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20. Facilitation threshold is defined as the smallest amplitude of the echo that evokes just noticeable facilitation.
21. The dash and slash mean, respectively, successive and simultaneous deliveries of two sounds for maximum excitation of combination-sensitive neurons. For instance, H_1-FM_2 means that FM_2 should be delivered after H_1 for best facilitation, and CF_1/CF_2 means that CF_1 and CF_2 should be delivered simultaneously. A multiple suffix—for instance, $FM_{2,3}$ in H_1-$FM_{2,3}$—means that either FM_2 or FM_3 delivered after H_1 effects the same or similar facilitation. The H_1-FM facilitation neurons are those whose response to FM is facilitated by H_1 or its components CF_1 and FM_1, so that this category includes all H_1-FM_2, H_1-FM_3, H_1-FM_4, H_1-$FM_{2,3}$, H_1-$FM_{2,4}$, H_1-$FM_{3,4}$, and H_1-FM_{2-4} facilitation units. The FM_1-FM-facilitation neurons are those whose response to FM is facilitated by the FM_1 component of H_1, but not by CF_1, so that this category includes FM_1-FM_2, FM_1-FM_3, and FM_1-$FM_{2,3}$. The CF_1/CF facilitation neurons are those whose response to CF is facilitated by CF_1, so that this category includes CF_1/CF_2, CF_1/CF_3, $CF_1/CF_{2,3}$, and $CF_1/CF_{3,4}$. A detailed investigation of the response properties of CF_1/CF facilitation neurons will be reported separately (N. Suga, W. E. O'Neill, T. Manabe, *Science*, in press).
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Reducing Epileptic Seizures Through Operant Conditioning of Central Nervous System Activity: Procedural Variables

Abstract. *Operant conditioning of the sensorimotor rhythm of the human electroencephalogram with time-outs contingent on epileptiform activity reduces epileptic seizure rates in patients whose seizures are not well controlled by medication. A comparison of this procedure with time-out training alone demonstrates that operant conditioning of the sensorimotor rhythm is neither necessary nor sufficient for seizure reduction.*

Operant conditioning, or biofeedback, of particular electroencephalographic (EEG) rhythms has been applied successfully as a treatment for epilepsy in humans who have not responded well to medication (*1-6*). With few exceptions (*3, 6, 7*), the method has involved operant conditioning of the sensorimotor rhythm (SMR). This rhythm is a 12- to 14-Hz sinusoidal waveform recorded from the scalp over the sensorimotor cortex. Operant conditioning of the SMR has been correlated with a reduction in the frequency of epileptic seizures (*4, 5*). Further, an increase in SMR activity has been assumed to reduce the seizure rate through a decrease in cortical excitability (*8*). There is reason, however, to question such a relationship between SMR conditioning and reduced seizure rate.

In every experiment in which reductions in seizure frequency were reported to follow SMR training, the conditioning procedure included a clearly signaled "time-out" contingent on EEG slow waves, spike activity, or high-voltage scalp electromyographic (EMG) activity. A time-out is a period during which reinforcement is not available. That is, SMR was not reinforced during epileptiform activity or gross body movements, and the unavailability of reinforcement was indicated to the subject by a signal.

The omission of reinforcement could act as an aversive stimulus. It has been established that time-outs punish skeletal behaviors (*9*). With respect to the SMR plus time-out (SMR + TO) procedure, the time-out may suppress EEG slow-wave and spike activity. The time-out might also lead to the development of either avoidance or escape responses, that is, the acquisition of some response that prevents or terminates activity associated with the time-out. A decrease in the probability of epileptiform activity might account for a decrease in the frequency of seizures preceded by such activity (*10*). Consequently, the procedural variable that leads to reduced seizure activity in SMR training procedures might be the signaled removal of reinforcement rather than the SMR training itself (*11-13*). We have now demonstrated that the SMR + TO procedure is no more effective than a time-out alone (TO) procedure.

Seven epileptic outpatients with long histories of responding poorly to medication were obtained from the epilepsy clinic at McMaster University Medical Centre. Each patient 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 reliably triggered the time-out circuit; and seizures described clinically as being poorly controlled by medication.

Medical files and interviews were used to determine the mean seizure rate, clinical history, seizure manifestation, medication schedule, and interictal EEG pattern. One or two 40-minute recording sessions were also used to determine whether interictal epileptiform activity reliably triggered the time-out circuit. Serum concentrations of prescribed medication were held constant throughout the experiment (*14*). Four subjects received TO training and three received SMR + TO training. Descriptions of each subject are presented in Table 1.

There were two 40-minute sessions per week over a period of 210 days. During a 30-day period before training began (eight sessions), seizure and EEG data were collected, but no feedback was delivered. The remaining 180 days were devoted to training sessions. Previous SMR investigations indicate that subjects who improve do so within 6 months of training. Subjects and their families were provided with small notebooks for detailed monitoring of auras and seizures. No records were kept by the one mentally retarded subject in each group; their data were obtained from family, friends, teachers, and counselors.

The training procedure was modeled after that of Lubar and Bahler (*4*). Each session consisted of 5 minutes of baseline recording without feedback, 15 minutes of feedback contingent on activity recorded alternately on each succeeding sessions from C_3-T_3 or C_4-T_4 (*15*), 15 minutes of feedback from the contralateral electrodes, and a final 5-minute baseline. Stimulus presentation and online data analysis were carried out by a computer (PDP Lab-8/E).

The EEG was monitored through silver-silver chloride scalp electrodes (Grass) connected to two matched EEG

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amplifiers (Grass 7P511) with filters set at 1 and 300 Hz. The output of the amplifier on which feedback was contingent was fed to two band-pass filters, a 12- to 14-Hz filter (Ross Systems Engineering) and a 4- to 7-Hz filter (Kron-Hite 335), both having roll-offs of 24 dB per octave. The computer used a maximum-minimum detection algorithm on the output of the 12- to 14-Hz filter to identify SMR waves (*16*). The occurrence of six SMR waves within 0.50 second was defined as an SMR burst. The 4- to 7-Hz filter output was fed to an integrator (Grass 7P3) (time constant = 0.5 second). Whenever this integrated slow-wave activity exceeded a voltage equivalent to that produced by a 5.5-Hz calibration sine wave with a peak-to-peak amplitude of 10 μV at the input of the 7P511 amplifier, a Schmitt trigger fired. In order to detect EMG and spike activity, the 7P511 amplifier output was also fed to a second integrator (Grass) (time constant = 0.1 second), calibrated so that a 50-μV, 10-Hz sine-wave calibration input to the amplifier produced an integrator output voltage just large enough to fire a second Schmitt trigger. The computer recognized the firing of either Schmitt trigger as a time-out event. Although this system would count nonepileptiform sharp waves and large-amplitude activity as time-out events, it does ensure that all epileptiform activity produces time-outs.

For all subjects, a buzzer and a small lamp indicated time-out events. For SMR + TO subjects, an SMR burst in the absence of time-out events produced a 0.50-second tone and advanced a digital light counter.

An informal shaping procedure was used with SMR + TO subjects in an attempt to increase both the probability and the amplitude of SMR bursts. During the first training session, the amplitude criterion was set so that a 13-Hz calibration sine wave of 2 μV peak-to-peak amplitude would produce SMR burst feedback. On succeeding sessions, the criterion was increased by approximately 0.44 μV if on the preceding session the subject had received a mean of two or more SMR-burst reinforcements per minute.

During pretraining and the first and last 5 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. The TO subjects were told to keep the time-out signals off as much of the time as possible. The 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.

Totals of each subject's reported seizures per 30-day period are presented in Table 2. The number of seizures decreases from pretraining for all but one subject in each group (*17*). A separate Wilcoxon matched-pairs signed-ranks

Table 1. Subject descriptions. N.A., not available.

Subject	Sex	Year of birth	Age at first seizure	Type of seizure	Auras	Medication	Mentally retarded
T_1	M	1948	6 months	Psychomotor	Yes	Valium, Mysolin, Dilantin	No
T_2	F	1957	9 months	Major, minor, temporal	Yes	Dilantin, phenobarbital	No
T_3	F	1962	4 months	Grand mal	N.A.	Mysolin	Yes
T_4	F	1950	19 years	Deja vu, psychomotor	No	Dilantin	No
ST_1	F	1955	12 years	Psychomotor	Yes	Mysolin	No
ST_2	M	1963	6 years	Tonic-clonic, drop, absence	Yes	Phenobarbital	Yes
ST_3	M	1951	5 years	Focal, grand mal	Yes	Dilantin, Mysolin	No

Table 2. Seizure and EEG variables. Number of seizures (S) and mean time-out (TO) and mean SMR time in seconds per minute. Medical-file estimates of seizure rates (not used in statistical tests) and right-hemispheric EEG data are given in parentheses. Data were analyzed with one-tailed Wilcoxon matched-pairs signed-ranks tests. N.S., not significant.

Subject	Variable	Blocks of 30 days							Changes from pretraining
		Pretraining	Training						
			1	2	3	4	5	6	
T_1	S	5 (8)	2	2	4	6	4	3	$\downarrow P < .05$
	TO	16.1 (20.7)	12.2 (17.3)	14.1 (21.4)	12.6 (22.5)	14.2 (25.7)	13.9 (22.2)	8.1 (19.4)	$\downarrow P < .025$ (N.S.)
	SMR	21.9 (26.6)	23.6 (23.2)	23.4 (23.9)	23.2 (25.2)	24.9 (27.9)	23.5 (25.0)	21.3 (23.9)	$\uparrow P < .05$ (N.S.)
T_2	S	3 (26)	4	2	4	13	2	21	N.S.
	TO	35.4 (33.0)	27.1 (31.0)	22.0 (29.3)	28.4 (32.7)	23.5 (28.7)	29.3 (33.6)	27.4 (35.6)	$\downarrow P < .025$ (N.S.)
	SMR	23.8 (25.1)	26.2 (27.0)	19.1 (18.5)	21.6 (26.8)	22.8 (26.5)	23.3 (25.3)	22.6 (28.5)	N.S. (N.S.)
T_3	S	9 (12)	5	3	2	4	3	2	$\downarrow P < .025$
	TO	55.1 (56.0)	47.8 (46.7)	44.3 (41.7)	54.4 (52.3)	48.5 (49.9)	49.8 (50.9)	52.3 (52.9)	$\downarrow P < .025$ ($\downarrow P < .025$)
	SMR	23.9 (25.4)	23.6 (24.1)	26.3 (27.3)	22.3 (22.0)	25.6 (26.2)	20.5 (23.9)	19.8 (24.7)	N.S. (N.S.)
T_4	S	14 (21)	6	8	2	9	5	3	$\downarrow P < .025$
	TO	13.9 (20.3)	9.9 (10.6)	11.6 (15.8)	16.9 (19.9)	15.6 (21.6)	22.4 (25.0)	12.3 (19.1)	N.S. (N.S.)
	SMR	19.8 (20.8)	22.0 (24.7)	23.0 (26.2)	22.2 (25.1)	22.9 (25.8)	23.4 (26.6)	19.1 (21.6)	$\uparrow P < .05$ ($\uparrow P < .025$)
ST_1	S	16	32	14	28	25	28	25	N.S.
	TO	38.2 (40.8)	24.7 (24.6)	24.3 (23.6)	26.9 (29.5)	29.3 (31.1)	32.3 (31.4)	30.3 (31.8)	$\downarrow P < .025$ ($\downarrow P < .025$)
	SMR	24.0 (24.0)	28.4 (28.6)	26.0 (28.7)	29.9 (25.6)	27.7 (27.9)	26.3 (27.2)	27.8 (27.9)	$\uparrow P < .025$ ($\uparrow P < .025$)
ST_2	S	72	61	72	59	47	64	60	$\downarrow P < .05$
	TO	43.1 (46.8)	41.6 (41.5)	40.8 (41.0)	37.2 (37.7)	40.5 (42.2)	41.2 (42.5)	41.5 (44.9)	$\downarrow P < .025$ ($\downarrow P < .025$)
	SMR	27.0 (27.3)	27.2 (30.0)	27.3 (28.1)	23.4 (28.3)	23.6 (26.9)	23.2 (29.9)	20.9 (19.9)	N.S. (N.S.)
ST_3	S	255 (375)	150	180	194	140	191	174	$\downarrow P < .025$
	TO	20.9 (24.2)	14.2 (15.9)	11.9 (15.1)	15.8 (21.4)	27.2 (30.4)	20.6 (26.3)	24.3 (21.6)	N.S. (N.S.)
	SMR	17.0 (19.5)	19.0 (22.2)	16.6 (21.1)	18.1 (22.1)	19.5 (23.8)	17.7 (20.7)	15.4 (15.1)	N.S. (N.S.)

test (one-tailed) for each subject tested the hypothesis that the number of seizures per 30-day period did not decrease from the pretraining value. This hypothesis was rejected for subjects T_1, T_3, T_4, ST_2, and ST_3; it was not rejected for subjects T_2 and ST_1.

Wilcoxon tests were used to determine whether (i) time-out time per minute decreased and (ii) 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 periods of each pretraining session, and each training session value was compared with the pretraining session mean. Separate tests were done for data from the left and right hemispheres of each subject. Three of the four TO subjects significantly decreased time-out in at least one hemisphere, as did two of three SMR + TO subjects. The SMR time increased in one hemisphere for subject T_1, and increased in both hemispheres for subjects T_4 and ST_1.

These results indicate that SMR training is not necessary for reductions in seizure frequency; they provide no evidence of a relationship between SMR time and seizure rate (*18*). Of the five subjects whose seizure rate decreased, only two showed an increase in SMR time; ST_1 increased SMR time significantly but showed no decrease in seizure rate.

Neither are these results entirely consistent with the hypothesis that reductions in time-out activity are necessary and sufficient for lowering seizure rate. The two subjects who failed to reduce seizure rates (T_2 and ST_1) significantly reduced time-out time, indicating that escaping or avoiding epileptiform activity during feedback training is not sufficient for lowering seizure rate. Furthermore, subject T_4 did not significantly reduce time-out time but did significantly reduce seizure rate.

Thus, SMR conditioning is not necessary for the reductions in seizure rate that have been reported to result from the SMR + TO procedure. Although TO training may be necessary, it is clearly not sufficient. The effective component of the time-out procedure is yet to be identified.

ARTHUR COTT
Department of Medicine, McMaster University, Hamilton, Ontario Canada L8S 4K1
RAYMOND P. PAVLOSKI
ABRAHAM H. BLACK
Department of Psychology, McMaster University

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11. We know of no experimental evidence that would suggest that SMR has any relationship to seizure frequency. Sterman (*12*) has failed to replicate his initial finding (*13*) that seizure latency following the administration of monomethylhydrazine is significantly longer in SMR-trained cats than in normal controls. Furthermore, Kaplan (*3*) used no time-out with two epileptics and found no changes in seizure frequency.
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17. Extra experimental factors were evident in these two cases. Subject ST_1 became pregnant during the first month of feedback, a condition which had once before grossly exacerbated seizures. Three sharp rises in the seizure rate of subject T_2 occurred at days 68, 114, and 159 from the start of feedback, concomitant with, respectively, the days that T_2 left an uneasy home situation, returned home, and realized that the home situation had not improved. Furthermore, the reliability of T_2's data is questionable, in that her pretraining seizure rate was estimated in her medical file to be eight times the rate she reported during the pretraining period. This subject's neurologist also indicated that he believed T_2 to have many more seizures than were reported.
18. This lack of relationship has also been reported in other published reports (*1*). We are aware of no data, including those reported by Sterman (*5*), demonstrating significant increases in SMR in groups of epileptic subjects receiving SMR training.
19. Supported by Ontario Mental Health Foundation grant 258-69D and Medical Research Council of Canada grant MA 5854. A.C. is an Ontario Mental Health Foundation Research Scholar. We thank Dr. A. Upton for providing medical supervision and assistance throughout this study.

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Plasticity: The Mirror of Experience

Abstract. *A simple avoidance training procedure during early development produces massive neural traces in visual and somatic cortices of kittens reared in a normal environment. A preponderance of cells in these areas had response preferences for the stimuli used during training. Furthermore, some of these cells exhibited properties never found in normal animals not receiving such training. It appears that, even in an environment in which many other stimuli are present, some early experiences powerfully affect brain development and the way in which other experiences exert their effect.*

One of the most interesting endeavors in neuroscience has been the search for neural modifications induced by experience and their loci in the brain. Lashley (*1*) named this "the search for the engram" and after many experiments concluded that memories had to be distributed because they could not be localized. Wiesel and Hubel have demonstrated in the visual cortex of cats that if sensory deprivation is enforced during a critical period of development that spans 4 to 8 weeks, substantial phenomena of neural plasticity result (*2, 3*). In 1970, Hirsch and Spinelli (*4*) demonstrated that controlled exposure to vertical lines for one eye and horizontal lines for the other during early development causes a preponderance of monocular cells in the visual cortex. Most important, the shape of receptive fields was remarkably similar to the shape of the stimuli viewed during development. Similar results have been obtained by others (*5*). In some of these experiments (*4, 5*), except for the controlled experience, the kittens were kept in a dark room at all times; that is, the exposures are delivered on a background of visual deprivation. We also showed that after our cats from the 1970 experiment acquired normal experiences binocularly for a year and a half, they also acquired new functional properties in some of their visual cortex cells: cells were found with binocular disk-shaped receptive fields (*6*). Cells with line-shaped receptive fields appeared to be still monocular and bound to the early experience.

Our memory hypothesis, that many responsive cells are actually shaped by the experience (*6*), might explain at least some of the effects observed. Alternatively, atrophy from disuse might have

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