REDUCTION OF HUMAN EPILEPTIC SEIZURE RATE VIA OPERANT CONDITIONING OF SCALP BIOELECTRIC ACTIVITY

BY

RAYMOND PAUL PAVLOSKI, B.S.

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AUTHOR: Raymond Paul Pavloski, B.S. (Pennsylvania State University)

SUPERVISOR: Professor Arthur Cott

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Abstract

A behavioral method for reducing the rate of seizure emission in epileptic outpatients was investigated. This procedure - operant conditioning of the electroencephalographic sensorimotor rhythm (SMR) with time-outs for epileptiform activity and large amplitude electromyographic activity - has been successfully applied to a variety of seizure disorders. Results from the first study reported in this thesis showed that neither SMR reinforcement nor changes in SMR density are necessary or sufficient for decreasing seizure frequency, and that changes in parameters of time-out activity are unrelated to changes in seizure rate. A second long-term study indicated that time-outs for either high- or low-voltage scalp electromyographic activity produced equivalent and significant reductions in seizure rate. Informal observations supplemented by pretraining psychometric test data and daily self-monitoring data suggest that the operant conditioning procedure effects clinical results by modifying subjects' behaviors in situations realted to seizure occurrence.

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Chapter 1

INTRODUCTION

> "An epileptic seizure is a state produced by an abnormal excessive neuronal discharge within the central nervous system. An epileptic seizure is therefore a symptom of disease". (Penfield and Jasper, 1954, p.20).

There is currently a great deal of interest in the application of behavioral principles and techniques to a variety of physical disorders. Not surprisingly, most of these pathologies have in the past been termed psychosomatic or functional, or have been thought to embody so-called "psychological" factors in addition to the presumed primary physical cause of complaint. In the first case the terms psychosomatic or functional are employed to describe a symptom or symptom complex for which no underlying disease process is evident. In the second case, it is recognized or suspected that vaguely-defined states such as excitement or extreme fatigue exacerbate the complaint. In neither case, however, are the psychological processes well-understood (Birk, 1973).

Human epilepsy provides an excellent example of this situation. The disorder is clearly defined in terms of an underlying physical pathology - as in the quotation that begins this chapter - and it has

been very successfully treated both pharmacologically and surgically (e.g., Lennox, 1960a, b; Rodin, 1968). Nevertheless, the contribution of psychological factors to the severity and frequency of epileptic seizures has been emphasized by numerous authors (see Chapter 2), and the response of an individual epileptic to pharmacologic treatment cannot be perfectly predicted (Rodin, 1968; Sibley, 1974).

Although there are relatively few clinical reports and even fewer experimental investigations of the application of learning principles to the reduction of epileptic seizures, the published reports do suggest that seizure frequency in humans can be reduced through behavioral intervention (Mostofsky and Balaschak, 1977). It will be shown in Chapter 2 that a wide variety of behavioral methods have been employed, and that very often a different combination of techniques has been utilized in order to treat each individual patient. This obviously makes evaluation of any given procedure difficult at best. It is important that claims made for the therapeutic value of certain procedures be tested experimentally.

The behavioral approach that is of major concern in this thesis is operant conditioning. Conceptually, attempts to reduce or to eliminate seizures through operant conditioning have focused both directly on overt behavior and indirectly on central nervous system (CNS) events believed to play a key role in the generation

of or active inhibition of the neuronal discharges underlying clinical seizures. In the former case, contingencies are arranged so that seizure-free behaviors are reinforced and seizures or behaviors that are highly predictive of seizures are punished or extinguished. In the indirect approach, operant conditioning techniques are employed to modify surface (scalp) recordings of bioelectric activity thought to represent cortical and subcortical events of presumed importance. The investigations reported in this thesis were conducted in order to test several explanations for the effectiveness of one such indirect intervention technique. This method involves operant conditioning of the electroencephalographic (EEG) sensorimotor rhythm (SMR), a 12-14 Hz sinusoidal waveform recorded over the sensorimotor cortex from scalp electrodes. In addition, a time-out for epileptiform activity and large amplitude electromyographic (EMG) activity is employed. That is, SMR is not reinforced during epileptiform activity or body movement, and the unavailability of reinforcement is signalled to the subject.

The SMR plus time-out procedure has been reported to yield clinically significant reductions in the frequency of pharmacologically-uncontrolled seizures of various etiologies and behavioral manifestations (Finley, 1977; Finley, Smith, and Etherton, 1975; Lubar, 1977; Lubar and Bahler, 1976; Seifert and Lubar, 1975; Sterman, 1973, 1977; Sterman and Friar, 1972; Sterman and MacDonald, 1978; Sterman, MacDonald, and Stone, 1974). Further, it has been assumed that an increase in SMR activity causally effects the reduction in seizure rate (e.g., Sterman, 1973). As discussed in the following chapter, however, there is reason

to question this putative relationship between SMR and seizure frequency. This question formed the starting point for the experiments reported in this thesis.

As mentioned previously, the SMR plus time-out procedure is one of many different types of behavioral methods used to ameliorate epileptic seizures in humans. A brief review of these interventions is provided in the next chapter, followed by a discussion of previous SMR research. Although it is difficult to recognize commonalities between the SMR plus time-out procedure and most of the other intervention techniques, this review is important for a number of reasons. It presents the evidence cited in support of the conclusion that behavioral methods are therapeutically effective for epileptics (e.g., Mostofsky and Balaschak, 1977). Second, it shows that most of the non-SMR procedures are conceptually limited to particular subject characteristics. Finally, it makes available results that can be useful in generating hypotheses regarding the mechanism underlying the therapeutic value of the SMR plus time-out precedure.

A considerable portion of the SMR review concerns methodological considerations, as does the rationale for the present investigation which is presented in Chapter 3. This is due, in part, to the fact that the data analyses reported in previous SMR investigations are not sufficient for the evaluation of experimental hypotheses. The greatest

contributors to this concern with methodology, however, are the population of subjects required and the state of knowledge that exists for the therapeutic technique. It has been recognized time and again that new problems in experimental design arise when the subjects are members of an extremely heterogeneous, ill-defined population (e.g., Davidson and Costello, 1969; Hersen and Barlow, 1976). In addition to the difficulties encountered in any clinical trial, especially those concerned with placebo effects (Jospe, 1974), many questions regarding basic procedural issues in the operant conditioning of responses other than directly observable, molar skeletal behaviors have not been answered (Black and Cott, 1977; Black, Cott, and Pavloski, 1977). An attempt is made in Chapter 3 to deal with these problems, first by recognizing that investigations of the type being considered must be exploratory, and second by determining what type of experimental design is best suited to the situation.

Reports of two long-term experiments are next, followed by a general discussion in Chapter 6. Because the results of this investigation do not support the hypothesis that seizure rate reductions are produced by learned changes in EEG activity, the applicability of certain social learning concepts to these results is considered here.

Chapter 2

BACKGROUND

As has been noted elsewhere (Mostofsky and Balaschak, 1977; Sterman, 1977), the formal application of behavioral techniques to the problem of controlling epileptic seizures has a relatively short history. There has been a dramatic increase in the reported application of learning principles to epilepsy over the past two decades, however, and at least some of the techniques that have been employed are relevant to the SMR plus time-out (SMR + TO) procedure. In this chapter previous SMR research will be discussed in relation to other non-surgical, non-pharmacologic treatments.

The main objective of the first section, which deals with non-SMR procedures, is to illustrate the variety of intervention techniques that have been employed in the management of seizures. It is remarkable that almost all of the studies that will be discussed reported success in reducing seizure frequency and/or severity. Unfortunately, many of these studies are case reports with few if any systematic data, especially baseline seizure data, reported (Adams, Klinge, and Keiser, 1973; Balaschak, 1975; Booker, Forster, and Klove, 1965; Daniels, 1975; de Weerdt and van Rijn, 1975; Dorcus and Schaffer, 1945; Efron, 1956; Feldman and Paul, 1976; Finley, Smith, and Etherton, 1975; Forster, Booker, and Ansell, 1966; Forster and Campos, 1964;

Forster, Paulsen, and Baugham, 1969; Forster, Ptacek, and Peterson, 1965; Gardner, 1967; Gottschalk, 1953; Ince, 1976; Iwata and Lorentzson, 1976; Johnson and Meyer, 1974; Parrino, 1971; Sterman and Friar, 1972; Wright, 1973, 1976). It is impossible, therefore, to give an evaluation of the extent to which seizure frequency and/or severity are affected by the various procedures.

Nevertheless, as pointed out by Mostofsky and Balaschak (1977), these case reports do suggest that behavioral techniques can be efficacious in reducing and sometimes eliminating epileptic seizures. Although they produce few data useful in evaluating the effectiveness of various treatments, they indicate that experimental evaluation of these procedures might prove fruitful (Blanchard and Young, 1974).

Procedures Not Employing SMR Conditioning

A number of case reports are based on epileptic seizures that can be reliably precipitated or inhibited by specific sensory stimulation. In the former case, visual stimulation hasusually been found to trigger seizures, although some cases of seizures provoked by certain complex auditory events have also been reported (e.g., Lennox, 1960a). Somatosensory stimulation (e.g., pressure applied to a limb contralateral to the epileptic focus) has most often been reported as an effective technique in aborting impending seizures (Symonds, 1961; Paulsen, 1963; see also the historical introduction by Lennox, 1960a). For this technique to be very effective, however, it is necessary that the epileptic have some warning sensation (aura) of an impending seizure so that the inhibitory sensory stimulus can be applied in time.

A classic paper dealing with the application of sensory inhibition in a systematic fashion was published by Efron (1956). He reported that administration of an unpleasant odor early in his patient's auras consistently aborted the grand mal seizures which otherwise inevitably followed the warning sensation. This effect was later conditioned to the sight of a bracelet and eventually to a visualization of the bracelet (Efron, 1957). The subject had a 26-year history of seizures, yet it was reported that the procedure resulted in a complete absence of seizures during a 14-month observation period.

Stevens (1962, 1967) has attempted to extend the usefulness of this technique. It was hoped that subjects could be trained to identify paroxysmal epileptiform EEG discharges so that an aura could be developed and put to use, presumably in the same manner as the aura of Efron's subject.

Stevens (1962) made a clicking sound followed by electric shock contingent on abnormal spike-and-wave discharges, and later omitted the clicking sound. Subjects could initially avoid the shock by pressing a key soon after the clicks began, and later by responding to their own paroxysmal discharges. Of 10 subjects, only one learned to avoid shocks in the absence of the discriminative clicking sound. In another study, an attempt was made to pair paroxysmal EEG activity with visceral responses to shock (Stevens, 1967). It was reasoned that subjects might be able to discriminate visceral responses that had been conditioned to abnormal EEG activity. Classical conditioning

did not occur, however, and it is not surprising that seizure rate was not altered.

The notion of sensory inhibition was also combined with detection of epileptiform EEG activity by Upton and Longmire (1975) and Upton and Saltarelli (1977). In a series of clinical trials, somatosensory and auditory stimulation were triggered from focal spike discharges while subjects were instructed to utilize strategies previously found to be correlated with depressed spiking (e.g., clenching the fist contralateral to the focus). Clinically significant reductions in seizure frequency were reported for 11 of 27 subjects who had been found recalcitrant to anti-epileptic medications. It was not established whether the subjects had learned to discriminate the occurrence of focal spiking. Therefore, the relative contributions of this variable and the learned sensory inhibition strategies cannot be evaluated.

Several different techniques have been tested with subjects who have seizures that are reliably triggered by specific stimuli. Forster and his colleagues (Booker, Forster, and Klove, 1965; Forster, Booker, and Ansell, 1966; Forster, Booker, and Gascon, 1967; Forster and Campos, 1964; Forster and Cleeland, 1969; Forster, Hansotia, Cleeland, and Ludwig, 1969; Forster, Klove, Peterson, and Bengzon, 1965; Forster, Paulsen, and Baughman, 1969; Forster, Ptacek, and Peterson, 1965; Forster, Ptacek, Peterson, Chan, Bengzon, and Campos, 1964) have employed

a desensitization or conditioned inhibition technique with patients suffering from startle (audiogenic), pattern, musicogenic, and stroboscope-induced seizures. For example, in some studies monocular or monaural stimuli which did not trigger photosensitive and startle seizures, respectively, were repeatedly presented until previous triggering by binocular or binaural stimuli was reduced or eliminated. As might be expected, this technique proved effective for only a short period of time following treatment, so that seizures were again triggered several days after the conditioning procedure had been administered. In the case of stroboscopic seizures, it was found that second-order conditioning to a click stimulus could be carried out (Forster, Ptacek, and Peterson, 1965; Forster et al., 1966). A portable device to generate clicks in response to flashing light was packaged in eyeglasses, and this eliminated seizure-occurrence in six subjects (Forster, 1969).

In this last case, it is not clear that the elimination of seizures was due to classical conditioning. The clicks could serve as a discriminative stimulus for an operant response incompatible with seizure-occurrence (e.g., shutting the eyes). One example of such a competing response strategy is provided by de Weerdt and van Rijn (1975), who trained a subject with reading epilepsy to hit his knee whenever reading particular, commonly-occurring letters.

Other treatment procedures have been based on the assumption that underlying conflicts on the one hand, or stressful everyday

situations on the other, exacerbate seizures. In these cases no well-specified stimulus is identified as triggering seizures, and the particular procedure followed is probably due in most part to the theoretical orientation of the clinician or investigator.

For example, several different psychotherapeutic procedures have been employed in the management of epileptic seizures. One such procedure is based on the concept that seizures are hysterical manifestations of psychic phenomena (Freud, 1924), and is therefore aimed at relating seizure emission to underlying conflicts so that these conflicts might be understood and resolved by the patient. Working within this framework, Gottschalk (1953) reported elimination of seizures in one child and one teenage boy, and marked reduction of seizure rate in a third child during the course of traditional psychoanalytic sessions.

Relaxation and desensitization have been employed in order to treat seizures thought to be exacerbated in stressful circumstances. Mostofsky and Balaschak (1977) present an unpublished case study of progressive muscle relaxation, but point out that in this case praise for successful reductions in seizure frequency may have contributed to the results. Ince (1976) gave a patient relaxation training with instructions to practice regularly, in addition to desensitization for anxiety, which was hypothesized to aggravate seizures. Desensitization and relaxation training were also employed by Parrino (1971) in a case study of one psychiatric inpatient diagnosed has having Greutzfeldt-Jakob syndrome, a degenerative neurological disorder. Anxiety-hierarchies were used in

the desensitization procedure, and the patient became seizure-free and remained so following discontinuation of anticonvulsants. The effects of desensitization and of operant conditioning of cortical alpha EEG activity were compared in the study by Cabral and Scott (1976). The two procedures were administered alternately to three subjects, with high densities of alpha activity considered as an index of relaxation. Decreased seizure rates were reported for each subject, with some EEG normalization apparently following initiation of alpha training. Johnson and Meyer (1974) administered relaxation training, followed by operant conditioning of low-amplitude EMG activity from various muscle groups, followed by operant conditioning of alpha and theta EEG activity. Although the authors do not make clear the rationale for this procedure, their goal was apparently providing the subject with an effective relaxation technique to compete with subjective tension reported during the epileptic aura. A clinically and statistically significant decrease in seizure rate was reported for the subject. Finally, Rouse, Peterson, and Shapiro (1975) reported that long-term reinforcement of occipital alpha activity was paralleled by a significant decrease in seizure rate in their one epileptic subject.

Feldman and Paul (1976) also focused on seizures presumably brought on by stressful circumstances. These authors had their patients watch videotapes of seizures that were hypothesized as being precipitated by emotional stimuli. Successful reductions in seizure frequency were throught to be based on the patients' recognition of seizure-precipitating

situations (as a result of watching the videotapes) and on future avoidance of or coping with such situations.

Daniels (1975) employed covert reward for imagined seizure-free behavior in imagined seizure-provoking scenes, and covert extinction for imagined seizures. Overt seizures were also treated as operant responses and ignored (i.e., extinction). Successful reduction of seizure frequency was observed in this case report.

Finally, a number of authors have attempted to reduce seizure rate by employing various combinations of reinforcement, extinction, and punishment. The object has been to reduce seizure behavior by eliminating existing contingencies or arranging new contingencies between overt behavior and reinforcers or punishment.

In some case studies, reinforcement was made contingent on a low number of seizures or on seizure-free behavior for a specified period of time, and shaping was used to gradually decrease overall seizure frequency. Although Balaschak (1975) is apprently the sole author who employed this technique exclusively, it has often been combined with punishment. Since institutionalized patients have generally been employed in these studies, the punishment aspect of the procedure was implemented by isolating the epileptic from social functions and from other patients when seizures occurred (Adams, Klinge, and Keiser, 1973; Iwata and Lorentzson, 1976). Assessment of these procedures is difficult primarily because the patients were neither observed constantly nor did they self-monitor seizures.

Of the studies employing punishment, those reported by Wright (1972, 1976) and Zlutnick (1972) made aversive stimulation contingent upon behaviors that reliably preceded seizures, and Wright (1976) also administered electric shock contingent on subclinical EEG abnormalities. Zlutnick, Mayville, and Moffat (1975) punished pre-seizure behaviors, and also reinforced the seizure-free behavior of one of their five subjects. Decreased seizure frequencies were reported on each of the above studies, but were especially large and consistent in four of the five subjects studied by Zlutnick et al (1975).

Dorcus and Schaffer (1945) provide the sole example of a seizure avoidance procedure. These authors instructed their patient to self-administer noxious asafetida three times daily until seizures improved; it was reported that seizures stopped within three days.

Finally, Gardner (1967) employed a combination of reinforcement and extinction. Successful seizure rate reduction was reported to follow from an intervention during which attention previously given to seizure behavior was discontinued and appropriate seizure-free behaviors were reinforced.

Taken together, the studies discussed thus far indicate that epileptic seizures can be modified behaviorally. Unfortunately, few experiments have been performed; control groups are almost uniformly non-existent. Thus, as mentioned previously, no evaluation of any procedure's effectiveness in reducing seizure rate and/or severity is possible.

As will be seen, this last point also applies to SMR conditioning. What sets the SMR studies apart from most of those already discussed, however, is a clearly stated neurophysiological hypothesis which explains the supposed anti-epileptic effects of SMR training. The research that led to the formulation of this hypothesis is described in the following section.

The Sensorimotor Rhythm

The SMR was first defined for the cat EEG, and has been studied intensively by Sterman and his colleagues (see review by Chase, 1974; Sterman, 1973, 1977). In an early experiment, Wyrwicka and Sterman (1968) attempted to condition SMR operantly. The 12-20 Hz spindle activity recorded from the coronal gyri of food-deprived cats was first detected visually, from EEG tracings, and 0.5 cc of milk presented to a cat on each SMR occurrence. Once SMR reliably occurred, a series of SMR conditioning, extinction, and non-SMR (desynchronized activity) conditioning sessions was instituted. Two important observations were made in this experiment. First, it was reported that SMR was conditioned. Second, complete behavioral immobility was displayed immediately prior to and during bursts of SMR. Wyrwicka and Sterman concluded that immobility was necessary but not sufficient for SMR, since immobility consistently preceded in time the EEG spindle activity but not all occasions of immobility were accompanied by SMR. It was proposed that both SMR and postural immobility reflected a

central nervous system state of inhibition established through reinforcement of the instrumental SMR response.

That a relationship between SMR training and epileptic seizure-resistance might exist was first proposed by Sterman, LoPresti, and Fairchild (1969). These investigators were attempting to specify the behavioral manifestations of CNS seizure activity produced by injections of monomethylhydrazine (MMH), an aircraft propellant. Six cats received 9 mg/Kg of MMH intraperitoneally (convulsive dose), and three of these cats had previously undergone SMR training. Although the onset latencies of restlessness, vomiting, vocalization, panting, salivation, hyperactivity, and subcortical seizure activity were about equal for the SMR-trained and untrained animals, a significant delay in escape behavior and convulsions (both behavioral and widespread cortical epileptiform activity) was reported for the SMR-trained animals. It was this finding that motivated Sterman and his colleagues to search for a human analogue to the feline SMR.

Sterman and Friar (1972) reported the existence of SMR in a human epileptic trained to produce this rhythm. The human SMR was said to be a saw-tooth waveform of 12-14 Hz recorded over the sensorimotor cortical area from scalp electrodes, similar to the en arceau rhythm described by Gastaut (1952), but detectable only through the use of high-gain amplifiers and sharp bandpass filters. The subject, who had participated in SMR training for 16 months at the time of publication,

was concurrently receiving anti-convulsant medication which did not adequately control her generalized major motor seizures. During training, each SMR burst activated a visual feedback device, and feedback was automatically disabled whenever epileptiform activity or high-voltage scalp EMG activity occurred. Each session was 30-60 minutes long, and one or two sessions were scheduled weekly.

Although no statistical analyses were performed on the data, the following changes were attributed to SMR training: (1) The percent-time SMR observed during pre-feedback baselines increased as training progressed; (2) Increases in percent-time SMR during feedback from pre-feedback baseline levels became greater as training progressed; and (3) There was a reduction in seizure rate.

Sterman and Friar (1972) proposed that the increase in percent-time SMR led to a generalized decrease in cortical excitability, which was reflected by the decrease in seizure frequency. They based their hypothesis on the following data: First, SMR in cats is related to repeated activation of a thalamocortical network (Howe and Sterman, 1967). Second, activation of this thalamocortical network is associated with the synchronous discharge of inhibitory thalamic neuronal pools (Andersen and Andersson, 1968; Howe and Sterman, 1967). Third, repeated electrical stimulation of partially isolated cat cerebral cortex, presumably assumed to be analogous to the thalamocortical activity underlying SMR, prevents the cortical supersensitivity resulting from cortical isolation (Rutledge, Rank, and Duncan, 1967).

Sterman and his colleagues have since reported data on five additional epileptics given SMR training for periods ranging from 6 to 18 months (Sterman, 1973, 1977; Sterman, MacDonald, and Stone, 1974). The pathologies of the four subjects include a major motor disorder, a mixed seizure disorder (petit mal variant), an adult petit mal disorder and two clonic-tonic disorders. Reductions in seizure frequency were reported in all cases. In these later studies it was reported that SMR training also resulted in increased SMR amplitude and a decrease in the percent-time that abnormal, low-frequency discharges were present during feedback. In addition, abnormal EEG patterns and seizure frequencies were said to return to pre-feedback levels within six weeks following discontinuation of training. However, no statistical descriptions or analyses of either seizure frequency or EEG changes were provided.

Similar results have been reported by Finley (1974, 1975, 1977; Finley, Smith, and Etherton, 1975) who employed one subject with atonic seizures and one subject with psychomotor seizures. Finley, however, did not observe a return of seizure rate to pre-treatment levels when non-contingent feedback was delivered for seven weeks following a year of SMR training. Lubar and his associates (Lubar, 1975, 1977; Lubar and Bahler, 1976; Seifert and Lubar, 1975) have reported decreased seizure rates in six out of eight subjects spanning a wide range of epilepsies. The training procedure employed by these investigators has paralleled that of Sterman, including the signalled interruption of feedback by abnormal slow-wave activity, spike discharges, and high-voltage scalp EMG.

Kaplan (1974, 1975) is the only SMR investigator to report negative findings; she reported that SMR training had no discernable effects on the clinical EEG's, seizure frequencies, or EEG power spectra of two epileptics (one with grand mal and one with akinetic seizures). Following this negative outcome, Kaplan enlisted three patients, all with stress-precipitated seizures (the akinetic epileptic from the first study, plus one patient with petit mal and one with psychomotor seizures), in a program in which the production of "low-frequency synchronous activity" (thought to be a mixture of alpha and mu, a sensorimotor cortex "resting rhythm"; see Kiloh, McComas, and Osselton, 1972) was reinforced. Although no EEG changes followed that could be attributed directly to training, seizure frequency decreased for all three subjects (although one subject's improvement immediately followed a change in medication). Kaplan concluded that these results were not due to training EEG-synchrony, since no changes were found in the EEG power spectra. The reductions in seizure frequency observed in this study and in SMR investigations were attributed to the subjects' learning to function at a lower level of arousal as a consequence of the relaxation presumably imposed by the feedback situation.

In summary, two hypotheses have been proposed to account for the decreases in seizure rate that have been reported in studies of SMR conditioning. The first hypothesis states that SMR is related to processes involved in seizure inhibition (Lubar and Bahler, 1976; Seifert and Lubar, 1975; Sterman, 1973, 1977; Sterman and Friar, 1972).

In particular, Sterman (1973) has proposed that seizure control is gained through overuse of thalamocortical inhibitory circuits which promotes a generalized decrease in cortical excitability. The second hypothesis (Kaplan, 1975) holds that SMR training per se has nothing to do with reduced seizure rate. Rather, the feedback situation is said to be structured so that subjects learn to function at a lower level of arousal, which produces a decrease in stress-related seizure incidence.

The first hypothesis is of special importance since it holds that the procedure directly influences CNS processes involved in the inhibition of paroxysmal discharges. SMR conditioning would be said to affect the disease process rather than its symptoms and signs, since it effectively isolates the tissue involved in seizure generation. Unfortunately, no experiments which could permit a test of this assumption have been reported.

There has not even been an effort made to separate the SMR reinforcement and time-out aspects of the SMR + TO procedure. These two variables have apparently been completely confounded in all of the SMR + TO studies that have been discussed. Possible effects of the time-out variable are considered below. However, it should be pointed out here that SMR + TO investigators have treated the time-out as no more than a necessary condition for SMR reinforcement.

Of the nine published studies referred to above, none report control groups in which SMR was not reinforced or in which SMR was reinforced but no time-outs were employed. Sterman (1977) has reported

preliminary data on two epileptics for whom reinforcements and time-outs were made contingent on SMR activity and low-frequency activity (presumably including slow waves considered as abnormal in the waking EEG; see Kiloh et al., 1972), alternately. That is, reinforcement was initially contingent on SMR with time-outs for slow activity; these contingencies were then reversed for an equivalent period of time, and finally the initial contingencies were reinstated. The data do indicate that reinforcing slow waves with time-outs for SMR does not reduce seizure frequency, but shed no light on the necessity or sufficiency of SMR increases for decreasing seizure rate. In the most recent SMR publication, Sterman and MacDonald (1978) have reported further results from the same study. Data for six subjects, in addition to the two reported on in the paper cited above, are presented. Two subjects were treated identically to the subjects described by Sterman (1977), except that reinforcement was initially contingent on slow-wave activity. Treatment of the remaining two pairs of subjects was analogous to treatment of the first two pairs, except that 18-23 Hz activity was substituted for SMR (defined in this paper as waves from 12-15 Hz). Subjects who initially began with reinforcement for either SMR or 18-23 Hz activity were terminated with the initial contingencies after one intermediate reversal, but the remaining subjects never finished with reinforcement for slow-waves. That is, training always ended with reinforcement for SMR or for 18-23 Hz activity. No rationale was given for this procedures. Two of the six subjects did not reliably decrease seizure rate; one of these subjects

received reinforcement for 18-23 Hz activity and the other received SMR reinforcement. This suggests that reinforcement for SMR is not necessary for decreasing seizure frequency.

Finley (1977) has reported using non-contingent reinforcement following the SMR + TO procedure, on one epileptic. Seizure frequency dramatically decreased during SMR + TO training. Although seizure rate increased with the initiation of non-contingent reinforcement, this increase was not statistically significant.

In fact, the author knows of no experimental evidence that would suggest that SMR has any relationship to seizure frequency. According to Sterman's (1973) hypothesis, SMR density should be inversely proportional to seizure rate within and perhaps also between subjects, even if no SMR training is administered. There has been no attempt to correlate these two variables prior to SMR training.

The relationship of SMR to seizure rate during SMR training is also unclear. Sterman (1976) has failed to replicate his initial serendipitous finding (Sterman et al., 1969) that seizure latency following the administration of MMH is significantly longer in SMR-trained cats than it is in normal, unoperated controls. Kaplan (1974, 1975) reported using SMR training with no time-outs on two epileptics and found no changes in seizure frequency. Finley (1977) found in two subjects that both percent-time SMR and seizure rate were correlated with trials, but that there was no significant correlation between seizure rate and percent-time SMR. In contrast to this last result, Kuhlman (1974, 1976)

reported that three non-epileptics could not even be trained to increase the density of 12-14 Hz sensorimotor activity, although three other normal subjects did increase 9-11 Hz activity, thought to be the mu rhythm; three of five epileptic subjects trained to increase 9-14 Hz activity showed decreases in seizure frequency (Kuhlman and Allison, 1977).

Kuhlman's (1974, 1976) failure to obtain significant increases in SMR density is especially troubling when one examines the evidence cited in support of the claim that subjects can enhance SMR. For example, although some method of SMR quantification was employed during pretraining in most of the SMR studies cited above (Finley, 1977; Finley et al., 1975; Lubar, 1977; Lubar and Bahler, 1976; Seifert and Lubar, 1975; Sterman, 1977), and during training by all previous investigators, there is little consistency in the method of quantification between studies, and often little consistency between subjects in the same study. With respect to pretraining EEG measures, Sterman (1977) shows a graph of percent-time SMR for one subject, with no description of the number of recordings or time per recording on which the data are based, and one sleep-EEG compressed power spectral array is shown for the other subject. Finley (1977) and Finley et al. (1975) graph one subject's percent-time SMR and percent-time slow-wave activity during a two week pretraining period, but once again neither the number of recordings nor the recording time is stated, and no pretraining data are given for the other subject. In the series of studies by Lubar and his

colleagues (Lubar, 1977; Lubar and Bahler, 1976; Seifert and Lubar, 1975), an estimate for each subject of the number of SMR bursts on which reinforcement was later made contingent was derived from a single 40-minute recording. In light of the large variability over time characteristic of most EEG measures (e.g., Kiloh et al., 1972), this seems grossly inadequate.

It is perhaps significant that in the latest published study Sterman and MacDonald (1978) refer to SMR only in passing, and discuss obtained decreases in seizure frequency in relation to normalization of EEG rather than increases in SMR. As pointed out below, results of single-cell studies make it unlikely that reinforcement of the rhythmic SMR activity leads to EEG normalization. Reduction of EEG abnormalities, if obtained, is more likely to follow from the time-out aspect of the SMR + TO procedure.

The Time-Out Variable

In each of the SMR + TO studies, the conditioning procedure included clearly signalled time-outs contingent on slow-waves, spike activity, and/or high-voltage EMG activity. A time-out is a period during which reinforcement is not available. That is, SMR was not reinforced during epileptiform activity or body movement or tension, and the unavailability of reinforcement was indicated to the subject by a signal.

In the studies discussed above, the time-out was considered as a necessary procedural variable (Finley, 1977; Lubar, 1977), since high voltage EEG spikes and sharp waves and EMG bursts could cause

the bandpass filter used in the SMR recognition circuit to "ring", producing SMR reinforcements. That is, the active analog filters used to detect SMR effectively suppress most EEG activity outside the SMR frequency band. However, high-voltage transients such as epileptiform spikes and sharp increases in EMG activity cause the filter to overshoot the input waveform and to resonate at its center bandpass frequency, so that one high-voltage spike would result in a damped train of SMR period sine waves in the filter's output. Therefore, it is necessary to gate SMR reinforcements with a circuit for detecting epileptiform activity and high-voltage scalp EMG activity.

In addition to serving this gating purpose, however, the omission of reinforcement could act as an aversive stimulus. Leitenberg (1965) has reviewed studies which demonstrate that this is a punishment procedure in that skeletal behaviors leading to time-out are suppressed. With respect to the SMR + TO procedure, the time-out may suppress the abnormal EEG activity and high-voltage scalp EMG activity on which it is contingent. The time-out might also lead to the development of either a discriminated avoidance or escape response; that is, the detection of stimuli related to the epileptiform activity that produces the time-out, and the acquisition of some response that prevents or terminates this activity. A decrease in the probability of epileptiform activity might account for a decrease in the frequency of seizures. The procedural variable that leads to the reduction of seizure activity in the SMR + TO procedure might be

the signalled removal of reinforcement rather than the SMR training itself.

There is some evidence that supports this notion. Operant conditioning of "normal" firing patterns in single-cells from alumina cream foci in monkeys leads to decreased seizure rates and is correlated with EEG desynchronization (Wyler and Fetz, 1974; Wyler, Fetz, and Ward, 1974). On the other hand, rhythmic EEG discharges akin to the human SMR were coincident with abnormal single-cell bursting (Wyler and Fetz, 1974).

Furthermore, although the results of studies in which epileptics were taught to escape or avoid epileptiform activity are not conclusive (Korein, Maccario, Carmona, Randt, and Miller, 1971; Ounstead, Lee, and Hutt, 1966), there is evidence that learned EEG desynchronization leads to reduced seizure rates. Wyler, Lockard, Ward, and Finch (1976) reinforced desynchronized EEG activity in four epileptics and obtained depressed seizure frequencies. A placebo-control subject who received operant conditioning of low EMG amplitude activity withdrew from the study after three weeks in order to be eligible for a change in medication.

In summary, there is no evidence for the hypothesis that increased SMR density is either necessary or sufficient for decreasing seizure frequency. There is also no indication that SMR density is even correlated with seizure rate, and it is questionable whether subjects can learn to increase SMR density.

It is possible that the time-out could be the variable responsible for the observed decreases in seizure rate. There is some evidence in support of the hypothesis that learned EEG desynchronization ameliorates seizures, although the effects of training epileptic subjects to escape signals contingent on epileptiform activity are not clear.

In general, a comparison of the SMR + TO reports with studies applying other non-medical techniques shows that few of the latter have been applied to a wide variety of seizure disorders. Indeed, most of these procedures are conceptually fixed to a particular pattern of seizure and/or pre-seizure events, either electrophysiological or behavioral.

That the effects of SMR + TO training have been replicated in a number of laboratories makes it evident that we are dealing with a robust phenomenon. Unfortunately, the deficiencies in methodology discussed above make any statements regarding the mechanism underlying amelioration of seizures purely speculative. In short, controlled experiments are required to test hypotheses regarding variables of presumed importance. The following chapter presents the type of experimental design chosen for this purpose and the rationale for this choice.

Chapter 3

RATIONALE

The two experiments described below were conducted in order to meet a set of objectives considered to be requisite for describing the mechanism by which SMR + TO training leads to decreases in seizure rate. Initially, predictions following directly from the hypothesis that amelioration of seizures is due to increased SMR density had to be tested. It was therefore necessary to determine: (1) if SMR density is related to seizure frequency, either prior to training or during training; (2) if increases in SMR density from pretraining values can be achieved; and (3) if any observed increases in SMR density are necessary or sufficient for decreasing seizure rate. These objectives follow logically from the discussion of previous SMR research presented in the last chapter, and they form the main focus of the first experiment of this thesis.

The rationale for studying the SMR + TO procedure is based on a number of considerations. First, SMR + TO training has in common with other non-medical approaches three strong arguments for further investigation: It circumvents harmful side-effects inherent in pharmacologic and surgical therapy, it has been successfully applied to patients unresponsive to various anti-epileptic pharmacologic regimens, and, if a short-term placebo-type mechanism is not responsible for the reductions in seizure rate, it may prove to be a curative form of

therapy.

In addition, it has been pointed out in Chapter 2 that this is the only non-medical approach which has been shown to be applicable to a wide range of seizure-types and which apparently does not depend upon a particular behavioral analysis of environmental seizure maintenance. Although operant conditioning of skeletal behaviors has also been applied to several seizure disorders, most of these reports are clinical case studies and their effects have been recorded for few subjects, often without replication. The punishment procedure employed by Wright (1973) and by Zlutnick and associates (Zlutnick, 1972; Zlutnick et al., 1975) accounts for six of the ten subjects participating in studies based on operant conditioning of skeletal behaviors, and requires that subjects emit behaviors highly predictive of impending seizures. Applications of operant conditioning of EEG activity other than SMR (Kaplan, 1975; Kuhlman, 1974, 1976; Kuhlman and Allison, 1977; Wyler et al., 1976) suffer from methodological deficiencies, including an absence of control groups. The results of these studies suggest that the SMR + TO procedure may effect decreases in seizure rate via desynchronization of EEG activity (Wyler et al., 1976), relaxation (Kaplan, 1975), or a placebo mechanism having no relationship to the bioelectric activity on which reinforcement is contingent (Kuhlman and Allison, 1977). That is, these studies might be useful in constructing alternatives to Sterman's (1973) hypothesis, but they fail to test that hypothesis.

A further aspect of the rationale concerns the independent variables chosen for manipulation and the type of experimental design utilized for assessing the effects of those manipulations. The studies described below were conceived as a means of describing various relationships that obtain between the operations involved in SMR + TO training, the responses presumably influenced by those operations, and seizure frequency. Most of the hypotheses that are generated from assumptions regarding the nature of those relationships can be tested in individual subjects. A basic tenet of the experiments reported below is that analyses of group data from factorial experimental designs are of limited value for the type of hypotheses tested in this relatively undeveloped field of research. Rather, intensive descriptive analyses of individual subject data are called for. There are a number of reasons for employing this type of data analysis.

The main hypothesis states that an elevated density of a particular EEG rhythm causally effects seizure reductions. There is no guarantee that any specific set of operations designed to bring about certain well-defined alterations in the EEG will in fact have their desired effects, or that other sets of operations (e.g., for control groups) will not bring about similar or even identical changes. This means that changes in seizure rate must be related to the putative causative agent (a change in SMR density) primarily, and only

secondarily to the operation that is presumed to influence that agent (reinforcing SMR).

Furthermore, individual tests of the relationship between the agent proposed to effect seizure reduction and changes in seizure rate can be useful in constructing new hypotheses. For example, if subjects who do not significantly increase SMR density as a function of training do not show decreases in seizure rate, and if only a percentage of those subjects who do increase SMR density decrease seizure rate; then an increase in SMR density would be considered necessary but not sufficient for decreasing seizure frequency. Such a result would also imply significant individual differences in the effectiveness of increasing SMR density, and thus indicate the existence of other important variables. Simple between-group analyses can, of course, be performed as a first step in evaluating the differential effectiveness of particular operations. This is not, however, the prime objective of the present investigation. It can even be predicted that the practical necessity of utilizing a small number of subjects with widely different pre-treatment seizure rates would lead to a large Type II error probability. Thus, a conservative acceptance of the null hypothesis of no difference (between groups, within groups, interactions) in seizure rate can be expected, regardless of the treatments being compared.

Chapter 4

EXPERIMENT I

Introduction

In order to determine whether elevated SMR densities are necessary and/or sufficient for decreasing seizure frequency, one group of subjects was given SMR + TO training and another group received only the time-out component of this procedure. Only those subjects in the SMR + TO group were expected to develop higher SMR densities, and all subjects were expected to exhibit depressed time-out densities. Thus, changes in seizure rate could be evaluated and related to changes in EEG activity in order to test the necessity and sufficiency of increased SMR density for decreasing seizure rate.

Prior to describing the methods employed in this experiment, two issues regarding data analysis should be considered. One issue concerns the evaluation of changes in seizure rate, and the other concerns the types of relationship that might be assumed to hold between SMR density and seizure frequency.

Because evaluations of changes in seizure frequency depend upon the measure of pretraining seizure rate, a description of pretraining data is necessary. An analysis of the effects of training on seizure rate might, for example, be based on a comparison of the

total number of seizures occurring during 30-day intervals of training to the number of seizures reported for a 30-day pre-training period. If the seizure rate tends to be consistently lower during training, it would be valuable to know something about the temporal pattern of seizure emission during pretraining. For example, a constant seizure rate during pretraining (i.e., a linear relationship between the cumulative number of pretraining seizures and days of pretraining), if followed by a consistently smaller seizure rate during training, would provide good evidence for the procedure's effectiveness. If the pretraining rate changed as a function of time, less confidence could be placed in a rate-shift during training, because the pretraining rate estimate would be suspect. The worst possible case would occur if the pretraining rate decreased as a function of time. It would then be reasonable to hold the hypothesis that any further decrease in rate observed during training merely continued the pretraining trend.

A similar problem exists in the case of more complex statistical tests suitable for an analysis of individual subject seizure data. Such tests might posit a Poisson process as the generator of seizure events (Feller, 1968). If seizure rate waxes and wanes during pretraining, then the probabilistic rate parameter central to tests of changes in seizure rate (Poisson test and exponential test) cannot be assumed to be constant (Cox and Lewis, 1966).

Because of the importance of pretraining seizure rate patterns, these data are described in some detail in the results of this experiment.

The second issue derives from consideration of the neurophysiological mechanism hypothesized to underlie the effectiveness of the SMR + TO procedure. It has been hypothesized (Sterman, 1973) that SMR + TO training reduces seizure frequency because high densities of SMR represent activity of a thalamocortical network that decreases cortical excitability. This hypothesis might, for lack of further explanation, be construed in two ways. It might be assumed that this hypothesis implies that in a population of epileptics, those with higher SMR densities will emit fewer seizures than those with lower SMR densities, and that increasing an individual epileptic's SMR density will lower that individual's seizure rate. This might be called a "strong" version of Sterman's hypothesis, since it posits both between- and within-subject seizure rate - SMR density relationships.

A weaker version of this hypothesis would hold that within any individual epileptic, an inverse relationship between SMR density and seizure rate exists. Thus, as an epileptic's SMR density waxes and wanes over time, seizure rate should decrease and increase, respectively. According to this interpretation, however, no between-subject correlation would exist. It could be, for example, that the same SMR density exists in two subjects with very different seizure frequencies. Nevertheless, increasing SMR density beyond this level would still be expected to decrease the seizure rates of both individuals. The EEG and seizure

data collected in this experiment were examined for both within- and between-subject SMR-seizure rate relationships.

Method

Subjects

Eight epileptic outpatients were obtained from the epilepsy clinic at McMaster University Medical Centre. Each patient who was chosen to be a subject met the following criteria: no major metabolic disorders; no sensory precipitation of seizures; seizures not primarily nocturnal; some motor involvement in clinical seizures; clear interictal epileptiform activity which triggered the time-out circuit reliably; and seizures described clinically as being poorly controlled by medication following various treatment procedures.

The patients' medical files and an interview between the patient and the experimenter were employed in order to determine the mean seizure rate, clinical history, seizure manifestations, medication schedule and interictal EEG pattern. A 40-minute recording session was also used to determine whether interictal epileptiform activity triggered the time-out circuit. After being accepted for participation, each patient remained under the care of Dr. Adrian Upton, director of the epilepsy clinic, who agreed to alter the anticonvulsants taken only if seizures became dangerously stronger or more frequent, to perform periodic medication serum level checks (a standard practice at the clinic), and to attempt to hold constant serum levels of prescribed medication. Serum levels were checked approximately once per month, and the amount of medication

changed if the levels were either above or below recommended levels.

Subjects were randomly assigned to one of two groups following acceptance. Four subjects were chosen to receive SMR + TO training, and four received TO training alone. Descriptions of each subject are presented in Table 1.

Procedure

Pretraining and training sessions

There were two 40-minute sessions scheduled per week, over a period of 210 days. An attempt was made to have each subject come at the same times each week, although exceptions to this were sometimes unavoidable. During a 30-day pretraining period (8 sessions), seizure and EEG data were collected as described below, but no feedback was delivered. The subjects were instructed to sit and relax, with eyes open, while bipolar EEG data were gathered from electrode sites C_3-T_3 and C_4-T_4 of the International Ten-Twenty System (Jasper, 1958). The remaining 180 days were devoted to training sessions. This time limit was chosen because the results of the previous SMR investigations suggest that subjects who improve do so within six months of training (Lubar, 1977).

The training procedure was modelled after that employed by Lubar and his colleagues (Lubar, 1975; Lubar and Bahler, 1976; Seifert and Lubar, 1975). Each session consisted of: five minutes of baseline recording without feedback; 15 minutes of feedback contingent on activity recorded alternately on each succeeding session from C_3-T_3 or C_4-T_4;

Table 1. Descriptions of subjects employed in Experiment I.

	Subject	Sex	Year of Birth	Age At first Seizure	Type(s) of Seizure	Auras	Medication	Mentally Retarded
TO	T1	M	1948	6 mo.	psychomotor	Yes	Valium Mysoline Dilantin	No
	T2	F	1957	9 mo.	major minor temporal	Yes	Dilantin Phenobar-bital	No
	T3	F	1962	4 mo.	grand mal	N/A	Mysoline	Yes
	T4	F	1950	19 yr.	deja vu psychomotor	No	Dilantin	No
SMR + TO	ST1	F	1955	12 yr.	psychomotor	Yes	Mysoline	No
	ST2	M	1963	6 yr.	tonic-clonic drop absence	Yes	Phenobar-bital	Yes
	ST3	M	1951	5 yr.	focal grand mal	Yes	Dilantin Mysoline	No
	ST4	M	1969	14 mo.	psychomotor	No	Dilantin	No

15 minutes of feedback from the contralateral electrodes; and a final 5-minute baseline. Stimulus presentation and on-line data analysis were carried out by a PDP Lab-8/E computer.

EEG was monitored through Grass silver/silver-chloride electrodes. After rubbing each electrode site with acetone, the electrodes were attached with small amounts of collodion and filled with conductive cream (Burton, Parsons, and Co. EKG Sol). Resistance levels between each pair of electrodes were kept below 5K ohms.

The scalp electrodes were connected to two matched Grass model 7P511 EEG amplifiers with half-amplitude filter settings at 1 and 300 Hz. The output of the amplifier on which feedback was contingent was fed to two bandpass filters, a 12-14 Hz active filter (Ross Systems Engineering) and a 4-7 Hz passive filter (Kronhite Model 335), both having rolloffs of 24 dB/octave. The computer utilized a maximum-minimum detection algorithm on the output of the 12-14 Hz filter in order to identify SMR waves. Samples were taken every two milliseconds, and at the amplifier sensitivity used (2 uV/mm), the system had a resolution of 0.33 uV. Therefore, any input to the analog-to-digital converter representing a wave with a smaller peak-to-peak amplitude $\geq$ 0.33 uV, and having a period such that (71 ± 1) msec $\leq$ period $\leq$ (83 ± 1) msec, was regarded as an SMR period wave. The occurrence of two maxima with no intervening minimum and the occurrence of two minima with no intervening maximum were disregarded,

and the number of such occurrences printed at the end of each session. Such "missed waves" never accounted for more than 5 seconds of any session. The observation of six SMR period waves within 0.50 sec was defined as an SMR burst (Lubar and Bahler, 1976).

Abnormal EEG activity and high-voltage EMG activity (time-out events) were detected in the following way. The 4-7 Hz filter output was fed to a Grass Model 7P3 integrator (TC = 0.5 sec). Whenever this integrated slow activity exceeded a voltage level equivalent to that produced by a 10 uV peak-to-peak amplitude 5.5 Hz calibration sine wave at the input of the 7P511 amplifier, a Schmitt trigger gate voltage was set. In order to detect EMG and spike activity (i.e., short rise time waves), the unfiltered 7P511 amplifier output was also fed to a second Grass integrator (TC = 0.1 sec), calibrated so that a 50 uV, 10Hz sine wave calibration input to the amplifier produced an integrator output voltage just large enough to set the gate output of a second Schmitt trigger. It was found, as indicated by Lubar and Bahler (1976), that almost all EMG activity and spike activity visible in the 7P511 output caused this second Schmitt trigger to fire. The computer recognized either Schmitt trigger output as a time-out event, with a resolution of 2 msec.

For all subjects, time-out events turned on a buzzer and illuminated a small white lamp (one cm in diameter). In addition, an oscilloscope display permitted subjects to view continuously the activity on which time-outs were contingent. The output of the integrator used to detect slow wave activity drove the horizontal sweep of the oscilloscope (sensitivity = one V/cm), and the integrator employed for EMG and

spike activity drove the vertical display (sensitivity = one V/cm). A red grease pencil was used to outline the perimeter of the upper right corner of the screen and the resting positions of the horizontal and vertical dimensions of the beam calibrated so that the dot produced would lie inside the circumscribed area only when neither integrator voltage met its time-out criterion.

For SMR + TO subjects only, an SMR burst in the absence of time-out activity produced a 0.50 sec tone and advanced a cumulative digital light counter. This counter was constructed of 10 lamps identical to the one used for time-out events. Each successive SMR burst illuminated one lamp; on the eleventh burst, all lights were extinguished.

Following Sterman (1973) and Lubar and Bahler (1976), an informal shaping procedure was utilized with SMR + TO subjects in an attempt to increase both the probability and the amplitude of SMR activity. During the first training session the amplitude criterion was set so that a 13 Hz calibration sine wave of 2 uV peak-to-peak amplitude would produce SMR burst feedback. On succeeding sessions, the criterion was increased by approximately 0.44 uV if on the preceding session the subject had received a mean of two or more SMR-burst reinforcements per minute. The amplitude criterion was never decreased.

During pretraining and the first and last five minutes of each training session, all subjects were instructed to sit and relax with eyes

open. All subjects were informed that time-out signals were produced by activity related to their epilepsy. TO subjects were told to keep the time-out signals off as much of the time as possible. SMR + TO subjects were told to produce as many SMR feedback signals as possible and that SMR feedback would not be available whenever the time-out signals occurred. Subjects were encouraged to explore different strategies with the restriction that they keep their eyes open. No specific strategies were suggested.

Collection of seizure data

Subjects and their families (and whenever possible other acquaintances) were provided with small notebooks in which times of medication administration and descriptions of seizures, including times of occurrence and ratings of intensity and duration, were recorded (see sample page in Appendix 1). In the cases of one mentally retarded subject in each group, no records were kept by the subjects themselves, although these subjects were encouraged to report seizures to family members. As mentioned above, seizure and medication recording was begun 30 days prior to the initiation of training, and continued for a period of at least 210 days. Six subjects also provided follow-up data for variable periods after discontinuation of training.

Results

There are four issues which previous SMR + TO studies have left indeterminate, and for which statistical descriptions and tests of

appropriate hypotheses are provided below. These issues involve: (1) changes in seizure rate as functions of SMR + TO training and TO training; (2) changes in SMR density and TO density as a function of training; (3) relationships of SMR density to seizure rate; and (4) relationships of TO density to seizure rate.

The analyses reported below indicate that: (1) significant decreases in seizure rate occurred in subjects from both groups; (2) changes in SMR density and TO density from pretraining were very small, even when these changes were statistically significant; (3) SMR density was unrelated to seizure rate; and (4) TO density was unrelated to seizure rate.

Analysis of Seizure Data

In order to examine pretraining seizure patterns, the cumulative number of seizures was plotted against days of pretraining for each subject in the TO alone group in Figure 1 and for each subject in the SMR + TO group in Figure 2. Inserts on each graph give the best fit linear regression equation and the coefficient of determination (r^2). Inspection reveals good linear fits for all subjects except ST1, whose seizure rate appears to climb rapidly, drop to zero, and then climb again. Although consistent variability of this sort is also exhibited by subjects ST2 and ST3, and much slower variations in seizure rate might be inferred in the cases of the remaining subjects, only in the case of ST1 is the seizure rate clearly not constant. Any analysis of this subject's seizure rate focusing on changes in the intervals between seizures would be suspect, since the duration of any interval is dependent upon the lengths of previous intervals (Cox and Lewis, 1966).

Figure 1

Regression of cumulative number of seizures on days of pretraining for subjects in the TO group.

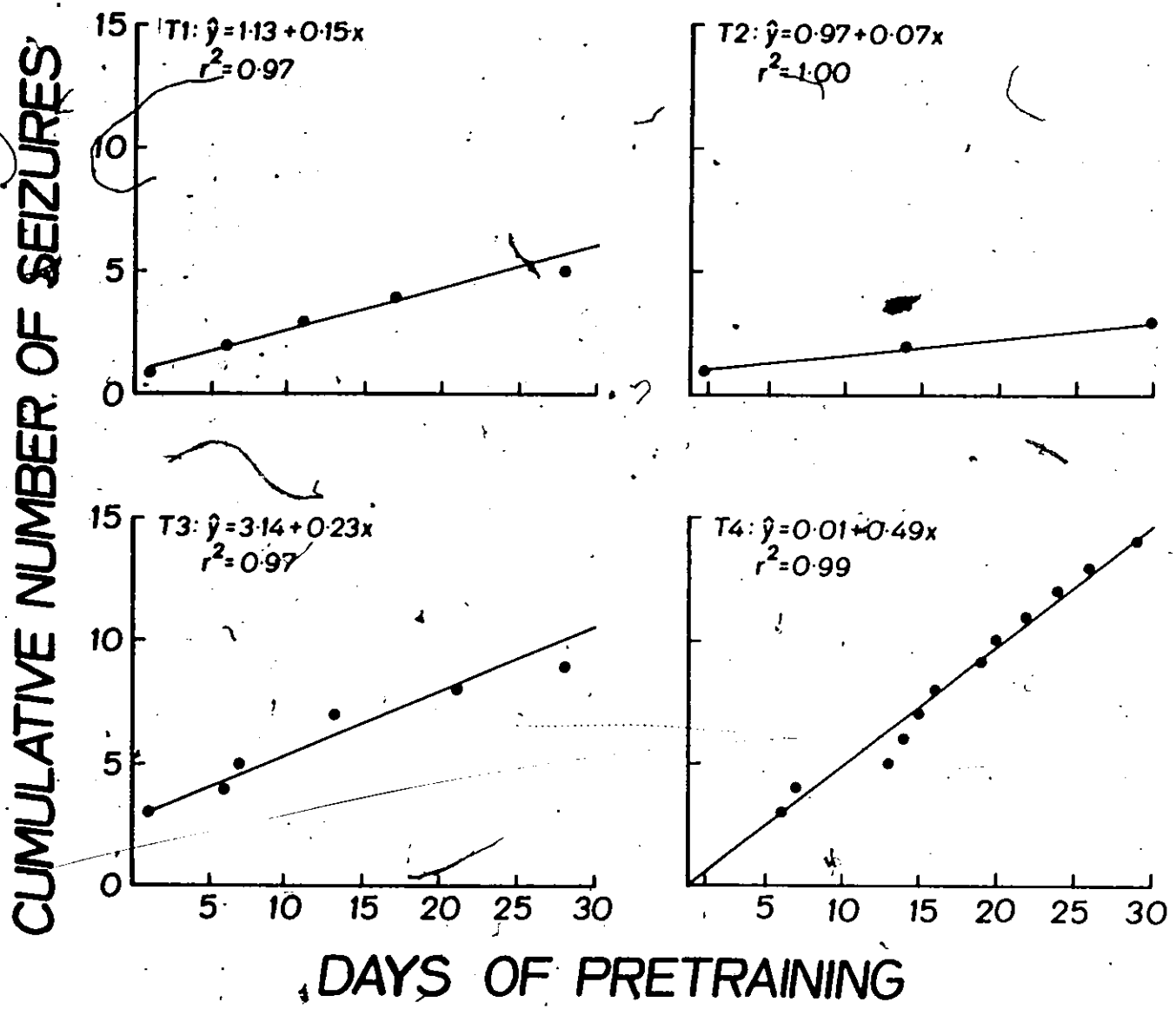
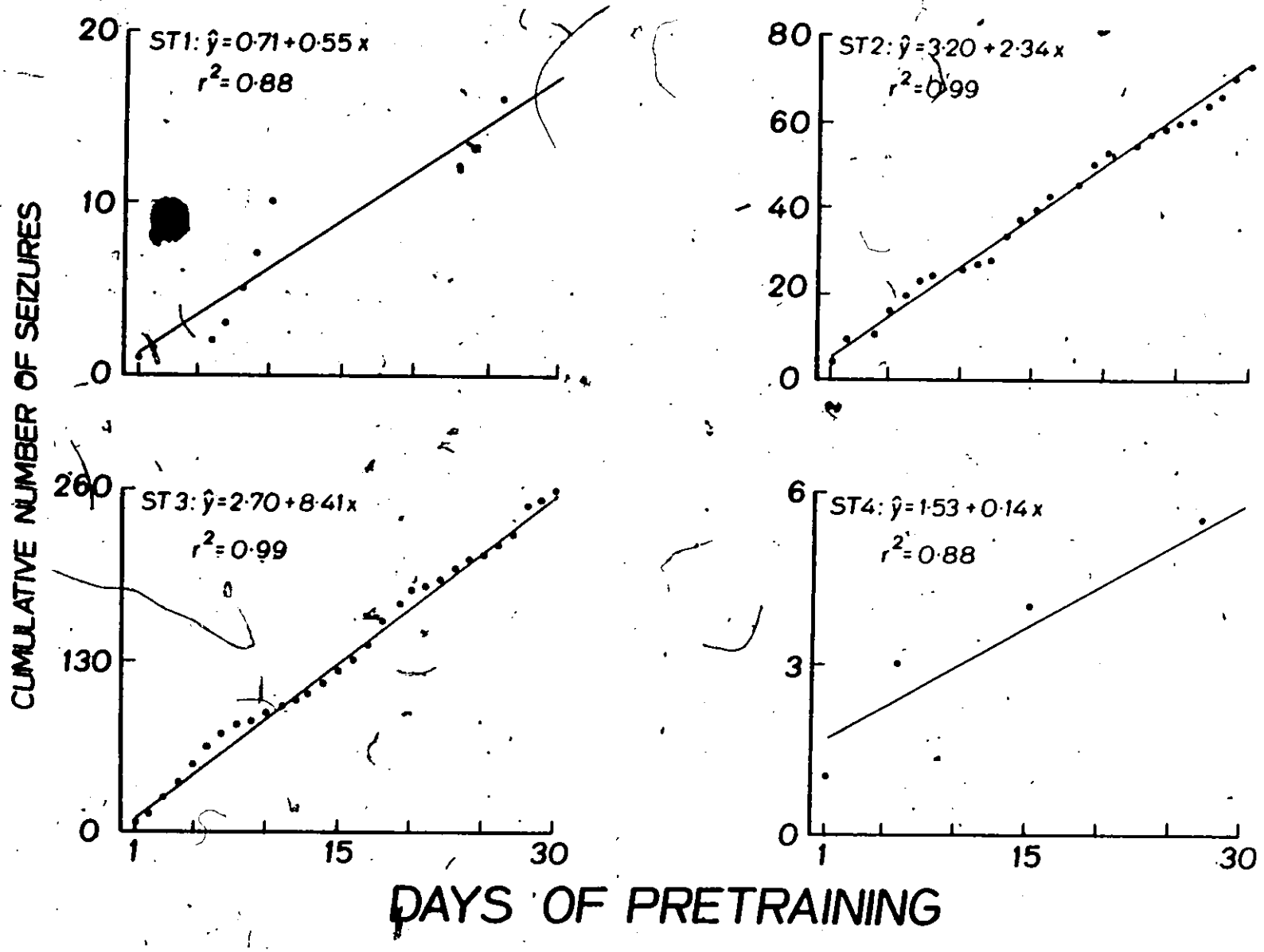

T1: ŷ = 1·13 + 0·15x
r² = 0·97
T2: ŷ = 0·97 + 0·07x
r² = 1·00
T3: ŷ = 3·14 + 0·23x
r² = 0·97
T4: ŷ = 0·01 + 0·49x
r² = 0·99
CUMULATIVE NUMBER OF SEIZURES
DAYS OF PRETRAINING
0
5
10
15
20
25
30

Figure 2

Regression of cumulative number of seizures on days of pretraining for subjects in the SMR + TO group.


ST1: ŷ = 0·71 + 0·55 x
r² = 0·88
ST2: ŷ = 3·20 + 2·34 x
r² = 0·99
ST3: ŷ = 2·70 + 8·41 x
r² = 0·99
ST4: ŷ = 1·53 + 0·14 x
r² = 0·88
CUMULATIVE NUMBER OF SEIZURES
DAYS OF PRETRAINING

In the interests of consistency, tests of changes in seizure rate in individual subjects from pretraining to the end of training will thus be limited to non-parametric analyses and tests of trend.

As a preliminary description of changes in seizure rate, totals of each subject's reported seizures per 30-day period are presented in Figure 3 for TO group subjects and in Figure 4 for SMR + TO group subjects. It is important to note that the widely different numbers of seizures exhibited by each subject required the use of differently scaled ordinates in these graphs. In order to compare estimates of pretraining seizure rate gained through the procedure described in the Method section with medical file estimates, the latter are also plotted, if available. The medical file estimates were made by the subjects' neurologist on the basis of records kept during hospital visits as inpatients as well as on the basis of verbal family reports. No detailed written records were kept by patients or their families prior to the pretraining phase of this experiment, so that the method of estimation differed from the present procedure. Available follow-up data are also plotted.

Inspection of these figures reveals the following. First, the number of seizures reported during pretraining is smaller than the medical file estimate of the pre-experimental seizure rate. Although these two estimates were arrived at in different ways, the consistently smaller value of the pretraining measure suggests one of three

Figure 3

Total reported seizures per 30-day period for TO group subjects. Note that the ordinates are scaled differently. The open circles appearing before the pretraining (PT) values (o) are estimates gained from medical file records (MF). Follow-up data are plotted for the three subjects who agreed to record seizures following termination of training.

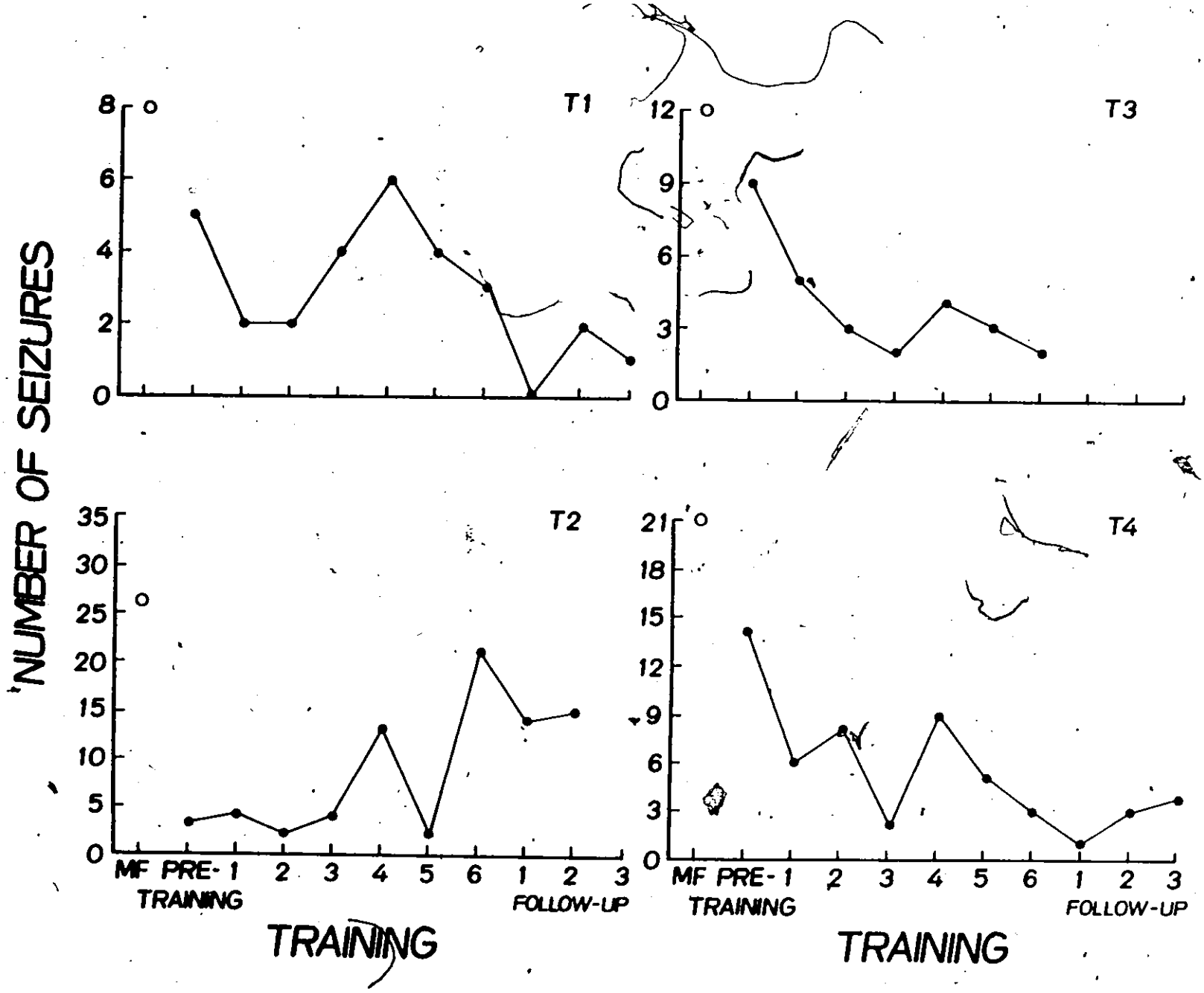
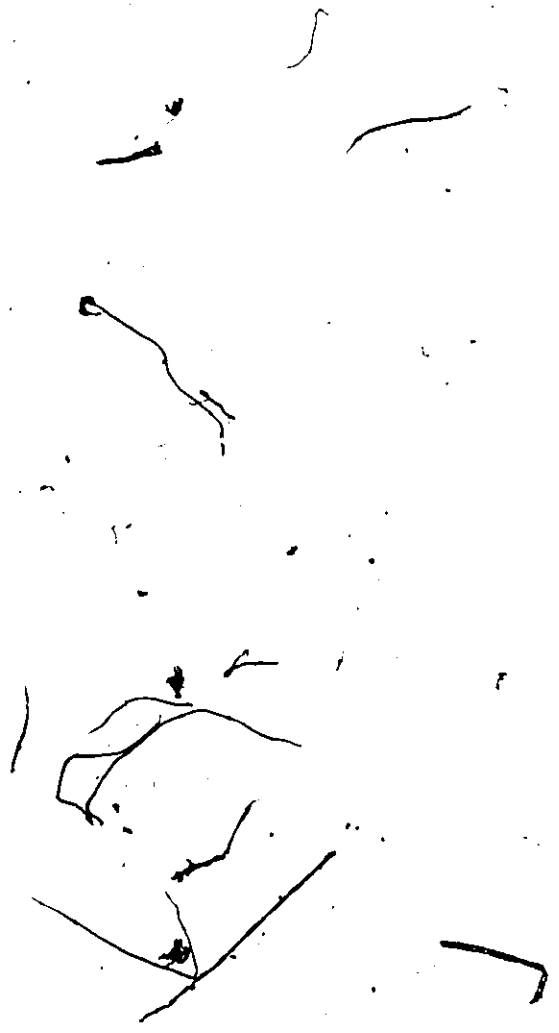
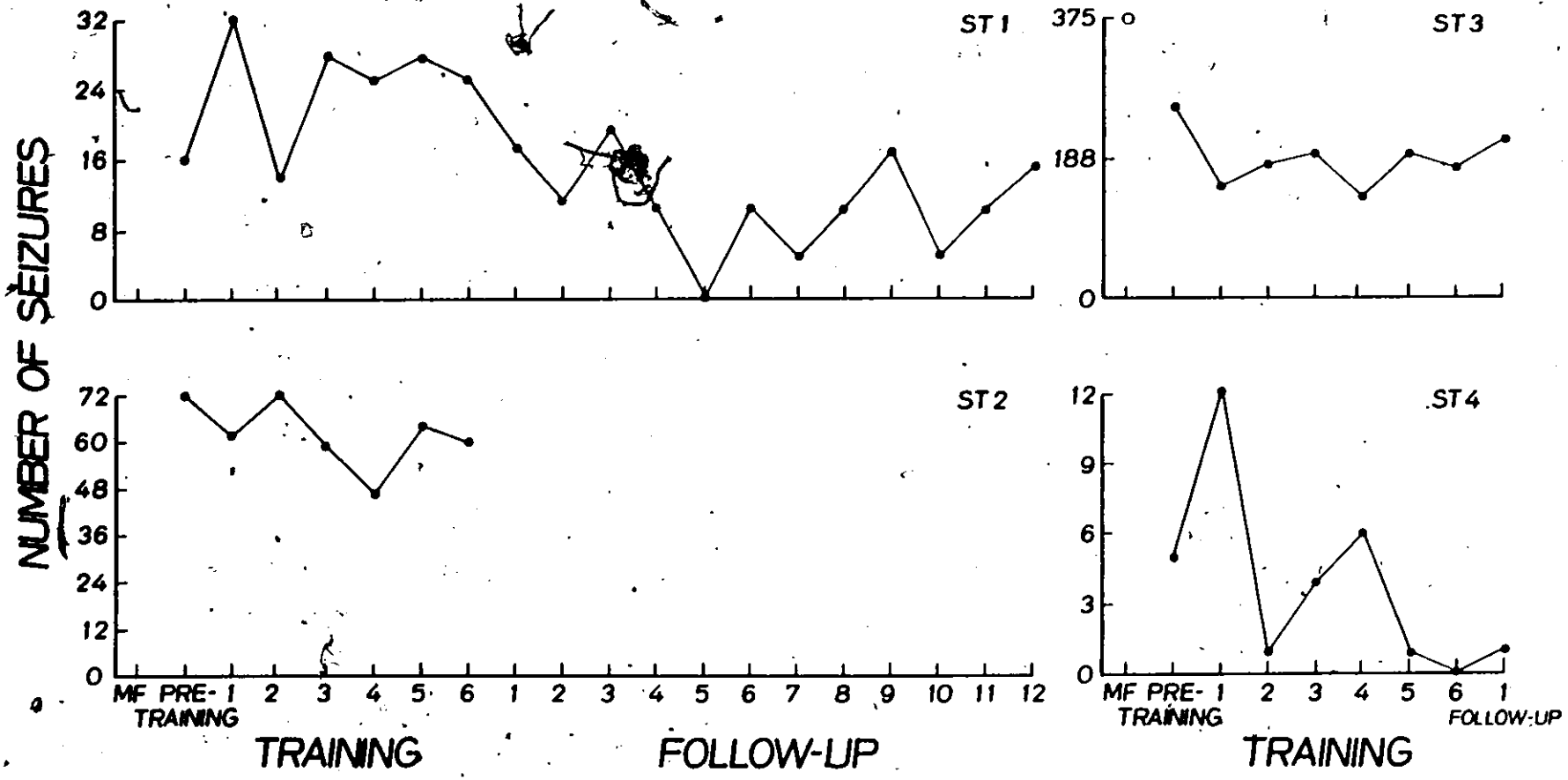

NUMBER OF SEIZURES
T1
T2
T3
T4
MF PRE-TRAINING
1 2 3 4 5 6
FOLLOW-UP 1 2 3
TRAINING

Figure 4

Total reported seizures per 30-day period for SMR + TO group subjects. Note that the ordinates are scaled differently. The open circles appearing before the pretraining values (o) are estimates gained from medical file records (MF). Follow-up data are plotted for the three subjects who agreed to record seizures following termination of training.




NUMBER OF SEIZURES
ST 1
ST 2
ST 3
ST 4
32
24
16
8
0
72
60
48
36
24
12
0
375
188
0
12
9
6
3
0
MF PRE-TRAINING 1 2 3 4 5 6 1 2 3 4 5 6 7 8 9 10 11 12
TRAINING
FOLLOW-UP
MF PRE-TRAINING 1 2 3 4 5 6 1
TRAINING
FOLLOW-UP

possibilities: that the medical file value is an overestimation; that there was a lack of compliance in keeping pretraining seizure records; or that the pretraining procedure led to decreases in seizure rate. No data bearing on these possibilities are available.

A visual comparison of reported seizures from pretraining to the end of training shows that the number of seizures decreases from pretraining for all but one subject in each group. Extra-experimental factors were clearly evident in these two cases. Subject ST1 became pregnant during the first month of training, a condition which had once before exacerbated seizures. Three sharp rises in the seizure rate of subject T2 occurred at days 68, 114, and 159 from the start of training, concomitant with, respectively, the days that T2 left home, returned home, and reported that her family relationship had not improved. Furthermore, the validity of T2's data is questionable. The neurologist indicated that he believed T2 to have many more seizures than were reported, and this was confirmed by a close companion of the subject. This subject's medical file also showed a pre-experimental rate eight times the value reported during the pretraining period.

Some evidence for the existence of seizure-exacerbating variables was also present in the records of the remaining subjects. The seizure rate of T1 fell initially, increased beginning at training day 97 (at which time T1 began running several miles daily, having every seizure between days 97 and 115 immediately after

running), then decreased again. Subject T3's slight increase in rate between training days 91 and 150 occurred during attendance at a summer camp, a rare change in the routine of this subject. T4 showed a remission at the same time, and this was concomitant with serious disagreements with her employer and ended when T4 quit the job. The seizure rate of ST2 increased prior to visits home from this subject's juvenile residence facility, ST3's lowest rate during the first 30 days of training subsequently increased with an increase in her work load which often required a 7-day, 10 hour per day work schedule, and the frequency of ST4's seizures initially increased concomitant with disciplinary problems at elementary school.

Follow-up data were provided by three subjects in each group, for variable periods of time. Subjects T1 and T4 actually show lower seizure rates during follow-up than for training, while the follow-up data for ST2, ST3, and ST4 are about the same as at the end of training. ST1's seizure rate during follow-up falls below the pretraining estimate.

A separate Wilcoxon Matched-Pairs Signed-Ranks Test (one-tailed) was employed for each subject to test the hypothesis that the number of seizures per 30-day training period did not decrease from its pretraining value. (The application of inferential statistics to single-subject data is considered in Appendix 2). This hypothesis was rejected for subjects T1, T3, T4, ST2, and ST3 at the level of significance shown in Table 2. The null nypothesis of no decrease was not rejected for

Table 2. Significance of one-tailed Wilcoxon Matched-Pairs Signed-Ranks Test on changes in seizure rate from pretraining values.

Subject	Seizure Rate Without Follow-Up	Seizure Rate With Follow-Up
T1	$p < 0.05$	$p < 0.01$
T2	N.S.	N.S.
T3	$p < 0.025$	N/A
T4	$p < 0.025$	$p < 0.005$
ST1	N.S.	N.S.
ST2	$p < 0.05$	N/A
ST3	$p < 0.025$	$p < 0.01$
ST4	N.S.	N.S.

subjects T2, ST1, and ST4. When follow-up data are included for these tests, the null hypothesis is still rejected for subjects T1, T4, and ST3, and is still not rejected for T2, ST1, and ST4. The significance levels obtained in these tests are given in Table 2.

This particular statistical test is, of course, only one way of evaluating changes in seizure rate. The null hypothesis of no decrease is rejected only if the seizure rates observed during training are consistently lower than the pretraining rate. In other words, with the small N of repeated observations available, the null hypothesis will be rejected only if the training procedure is immediately effective and remains so. The Wilcoxon test will not reject the null hypothesis if the procedure becomes effective at some point well into training. This is not a problem for any subject except ST4, whose low seizure rate at the end of training does not make much impact on the signed-ranks employed in arriving at the W-statistic.

Another, more descriptive method of examining changes in seizure rate employes comparisons of the best fit equations for cumulative seizure rate during pretraining and training. Because this procedure can be used with any order polynomial, an equation to fit a cumulative seizure record that changes slope many times can be found. The method described by Kendall (1973) was used to find, first, the lowest order polynomial yielding a low residual

or error variance when fit to the cumulative number of seizures during training, and second, moving averages of the same order polynomial to describe the smooth aspects of the cumulative record. This technique is described in Appendix 3.

Table 3 gives the residual variance after polynomials of order one through five were removed from the relation of cumulative seizure number to days of training. All of these variances are quite low. This is to be expected, since it is unlikely that a summated variable will deviate much from a linear function of time. Subjects T2 and ST1 can be eliminated from this analysis, since it is obvious that no decrease in seizure rate occurred. Of the remaining subjects, no appreciable decreases in error variance occur when polynomials of order more than one are removed from the data of T1, T3, or ST3. For subjects T4, ST2, and ST4, the largest decrement in residual variance takes place as we move from a linear to a quadratic equation. It was decided, therefore, to represent the data of subjects T1, T3, and ST3 with linear equations, and the data of subjects T4, ST2, and ST4 with quadratic equations.

Best-fit linear regression equations were calculated for T1, T3, and ST3, and 15-point moving averages were calculated for T4, ST2, and ST4. The resulting plots are shown in Figures 5 and 6, where they are compared to the best-fit linear equations for the cumulative pretraining seizure data.

Table 3. Residual variance in estimated cumulative treatment series after removal of polynomials of order one through five from cumulative training seizure number.

Subject	Order of Polynomial Removed 1	2	3	4	5
T1	0.067	0.043	0.039	0.037	0.037
T2	0.860	0.566	0.518	0.497	0.485
T3	0.050	0.034	0.030	0.029	0.028
T4	0.165	0.095	0.082	0.076	0.073
ST1	1.841	0.482	0.307	0.251	0.227
ST2	3.475	0.783	0.616	0.540	0.495
ST3	0.051	0.046	0.043	0.039	0.037
ST4	0.193	0.097	0.084	0.079	0.075

Figure 5.

Best-fit linear regression equations for the pretraining (PT) cumulative seizure number of subjects T1, T3, and T4, extended to 180 days to illustrate the predicted number of seizures with no treatment intervention. Plotted on the same graphs are the best-fit linear regression equations for the cumulative training seizure number (T) of subjects T1 and T3, and a set of 15-point moving averages based on a second-order polynomial for subject T4. Coefficients of determination (r^2) are given for each equation.

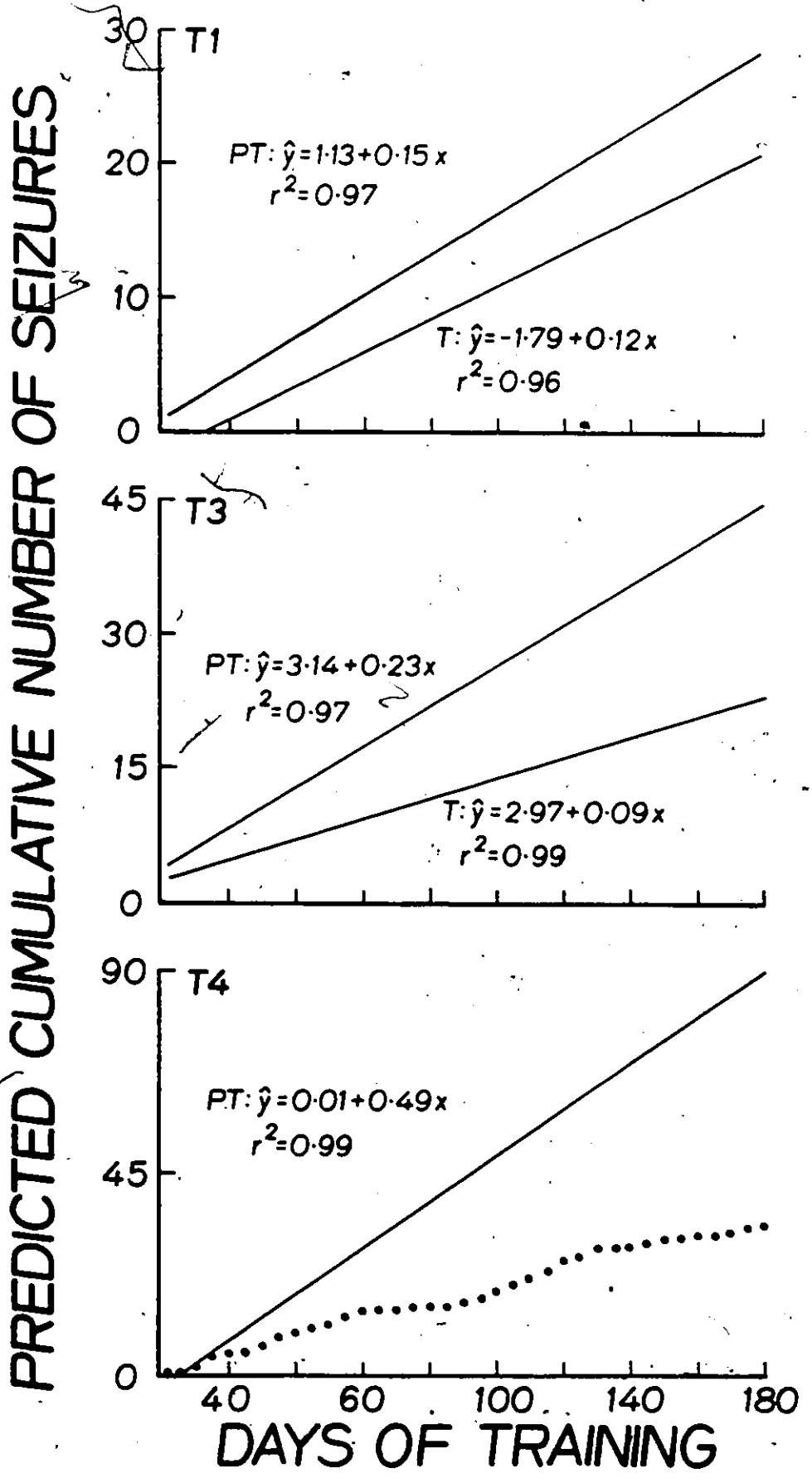
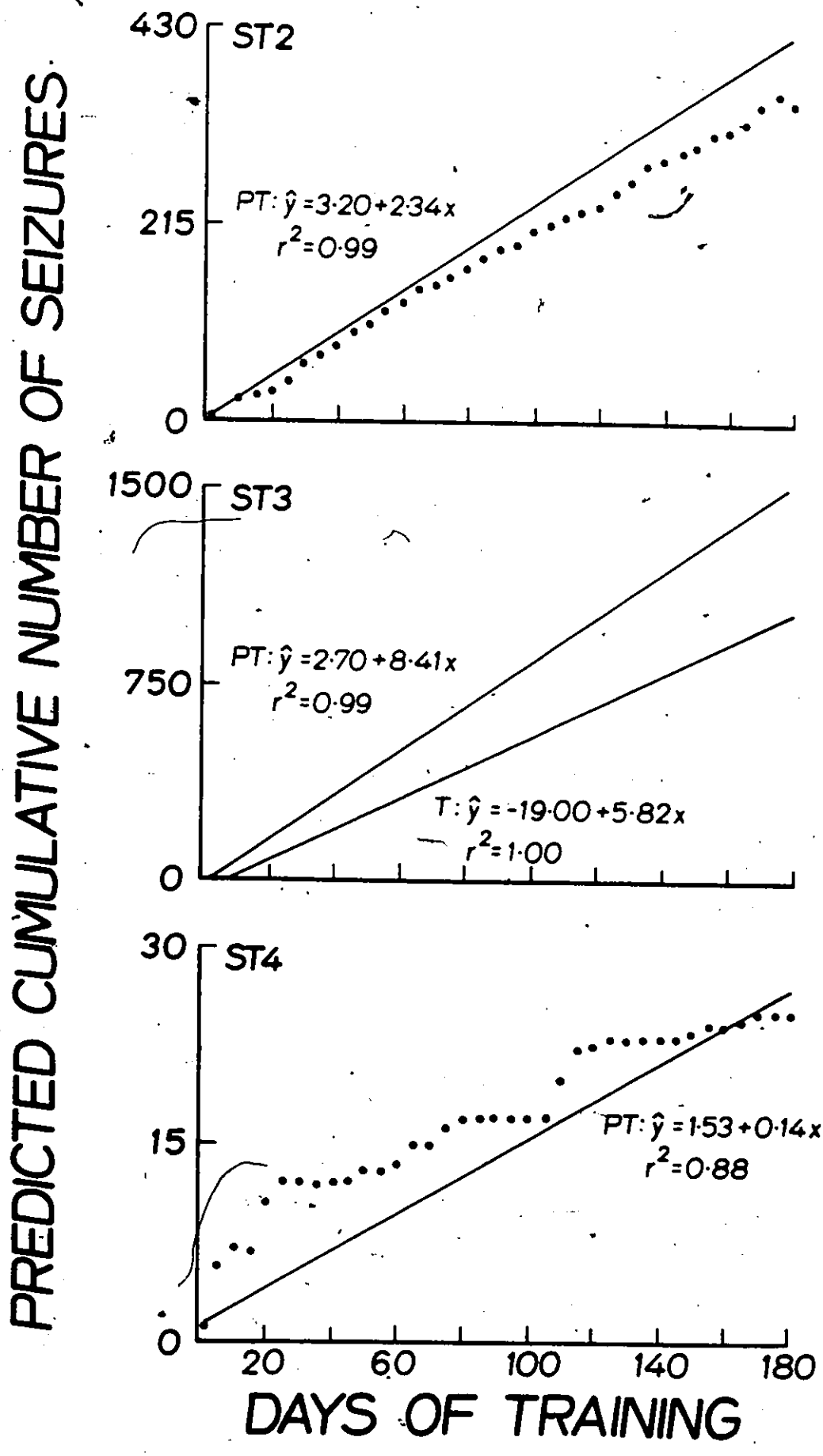

T1
PT: ŷ = 1·13 + 0·15 x
r² = 0·97
T: ŷ = -1·79 + 0·12 x
r² = 0·96
T3
PT: ŷ = 3·14 + 0·23x
r² = 0·97
T: ŷ = 2·97 + 0·09 x
r² = 0·99
T4
PT: ŷ = 0·01 + 0·49 x
r² = 0·99
PREDICTED CUMULATIVE NUMBER OF SEIZURES
DAYS OF TRAINING
0
10
20
30
15
45
90
40
60
100
140
180

Figure 6.

Best-fit linear regression equations for the pretraining (PT) cumulative seizure number of subjects ST2, ST3, and ST4, linear regression equation for the training (T) cumulative seizure number of ST3, and 15-point moving averages (quadratic) for the cumulative training seizure number of ST2 and ST4 are plotted. See caption of Figure 5 for other details.


PREDICTED CUMULATIVE NUMBER OF SEIZURES
430
215
0
ST2
PT: ŷ = 3·20 + 2·34x
r² = 0·99
1500
750
0
ST3
PT: ŷ = 2·70 + 8·41x
r² = 0·99
T: ŷ = -19·00 + 5·82x
r² = 1·00
30
15
0
ST4
PT: ŷ = 1·53 + 0·14x
r² = 0·88
20
60
100
140
180
DAYS OF TRAINING

For all subjects except ST4, these graphs provide little information other than that given by Figures 3 and 4, and confirmed by the Wilcoxon tests. The graph of subject ST4's data, however, clearly illustrates how seizure rate changed during training. The most significant aspect of this plot shows that seizure rate approached zero during the final 60 days of training, and follow-up data (see Figure 4) indicate that this trend continued after termination of training.

In summary, five of the eight subjects decreased seizure frequency from the estimated pretraining rate, as assessed by a Wilcoxon Matched-Paris Signed-Ranks Test. Three of these subjects received TO training and the remaining two received SMR + TO training. Inspection of cumulative seizure number during training, when compared to projected pretraining cumulative seizure number, shows impressive, as well as statistically significant decreases in seizure rate, for two TO subjects (T3 and T4) and for one SMR + TO subject (ST3). This inspection also suggests a significant decrease in seizure rate for subject ST4.

A statistical analysis of group seizure data was also performed. However, it was pointed out in Chapter 3 that the small number of subjects available, together with the high between-subject variance in seizure frequency (during both pretraining and training periods) produces a Type II error of magnitude sufficient to obscure both between- and within-group changes in seizure rate. A 2 X 7 (groups by 30-day blocks during pretraining and training) repeated measures analysis of

variance (described in section 7.2 of Winer, 1971) performed on the seizure rate data confirmed these expectations. As illustrated in Table 4, no F-ratios greater than those required to reject null hypotheses at the 0.05 level of significance were obtained.

Analysis of EEG Data

As in the case of seizure data, Wilcoxon tests were employed to determine whether time-out time per minute decreased and the time per minute during which SMR period waves were present increased as a function of training. Each of these variables was averaged over the feedback periods of each training session and over corresponding 30-minute periods of each pretraining session, and each training session value was compared to the mean value of the pretraining sessions. Separate tests were done for the left and right hemisphere data of each subject. As shown in Table 5, three of the four TO group subjects significantly decreased time-out time in at least one hemisphere, as did two of the four SMR + TO subjects. SMR time increased in one hemisphere for subject T1, and increased in both hemispheres for subjects T4, ST1, and ST4.

Analyses of variance identical to those performed for the seizure rate data were applied to the left- and right-hemisphere measures of mean SMR time per minute and mean time-out time per minute. Tables 6 and 7 summarize the results of these analyses. With the exception of a significant decrease in the right hemisphere mean time-out time per minute ($F(6,36) = 3.91$, $p < 0.01$), no changes in group EEG data were observed, and no between-group differences

Table 4. Summary of 2 X 7 repeated measures analysis of variance performed on seizure rate data.

Source	SS	df	MS	F
Between Subjects				
A (Groups)	55692.10	1	55692.10	2.46
Subjects within groups	135661.00	6	22610.20	
Within Subjects				
B (Blocks of 30 days)	1230.13	6	205.02	1.03
AB	1253.19	6	208.86	1.05
B x subjects within groups	7185.06	36	199.58	
Total	201021.00	55		

Table 5. Mean time-out time per minute (TO) and mean SMR time per minute (SMR) recorded from left (L) and right (R) hemisphere electrodes (Hem) during pretraining and 30-day blocks of training. Times are given in seconds. Significance levels of predicted changes found in one-tailed Wilcoxon Matched-Pairs Signed-Ranks Tests are shown in the last column.

Subject	Variable	Hem	Pretraining	Training 1	2	3	4	5	6	Changes From Pretraining
T1	TO		16.1	12.2	14.1	12.6	14.2	13.9	8.1	$p < 0.025$
	SMR		20.7	17.3	21.4	22.5	25.7	22.2	19.4	N.S.
		L	21.9	23.6	23.4	23.2	24.9	23.5	21.3	$p < 0.05$
		R	26.6	23.2	23.9	25.2	27.9	25.0	23.9	N.S.
T2	TO	L	35.4	27.1	22.0	28.4	23.5	29.3	27.4	$p < 0.025$
		R	33.0	31.0	29.3	32.7	28.7	33.6	35.6	N.S.
	SMR	L	23.8	26.2	19.1	21.6	22.8	23.3	22.6	N.S.
		R	25.1	27.0	18.5	26.8	26.5	25.3	28.5	N.S.
T3	TO	L	55.1	47.8	44.3	54.4	48.5	49.8	52.3	$p < 0.025$
		R	56.0	46.7	41.7	52.3	49.9	50.9	52.9	$p < 0.025$
	SMR	L	23.9	23.6	26.3	22.3	25.6	20.5	19.8	N.S.
		R	25.4	24.1	27.3	22.0	26.2	23.9	24.7	N.S.
T4	TO	L	13.9	9.9	11.6	16.9	15.6	22.4	12.3	N.S.
		R	20.3	10.6	15.8	19.9	21.6	25.0	19.1	N.S.
	SMR	L	19.8	22.0	23.0	22.2	22.9	23.4	19.1	$p < 0.05$
		R	20.8	24.7	26.2	25.1	25.8	26.6	21.6	$p < 0.025$
ST1	TO	L	38.2	24.7	24.3	26.9	29.3	32.3	30.3	$p < 0.025$
		R	40.8	24.6	23.6	29.5	31.1	31.4	31.8	$p < 0.025$
	SMR	L	24.0	28.4	26.0	29.9	27.7	26.3	27.8	$p < 0.025$
		R	24.0	28.6	28.7	25.6	27.9	27.2	27.9	$p < 0.025$
ST2	TO	L	43.1	41.6	40.8	37.2	40.5	41.2	41.5	$p < 0.025$
		R	46.8	41.5	41.0	37.7	42.2	42.5	44.9	$p < 0.025$
	SMR	L	27.0	27.2	27.3	23.4	23.6	23.2	20.9	N.S.
		R	27.3	30.0	28.1	28.3	26.9	29.9	19.9	N.S.
ST3	TO	L	20.9	14.2	11.9	15.8	27.2	20.6	24.3	N.S.
		R	24.2	15.9	15.1	21.4	30.4	26.3	21.6	N.S.
	SMR	L	17.0	19.0	16.6	18.1	19.5	17.7	15.4	N.S.
		R	19.5	22.2	21.1	22.1	23.8	20.7	15.1	N.S.
ST4	TO	L	16.6	31.2	33.5	49.7	55.1	54.8	39.9	N.S.
		R	26.9	21.1	33.2	50.0	54.7	53.8	40.6	N.S.
	SMR	L	20.4	21.8	26.6	28.2	26.1	28.2	21.4	$p < 0.025$
		R	19.6	21.5	25.3	25.8	27.1	26.8	22.7	$p < 0.025$

Table 6. Summary of 2 X 7 repeated measures analyses of variance performed on mean SMR time per minute recorded from the left and right hemisphere electrodes.

Left					Right				
Source	SS	df	MS	F	Source	SS	df	MS	F
Between Subjects					Between Subjects				
A (Groups)	9.59	1	9.59	0.16	A (Groups)	0.40	1	0.40	0.01
Subjects within groups	363.75	6	60.62		Subjects within groups	206.30	6	34.38	
Within Subjects					Within Subjects				
B (Blocks of 30 days)	58.82	6	9.80	2.22	B (Blocks of 30 days)	69.09	6	11.51	2.02
AB	10.42	6	1.74	0.39	AB	38.88	6	6.48	1.13
B x Subjects within groups	159.07	36	4.42		B x Subjects within groups	205.62	36	5.71	
Total	601.65	55			Total	520.29	55		

Table 7. Summary of 2 X 7 repeated measures analyses of variance performed on mean time-out time per minute recorded from the left and right hemisphere electrodes.

Left					Right				
Source	SS	df	MS	F	Source	SS	df	MS	F
Between Subjects					Between Subjects				
A (Groups)	507.09	1	507.09	0.36	A (Groups)	140.90	1	140.90	0.14
Subjects within groups	8413.86	6	1402.31		Subjects within groups	6046.80	6	1007.80	
Within Subjects					Within Subjects				
B (Blocks of 30 days)	378.98	6	63.16	1.75	B (Blocks of 30 days)	686.11	6	114.35	3.91*
AB	218.11	6	36.35	1.01	AB	99.66	6	16.61	0.57
B x subjects within groups	1300.74	36	36.13		B x subjects within groups	1052.08	36	29.22	
Total	10818.80	55			Total	8025.55	55		

*$p < 0.01$

or interactions were found.

Although these analyses indicate that statistically significant increases in SMR density occurred in particular subjects, and significant decreases in time-out activity were revealed both within and across subjects, the actual changes in the mean times from pretraining to training were very small. The values found for these measures are presented in Table 5. Small increases in SMR density were not unexpected; although Lubar and Bahler's (1976) graph of changes in SMR activity might lead one to expect larger increases, their measure was based on the ratio of SMR density during feedback to SMR density during baseline recordings. However, the results obtained for time-out density were a surprise to the experimenter. During each training session, the subjective impression was that subjects could in fact decrease time-out time, and subjects often expressed satisfaction with their performance.

Two different post-hoc explanations might be given for these results. First, subjects usually showed the greatest decrease in time-out density during the first two 30-day blocks of training. This can be confirmed from perusal of the entries in Table 5 and from the plots of mean time-out time per minute shown in Figures 7 and 8. Subjects appeared to lose motivation for performing well at training sessions once they had reported feeling in control of the feedback, and once seizure rate began to decrease.

Figure 7.

Mean number of time-out events per minute, mean time-out time per minute, and mean time per time-out are plotted against blocks of 30 days, for each TO group subject. Left- and right-hemisphere data are given separately.

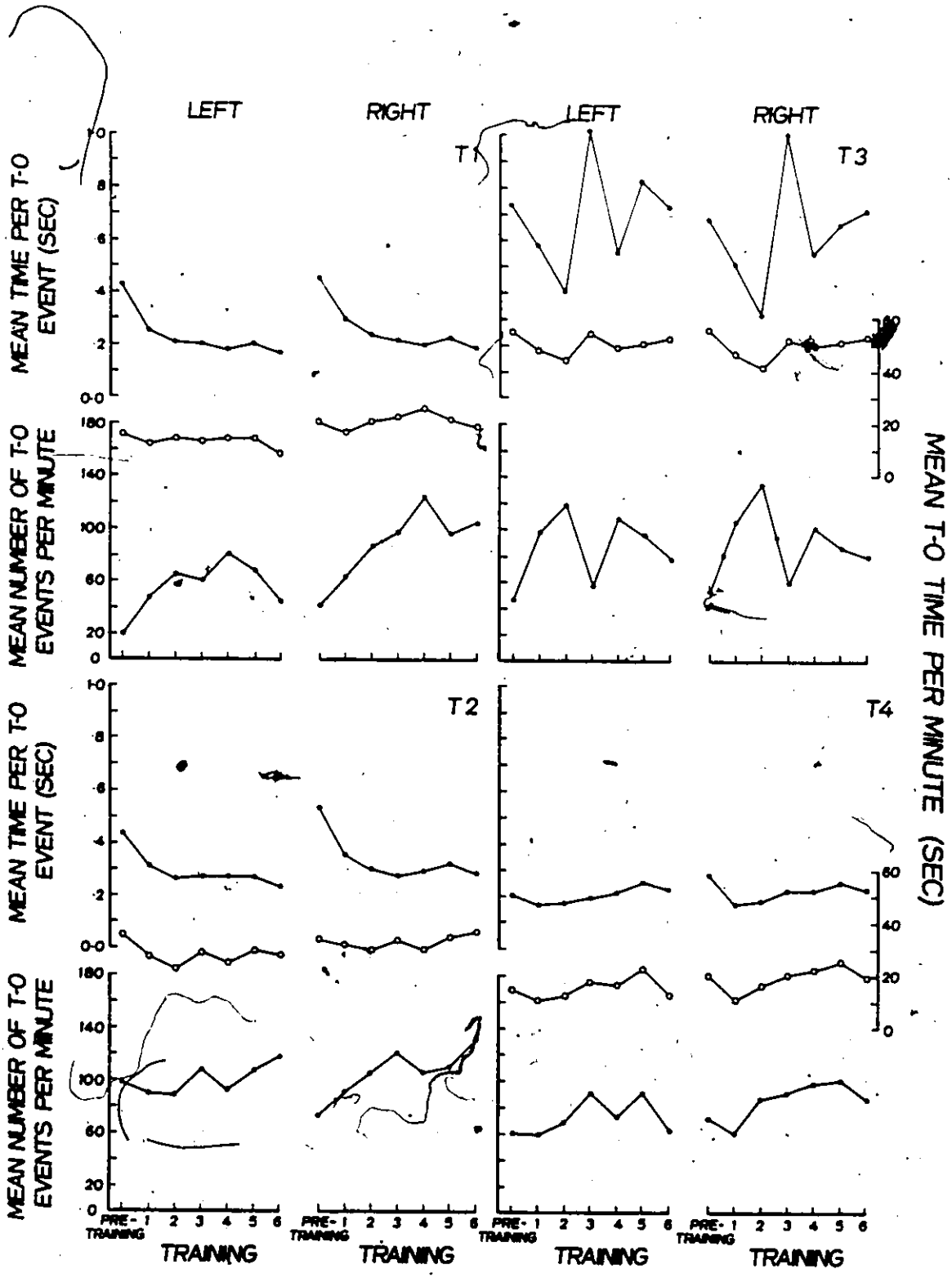
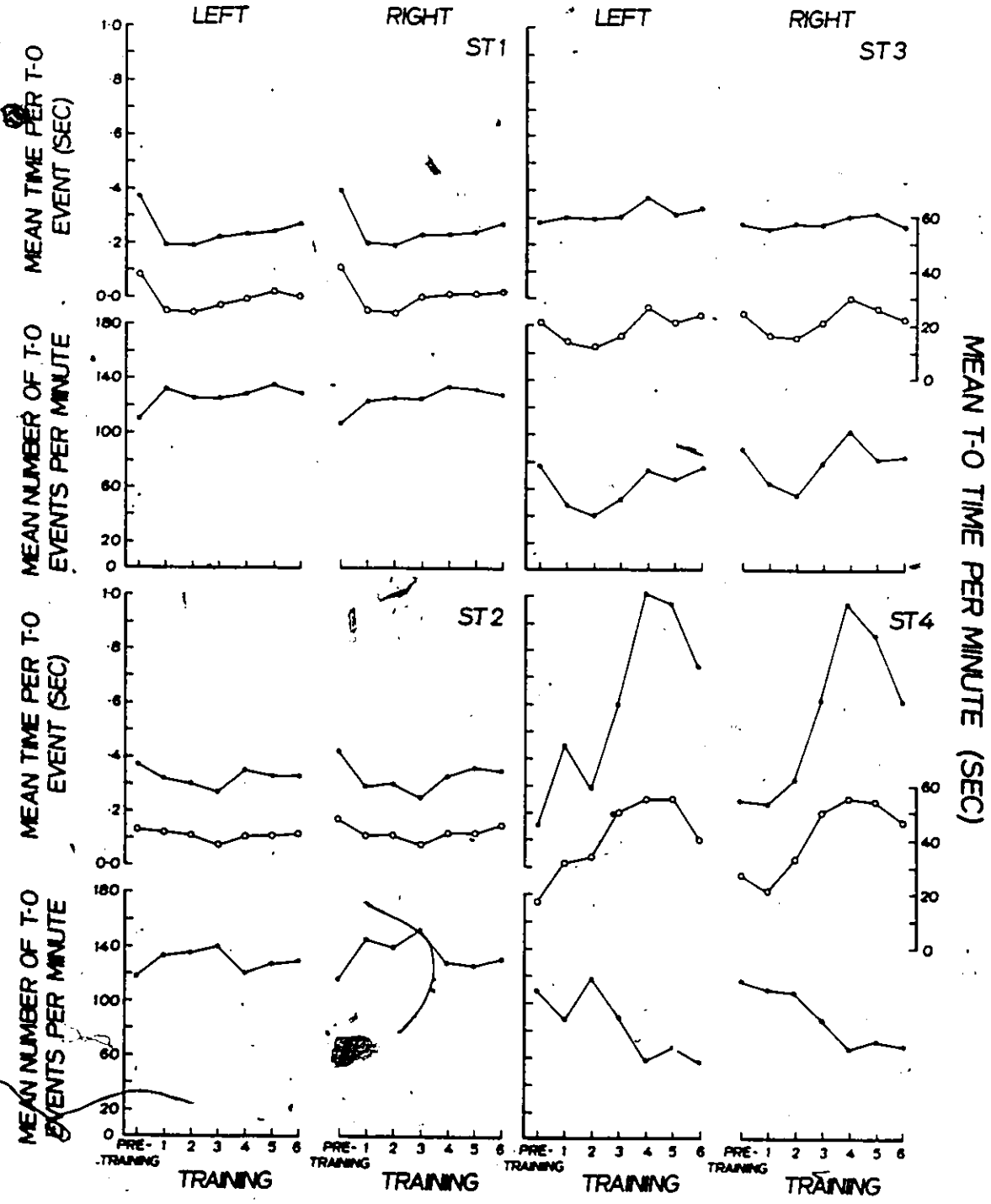

LEFT
RIGHT
LEFT
RIGHT
T1
T3
T2
T4
MEAN TIME PER T-O EVENT (SEC)
MEAN NUMBER OF T-O EVENTS PER MINUTE
MEAN T-O TIME PER MINUTE (SEC)
PRE-TRAINING
1 2 3 4 5 6
TRAINING

Figure 8.

Mean number of time-out events per minute, mean time-out time per minute, and mean time per time-out event are plotted against blocks of 30 days, for each SMR + TO group subject. Left- and right-hemisphere data are given separately.


LEFT
RIGHT
LEFT
RIGHT
ST1
ST3
ST2
ST4
MEAN TIME PER T-O EVENT (SEC)
MEAN NUMBER OF T-O EVENTS PER MINUTE
MEAN T-O TIME PER MINUTE (SEC)
PRE-TRAINING
TRAINING
1·0
·8
·6
·4
·2
0·0
180
140
100
60
20
0
60
40
20
0
1 2 3 4 5 6

Second, it was discovered that although mean time-out time per minute did not change very much, other measures of time-out activity were modified to a greater degree. As shown in Figures 7 and 8, subjects T1, T2, and ST1 decreased substantially the mean duration of each time-out event, while ST2 showed a smaller but nonetheless impressive decrease in this variable. It might be conjectured that these subjects could escape time-out activity, but that this activity could not be avoided. Given a constant and unlaterable amount (i.e., total time) of time-out activity, an escape strategy would decrease the duration of each time-out event and increase the number of time-out events.

The data of the remaining subjects show no consistent effects of this sort, aside from ST4's somewhat bizarre decrease in the number of time-outs with concomitant increases in the duration of each time-out and mean time-out time per minute. Subject T4 decreased time-out duration in one hemisphere. ST3 exhibited a constant time-out duration with number of time-outs and mean time-out time per minute first decreasing and then increasing again. Subject T3's data followed a different pattern; the duration decreased and the number of time-outs increased during the first 60 days of training, producing a net decrease in mean time-out time per minute.

Because of this extreme variability in performance, no between-group differences, within-subject effects, or interactions would be expected in a group analysis of time-out duration. This was confirmed

by a 2 X 7 repeated measures analysis of variance, summarized in Table 8.

Clinical evaluations of EEG recordings are in agreement with these findings. The clinical impressions noted during both pretraining and training EEG reports are summarized in Table 9. No EEG normalization occurred during training.

It is difficult to provide a summary statement regarding these data. Aside from the overall failure to produce large increases in SMR activity, and the small but statistically significant overall decrease in mean time-out per minute recorded from the right hemisphere, no consistent effects were observed. The poor performance of these subjects will be considered further in discussion of this experiment, following analyses of relationships between EEG data and seizure frequency.

Relationships Between SMR Activity and Seizure Data

The predicted between-subject relationship of SMR density to seizure frequency was investigated by regressing the mean SMR density recorded during pretraining sessions against total seizures during pretraining. The data from all subjects were employed in this analysis, and the left and right hemisphere densities were both used in order to increase the number of data points. The resulting best-fit linear equation is graphed in Figure 9, and an insert gives the coefficient of determination. Unfortunately, most of the data points are bunched together, and the correlation coefficient is not significant ($r = 0.45$ and with 14 degrees of freedom the required

Table 8. Summary of 2 X 7 repeated measures analyses of variance performed on mean duration per time-out, recorded from the left and right hemisphere electrodes.

	LEFT					RIGHT			
Between Subjects	SS	df	MS	F	Between Subjects	SS	df	MS	F
A (Groups)	3198.00	1	3198.00	0.01	A (Groups)	3099.00	1	3099.00	0.02
Subjects within groups	1724900.00	6	287483.00		Subjects within groups	1138440.00	6	189740.00	
Within Subjects					Within Subjects				
B (Blocks of 30 days)	148427.00	6	24737.80	1.04	B (Blocks of 30 days)	165988.00	6	27664.70	1.39
AB	177315.00	6	29552.50	1.24	AB	139501.00	6	23250.20	1.17
B x subjects within groups	858808.00	36	23855.80		B x subjects within groups	713680.00	36	19824.50	
Total	2912650.00	55			Total	2160710.00	55		

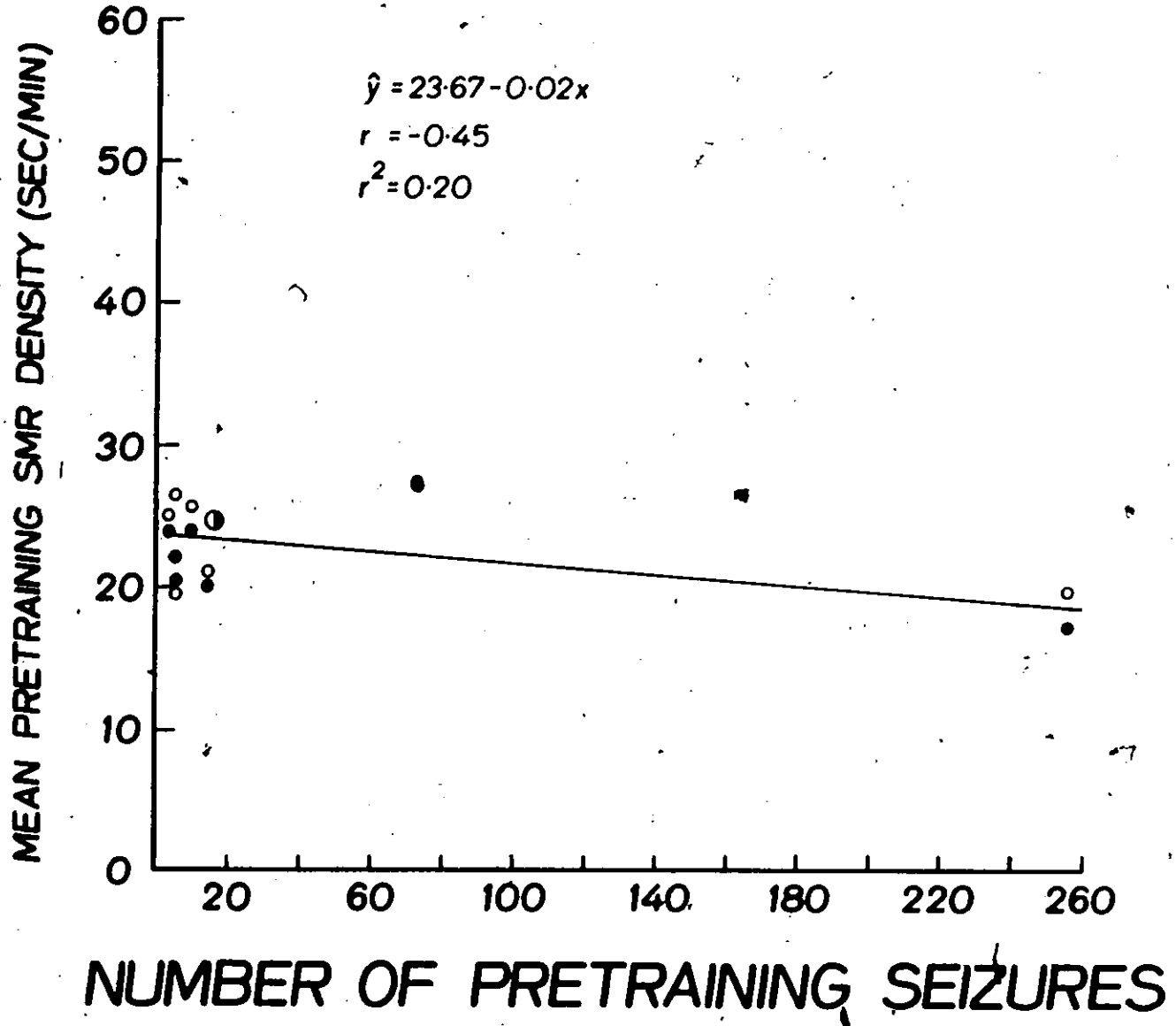
Table 9. Summaries of pretraining and training period clinical EEG reports.

Subject	Clinical Impression
T1	Abnormal slow-wave bursts over right frontal and fronto-temporal regions.
T2	Bursts of polyspike and slow-wave activity diffusely on both sides.
T3	Diffuse excess slow-wave activity with focal features over right fronto-temporal and mid-temporal regions.
T4	Excess slow activity over the left hemisphere, particularly over left mid- and posterior-temporal regions.
ST1	Irregular bilateral temporal sharp-wave activity.
ST2	Right-sided mid-temporal focal sharp waves.
ST3	Almost continuous bursts of spike-and-wave and polyspike-and-wave discharges bilaterally.
ST4	Abnormal slow-wave activity with a left fronto-temporal to mid-temporal focus.

Figure 9.

Mean SMR time per minute recorded during pretraining sessions is graphed as a function of the total number of pretraining seizures, for all subjects. Also plotted is the best fit linear regression equation and the coefficient of determination (r^2).

• Left ○ Right


$\hat{y} = 23{\cdot}67 - 0{\cdot}02x$
$r = -0{\cdot}45$
$r^2 = 0{\cdot}20$
MEAN PRETRAINING SMR DENSITY (SEC/MIN)
60
50
40
30
20
10
0
20
60
100
140
180
220
260
NUMBER OF PRETRAINING SEIZURES

r at $\alpha = 0.05$ equals 0.497).

The within-subject relationship between SMR density and seizure rate was explored by regressing each subject's mean SMR density, calculated for each block of 30 days, against that subject's number of seizures for the same 30-day period. Separate regressions were performed for the left- and right-hemisphere data of each subject. Although this procedure does reduce the degrees of freedom and thus increase the magnitude of the coefficient of correlation required to reject the null hypothesis of $r = 0$ at any given level of significance, it reduces the variability of the EEG data. It will be recalled that some subjects performed well when reinforcement was contingent on activity recorded from one set of electrodes, but not from the other set.

These data are plotted in Figures 10 and 11, together with the best-fit linear regression equations and r^2 values. Only one of these correlations achieved significance ($\alpha = 0.05$), and this shows a positive relationship between SMR density and seizure rate (right hemisphere SMR density of subject T1). One other correlation approached the value of 0.754 (required with 5 degrees of freedom at $\alpha = 0.05$), and this shows a positive relationship as well (left hemisphere SMR density of subject ST1).

These results confirm Finley's (1977) finding that SMR density is not correlated with seizure frequency. They will be discussed in more detail below.

Figure 10.

Mean SMR time per minute, calculated for each 30-day block, is plotted against the number of seizures per 30 days, for each TO group subject. Left- and right-hemisphere data are given separately. Also shown are the best-fit linear regression equation and r^2 value for each plot.

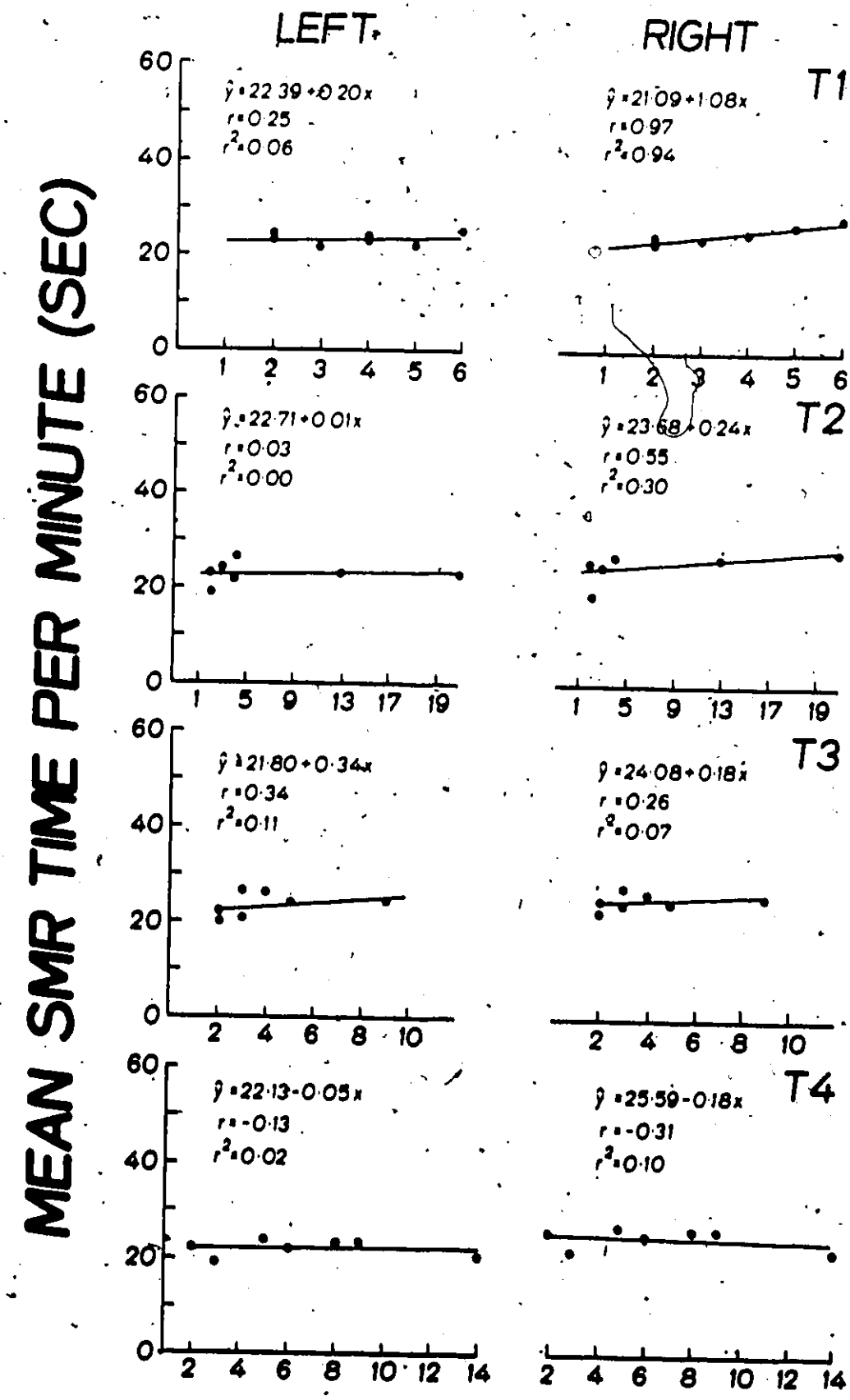
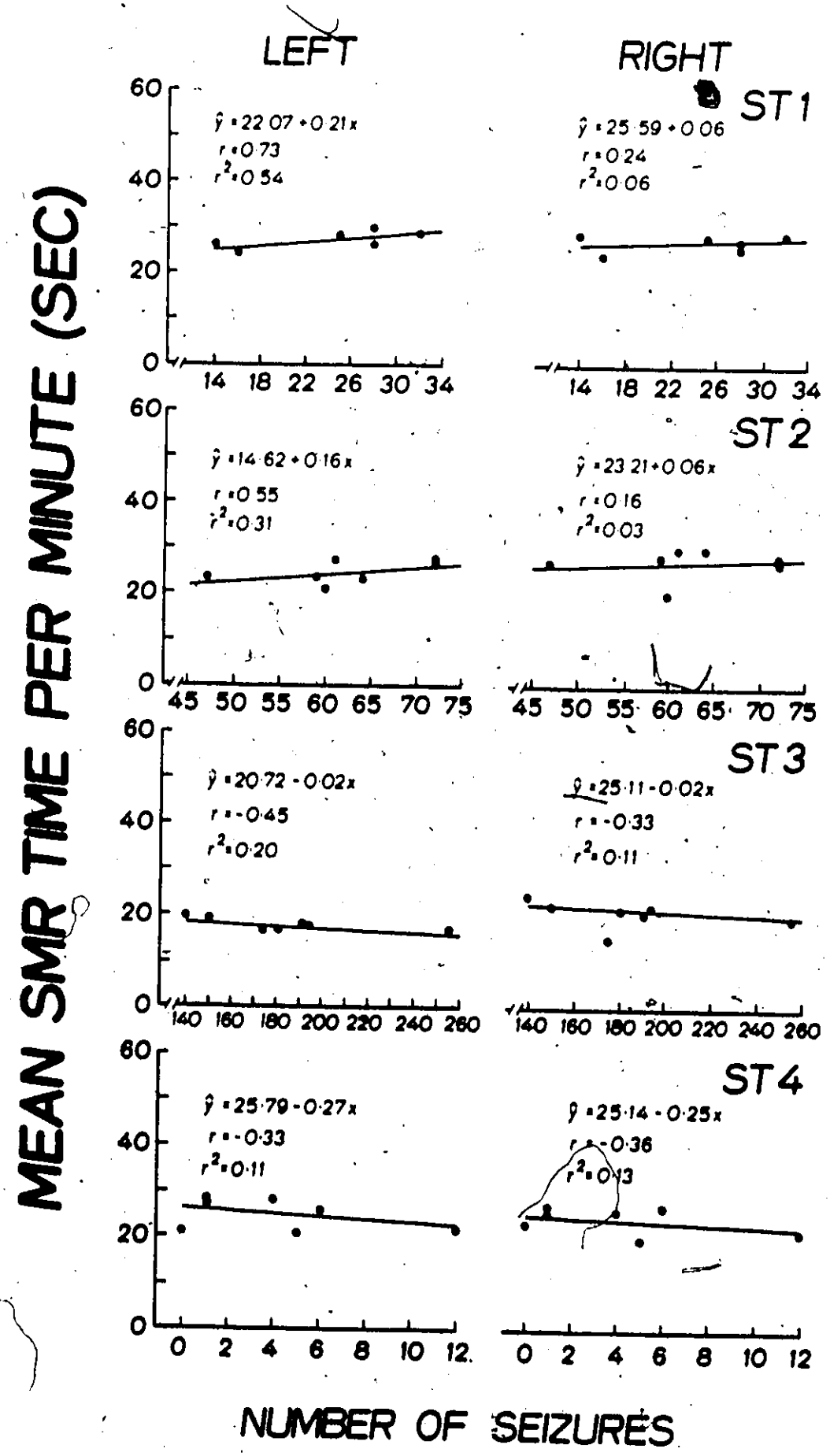

LEFT
RIGHT
T1
$\hat{y}$ = 22·39 + 0·20x
r = 0·25
r^2 = 0·06
$\hat{y}$ = 21·09 + 1·08x
r = 0·97
r^2 = 0·94
T2
$\hat{y}$ = 22·71 + 0·01x
r = 0·03
r^2 = 0·00
$\hat{y}$ = 23·68 + 0·24x
r = 0·55
r^2 = 0·30
T3
$\hat{y}$ = 21·80 + 0·34x
r = 0·34
r^2 = 0·11
$\hat{y}$ = 24·08 + 0·18x
r = 0·26
r^2 = 0·07
T4
$\hat{y}$ = 22·13 - 0·05x
r = -0·13
r^2 = 0·02
$\hat{y}$ = 25·59 - 0·18x
r = -0·31
r^2 = 0·10
MEAN SMR TIME PER MINUTE (SEC)
NUMBER OF SEIZURES

Figure 11.

Mean SMR time per minute, calculated for each 30-day block, is plotted against the number of seizures per 30 days, for each SMR + TO group subject. Left- and right-hemisphere data are given separately. Also shown are the best-fit linear regression equation and r^2 value for each plot.


LEFT
RIGHT
ST 1
ST 2
ST 3
ST 4
$\hat{y}$ = 22 07 + 0 21x
r = 0 73
r^2 = 0 54
$\hat{y}$ = 25 59 + 0 06
r = 0 24
r^2 = 0 06
$\hat{y}$ = 14 62 + 0 16x
r = 0 55
r^2 = 0 31
$\hat{y}$ = 23 21 + 0 06x
r = 0 16
r^2 = 0 03
$\hat{y}$ = 20 72 - 0 02x
r = -0 45
r^2 = 0 20
$\hat{y}$ = 25 11 - 0 02x
r = -0 33
r^2 = 0 11
$\hat{y}$ = 25 79 - 0 27x
r = -0 33
r^2 = 0 11
$\hat{y}$ = 25 14 - 0 25x
r = -0 36
r^2 = 0 13
MEAN SMR TIME PER MINUTE (SEC)
NUMBER OF SEIZURES

Relationships Between Time-Out Activity and Seizure Rate

As discussed in Chapter 2, it is possible that the time-out component of the SMR + TO procedure is the variable that leads to decreases in seizure frequency. More specifically, it was indicated that a decrease in time-out density might promote a reduction in seizure frequency. This hypothesis might be given in strong and weak versions similar to the two interpretations of Sterman's (1973) hypothesis. Thus, both between- and within-subject relationships between seizure rate and time-out density must be examined, with positive correlations expected in both cases. The same procedures followed for SMR density were used for time-out density.

Pretraining time-out density is graphed against pretraining seizure rate in Figure 12, for all subjects. Despite the small number of data points, it is clear that no strong relationship exists.

Within-subject relationships between time-out density and seizure frequency were examined by regressing each subject's mean time-out time per minute, calculated over 30-day blocks, against the number of seizures reported for each 30-day block. As in the case of SMR density, separate regressions were performed for the left- and right-hemisphere data of each subject. Plots of each subject's data with the best-fit linear regression equations are presented in Figures 13 and 14. Only one coefficient of correlation was significant (right hemisphere time-out density of subject TT).

Figure 12.

Mean time-out time per minute recorded during pretraining sessions is graphed as a function of the total number of pretraining seizures, for all subjects. Also plotted is the best-fit linear regression equation and the coefficient of determination (r^2).

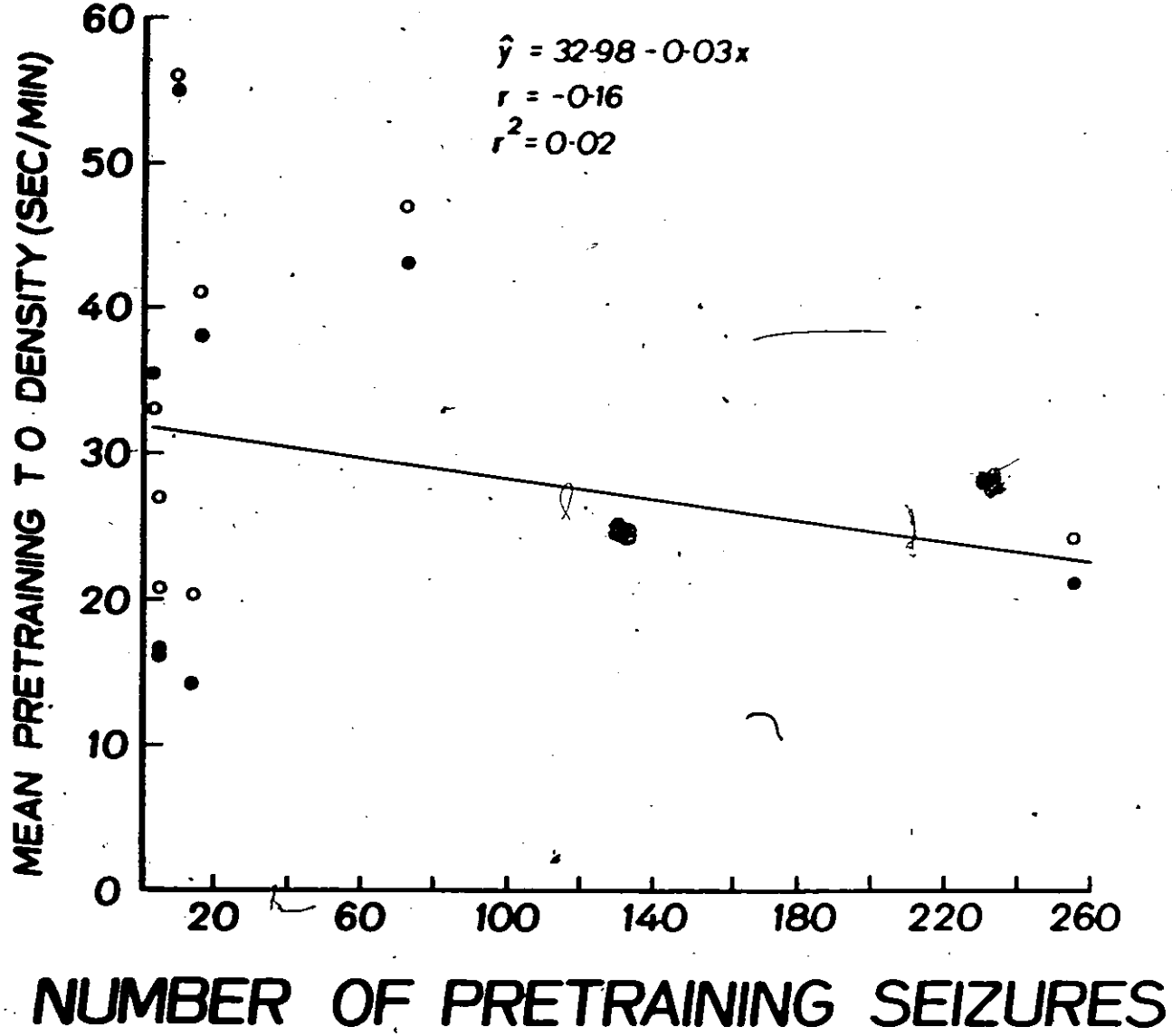

$\hat{y}$ = 32·98 - 0·03x
r = -0·16
r^2 = 0·02
MEAN PRETRAINING T O DENSITY (SEC/MIN)
0
10
20
30
40
50
60
20
60
100
140
180
220
260
NUMBER OF PRETRAINING SEIZURES

Figure 13.

The mean number of time-out events per minute, mean time-out time per minute (i.e., time-out density), and mean duration of each time-out event, calculated for each block of 30 days, are plotted against the number of seizures per 30 days for each TO group subject. Left- and right-hemisphere data are given separately. Also shown are the best-fit linear regression equation and r^2 value for each plot.

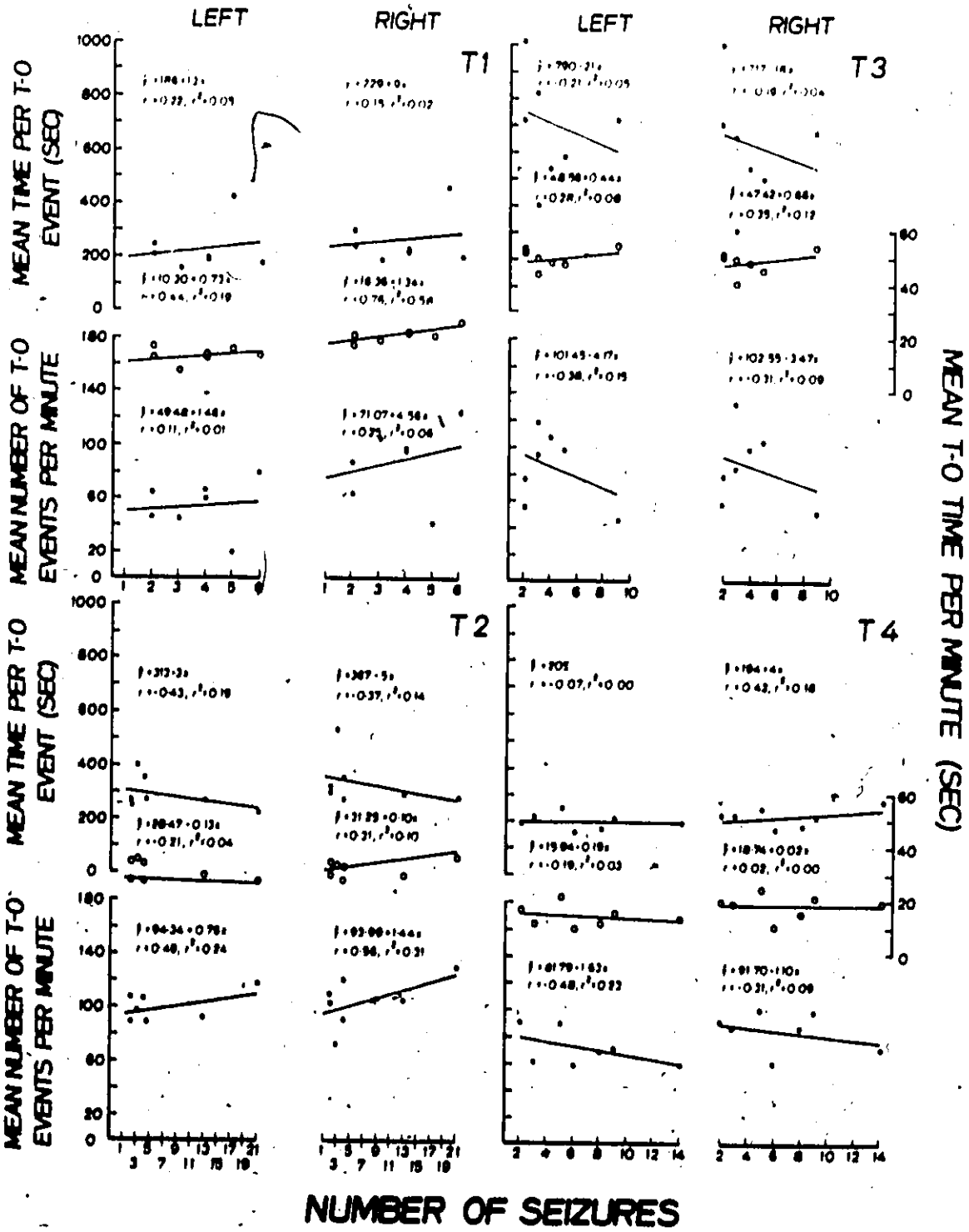
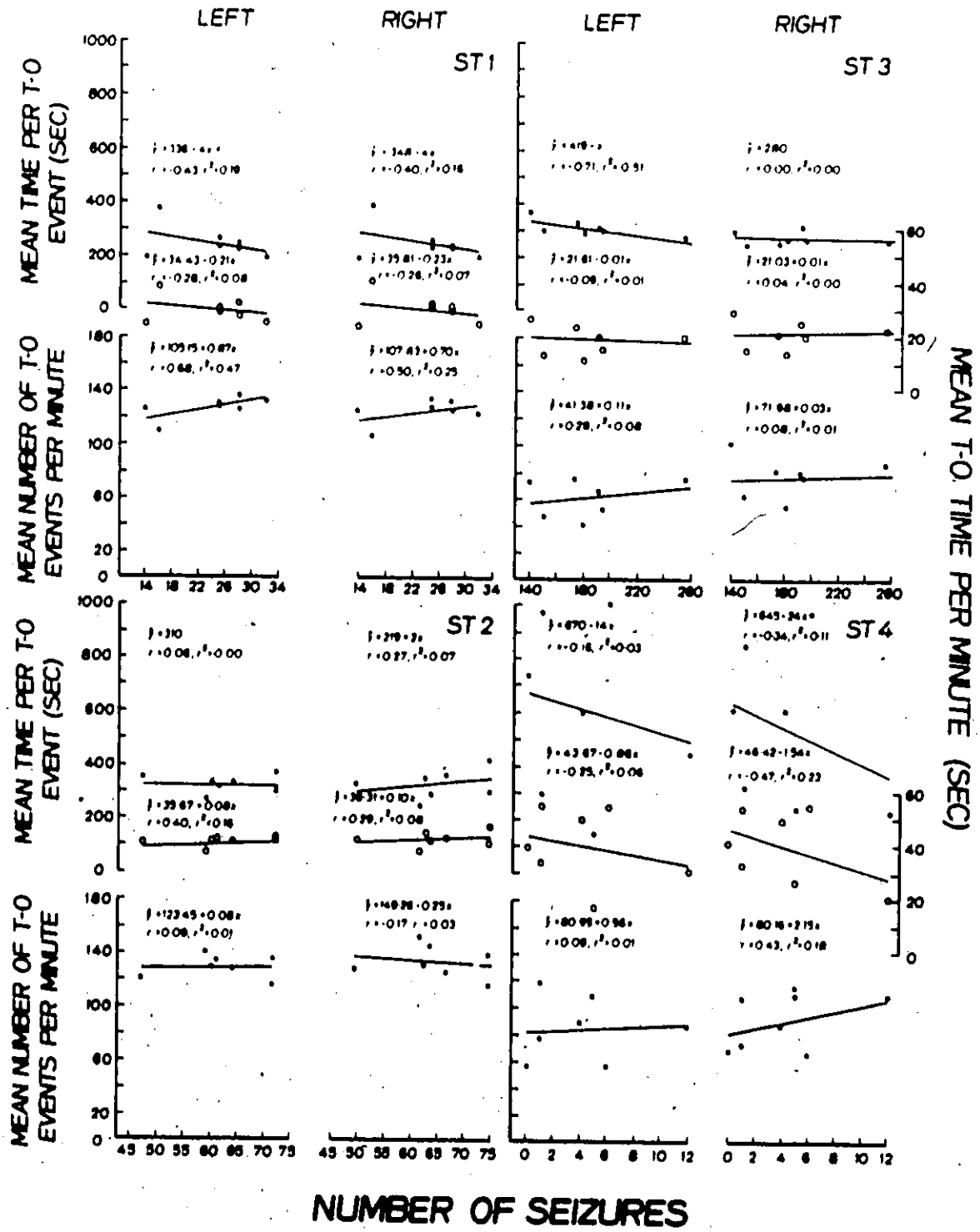

LEFT
RIGHT
LEFT
RIGHT
T1
T3
T2
T4
MEAN TIME PER T-O EVENT (SEC)
MEAN NUMBER OF T-O EVENTS PER MINUTE
MEAN T-O TIME PER MINUTE (SEC)
NUMBER OF SEIZURES

Figure 14.

The mean number of time-out events per minute, mean time-out time per minute (i.e., time-out density), and mean duration of each time-out event, calculated for each block of 30 days, are plotted against the number of seizures per 30 days for each SMR + TO group subject. Left- and right-hemisphere data are given separately. Also shown are the best-fit linear regression equation and r^2 value for each plot.


LEFT
RIGHT
LEFT
RIGHT
ST 1
ST 3
ST 2
ST 4
MEAN TIME PER T-O EVENT (SEC)
MEAN NUMBER OF T-O EVENTS PER MINUTE
MEAN T-O TIME PER MINUTE (SEC)
NUMBER OF SEIZURES

Because some subjects (especially T1, T2, and ST1) showed changes in the mean duration of each time-out and in the mean number of time-outs per minute that were larger than the decreases in mean time-out time per minute, the former two variables were also regressed on seizure rate. Plots of these variables are also given in Figures 13 and 14, together with the best-fit linear equations and r^2 values. Of the 32 correlations calculated, none were significant at $\alpha = 0.05$.

Discussion

The results of this experiment are rather complex. Although they fail to clearly identify a set of variables important for producing decreases in seizure frequency, they do show that no presently-held hypothesis regarding mechanisms underlying seizure reduction is tenable.

One unexplained finding is the large difference found between medical record and pretraining records of seizure rate. As indicated in presentation of the results, this finding can be interpreted in several ways. It is unfortunate that there are no data permitting evaluation of the various alternative interpretations. It is interesting, however, that even though Sterman et al. (1974) and Lubar and Bahler (1976) do not give detailed descriptions of their method for collection of pretraining seizure data, these investigators do imply the pretraining estimates were gained from subject interviews and medical records. If this were their method, then the changes in seizure rate attributed to training might be grossly exaggerated.

A primary result of the present experiment is that the reductions in seizure rate had no apparent relationship to either group treatment (SMR + TO versus TO) or EEG activity (SMR density or time-out density, number, or duration).

Of the subjects showing depressed seizure rates, three received TO training and two (according to Wilcoxon tests) or three (according to comparisons of the cumulative number of pretraining and training seizures) received SMR + TO training. A regression of pretraining SMR density on seizure rate yielded a negative but non-significant correlation. Of the five (or six) subjects who decreased seizure rate, only two (or three) increased SMR density, while one subject (ST1) who did not decrease seizure rate did increase SMR density. Regressions of each individual's SMR density, during training, on seizure rate failed to produce one significant negative correlation. It logically follows from these results that neither SMR conditioning nor an elevated SMR density is sufficient or even necessary for the reductions in seizure rate which have been reported to result from the SMR + TO procedure.

A situation of equivalent complexity exists with respect to the time-out variable. No obvious relationship between pretraining seizure rate and time-out density was found. The two subjects who clearly failed to reduce seizure rates did significantly reduce time-out time, indicating that avoiding the activity on which time-outs were contingent is not sufficient for lowering seizure frequency.

Also, two subjects who did not significantly decrease time-out time did show a significant reduction in seizure rate. Regressions of each subject's time-out density averaged over 30-day blocks on seizure rate per block yielded only one significant correlation. Identical regressions performed for two other parameters of time-out activity failed to produce a significant correlation. These results indicate that time-out training is not sufficient for decreasing seizure rate, although it may be necessary. A depressed time-out density is neither necessary nor sufficient.

Now it might be argued that the failure to find relationships between SMR density and seizure rate or between parameters of time-out activity and seizure rate is due to the poor performance of the subjects. According to this argument, the procedure followed did produce a decrease in seizure frequency by some mechanism other than learned control of EEG activity. However, it was inadequate for altering EEG activity by more than small, though often statistically significant, amounts.

Such an argument can be rejected for several reasons. First, there are no data available which would suggest that increases in SMR density or decreases in time-out density, from pretraining values, can be obtained with the SMR + TO procedure. As pointed out in Chapter 2, the EEG data from previous SMR + TO investigations are too meager even for concluding whether changes in SMR density can be achieved. The graphical presentations employed in previous studies often were based

on an unidentified number of recordings for unidentified time durations (Finley, 1977; Finley et al., 1975; Sterman, 1977), or else the pretraining EEG measures were gathered in a single 40-minute recording session (Lubar, 1977; Lubar and Bahler, 1976; Seifert and Lubar, 1975). This latter practice does not even allow for the possibility that the subject's first session will yield a recording with much EMG activity and therefore much time-out activity. Both problems are compounded by the use of power spectra calculated over short periods of time (less than one minute) for selected sessions (e.g., Sterman, 1973, 1977; Sterman et al., 1974). Even if all of the EEG data collected were subjected to such analysis, presentation of power spectral graphs confounds the abundance (i.e., percent-time or density) and amplitude of SMR activity, since power is a function of both variables. Further, a power spectrum can be mistakenly interpreted to demonstrate much larger changes in SMR and time-out activity than were obtained, since power is proportional to the square of amplitude.

There is another reason that such an explanation of the present results must be rejected. It would have to be supposed that the decreases in seizure frequency observed in the present experiment were due to the action of some sort of complex variable or set of variables with relatively long-lasting effects. A similar effect would have to be posited to exist in other SMR + TO studies, and if it is being argued that large changes in EEG

activity were achieved in those studies (even though no evidence for this is available), then presumably subjects in those studies would exhibit decreases in seizure rate greater than those obtained in the present experiment. As discussed in Chapter 2, the methods of pretraining seizure data collection used by previous investigators are problematic, so that a comparison of the present results with those of other studies would be of questionable utility. The changes in seizure rate observed here are, nevertheless, representative of those reported in other studies.

Since no causative role can be attributed to SMR, the time-out becomes the procedural variable of prime importance for further study. It was concluded that appropriate changes in parameters of time-out activity are neither necessary nor sufficient for decreasing seizure frequency, and that although time-out training is not sufficient, it may be necessary.

It is important to note that questions regarding the possible roles of time-out activity in decreasing seizure rate are very different from questions about epileptiform activity. Subjects could alter parameters of time-out activity by manipulating EMG activity and without altering epileptiform activity. Conversely, the density of epileptiform activity could conceivably change with no detectable alteration in time-out density. Thus, a decrease in epileptiform activity could well be the agent responsible for ameliorating seizures. There is some evidence that normalization of interictal

EEG activity could act to reduce seizure rate (see Chapter 2). Unfortunately, the studies of human epileptics which provide evidence for this hypothesis (Sterman and Macdonald, 1978; Wyler et al., 1976) suffer from many of the methodological deficiencies apparent in SMR reports. In particular, none has employed a control group which would permit a test of the hypothesis that training decreased densities of epileptiform activity is sufficient or necessary for reducing seizure rate. The placebo-control subject of Wyler et al. (1976) dropped out of the study after only three weeks of training, and Sterman and Macdonald's (1978) reinforcement of 6-9 Hz activity with time-outs for 12-15 Hz or 18-23 Hz activity is not a suitable control. In addition to failing to meet a prime requirement of a placebo control (see below), this latter procedure may well have increased epileptiform activity. It is mandatory that the effects of the control procedure not be incompatible with the hypothetical causative agent; the hypothesis that a decrease in epileptiform activity promotes seizure reduction cannot be tested with a control group in which epileptiform activity is increased.

This brings up the question of the type of controls that would be appropriate, and therefore addresses the problem of identifying an alternative to the hypothesis that a time-out contingent (at least partially) on epileptiform activity is necessary for reducing seizure frequency. Such alternatives are generally referred to as placebos, insofar as the only available physiological

explanation of desired clinical effects is challenged. Some SMR investigators dismiss the possibility that seizure reductions are produced via mechanisms other than learned control of EEG activity on the grounds that placebos produce only short-term effects while the greatest changes in seizure rate are seen only after several months of training (e.g., Sterman and Macdonald, 1978), or because "non-contingent reinforcement" does not affect seizure frequency (Kuhlman and Allison, 1977). Neither of these arguments is adequate.

By arguing that placebos produce only immediate or short-term effects, and then stating that long-term clinical effects were in fact observed, it is implied that the beneficial results obtained must have been the result of EEG training. But this erroneous conclusion is based on the a priori definition of all non-experimental effects as short-term, as not requiring some type of learning that might be secondary to the experimenter's intentions. When used in this way, the term "placebo" essentially provides an excuse for not running control groups. In fact, Sterman and Macdonald's (1978) claim that greater decreases in seizure rate occur as training progresses can be questioned, since training time in their study was confounded with type of training (see Chapter 2). Furthermore, a trend for seizure rate to decrease over training time occurred for only four of Sterman and Macdonald's (1978) eight subjects. In one of the latter cases the mean change (over 15 months) was 1.1 seizures per

month; in another the mean change from the first to the last 3 months of training was 2 seizures per month. Overall, seizure rate appears to decrease immediately. This also occured in the present experiment. Such a result would be unlikely if changes in seizure frequency depended upon a gradual, learned change in neurophysiological function.

Second, so-called non-contingent reinforcement or false feedback is an inadequate control procedure for reinforcement of activity believed to produce clinical effects. In operant conditioning paradigms such as the SMR + TO and TO procedures there are actually two variables of importance: the "relatedness" of the response being reinforced to the desired outcome (e.g., a decrease in epileptiform activity is believed to produce a decrease in seizure frequency because the presence of epileptiform activity and seizure occurrence are related), and the presence of a contingency that is detectable by the subject. It is clear that in false-feedback or non-contingent reinforcement control procedures such as that used by Kuhlman and Allison (1977), subjects easily detect the absence of a true response-feedback contingency (Budzynski, Stoyva, Adler, and Mullaney, 1973; Stern and Pavloski, 1973; Strayer, Soctt, and Bakan, 1973). In such procedures, then, both variables present in the experimental condition are absent in the control condition (Cott, 1978).

In order to collect data relevant to the hypothesis that learned decreases in abnormal interictal EEG activity causally effect

reductions in seizure frequency, it is necessary to employ a control group in which some response unrelated to seizure disorders is reinforced, so that a detectable response-reinforcer contingency is preserved. Although it might appear that such a procedure should on physiological grounds have no impact on seizure occurrence, informal observations made in the present experiment indicate that a time-out for epileptiform activity may not be a necessary component of the procedure.

In interviews prior to their acceptance as subjects, the patients chosen for participation attributed their seizures either to a complicated organic process over which they have no control, or to the unsuccessful efforts of physicians to control their seizures. Yet, in this same interview these patients also offered information indicating that they believed their seizures to be more likely in certain situations which might be termed "stressful". There is, in fact, a good deal of data showing that situational or environmental events (Booker, Forster, and Klove, 1965; Gastaut, Regis, Dongier, and Roger, 1956; Martinek and Horak, 1970; Pitha, 1938), as well as particular responses (Fabisch and Darbyshire, 1965; Goldie and Green, 1959; Liddell, 1965) and vaguely-defined states such as excitement and fatigue (Bennett, 1963, 1964; Gastaut and Tassinari, 1966; Livingston, 1956; Weinberg, 1945) have a temporal relationship with seizure occurrence. Furthermore, many of the studies reviewed in Chapter 2 present treatment procedures based on the assumption that these relationships are not merely correlational, but that certain

classes of environmental and behavioral events causally influence seizure emission. Therefore, epileptic patients may be incorrect in assuming that they can exert little or no self-control over seizures.

Keeping this in mind, let us consider what behavioral effects the SMR + TO and TO procedures might have, aside from alterations in the parameters of SMR and time-out activity. One such effect, mentioned previously, concerns the unsolicited reports by subjects that self-control over signals believed to be directly related to epileptiform activity had been achieved. It can be tentatively suggested, then, that one function of the conditioning procedures is to allow subjects to perceive control over epilepsy-related brain activity. Although there are no data gathered from epileptics that could tell us what behavioral changes would follow such a manipulation, certain social-psychological experiments and theories do seem applicable.

For example, experiments dealing with the notion of locus of control (LOC), a concept central to social learning theory (Phares, 1976), support the idea that perceived control over the feedback signals could affect behaviors which influence seizure occurrence. Locus of control refers to an individual's expectancies that actions will produce environmental effects favorable for that individual, sometimes generalized over different types of situations but more often specific to a particular task. A good deal of research has been conducted in order to ascertain relationships between measures of internal (i.e., self-control) versus

external (i.e., control by "fate" or by other individuals) perceived LOC, such as scores on Rotter's (1966) internal-external scale, and behaviors thought to be indicative of mastery over one's environment (Phares, 1976). It has been shown that internal scores are correlated with greater efforts to seek information relevant to mastery (Davis and Phares, 1967; Williams and Stack, 1972), better or more effective use of available information (Phares, 1968), and a greater awareness of reinforcement contingencies (Ude and Vogler, 1969).

Other studies have been concerned with the effects that certain manipulations have on internal-external scores. Eisenman (1972) found that experience in experiments involving guessing resulted in a shift towards an externalorientation, while experiments in which subjects were in control produced a shift towards an internal perception of LOC. Norwicki and Barnes (1973) reported that emphasizing relationships between behavior and reinforcement to inner-city adolescents attending a summer camp was followed by lower (i.e., more internal) scores, and there is also some support for the notion that successful behavioral therapeutic procedures result in a shift towards internal LOC (Smith, 1970; Dua, 1970; Gillis and Jessor, 1970).

These findings are relevant to the present investigation. The subjects employed in the present experiment have all had a long history of epilepsy, and have been passed from one physician to another, each time having medications changed; yet seizures remained uncontrolled.

Although psychometric tests have not been administered to these patients, it seems entirely consistent with the social learning literature to describe them as externals, at least with respect to their epileptic seizures.

During their participation in the experiment, these subjects were required to keep careful records of the time, place, and other circumstances surrounding their seizures, and during the conditioning or training phase of the experiment subjects reported that they perceived control over feedback which they believed to be related to their disorders. That is, they were engaged in a program which should: (1) make salient contingencies between environmental events and their seizures, and/or contingencies between certain behaviors and their siezures; and (2) provide them with opportunities to perceive control over signals believed to be derived from a process that they had considered to be beyond self-control, and that is directly related to their seizures (the role of a true response-reinforcer contingency in leading to perceived control has not, however, been established).

The social learning literature suggests that such a program should result in a shift towards internal LOC perception with respect to seizures, and internal LOC is generally correlated with better recognition and use of environmentalinformation relevant to control. Missing in this analysis is the means by which both beliefs regarding control and behaviors leading to reductions in seizure rate might be acquired and maintained.

Certain experiments performed under the rubric of attribution theory (Jones, Kanouse, Kelley, Nisbett, Valins, and Weinder, 1972) may pertain to the acquisition of beliefs and behaviors leading to reductions in seizure rate. The general conclusion based on this research is that inferences which subjects make from their behavior in an experimental situation may function as hypotheses to be tested in other suitable circumstances (Nisbett and Valins, 1972). It can be argued on the basis of this research that epileptic subjects might develop hypotheses on the basis of their perceived control over feedback signals, and test these hypotheses in situations in which seizures are likely. Unfortunately it is not clear what form these hypotheses might take. This is an empirical question which would probably have a different answer for each subject.

Following a different theoretical orientation, Bandura (1977) has suggested that expectations of personal efficacy (i.e., expectations that one can successfully execute behaviors required to produce certain outcomes) determine the existence, strength, and persistence of coping behaviors in threatening situations. It is proposed that a theoretical framework in which personal efficacy is the central concept integrates data from operant learning studies and modelling studies, and from cognitive analyses of learning and motivation. Theoretical predictions that diverse psychological procedures effect desired behavioral outcomes by modifying personal efficacy expectations have been partially tested and confirmed in comparisons of phobic behavior treatment procedures. Application of the self-efficacy concept to the present case would lead to the prediction that performance in EEG training

procedures should strengthen expectations of personal efficacy and thus lead to the initiation of behaviors that might, on the basis of presumed situation-seizure contingencies, reduce the probability of seizure occurrence. Avoidance of seizures would in turn reinforce and therefore maintain these behaviors.

It should be emphasized that this discussion is not intended to be an outright rejection of the idea that subjects reduce seizure frequency via learned changes in EEG activity. It is, rather, an attempt to demonstrate that a non-physiological explanation of decreases in seizure rate may be a viable alternative to a physiological hypothesis which may be more appealing, but that has very little empirical support. Clearly, the next stage of this investigation must provide evidence bearing on the necessity of epileptiform activity time-outs for reductions in seizure rate. The experimental manipulations employed for this purpose should at least satisfy the requirements set out in our discussion of an adequate placebo control. They can, in addition, provide some evidence relevant to the hypothesis that a non-physiological mechanism influences seizure rate. The following experiment was designed in order to meet these criteria.

Chapter 5

EXPERIMENT II

Introduction

The purpose of this experiment was to determine whether certain control procedures not employing EEG conditioning could produce decreases in seizure frequency. Two groups of subjects were utilized. One group received time-outs for high-voltage scalp EMG and the other group received time-outs for low-voltage EMG. The rationale for employing these groups is based on three hypotheses regarding mechanisms underlying the seizure rate reductions obtained with the SMR + TO and TO procedures.

The first hypothesis is that a time-out contingent (at least partially) on epileptiform EEG activity is a necessary condition for reducing seizure frequency (e.g., Wyler et al., 1976). A corollary to this hypothesis is that time-outs for responses unrelated to epileptiform activity should not result in lower seizure frequencies.

Kaplan's (1975) suggestion that EEG training procedures ameliorate seizures by promoting relaxation forms the second hypothesis. According to this hypothesis, epileptics whose seizures are precipitated or exacerbated by stressful circumstances should also decrease their seizure rates as a result of other relaxation-training procedures. Therefore, progressive muscle relaxation and operant conditioning of low EMG levels from various muscle groups should be effective in lowering

seizure frequency (Blanchard and Young, 1974). Training a response incompatible with relaxation (e.g., increased EMG levels) should not be an effective procedure.

The third hypothesis was generated on the basis of informal observations made in the previous experiment, and can be stated as follows: Any procedure that establishes in subjects a belief that self-control over phenomena involved in seizure-generation has been attained, and which makes salient situational and/or behavioral correlates of seizure activity, leads to the learning of behaviors that decrease seizure probability. Like the second hypothesis, this idea was judged to be a viable alternative to the notion that time-outs for epileptiform activity are necessary for attaining decreases in seizure frequency. As such, it was not tested in the present experiment. Rather, the strategy of using a group of subjects not expected to improve on the basis of either the first or second hypotheses was employed. The rationale for using a high-EMG time-out and low-EMG time-out group follows from this strategy.

As a first consideration, it was deemed necessary to use only scalp electrodes during the prcoedure so that subjects would believe the time-outs to be derived from EEG activity. This is certainly a condition that any control group for the TO group of the first experiment must fulfill. In addition, it is required for gathering data relevant to the hypothesis regarding belief in control.

Aside from the necessity of scalp electrodes, the first hypothesis demands that subjects receive contingent feedback or time-out signals for activity unrelated to epileptiform EEG patterns. Conceptually, this is simple. But empirically, there is no a priori reason to assume that any particular scalp bioelectric activity is unrelated to epileptiform activity. EMG potentials were chosen because they are derived from skeletal muscle, a non-neural source, because most EEG activity could be electronically filtered from the signal before time-out criteria are imposed, because it was thought that the distribution in time of EMG time-outs would not be radically different from the distribution of EEG plus EMG time-outs, and finally because EMG could be monitored and recorded from the same set of electrodes.

Even with the choice of EMG, however, two problems still exist. EMG levels meeting the criteria for time-out activity might be correlated with epileptiform activity, and certain types of high-frequency abnormal EEG could conceivably meet these criteria if they are not filtered from the signal. There is one way to avoid these problems and to concomitantly collect data bearing on the second and third hypotheses. This is, of course, to make time-outs contingent on high-voltage EMG for some subjects and on low-voltage EMG for others. Then the first hypothesis is testable, while data concerning the relaxation and belief-in-control hypotheses are available.

According to the first hypothesis there should be no reduction of seizure rate in either group unless one of the EMG time-outs is correlated

with EEG plus EMG time-outs. If the subjects who improve are restricted to one of the groups, then the EEG and EMG data of each subject can be examined for such confoundings.

If the first hypothesis is rejected, then each subject's data can be examined to determine whether relationships between changes in EMG time-out activity and changes in seizure rate exist. Considering lowered EMG voltage levels as one facet of relaxation (and high EMG levels as incompatible with relaxation), the second hypothesis would be supported if only those subjects showing depressed EMG activity decreased seizure frequency. The sufficiency of lowered EMG activity would be rejected if decreased EMG voltages were not in all cases accompanied by reduced seizure frequencies.

If the first hypothesis is rejected and the second hypothesis is not supported, there would be no reason to believe that either training subjects to alter certain types of EEG or EMG activity or that actual changes in these types of activity are either necessary or sufficient for lowering seizure frequency. That is, no purely physiological explanation for the success of treatment would be adequate. While this is not equivalent to accepting the third hypothesis - indeed this hypothesis is not even testable in this experiment - it would suggest that an attempt be made to generate psychological rather than physiological descriptions of the successful seizure-reducing procedures. As noted in Chapter 4, the belief-in-control hypothesis was devised on the basis of an apparent fit between subject interview data and a rather large body of social

learning data.

A number of predictions can be generated from this hypothesis, two of which might be testable in the present experiment. First, subjects who do not believe that they have achieved control over the time-outs should not decrease seizure rate. Second, subjects who do believe, prior to treatment, that they have good self-control over seizures should not improve.

Method

Subjects

Six epileptic outpatients were obtained from Drs. A. Upton, G. Kirschberg, D. Levy, and J. Marotta. An attempt had been made to procure at least eight patients for this experiment. Unfortunately, imposition of the criteria for acceptance of subjects described in Experiment I made this impossible. One additional subject declined to participate, and one subject could not attend twice-weekly sessions.

All criteria for subject acceptance and for control of anti-epileptic medication serum levels paralleled the methods described in the first experiment. For three randomly chosen subjects time-outs were contingent on high-voltage scalp EMG (group H) and for the remaining subjects time-outs were contingent on low-voltage scalp EMG (group L). Descriptions of each subject are presented in Table 10.

Procedure

Pretraining and training sessions

As in Experiment I, there were two 40-minutes sessions per week. The pretraining period was extended from 30 to a minimum of 60 days, however, to help ensure valid estimates of seizure rates for those subjects with

Table 10. Descriptions of subjects employed in Experiment II.

	Subject	Sex	Year of Birth	Age at First Seizure	Type(s) of Seizure	Auras	Medication	Mentally Retarded
Low-Voltage EMG	L1	F	1954	7	Petit mal Grand mal	No	Mysoline Zarontin Diamox	Yes
	L2	M	1956	12	Petit mal Grand mal (rare)	Yes	Tegretol Rivotril Sodium- Valproate	No
	L3	F	1924	32	Psychomotor	No	Mysoline Phenobarbital	No
Time-Out For								
	H1	M	1960	8	Petit mal Grand mal Psychomotor	No	Dilantin Tegretol Zarontin	No
High-Voltage EMG	H2	F	1944	17	Psychomotor Myoclonic	Yes	Tegretol Phenobarbital	No
	H3	F	1955	12	Grand mal Psychomotor	Yes	Dilantin Mysoline Phenobarbital	No

relatively infrequent seizures. Twice-weekly training sessions were scheduled for the subsequent 180 days.

During the first 30 days of pretraining, subjects collected seizure data but did not attend recording sessions. In several cases (see below) it was possible to extend this period beyond 30 days. During the remaining 30 days of pretraining subjects continued to collect seizure data and attended 8 pretraining EEG-EMG recording sessions. All data were gathered from electrode sites C_3-T_3 and C_4-T_4 (Jasper, 1958).

The procedure followed during the 180-day training period was identical to that employed for the TO group in Experiment I, except that time-out signals were contingent on high-voltage EMG for group H and on low-voltage EMG for Group L. Wide-band data were also recorded on an Ampex FM tape recorder for subsequent off-line analysis. As in the first experiment, the electrode sites on which time-outs were contingent were alternated within and between sessions. Stimulus presentation and on-line data analysis were carried out by a PDP Lab-8/E computer.

EEG and EMG were monitored through Grass silver/silver-chloride electrodes connected to two matched Grass model 7P511 wide-band amplifiers with half-amplitude filter settings at 1 and 1000 Hz. The output of the amplifier on which feedback was contingent was fed to two bandpass filters, a 12-14 Hz active filter (Ross Systems Engineering) and a 30-300 Hz passive filter (Krohnhite Model 335), both having rolloffs of 24 dB/octave.

Output from the 30-300 Hz filter was fed to a Grass model 7P3 integrator (TC = 0.05 sec) for imposition of time-out criteria. The integrated EMG signal formed the input to Schmitt triggers calibrated to set theiroutput gates for high and low amplitude EMG, respectively. When the filtered, integrated signal exceeded a voltage equivalent to that produced by a 6 uV peak-to-peak amplitude 70 Hz calibration sine wave at the input of the 7P511 amplifier, the high-level Schmitt trigger gate was set. The low-level gate set when the signal fell belowa voltage produced by a 6 uV peak-to-peak 70 Hz calibration sine wave at the 7P511 input. These calibration parameters were determined empirically, on a trial and error basis, during the pretraining recording sessions. Visual inspection of the wide-band 7P511 output revealed that subjects generally produced either very high voltage EMG activity (i.e., > 200 uV), or that no EMG activity whatsoever could be discerned in the recording. With the Schmitt triggers calibrated as described above, the high-level Schmitt trigger always fired when high-amplitude EMG was obvious in the oscillograph recording, and the low-level gate set when no EMG activity was detected visually. The Schmitt trigger outputs were switch selectable, so that the appropriate signal would be sent to the computer's digital input.

With one exception, time-out activity during the feedback periods of training sessions was displayed in the manner described in the first experiment. Since time-out signals were now contingent on only one

integrated signal, the oscilloscope screen was divided only by a horizontal line. Vertical movement of the beam was calibrated so that the dot produced would lie above this line only when the appropriate time-out criterion was not met.

Each subject was given instructions identical to those utilized for the TO group subjects of Experiment I. Each subject was told that the time-out signals were produced by activity related to the epileptic disorder.

Collection of questionnaire data

A face-valid "perception of control of seizures" questionnaire has been developed and is reproduced in Appendix 1. This questionnaire and Collins' (1974) version of Rotter's (1966) internal-external scale was administered to all subjects except L1 (who was apparently unable to comprehend the questions asked) at the initial pretraining interview.

Collection of seizure data

Subjects and their families and companions were provided with small notebooks in which times of medication administration and descriptions of seizure activity were recorded. These notebooks were identical to those used in the first experiment, and a sample page is shown in Appendix 1.

Two subjects from each group (L1, L2, H2, H3) also agreed to keep records of major activities, moods, places, companions and subjective seizure likelihood estimates for every waking two-hour period during each day of pretraining and training. A page of the diary issued these subjects is illustrated in Appendix 1. It was hoped that these records would provide information regarding changes in the probabilities of the

subject encountering various situations in which seizures might be highly likely to occur, and changes in the conditional probabilities of seizures given such situations.

Results

The results of this experiment have been placed in six categories in order to simplify their presentation. In order of discussion, these categories are: (1) analysis of seizure data; (2) analysis of EMG data; (3) relationships between EMG activity and seizure rate; (4) relationships between EMG activity and EEG activity; (5) relationships between psychometric measures and seizure rate; and (6) analysis of behavioral (diary) data.

Analysis of Seizure Data

Pretraining seizure patterns were examined as in Experiment I, by plotting the cumulative number of seizures against days of pretraining. The data for groups H and L are presented in Figures 15 and 16, respectively. Inserts on each graph give the best fit linear regression equation and coefficient of determination. The graph for each subject except L2 is divided by one dashed line at the day prior to the initiation of EEG - EMG recording sessions. The plot of L2's data is divided by two dashed lines - one at the day prior to the first EEG - EMG recording sessions, and another at the day on which this subject's medication was supplemented by sodium valproate. As shown in Figure 16, L2's pretraining period was extended by 30 days so that any change in seizure rate produced by the new medication might be noted. It is clear from the plot of cumulative seizure number

Figure 15

Regression of cumulative number of seizures against days of pretraining for group H subjects. The dashed vertical line divides the first (prior to laboratory recording sessions) and second (during laboratory recording sessions) phases of the pretraining period.

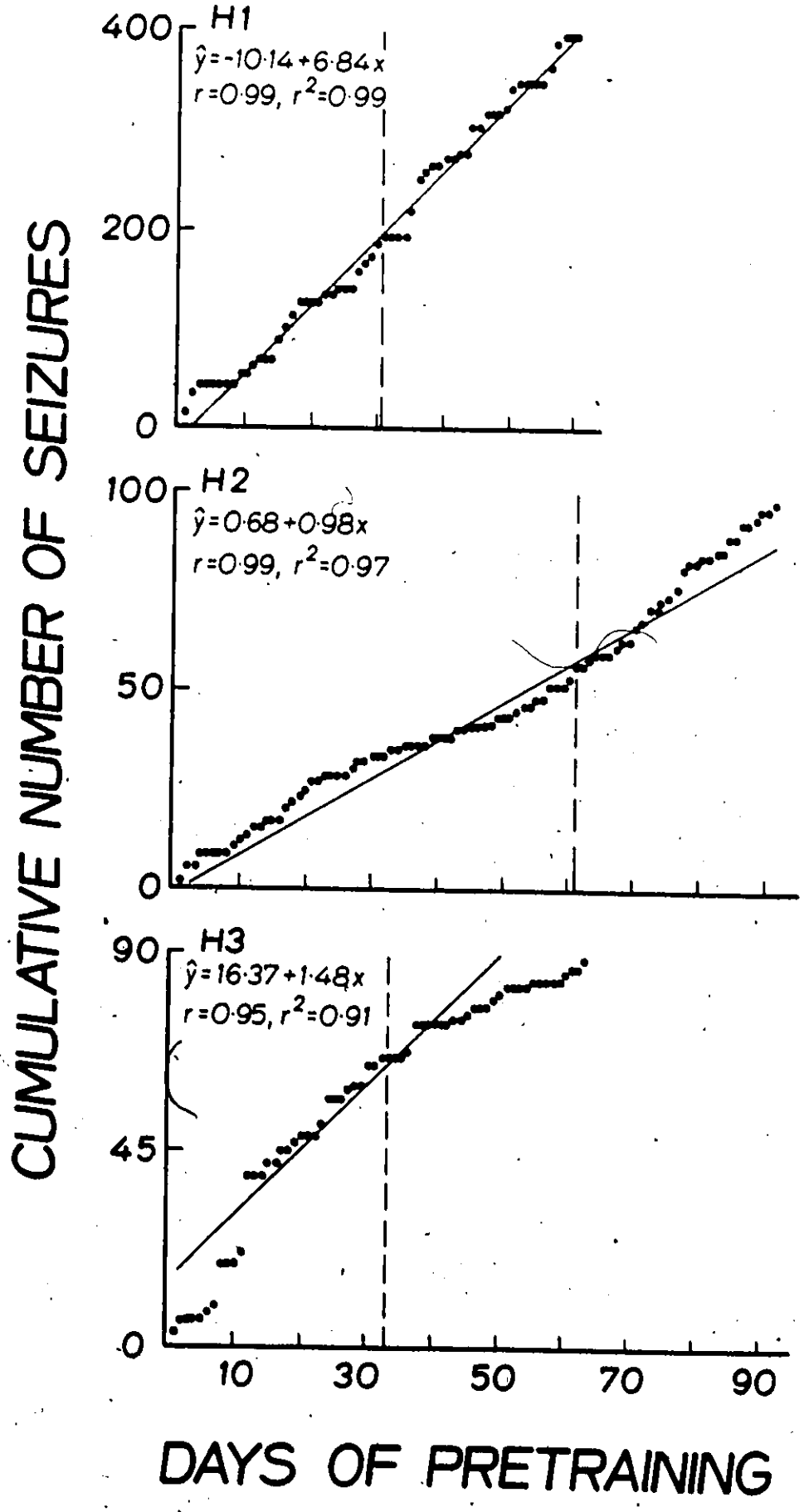
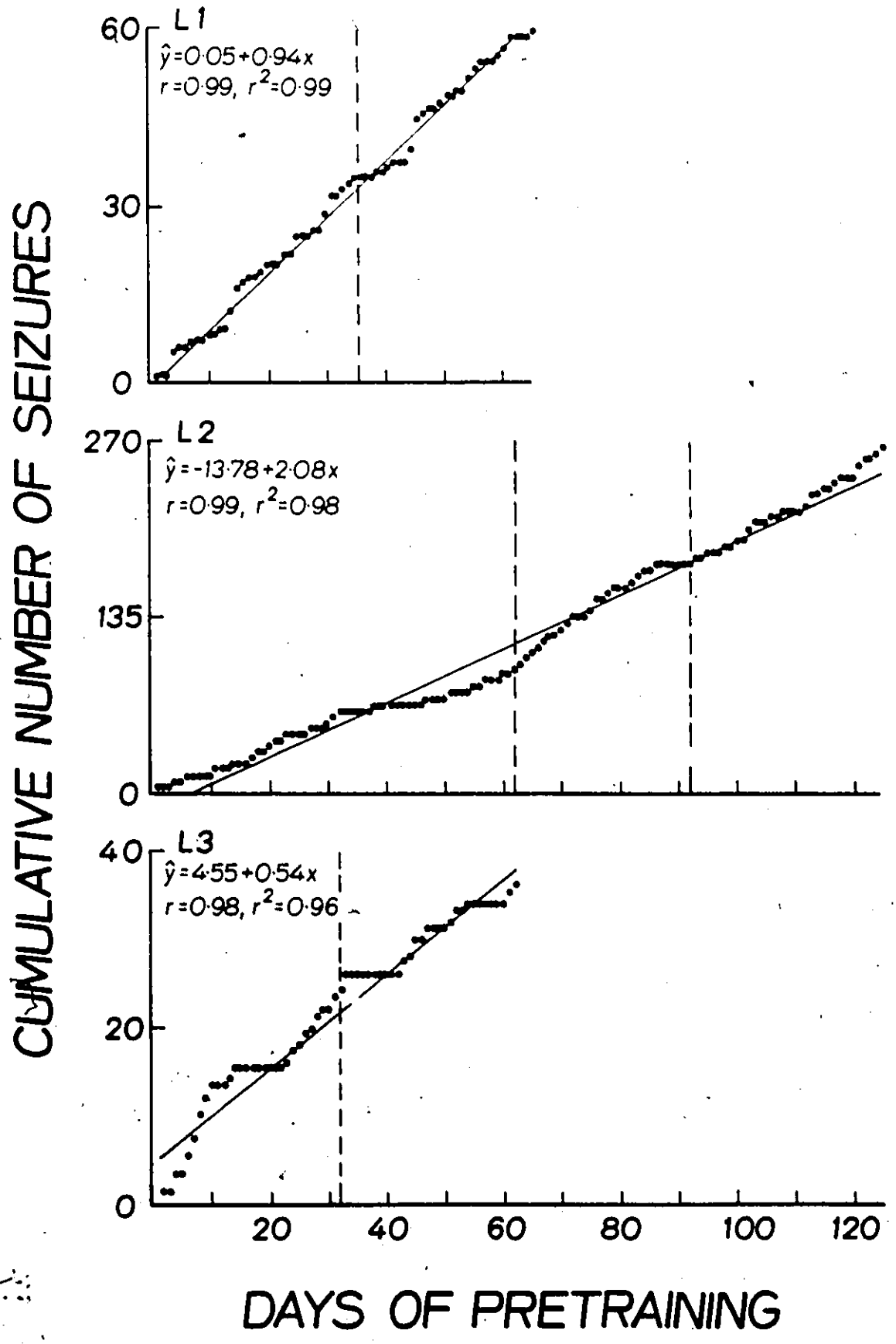

H1
ŷ=-10·14+6·84x
r=0·99, r²=0·99
400
200
0
H2
ŷ=0·68+0·98x
r=0·99, r²=0·97
100
50
0
H3
ŷ=16·37+1·48x
r=0·95, r²=0·91
90
45
0
10
30
50
70
90
CUMULATIVE NUMBER OF SEIZURES
DAYS OF PRETRAINING

Figure 16

Regression of cumulative number of seizures against days of pretraining for group L subjects. For subjects L1 and L3, the vertical dashed line separates pretraining phases one and two. For subject L2 the first (left) dashed line serves the same purpose; the second dashed line indicates the day on which this subject's neurologist altered anti-epileptic medication (i.e., sodium valproate was added to the existing drugs).


L1
ŷ=0·05+0·94x
r=0·99, r²=0·99
60
30
0
L2
ŷ=-13·78+2·08x
r=0·99, r²=0·98
270
135
0
L3
ŷ=4·55+0·54x
r=0·98, r²=0·96
40
20
0
20
40
60
80
100
120
CUMULATIVE NUMBER OF SEIZURES
DAYS OF PRETRAINING

that no such effect occurred.

Only the data of subjects H3 and L3 deviate markedly from a linear relationship with time. In both cases, there is an obvious decrease in seizure frequency beginning at the first recording session. The seizure rate of H3 decreased from 66.4/30 days prior to the first recording session to 26/30 days during recording. The rates for L3, for the same periods of time, were 21.6/30 days and 13/30 days.

An opposite trend was found for subjects H2 (a change in rate from 27.5/30 days to 42/30 days) and L2 (a change from 45.9/30 to 81/30 days). Inspection of Figure 15 shows, however, that there are two distinct seizure rates during the first phase of pretraining for H2, and that only one of these rates had yet appeared in the second phase.

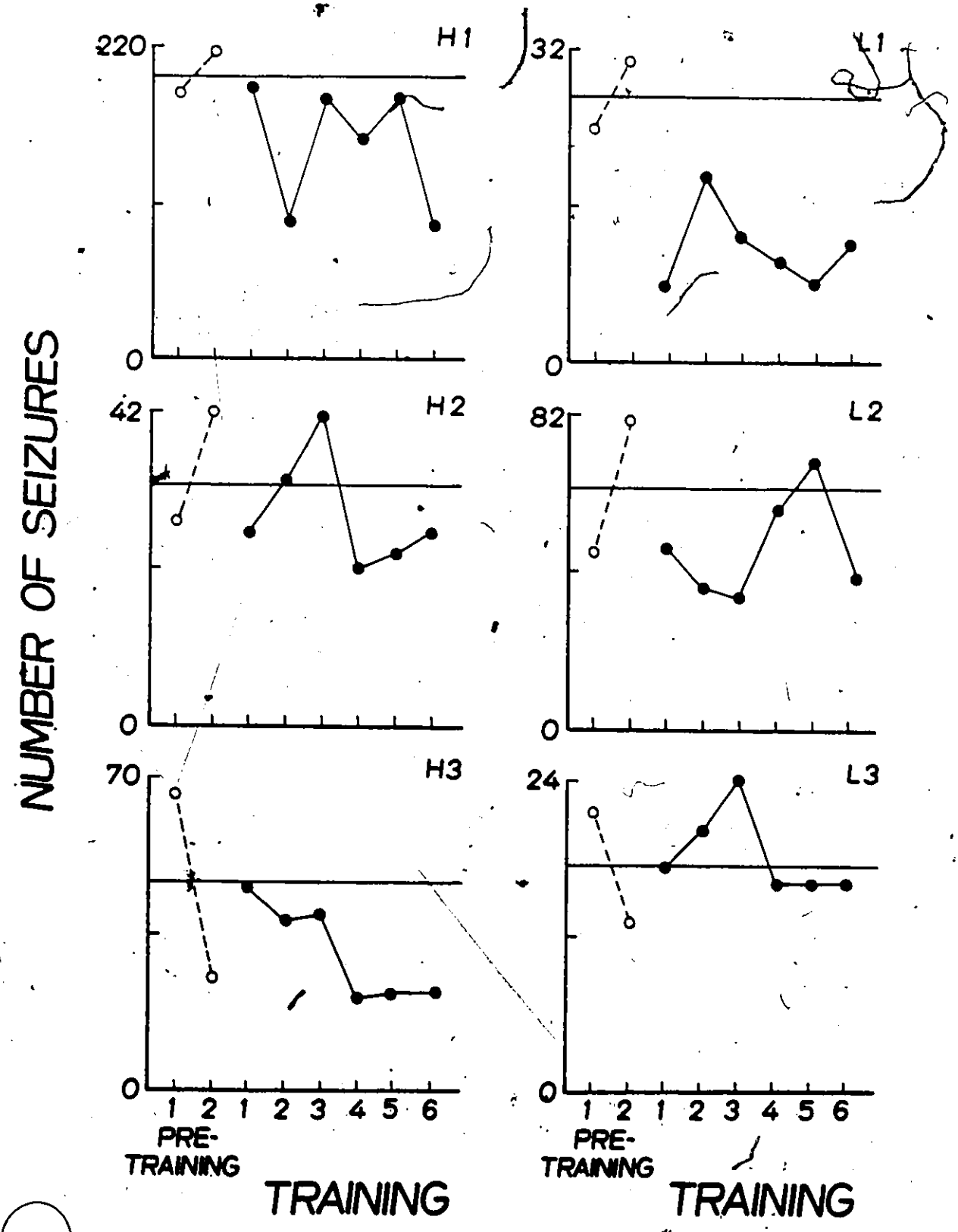
The shifts in seizure frequency from the first to the second phase of pretraining are shown more clearly in Figure 17, where the pretraining seizure rate, per 30 days, is plotted for the periods prior to and during laboratory recording sessions (open circles). The mean overall pretraining rate is given by a horizontal line on each graph, and seizure rates during the six 30-day periods of training are plotted as closed circles.

Changes in seizure frequency from pretraining to training were evaluated in three ways. Each of the methods used was based on certain assumptions regarding the cause of shifts in seizure rate from the first to the second phase of pretraining.

The first assumption is that changes in seizure frequency within the pretraining period were produced by attendance at laboratory sessions.

Figure 17

Number of seizures per 30 days are plotted against blocks of pretraining and training for all subjects. The first and second phase pretraining estimates are denoted by open circles connected by a dashed line, the overall pretraining estimate is given by a horizontal line running the extent of each graph, and the training data are represented by closed circles.


NUMBER OF SEIZURES
H1
220
0
L1
32
0
H2
42
0
L2
82
0
H3
70
0
L3
24
0
1 2 1 2 3 4 5 6
PRE-TRAINING
TRAINING
1 2 1 2 3 4 5 6
PRE-TRAINING
TRAINING

This assumption dictated the first two analyses. Seizure rates during training were compared to the phase one estimate of seizure frequency in order to reveal the effects of attendance at laboratory sessions plus the effects of training. In the second analysis, the seizure frequency observed during the second phase of pretraining was used as the estimate of the pre-intervention seizure rate. This was, of course, the method employed in the first experiment, and it was chosen so that the effects of training per se would be observable.

The third analysis was based on the assumption that attendance at laboratory training sessions had no effect on seizure frequency. Rather, any differences observed between the first and second phase seizure rates were assumed to reflect only an overall temporal pattern in the frequency of seizure emission. Under this assumption, the seizure frequency reported over both phases of pretraining was taken as the best estimate of the pre-intervention rate. A visual comparison of the total number of seizures reported during the entire duration of pretraining, to the total number of seizures reported during training periods of equivalent duration, is given in Figure 18.

Wilcoxon Tests (one-tailed) were employed for each subject in order to test the hypothesis that the number of seizures per 30-day training period did not decrease from each of the three pretraining rates described above. Thus, three tests were performed for each subject. The results of these tests are summarized in Table 11. The null hypothesis

Figure 18

Alternative representation of changes in seizure rate. Shown are the total number of pretraining seizures and the total number of seizures reported during training periods of equivalent duration.

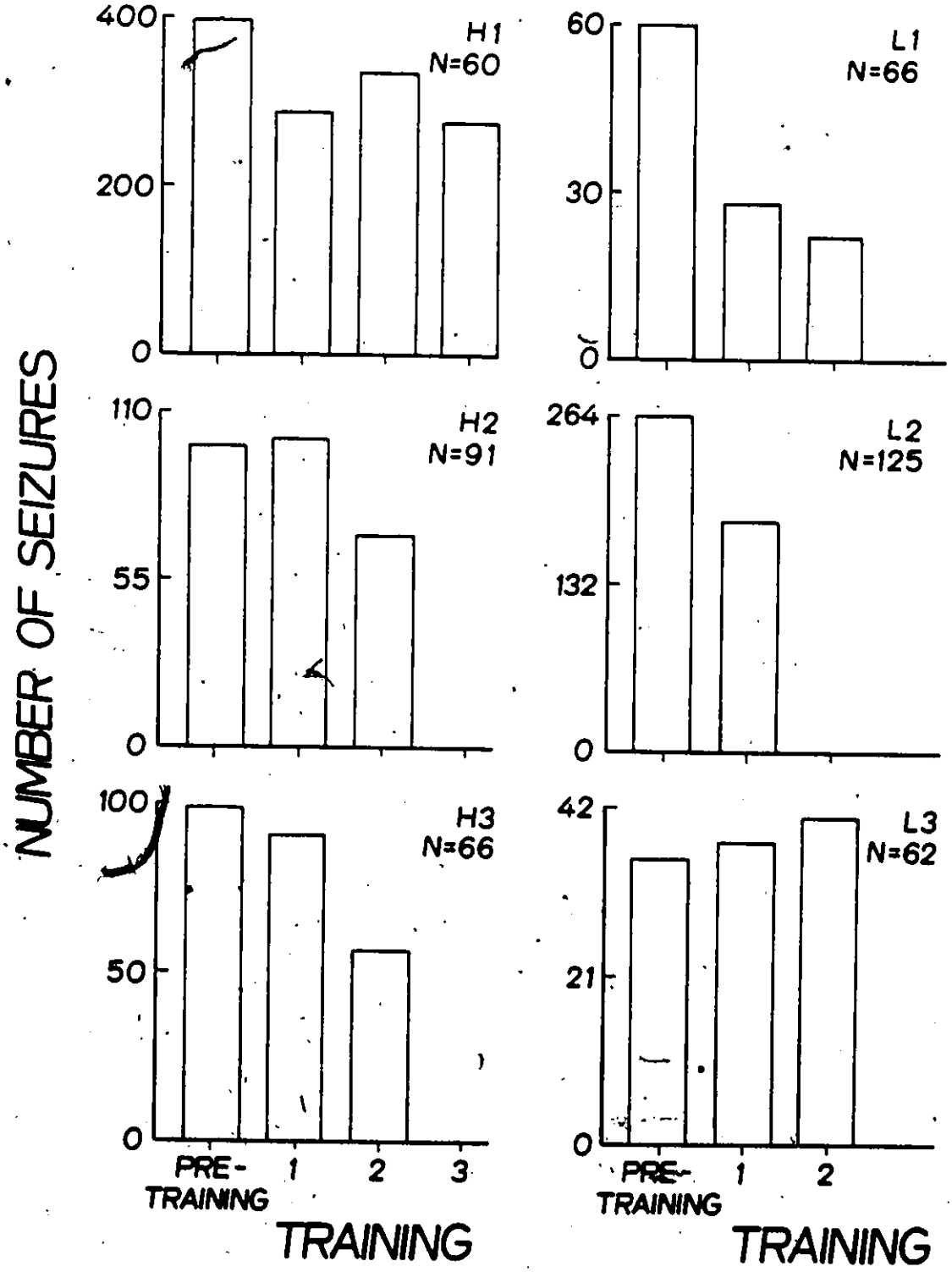

NUMBER OF SEIZURES
400
200
0
H1
N=60
60
30
0
L1
N=66
110
55
0
H2
N=91
264
132
0
L2
N=125
100
50
0
H3
N=66
42
21
0
L3
N=62
PRE-TRAINING
1
2
3
TRAINING
PRE-TRAINING
1
2
TRAINING

Table 11. Significance of one-tailed Wilcoxon Matched-Pairs Signed Ranks Tests on changes in seizure rate.

Subject	30-day Data from First Pretraining Period	30-day Data from Second Pretraining Period	30-day Data from Combined Pretraining Periods
H1	N.S.	$p < 0.025$	$p < 0.025$
H2	N.S.	$p < 0.025$	N.S.
H3	$p < 0.025$	N.S.	$p < 0.025$
L1	$p < 0.025$	$p < 0.025$	$p < 0.025$
L2	N.S.	$p < 0.025$	$p < 0.05$
L3	$p < 0.05$	N.S.	N.S.

of no decrease was rejected for three subjects (H3, L1, L3) on the basis of the first pretraining estimate, for four subjects (H1, H2, L1, L2) on the basis of the second pretraining estimate, and for four subjects (H1, H3, L1, L2) on the basis of the combined pretraining estimate.

Three 2 X 7 (groups by 30-day blocks) repeated measure analyses of variance were performed on the seizure rate data, employing the first, second, and combined pretraining estimates of seizure frequency. Prior to performance of these analyses, visual inspection of the data suggested the existence of a monotonic relationship between cell means and cell variances. This was confirmed by regression analyses which indicated that cell variances were directly proportional to the squares of cell means (see Appendix 4). Therefore, a logarthmic transformation was used to stabilize the variances (Winer, 1971, pp. 397-402).

As shown in Table 12, employing the first phase pretraining seizure rate estimate yielded a significant within-subject effect reflecting an overall decrease in seizure frequency ($F(6,24) = 3.02$, $p < 0.05$), but no group effect or group-training interaction. Tests on the difference between all possible pairs of means were performed via the Neuman-Keuls procedure, and the results shown in Table 12. From top to bottom, the lower portion of this table gives the cell means, the differences between all pairs of ordered means and a listing of pairs that are significantly different ($\alpha = 0.05$). The most important aspect of the direct tests on main effects is that all training period means are

Table 12. Summary of 2 X 7 Repeated measures analysis of variance performed on log seizure rate data using phase one estimate of pretraining (PT) rate, and Newman-Keuls tests on main effects.

Source	SS	df	MS	F
Between Ss				
A (groups)	1.45	1	1.45	1.69
Ss within groups	3.42	4	0.86	
Within Ss				
B (blocks of 30 days)	0.28	6	0.05	3.02*
AB	0.08	6	0.01	0.88
B x Ss within groups	0.37	24	0.02	
Total	5.60	41		

	PT	1	2	3	4	5	6
Means	9.91	9.16	9.24	9.51	8.80	8.92	8.62

Differences in Ordered Means†

Block	6	4	5	1	2	3	PT
6		0.18*	0.30*	0.54*	0.62*	0.89*	1.29*
4			0.12	0.36*	0.44*	0.71*	1.11*
5				0.24*	0.32*	0.59*	0.99*
1					0.08	0.35*	0.75*
2						0.27*	0.67*
3							0.40*

*p < 0.05

†Standard error of each mean equals 0.25

significantly lower than the mean log pretraining rate ($\alpha = 0.05$). This indicates that significant reductions in seizure rate occurred immediately after training began.

Identical tests were conducted using the second phase pretraining seizure rate estimate, and the combined phase one-phase two estimate. The results of these analyses are given in Tables 13 and 14, respectively. In both cases, a significant within-group effect of training occurred ($F(6,24) = 2.51$, $p < 0.05$ using the second phase estimate, and ($F(6,24) = 3.66$, $p < 0.05$ using the combined estimate). There were no significant group effects or interactions, and the Newman-Keuls results are identical to those given in Table 12.

In summary, Wilcoxon tests employing the three different estimates of pretraining seizure frequency showed that three or four of the six subjects decreased seizure rate. Repeated measures analyses of variance, also conducted separately for each estimate of pretraining seizure frequency indicated significant decreases in seizure rate, regardless of which pretraining estimate was utilized. Finally, direct tests on the main effect of training showed that all training means were lower than each estimate of the pretraining seizure frequency.

Analysis of EMG Data

The mean density of time-out activity during baseline periods of each pretraining and training session, and during feedback periods of each training session and corresponding periods of each pretraining

Table 13. Summary of 2 X 7 repeated measures analysis of variance performed on log seizure rate data using phase two estimate of pretraining (PT) rate, and Newman-Keuls tests on main effects.

Source	SS	df	MS	F
Between Ss				
A (groups)	1.34	1	1.34	1.42
Ss within groups	3.77	4	0.94	
Within Ss				
B (blocks of 30 days)	0.25	6	0.04	2.51*
AB	0.09	6	0.01	0.84
B x Ss within groups	0.41	24	0.02	
Total	5.86	41		

Block

Training

	PT	1	2	3	4	5	6
Means	9.87	9.16	9.24	9.51	8.80	8.92	8.62

Differences in Ordered Means#

Block

	6	4	5	1	3	2	PT
6		0.18*	0.30*	0.54*	0.62*	0.89*	1.25*
4			0.12	0.36*	0.44*	0.71*	1.07*
5				0.24*	0.32*	0.59*	0.95*
1					0.08	0.35*	0.71*
3						0.27*	0.63*
2							0.36*

*$p < 0.05$

#Standard error of each mean equals 0.05

Table 14. Summary of 2 X 7 repeated measures analysis of variance performed on log seizure rate data using combined pretrainino (PT) rate estimate, and Newman-Keuls tests on main effects.

Source	SS	df	MS	F
Between Ss				
A (groups)	1.38	1	1.38	1.54
Ss within groups	3.59	4	0.90	
Within Ss				
B (blocks of 30 days)	0.29	6	0.05	3.66*
AB	0.09	6	0.01	1.13
B x Ss within groups	0.31	24	0.01	
Total	5.66	41		

	Block						
	Training						
	PT	1	2	3	4	5	6
Means	9.94	9.16	9.24	9.51	8.80	8.92	8.62

Differences in Ordered Means/

	Block						
	6	4	5	1	2	3	PT
6		0.18*	0.30*	0.54*	0.62*	0.89*	1.32*
4			0.12	0.36*	0.44*	0.71*	1.14*
5				0.24*	0.32*	0.59*	1.02*
1					0.08	0.35*	0.78*
2						0.27*	0.70*
3							0.43*

*p < 0.05

/Standard error of each mean equals 0.05

session is presented in Figure 19 for group H subjects and in Figure 20 for group L subjects. Left and right hemisphere data are plotted separately, and standard errors are shown so that the within-subject variability, per 30-day period, can be examined.

These figures reveal three main points. First, the within-subject variability during baseline periods is much larger than during feedback periods. However, it should be kept in mind that the mean density for the feedback period of each session is based on a time duration three times greater than that employed for the baseline period mean (i.e., each session yielded 10 minutes of baseline data and 30 minutes of feedback data).

The second point is that all group H subjects clearly decreased time-out density during feedback periods, while the baseline data for each of these subjects are highly variable. It is clear from the small standard errors shown for the feedback period data that within-subject statistical analyses will yield significant decreases in time-out density for each subject in group H.

The third point is that decreases in time-out activity from the pretraining data are evident for only one subject in group L. Subjects in both groups showed considerable EMG activity during pretraining sessions, and each subject initially reacted to the first feedback session by becoming very still and quiet. This was, of course, a good strategy for the group H subjects, since it tended to reduce EMG amplitude and therefore avoided time-out signals. For group L subjects, quiet attentiveness to the feedback

Figure 19

Mean time-out density (time per minute) during baseline and feedback periods is plotted against 30-day blocks of pretraining and training, for group H subjects. Vertical bars represent standard errors of the mean for each block of days. Left and right hemisphere data are shown separately.

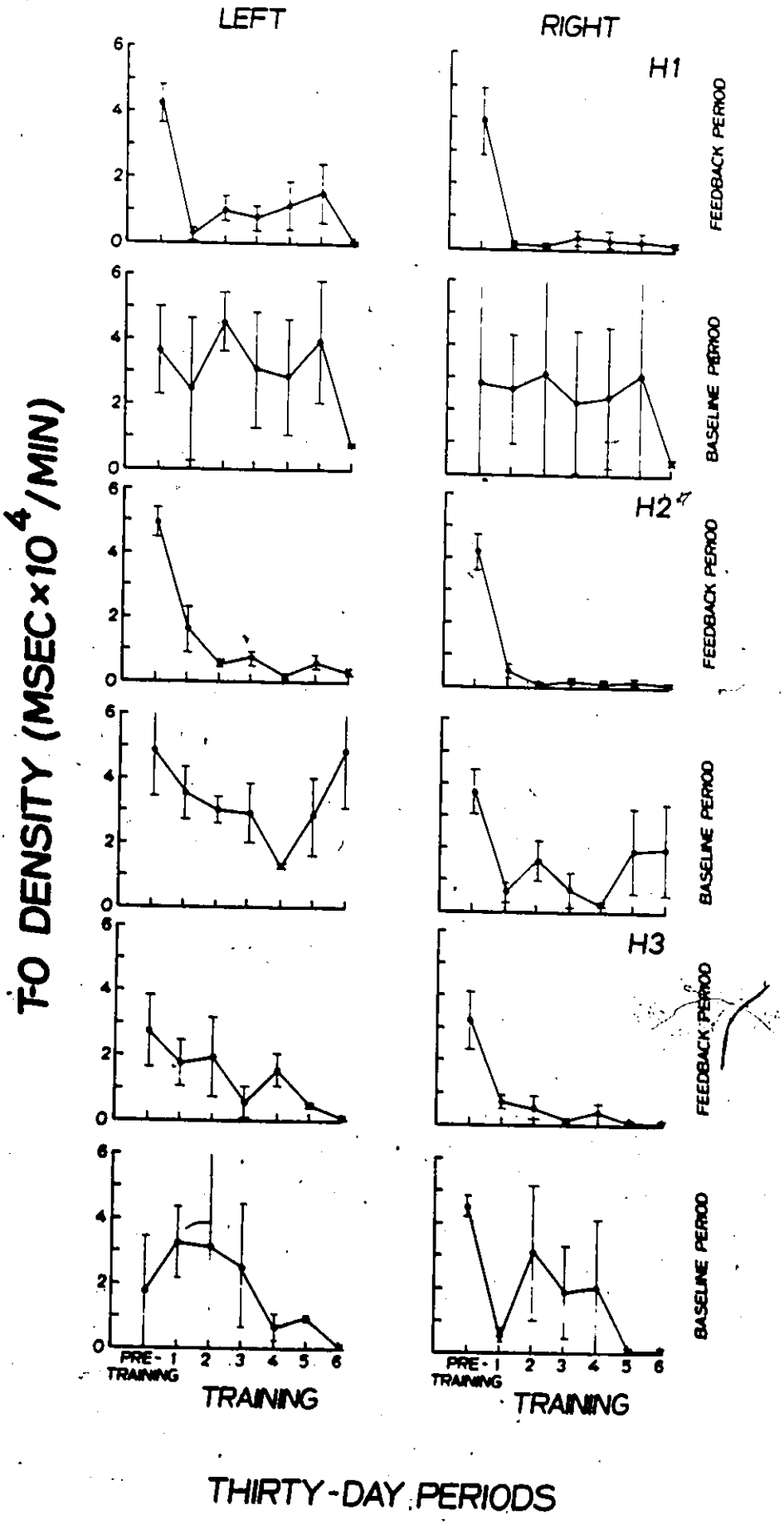
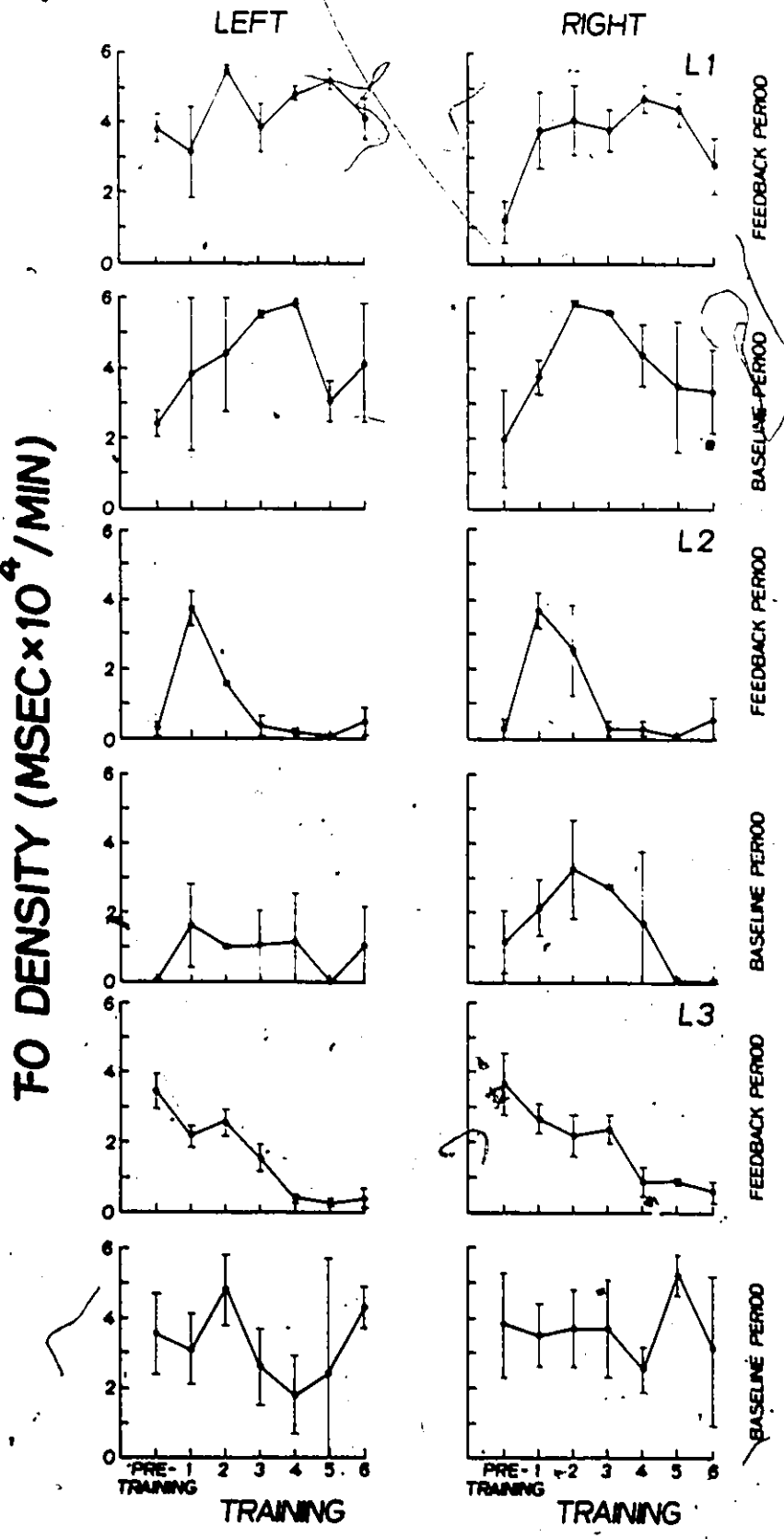

LEFT
RIGHT
H1
H2
H3
FEEDBACK PERIOD
BASELINE PERIOD
FEEDBACK PERIOD
BASELINE PERIOD
FEEDBACK PERIOD
BASELINE PERIOD
T-O DENSITY (MSEC×10⁴/MIN)
0
2
4
6
PRE-TRAINING
1
2
3
4
5
6
TRAINING
TRAINING
THIRTY-DAY PERIODS

Figure 20

Mean time-out density during baseline and feedback periods is plotted against 30-day blocks of pretraining and training, for group L subjects. Vertical bars represent standard errors of the mean for each block of days. Left and right hemisphere data are shown separately.


LEFT
RIGHT
L1
L2
L3
FEEDBACK PERIOD
BASELINE PERIOD
FEEDBACK PERIOD
BASELINE PERIOD
FEEDBACK PERIOD
BASELINE PERIOD
FO DENSITY (MSEC×10⁴/MIN)
0
2
4
6
PRE-TRAINING
1
2
3
4
5
6
TRAINING
THIRTY-DAY PERIODS

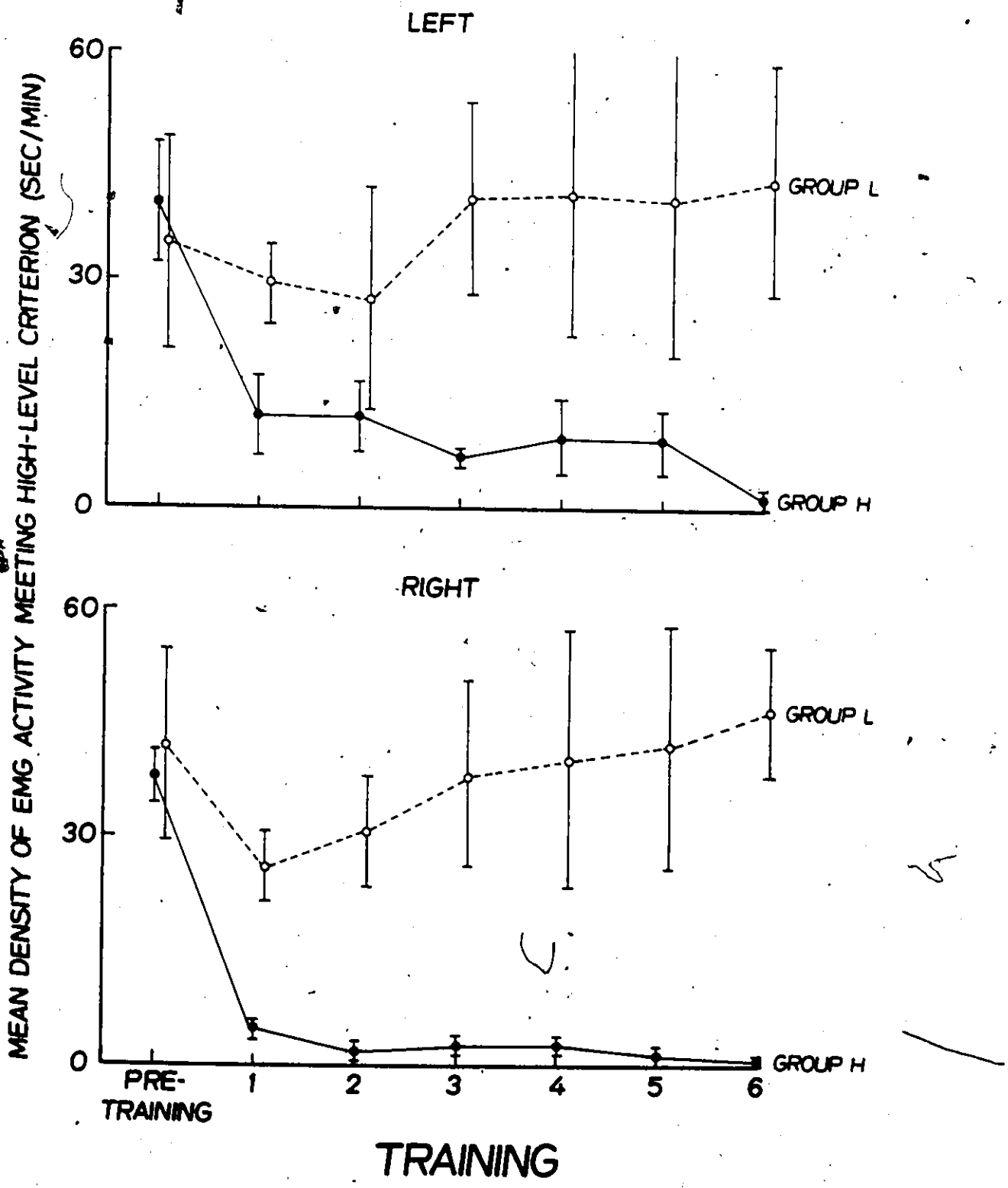
was a very poor strategy since it tended to produce a good deal of time-out activity. As training progressed L2 and L3 began to tense facial muscles as an avoidance strategy; this was highly visible to the experimenter and was also, as shown in Figure 20 an effective strategy. For subject L1 a similar strategy was effective in temporarily escaping the time-out signals, but did not produce prolonged periods of high-amplitude EMG activity. In spite of the poor avoidance performance of L1, this subject repeatedly insisted that she could control time-out activity.

An alternative visualization of EMG data is given in Figure 21 where group means and between-subject standard errors of EMG activity meeting the high-level criterion are plotted. It will be remembered that the criteria for high- and low-amplitude EMG activity had an identical cutoff point (i.e., 6uV at 75 Hz). Therefore, subtracting the mean time-out density of each group L subject from 60 seconds yields the density of activity meeting the criterion for the group H time-out. This allows direct comparison of the two groups on the basis of one variable. Figure 21 demonstrates that, as a group, H-subjects decreased substantially the density of high-amplitude EMG activity, while L-subjects did not alter this density from its pretraining activity.

Both the within-subject changes and between-group differences were confirmed by statistical tests. As was done for the EEG data in

Figure 21

Group mean densities of left and right hemisphere EMG activity meeting the high-amplitude criterion (i.e., time-out density for group H, 60 seconds per minute minus time-out density for group L) during feedback periods, are plotted against 30-day blocks of pretraining and training. Vertical bars represent standard errors of group means for each block.


LEFT
60
30
0
GROUP L
GROUP H
RIGHT
60
30
0
GROUP L
GROUP H
MEAN DENSITY OF EMG ACTIVITY MEETING HIGH-LEVEL CRITERION (SEC/MIN)
PRE-TRAINING
1
2
3
4
5
6
TRAINING

Experiment I, Wilcoxon tests were employed to determine whether time-out time per minute decreased as a function of training. The density of EMG activity meeting the high-level criterion was averaged over the feedback periods of each training session and over corresponding 30-minute periods of each pretraining session, and each training session value was compared to the mean value of the pretraining sessions. Separate tests were performed for the left and right hemisphere data of each subject. As shown in Table 15, all three of the group H subjects significantly decreased, and subject L3 significantly increased the density of high-amplitude EMG activity, in both hemispheres.

In order to evaluate group changes in EMG activity, 2 X 7 repeated measures analyses of variance were applied to the left and right hemisphere measures of mean high-amplitude EMG activity per minute. Table 16 summarizes the results of these analyses. As implied by Figure 21, a significant group x training interaction occurred for data from both the left ($F(6,24) = 3.79$, $p < 0.01$) and the right hemispheres ($F(6,24) = 3.42$, $p < 0.05$).

Tests on the simple main effects of training were performed (as described by Winer, 1971, pp. 529-532). These tests revealed a significant effect of training in group H for both the left ($F(6,24) = 4.60$, $p < 0.01$) and right hemisphere data ($F(6,24) = 6.42$, $p < 0.01$); and no significant effect of training in group L for either the left ($F(6,24) = 1.23$) or right hemisphere ($F(6,24) = 1.85$). These results are in complete agreement with the impressions gained from Figure 21.

Table 15. Mean density of EMG activity meeting high-level criterion recorded from left (L) and right (R) hemisphere electrodes during feedback periods of pretraining and 30-day blocks of training. Times are given in seconds per minute. Significance levels of predicted changes (decreases for group H subjects, increases for group L subjects) found in Wilcoxon Matched-Pairs Signed-Ranks Tests are shown in the last column.

Subject	Hemisphere	Pretraining	Training 1	2	3	4	5	6	Significance of Predicted Changes from Pretraining
H1	L	43.3	3.1	11.2	8.3	12.3	16.3	0.4	$p < 0.005$
	R	39.5	1.9	1.5	4.3	3.1	3.3	1.8	$p < 0.005$
H2	L	48.9	16.2	5.5	6.7	1.5	6.1	3.3	$p < 0.005$
	R	41.6	4.9	0.8	2.4	1.0	1.5	0.9	$p < 0.005$
H3	L	27.2	17.0	18.9	5.3	14.7	4.6	0.5	$p < 0.005$
	R	32.0	6.5	4.0	0.8	2.9	0.0	0.0	$p < 0.005$
L1	L	21.3	28.2	3.9	21.3	10.6	6.7	18.4	N.S.
	R	48.2	21.9	19.0	22.2	12.6	16.2	31.7	N.S.
L2	L	57.2	22.4	43.7	56.3	58.1	58.7	55.3	N.S.
	R	56.5	22.7	34.5	57.0	56.9	58.9	53.5	N.S.
L3	L	24.9	37.7	33.4	44.5	56.3	57.1	55.6	$p < 0.005$
	R	22.6	33.3	38.0	35.7	51.1	51.1	53.9	$p < 0.005$

Table 16. Summary of 2 X 7 repeated measures analyses of variance performed on mean density of EMG activity meeting high-level criterion, recorded from the left and right hemisphere electrodes.

Left					Right				
Source	SS	df	MS	F	Source	SS	df	MS	F
Between Ss	10728.32	5			Between Ss	11924.48	5		
A (groups)	5971.44	1	5971.44	5.02	A (groups	9816.48	1	9816.48	18.63*
Ss within groups	4756.88	4	1189.22		Ss within groups	2108.00	4	527.00	
Within Ss	5915.62	36			Within Ss	6199.10	36		
B (blocks of 30 days)	1227.28	6	204.55	2.04	B (blocks of 30 days)	2449.88	6	408.31	4.85**
AB	2280.65	6	380.11	3.79**	AB	1727.95	6	287.99	3.42*
B x Ss within groups	2407.69	24	100.32		B x Ss within groups	2021.27	24	84.22	
Total	16643.94	41			Total	18123.58	41		

* $p < 0.05$

** $p < 0.01$

A comparison of these subjects' performance with that of the subjects employed in the first experiment indicates that avoidance of signals contingent on high-amplitude EMG activity is much more easily achieved than avoidance of signals contingent on a combination of high-amplitude EMG activity and abnormal EEG activity. This suggests that the poor performance found in the first experiment was due to the EEG component of the time-out. The degree to which subjects could avoid low-amplitude EMG activity is less clear. There is no question that subject L1 failed to reduce the density of this activity while L3 clearly and significantly succeeded at the task. L2's data present a problem in that this subject's extremely low pretraining density produced a floor effect. Overall, group H decreased and group L did not change the density of high-amplitude EMG activity.

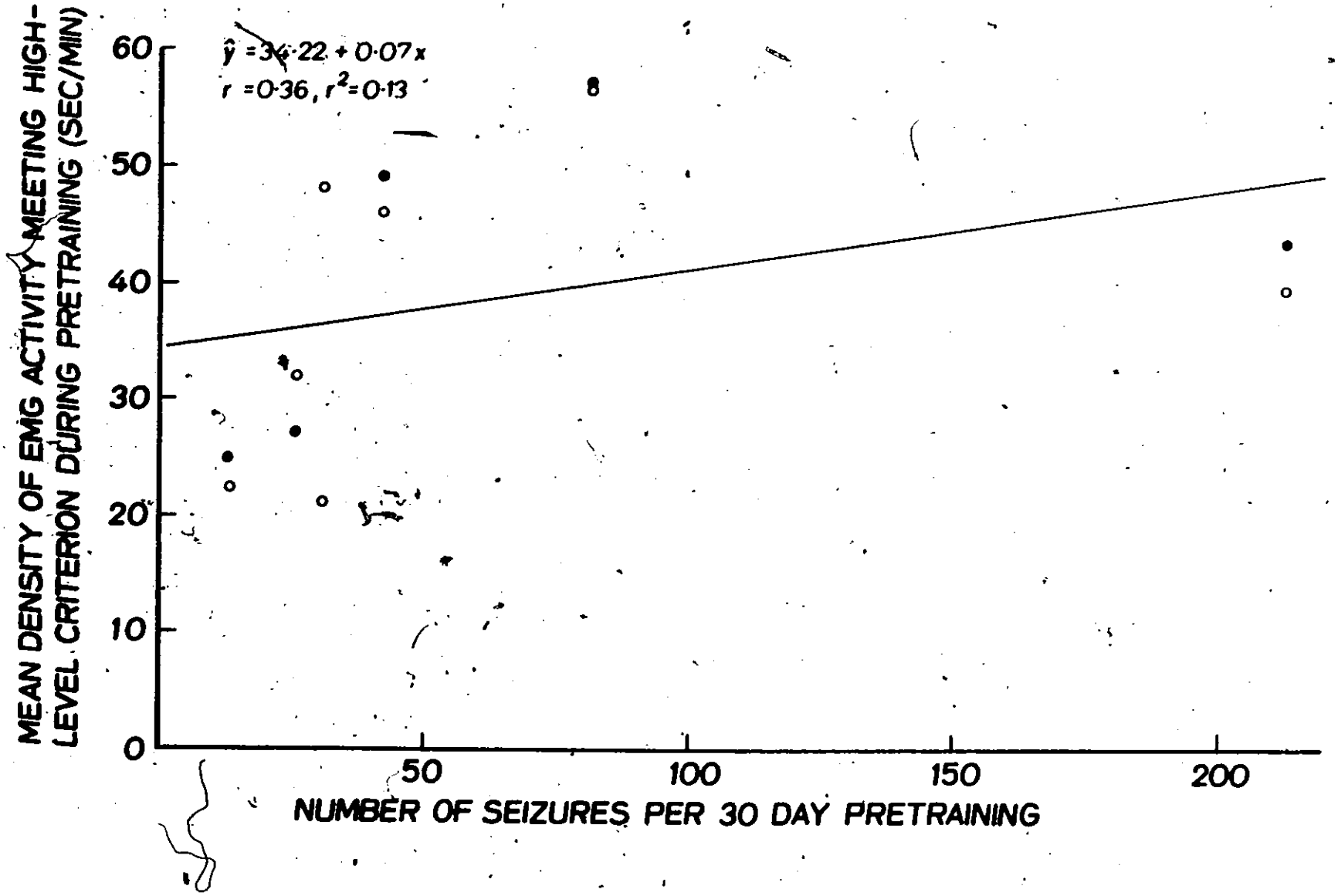
Relationships Between EMG Activity and Seizure Rate

It follows from Kaplan's (1975) hypothesis that trained decreases in the density of high-amplitude EMG activity should lead to a decrease in the probability of stress-related seizures, given an assumed relationship between high-amplitude EMG activity and relaxation.

The mean pretraining density of high-amplitude EMG activity was regressed on seizure rate during the second phase of pretraining in order to determine whether a pre-intervention relationship held between these two variables. Inspection of Figure 22 reveals a positive but non-significant linear trend between subjects.

Figure 22

Each subject's mean pretraining density of EMG activity meeting the high-amplitude criterion is plotted against that subject's seizure rate during the second phase of pretraining. The best-fit regression line is also shown. Left hemisphere densities are given by closed circles and right hemisphere densities are given by open circles.


$\hat{y} = 34{\cdot}22 + 0{\cdot}07x$
$r = 0{\cdot}36, r^2 = 0{\cdot}13$
MEAN DENSITY OF EMG ACTIVITY MEETING HIGH-LEVEL CRITERION DURING PRETRAINING (SEC/MIN)
0
10
20
30
40
50
60
50
100
150
200
NUMBER OF SEIZURES PER 30 DAY PRETRAINING

The within-subject relationship between high-amplitude EMG density and seizure rate was evaluated by regressing each subject's mean high-amplitude EMG density, calculated for blocks of 30 days, against that subject's number of seizures for that 30-day period. Separate regressions were performed for the left and right hemisphere data of each subject. These data are plotted in Figures 23 and 24 for the group H and group L subjects, respectively. One significant positive correlation was found, for the right hemisphere data of subject L1 ($r = 0.80$, $p < 0.05$). It will be recalled that this subject never decreased the density of the low-amplitude EMG activity; the positive correlation is the result of the simultaneous occurrence of a step-increase in low-amplitude EMG activity and a step-decrease in seizure rate from pretraining to the first 30-day block of training. There were no significant negative correlations.

Results given in the previous section showed that subjects H1, H2 and H3 significantly decreased the density of high-amplitude EMG activity; subject L3 significantly decreased, and L1 and L2 showed no significant change in this density from the pretraining mean. Analyses of changes in seizure rate from the values found during the pretraining period from which the EMG density estimates were obtained showed that subjects H1, H2, L1 and L2 significantly decreased seizure frequency. Thus, two of the three subjects who significantly decreased the density of high-amplitude EMG activity also decreased seizure frequency, as did both subjects who showed no change in high-amplitude

Figure 23

The mean density of criterion high-amplitude EMG activity, calculated for each 30-day block, is plotted against the number of seizures per 30 days, for each group H subject. Left and right hemisphere data are given separately, and the best fit linear regression line is shown for each plot.

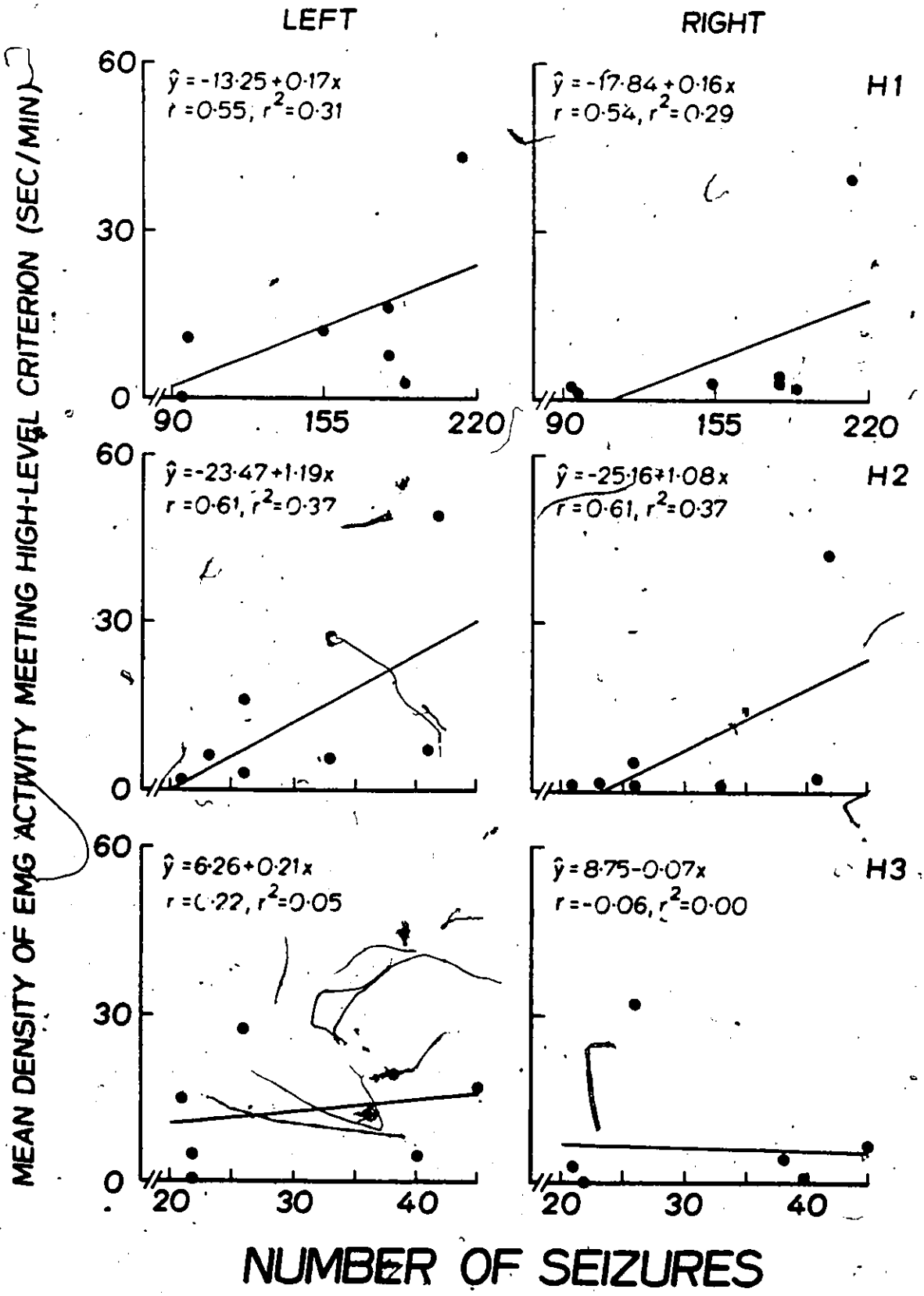
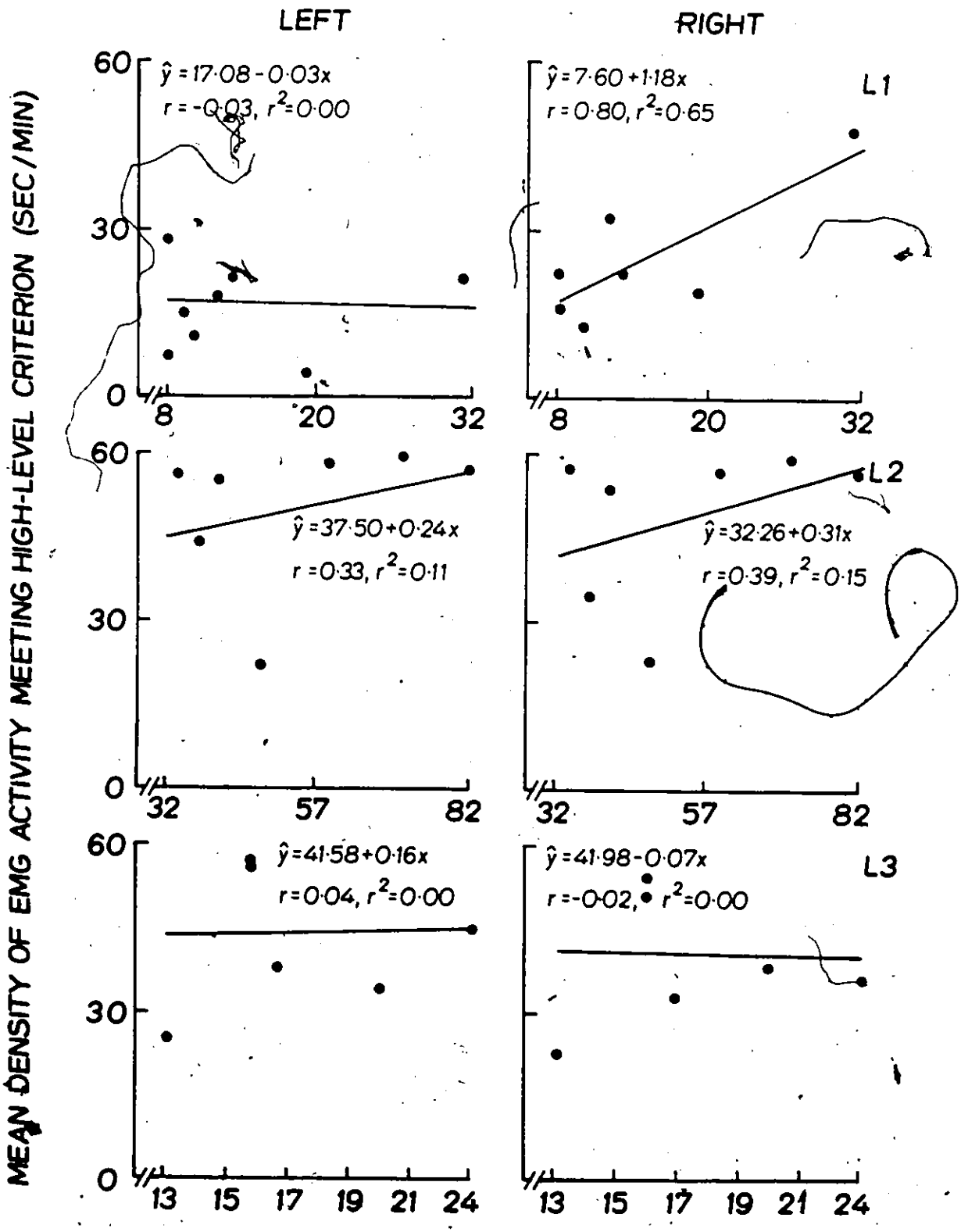

LEFT
RIGHT
H1
H2
H3
$\hat{y}$ = -13·25 + 0·17x
r = 0·55, r^2 = 0·31
$\hat{y}$ = -17·84 + 0·16x
r = 0·54, r^2 = 0·29
$\hat{y}$ = -23·47 + 1·19x
r = 0·61, r^2 = 0·37
$\hat{y}$ = -25·16 + 1·08x
r = 0·61, r^2 = 0·37
$\hat{y}$ = 6·26 + 0·21x
r = 0·22, r^2 = 0·05
$\hat{y}$ = 8·75 - 0·07x
r = -0·06, r^2 = 0·00
60
30
0
90
155
220
20
30
40
MEAN DENSITY OF EMG ACTIVITY MEETING HIGH-LEVEL CRITERION (SEC/MIN)
NUMBER OF SEIZURES

Figure 24

The mean density of criterion high-amplitude EMG activity, calculated for each 30-day block, is plotted against the number of seizures per 30 days, for each group L subject. Left and right hemisphere data are given separately, and the best-fit linear regression line is shown for each plot.


LEFT
RIGHT
MEAN DENSITY OF EMG ACTIVITY MEETING HIGH-LEVEL CRITERION (SEC/MIN)
ŷ = 17·08 - 0·03x
r = -0·03, r² = 0·00
ŷ = 7·60 + 1·18x
r = 0·80, r² = 0·65
L1
ŷ = 37·50 + 0·24x
r = 0·33, r² = 0·11
ŷ = 32·26 + 0·31x
r = 0·39, r² = 0·15
L2
ŷ = 41·58 + 0·16x
r = 0·04, r² = 0·00
ŷ = 41·98 - 0·07x
r = -0·02, r² = 0·00
L3
60
30
0
8
20
32
57
82
13
15
17
19
21
24
NUMBER OF SEIZURES

EMG density. Further, subject H3 showed a significant decrease in time-out activity but did not significantly decrease seizure rate from the second phase pretraining estimate. This suggests that reductions in the density of high-amplitude EMG activity are neither necessary nor sufficient for decreases in seizure frequency.

Relationships Between EMG Activity and EEG Activity

The results presented in the previous section make it extremely unlikely that the observed reductions in seizure rate could be due to confoundings between EMG and EEG activity. Such an explanation of the decreases in seizure frequency demands consistency in the relationship between EMG activity and seizure frequency, and this was not observed. Subjects H1 and H2 decreased both seizure rate and the density of high-voltage EMG activity, while H3 decreased time-out activity but showed no decrease in seizure rate from the second phase pretraining estimate. Subject L1 showed no change in high-amplitude EMG density in one hemisphere but an increase in the other, while L2 first decreased and then increased this density; yet both subjects reduced seizure rate. Finally, L3 significantly increased high-amplitude EMG density but did not decrease seizure rate from the phase two estimate.

Ideally, any conclusions regarding the existence of EMG-EEG confoundings should be based on cross-correlations between EMG amplitude and some measure of the degree of EEG abnormality. A conceptually simple technique would involve construction of a 2 X 2

matrix for each block of pretraining and training, containing as entries the number of EEG abnormalities and "normalities" given criterion high-amplitude EMG activity and given the absence of criterion high-amplitude EMG activity. These matrices could then be employed in chi-squared tests (Maxwell, 1961). This would permit statement of the probability of observing an EEG abnormality given the presence or absence of high-amplitude EMG activity, for each block of training; comparisons of matrices would indicate whether the degree of confounding changed as a function of training.

Unfortunately, there is no accepted method for the automatic detection of EEG abnormalities, and this is required for statistical analysis. It is possible, however, to draw some tentative conclusions regarding the presence of confoundings.

By definition, whenever criterion high-amplitude EMG activity was present, the criterion for the EMG + EEG time-out activity of the first experiment was exceeded. This is guaranteed by the integrator calibrations employed in the two experiments. Therefore, group L subjects who did not increase their time-out activity did not decrease the time-out activity measured in Experiment I. With the possible exception of L1's right hemisphere performance (see Figure 20), no group L subject decreased the density of high-amplitude EMG activity in either hemisphere, and therefore no decrease in EEG + EMG time-out activity occurred.

Furthermore, visual inspection of polygraph chart recordings

revealed no decrease in abnormal EEG activity. This is, admittedly, based on subjective interpretation and therefore highly limited as an explanatory vehicle. Nevertheless, well-described abnormal EEG patterns were present throughout training. Summaries of clinical EEG reports are given in Table 17. Figure 25 illustrates the relationship between EMG amplitude and output of the EMG integrator, and Figure 26 shows examples of oscillograph recordings made from each subject during: (1) the first pretraining session, (2) the first training session, and (3) the last training session. Aside from expected changes in EMG activity, no changes are visible in the EEGs from pretraining to the end of training. This is especially clear for group H subjects.

Relationships Between Psychometric Measures and Seizure Rate

Table 18 presents the results of the seizure locus of control and overall (Collins) locus of control tests that were administered to subjects prior to training. As indicated in the second column of this table, the possible seizure LOC scores can range from 0 to 7; since each "external" alternative receives a score of 1, 0 represents maximum internal perception and 7 is indicative of maximum external perception of control (see Appendix 1). Scores on the four factors of the Collins (1974) test are given in the next columns, followed by the sum of these four scores. For each of the four factors (I-IV), a high positive or external score reflects a belief that the world is: (I) Difficult, (II) Unjust, (III) Governed by Luck, and (IV) Politically Unresponsive. The range of possible scores is given at the head of

Table 17. Summaries of pretraining and training clinical EEG reports.

Subject	Clinical Impression
H1	Large amounts of bilateral synchronous slow wave bursts.
H2	Left-sided mid-temporal sharp waves and poly-spike discharges.
H3	Left temporal spike-and-wave focal activity.
L1	Bursts of left frontal, temporal, and parietal spike activity.
L2	Diffuse slow-wave bursts bilaterally, focal left fronto-temporal sharp-wave activity and spike-and-wave forms.
L3	Some irregular temporal activity, but otherwise normal.

Figure 25

Record of subject L2 shows the EEG recorded from left (bottom trace) and right (top trace) electrodes, with the resultant EMG integrator output. The criterion employed to distinguish low and high levels of EMG amplitude is marked C. Note that a downward deflection of the integrator tracing denotes a higher EMG amplitude. In the top portion of the figure the integrator is fed by the right hemisphere EMG and in the bottom portion it is fed by the left hemisphere EMG. Each record represents approximately 50 seconds, and the vertical bar represents a peak-to-peak amplitude of 250uV. Paper speed = 6 mm/sec, amplifier sensitivity = 2 uV/mm.

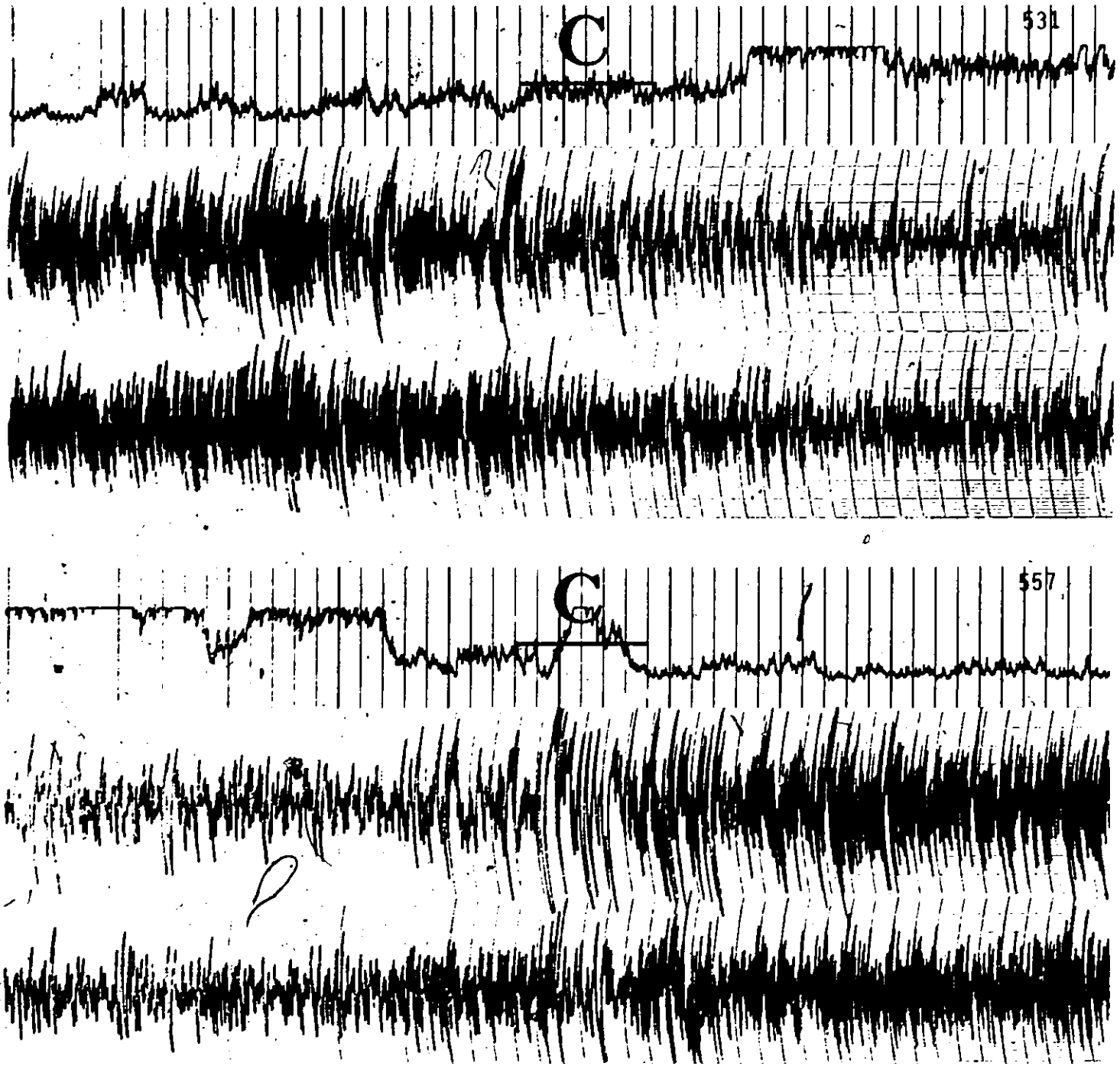

C
531
C
557

Figure 26

A 50-second portion of the unfiltered oscillograph recordings made midway (at minute 20) through the first pretraining session (PT1), first training session (T1), and last training session (TL) of each subject is shown. The upper portion of each pair of traces is from the right hemisphere electrodes and the bottom portion is from the left hemisphere electrodes. With the exceptions of subject H1 and L2, these recordings show clearly a decrease in EMG abundance for group H subjects and an increase for group L subjects. The recording for L2 illustrates the floor effect revealed in the analysis of this subject's time-out density. The vertical bar represents a peak-to-peak amplitude of 250uV. Paper speed = 6 mm/sec, amplifier sensitivity = 2 uV/mm.

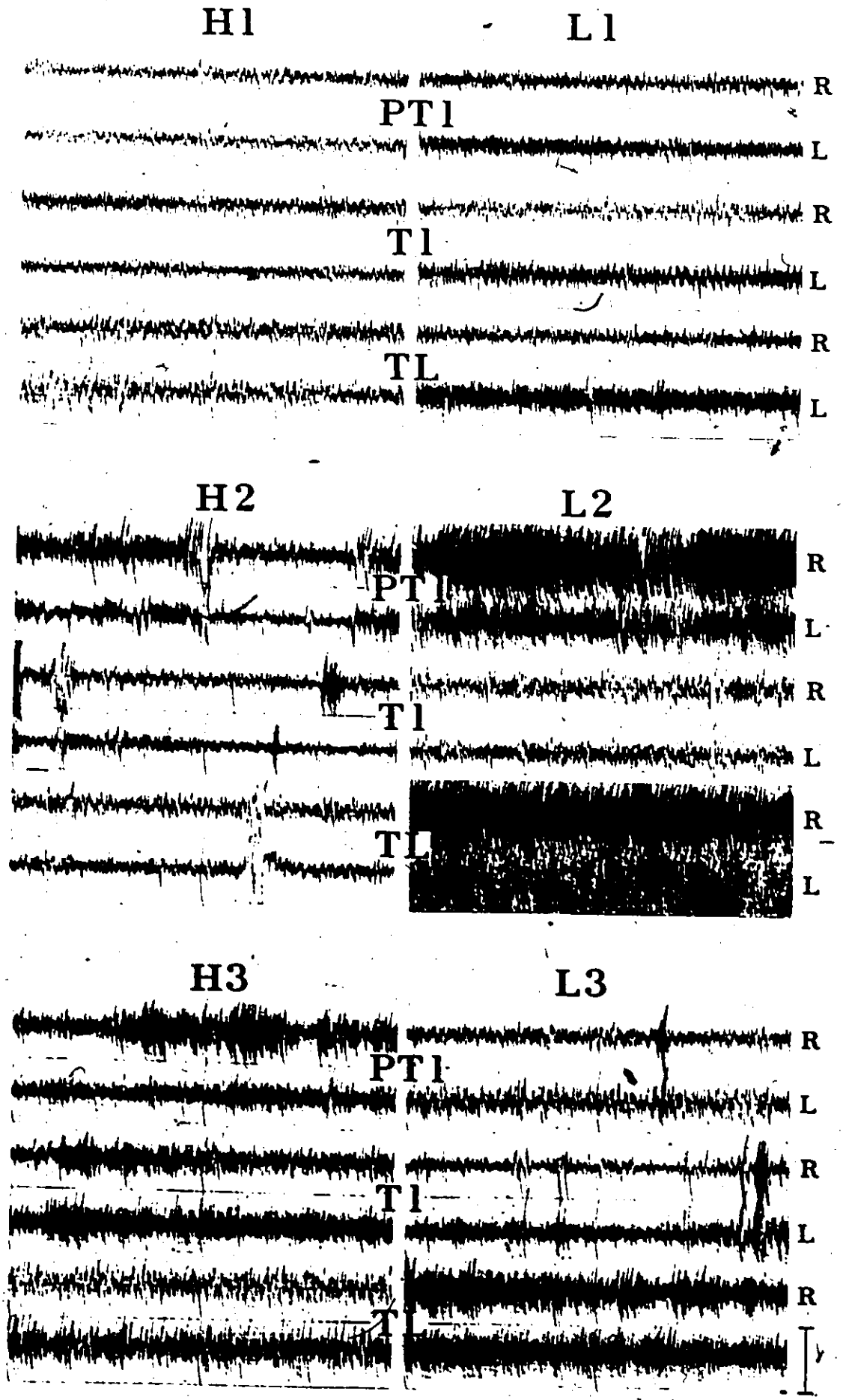

H1
L1
R
PT1
L
R
T1
L
R
TL
L
H2
L2
R
PT1
L
R
T1
L
R
TL
L
H3
L3
R
PT1
L
R
T1
L
R
T

Table 18. Results of pretraining psychometric tests. Scoring is explained in the text.

Belief In Control As Measured by Collins' LOC

Subject	Seizure LOC (0 to 7)	FACTOR I (-22 to 22)	II (-22 to 22)	III (-14 to 14)	IV (-16 to 16)	Sum
L1*	--	--	--	--	--	
L2	6	+3	-1	-3	+6	+ 5
L3	5	+6	-2	-1	+6	+ 9
H1	4	-3	-20	-8	0	-31
H2	2	-3	-9	-9	-2	-23
H3	3	+6	0	0	+1	+ 7

* This subject is mentally retarded and could not complete the psychometric test forms.

each column, with negative scores indicative of an internal perception of control.

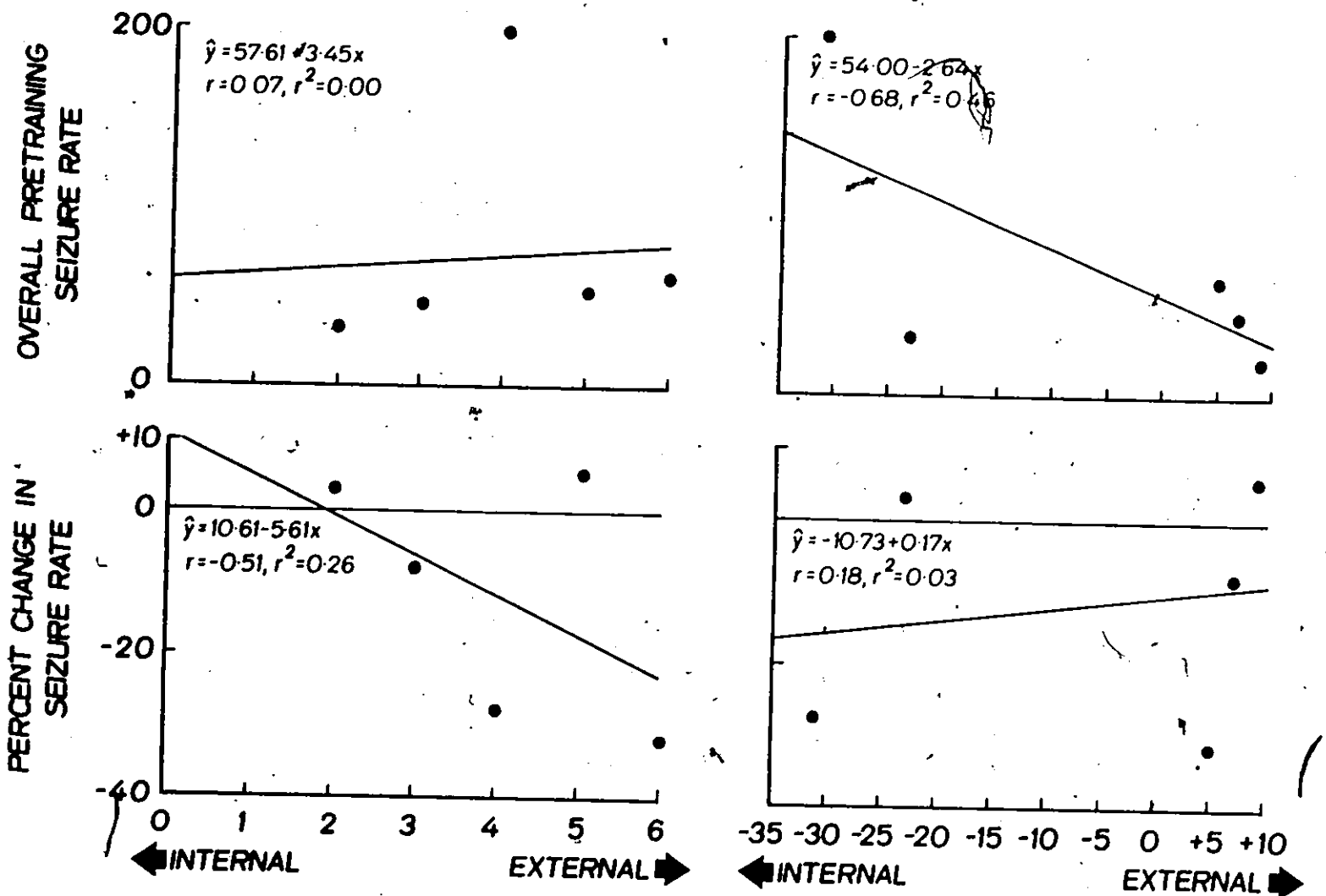
As can be seen in Table 18, the results of these tests were highly variable. On the seizure LOC test in particular (column 2), each subject scored differently so that five of the possible eight scores were obtained. It will be recalled that subject L1, who is mentally retarded, was unable to complete the test forms.

The overall pretraining seizure rate, and the percent change in seizure rate from the overall pretraining estimate to the rate during the initial period of training equivalent to the duration of pretraining, are plotted against the seizure locus of control scores and total Collins locus of control score in Figure 27. It was expected that baseline seizure rate would be directly proportional to test scores (i.e., high test scores indicate an external orientation), and that the percent-change in seizure rate would be inversely proportional to the test results. Although none of the correlations between test scores and seizure rate data was significant, it is clear that the plots for the seizure locus of control data are in the expected directions, but that the plots for the Collins' scores are contrary to what was expected.

These results, while not terribly encouraging, are not surprising either, given the small number of subjects. The seizure locus of control results, with the exception of the data of subject H1 (the point furthest from the regression line in both plots), are, in terms of rank order, exactly as predicted.

Figure 27

The overall pretraining seizure rate and percent-change from this rate are plotted against seizure and overall Collins locus of control (LOC) scores for all subjects but L1. Best-fit linear regression lines are shown for each plot.


OVERALL PRETRAINING SEIZURE RATE
200
0
ŷ = 57·61 + 3·45x
r = 0·07, r² = 0·00
ŷ = 54·00 - 2·64x
r = -0·68, r² = 0·46
PERCENT CHANGE IN SEIZURE RATE
+10
0
-20
-40
ŷ = 10·61 - 5·61x
r = -0·51, r² = 0·26
ŷ = -10·73 + 0·17x
r = 0·18, r² = 0·03
0 1 2 3 4 5 6
INTERNAL
EXTERNAL
-35 -30 -25 -20 -15 -10 -5 0 +5 +10
INTERNAL
EXTERNAL
SEIZURE LOC SCORE
OVERALL LOC SCORE

Analysis of Behavioral (Diary) Data

The results presented thus far do not support the hypothesis that trained changes in any of the measured parameters of EMG and EEG activity produce decreases in seizure rate. It is possible that subjects learn to control some parameter of scalp bioelectric activity that was not measured, and that changes in the value of this parameter promoted a lowered seizure frequency. It would be predicted on the basis of this hypothesis that either only one group should decrease seizure rate or that only those subjects showing a particular change in time-out density would improve, assuming that changes in the unknown parameter are related to either type of treatment or the response on which time-outs are contingent. Since neither of these cases was observed, there is no support for this hypothesis.

There are, of course, a variety of other, non-physiological, mechanisms that might underlie decreases in seizure rate. If a subject came to recognize situations in which seizures are likely to occur, the subject might escape or avoid such situations, or perhaps responses incompatible with seizures could be learned. In addition, the subject's participation in the experiment may have indirectly modified the responses of family members and close acquaintances to the subject's seizures. For example, if seizures had been reinforced by family members prior to experimental intervention, then a change in their behavior might tend to extinguish seizures.

The central assumption underlying this sort of analysis is that seizures should occur in only a subset of the situations encountered by subjects. Each situation might be defined by the presence of unconditioned or classically conditioned stimuli for seizures, by discriminative stimuli signalling the presence of a contingency between a reinforcer and operant aspects of seizure behavior, and so on. In each case, seizure rate could decrease if the probability of the situation occurring decreases or if the behavior of the subject or of other people changes in some fashion.

The diary data collected by subjects H2, H3, L1, and L2 were examined in order to determine: (1) whether seizure occurrence was limited to a subset of the activities or situations described by each subject; and (2) whether the frequency of these situations and/or of seizures in these situations decreased with a drop in seizure frequency.

It will be recalled that subjects were requested to record the place, activity, and companions accounting for the majority of each two-hour block of time, as well as their predominant mood and subjective perception of seizure likelihood (see Appendix 1). Unfortunately, there was a good deal of missing data for the companion, mood, and seizure likelihood information. In addition, preliminary analysis of the "place" data indicated that these entries often overlapped with, but provided less information, than the "activity" entries. For these reasons, analysis of the diary data was confined to a description of activities recorded during pretraining and

during the training block which yielded the lowest seizure rate for each subject. The data were tabulated by assigning a number to each activity encountered in the diary; a different number was used whenever there was any doubt concerning the equivalence of the subject's entry to an activity that had previously been coded. Two activities given the same number were therefore placed in the same category.

The first column of entries in Table 19 gives the ratio of the number of activity-categories for which at least one seizure had been recorded during the first phase of pretraining (abbreviated PT1), to the total number of activity-categories. This number served as an index of how widespread seizures were prior to the initiation of laboratory sessions. In each of the four cases, seizures occurred in only a subset of the categories found, ranging from a low of 24% of all categories for H2 to a high of 67% for L2.

The entries given in the second column for PT1 show, however, that those categories associated with seizures occurred more often, overall, than the remaining categories. These entries are the total number of activities in the categories associated with at least one seizure in PT1 (abbreviated by AS), divided by the total number of activities (number of activities per category, summed over all categories). The ratios are therefore proportional to the percent-time spent by each subject in activities associated with seizure occurrence. Each of these numbers is greater than 0.50, indicating that more than 50% of the two-hour blocks in PT1 contained

Table 19. Breakdown of activity data showing changes in the frequency of activities associated in pretraining phase one (PT1) with seizures (AS activities), changes in the conditional probability of AS activities given seizure occurrence (P(AS/S)), and changes in the conditional probability of a seizure given an AS activity (P(S/AS)).

Subject	Block	(Number of activity categories associated with at least one seizure)/(Total number of categories)	(Number of activities in categories associated in PT1 with at least one seizure)/(Total number of activities)	P(AS/S)	P(S/AS)	Number of seizures per 30 days
H2	PT1	0.24	0.70	1.00	0.07	27.5
	PT2		0.66	0.75	0.09	42
	TL		0.54	0.75	0.06	21
H3	PT1	0.42	0.90	1.00	0.10	66.4
	PT2		0.81	0.65	0.04	26
	TL		0.88	0.54	0.03	21
L1	PT1	0.50	0.81	1.00	0.07	24.1
	PT2		0.71	0.36	0.06	31
	TL		0.58	0.50	0.02	8
L2	PT1	0.67	0.98	1.00	0.10	45.9
	PT2		0.99	1.00	0.15	81
	TL		0.94	0.91	0.06	34

entries of activities that were associated with the occurrence of one or more seizures, for each subject.

Finally, the PT1 entries in the last three columns represent, respectively: (a) an estimate of the conditional probability of an AS activity (i.e., an activity in a category associated with at least one seizure in PT1) given that a seizure occurred (which is by definition equal to 1.00 for the first phase of pretraining); (b) an estimate of the conditional probability of a seizure given the occurrence of an AS activity; and (c) the number of seizures reported per 30 days. It is interesting to note that the entries in the second and fourth data columns are highest for subjects H3 and L2, who also had the highest PT1 seizure rates. This shows that these subjects spent proportions of time greater than H2 or L1 engaged in activities associated with one or more seizures, and that they were also more likely than H2 or L1 to have a seizure given that they were engaged in such activities.

Inspection of the entries in the PT2 (second phase of pretraining) and TL (block of training yielding the lowest seizure rate) rows shows how the proportion of AS activities and conditional probabilities change as seizure rate is altered. For all four subjects, there was a decrease both in the proportion of AS activities and in the conditional probability of a seizure given an AS activity as seizure rate decreased. In the cases of subjects H2, H3 and L2 the majority

of seizures occurred in the presence of AS activities during PT2 and TL (see column 3); in the case of L2, it appears that the joint decrease in the frequency of AS activities and in the conditional probability of a seizure given an AS occurrence is responsible for the drop in seizure rate.

In summary, this analysis shows that seizure occurrence is confined to a subset of each subject's activities prior to experimental intervention, and that these activities are coincident with the majority of each subject's seizures even when seizure rate drops to its lowest value (column 3 in Table 20). Given these observations, it seems reasonable to assume that the experimental treatment produces a decrease in seizure rate by ultimately lowering both the frequency of activities initially associated with seizures and the conditional probability of a seizure given the occurrence of such an activity.

Discussion

The results of this experiment indicate that a time-out contingent on epileptiform activity is not a necessary procedural condition for decreasing seizure frequency in medically-controlled epileptics. They also show that decreases in seizure rate occur when time-outs are given for either high- or low-amplitude scalp EMG activity. Although two of the group L subjects did not significantly decrease time-out density, the overall lack of relationship between density of high-amplitude EMG activity and seizure rate suggests that modification of EMG activity is not

responsible for amelioration of seizures. The predicted monotonic relationships between pretraining locus of control scores and pretraining seizure rate, and between locus of control scores and magnitude of changes in seizure rate were not found, although a larger sample size might have revealed such relationships. Finally, the analyses of diary data demonstrate that seizures occur in a subset of subjects' activities, and that decreases in both the frequency of these activities and in the conditional probability of seizures given these activities occur in conjunction with overall decreases in seizure frequency.

Another outcome of this experiment is related to choice of the length of the pretraining period from which seizure rate estimates were obtained. Although the duration of this period was increased from the first experiment, there was much within-subject variability during pretraining, especially when the first and second phase estimates are compared. As pointed out in Chapter 2, most previous studies have used shorter pretraining periods than those utilized in this experiment, or have relied on records collected prior to pretraining subject interviews, or have failed altogether to state the method employed to estimate pretraining seizure rate. In other words, there was no reason to believe that the pretraining durations employed in this experiment would not produce a linear relationship between cumulative seizure number and days of pretraining.

In fact, these relationships did conform rather well to linear functions within each phase of pretraining. However, two subjects showed large increases in seizure rate from the first to the second phase, and two subjects showed large decreases. As pointed out in the Results, there is no information available that would permit an evaluation of the causes of these changes. Fortunately, analyses based on three different assumptions regarding the shifts in rate all indicated that significant decreases in seizure rate were obtained in subjects from both groups.

Nevertheless, it is clear that longer pretraining periods are required if such unexpected shifts in seizure rate are to be accounted for. Perhaps a reasonable method for future research would be to continue collection of pretraining seizure data until seizure rates for a period of time equivalent to the duration of time that subjects are to attend laboratory sessions could be predicted with a satisfactory degree of accuracy (e.g., an error no greater than ± 5%) for all subjects.

Performance of subjects on the EMG tasks was much better than time-out performance in the first experiment. As expected, group H subjects attained large decreases in time-out density. Two of the group L subjects performed poorly, but there was a definite floor effect in the case of subject L2.

The observation of a group by time interaction in analyses of criterion high-amplitude EMG density is very important. It demonstrates that overall performance was as expected, and suggests

that the poor performance of subjects in the first experiment was not due to a fundamental deficiency in the operant conditioning procedure. It can be inferred from the present results that decreasing the density of epileptiform activity is much more difficult than decreasing the density of high-amplitude EMG activity recorded from the same scalp electrode placements.

The step decrease in time-out density from pretraining to the first 30-day block of training was accompanied by a step decrease in seizure rate in subjects H1 and H2. Aside from this, no relationship between EMG activity and seizure rate was found. Taken in conjunction with the lack of relationship between EMG activity and abnormal EEG activity, and between group treatment and seizure rate, this result shows that neither the response on which the time-out is contingent nor actual changes in this response are crucial for decreasing seizure frequency. It must be concluded that trained alterations in EMG activity do not play a causative role in depressing seizure rate. This, of course, raises questions about the type of mechanism that might provide a reasaonble explanation for the seizure rate results.

Pretraining locus of control scores did not show the expected monotonic relationships to seizure rate variables. As pointed out in the Results, this should not be too surprising given the small sample of subjects available. It is interesting that the trends between overall locus of control and the seizure rate variables were

opposite to what was predicted, while the relationships of seizure rate variables to seizure locus of control scores were as expected, though not significant. It would be reasonable to argue that overall locus of control should not be predictive of either seizure rate or of changes in seizure rate. However, the expected relationships of seizure rate variables to seizure locus of control scores were destroyed only by the responses of subject H1.

The diary data are provocative in the absence of a tenable physiological explanation for the seizure rate results. They indicated the existence of a subset of subject activities which can be predicted to have occurred with some reliability each time a seizure occurs, even as the overall frequency of these activities decreases. While these results are based on limited data and must therefore be considered tentative, they do suggest that seizure-precipitating situations exist. It can then be hypothesized that the operant conditioning procedure decreases seizure rate by modifying the behavior of subjects in such situations. These data also suggest that the experimental procedures are affecting seizure rate, and not merely seizure-reporting behavior. If the latter were the case, no change in the probability of activities associated with seizures would be expected.

Clearly, more sensitive instruments are required before hypotheses regarding the effects of the training procedures on responses in seizure-precipitating situations can be formulated. It would be

useful to categorize pretraining diary data so that labels can be placed on sets of activities such that seizures never occur, occur with low probability, and occur with high probability. Descriptions of these situations and of subjects' behaviors in these situations, more detailed than those gathered in the present study, would be required in the seizure recording books. Comparisons of classifications of behavior in each of the categories described above, during pretraining and training, would provide data on how behavior is altered in each type of category.

In summary, the results of this experiment indicate that time-outs for epileptiform EEG activity are not necessary for reducing seizure rate. Time-outs contingent on either high- or low-amplitude EMG activity lead to equivalent and significant decreases in seizure frequency, and no relationship between changes in EMG activity and seizure rate exists. This strengthens the contention, made on the basis of results from the first experiment, that the operant conditioning procedure effects reductions in seizure frequency by altering the behavior of subjects in seizure-provoking situations. A mediative locus of control construct may or may not prove to be a link between the procedure and its ultimate clinical effects. The seizure locus of control and diary data, while not providing strong support for this idea, do in general confirm expected relationships.

Chapter 6

GENERAL DISCUSSION AND CONCLUSIONS

The experimental questions first posed in this thesis concerned the necessity and sufficiency of SMR training and changes in SMR density for producing decreases in the seizure rates of medically uncontrolled epileptic outpatients. Results obtained in Experiment I provided no evidence for any relationship between SMR and seizure rate. The results of this study regarding the possible contribution of changes in abnormal EEG activity were negative. Following the hierarchical approach outlined in Chapter 3, it was then shown that utilization of time-out signals contingent on either high- or low-amplitude scalp EMG activity produced equivalent decreases in seizure rate. Therefore, it would now appear not unreasonable to hold the hypothesis that operant conditioning of scalp bioelectric activity is not even necessary for reducing seizure frequency.

It is true that the groups employed in the second study were not directly compared to an SMR plus EEG-EMG time-out group or to an EEG-EMG time-out group. Because of this, it might be argued that no unambiguous conclusion regarding the relative contribution of EEG training can be made. However, the changes in seizure rate found in the two experiments were not very different. In fact, statistical analyses of group data revealed a significant overall decrease in seizure rate in the second, but not in the first experiment. When

considered in conjunction with the very small changes in SMR and time-out density found in the first study, these results seem strong enough to reject the notion that EEG conditioning is necessary for ameliorating seizures.

A second possibility is that a better shaping procedure might have led to larger changes in SMR activity and therefore presumably to much larger decreases in seizure rate in the SMR + TO group. There are, however, no grounds for this argument. The procedures followed in Experiment I were modelled after those of previous SMR investigators as far as the methodological descriptions provided in published reports would allow. The casual reader of these reports might in fact get the impression that increases in SMR density larger than those observed in this thesis were obtained. As pointed out in Chapter 2, however, the inadequate methodologies, reporting of data collection procedures, and data analysis evident in these reports make impossible an evaluation of changes in any parameters of EEG activity. Certain of these deficiencies were corrected in later reports (e.g., Finley, 1977; Kuhlman and Allison, 1977), and these depict a failure to confirm earlier claims of changes in SMR and of relationships between SMR and seizure rate.

The lack of expected changes in parameters of EEG activity, together with the rapidity of effects on seizure rate and the analysis of diary data carried out in the second study suggest an alternative to a physiological explanation of therapeutic effects. The important

elements in this explanation, and therefore the therapeutically-effective components of the operant conditioning procedure are unclear. A shift in subjects' perception of control over seizures was hypothesized as an important variable, but it must be understood that changes in this variable might just as easily passively follow from a decrease in seizure rate.

A number of control groups for the EMG procedures would be useful. If perception of control over time-out signals is hypothesized to be a necessary condition for decreasing seizure rate, then the degree of control that subjects can possibly attain might be degraded in a control group. For example, signals which produce time-outs might be substituted for subjects' EMG on a random basis during each session. A second possibility would be to instruct subjects that the experimenter is actively modifying their epileptic brain activity with a machine, and that best effects will occur if the subject keeps the time-out signals off. In the first case belief in control might be attained, but to a lesser degree than for subjects who are always receiving true feedback. Subjective perception of control might be measured after each session in order to establish the effectiveness of this manipulation. In the second case, the subjects are given a passive role; they can be required to attain control over time-outs, but should believe that the real agent of changes is the experimenter's machine.

From a clinical point of view, the most promising research would involve development of a procedure to reduce seizure rate without reliance on expensive equipment. It is clear that clinicians have in fact already applied several psychiatric and psychological models to the problem of seizures (Chapter 2). If it is found that perceived control is the important variable in the procedures investigated in this thesis, then it should prove possible to shift perceptions of control in a psychotherapeutic setting (e.g., Bandura, 1977; Goldfried and Merbaum, 1973). Applications of social learning theory (Phares, 1976) and of Bandura's (1977) self-efficacy concept predict that a variety of behavioral treatment procedures should lead to decreases in seizure rate. Replications of the behavioral treatment studies reviewed in Chapter 2, with pre- and post-treatment measures of self-efficacy and perceived control, would help to clarify the predictive power of these constructs and to integrate the various behavioral approaches to the treatment of epilepsy.

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Appendix 1

SELF-MONITORING FORMS AND PERCEPTION

OF CONTROL OVER SEIZURES QUESTIONNAIRE

A blank sheet from the seizure-recording notebooks used by subjects in both experiments is illustrated in Figure 1.1. Subjects were supplied with these notebooks on demand, and each notebook contained 30 blank forms.

A page from the diaries kept by subjects H2, H3, L1, and L2 in Experiment II is shown in Figure 1.2. Each notebook contained forms for a period of five days. The abbreviations for places and moods shown above the blank form were printed on the inside front cover of each notebook.

The face-valid perception of control over seizures questionnaire is shown in Figure 1.3. All Experiment II subjects with the exception of L1 completed this questionnaire at a pretraining interview with the experimenter. Scoring is explained in the figure caption.

Figure 1.1

Sample form from the seizure recording notebooks employed by epileptic outpatients in Experiments I and II.

Month:_____ Day:_____ Time:_____ AM PM
Check if: Aura___ and/or Seizure___
Approximate duration of: Aura _____ and/or Seizure _____
If Aura, was it: Very vague___ Definite___ Very Intense___
If Seizure, was it: Mild___ Average Strength___ Very strong___
Medication last taken on: Day:____ Time:____ AM PM
Type of Medication and Amount:

_____

Describe Aura and/or Seizure, including place, what you did and what you felt before, during and after (use back of sheet):

_____

_____

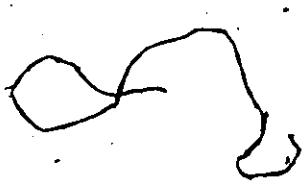


Figure 1.2

Blank page from the diary used by Experiment II subjects H2, H3, L1 and L2.

SELF MONITORING FORM

Place (Categories):

H - home
W - work
R - restaurant
Rec - recreation (party, etc.)
O - other (please specify)

Mood (Categories):

A - anxious
B - bored
C - tired
D - depressed
E - angry
H - happy
R - relaxed
O - other (please specify)

Date	Place	Activity	With Whom	Mood	Seizure Likelihood (0-10)	Comments
AM 12-2						
2-4						
4-6						
6-8						
8-10						
10-12						
PM 12-2						
2-4						
4-6						
6-8						
8-10						
10-12						

Figure 1.3

The perception of control over seizures questionnaire is shown as it was presented to subjects. Items 1 and 5 are fillers and were not scored. Responses 2b, 3a, 4a, 6b, 7b, 8a, and 9a were each scored with one point and judged as indicative of an external perception of control. Therefore a score of 7 represents maximum external perception and a score of zero represents maximum internal perception of control.

Questionnaire

1. a. Medication for epilepsy is getting better all the time.
   b. Doctors will never understand epilepsy.
2. a. Most epileptics have a lot more control over seizures than they think.
   b. As far as epilepsy is concerned, once you've got it you must accept seizures as they come.
3. a. Epilepsy is different from some other diseases, since you never know when a seizure will happen.
   b. People who have epilepsy are likely to have seizures in situations which make them upset.
4. a. What I do and where I am has no influence on the chance of my having a seizure.
   b. There are situations in which seizures are likely, and if I do nothing about them then the seizure is my own fault.
5. a. It's almost impossible for an epileptic to get a good job.
   b. Capable people who have epilepsy don't let it stand in the way of their success.
6. a. Now that I think about it, it's clear that having seizures might help avoid unpleasant situations.
   b. Having seizures does not change every day situations very much.
7. a. Taking drugs is not the only way to avoid having seizures.
   b. We epileptics are the victims of forces that we can neither understand nor control.
8. a. There is no sense in pretending that I can exert any real control over my seizures.
   b. Although I don't like to admit it, having a seizure might be a good way of getting something that I want.

9. a. Most people don't realize the extent to which the lives of epileptics are controlled by their seizures.

   b. Luck has nothing to do with the number of seizures that epileptics have.

Appendix 2

STATISTICAL ANALYSIS OF SINGLE-SUBJECT DATA

The application of inferential statistics to single-case data is, to say the least, a controversial issue (Kazdin, 1976). It has been argued that single-subject data should not be subjected to statistical analysis (Michael, 1974), although the arguments cited in defense of this viewpoint are not convincing (Davidson & Costello, 1969; Kazdin, 1976).

Of more concern here is the choice of a statistical test. The *t* and *F* tests that are generally utilized in order to test the null hypothesis of no treatment effect cannot be indiscriminately applied to single-case data. Application of these tests is based on the assumption that the error components of pairs of observations are independent. In other words, the expected value of the correlations for pairs of observations is assumed to be zero (Winer, 1971). If a correlation is significantly different from zero, then the estimates of variability based on those observations will be deflated and hence result in artificially high statistics. Further, the degrees of freedom estimate based on the number of observations will be inappropriate, since this estimate assumes independent observations.

In the case of the single-subject data collected in this thesis, application of the *t*-statistic to test null hypotheses of zero difference between pretraining and training scores (i.e., of mean seizure rate and mean time-out density) might be incorrect. For moderate positive correlations between successive observations (autocorrelations) the actual level of significance will be considerably lower than that

stated for the test, and for negative autocorrelations the actual level will exceed the nominal level (Scheffe, 1959). In other words, the usually-employed parametric tests are not robust to significant dependence between serial observations (Glass, Wilson, and Gottman, 1975).

Variations of the t test and analysis of variance have been proposed in order to deal with this problem (Gentile, Roden, and Klein, 1972; Shine and Bower, 1971). These proposals have been criticized on several grounds (Hartmann, 1974; Kratochwill, Alden, Demuth, Dawson, Panicucci, Arntson, McMurray, Hempstead, and Levin, 1974; Thoresen and Elashoff, 1974). While the variations may sometimes be of some utility, the solutions proposed for dealing with serial dependency are effective only for certain patterns of data.

An alternative approach to testing treatment effects in single cases is based on the methods of time-series analysis (Kazdin, 1976). In this approach, a number of models are selected as possible representations of the pattern of serial dependence. Glass et al. (1975), for example, consider two possibilities: the autoregressive model and the moving averages model. In the autoregressive model, the observation at time t (z_t) is represented as a weighted sum of past observations plus a normally distributed random component, a_t:

$$z_t = \phi_1 z_{t-1} + \phi_2 z_{t-2} + \cdots + \phi_p z_{t-p} + a_t.$$

In the moving averages model, z_t is considered as a weighted sum of random shocks to the system on which observations are made:

$$z_t = a_t - \theta_1 a_{t-1} - \theta_2 a_{t-2} - \cdots - \theta_q a_{t-q}.$$

Having made the assumption that one of these models can adequately represent the data, the next step is to compute the lag 1 autocorrelations for the pretreatment and treatment data separately, and to determine if these correlations are significantly different from zero. If the null hypothesis is not rejected in either case, then the data can be treated as independent observations and therefore be subjected to traditional parametric or non-parametric analyses. Otherwise, autocorrelations of lag greater than 1 must be computed in order to illuminate the structure of the series - that is, to estimate the parameters of the model assumed to underlie the pattern of data. Once these estimates are available the data can be transformed by a linear model from which equations for the desired statistics can be derived (e.g., Glass et al., 1975, Chapter 6).

Although time-series analysis deals with the problem of serial dependency much more effectively than the previously-mentioned variations on traditional t- and F-tests, it also presents some new problems. As Glass et al. (1975) indicate, it is often unclear just which model should be assumed to underlie the observed data. In a three-parameter model presented by these authors, an observed series can often be equally-well represented by several different sets of parameter values. Furthermore, estimates of the combined pretreatment

and treatment variance and other statistics (e.g., t) are derived from an approximate solution to a matrix equation. Finally, the combining of pretreatment and treatment autocorrelation estimates is problematic. This last point is especially troublesome, since the entire process of parameter estimation is based upon the estimated magnitude of an autocorrelation to represent the entire series of observations.

Fortunately, most of these problems were avoided in analyzing data from Experiment I and Experiment II. As shown in the Results sections of these two experiments, all single-subject data were analyzed by means of Wilcoxon Matched-Pairs Signed-Ranks Tests (also termed the One-Sample Wilcoxon Test - see Hajek, 1969, pp. 102-109). Two assumptions are required for application of this test: the random variables underlying observed values are assumed to be independent and are assumed to be governed by a common continuous and symmetric distribution function. It will be shown below that the required independence of the random variables was in fact achieved. That the assumption of a symmetric distribution function was met can be easily demonstrated as follows.

In the most common application of this test, the effect of some treatment A is tested on N pairs of subjects. Following Hajek (1969), it is assumed that the location parameter or value of each observation is a sum of two components: one due to the presence or absence of A, and the second due to individual differences. Thus, the two observations made on each subject are given by

$$X_i = X_i^0 + u_i + \Delta, \qquad Y_i = Y_i^0 + u_i, \qquad 1 \leq i \leq N,$$

where $(X_1^0,\ldots,X_N^0,Y_1^0,\ldots,Y_N^0)$ are identically distributed independent random variables. Therefore $X_i^0 - Y_i^0$ and $Y_i^0 - X_i^0$ are identically distributed, and $Z_i = X_i - Y_i$ has a symmetric distribution about zero if $\Delta = 0$; i.e.,

$$F(x) = P(Z_i^0 \leq x) = P(-Z_i^0 \leq x)$$
$$= P(Z_i^0 \geq -x) = 1-P(Z_i^0 < -x)$$
$$= 1-F(-x).$$

In the present case, N observations are collected on each subject, and N-1 treatment observations are to be compared to a pretreatment value. With the assumption of independence in mind, we have

$$X_i = X_i^0 + u_i + \Delta$$

for treatment observations, and

$$Y = Y^0 + u_i$$

for pretreatment. Then the differences $X_i^0 - Y^0$ and $Y^0 - X_i^0$ will be identically distributed, and $Z_i = X_i - Y$ has a symmetric distribution about zero, as above.

With respect to independence of observations, inspection of the raw data (e.g., number of seizures per day, mean time-out density per minute per session) for pretraining and training demonstrated no obvious serial dependence between successive observations. For example, the plots of cumulative pretraining seizure rate shown in Figures 1, 2, 15 and 16 do not reveal a serial dependency. While it might be argued that the training-period data would be more likely to show serial dependence because of a trend due to learning, this was found not to be the case. Lag 1 autocorrelations were computed for several cases in which large changes occurred from pretraining to training. This was done, for example, for the seizure data of subject T4 in Experiment I

and for the electromyogram (EMG) time-out data of subject H3 in Experiment II (i.e., Figures 3 and 19). The resulting autocorrelations and z-scores are illustrated for both pretraining and training in Table 2.1. None of the autocorrelations is significantly different from zero, even at $\alpha = 0.10$.

The lack of dependence in training data would be rather surprising if trends were present. As discussed in the results of the experiments, however, step-changes in variable values generally occurred from pretraining to training, so that each series of data is in fact stationary. This permits application of the Wilcoxon Test, which allows comparison of pretraining and training values with no assumption regarding the form of the underlying distribution.

Table 2.1. Mean value ($\bar{x}$), lag 1 sample autocorrelation (r), standard error of r(s_r), and observed z-statistic (z_{obs}) for pretraining and training seizure data of subject T4 (Experiment I) and left- and right-hemisphere EMG time-out density data of subject H3 (Experiment II).

	Subject T4		Subject H3			
	Pretraining	Training	Pretraining		Training	
			Left	Right	Left	Right
$\bar{x}$	0.47	0.18	28.28	31.97	11.37	2.81
r	0.02	0.03	0.33	-0.38	0.24	0.10
s_r	0.18	0.07	0.45	0.41	0.19	0.18
z_{obs}	0.10	0.41	0.72	-0.92	1.25	0.58

Appendix 3

METHOD FOR FINDING AND FITTING POLYNOMIALS TO CUMULATIVE SEIZURE DATA (CHOOSING AND FITTING APPROPRIATE MOVING AVERAGES)

If it is desired to fit a polynomial of order p to 2m+1 points, then the function

$$\sum_{-m}^{m} (U_t - a_0 - a_1 t - \ldots - a_p t^p)^2$$

must be minimized. Differentiation with respect to a_0 and the coefficients of t leads to the p+1 equations

$$\Sigma U_t t^j - a_0 \Sigma t^j - a_1 \Sigma t^{j+1} - a_2 \Sigma t^{j+2} - \ldots - a_p \Sigma t^{p+j} = 0,$$

for $j = 0, 1, \ldots, p$.

The solution for a_0, the value of the series at t=0, then depends upon values given by the sum Σt^j and linear functions of the u's given by $\Sigma t^j U_t$. Therefore the polynomial trend value at any point t=k is a linear average of values of the series from u_{k-m} to u_{k+m}. Kendall (1973) gives the weights required to compute moving averages based on polynomials of order two through five, based on 5,7,9,...,21 points of a series.

For end effects (i.e., the first and last m terms of the series), solutions are required for $a_1, a_2, \ldots, a_m$. These have been calculated by Cowden (1962) for linear through quintic polynomials and for 3,5,7,...,25 points of a series.

Choice of a moving average, that is, the lowest order polynomial that adequately depicts the trend of the series, is not quite so straightforward. Kendall (1973) suggests that what is termed the variate-difference method provides a guideline of sorts. This method is based on the following reasoning (Kendall, 1973, pp. 47-54).

Suppose that a time-series can be represented by a polynomial together with a superposed (i.e., additive or multiplicative) random element. Since the differences of a polynomial of order p are represented by a polynomial of order p-1, then successive differencing p+1 times should remove the p^{th} order polynomial, leaving only elements of a random series. Letting Δ^r represent the r^{th} forward difference, we have by definition

$$\Delta U_t = U_{t+1} - U_t,$$

$$\Delta^2 U_t = U_{t+2} - 2U_{t+1} + U_t,$$

$$\Delta^r Ut = U_{t+r} - \binom{r}{1}U_{t+r-1} + \binom{r}{2}U_{t+r-2} + \ldots \pm (-1)^r U_t.$$

Now let u have zero mean (this does not limit the generality of what follows). Then

$$E(\Delta^r U_t) = 0,$$

and if u_t has the same variance var u for all t, then

$$\text{var } (\Delta^r U_t) = \text{var } U \left(1 + \binom{r}{1}^2 + \binom{r}{2}^2 + \ldots + 1 \right).$$

But

$$1 + \binom{r}{1}^2 + \binom{r}{2}^2 + \ldots 1 = \binom{2r}{r}.$$

Therefore,

$$\text{var } (\Delta^r U_t) = \binom{2r}{r} \text{ var } U,$$

and

$$V_r = \text{var } U = \text{var } (\Delta^r U_t)/\binom{2r}{r}.$$

This shows that if we take the r^{th} differences of the series, calculate the variance and divide by $\binom{2r}{r}$, we should have an estimate of var u, the variance of the random element, providing that the differencing has removed polynomial trend. The variate-difference method proceeds by successive differencing until V_r settles down to a constant. Several possible pitfalls are discussed by Kendall (1973, pp. 49-54).

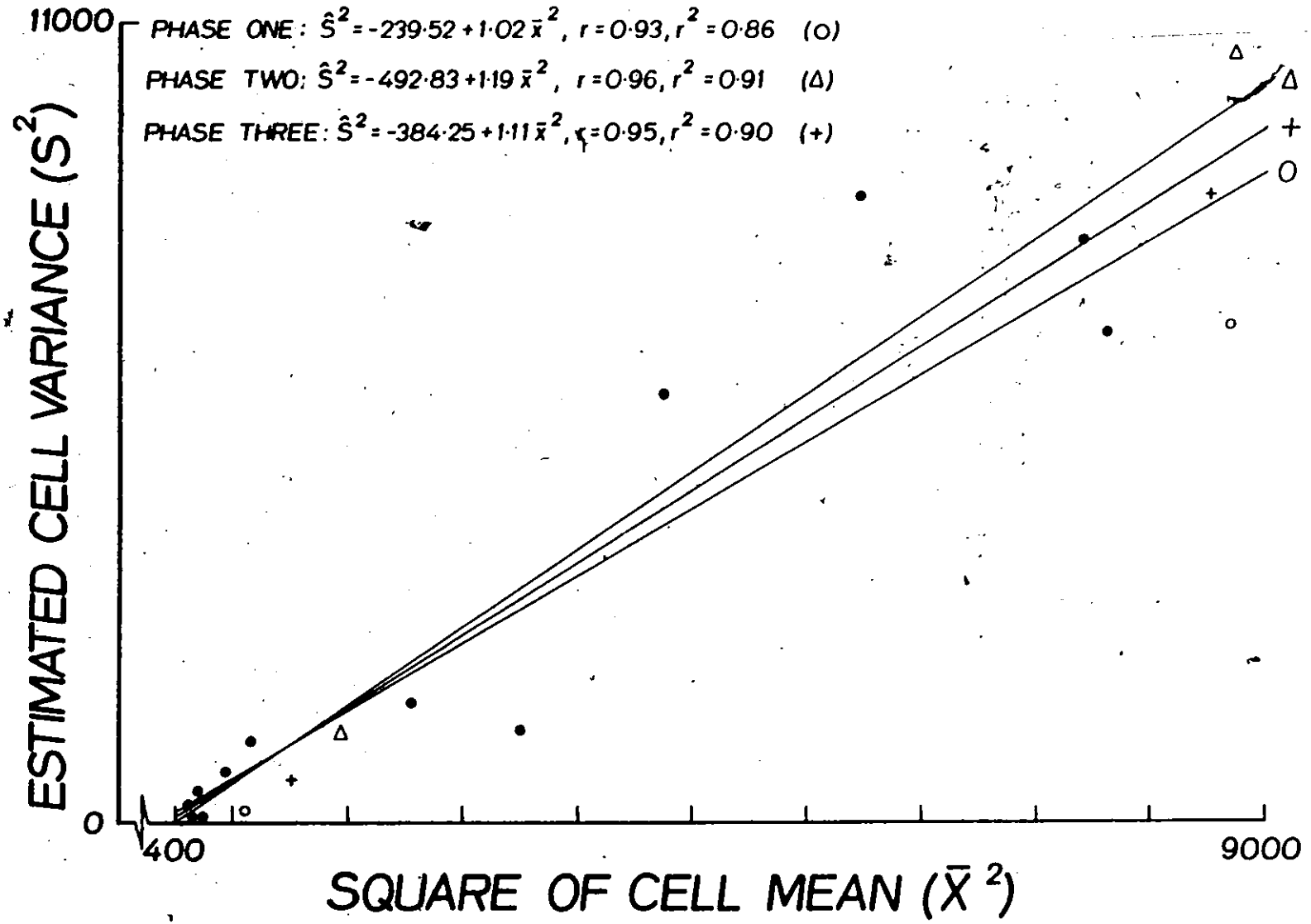
Appendix 4

DEPENDENCE OF ESTIMATED CELL VARIANCE UPON ESTIMATED CELL MEAN SEIZURE RATE (EXPERIMENT II)

Figure 4.1 shows a monotonic relationship between the mean seizure rates over blocks of days and the cell variances. As shown in this figure, a linear relationship between the estimated cell variance and the squared estimate of the mean seizure rate exists regardless of the pretraining seizure rate estimate employed.

Figure 4.1

The estimated cell variances are plotted against the squares of mean seizure rates for each block. Theopen circles denote the first phase pretraining estimates, the open triangles denote the second phase pretraining estimates, the plus signs indicate the combined pretraining estimates, and the closed circles represent training period data. Three linear regression equations were calculated, one for each of the pretraining estimates. The regression lines are marked by the appropriate symbols.


11000
PHASE ONE: $\hat{S}^2 = -239{\cdot}52 + 1{\cdot}02\,\bar{x}^2$, $r = 0{\cdot}93$, $r^2 = 0{\cdot}86$ (O)
PHASE TWO: $\hat{S}^2 = -492{\cdot}83 + 1{\cdot}19\,\bar{x}^2$, $r = 0{\cdot}96$, $r^2 = 0{\cdot}91$ (Δ)
PHASE THREE: $\hat{S}^2 = -384{\cdot}25 + 1{\cdot}11\,\bar{x}^2$, $r = 0{\cdot}95$, $r^2 = 0{\cdot}90$ (+)
ESTIMATED CELL VARIANCE (S^2)
0
400
9000
SQUARE OF CELL MEAN ($\bar{X}^2$)
Δ
+
O