The Effect of Variable Duration One Hertz Interference on Kindling

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SUMMARY: *Experiments were conducted to evaluate the effect of various durations of 1-Hz brain stimulation on kindling behaviour induced by 60-Hz sine wave stimulation. In two experiments the effective threshold intensity (ETI) to elicit a convulsion was determined on four separate occasions with 5 days of daily trials interspersed between determinations. On each day experimental rats were stimulated with 1-Hz current on the first and third trials for 5, 15, 30, 60, 120, 180, or 600 seconds duration and with 60-Hz current for 30 seconds on the second trial. A steady increase in the intensity required to elicit a convulsion with 60-Hz current from ETI_2 to ETI_4 resulted for all rats with durations of 15 seconds or greater. Rats stimulated only with 60-Hz sine waves, and those in the 5 second group. maintained relatively stable values from ETI_1 to ETI_4, with a slight decline occurring. Suppression of convulsive behavior on daily trials was modest in the 15 second group, pronounced with the 30 second group, and drastic with the other groups. The 600 second group had the greatest suppressive effect operating. The suppression effect did not appear to be due to tissue damage inasmuch as most of the experimental rats (except the 600 seconds one) convulsed again at previous low ETI levels following a 15 or 16 day rest at the end of the experiment. This result suggests that the suppression effect is a relatively transient event.*

RÉSUMÉ: *Des expériences furent faites pour évaluer l'effet de stimulations cérébrals de 1-Hz de durées variables sur le comportement kindling créé par une stimulation à onde sinusoidale de 60-Hz. Lors de 2 expériences l'intensité seuil (ETI) efficace à produire une convulsion fut déterminée 4 fois avec une période de 5 jours d'essais journaliers entre les déterminations. Chaque jour les râts expérimentaux furent stimulés avec un courant de 1-Hz au premier et troisième essai pour des durées de 5, 15, 30, 60, 120, 180 ou 600 secondes et avec un courant de 60-Hz pour 30 secondes au deuxième essai. Nous avons noté chez tous les rats, pour des durées de 15 secondes ou plus, une augmentation régulière de l'intensité requise pour provoquer une convulsion avec du courant de 60-Hz de ETI_1 à ETI_4. Les rats stimulés seulement avec les ondes 60-Hz, ainsi que ceux dans le groupe de 5 secondes, demeurent à peu près stables de ETI_1 à ETI_4. La suppression des convulsions lors des essais quotidiens fut modeste dans le groupe 15 secondes, marquée dans le groupe 30 sec et remarquable dans les autres groupes, dont surtout celui à 600 secondes. Il ne semble pas que cet effet suppressif (sauf à 600 sec) soit le résultat de lésion tissulaire car, après un repos de 15 à 16 jours, les animaux ont de nouveau répondu par des convulsions aux niveaux ETI bas. Il semble donc que l'effet suppressif soit un évènement transitoire.*

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The kindling effect has been investigated in a number of laboratories (Gaito, 1976b; Goddard, et al., 1969; Racine, 1972; Wada and Sato, 1975). This effect involves a change from normal exploration (Stage 1 — NE) to behavioral automatisms (Stage 2 — BA, chewing, eye closure on ipsilateral side, salivation) and finally to clonic convulsions (Stage 3 — CC) in response to electrical stimulation of a specific brain site (e.g., amygdala). During Stage 3, the rat usually stands on its hind paws and bilateral convulsions of the forelimbs occur. One of the distinctive features of the kindling effect is that once the clonic convulsion stage has been achieved, subsequent stimulation trials will reliably elicit the convulsions, even if weeks or months are allowed to elapse between stimulations. A permanent change that is not due to tissue damage is thought to occur in the brain as a result of kindling (Goddard et al., 1969; Racine, 1978). Behavioral, chemical, electrophysiological, and neurological aspects of this effect have been investigated by many researchers (Gaito, 1976a; Racine, 1978).

Goddard et al. (1969) indicated that there was a reduced probability of eliciting a convulsion at a given intensity for frequencies above and below 60-Hz. It seemed possible that some frequencies other than 60-Hz might interfere with 60-Hz brain stimulation events. With a few rats some frequencies below and above 60-Hz were evaluated, viz., 30, 20, 15, 10, 5, 3, and 1; 100, 150, 200, 300, 400, 500, 1000, 2000, and 4000. Stage 2 or 3 behavior was observed at all frequencies except 3-Hz and 1-Hz, although greater intensities than for 60-Hz were required to elicit these behaviors (Gaito, 1979a).

https://doi.org/10.1017/S0317167100023702 Published online by Cambridge University Press

In this attempt to determine frequencies which might be used as potential interference agents, two criteria were used:

(a) Stage 2 or 3 behavior should not usually be elicited with low or moderate intensities, e.g., up to 560 μA; (b) No consistent convulsion pattern should be elicited even at higher intensities. Only 3-Hz and 1-Hz stimulation met these criteria. Seldom did Stage 2 or 3 behavior occur below an intensity of 560 μA; Stage 1 behavior was the typical response in almost all cases. Furthermore, although convulsions did occur at intensities greater than 560 μA, stable convulsion patterns on successive trials of stimulation did not occur. Thus, 3-Hz, and later 1-Hz, were evaluated as potential "interference agents".

In the first exploratory experiments, Gaito (1979a) found that stimulation with a series of trials of 3-Hz sine wave current following the induction of convulsive behavior with a number of trials of 60-Hz stimulation produced a suppression of convulsions in 14 of 23 rats; these 14 rats showed a return to Stage 1 behavior during subsequent test trials with 60-Hz stimulation. In a second set of experiments, 3-Hz stimulation suppressed convulsions in 13 of 16 rats when 60 clonic convulsion (CC) trials were followed by 36 trials of 3-Hz stimulation at double the intensity of 60-Hz stimulation (Gaito, 1979b). This interference effect was obtained both for unilateral and bilateral stimulation with 3-Hz sine waves. In other experiments in this set, the convulsive tendency of rats was suppressed 50% and 81%, respectively, by one and two trials of 3-Hz stimulation before and after a single trial of 60-Hz stimulation daily.

In a third set of experiments (Gaito, Nobrega and Gaito, 1979), 3-Hz stimulation again produced suppression tendencies, i.e., previously convulsing rats showed Stage 1 behavior. Likewise, suppression tendencies resulted within a number of blocks of daily trials over 10 days in which one trial of 3-Hz stimulation preceded and followed stimulation by 60-Hz sine waves. The degree of suppression varied between 20 and 80% in these blocks of trials. In this last set of experiments, the effective threshold intensity (ETI) required to precipitate a convulsion was determined before and after each 10 day block. The mean ETI steadily increased over five determinations for the group stimulated with 3-Hz sine waves, whereas the ETI remained approximately constant or decreased slightly for a control group of rats which received no stimulation on Trials 1 and 3 each day.

In another experiment, the interference effect of 1-Hz brain stimulation was evaluated. When 15 seconds duration of stimulation with 1-Hz current was used on Trials 1 and 3 each day, and 30 seconds duration of stimulation with 60-Hz current occurred on Trial 2, little increase resulted in ETI values over four determinations and the maximum suppression of convulsions was about 15%. However, when 1-Hz stimulation was continued for 120 seconds, the effect was drastic; ETI values increased substantially and a 90% suppression of convulsions occurred.

The results of this preliminary experiment indicated that duration of stimulation might be a significant variable relative to the interference effect. The present experiment was conducted to evaluate a number of other durations of stimulation, viz., 5, 30, 60, 120, 180, and 600 seconds. Thus, over this experiment and the preliminary one, the following durations with 1-Hz stimulation were evaluated: 5, 15, 30, 60, 120, 180, and 600 seconds, as well as 0 seconds, the nonstimulation control condition.

METHODS

Fifty-five male rats (approximately 120-150 days of age) had nichrome bipolar electrodes implanted in one amygdala. The brain coordinates for electrode implantation were the same as in many experiments in our laboratory: .5 mm posterior to bregma, 4.5 mm from midline, 8.5 mm from skull (Gaito, 1976b). Thirty-seven rats were of the Wistar strain; the other 18 were Hooded rats. Previous research in our laboratory indicated no differences between Wistar and Hooded males in suppression aspects. The Wistar and Hooded rats were distributed almost equally among the various control and experimental groups.

Stimulation was not imposed until at least seven days after surgery. Then the 55 rats were stimulated with 60-Hz sine waves for 30 seconds during three trials on the first day. Approximately one hour intervened between each trial. A Lafayette Stimulator was used; the intensity was 100 μA. On the first trial of the second day, the 60-Hz current was increased gradually until a Stage 2 or 3 response was elicited. Then 15 μA was added to allow for day-by-day threshold fluctuations. This was the effective threshold intensity (ETI_1). Two further trials of stimulation at this intensity were provided to check on the stability of ETI_1.

Then, each of seven rats in one group was stimulated with 1-Hz sine waves for 5 seconds on Trials 1 and 3 the next day, and for four days thereafter, at twice the ETI_1 value. Trial 2 was a routine kindling trial with 60-Hz sine waves; the intensity was ETI_1 for 30 seconds duration. One hour intervened between each of the three trials. These rats constituted Group 1 (1-60-1, 5 seconds). The 1-Hz stimulator was one which had been constructed in the electronics shop of the Department of Psychology at York University. There were five other experimental groups. Each rat in groups 2 to 6 was stimulated with 1-Hz current for 30, 60, 120, 180, and 600 seconds, respectively, at double the ETI_1 values on Trials 1 and 3, and with 60-Hz current on Trial 2. There were eight, seven, six, six, and eight rats in groups 2 to 6, respectively. Thirteen other rats received 60-Hz stimulation on Trial 2, but on Trials 1 and 3 each rat was placed in the apparatus without stimulation (Group 7, X-60-X, 0 seconds). Following this 5 day period, rats from all groups had ETI_2 determined over six trials during two days. Then another block of 5 days of stimulation occurred in which each group was treated in the same fashion as during the 5 day block of trials prior to the ETI_2 determination. This alternation of ETI determinations and a 5 day block of trials was continued through the ETI_4 determination. Then all rats were rested for 15 or 16 days and ETI_5 was determined on one trial.

At the end of the experiment, histological analyses were performed on most rats. The animals were sacrificed with an overdose of sodium pentobarbital and perfused with saline and formalin. The brains were extracted and placed in a 10% formalin solution. Each brain was frozen and 50 micron sections were mounted on microscopic slides; these slides were placed in a photographic enlarger and used to obtain information concerning the presence or absence of lesions around electrode tips (of primary interest) and electrode site (of secondary interest because all rats reached the convulsion stage). The enlargement was approximately ten-fold.

RESULTS

The histological analyses indicated that the electrode tips were in the amygdala in most rats and in nearby structures for a few rats. No definite lesions were observed around the electrode tips for any rats. The tissue around electrode tips for rats stimulated with 1-Hz and 60-Hz current was indistinguishable from that of rats which had been exposed only to 60-Hz stimulation.

The mean ETI values are indicated in Table 1. As in previous experiments the control rats, those subjected to no stimulation on Trials 1 and 3 (0 seconds group), showed a gradual decrease over the four determinations, with the greatest decrement occurring between ETI_1 and ETI_2. The mean ETI values are slightly larger for the 5 second group from ETI_2 to ETI_4 than for the 0 seconds of stimulation. The 15 seconds condition (from the preliminary experiment) produced very little increase in ETI. The 30 second group had the steady increase over ETI determinations, which had been typical of rats stimulated in previous experiments at this duration with both 1-Hz and 3-Hz current. The other four groups showed a pronounced increase over the determinations, with the 60 seconds group affected the least and the 600 seconds rats having the greatest effect. The increment for the 600 seconds group was drastic, about 300 μA from ETI_1 to ETI_2 determinations. At the ETI_2 determination, four of the eight rats did not convulse at 560 μA and were not used for further stimulations. At the ETI_3 determination, the remaining four rats in this group did not convulse at this intensity. Thus, none of the 600 seconds rats were used for Block 3 or for ETI_4 determination.

TABLE 1

Mean ETI Values (in Microamperes)

GROUPS (in seconds)		ETI DETERMINATIONS 1	2	3	4	5+
0	(13)*	246	195	172	140	126
5	(7)	240	231	227	208	186
15	(13)**	184	206	227	246	---++
30	(8)	208	244	280	339	200
60	(7)	206	328	424	456	227
120	(6)	216	329	538	---***	229
180	(6)	288	453	570	---***	310
600	(8)	188	482	---+++	---+++	423

* Number of rats at beginning of the experiments in parentheses.
\+ Determined after a 15 or 16 day rest following the previous ETI determination.
** From preliminary experiment.
++ Rats in the preliminary experiment were not stimulated at this point.
*** Only one rat convulsed at 560 μA.
+++ No rats convulsed at 560 μA.

For the 120 and 180 seconds groups, only one rat convulsed consistently during ETI_4 at the upper limit of 560 μA. Furthermore, in these groups some rats did not convulse during ETI_2 and ETI_3 determinations. In the 120 seconds group, 4 rats convulsed on the ETI_2 determination and 2 of the 6, on the ETI_3 determination. For the 180 seconds group, 5 convulsed on the ETI_2 determination and 3 of the 6, on the ETI_3 determination. In each case of nonconvulsion, an ETI value of 585 was assigned to that rat. (Twenty-five was arbitrarily added to the upper limit of 560 μA).

The mean composite score over three blocks of trials also showed the suppression effect (Table 2). The minimum and maximum scores, respectively, for composite score over 5 trials are 5 and 15. Each rat receives a score of 1 for Stage 1 behavior, a score of 2 for Stage 2 responses, and a value of 3 for each convulsion. The 0 and 5 seconds groups had the greatest kindling progression over the three

TABLE 2

Mean Composite Score

GROUP	BLOCK OF TRIALS 1	2	3
0	11.1	14.8	15.0
5	10.5	15.0	15.0
15	10.7	13.1	13.1
30	10.0	13.6	12.3
60	10.1	12.0	12.5
120	9.2	9.8	11.0
180	7.5	7.6	9.0
600	6.0	5.8	5.0

https://doi.org/10.1017/S0317167100023702 Published online by Cambridge University Press

blocks of trials. The 15, 30, and 60 seconds groups had moderate increases in mean score whereas the other groups had little or no increments. In general, within each block, there was a gradual decrement in the mean composite score with increasing periods of stimulation with 1-Hz current.

The first block of trials usually showed the smallest interference effect because behavior was not as stable at this early stage as it was later, and ETI_1 was not as reliable as later ETI determinations. However, by the second block of trials the effect was apparent. Table 3 shows the mean composite score for the five days of trials within the second block of trials. The minimum and maximum scores, respectively, for each trial and each rat is 1 and 3. Again, there was a gradual decrement on each day from the control group to the rats stimulated for 600 seconds, especially after 3 days. Most rats in the control group (0 seconds group) and the 5 seconds group had a value close to 3.0 on every trial, i.e., most rats convulsed on each trial, whereas fewer convulsions occurred for the other groups. The 600 seconds rats showed no Stage 2 or 3 behavior from day 3 onward. Only four of the eight rats were available for Block 2 trials; the other four showed only Stage 1 behavior on ETI_2 determination at 560 μA and were not used thereafter.

The mean value for the five trials showed a gradual decrease from the 0 and 5 seconds groups to the 600 seconds group. The means indicate the following results. The control rats and the 5 seconds group had a mean of 3.0 or close to it (definite Stage 3 behavior). The 15, 30, and 60 seconds groups showed a mean 2.7, 2.6, and 2.4 respectively, which can be considered as middle Stage 2 behavior. Early Stage 2 behavior was apparent for the 120 seconds group with a mean of 2.0. The 180 seconds rats had a mean of 1.5, a value equivalent to the middle portion of Stage 1. The mean for the 600 seconds group was 1.2, early Stage 1 behavior.

The ETI_5 value was determined after a 15 or 16 days rest. For the 0 seconds group, all rats were below, at, or just above the lowest ETI value, ETI_4. The 5 seconds group ws similar, with the 7 rats near the low ETI point (ETI_4). The lowest ETI for other experimental rats was ETI_1. The 7 rats in the 30 seconds group were near the lowest ETI point. In the 60, 120, and 180 seconds groups, 15 of the 19 rats convulsed at or near the ETI_1 point. However, none of the 8 rats in the 600 seconds group returned to previous low ETI values. This duration of stimulation produced an effect lasting beyond 16 days. If the rats in the 600 seconds group are excluded, most other experimental rats showed a return to low ETI values.

DISCUSSION

Even though the number of rats in each duration group was small, the results were clear. There was a gradual increase in interference effects as the duration of stimulation with 1-Hz increased (Tables 1, 2, 3). The 5 seconds condition had little or no effect and was almost equivalent to the control rats (0 seconds stimulation). The effect at 15 seconds was modest. By 30 and 60 seconds the effect was more pronounced. With 2, 3, and 10 minutes of stimulation the effect was drastic; almost all rats failed to convulse at an intensity of 560 μA after the third block of trials.

The ETI determination after 15 or 16 days of no stimulation (ETI_5) indicated some interesting results. The mean ETI_5 value in Table 1 for the 0 and 5 seconds group is lower than any previous ETI. Thus, there is a steady decline for both groups. Although the mean ETI increases from ETI_1 to ETI_4 with the 30 seconds group, the mean for ETI_5 is lower than ETI_1. The mean ETI_5 for the 60, 120, and 180 seconds group are just above the ETI_1 value. Thus, the suppressive effect appears to have dissipated, or nearly so, in these groups by 15 or 16 days. However, the effect with the 600 seconds group is drastic; massive increases occur in mean ETI values over determinations and no return to low ETI levels on the ETI_5 determination is present.

TABLE 3

Mean Composite Score in Block 2

	DAY						
GROUP	**0+**	**1**	**2**	**3**	**4**	**5**	**M***
0	2.9	2.9	2.9	2.9	3.0	3.0	2.9
5	2.8	3.0	3.0	3.0	3.0	3.0	3.0
15	2.8	2.7	2.8	2.8	2.5	2.5	2.7
30	2.9	2.9	2.9	2.9	2.4	2.1	2.6
60	3.0	2.8	2.7	2.4	2.1	1.9	2.4
120	3.0	2.8	2.0	2.0	1.5	1.5	2.0
180	3.0	2.4	1.8	1.0	1.0	1.3	1.5
600**	3.0	2.0	1.3	1.0	1.0	1.0	1.2

\+ Mean score for last trial of ETI_2 determination.

* Mean score per trial in Block 2.

** n = 4; 4 rats did not convulse at 560 μA during ETI_2 determination.

https://doi.org/10.1017/S0317167100023702 Published online by Cambridge University Press

The ETI_5 determination allows one to place the various duration groups into three categories. The first consists of 20 rats in the 0 and 5 seconds groups; all rats showed a low ETI response on ETI_5. For the other groups (except the 600 seconds one), 23 of 27 rats had a response similar to the previous low ETI response, ETI_1, i.e., most rats convulse at previous low threshold values. Finally, of the 8 rats in the 600 seconds group, none showed a low ETI response for the ETI_5 determination. Thus, these data indicate that the suppression effect is a relatively transient one for all durations except the 600 seconds one.

The interference effects of 1-Hz and 3-Hz stimulation on kindled behavior produced by 60-Hz stimulation which we have observed are one class of interference effects noted within the kindling paradigm. There are two other classes of interference effects which can be considered to be similar.

1. Mucha and Pinel (1977) reported that repeated, periodic stimulation with 60-Hz current had a decremental effect on both motor seizures and on after-discharges in the EEG. The effect on the class of motor seizure (or severity of convulsion) had dissipated by 20 minutes, but the duration of seizure was still reduced 90 minutes later. After-discharge duration was reduced through a 45 minute period but was back to usual levels by 90 minutes. This interference effect is a type of unilateral stimulation interference.

We have used a one hour intertrial interval consistently in our research. Thus, we would not note any effect on the occurrence or non-occurrence of a convulsion, i.e., we are well beyond the 20 minute interval for dissipation of interference effects on the motor seizure (Mucha and Pinel, 1977). Furthermore, we used 30 seconds of stimulation in contrast to the one second used by Mucha and Pinel. Presumably 30 seconds of stimulation would offset any interference effect. A one second stimulation situation should be a more sensitive means of detecting this type of interference.

Although we have not noted the type of interference reported by Mucha and Pinel, we have observed another event which may be similar. With many convulsions, e.g., 60 or more, a number of rats stop convulsing when the current is terminated at the beginning of a convulsion, whereas the typical response is to continue convulsing well beyond the offset point. This result may be similar to the Mucha and Pinel event in which duration of motor seizures are reduced up to 90 minutes after stimulation with 60-Hz current.

2. Another type of interference is that involving successive stimulation of two homologous brain sites, e.g., the amygdalae. McIntyre and Goddard (1973) noted negative transfer or interference in latency data when stimulating a secondary site, following stimulation of a primary site to a convulsion 24 hours before. They also noted an interference effect when stimulating the primary site again; some rats did not convulse on the first trial in contrast to control rats which had not been stimulated in the secondary site.

We have extended this sequential alternation of stimulation from primary site to secondary site, to primary site, etc. over 10 or more phases of stimulation in which each phase involved six convulsions. There was a predominant tendency for increased latency to be present in the secondary site for most rats over all or most phases of stimulation (Gaito, 1976b).

Thus, there are both interfrequency and intrafrequency interference effects. The former one is the suppression effect. The latter type consists of unilateral and alternating stimulation aspects. With unilateral stimulation of a brain site, interference to later stimulation develops as a result of each stimulation event and lasts for a short period of time. In the alternating stimulation case, stimulation of one brain site sets up interference effects to later stimulation of the homologous brain sites. This last type of interference effect is assumed to result because of inhibitory effects of the one brain site on the other (McIntyre and Goddard, 1973; Nobrega and Gaito, 1978). Thus, stimulation of the primary site may set up an inhibitory process relative to later stimulation of the homologous site in the opposite hemisphere as well as an inhibitory process at the primary site which would interfere with later stimulation of the primary site. The McIntyre and Goddard and Mucha and Pinel results are consistent with this interpretation.

The exact basis for the 1-Hz and 3-Hz suppression effect is not clear at this time. Presumably it involves some modification of the brain process responsible for kindling, or else another process is developed which is antagonistic to the brain kindling process.

One possible basis for the suppression effect is that lesions are produced by the 1-Hz and 3-Hz stimulation, and the damage raises the threshold for Stage 2 or 3 responses. However, this explanation does not seem to be appropriate. Our histological analyses in the previous and present research indicated that the tissue around the electrode tips of rats subjected to intensities of 560 μA or lower with 1-Hz or 3-Hz current appeared similar to that of rats subjected only to 60-Hz stimulation. Obviously, such analyses are of gross nature and could miss subtle lesions.

A more important consideration is the apparent transient nature of the suppression effect, in that a time decay of the suppression event is indicated under certain conditions. This decay was suggested by the ETI_5 determinations in which most experimental rats (except those in the 600 seconds group) convulsed near the previous low threshold intensity. Furthermore, some of our recent results (research underway) indicated that the intertrial interval was important for the effect. With 1 or 3 hour intervals between trials and a duration of 120 seconds, the effect was pronounced. However, with a 24 hour interval and the same duration, the effect was present but modest. For example, increases from one ETI determination to the next averaged more than 100 μA with 1 or 3 hour intervals (see Table 1, 120 seconds group). However, the average increment with a 24 hour interval was about 30 μA. Furthermore, all rats convulsed at or below 560 μA (the upper limit used) during ETI determinations for the 24 hour interval, but some rats in the 1 and 3 hour intervals experiment did not convulse at this limit. In Table 1, 5 of the 6 rats in the 120 seconds group did not convulse

https://doi.org/10.1017/S0317167100023702 Published online by Cambridge University Press

during the ETI_4 determination. Further research with intervals of 24 hours and longer are anticipated to gain information concerning the possible time decay of the suppression effect.

Thus, even though tissue damage is a possible explanation for the suppression results, the above evidence indicating a time decay of the suppression effect seems to suggest that the effect is not due to lesions. If lesions were responsible for the suppression events, one would expect the ETI values to increase (Goddard et al, 1969; Racine, 1978). However, the increasing ETI should be more permanent in nature, with little or no decreases over time, i.e., tissue damage would not be considered of such short term nature as the time periods observed in our experiments.

These data indicating the transient nature of the suppression effect suggest that this effect may be similar to the "aftereffect" of McIntyre and Goddard (1973). They found an interference effect with stimulation of the primary site a second time if secondary site stimulation intervened between the two stimulations of the primary site. This interference was not present if an interval of 14 days or more occurred prior to the second time of stimulating the primary site.

Ultimately, these interfrequency interference effects might have important implications relative to the kindling effect and to brain function in general. Furthermore, a frequency that can suppress convulsions induced by another frequency might prove worthwhile as a potential anticonvulsant in some types of human epilepsy, e.g., focal epilepsy.

ACKNOWLEGEMENTS

This research was supported by a grant from the Atkinson Charitable Foundation (Toronto).

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