memory loss

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Memory and Convulsive Stimulation: Effects of Stimulus Waveform

NB — brief no better

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Electrical stimulation with brief pulses can produce a seizure requiring less energy than conventional sine-wave stimulation, and it has been suggested that brief-pulse stimulation might reduce the memory loss associated with electroconvulsive therapy (ECT). The authors evaluated the effects of electroconvulsive hock (ECS) on memory in mice by using various waveforms, current intensities, training-ECS intervals, pulse widths, and stimulus durations. When equated for ability to produce seizures, low-energy, brief-pulse stimulation caused as much amnesia as sine-wave stimulation and sometimes more. In the absence of comparisons of the amnesic effects of brief-pulse and sine-wave stimulation in humans, the use of brief pulses for administering ECT is unwarranted.

Of all the risks and side effects associated with ECT, memory dysfunction has received the most attention; a good deal is now known about its severity and duration (1, 2). Recently there has been interest in reducing the effects of convulsive treatment on memory by optimizing the characteristics of the electrical stimulus (e.g., waveform, current, and total electrical energy). Because delivery of electrical energy in excess of the minimum energy needed to elicit a seizure increases memory dysfunction (3, 4), it has sometimes been proposed that any procedure which reduces the electrical energy used in convulsive stimulation should reduce memory loss (5, 6). In particular, it has been suggested that treatment with brief square-wave pulses instead of conventional sine-wave stimulation could minimize the amnesic effects of ECT, because brief-pulse stimulation can elicit seizures with approximately one-third the electrical energy associated with conventional sine-wave stimuli (5–8).

It is possible, however, that reducing total electrical energy will decrease memory loss only if the ability of the electrical stimulus to produce seizures is also reduced. If this is true, then even though brief-pulse stimulation can produce a seizure with less electrical energy than sine-wave stimulation, memory loss might be similar if these two waveforms were both given at seizure threshold. Moreover, if some specific features of a stimulus waveform contribute to memory loss, such as rate of increase of current intensity, then brief-pulse stimulation might impair memory even more than sine-wave stimulation.

The available data (9, 10) on the effects of brief-pulse stimulation and sine-wave stimulation suggest that they are therapeutically equivalent, but to our knowledge a clear comparison of their effects on memory has not yet been accomplished (for review see 9, 11). We undertook this study to compare the amnesic effects on mice of convulsive stimulation with different waveforms, including sine-wave and brief-pulse stimulation. By standardizing the waveforms according to their seizure thresholds, we were able to determine directly whether total electrical energy contributes to amnesia and whether brief-pulse stimulation can minimize amnesia.

METHOD

Male Swiss albino mice (35–50 g) were housed for at least 4 days before training. Memory was assessed with the one-trial, step-through passive avoidance task, a standardized and much used method for investigating the amnesic effects of convulsive stimulation and other agents on rodents (12). Each animal was used only once. For training, a mouse was placed into the start compartment facing a door that blocked the entrance to a dark inner compartment. After a 10-sec delay, the door was opened. When mice entered the dark compartment and touched the rear floor plate of this area, they received a 65-mA foot shock. The mice were confined in the inner compartment for 5 sec and then allowed to escape back into the safe outer compartment.

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To test retention, this procedure was repeated 24 hours later, except that no foot shock was delivered. The time taken by mice to step into the dark compartment and touch the rear plates (step-through latency) was recorded automatically and taken as the measure of retention. A long step-through latency was taken to reflect good retention of the punishing foot shock, and a short step-through latency was taken to reflect poor retention. A maximum step-through time was allowed, and mice not stepping into the dark compartment within the allotted time were assigned the maximum score. In experiment 1 this time was 300 sec, and in experiments 2 and 3 it was 600 sec. For data analysis each step-through latency was log-transformed to normalize the distribution of scores.

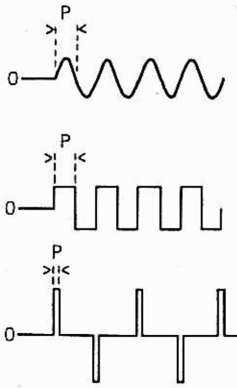
The three different constant current waveforms are shown in figure 1. The apparatus delivering these waveforms consisted of a waveform generator and a constant current amplifier. During stimulation, an oscilloscope was used to measure the voltage across the electrodes as well as the current through the electrodes. The duration of the pulse series and the width of the individual pulses could be varied.

Current was delivered to each mouse through transcorneal electrodes covered with small cotton sponges that were coated in saline before each treatment. The mice were hand held during administration of electroconvulsive shock (ECS) and were given air from an automatic pump afterward. With this procedure 11% of the mice died during the experiments. Current was delivered at three intensities, which were designated as low, medium, and high. The low current intensity was that intensity required to produce a clonic-tonic seizure in 50% of the animals. The medium current intensity was the minimum intensity needed to produce a clonic-tonic seizure in 100% of animals. The high current intensity was calculated to be 25% greater than the current needed to produce 100% seizures. The low and medium current intensities were established to the nearest milliampere in pilot studies by subjecting different groups of 10 mice to a stepwise series of current intensities.

For each mouse used in the experiments, the total electrical energy developed at each current intensity was calculated from the following formula: electrical energy (joules) = voltage (volts) × intensity (amperes) × time (seconds). This calculation provided a measure of the electrical energy developed between the two electrodes. Because it cannot be determined directly how much energy is dissipated through the skull, the calculated value is an estimate of the electrical energy passing through the brain.

To compare the duration of cortical seizures associated with the two critical waveforms under study, we measured the duration of seizures electrographically through skull screws in separate groups of mice that received either sine-wave (N=8) or brief-pulse (N=10) stimulation. The medium current intensity was used, and the current characteristics were the same as in experiment 1. The mean duration of seizures with sine-wave stimulation was 9.4±0.5 sec, and with brief-pulse stimulation it was 9.3±0.6 sec; the difference was nonsignificant.

FIGURE 1
Three Constant Current, Bidirectional Waveforms Used to Deliver Electroconvulsive Shock to Mice



Waveform (60 Hz)	Stimulus Duration (sec)	Pulse Width (P) (msec)
Sinusoidal (sine wave)	0.09–0.2	8.3
Bipolar square (square wave)	0.2	8.3
Bidirectional brief pulse (brief pulses)	0.4–1.0	0.4–0.8

RESULTS

Experiment 1

The first study evaluated the amnesic effects of the three waveforms across a wide range of experimental conditions. Each waveform was given at three current intensities (low, medium, and high) and at three different times after training (10, 30, and 90 min). This design resulted in 27 separate groups (3 waveforms × 3 current levels x 3 training-ECS intervals) among the 620 mice. In addition, there were 138 control mice.

The three current intensities (peak to peak) of the sine wave were 26, 36, and 45 mA. We selected a duration of sine-wave stimulation of 0.2 sec, a value commonly used for convulsion stimulation in experimental studies of animals (13). For the square wave, the three current intensities (peak to peak) were 19, 28, and 35 mA. The duration of the square-wave stimulation was 0.2 sec, and the width of each pulse was 8.3 msec. For brief-pulse stimulation the three current intensities (peak to peak) were 35, 46, and 58 mA. The width of each pulse was 0.4 msec. The duration of brief-pulse stimulation was 0.8 sec, which is longer than the duration of sine-wave stimulation, as is the case when brief-pulse stimulation is used with psychiatric patients (14).

Figure 2 shows the effects of training-ECS interval, current intensity, and waveform on performance of the step-through response at 24 hours after training. For each of these conditions the results for all 620 mice

TABLE 1
Effects of Electroconvulsive Shock Waveforms and Their Characteristics on 24-Hour Retention of a Passive Avoidance Habit in Mice

Group	N	Waveform	Pulse Width (msec)	Stimulus Duration (sec)	Current Intensity (mA)	Electrical Energy (J)	Retention (log sec)[a]	
							Mean	SEM
Experiment 2								
1	43	Sine wave	8.3	0.2	36	.063	2.04	0.06
2	42	Brief pulses	0.4	0.8	46	.022	1.98	0.08
3	43	Brief pulses	0.6	0.53	46	.022	1.88	0.07
4	42	Brief pulses	0.8	0.4	46	.022	1.82	0.06
5 (controls)	20						2.43	0.08
Experiment 3								
1	37	Sine wave	8.3	0.09	46	.045	2.03	0.08
2	40	Brief pulses	0.4	0.8	46	.022	2.08	0.07
3	35	Sine wave	8.3	0.2	36	.063	2.22	0.05
4	37	Brief pulses	0.4	1.0	36	.017	2.07	0.07
5 (controls)	32						2.34	0.07

[a] A high score signifies good retention.

Experiment 2

Five groups of mice were trained in the step-through avoidance task and tested for retention 24 hours later. All mice were given ECS 30 min after training at the medium current intensity (the minimum intensity needed to produce seizures in 100% of the mice). Group 1 was given the sine wave and groups 2–4 received brief pulses; the amount of electrical energy was the same as in experiment 1. The fifth group was a control group not given ECS. The results are shown in table 1. The control group exhibited better retention than any of the four groups receiving ECS (Dunnett's $t_s>3.0$, $p<.01$). In keeping with the results of experiment 1, groups 1 and 2 did not differ significantly. Increasing the pulse width of the brief pulses (groups 2–4) from 0.4 msec (group 2) to 0.8 msec (group 4) gradually increased their amnesic effect such that one of the groups receiving brief pulses (group 4) was more amnesic than the group (group 1) receiving sine waves (Tukey's $q=3.38$, $df=1, 42$, $p<.05$). This occurred despite the fact that less energy was delivered by brief pulses (.022 J) than by sine waves (.063 J).

Experiment 3

In experiment 1, sine-wave and brief-pulse stimulation exerted similar amnesic effects when the current intensity and duration of the waveforms were set to equate their ability to produce seizures. Experiment 2 replicated this finding and showed in addition that some configurations of brief pulses caused even more amnesia than the sine wave. In that study, the current intensity of the brief pulses was always 46 mA (peak to peak), and the current intensity of the sine wave was always 36 mA (peak to peak).

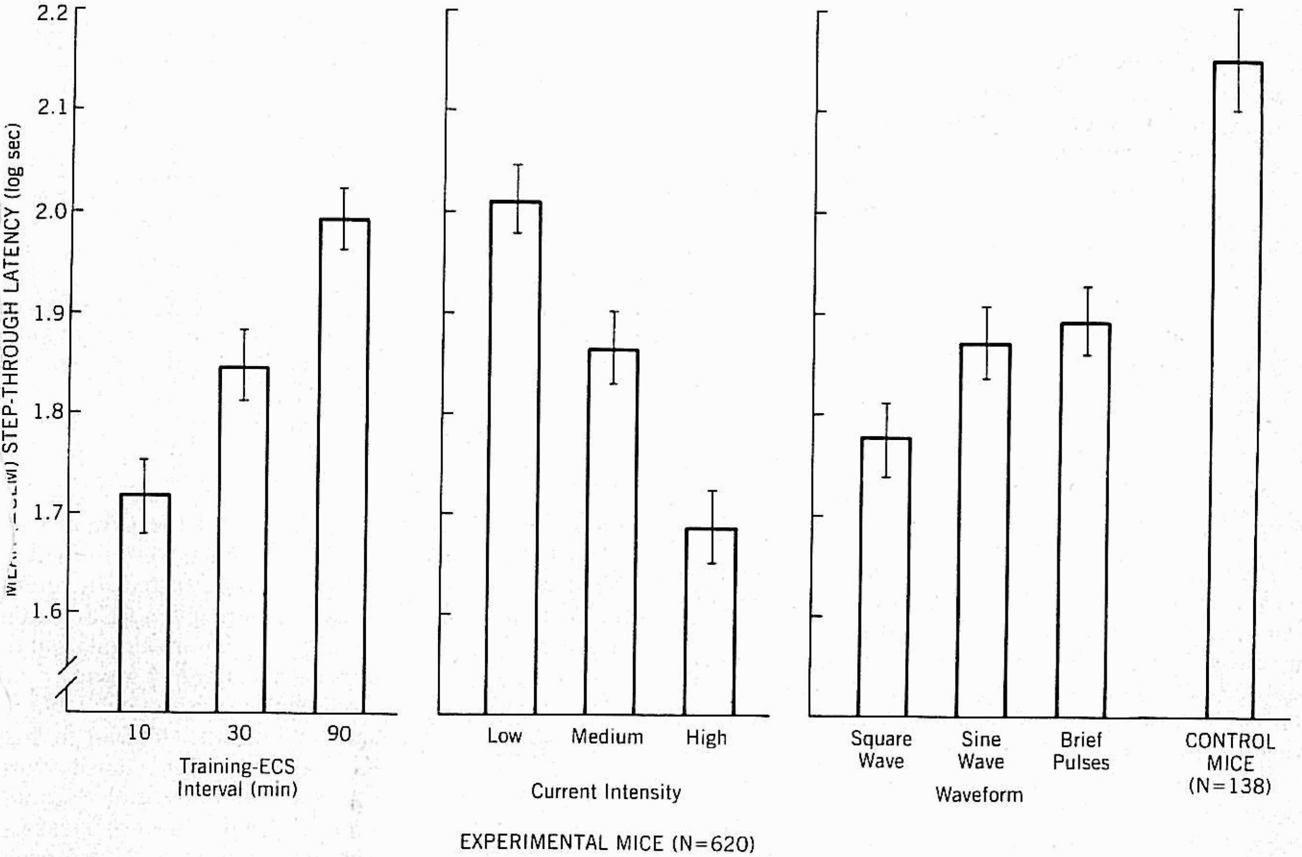
Experiment 3 compared the amnesic effects of brief-pulse and sine-wave stimulation when they had the same current intensity as well as the same ability to produce seizures. To equate these two characteristics for both waveforms, the duration of the stimuli wa altered as needed. Five groups of mice were trained i the step-through avoidance task and tested for retention 24 hours later. Groups 1–4 were given ECS 30 min after training and received the minimum stimulation to produce a seizure; group 5 was a control group.

ECS characteristics and results are shown in table 1. The retention of the control group was superior to that of the groups given ECS. When current intensity was 46 mA peak to peak, sine-wave and brief-pulse stimulation exerted amnesic effects that were not measurably different. When current intensity was 36 mA peak to peak, brief-pulse stimulation produced more amnesia than sine-wave stimulation, but this difference fell short of significance ($t=1.68$, $df=70$, $.05<p<.1$). These findings indicate that sine-wave stimulation produced a degree of amnesia similar to that of brief-pulse stimulation, even when the two waveforms were equated for both current intensity and the ability to produce seizures.

DISCUSSION

In these three experiments brief-pulse stimulation resulted in as much or more amnesia than sine-wave stimulation. Indeed, it was not possible to construct a low-energy, brief-pulse stimulus that, after equating for seizure-producing efficiency, caused less amnesia than a conventional sine-wave stimulus. Accordingly, total electrical energy is not the only factor determining the effects of convulsive current on memory. Waveforms can deliver considerably different amounts of electrical energy but exert similar amnesic effects (figure 2). In addition, for two different waveforms, more amnesia can occur after stimulation with that waveform delivering less electrical energy (table 1, experiment 2). Because the square-wave stimulus was the most deleterious to memory (figure 2) and because

FIGURE 2
Effects of Training-Electroconvulsive Shock (ECS) Interval, Current Intensity, and Waveform on 24-Hour Retention[a] of a Passive Avoidance Habit in Mice



[a] A high score signifies good retention.

were collapsed across the two other conditions. A three-way analysis of variance indicated that each of the three factors exerted a significant effect on step-through behavior. First, lengthening the interval between training and administration of ECS lengthened step-through latencies (F=16.5, df=2, 593, p<.001), indicating decreasing amnesia. Second, increasing current intensity shortened step-through latencies (F=22, p<.001), indicating increasing amnesia. Finally, waveform also had a significant influence on step-through latency (F=3.1, p<.05). Separate comparisons of each waveform with the Tukey HSD test (15) indicated that the square wave produced more amnesia than either sine-wave (p<.01) or brief-pulse (p<.01) stimulation. The amnesic effects of sine-wave and brief-pulse stimulation were not measurably different.

We further evaluated the effects of sine-wave and brief-pulse stimulation by comparing results at the medium (30 min) training-ECS interval (combining the results from all three current intensities) and at the medium level of current intensity (combining the results from all three training-ECS intervals). For mice given ECS 30 min after training, the sine-wave and brief-pulse stimulation produced almost identical step-through latencies (sine wave=1.98 log sec, N=61; brief pulses=1.99 log sec, N=76). For mice given the medium level of current intensity, the two waveforms also produced virtually identical step-through latencies (sine wave=2.03 log sec, N=63; brief pulses=2.00 log sec, N=76).

Electrical energy was calculated for each of the waveforms by computing the average number of joules developed at the three current intensities. The sine wave delivered an average of .063 J; the square wave, .078 J; and the brief pulses, .022 J. Thus, the brief pulses delivered considerably less energy than the sine wave but produced no less amnesia. Moreover, the square wave delivered only slightly more energy than sine wave but produced considerably more amnesia. Apparently, electrical energy is not the only factor that determines the degree of amnesia. The next experiment makes the same point in a different way by showing that even when waveforms deliver an identical amount of electrical energy during ECT they can nevertheless exert markedly different effects on memory.

Directional Effects of Skin Temperature Self-Regulation on Regional Cerebral Blood Flow in Normal Subjects and Migraine Patients

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Vascular headache of the migraine type is associated with vasomotor changes in cerebral arteries. The authors studied whether skin temperature training (biofeedback) reduces the frequency, severity, and duration of these headaches by measuring the regional cerebral blood flow in 11 migraine patients and 9 normal volunteers using the noninvasive ^{133}Xe inhalation technique. Half of each group was randomly assigned to a hand-warming or a hand-cooling group. Cerebral blood flow increased in several regions of the left hemisphere to a statistically significant degree only for the migraineurs who were in the hand-warming group. The pattern of vasomotor regulation apparently differs between migraine subjects and normal subjects. The migraineurs' headache symptoms were affected by both warming and cooling, but warming produced more salutary effects.

Vascular headache of the migraine type is a general headache classification characterized clinically by recurrent attacks of head pain that show considerable variation in frequency, severity, and duration (1). The attacks are often unilateral in onset, pulsating, and associated with nausea, vomiting, photophobia, and phonophobia (2, 3). The subclassification, "classic migraine," is distinguished by a transitory prodrome consisting of conspicuous neurologic manifestations that may consist of visual, sensory, or motor disturbance. "Common" or "atypical" migraine is characterized by its lack of an aura prior to the headache.

Recent estimates suggest that approximately 15%–20% of men and 23%–29% of women have migraine headaches (4) and that a positive family history is found in at least 60% of the cases (5). Traditionally, migraine headache has been treated pharmacologically; however, given the difficulties encountered in headache medications (nonresponsiveness, contraindications, habituation, adverse effects, and addiction), the advent of an effective nonpharmacological treatment has created considerable interest.

Since the initial pilot research at the Menninger Foundation (6), there has been a proliferation of independent research studies confirming the therapeutic efficacy of biofeedback hand temperature control in reducing the frequency, severity, and duration of migraine headaches (7). Several follow-up studies, some up to 5 years in duration, have demonstrated that initial gains in headache improvement may be maintained over extended periods of time with continuation of daily home practice in hand-warming (8). The theoretical basis for biofeedback-induced improvement in migraine was described by Sargent and associates (7) and Stroebel and Glueck (9). The theoretical basis for biofeedback improvement in migraine is unclear, but of the mechanisms suggested a common feature involved the hypothesis that hand-warming is associated with a decrease in sympathetic outflow, which is thought to stabilize or counter the vasomotor changes known to occur in migraine. These theories have been detailed elsewhere (7). Recently the American Association for the Study of Headache (10) supported biofeedback as a valid form of headache therapy.

It has been suggested that migraine symptoms are due to an increased sympathetic outflow to the cerebral vessels; this outflow is thought to be associated with the byphasic (constriction followed by dilatation) response, which results in the clinical syndrome of migraine. The present investigation was designed to assess whether the control of skin temperature may be associated with changes in regional cerebral blood flow in female migraineurs and normal subjects.

The following null hypotheses were examined in this study.

1. Volitional hand-warming is not associated with any consistent change in cerebral blood flow.
2. No difference exists between the effects of volitional hand-warming or hand-cooling on regional cerebral blood flow.

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high current intensity is more deleterious to memory than low current intensity (figure 2), it seems possible that for any waveform the duration of maximum current intensity contributes to memory loss.

Although these findings suggest that brief-pulse stimulation offers no advantage over sine-wave stimulation insofar as memory loss is concerned, it is possible that these results obtained with mice may not be applicable to human patients in all respects. For example, compared with the transcorneal electrode placement used with mice, the typical bitemporal scalp electrode placement used with human patients might differentially distribute the current associated with sine-wave and brief-pulse stimulation. Therefore, the effects of the two waveforms on humans could be different than those described here.

In any case, these results lead to the following general conclusions about convulsive stimulation and memory loss. 1) Memory loss is increased by increasing the electrical energy of any particular waveform above the minimum needed to produce a seizure. 2) When different waveforms are equated for their ability to produce a seizure, memory loss is not necessarily reduced by waveforms that deliver low electrical energy; in particular, compared with conventional sine-wave stimulation, brief-pulse stimulation appears to produce as much or more amnesia. 3) In the absence of direct comparisons of the amnesic effects of sine-wave and brief-pulse stimulation in humans, brief-pulse stimulation for convulsive therapy seems unwarranted.

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