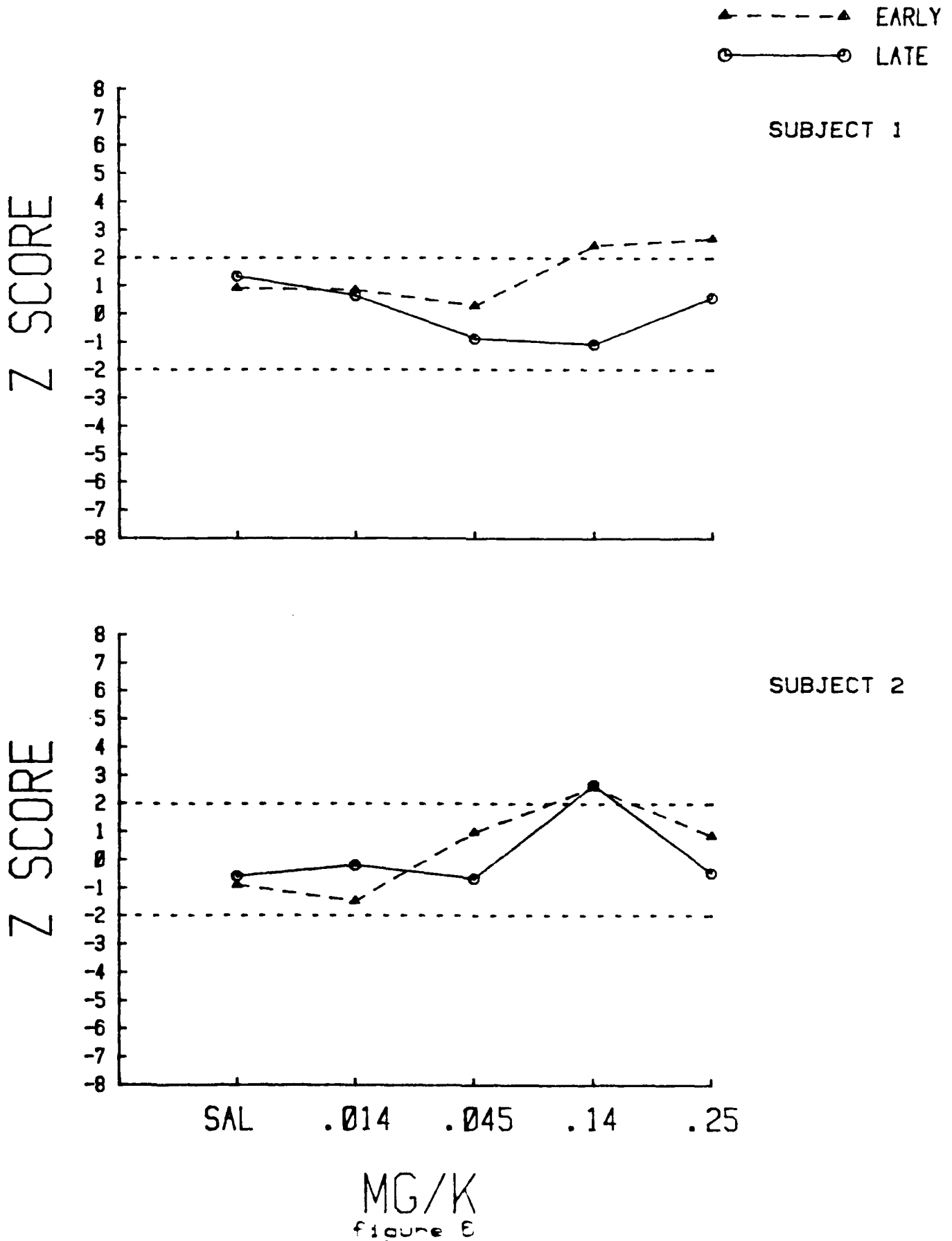


figure 8

ATROPINE
NUMBER OF FIXATIONS TO FIND TARGET

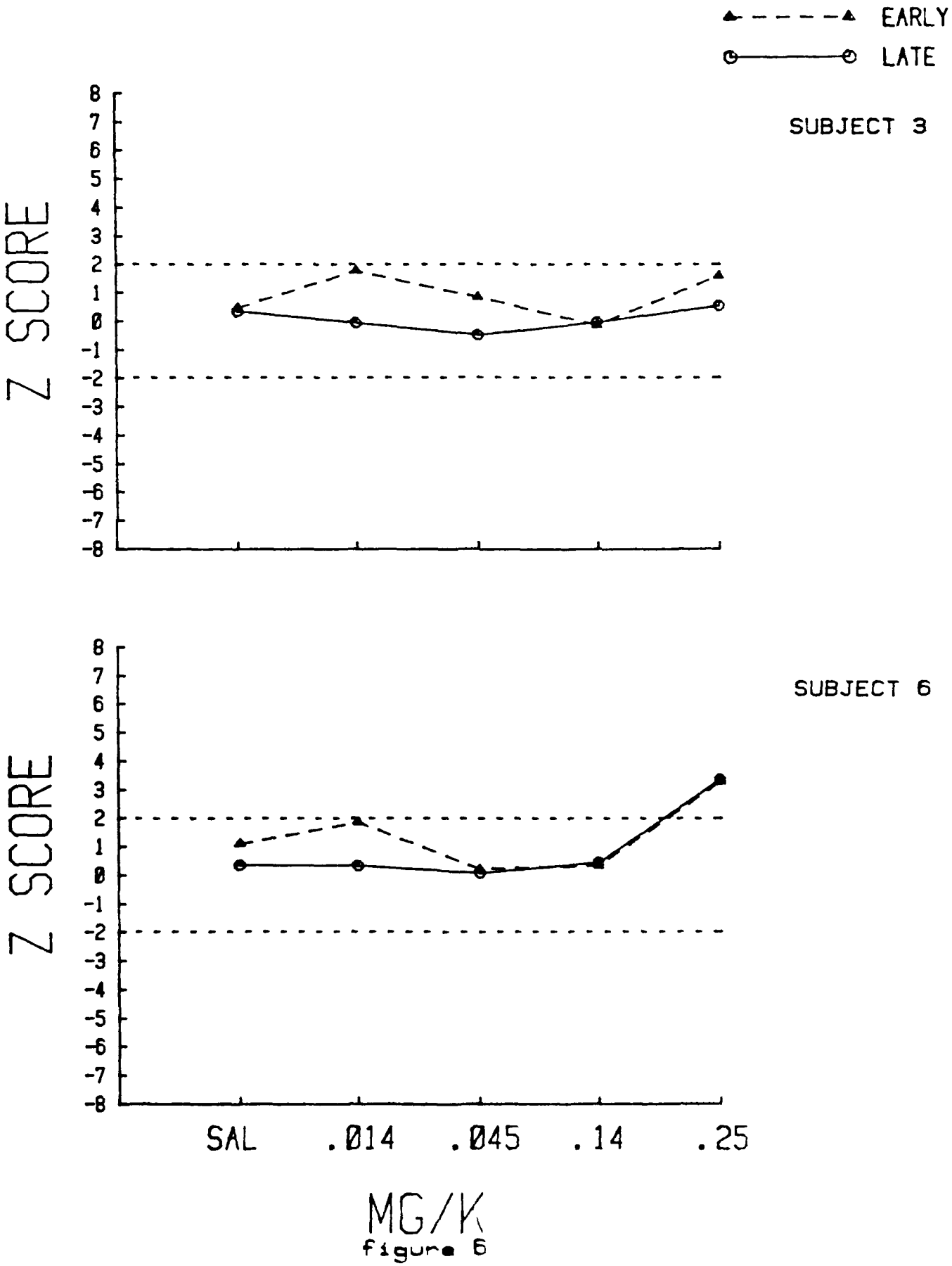


figure 6

ATROPINE: TRACKING - PRED. GAIN

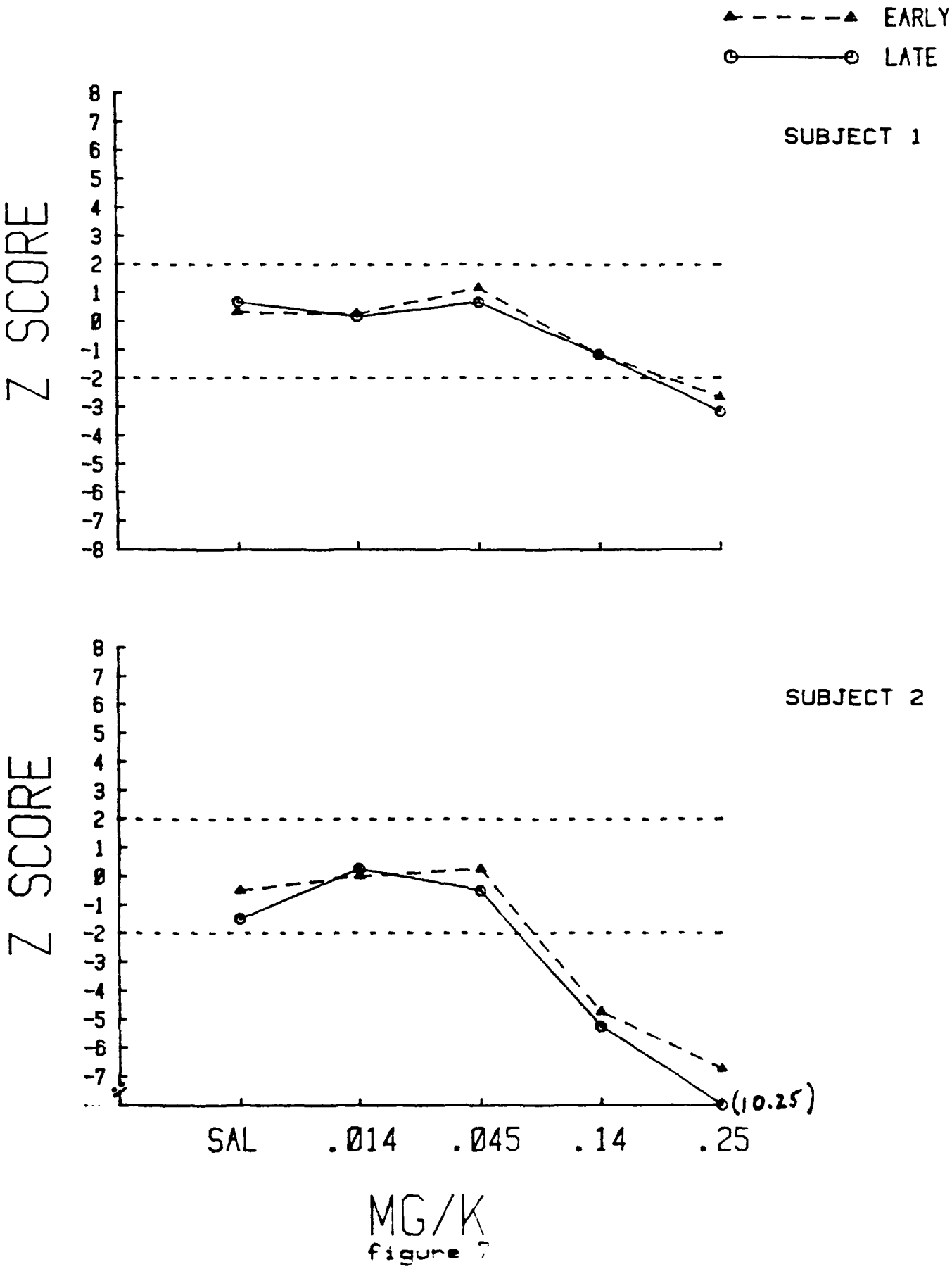
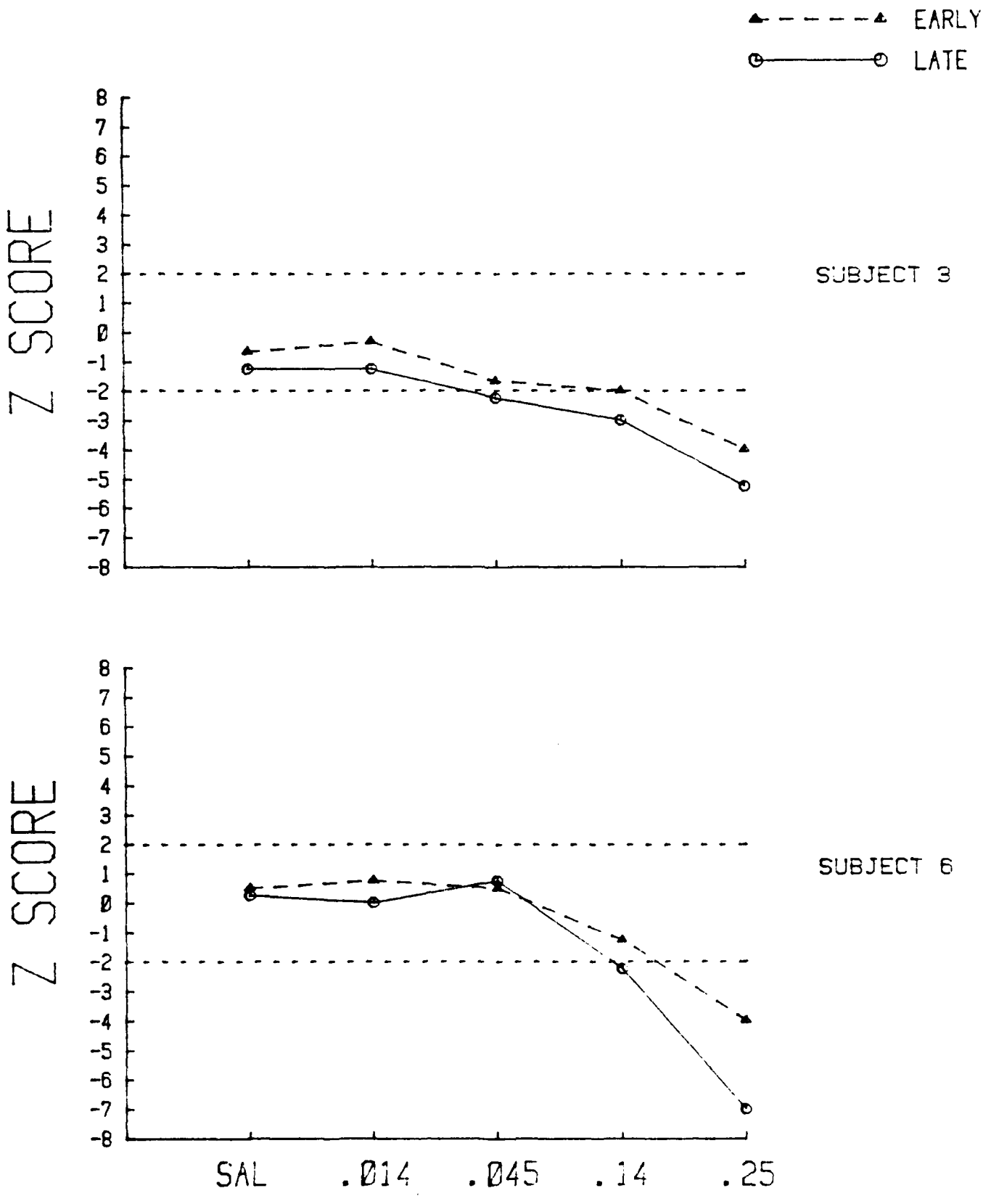


figure 7


ATROPINE: TRACKING - PRED. GAIN
EARLY
LATE
Z SCORE
SUBJECT 3
SUBJECT 6
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
SAL
.014
.045
.14
.25

MG/K

figure 7

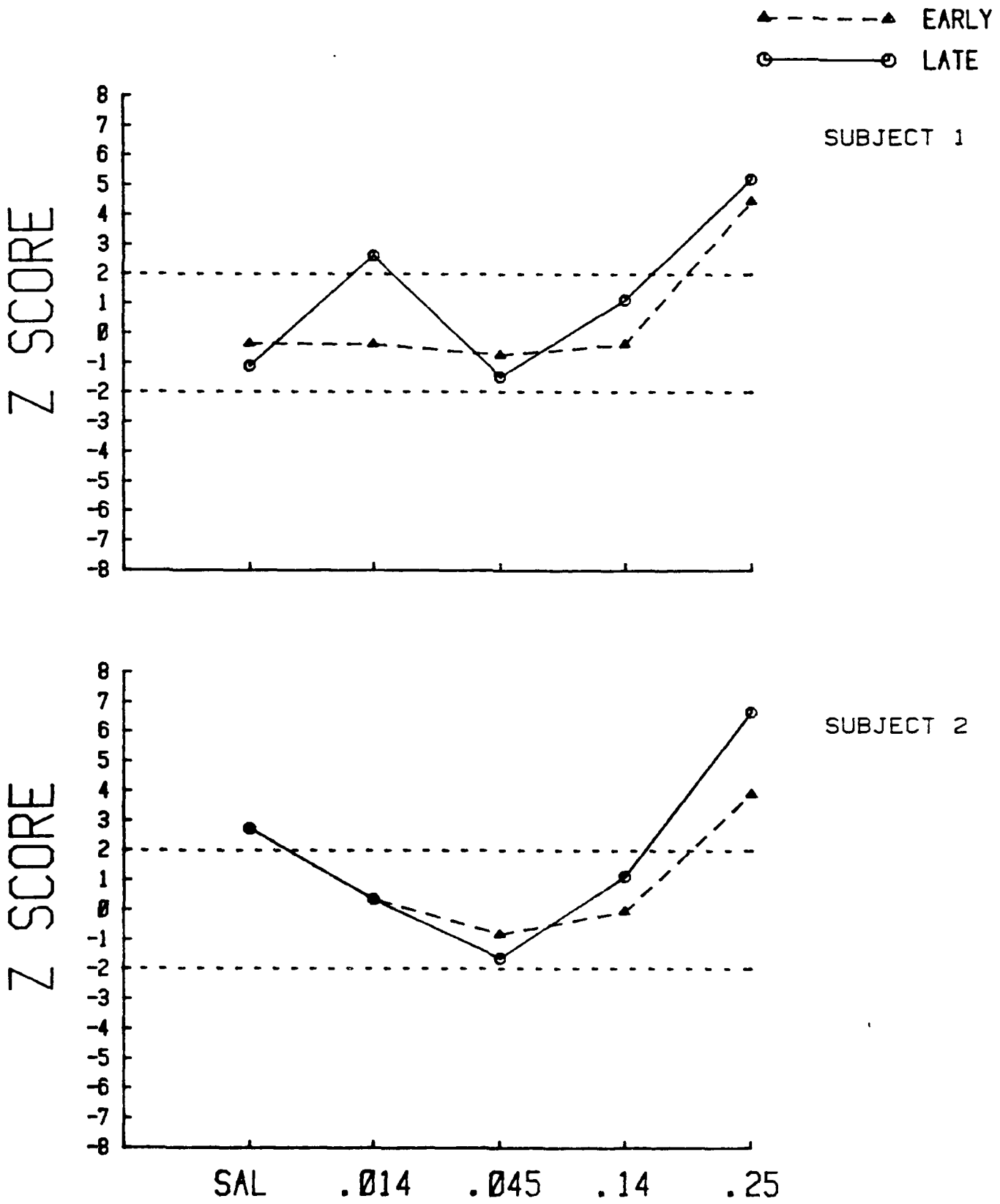

ATROPINE: TRACKING - PRED.
PHASE
EARLY
LATE
SUBJECT 1
SUBJECT 2
Z SCORE
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
SAL
.014
.045
.14
.25
MG/K

figure 7

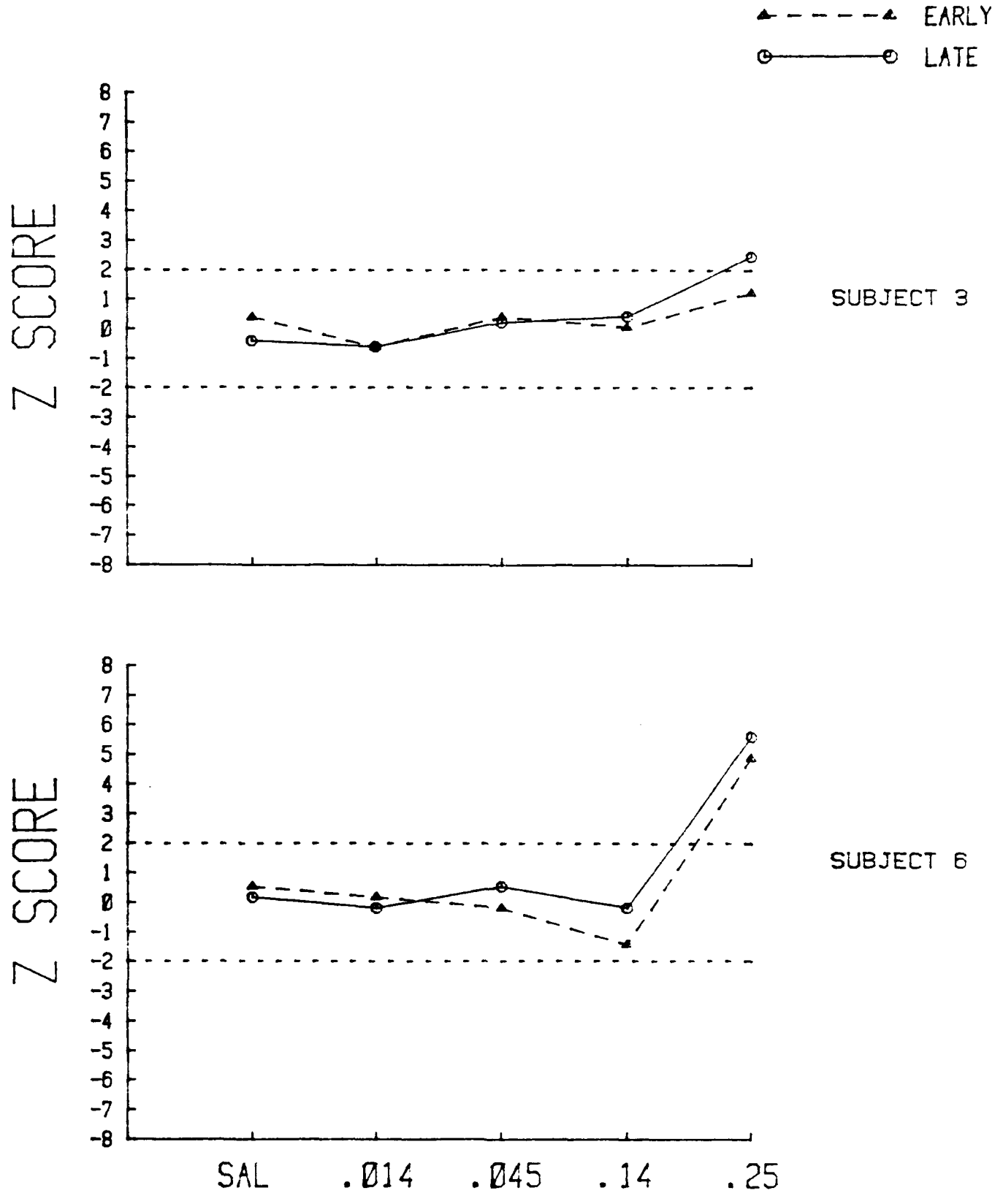

ATROPINE: TRACKING - PRED.
PHASE
EARLY
LATE
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
SUBJECT 3
Z SCORE
SUBJECT 6
SAL
.014
.045
.14
.25
MG/K

figure 7

PRALIDOXIME

1 and 2 mg/K

No abnormalities were detected at these levels of pralidoxime either during the Search or Tracking trials with the drugs. During the course of the project at the suggestion of the contract officer the 1 mg/K dose was dropped from the protocol and a higher 16 mg/K was added.

4mg/K

Neurological status: Normal

Oculomotor: The eye records were essentially normal with the occasional appearance of some excessive blinking.

Visual Search: Normal

Target Tracking: Statistically real but slight decrements in the gain of the tracking occurred in two subjects. Tracking was still quite good in these cases, the phase of the eye velocity was normal, and to the eye the tracking performance appeared normal.

8mg/K

Neurological status: Normal.

Oculomotor: The record revealed some drift in fixations particularly affecting the vertical channel (figure 8). This made it difficult for the monkeys to fixate the center of the screen long enough to initiate the trial. During tracking of the horizontally moving target this vertical drift caused them to follow the target's motion but to do so holding a fixation point that was slightly offset above the target. The shift in vertical offset occurred within 4 minutes and lasted to about 1/2 hour after drug injection.

Visual Search: Performance remained quite competent for the most part, but borderline decrements occasionally appeared. One subject took a slightly longer time to find the target; one subject found the target less often. There was also a tendency to undershoot the target. Normally, the gaze of monkeys closed to within 0.5 degrees of the target, but at this dose their closest fixations were typically 1.0 off the mark.

Target tracking: Normal, with borderline decrement occurring during the Early session in the gain of one subject (6).

16 mg/K

Neurological status: Normal

Oculomotor: The monkeys displayed the same changes as reported above for 8 mg/K., and the abnormalities were not noticeably worsened at 16 mg/K.

Visual Search: Testing was erratic and intermittent and this was reflected in a reduced percentage of successful presentations in one of the two subjects tested at this dosage. However, on successful trials the targets were found within a normal range of time and number of fixations.

Table 10. Pralidoxime. "Worst case" Session scores: Subject 4; Dose: 16mg/K; Session: Early

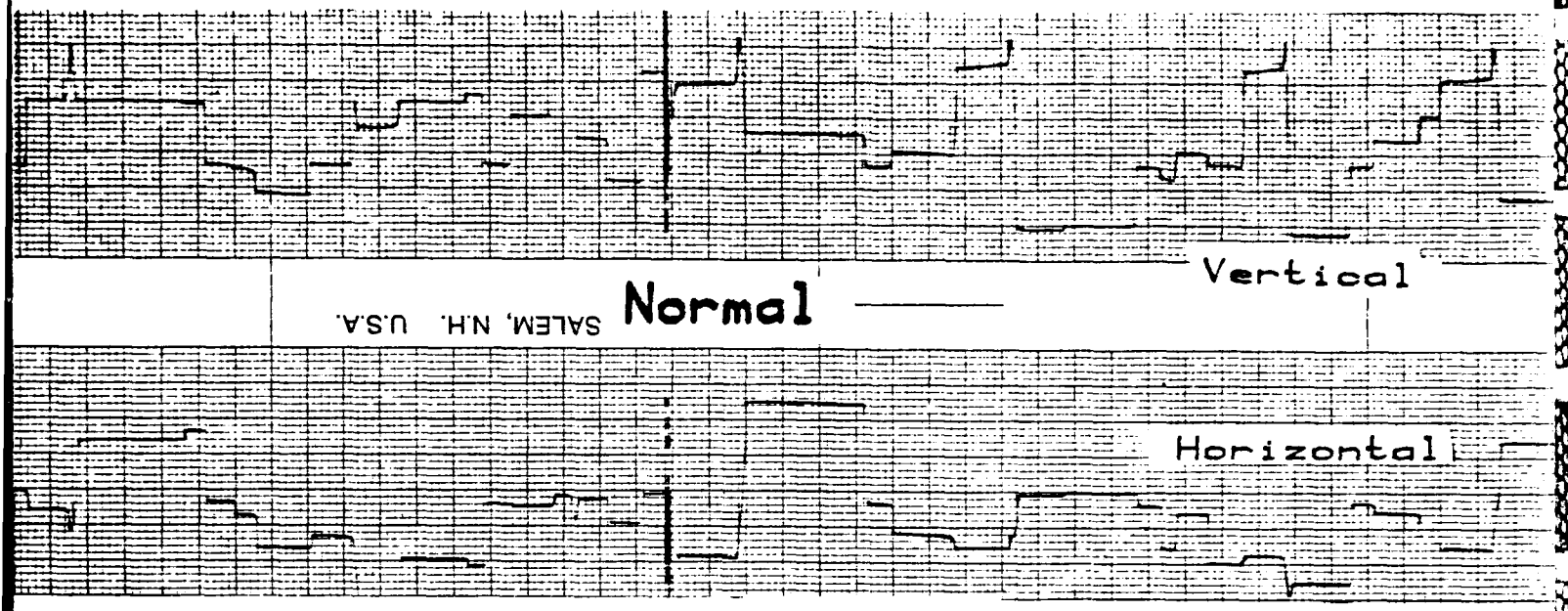
	Baseline Avg./	Std.	Drug Avg.
Percent of targets fixated	97.8	2.4	43.1
ON SUCCESSFUL TRIALS:			
Time required to fixate target (msec)	335	56	320
Number of fixations to find target	1.36	0.15	1.09

Target Tracking: Subjects 2 and 6 both displayed reliable decrements in both the gain and phase of their tracking performance. At its worst, however, (figure 9 and table 11) tracking performance did not break down entirely. Again, the effect appears to be one of oculomotor weakness. The position traces of figure 9 indicate that pursuit was not punctuated by excessive saccades but was reduced in the amplitude and therefore the velocity of the pursuit.

Table 11. Pralidoxime- "Worst case" session scores for Target Tracking. Subject 6; Dose: 16 mg/K; Session: Early.

	Baseline Avg/	Std	Drug Avg.
Gain	0.66	0.04	0.37
Phase (Lag in msec)	2.2	8.6	74.2

Pralidoxime
Eye Position During Search



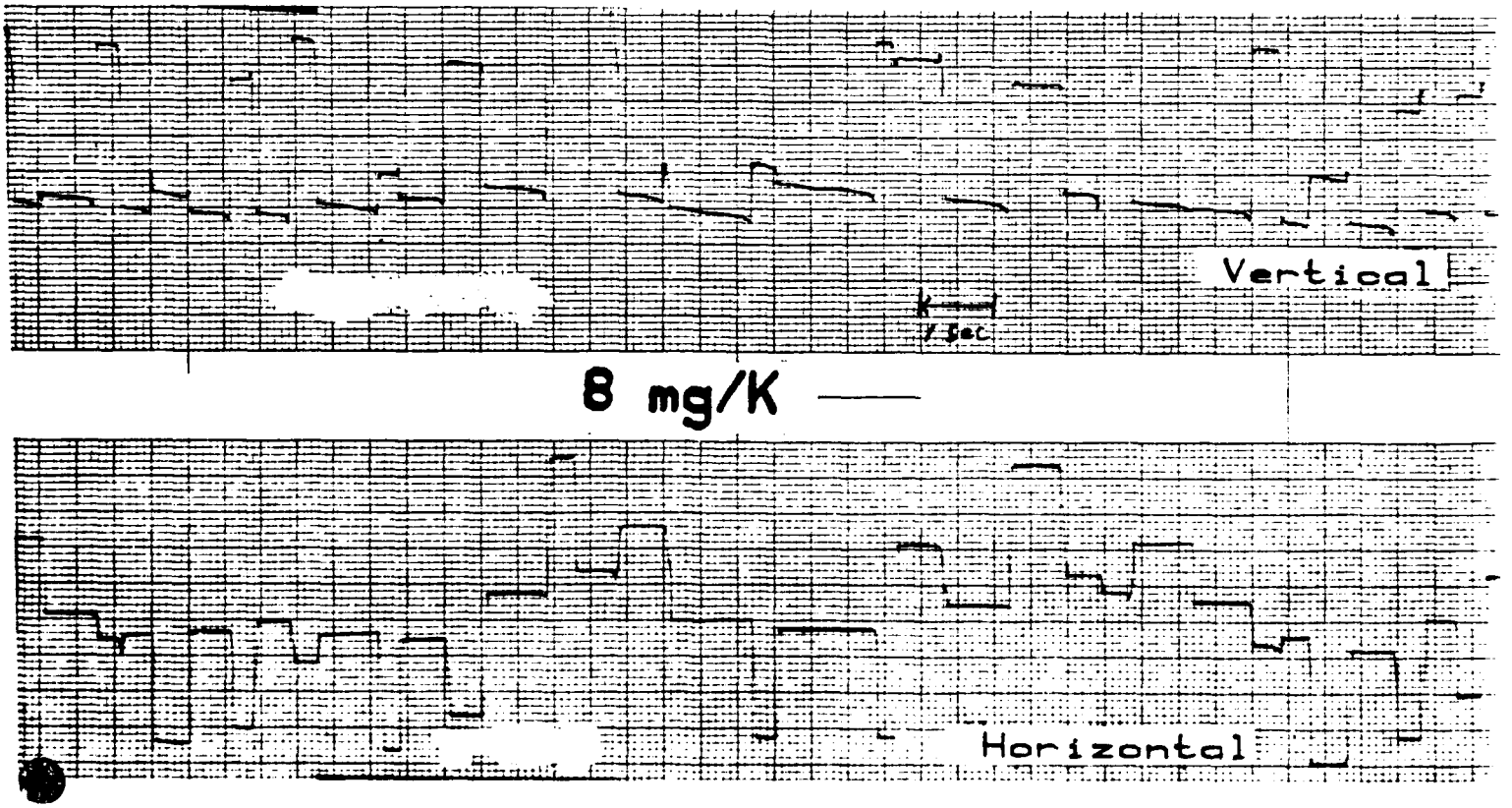
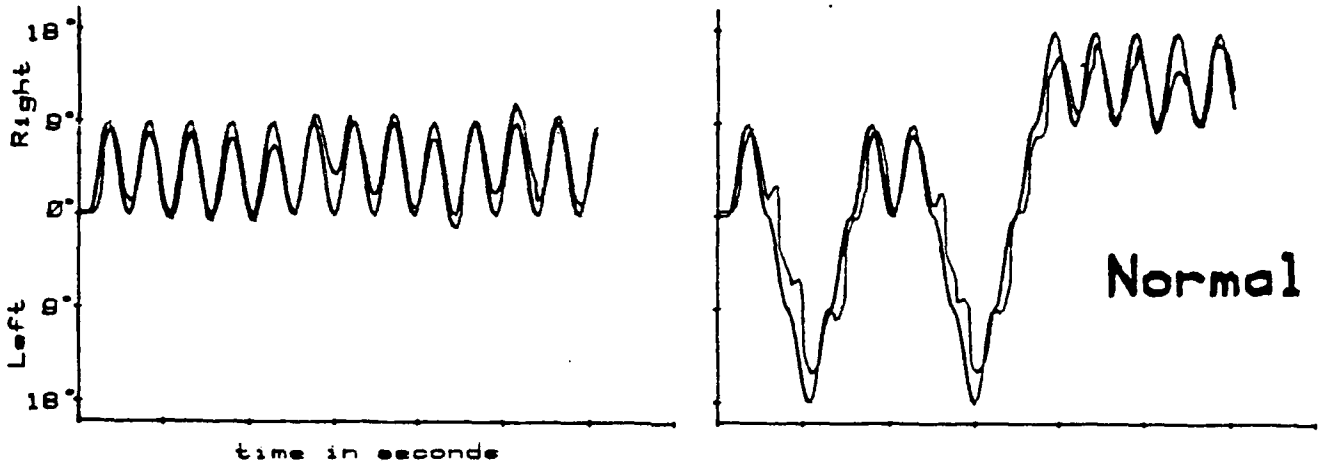
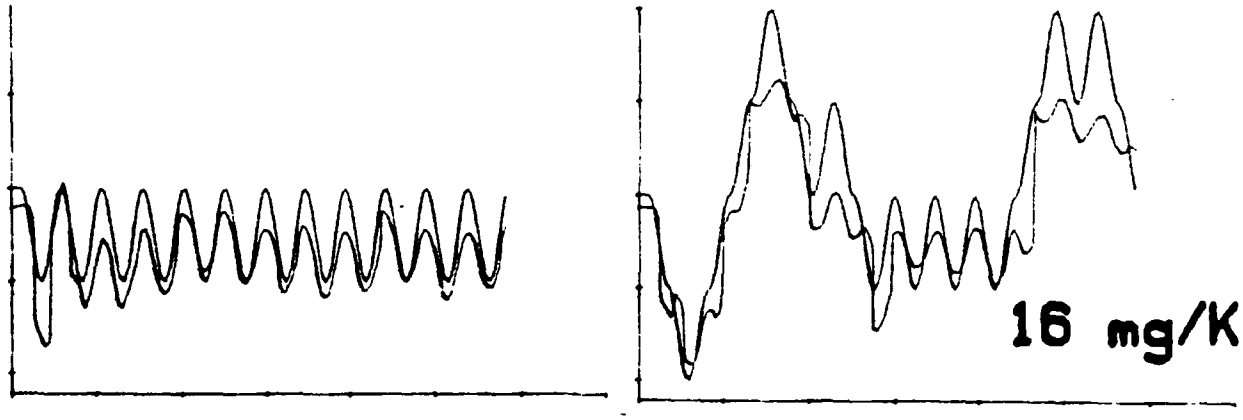


figure 8

Pralidoxime

Eye Position During Tracking





Predictable

Unpredictable

figure 9

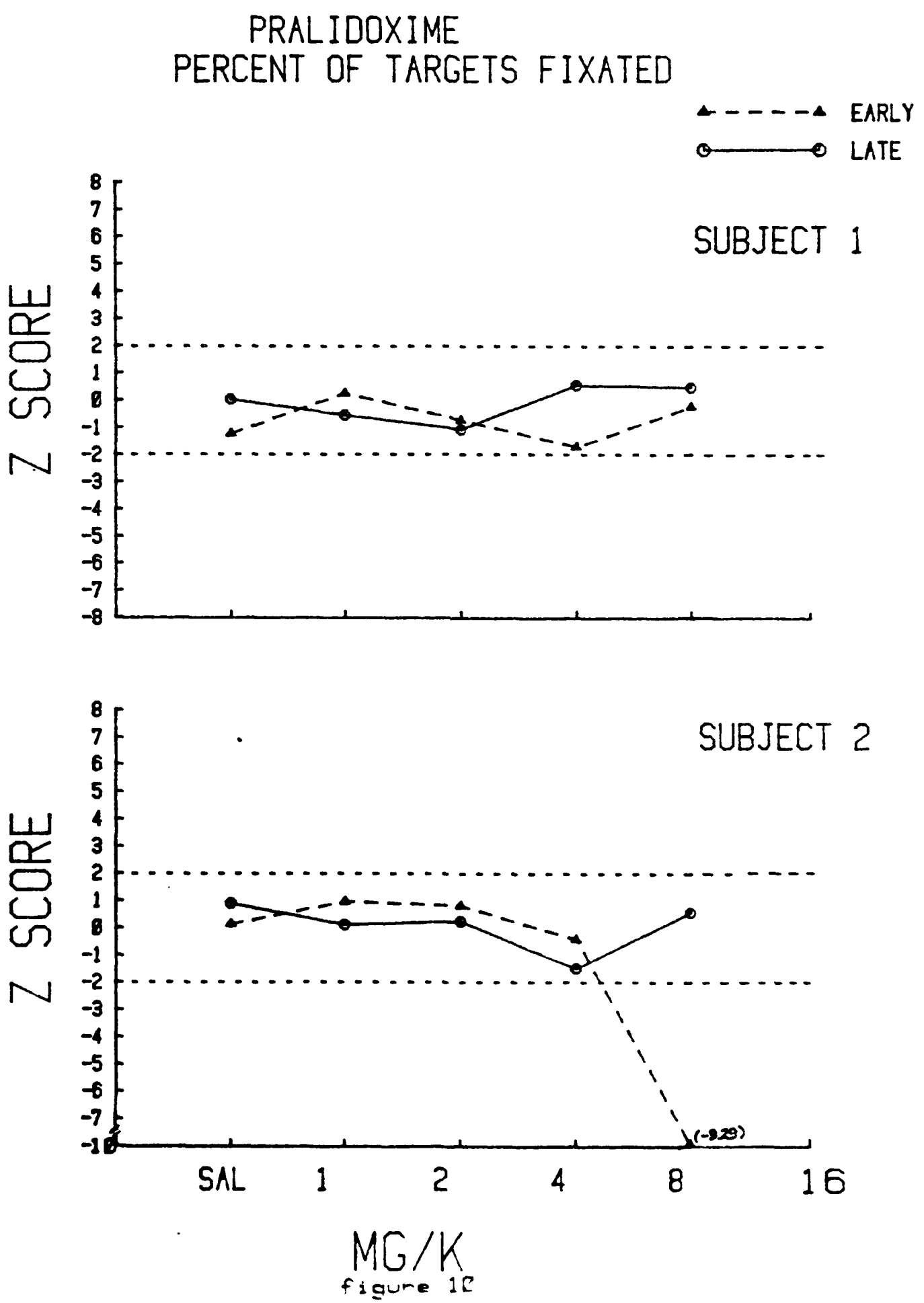

PRALIDOXIME
PERCENT OF TARGETS FIXATED
EARLY
LATE
SUBJECT 1
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
SUBJECT 2
Z SCORE
-10
(-9.29)
SAL
1
2
4
8
16
MG/K

figure 1C

PRALIDOXIME
PERCENT OF TARGETS FIXATED

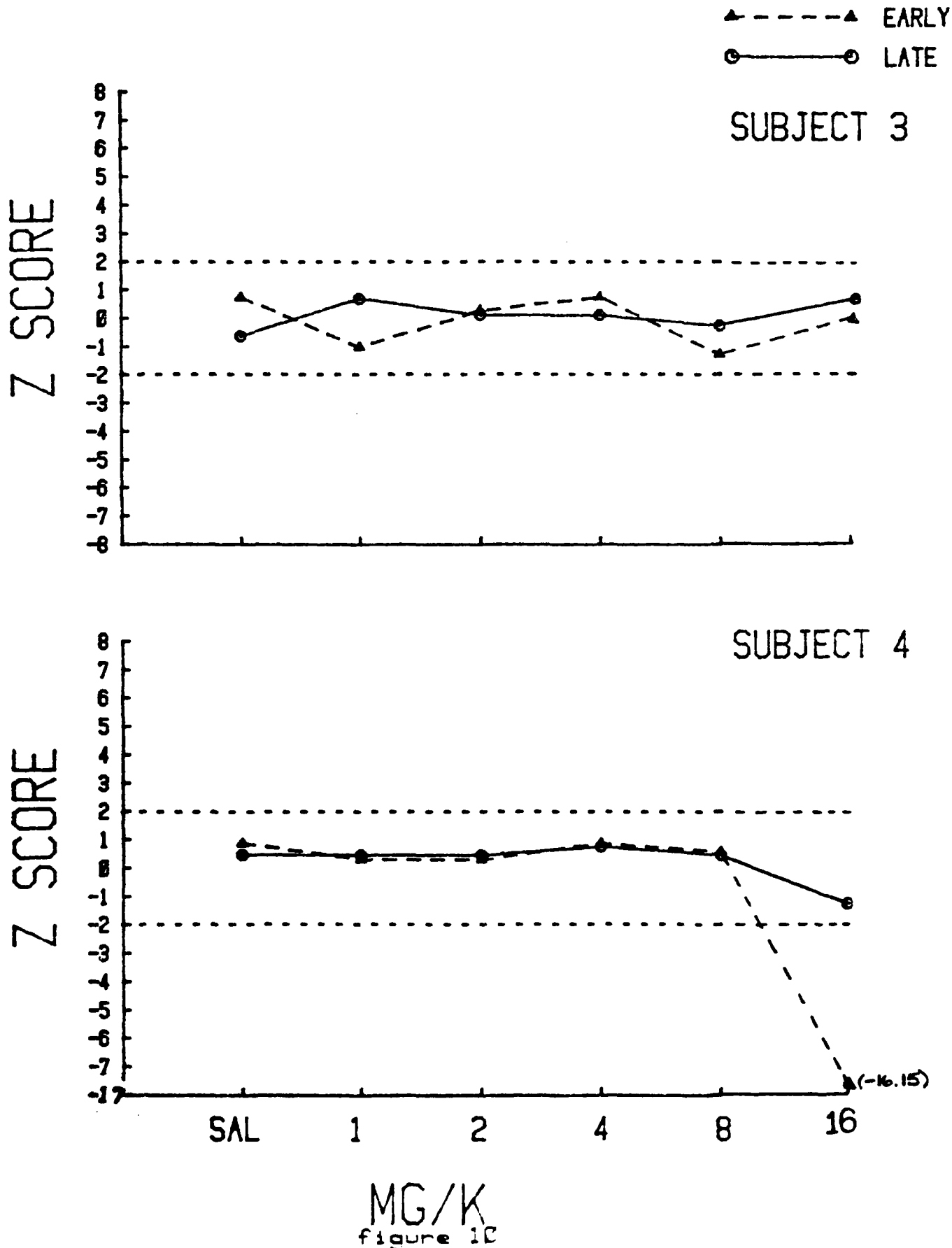


figure 1C

PRALIDOXIME
TIME TO FIXATE TARGET

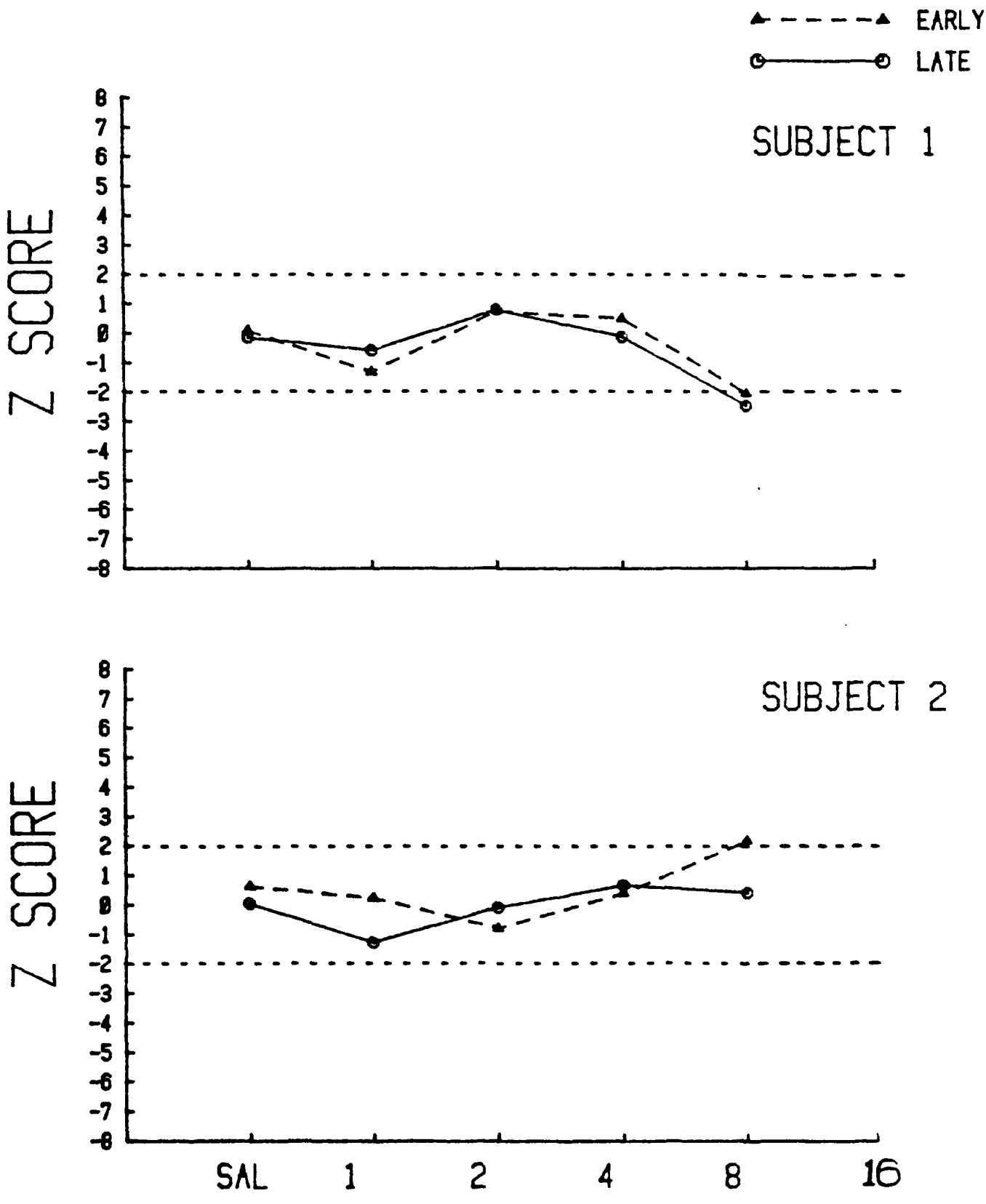


figure 1B

PRALIDOXIME
TIME TO FIXATE TARGET

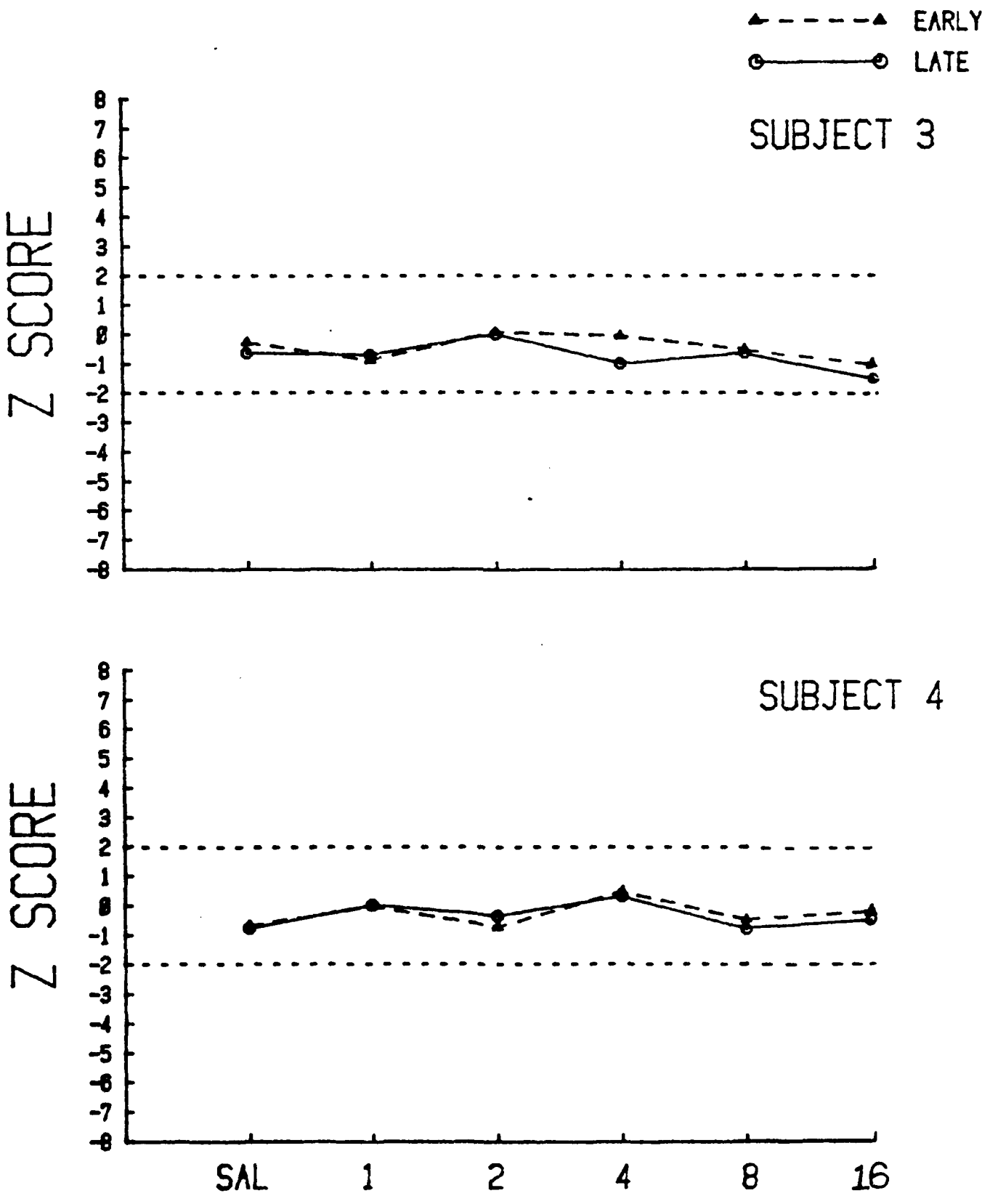


figure 1C

PRALIDOXIME
NUMBER OF FIXATIONS TO FIND TARGET

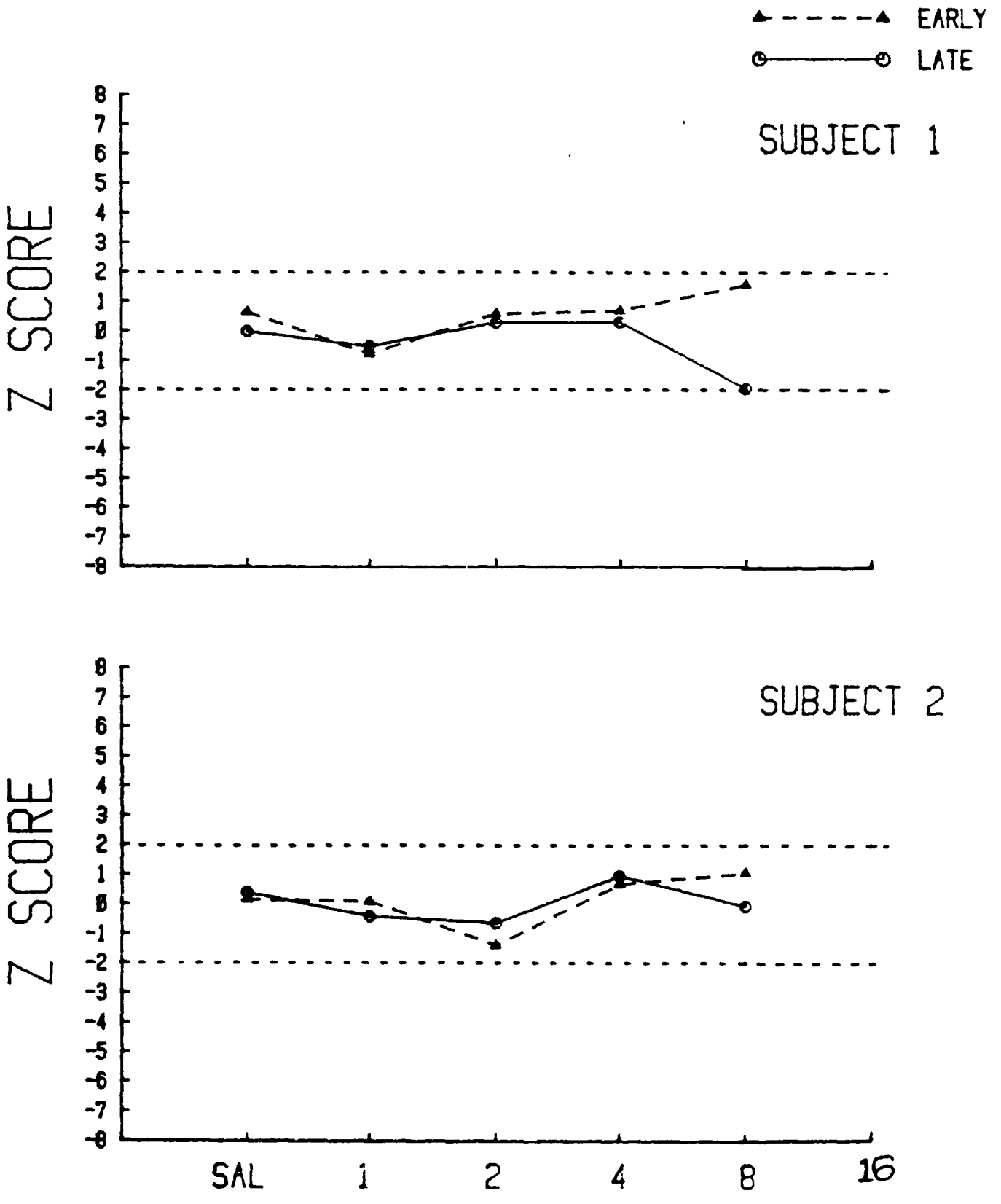


figure 1C

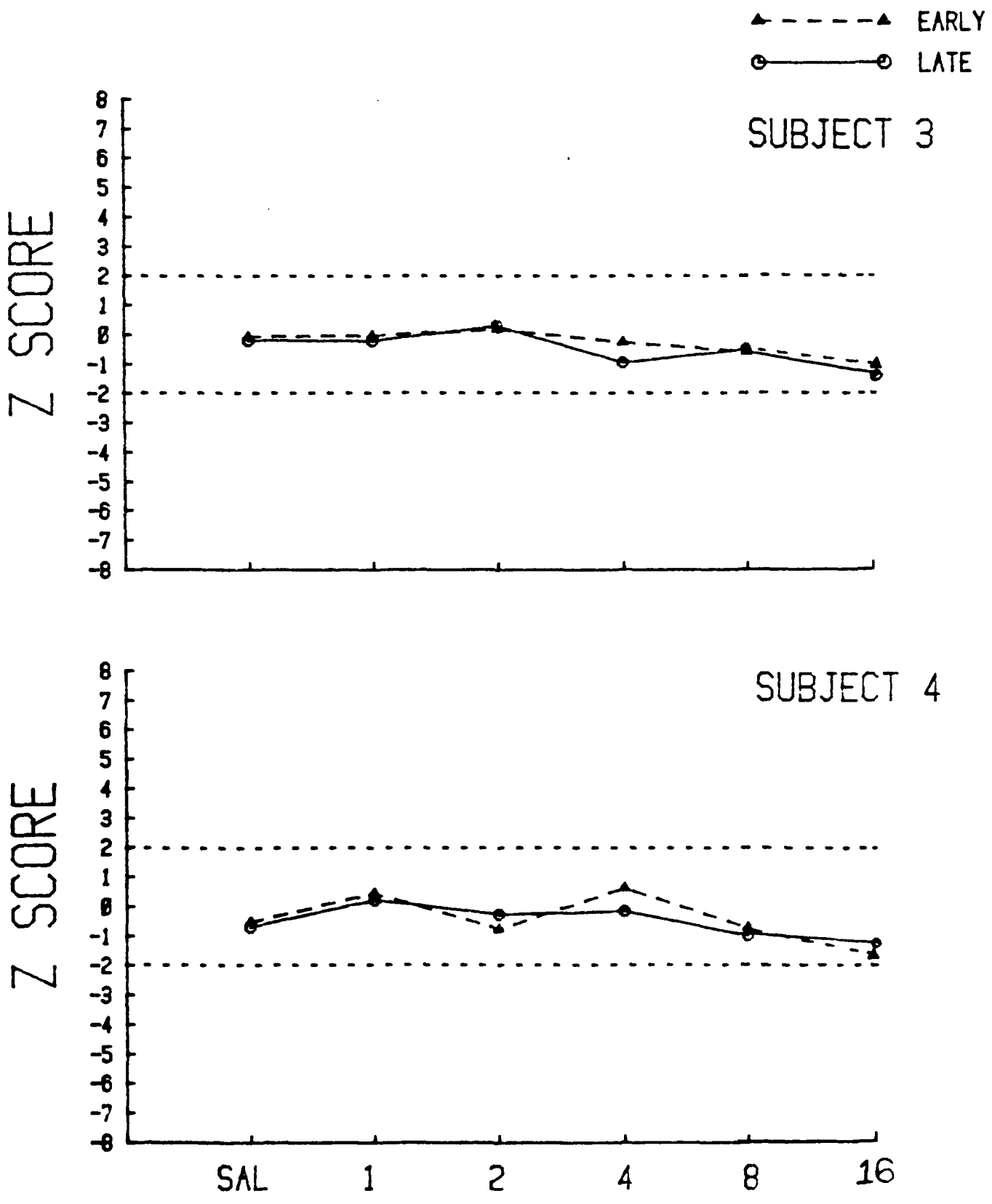

PRALIDOXIME
NUMBER OF FIXATIONS TO FIND TARGET
EARLY
LATE
SUBJECT 3
SUBJECT 4
Z SCORE
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
SAL
1
2
4
8
16
MG/K

figure 10

PRALIDOXIME: TRACKING GAIN

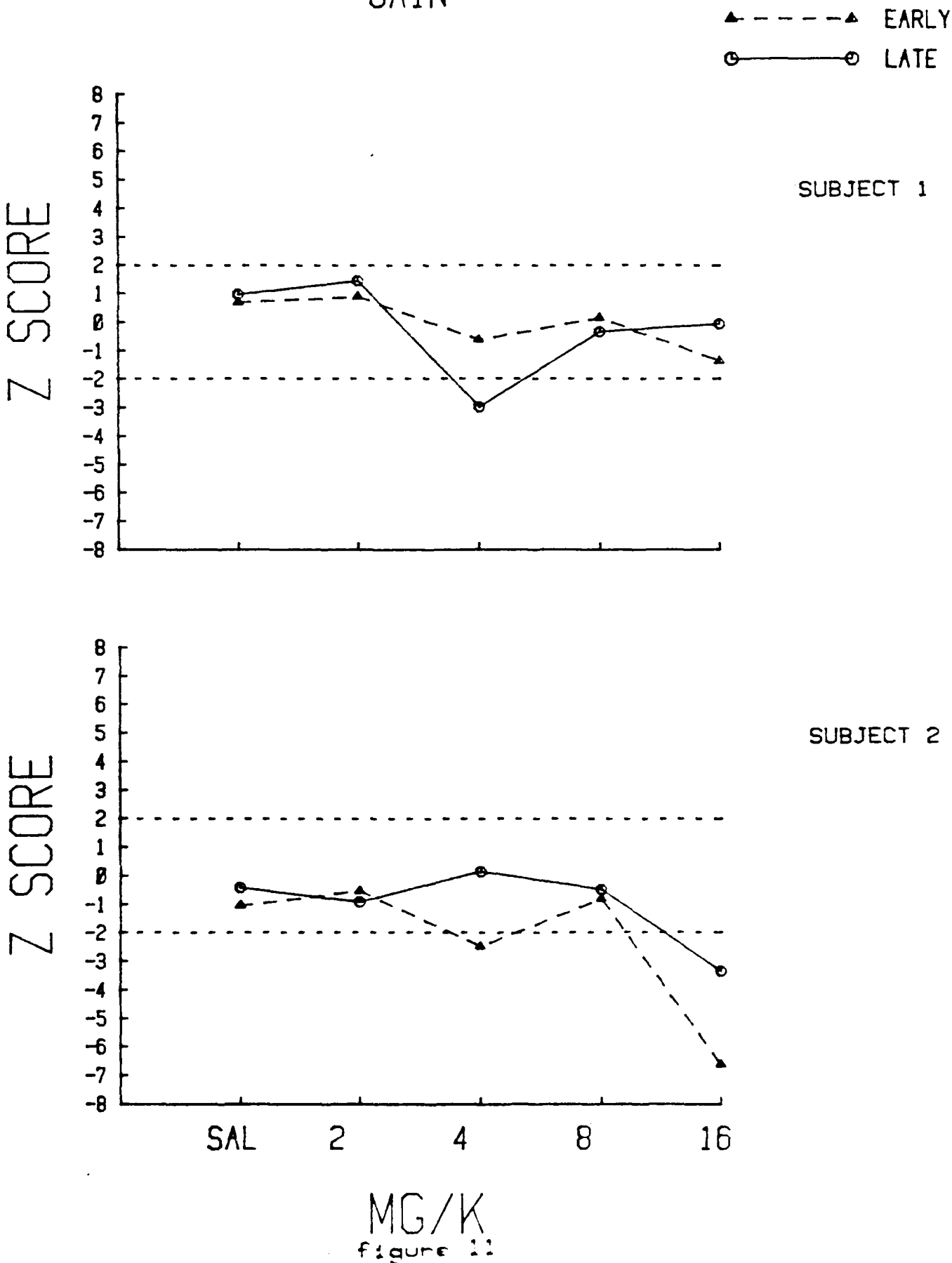


figure 11

PRALIDOXIME: TRACKING GAIN

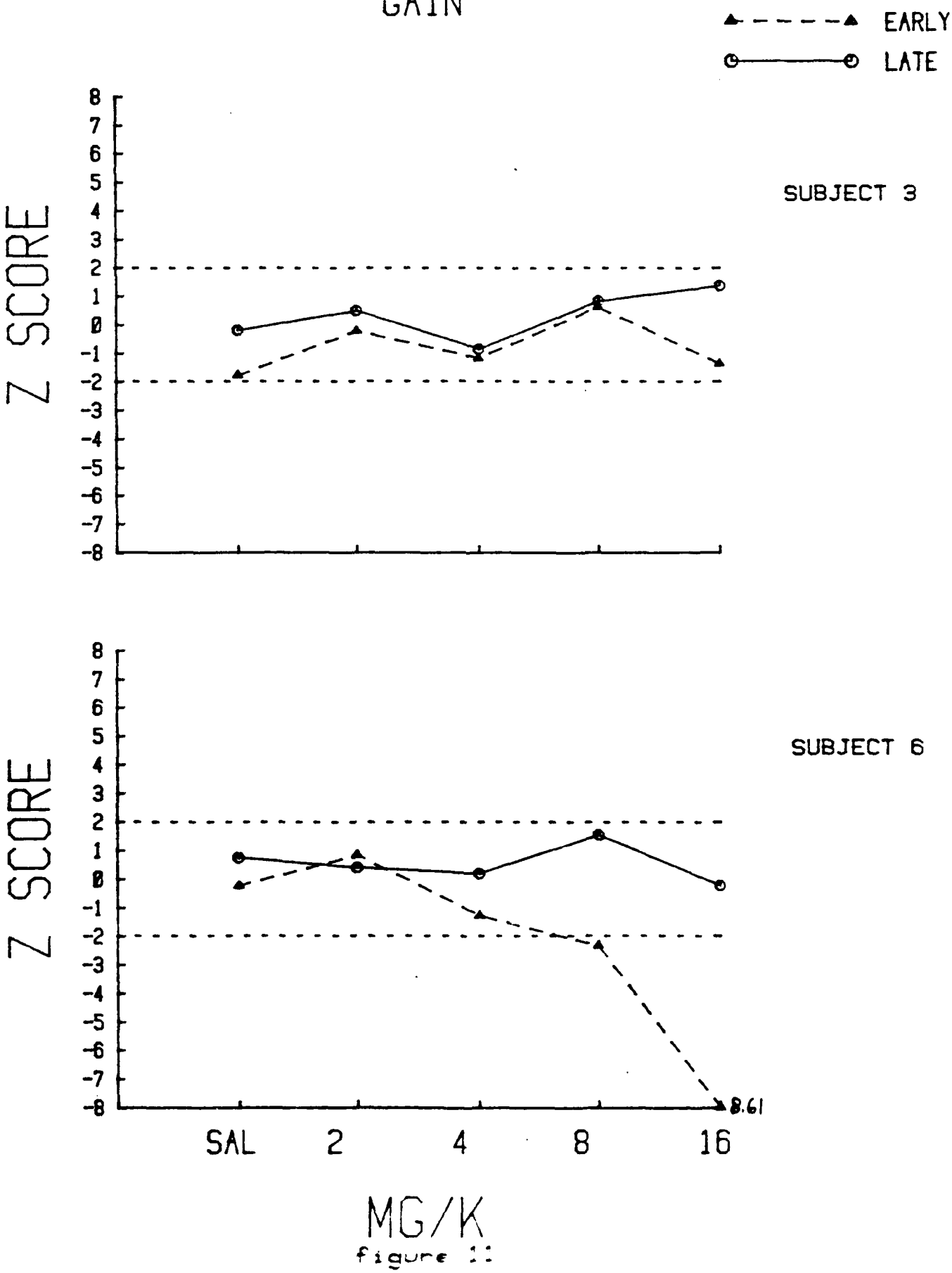


figure 11

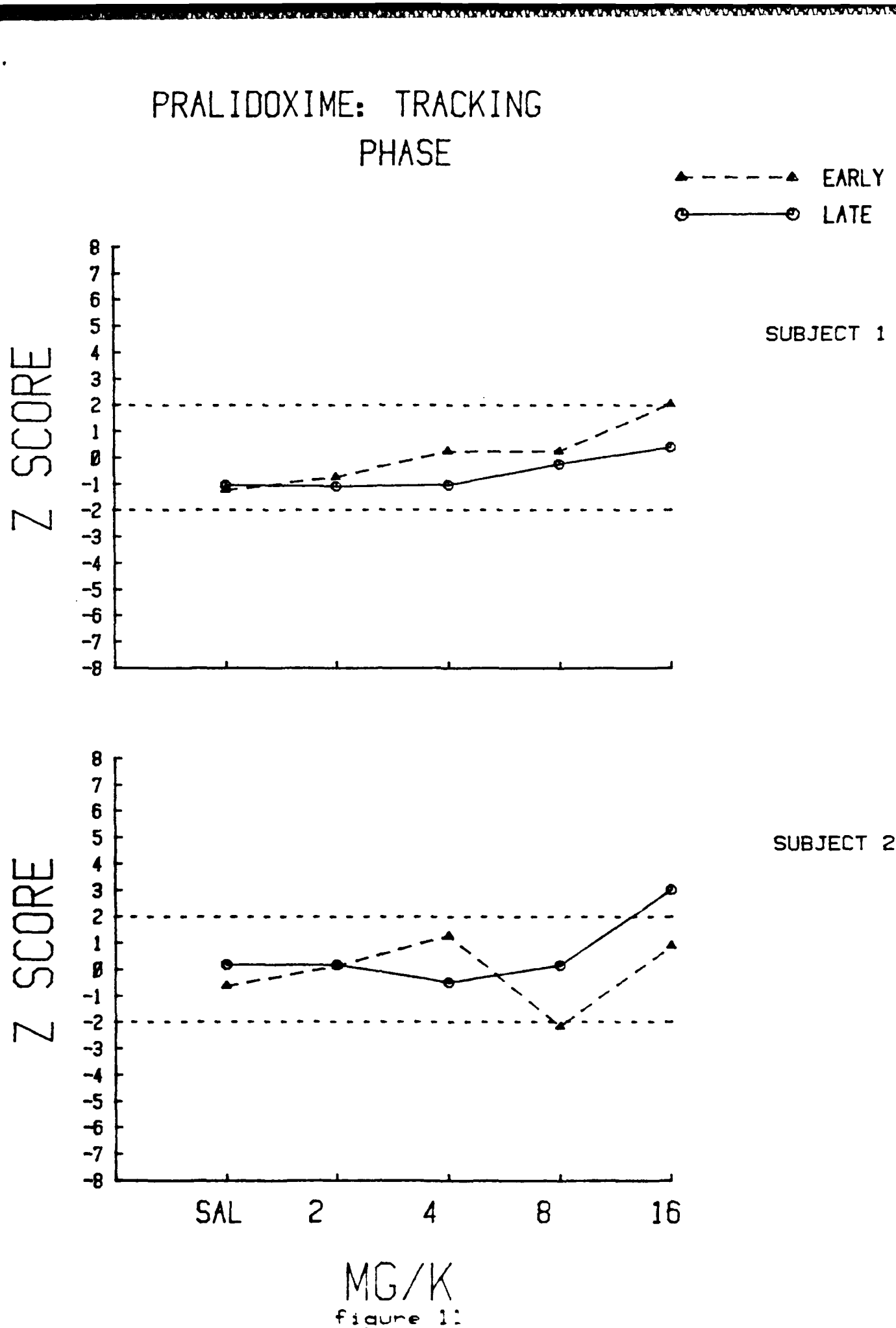

PRALIDOXIME: TRACKING
PHASE
EARLY
LATE
SUBJECT 1
SUBJECT 2
Z SCORE
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
SAL
2
4
8
16
MG/K

figure 1:

PRALIDOXIME: TRACKING PHASE

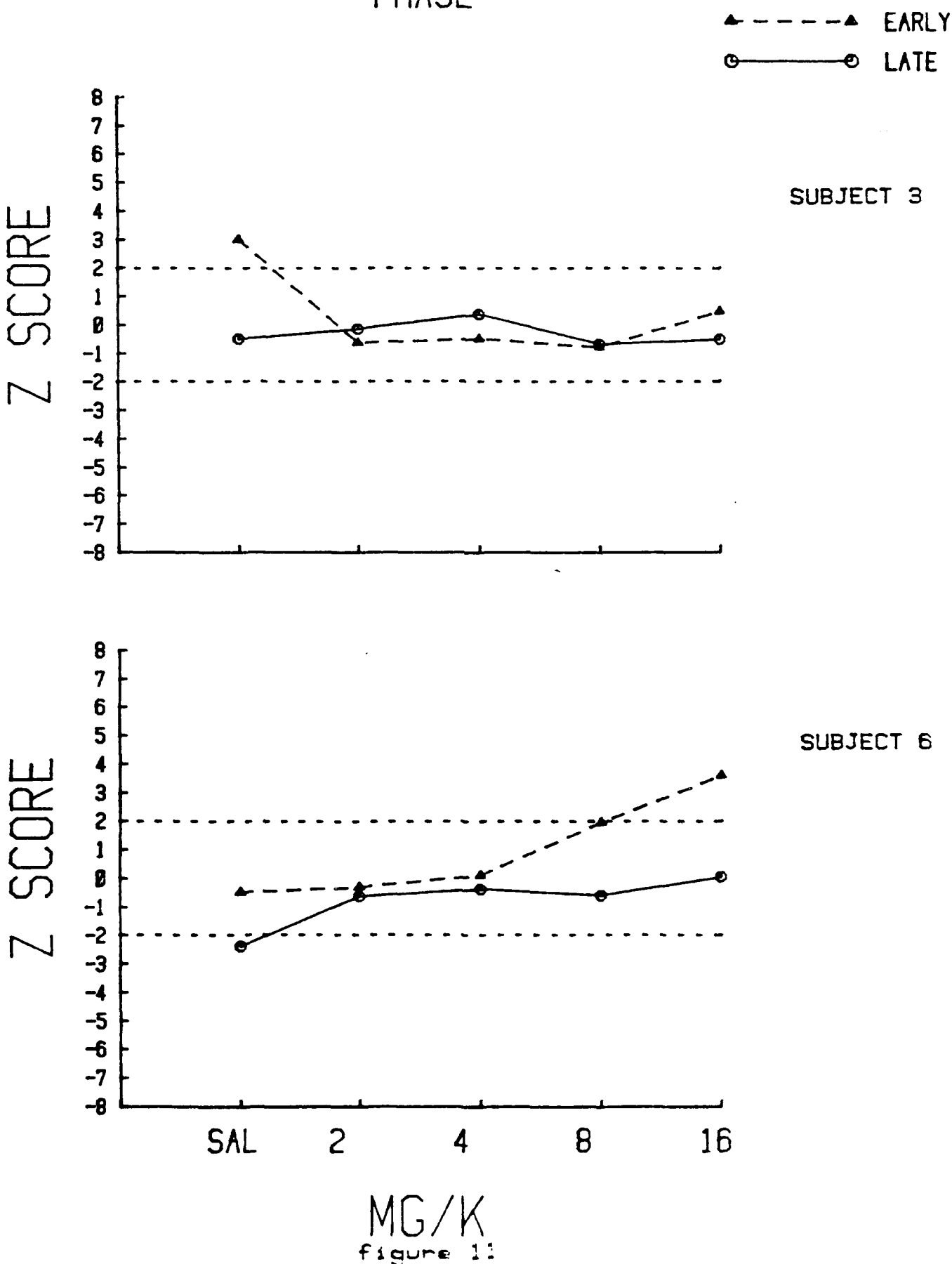


figure 11

PHYSOSTIGMINE

.025 mg/K

Neurological status: Normal, except that at every dose of this agent the monkeys made chewing noises indicative of a dry mouth.

Oculomotor: Normal

Visual Search: Normal

Target Tracking: Normal, but with borderline decrement in the phase of two subjects

.050 mg/K

Neurological status: The monkeys showed evidence of having dry mouths. One subject (3) appeared quite excited and fearful after injection. Otherwise the neurological status was normal.

Oculomotor: The polygraph record indicated occasional jitter when trying to hold a fixation point, increasing the microsaccadic corrections needed to hold the eye position. This was not a consistent finding and, in general, the eye movements seemed well-formed.

Visual Search: Performance remained competent. Borderline decrements in the success rate at finding targets appeared in one subject. An abnormal but slight increase in the time to find the target occurred in two subjects (2,3).

Target tracking: One of the four subjects had a substantial loss in the Gain of its performance (1), the other animals were normal on this measure. Phase was slightly increased in one subject.

0.075 mg/K

Neurological status: Normal, with no obvious muscle weakness, ptosis, vomiting, or pupillary signs. The monkeys appeared restless and made swallowing movements characteristic of animals experiencing a dry mouth.

Oculomotor: the polygraph record had obvious changes at this dose. Abnormalities were more obvious in the Early session and appeared as hypometric fixations that resulted in a stepwise progression of small saccadic jumps across the screen (figure 12). The fast, or saccadic component of the eye movement was less affected causing the eyes to overshoot and then fall-back to a hypometric fixation point.

Visual search: Consistent decrements in visual search appeared at this dose. Three of the four subjects had lower rates of success at finding the targets, and all four required more time to find them on successful trials. Many sessions occurred in which performance was within normal limits, however. The abnormalities were as equally likely to occur in the Early as in the Late session. The decrements do not appear to be motivational; the monkeys performed the test vigorously and without pause.

Target tracking: Real but inconsistent decrements occurred. Two subjects (1,2) had clear abnormalities in both the gain and phase of their tracking movements, the other two subjects appeared quite normal. In the abnormal pair, the decrements spanned the Early and Late sessions. The eye position records in figure 13 show the worst case of tracking performance. Tracking is considerably degraded from normal. Still, the monkey appears to be attempting to follow the target. Its better performance on the Predictable target indicates that the predictive component of pursuit is intact.

Table 12. Physostigmine. "Worst case" Session scores on Visual Search. Subject 3; Dose: .075 mg/K; Session: Early

	Baseline Avg./Std		Drug Avg.
Percent of targets fixated	98.4	1.4	88.9
ON SUCCESSFUL TRIALS:			
Time required to fixate target (msec)	271	15	336
Number of fixations to find target	1.07	0.05	1.11

Table 13. Physostigmine. "Worst case" Session scores on Target Tracking. Subject 2; Dose: .075 mg/K; Session: Late

	Baseline Avg./Std		Drug Avg.
Gain	0.60	0.07	0.28
Phase (Lag in msec)	34	4	99

Physostigmine

Eye Position During Search

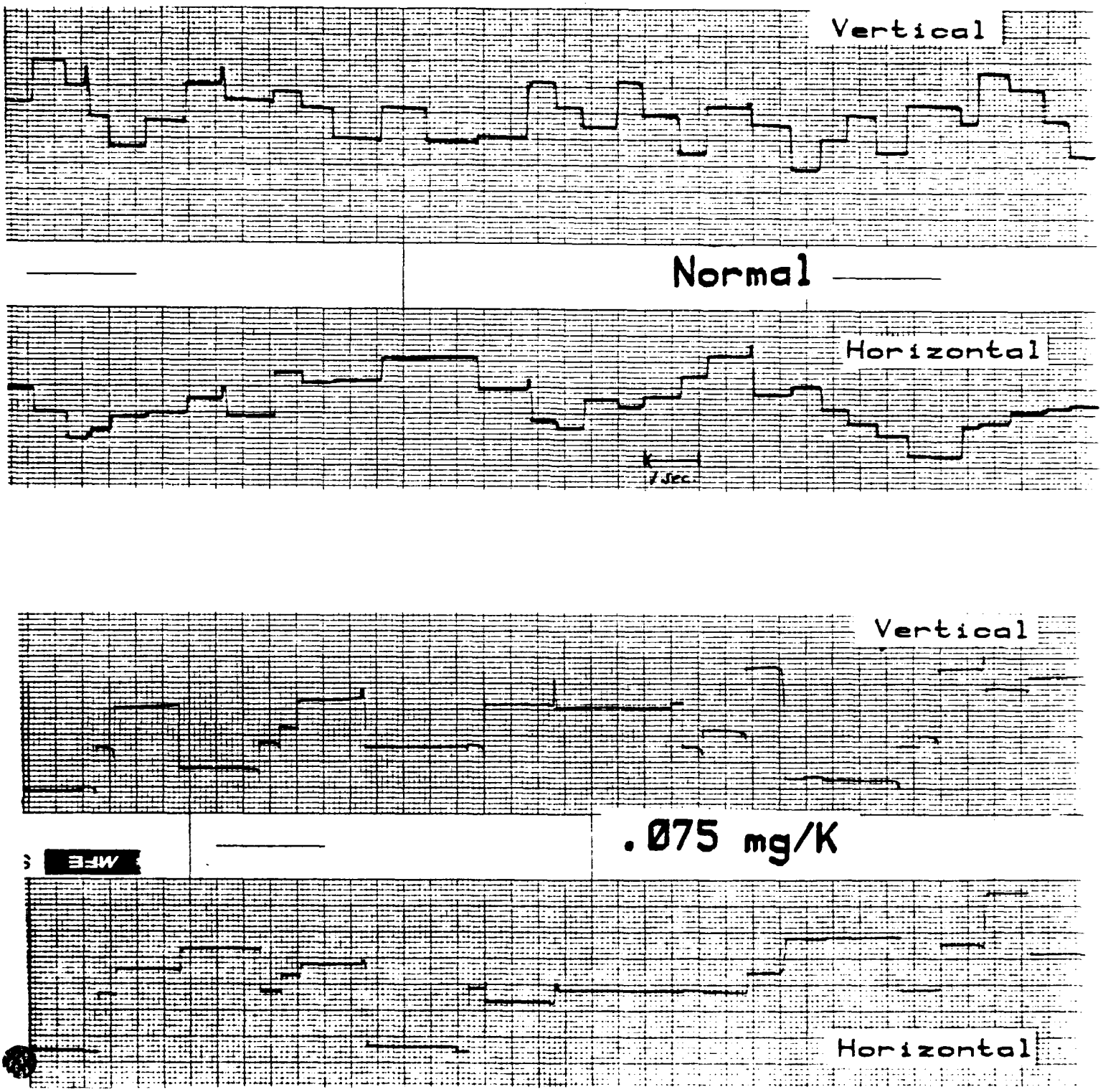


figure 12

Physostigmine
Eye Position During Tracking

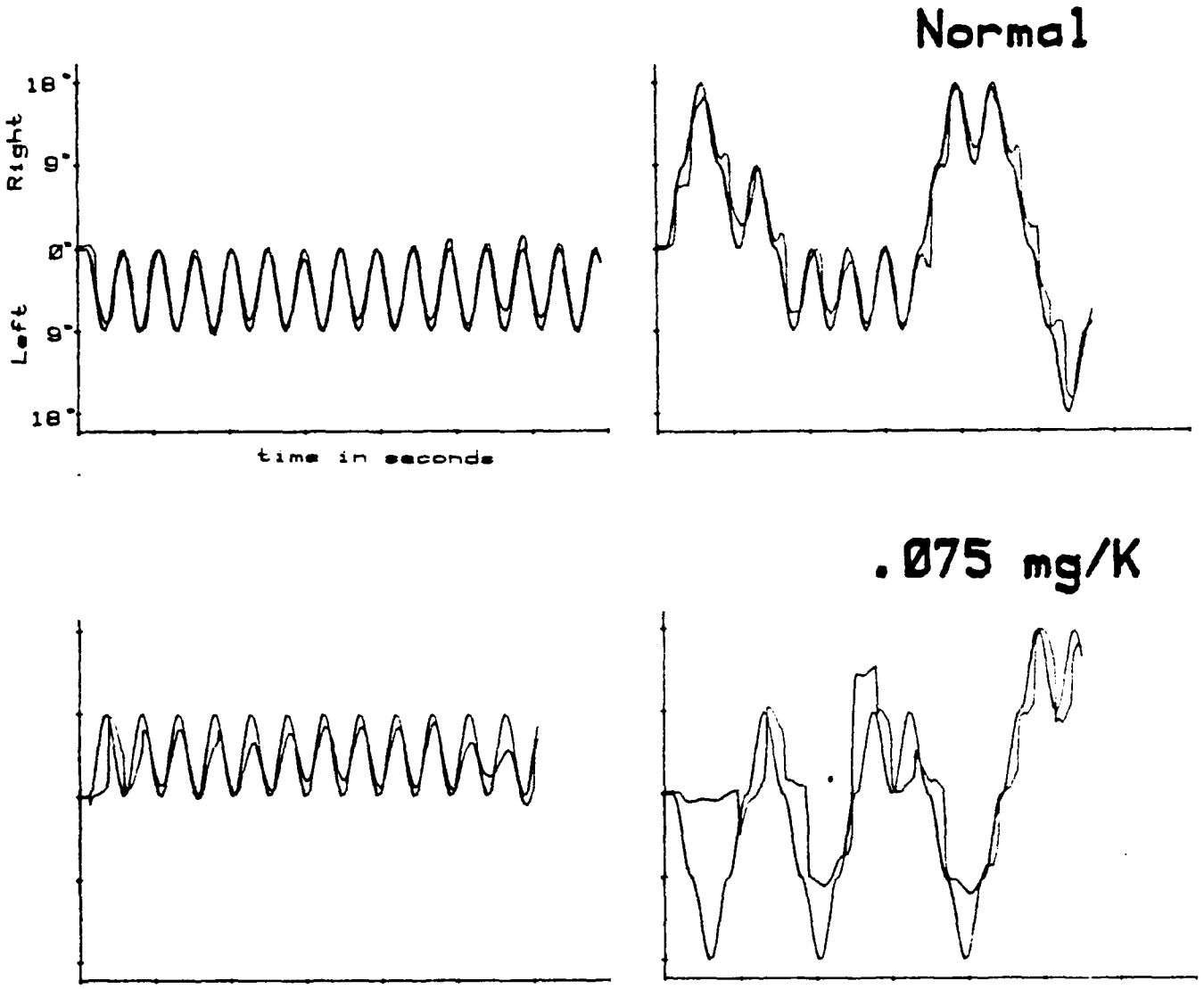


figure 13

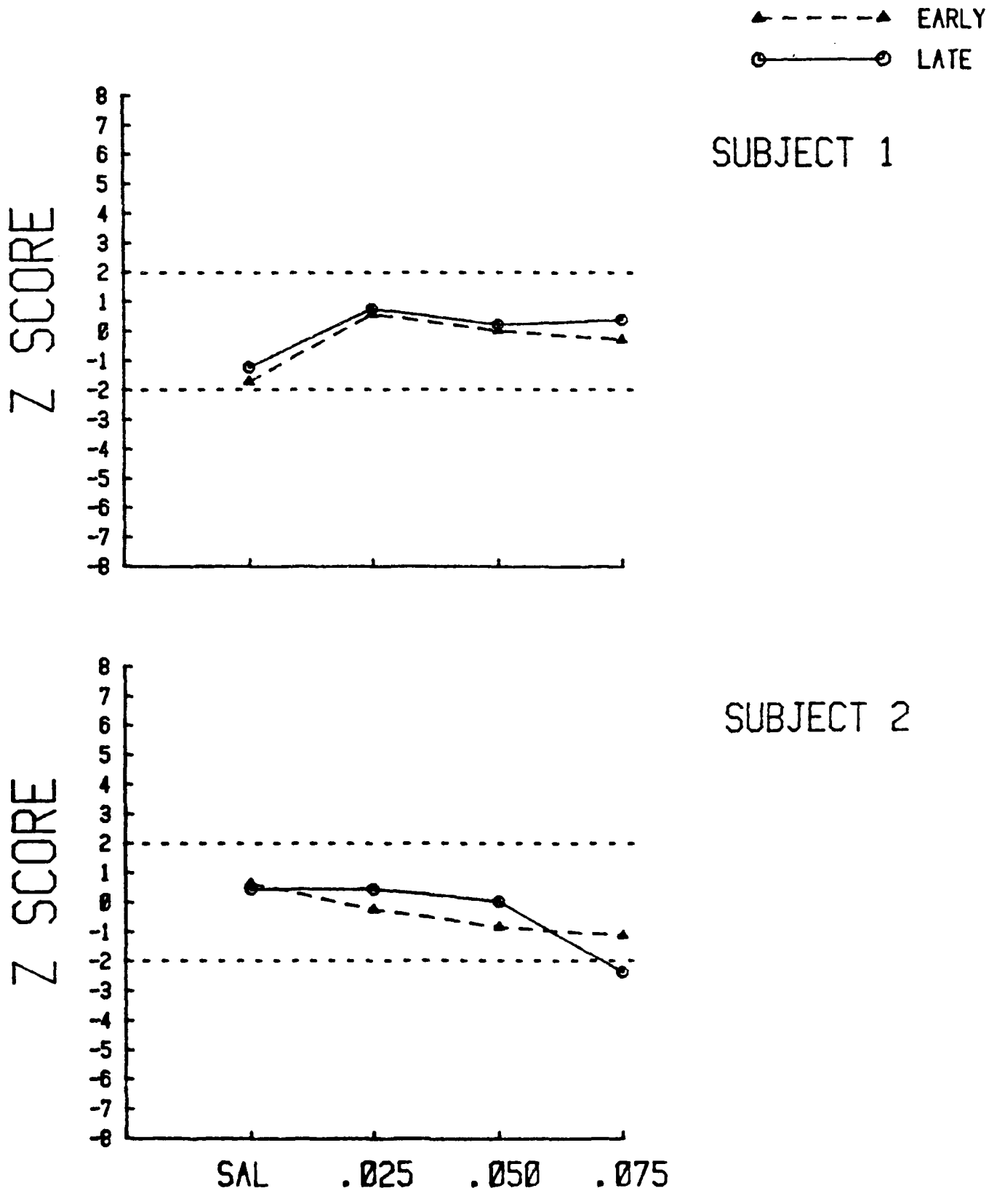

PHYSOSTIGMINE
PERCENT OF TARGETS FIXATED
EARLY
LATE
SUBJECT 1
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
SUBJECT 2
Z SCORE
SAL
.025
.050
.075

figure 14

PHYSOSTIGMINE
PERCENT OF TARGETS FIXATED

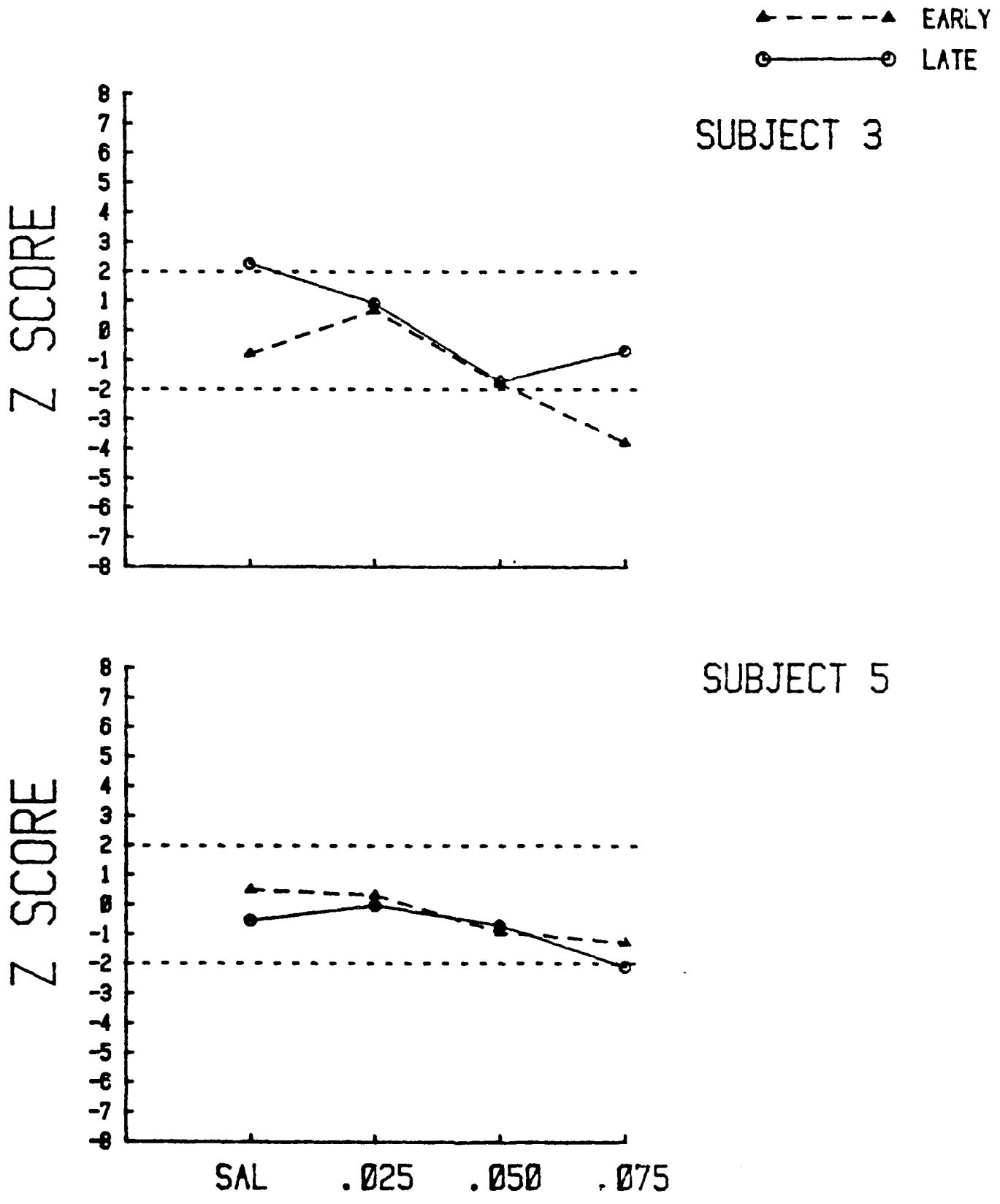


figure 14

PHYSOSTIGMINE
TIME TO FIXATE TARGET

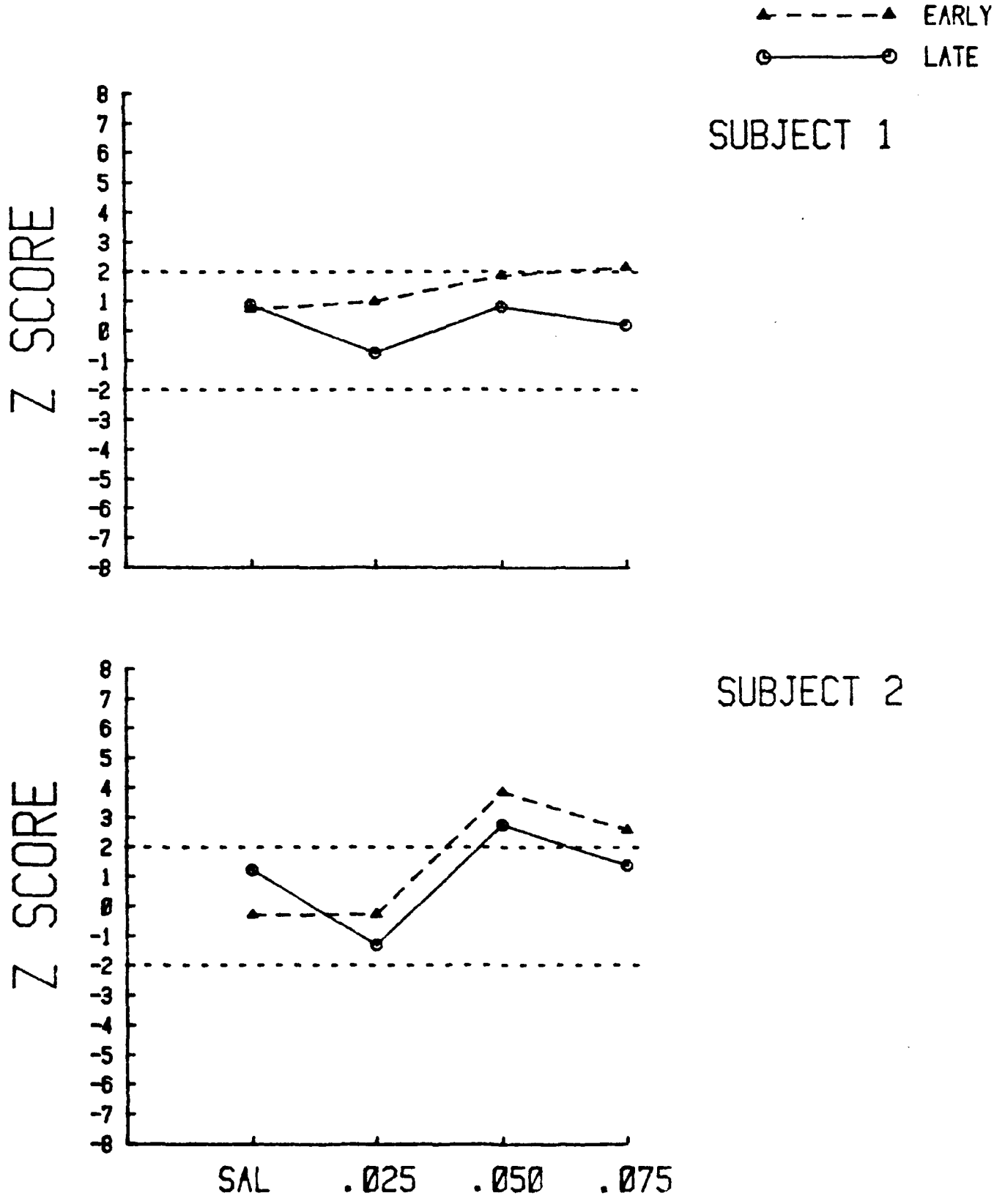


figure 14

PHYSOSTIGMINE
TIME TO FIXATE TARGET

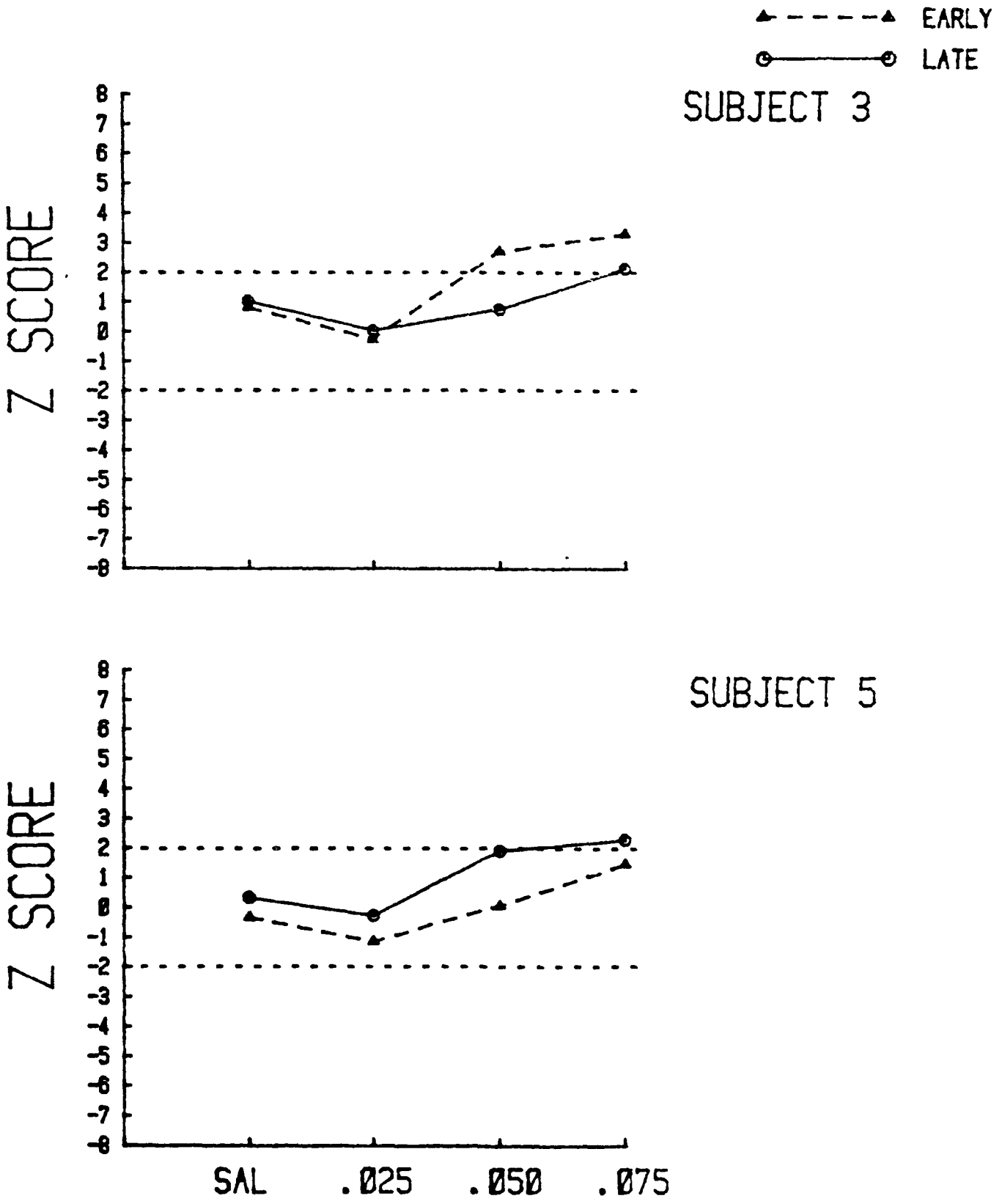


figure 14

PHYSOSTIGMINE
NUMBER OF FIXATIONS TO FIND TARGET

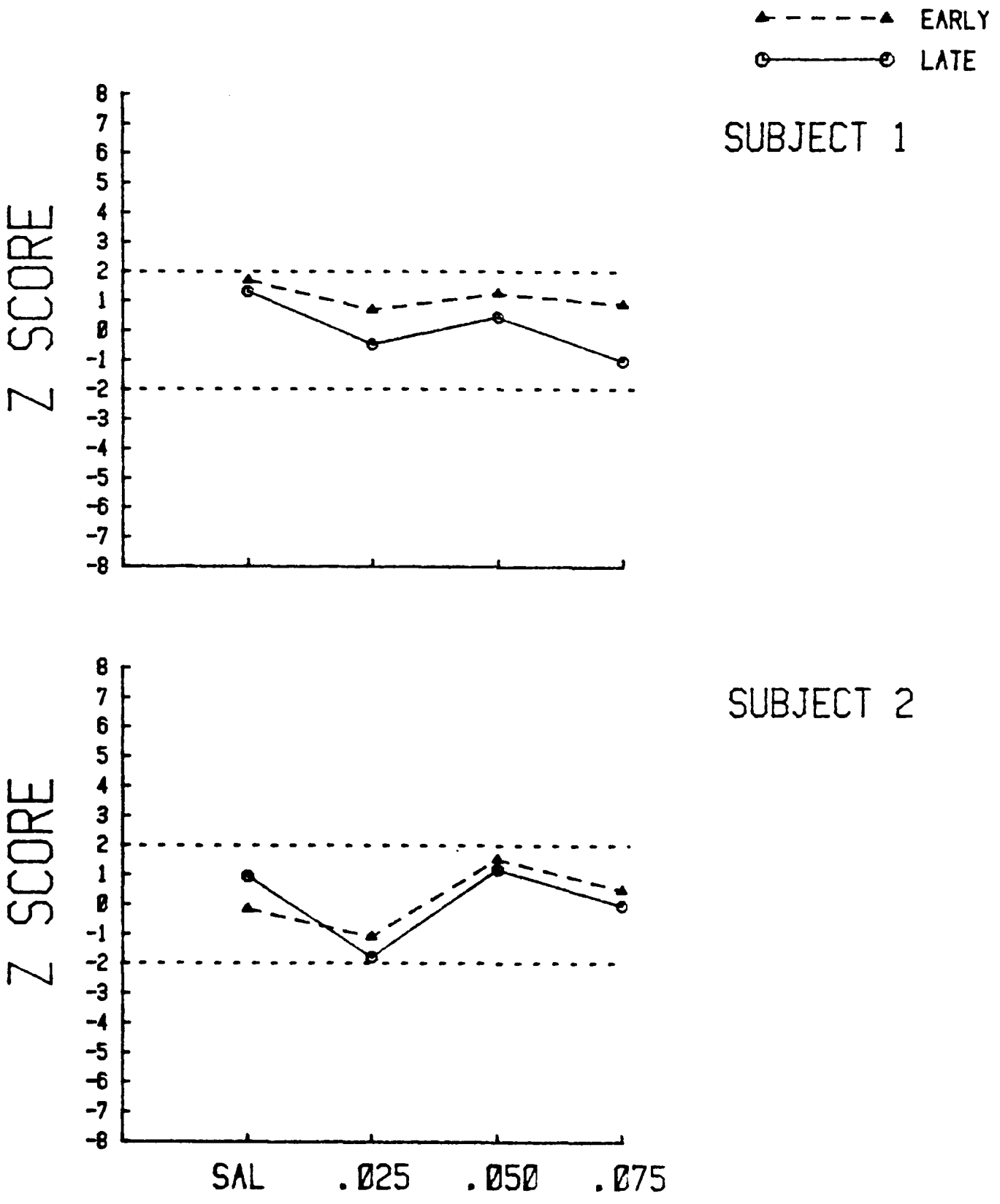


figure 14

PHYSOSTIGMINE
NUMBER OF FIXATIONS TO FIND TARGET

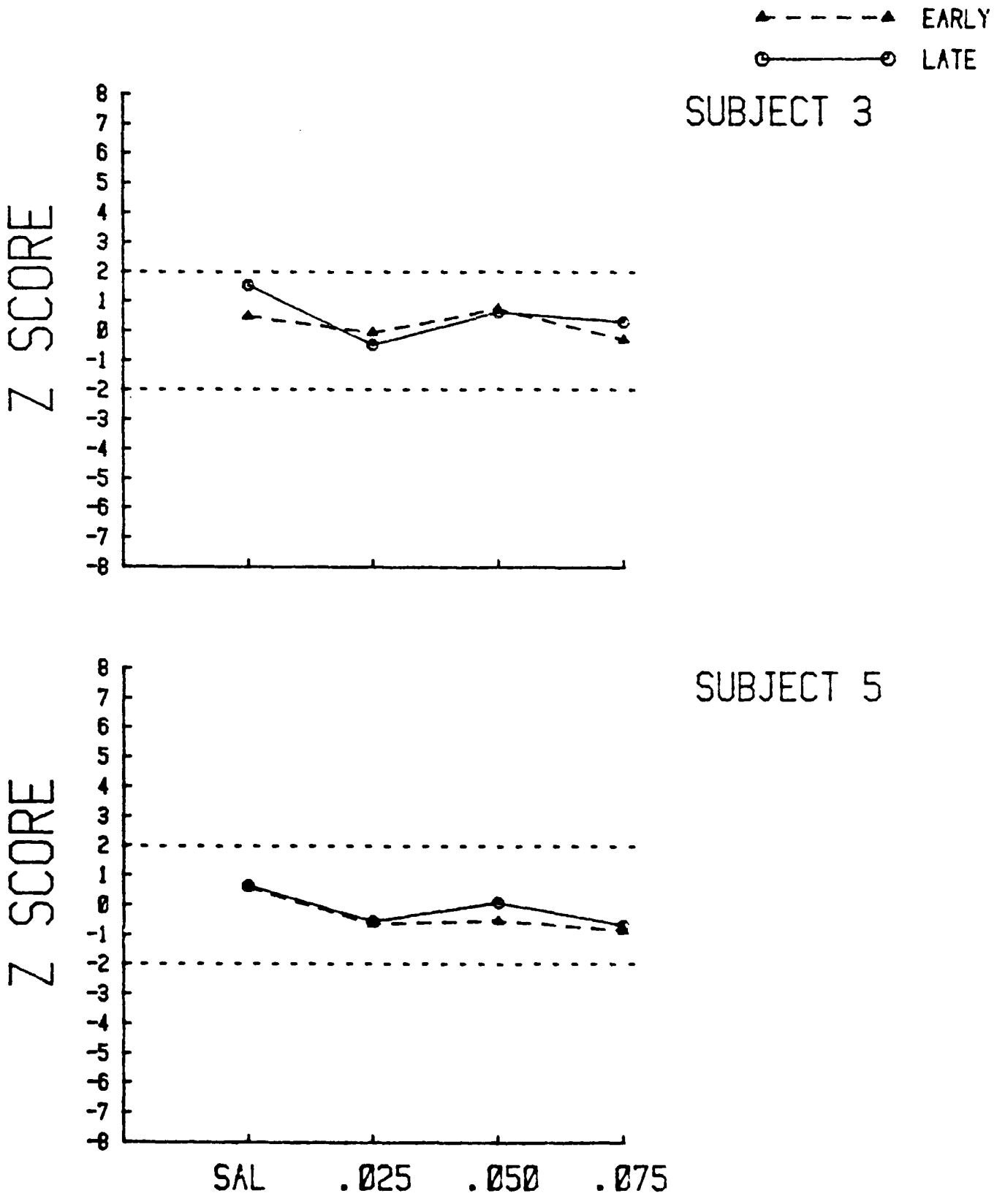


figure 14

PHYSOSTIGMINE: TRACKING GAIN

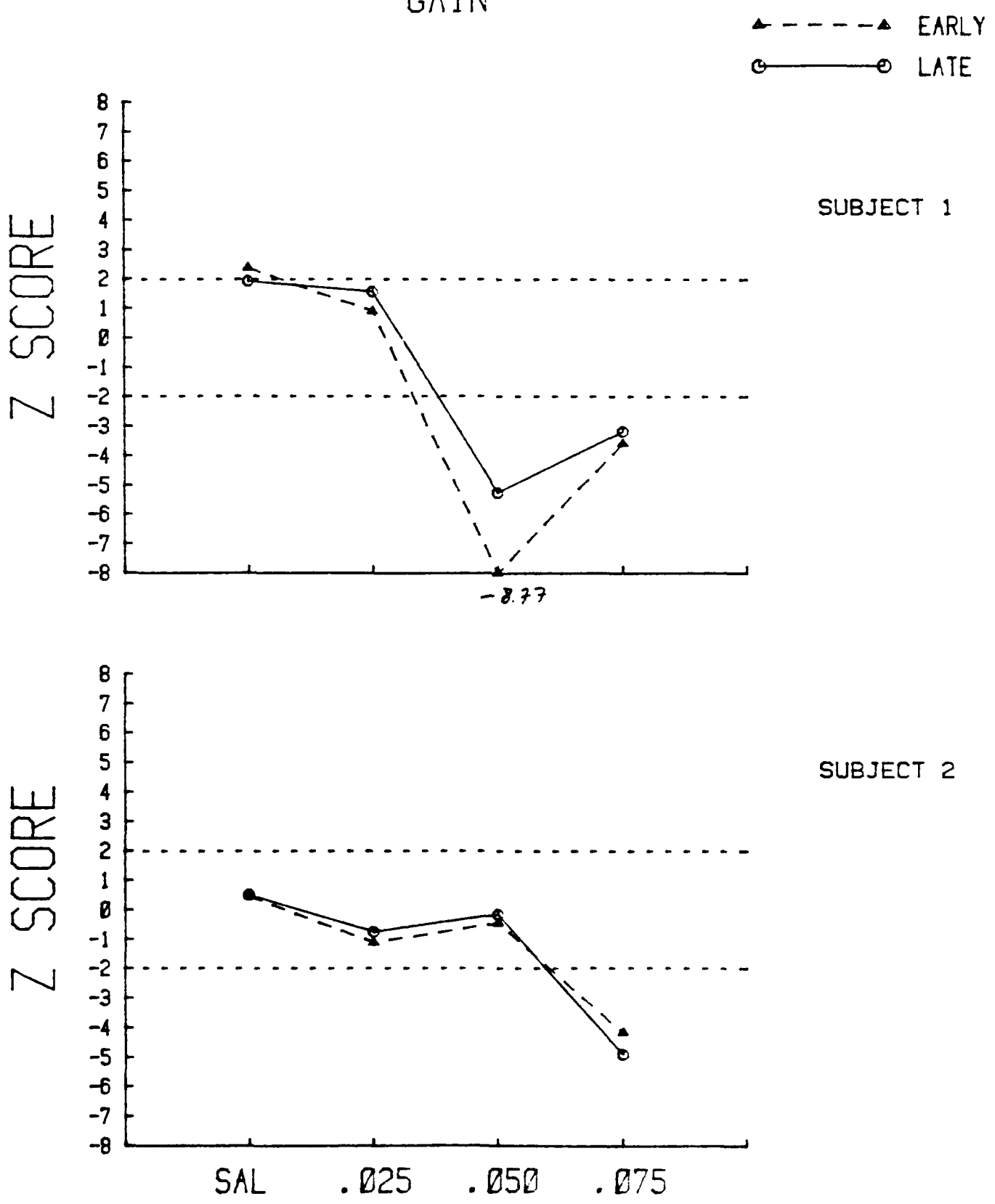


figure 15

PHYSOSTIGMINE: TRACKING GAIN

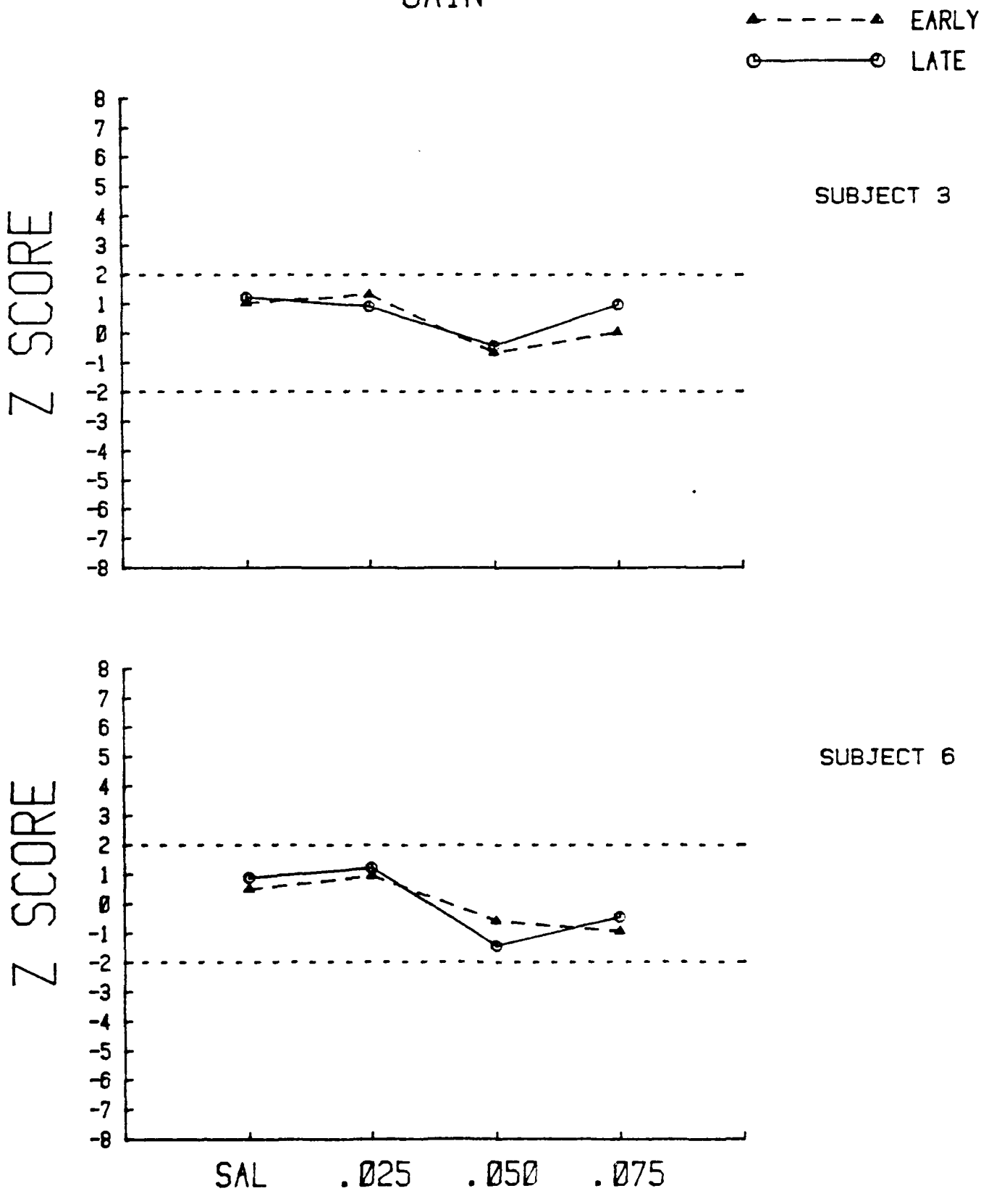


figure 15

PHYSOSTIGMINE: TRACKING PHASE

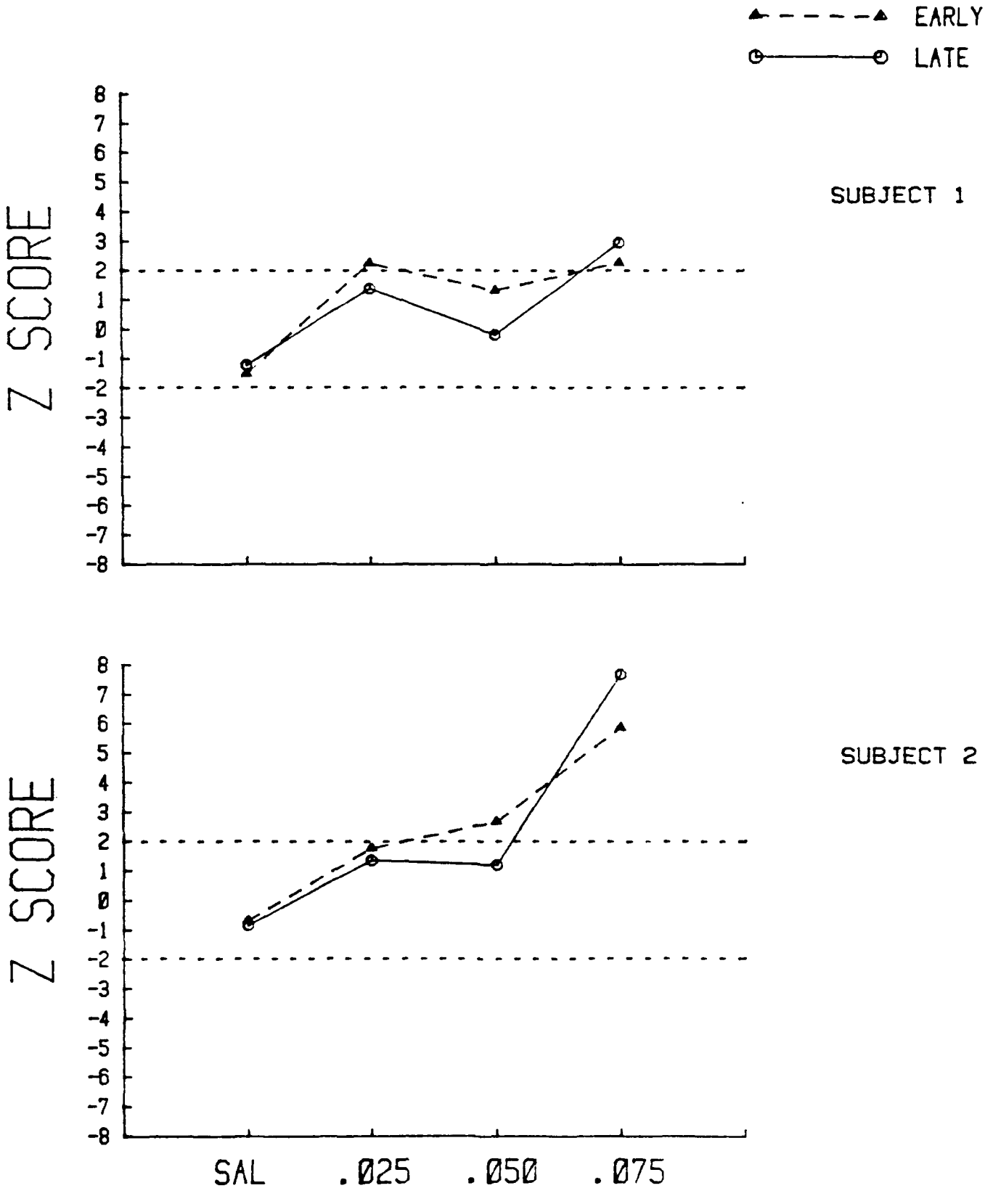


figure 15

PHYSOSTIGMINE: TRACKING PHASE

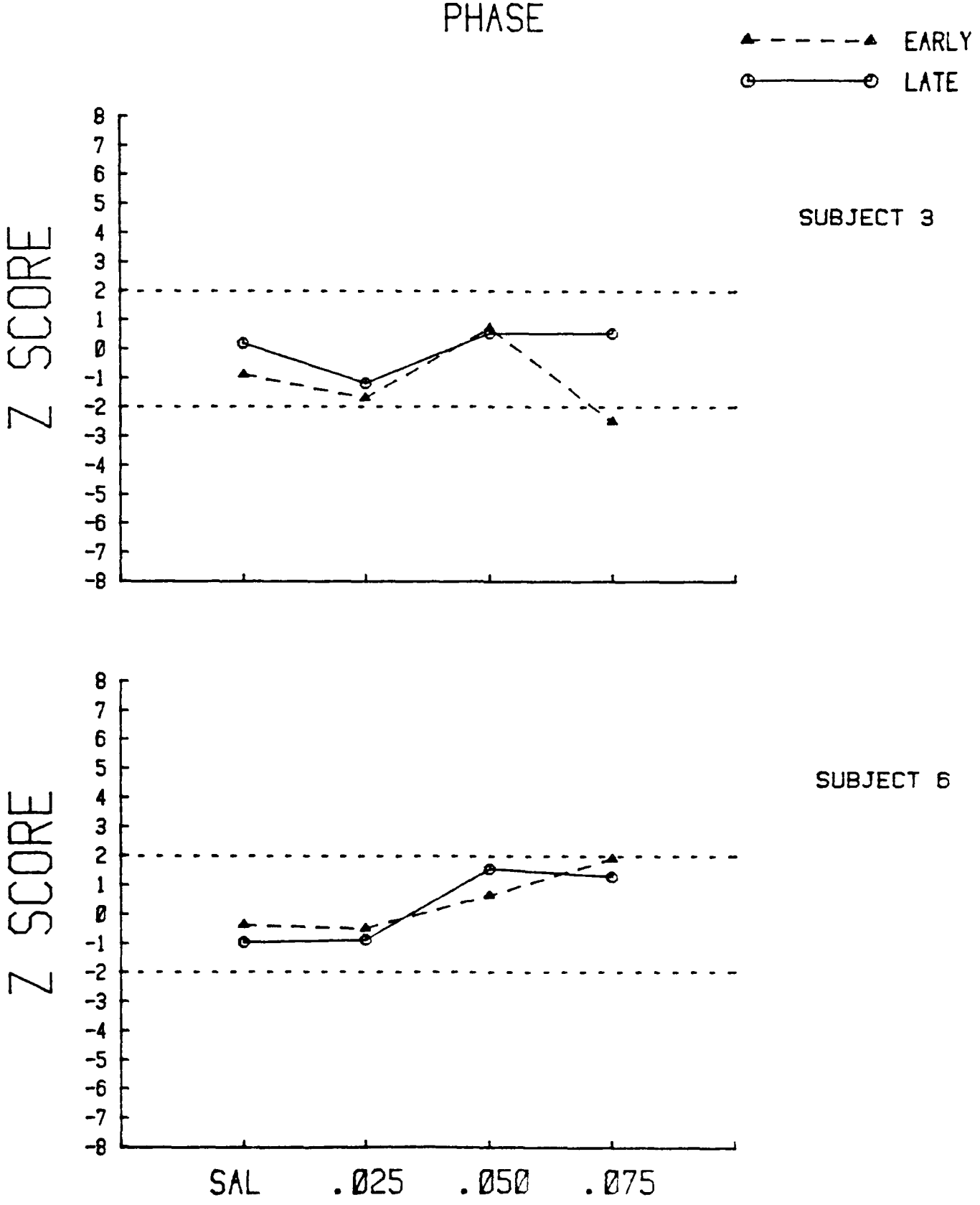


figure 15

PYRIDOSTIGMINE

The protocol for this agent differed from that of the other drugs. It called for the chronic administration of 7 mg/K of pyridostigmine to be given orally twice daily (embedded in a banana) over a period of 14 days. The banana was given without the drug for the following 14 days. Performance on Visual Search was collected periodically during these two weeks and compared to baseline sessions collected before and after the drug period. The data were expressed as Z scores as with previous agents (figure 18). The abscissa of the graphs was changed for the later Target Tracking trials. Instead of Z scores of relative performance they plot actual daily scores of the testing session collected during and after the 14 day period of the drug trial (figure 19).

RESULTS- Pyridostigmine was without observable effect. The monkeys appeared quite normal neurologically. Their performance on both the Visual Search and Tracking tasks remained normal.

During the early portion of the drug period subject 3 showed a slight elevation of its Phase (increased lag). This is an isolated and unconvincing decrement, especially since it returned to baseline while the drug trial progressed.

Pyridostigmine

Eye Position During Search

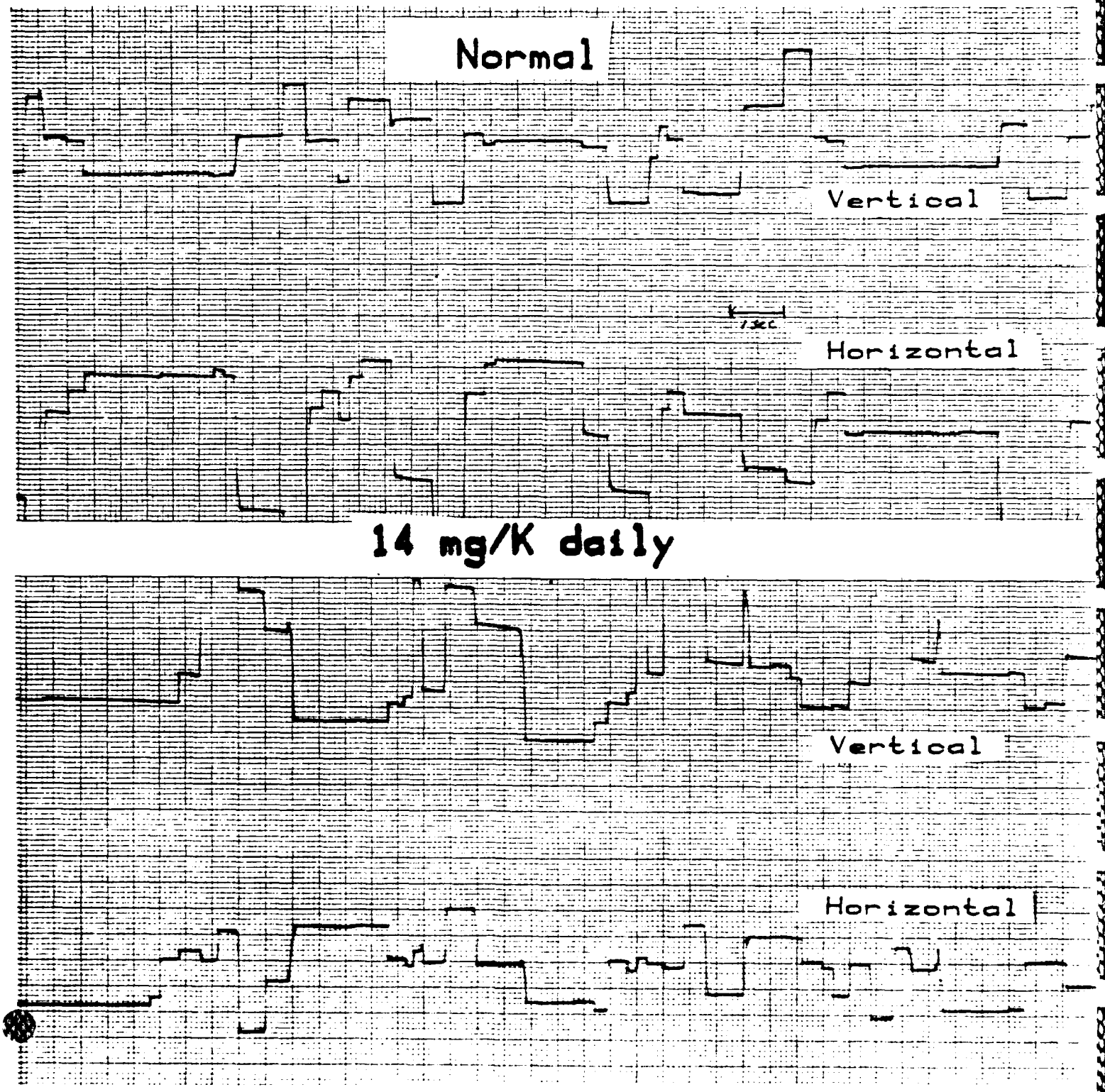
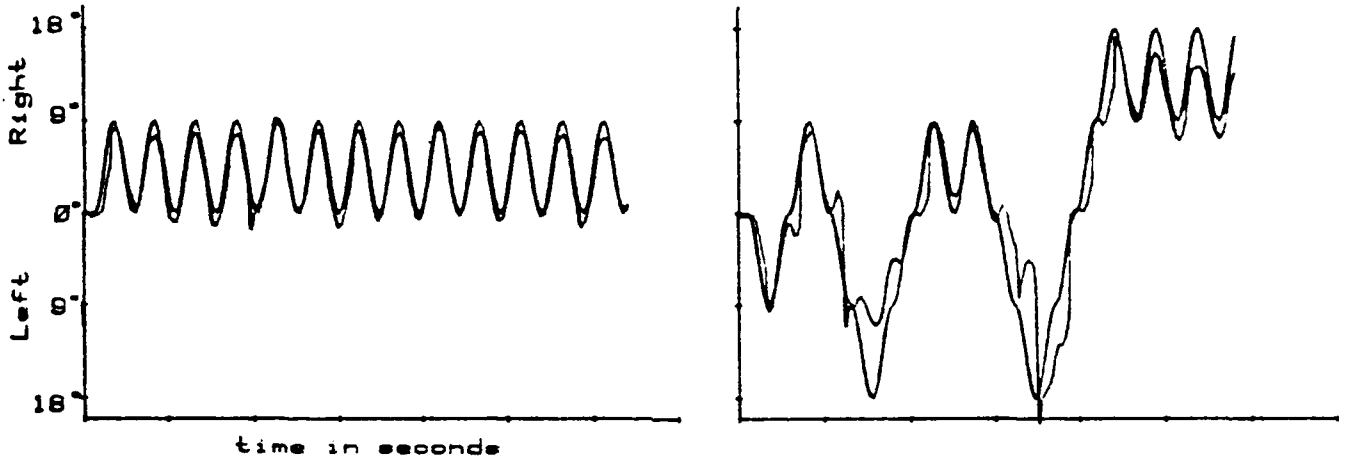


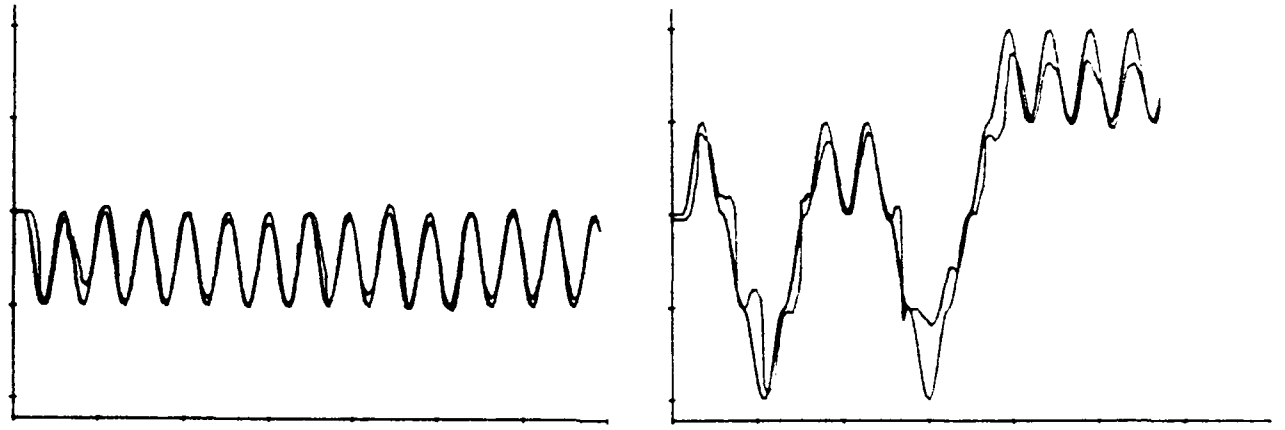
Figure 18

Pyridostigmine
Eye Position During Tracking

Normal



14 mg/K daily

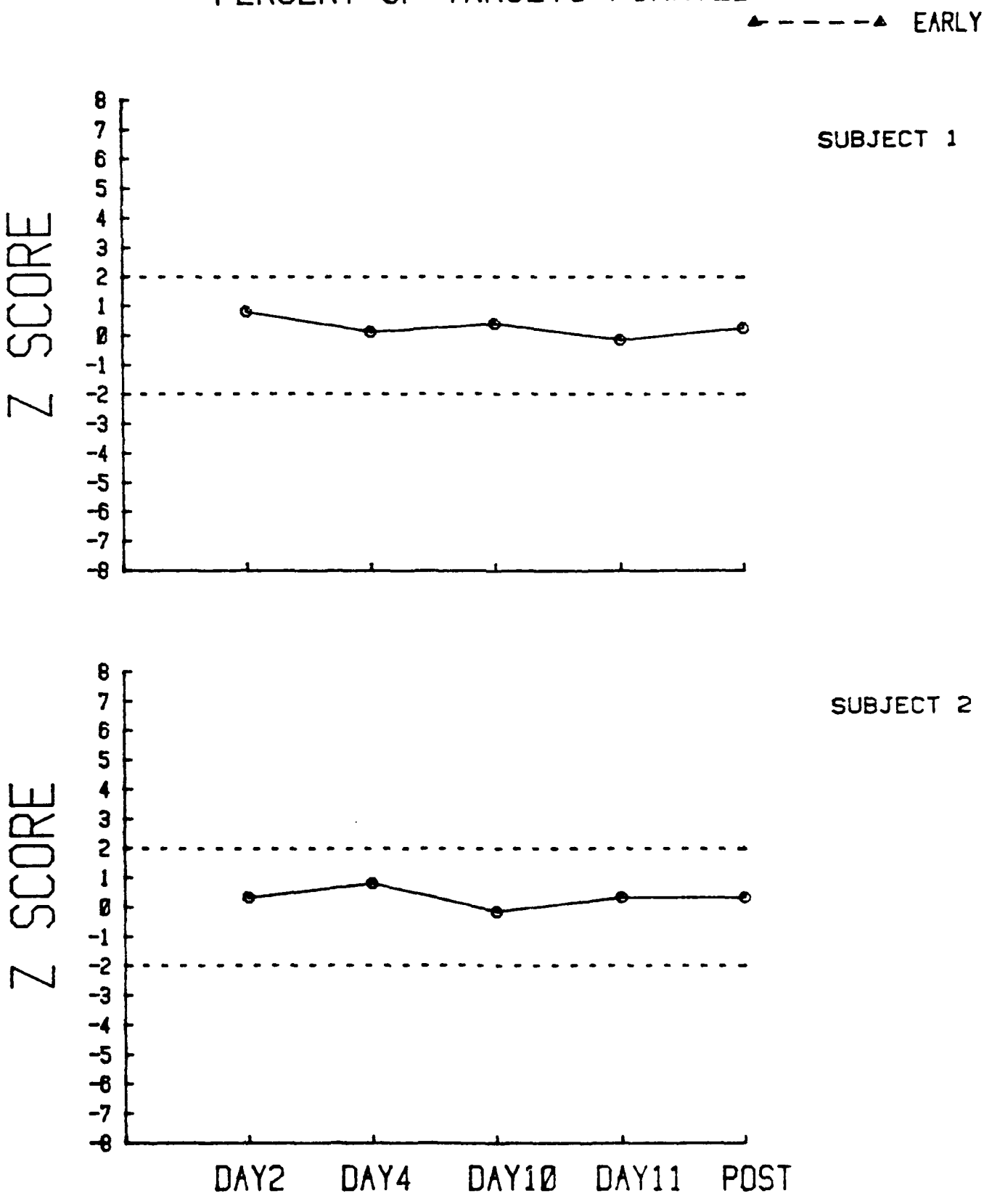


Predictable

Unpredictable

figure 17

PYRIDOSTIGMINE - VISUAL SEARCH
PERCENT OF TARGETS FIXATED



MG/K

figure 18

PYRIDOSTIGMINE - VISUAL SEARCH
PERCENT OF TARGETS FIXATED

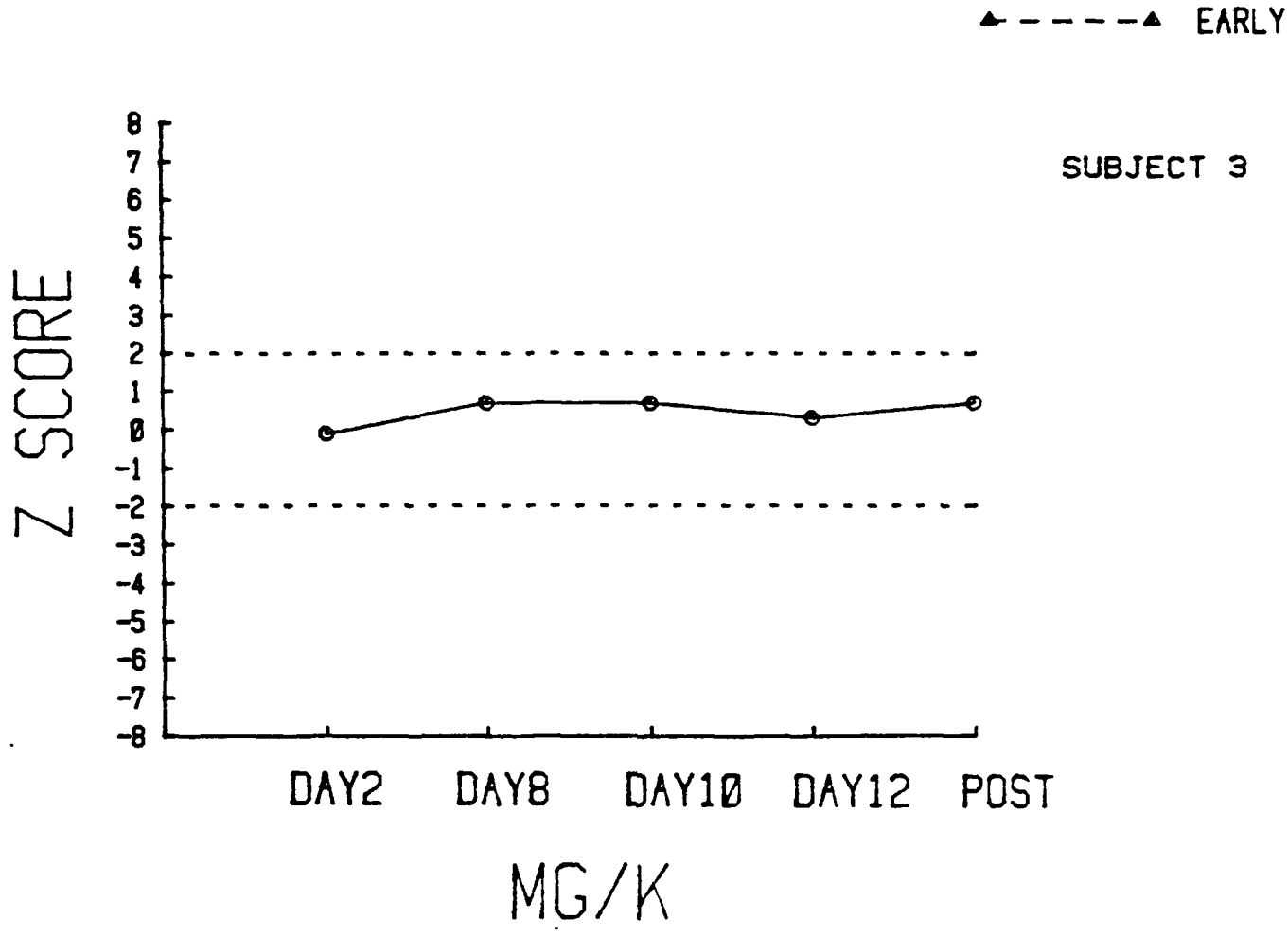
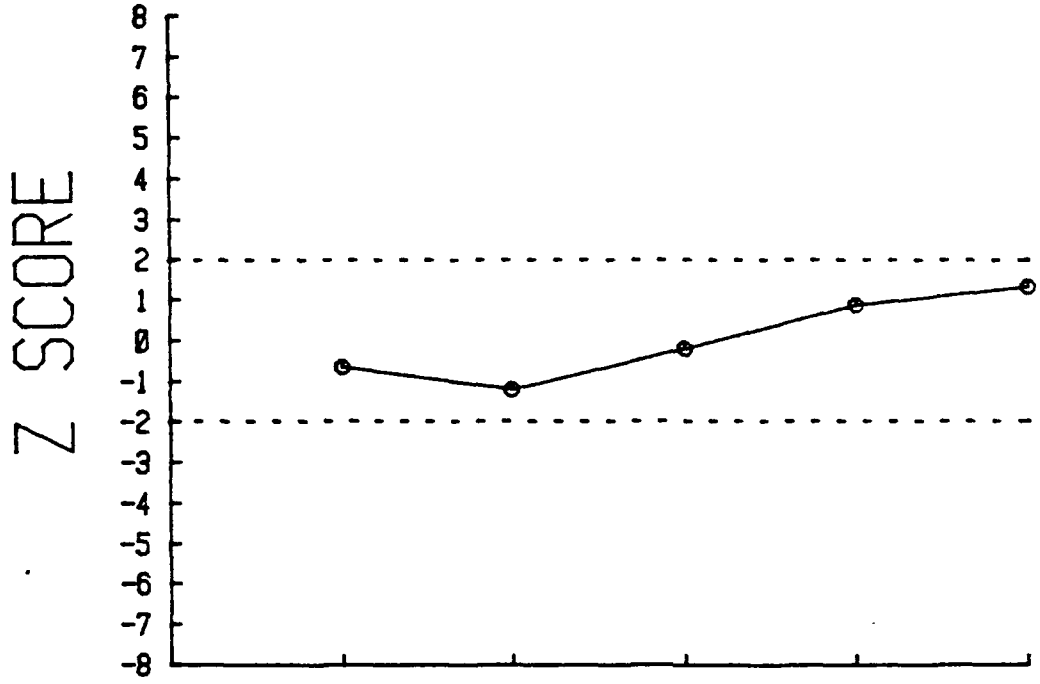


figure 18

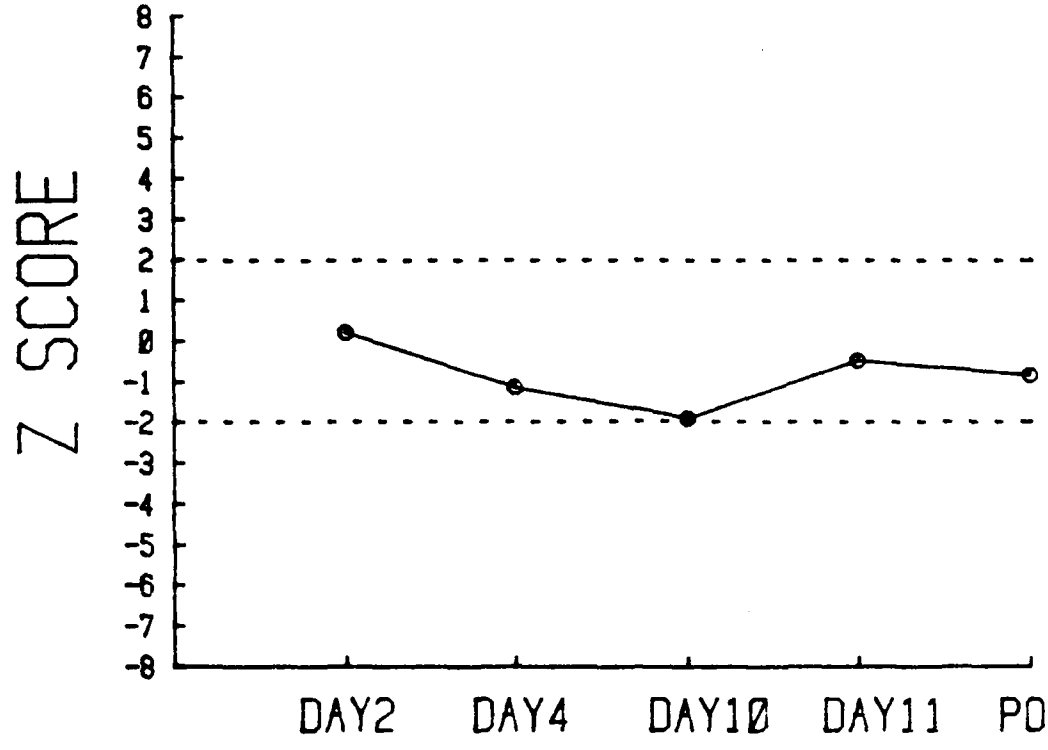
PYRIDOSTIGMINE - VISUAL SEARCH
TIME TO FIND TARGET

▲- - - - -▲ EARLY

SUBJECT 1



SUBJECT 2



MG/K

figure 18

PYRIDOSTIGMINE - VISUAL SEARCH
TIME TO FIND TARGET

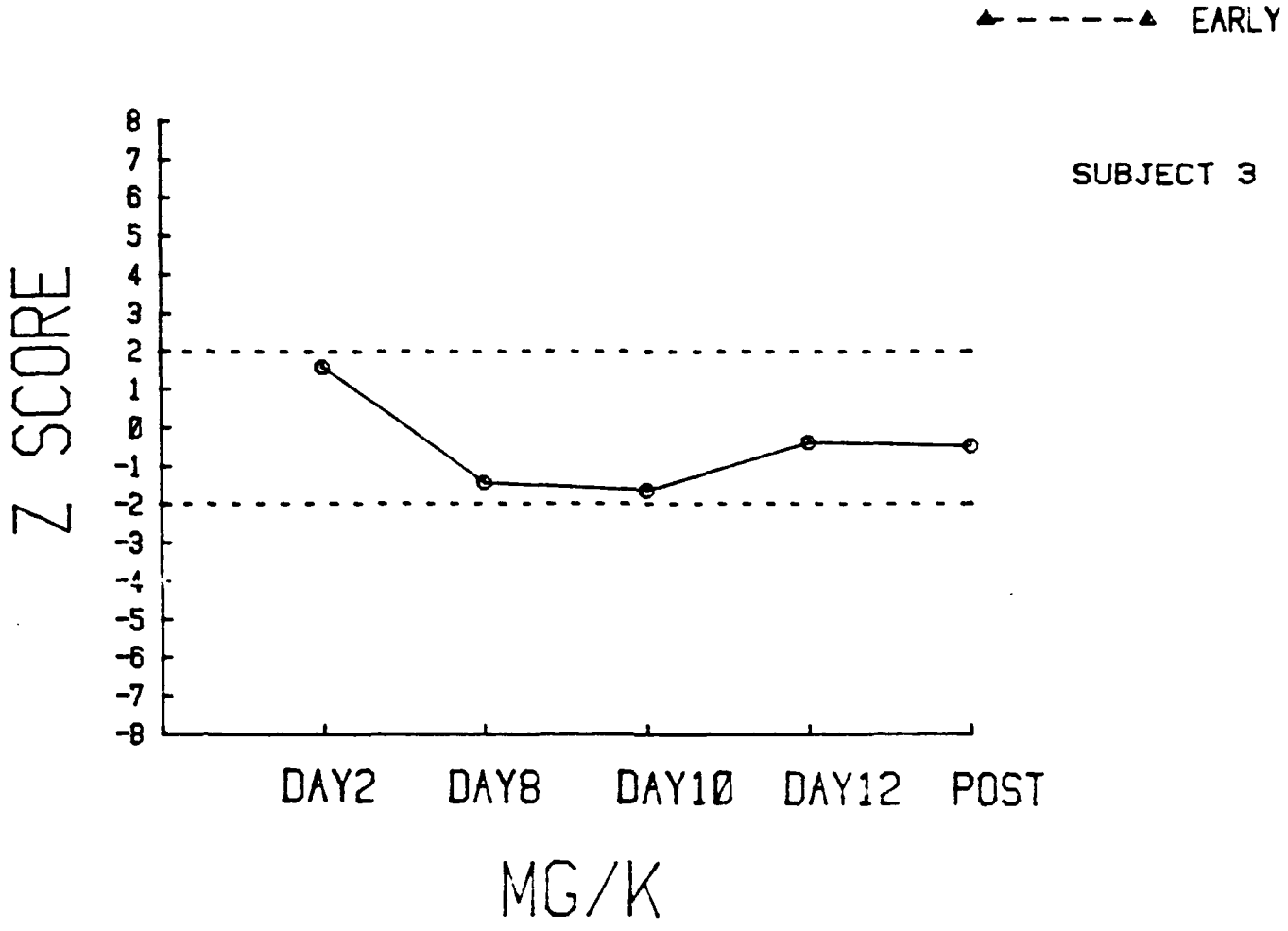


figure 18

PYRIDOSTIGMINE - VISUAL SEARCH
NUMBER OF FIXATIONS TO FIND TARGET

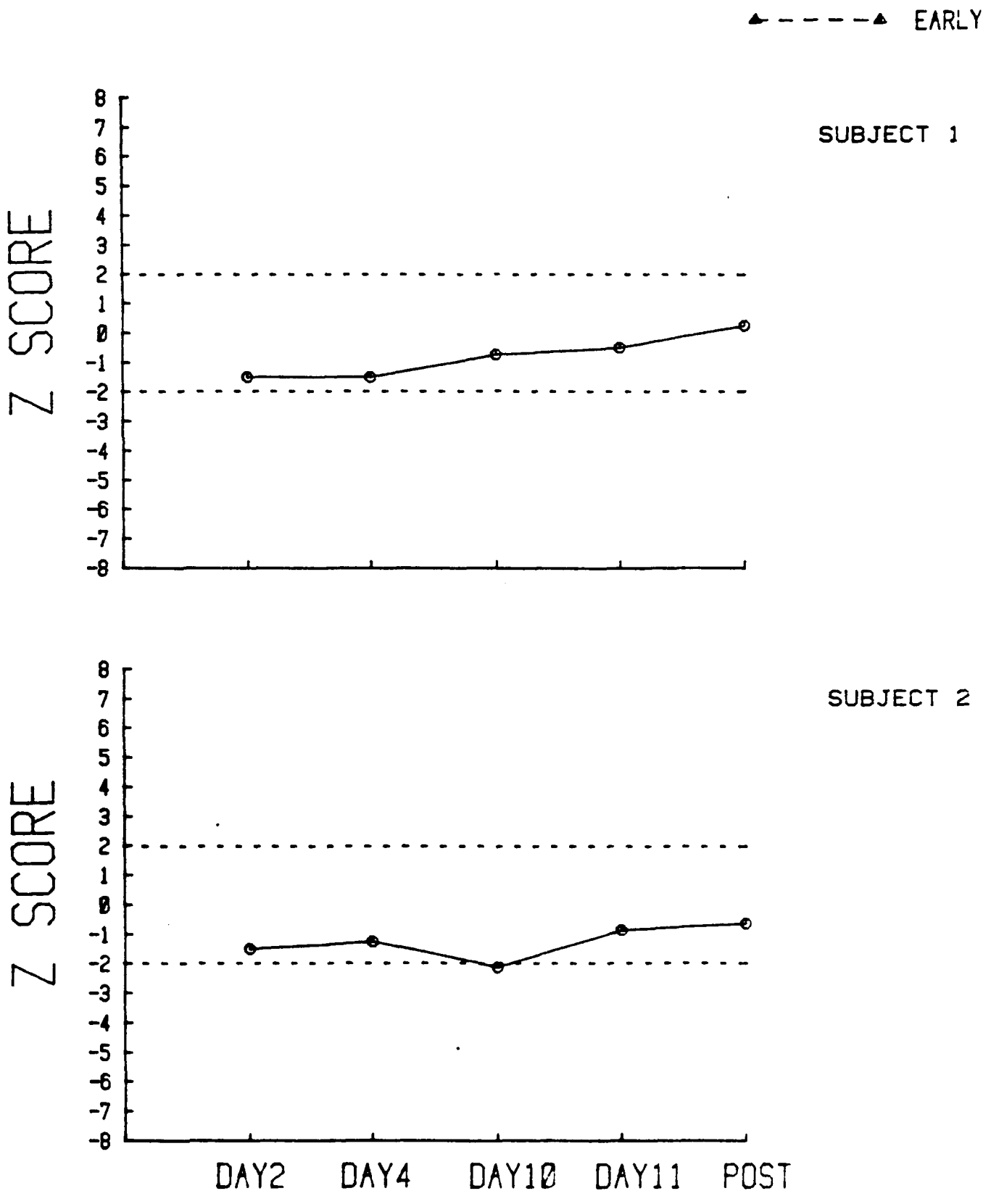


figure 18

PYRIDOSTIGMINE - VISUAL SEARCH
NUMBER OF FIXATIONS TO FIND TARGET

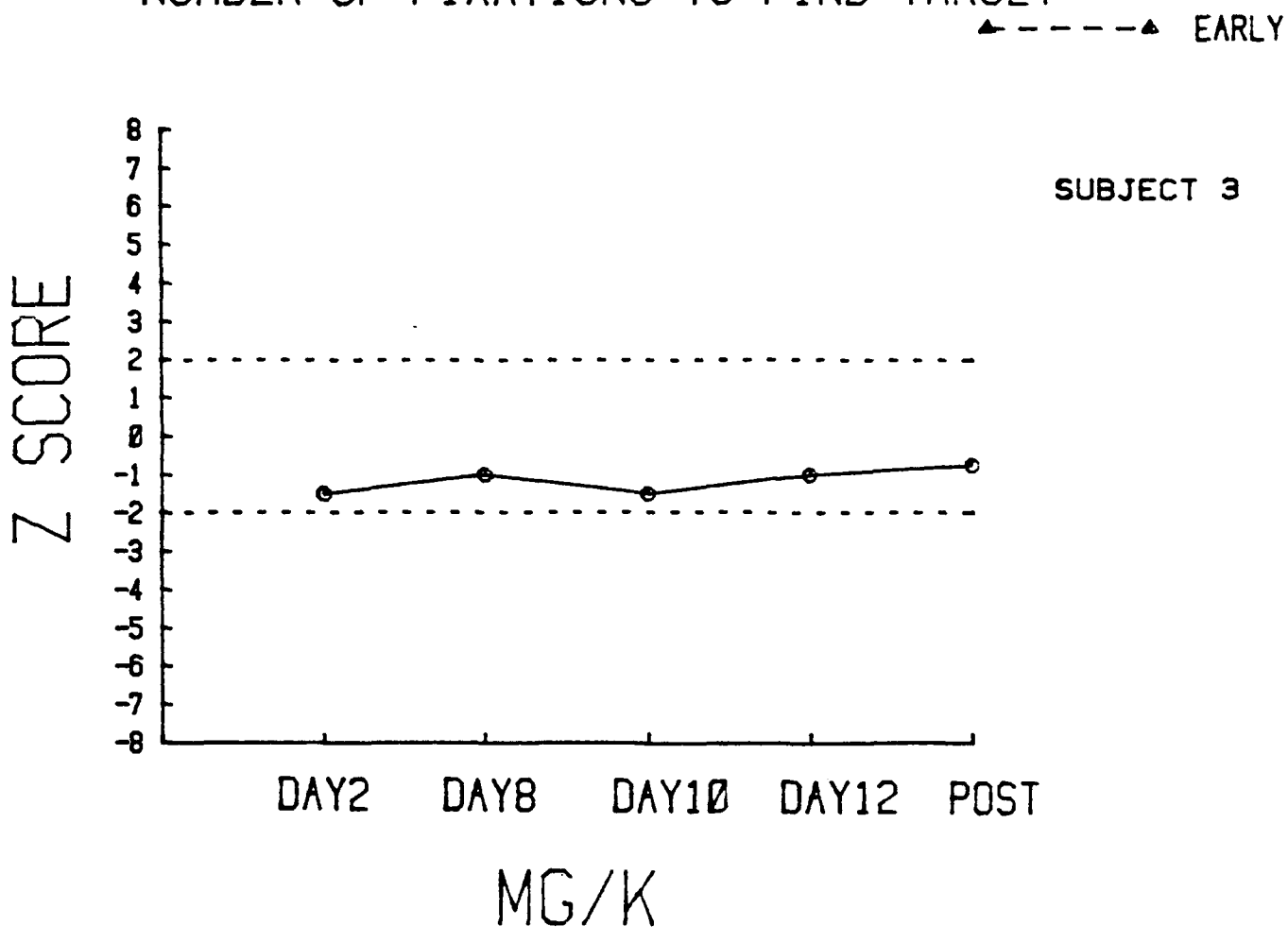
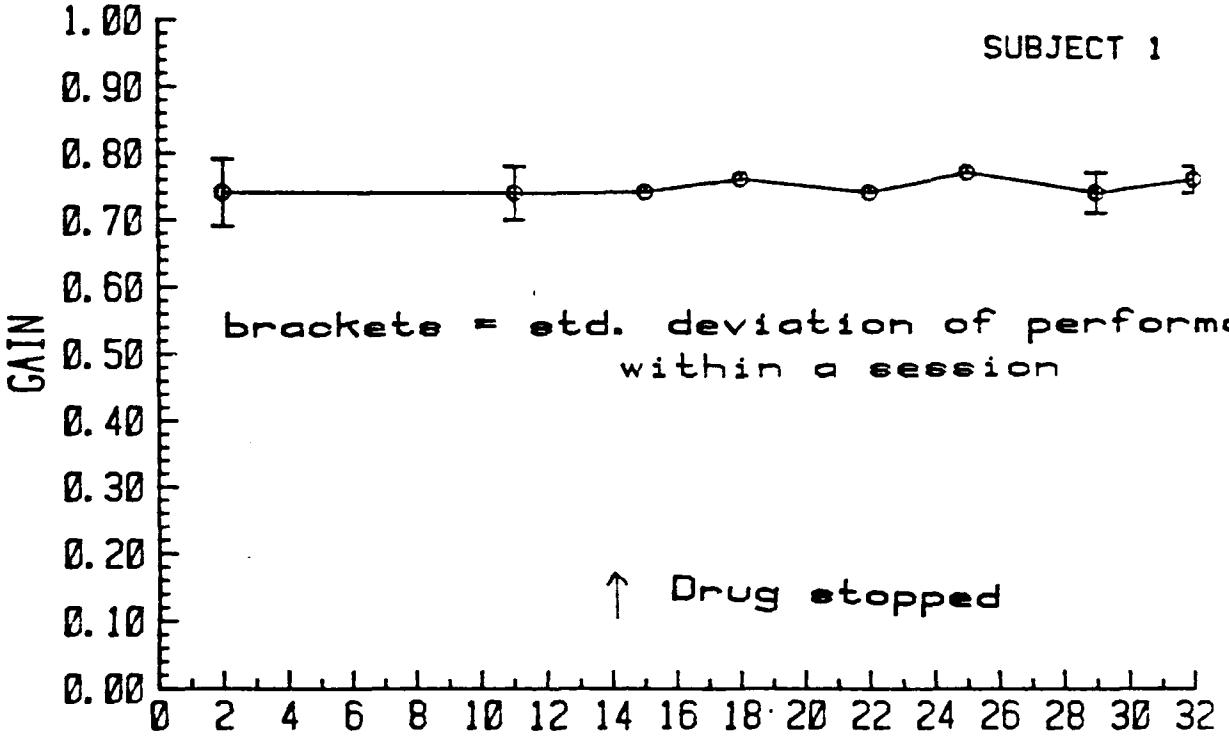


figure 18

PYRIDOSTIGMINE: TRACKING

GAIN



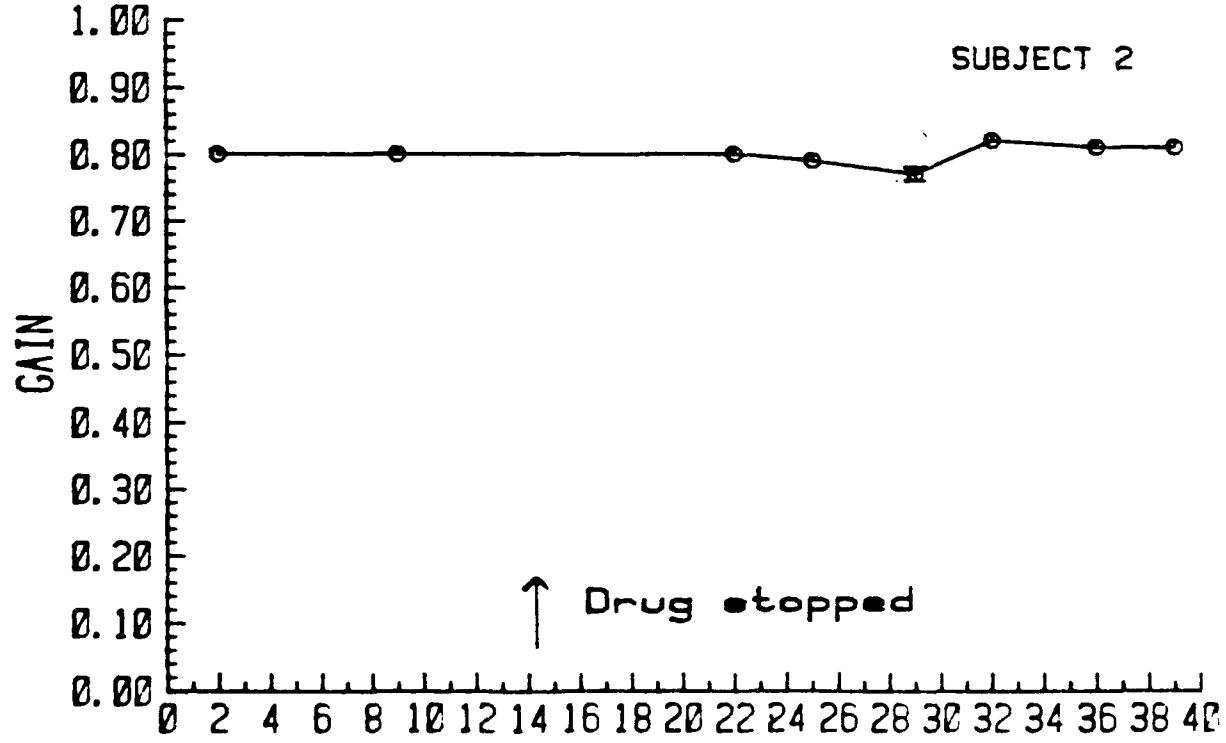
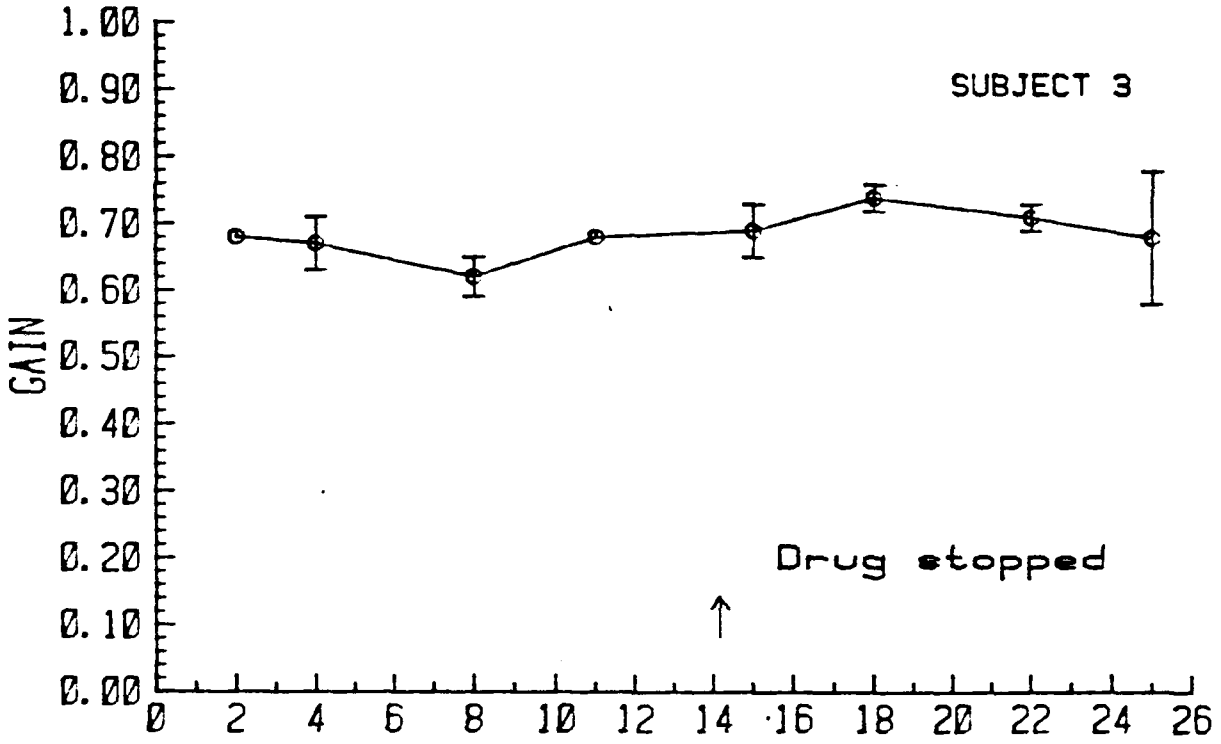


figure 19

PYRIDOSTIGMINE: TRACKING

GAIN



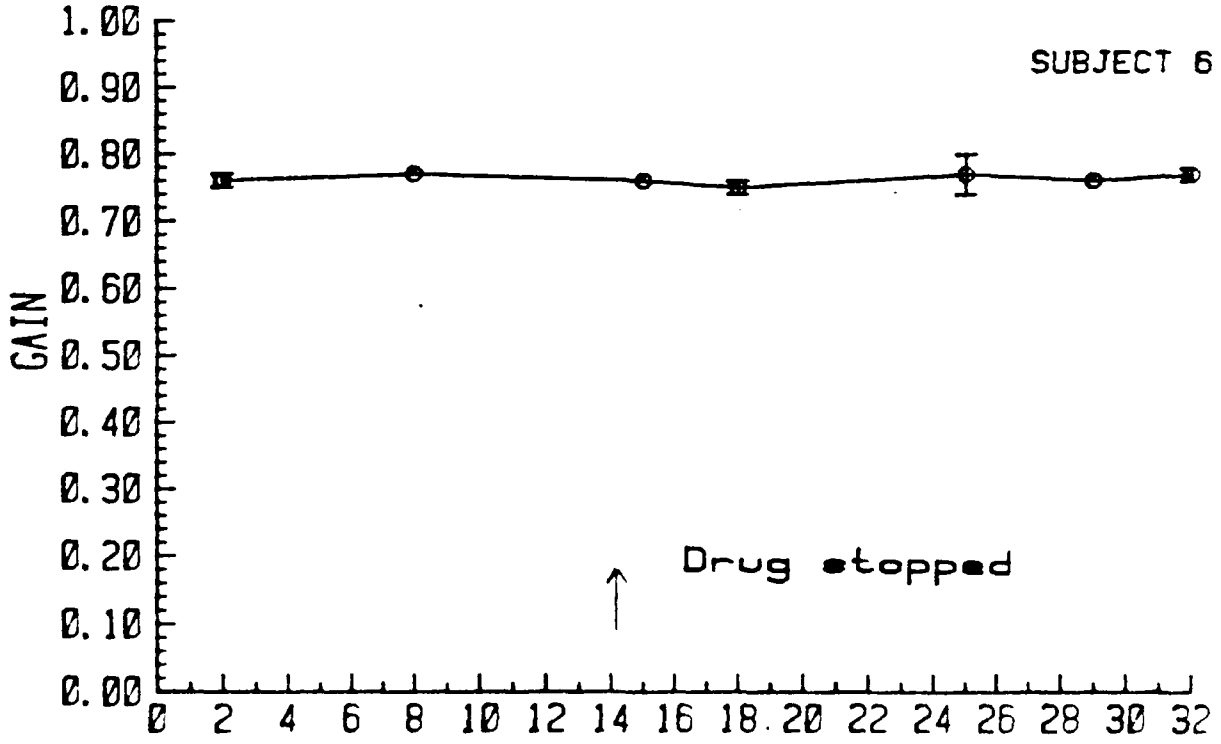
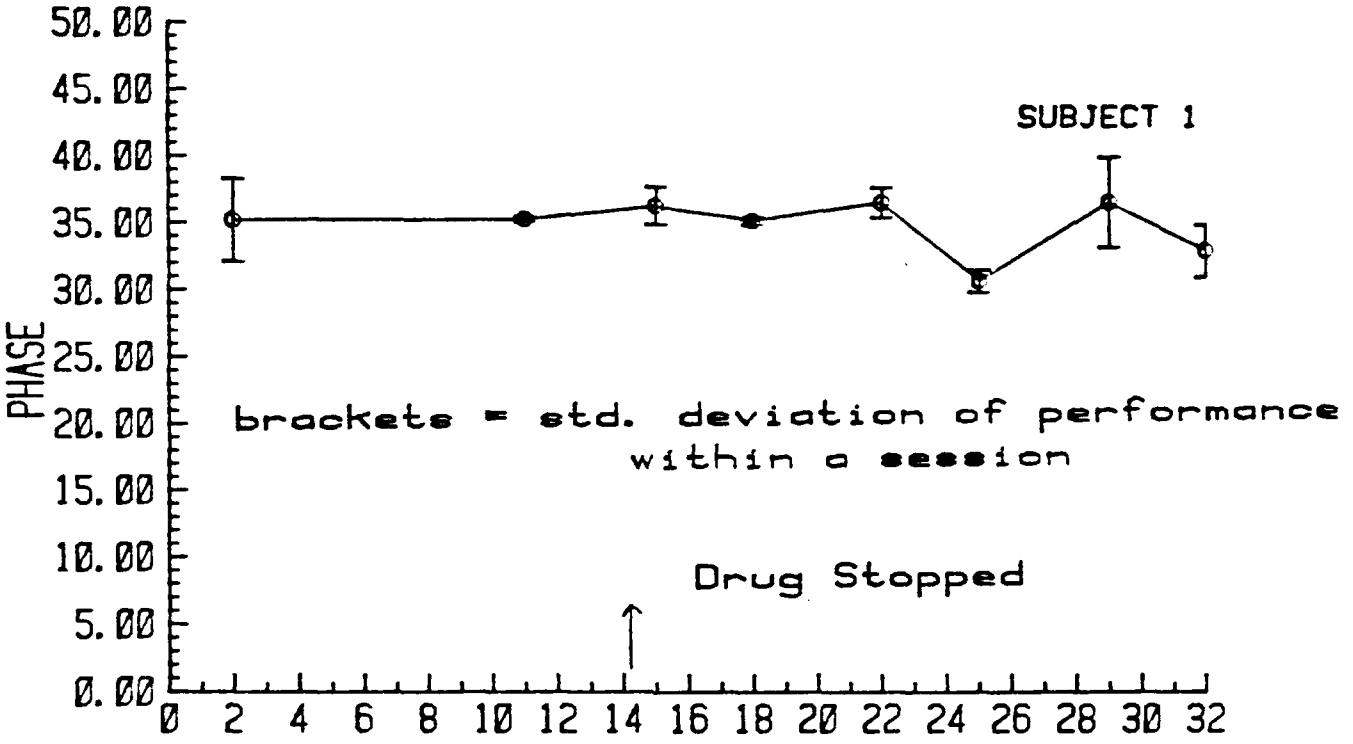


figure 19

PYRIDOSTIGMINE: TRACKING

PHASE



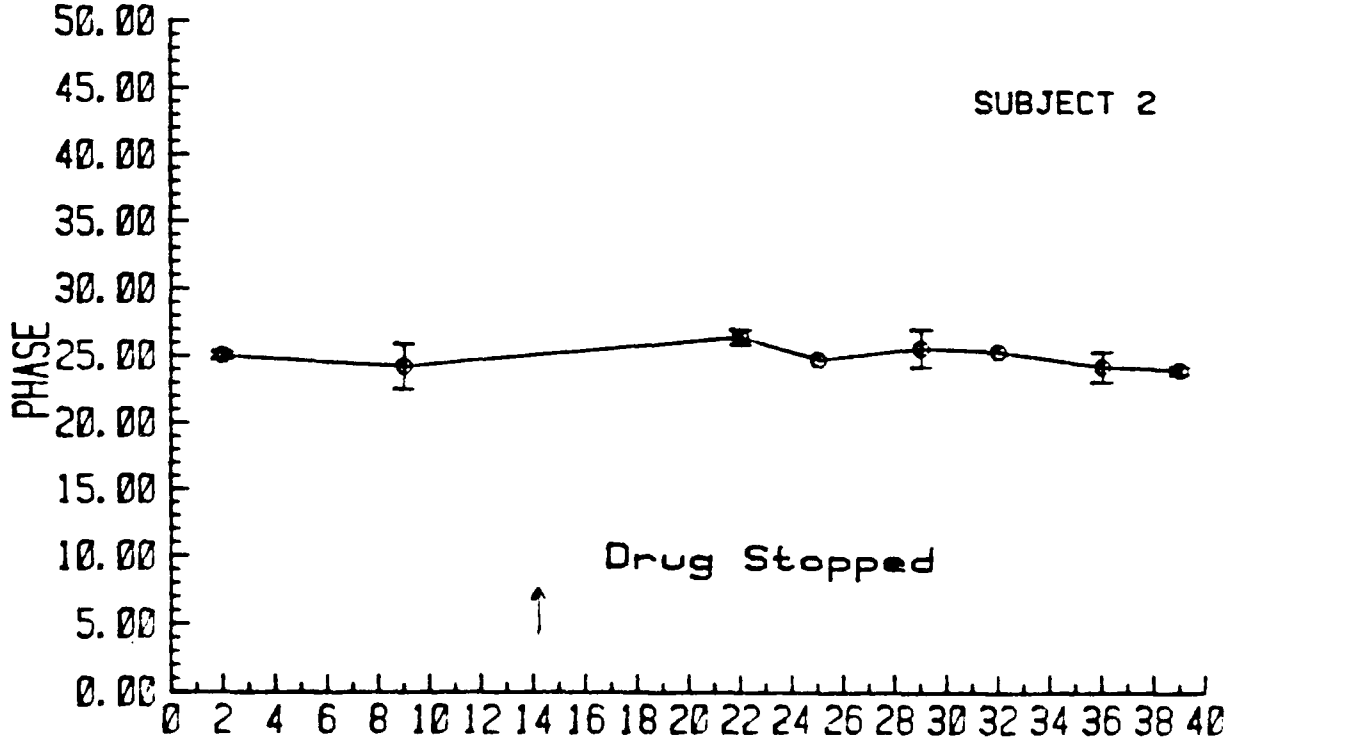


Figure 19

PYRIDOSTIGMINE: TRACKING

PHASE

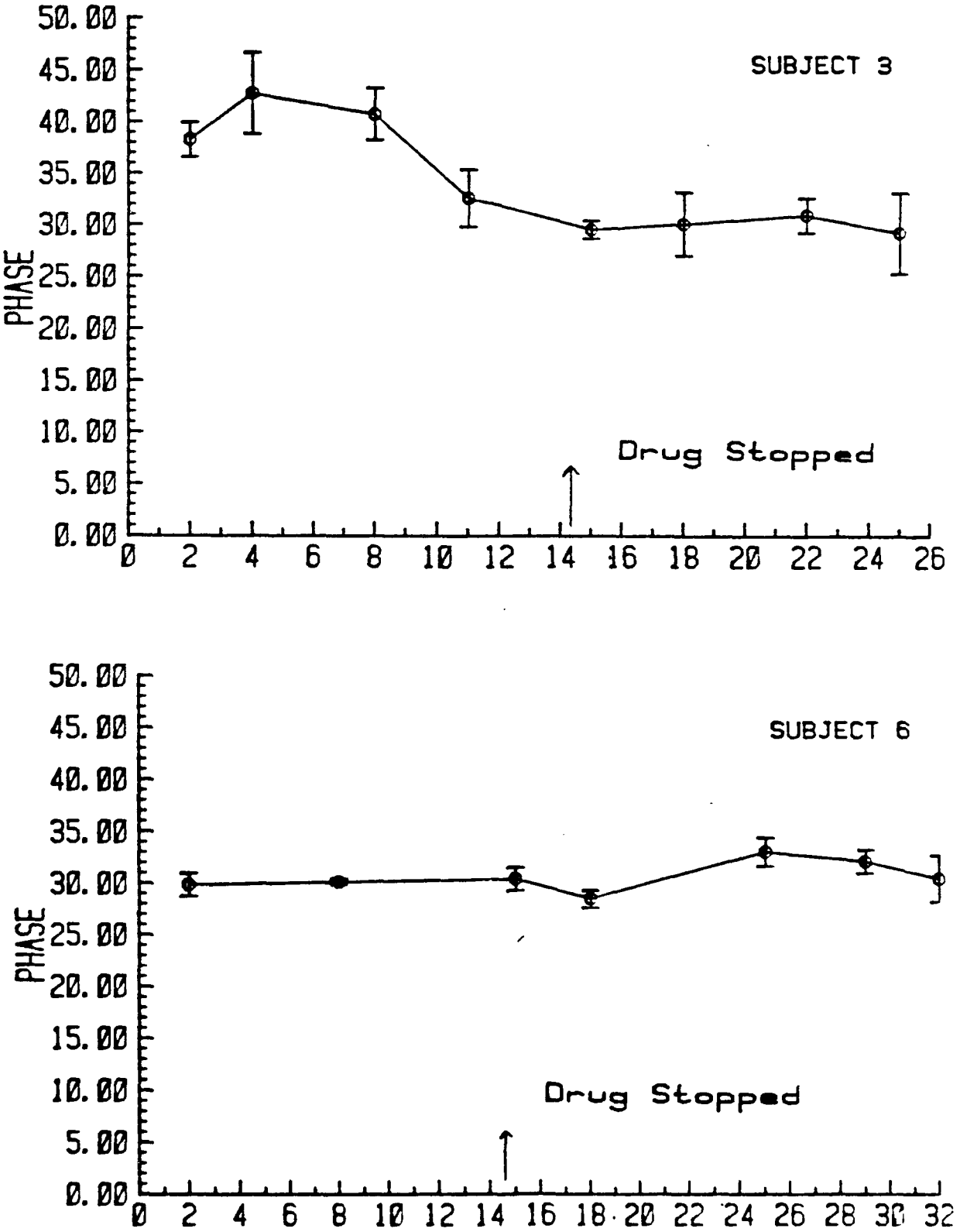


figure 19

.014 mg/K atropine + 1.0 mg/K pralidoxime

Neurological status: Normal, but for a hint of mydriasis

Oculomotor: Normal

Visual Search: Normal

Target Tracking: Time did not permit testing for the effects of this agent on the Target Tracking test before completion of the contract period.

.045 mg/K atropine + 2.0 mg/K pralidoxime

Neurological status: Slight to moderate mydriasis but no other neurological symptoms.

Oculomotor: the polygraph record showed subtle effects that included slowed saccadic velocities and fragmented fixations. These appeared in both Early and Late sessions.

Visual Search: Normal

0.14 mg/K atropine + 4.0 mg/K pralidoxime

Neurological and Oculomotor status: These were much the same as at the previous lower dose. The mydriasis was obvious but not severe. Fixations were often interrupted by small shifts of gaze and eye blinks but the monkeys were able to hold a point of gaze without much drift.

Visual Search: Normal

0.25 mg/K atropine + 8.0 mg/K pralidoxime

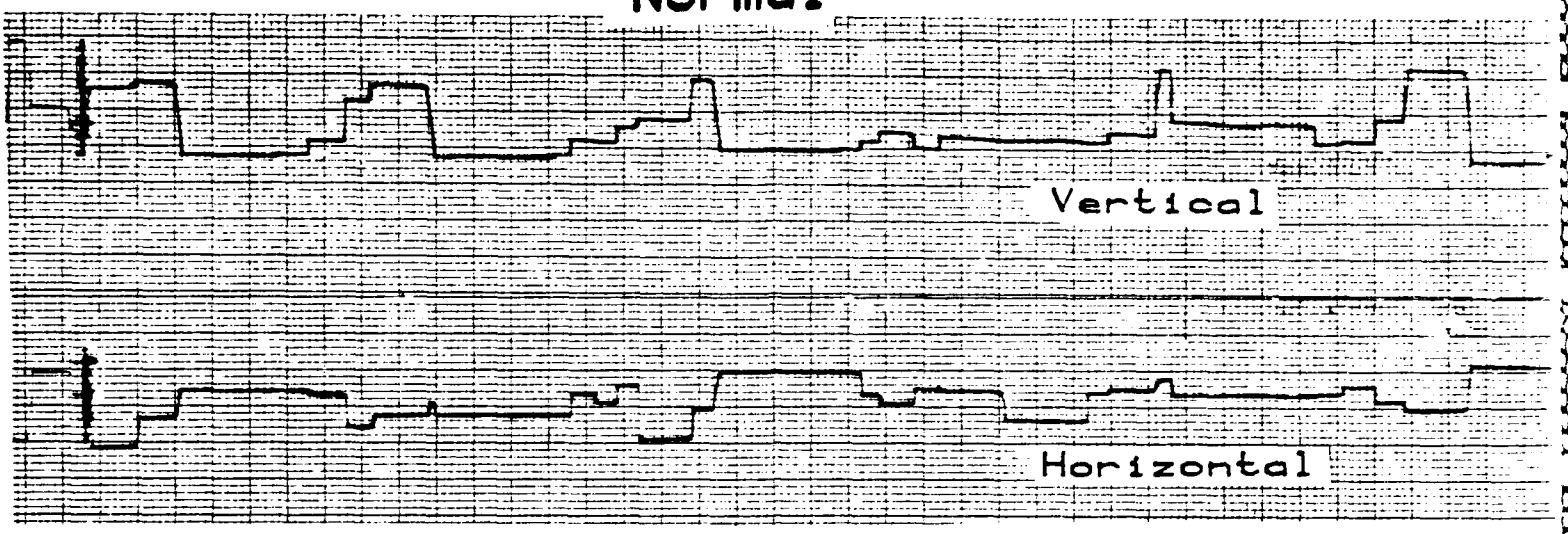
Neurological and Oculomotor status: Similar to and not worse than at the previous lower doses.

Visual Search: Normal, except for performance during one Late session with one subject (1).

Table 14. Atropine/Pralidoxime. "Worst case" Session scores on Visual Search. Subject 1; Dose: .25 mg/K atropine + 8.0 mg/K pralidoxime; Session: Late

	Baseline Avg./Std		Drug Avg.
Percent of targets fixated	98.3	1.6	98.6
ON SUCCESSFUL TRIALS:			
Time required to fixate target (msec)	308	13	365
Number of fixations to find target	1.22	0.07	1.5

Atropine/Pralidoxime
Eye Position During Search



.25/8 mg/K

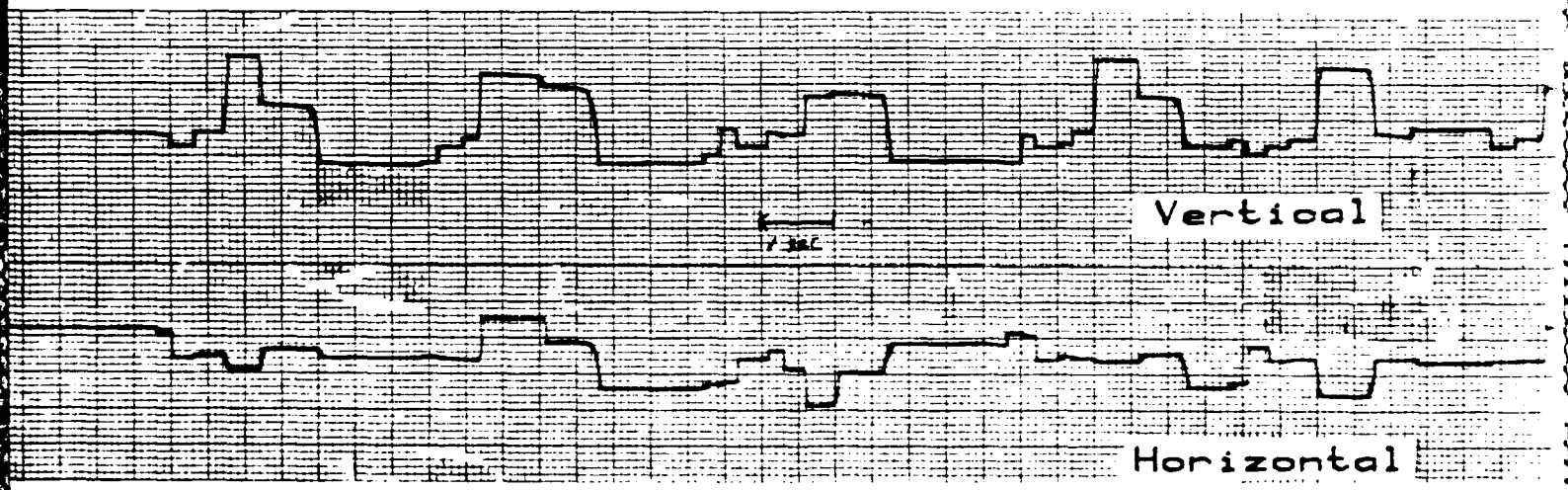


Figure 20

ATR-PAM
PERCENT OF TARGETS FIXATED

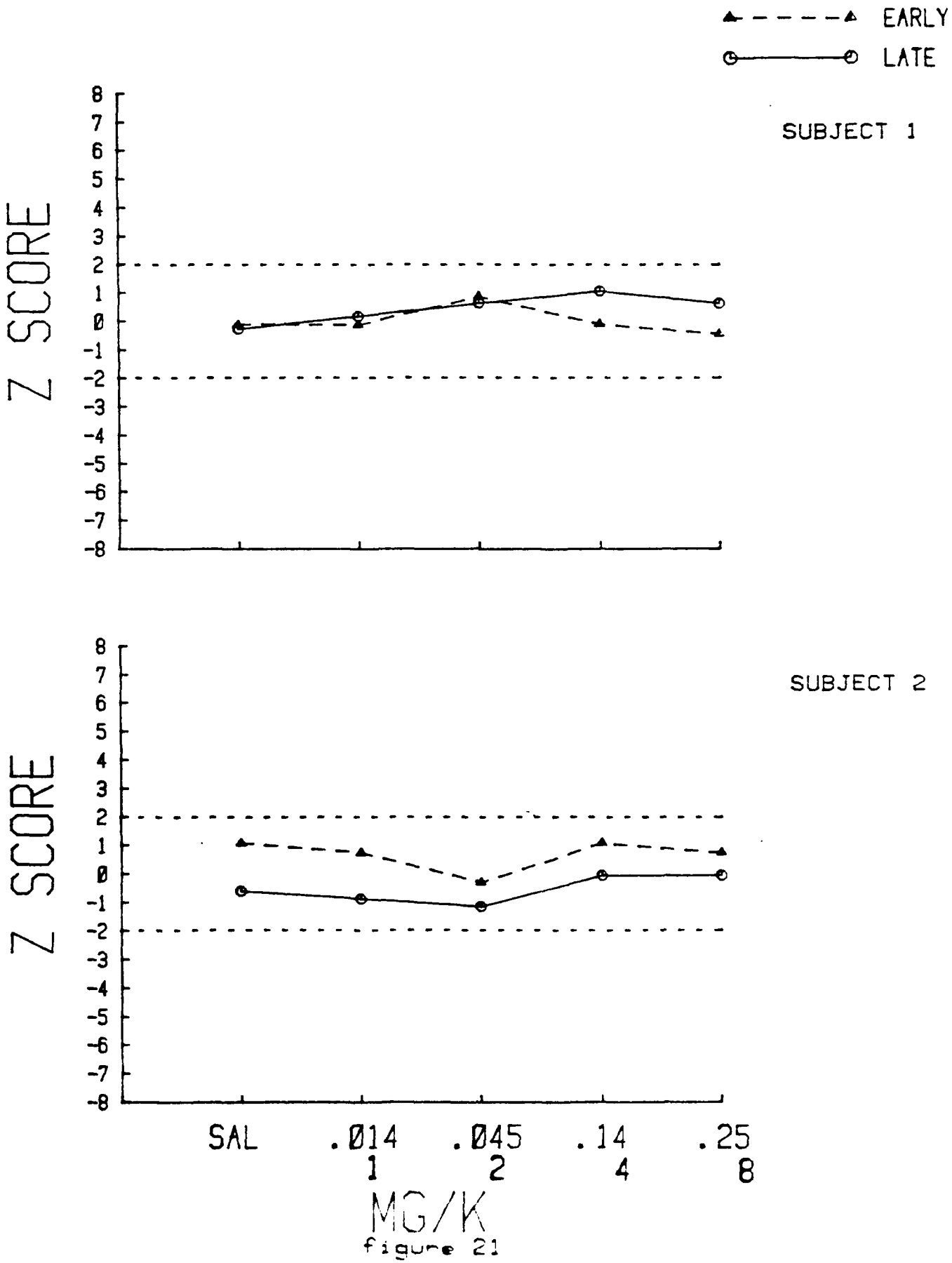
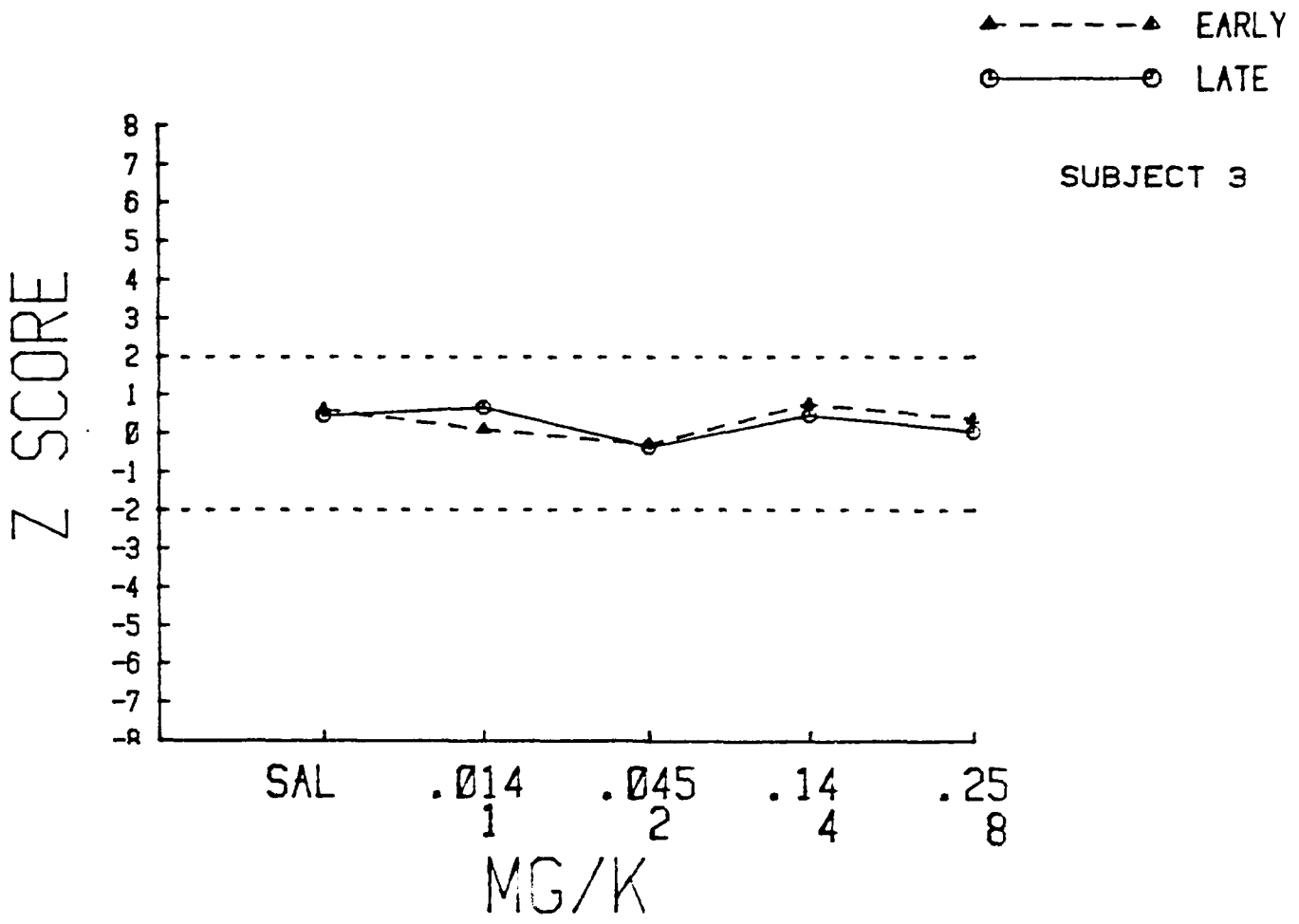


figure 21


ATR-PAM
PERCENT OF TARGETS FIXATED
EARLY
LATE
SUBJECT 3
Z SCORE
8
7
6
5
4
3
2
1
Ø
-1
-2
-3
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-5
-6
-7
SAL
.Ø14
1
.Ø45
2
.14
4
.25
8
MG/K

figure 21

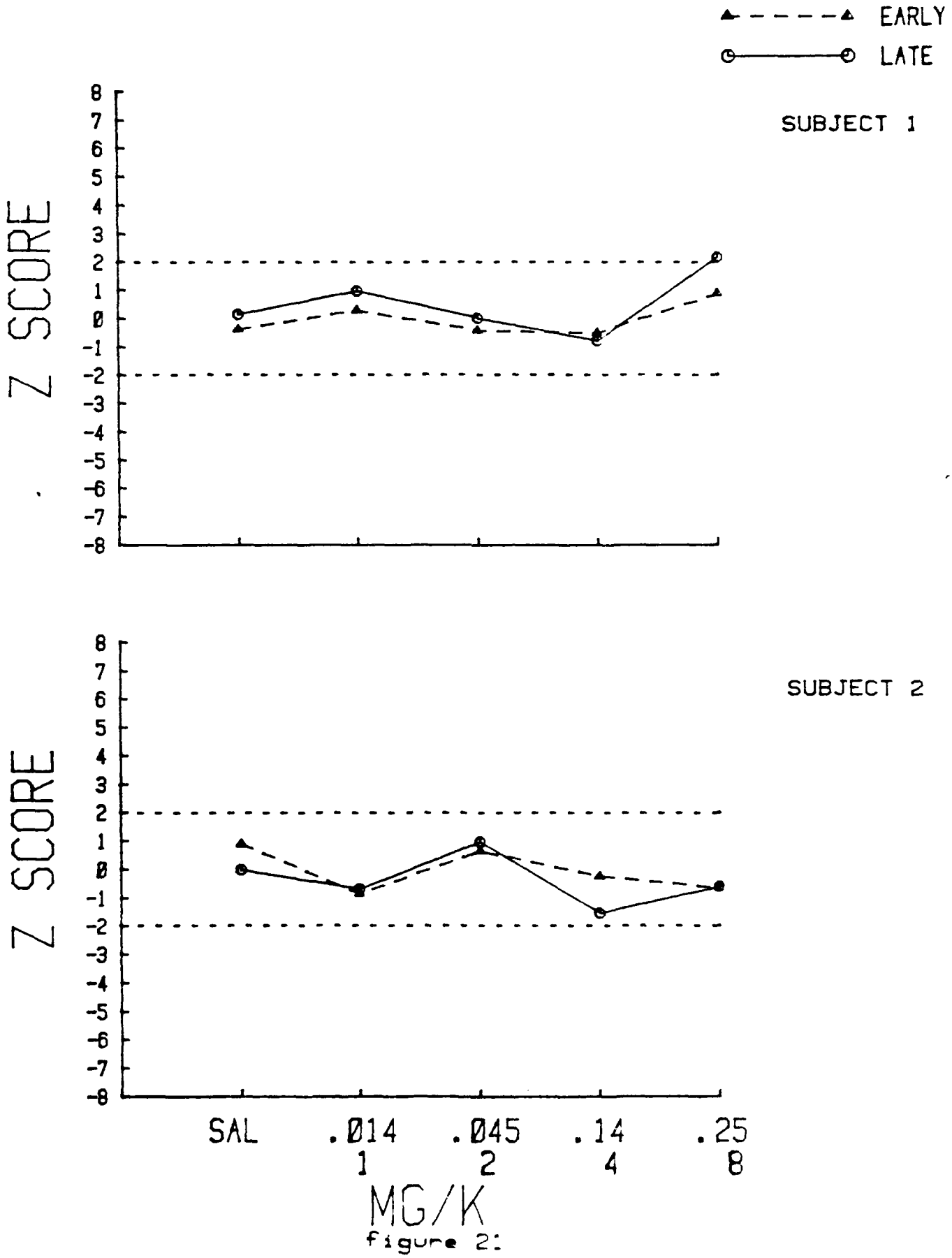
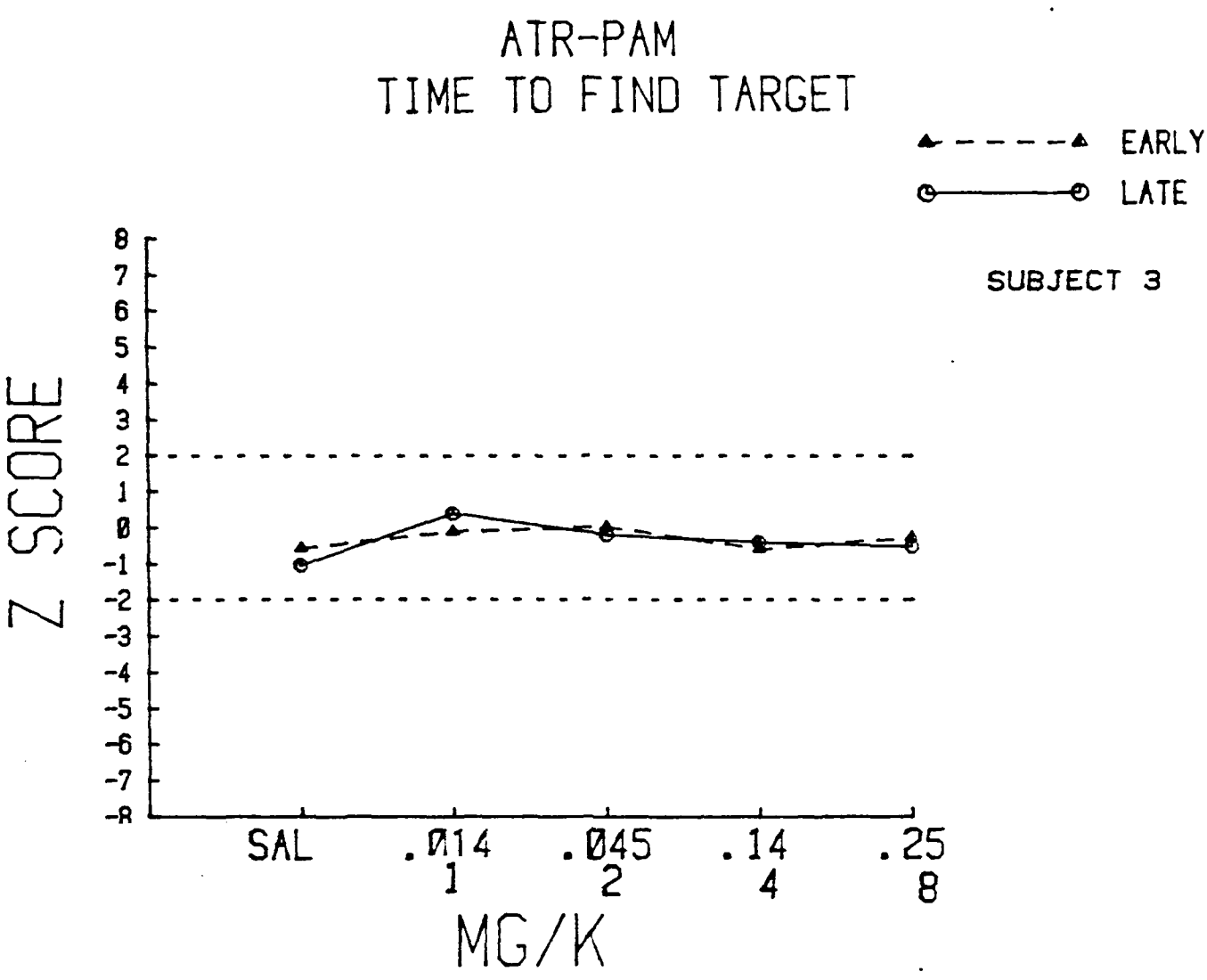

ATR-PAM
TIME TO FIND TARGET
EARLY
LATE
SUBJECT 1
SUBJECT 2
Z SCORE
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
SAL
.014
1
.045
2
.14
4
.25
8
MG/K

figure 2:


ATR-PAM
TIME TO FIND TARGET
EARLY
LATE
SUBJECT 3
Z SCORE
8
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6
5
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3
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SAL
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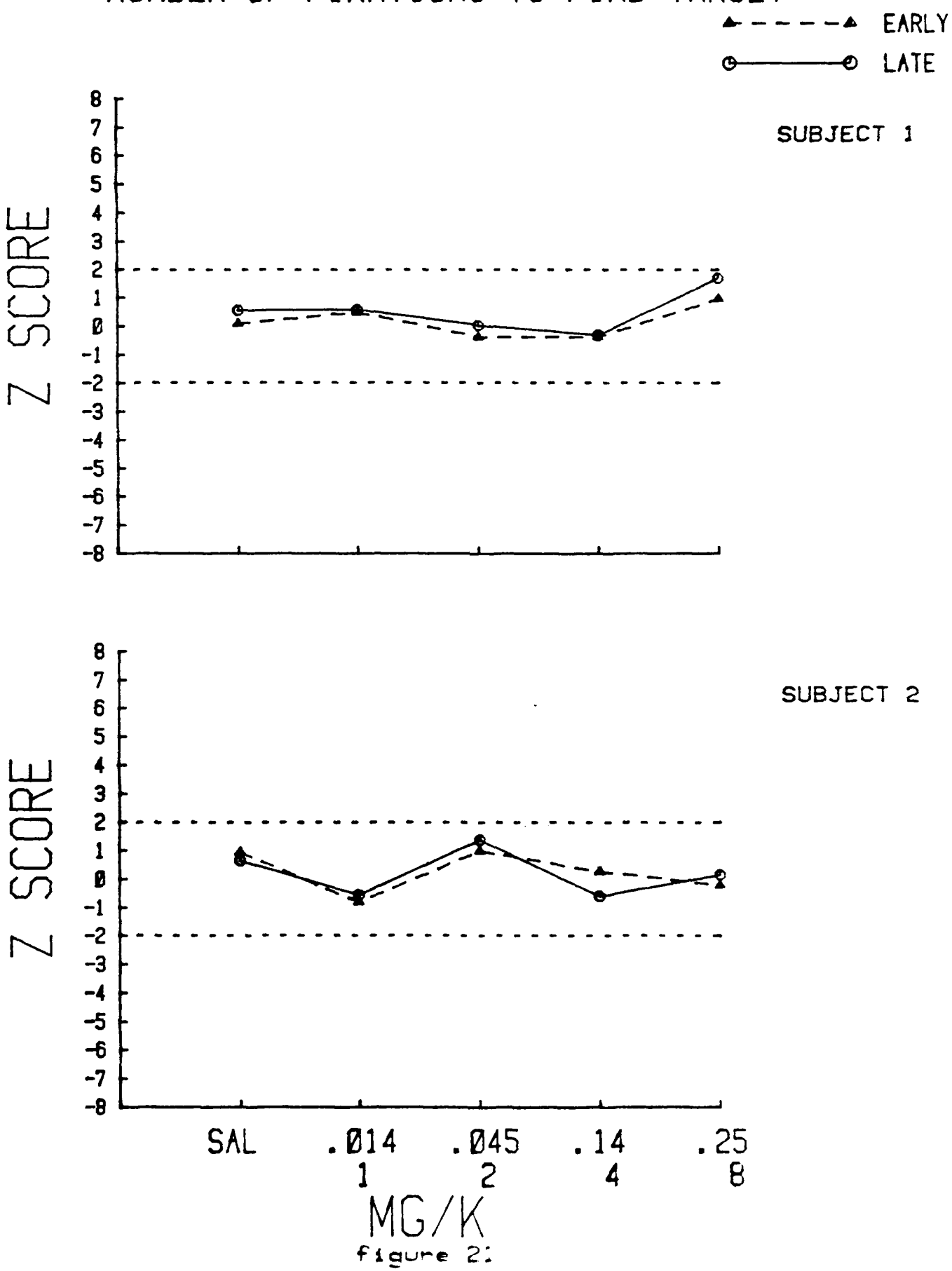
MG/K

figure 2:


ATR-PAM
NUMBER OF FIXATIONS TO FIND TARGET
EARLY
LATE
SUBJECT 1
SUBJECT 2
Z SCORE
8
7
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3
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-1
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SAL
.014
1
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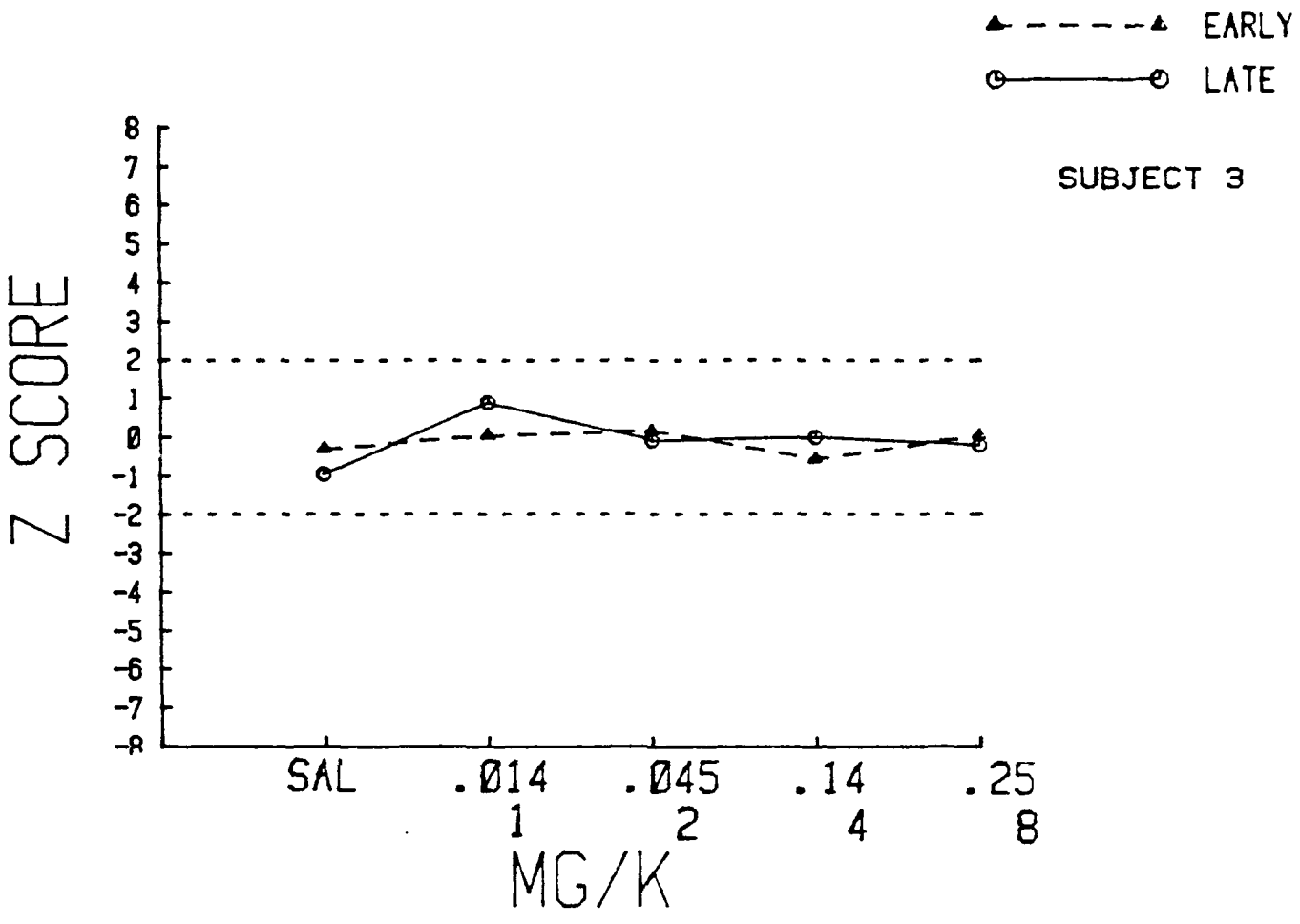
2
.14
4
.25
8
MG/K

figure 2:


ATR-PAM
NUMBER OF FIXATIONS TO FIND TARGET
EARLY
LATE
SUBJECT 3
Z SCORE
8
7
6
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4
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-1
-2
-3
-4
-5
-6
-7
-8
SAL
.014
1
.045
2
.14
4
.25
8
MG/K

figure 21

REPORT SUMMARY:

The experiments measured the effects of several cholinospecific agents on performance of tasks that attempted to provide an animal model of skills required of military personnel in the field. The results were that doses thought to provide protection against organophospate poisoning had no or only subtle effects on visual search and tracking. These agents at the doses tested certainly were not life threatening. They caused no generalized motor weakness, vomiting, or respiratory distress. They never entirely stopped the monkeys from trying to perform the tests, and never reduced performance to random responses. When statistically real decrements did occur they appeared with consistency only at the highest doses.

Besides the obvious species difference, some considerations must be kept in mind when using these results to predict human performance under analogous circumstances. One is the adequacy of the behavioral tasks as an animal model of important military skills. The tasks were designed to be difficult so as to reveal subtle effects of the tested agents. They did appear difficult in that the monkeys required several weeks of training to achieve asymptotic levels of performance. Human observers first attempting the Visual Search test were much less successful than the practiced monkeys at finding the targets.

On the other hand the monkeys by the time they entered the drug trials displayed excellent performance of both tasks. On the Visual Search test their performance approached a theoretical ideal. They could detect a target prior to moving their eyes from the center of the screen and required only 100 msec beyond the minimum reaction time for monkeys to initiate a saccadic eye movement. Performance on the tracking test was slightly less perfect and seemed a more sensitive indicator of drug related decrements. Still, at the start of the drug trials the monkeys could pursue the predictable targets with almost no lag and with high gain.

Secondly, the repeated-measures design of the study raises the question of the independence of the results of the several drug trials. Repeated trials with the same agent and with other agents did not appear to gradually degrade baseline performance. Thus, our tests did not reveal chronic effects of repeated exposure to cholinergic agents. However, the opposite possibility that repeated measures shaped a tolerance for the drugs can not be ruled out by our protocol.

With these cautions in mind it would appear that good visual-motor performance can be sustained through the lower dose range of all the drugs tested. The two week chronic administration of pyridostigmine had no observable effect. The combination of atropine/pralidoxime was benign even at the highest tested dose. Atropine, physostigmine, and pralidoxime did impair performance at the highest dose level. Even in these cases the subjects were able to maintain their motivation for testing and still managed competent visual search and moderately good tracking of moving targets.

The tasks tested several kinds of skills. There were visual, cognitive and motor components to the tasks. To the extent these components can be factored the deficits that did occur seem to represent mainly motor deficiencies. In spite of the pupillary mydriasis there were no obvious

visual disturbances (1). The high rate of success in finding targets on the Visual Search test indicate that the monkeys had little trouble detecting the visual target amongst its background distractors. Drug effects mainly increased the time and number of fixations needed to fixate the target. Inspection of the impaired trials indicated that the first eye movement from the center of the screen was usually in the appropriate direction toward the target. Thus, the target had been detected, but the resulting fixation fell short and required correction.

The monkeys appeared quite able to handle the cognitive load of the tasks. The Tracking task particularly was designed to measure a cognitive component. The monkeys learned to expect a target that moved with a sinusoidal trajectory. Their expectation was revealed by the result that they could track a sinusoidal target with virtually no lag and moved their eyes in a sinusoidal trajectory even when the target failed to do so. This cognitive component was largely undisturbed by the drugs. Gain of tracking was sometimes reduced. Phase of tracking increased but was always better than the 125 msec lag behind the target expected of an animal that had no prediction about the trajectory of the target. Even on Unpredictable trials when pursuit was erratic, the tendency to expect a sinusoidal trajectory was still revealed in the record.

The decrements do not appear to stem from a loss of motivation. The monkeys initiated the target presentations themselves, thus controlling the rate of testing. They persevered at trying to carry out the tasks through the trials when they performed most poorly. There were few interruptions in testing, and no indication that the monkeys were uninterested in the reward of orange drink.

Thus, by default and by more direct evidence the decrements that did occur seemed to represent an impairment in the oculomotor system. The pattern varied among the agents. Pralidoxime produced a significant gaze paresis which kept the animals from moving their eyes to eccentric eye positions. Atropine slowed saccadic velocities, caused fixations to drift, and introduced microsaccadic quivers in the record that fragmented the fixations. Of these, only the drifting fixations might be interpreted as resulting from a degraded visual acuity rather than a motor problem. However, the drift also occurred during spontaneous fixations in the dark. Physostigmine caused a "pulse overshoot" that initially drove they eyes beyond the intended fixation point. Such a pulse-step mismatch can be modeled by impairments at several points in the motor system from the cerebellum peripherally to the neuromuscular junction in the orbit (7). While loss in visual ability cannot entirely ruled out as partly responsible for slowing search or degrading tracking, the impairments are at least all consistent with the interpretation of a decrement in oculomotor function.

However, the main outcome of the study remains that the decrements resulting from these agents were subtle through most of the range of tested doses. Particularly encouraging for therapeutic considerations was the absence of any decrement from chronic administration of pyridostigmine.This agent holds considerable promise as a prophylactic against organophosphate poisoning (9).

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