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CHAPTER 4

LEARNING MOTIVATED BY SUBCORTICAL STIMULATION: The "Start" and the "Stop" Patterns of Behavior

JOHN C. LILLY

In 1954, Olds and Milner demonstrated that rats can be trained to start trains of electrical stimuli in certain loci in the brain.[14] About the same time, Delgado, Roberts and Miller[2] showed that cats could be trained to shut off electrical stimuli in other systems than those described by Olds and Milner.[14] Cohen, Brown, and Brown[1] showed similar results.

About one year ago we started mapping the sites for elicitation of each of these trained reaction patterns in the monkey's brain. As we proceeded we mapped many additional reactions, many of which confirm Hess's observations in the cat.[4] It was found necessary to do parametric studies of the electrical stimuli on several reactions as well as on these two (see the author's appendix to this paper); it was necessary to record the learning sequences. Three or four weeks' time was spent studying intensively one key zone at a time. At this time a complete map cannot be presented; to date we are less than a tenth of the way through the brain, but some of the material illustrates a few of the dimensions of the problems involved.

The neurophysiologist has been given a powerful investigative tool; the whole animal can be trained to give behavioral signs of what goes on inside, in addition to the electrical and neuronal signs picked up inside the brain. As we will show, the animal can give certain thresholds, which we eventually can relate to the electrical records. We can now find some of

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the behavioral correlates of certain neurophysiologic events, in addition to those already given by Gastaut,[3] Morrell,[12] Jasper,[5] Jouvet.[6] We are in the position of being able to guess with less margin of error what a man might feel and experience if he were stimulated in these regions and to help those who work on man with more detailed knowledge of dangers formerly vaguely known and now beginning to be better understood.

Materials and Methods

Three monkeys have been studied, 1 for 4 months, 1 for 6 months, and 1 for 12 months; in the first 2 animals about 500 zones have been studied, in the latter, 8 zones. The 500 zones were explored by a moveable "roving" electrode system, implanted in the skull in Horsley-Clarke coordinates. Each roving electrode is sent into the brain through a guiding track in a stereotaxic button implanted in the skull, through a soft plastic, bacteria-proof barrier between 2 layers of lucite. A small lightweight gage allows the operator to push each needle electrode to any desired depth in the brain from the pial surface to the base of the skull, usually 1-mm. steps are explored along each electrode track. Typical cases give 35 to 40 zones explored and studied for each track in the brain of the monkey.

The electrodes are of the coaxial type: #316 stainless steel wire, teflon-insulated, in a #24 hypodermic needle tube. The outside tube and a stainless steel ring (¾ in. in diameter) on the dura are the diffuse return electrode for current from the small exposed tip of the wire (1-mm. length).

The stimulating current used is of the pulse-pair type previously described[9] and consists of a pair of pulses (20–60 microseconds in duration) of opposite direction and of equal charge passed through the brain within 0.1–0.3 millisecond.

The stimulator circuits allow full control of the pulse-pair repetition rate, the number of pulse-pairs in each train, the train repetition rate, and the change of the value of the pulse-pair amplitude with time within each train (shape of the envelope of each train). Two complete stimulator assemblies allow simultaneous and independent stimulations at 2 or more electrodes. The value of current in all stimuli and electrode resistances are measured on a cathode ray oscilloscope.[8]

For the training with the 2 different types of regions which give the "start" and the "stop" patterns, a single type of trigger circuit is used, applied to 2 opposite kinds of control of the stimuli.

After much experience with microswitches for triggers, we found that a "body capacitance" (BC) trigger circuit allowed faster training, less

fatigue, higher and steadier rates, and more operations by the monkey per day than did the microswitches. The circuit used is a 3-megacycle crystal oscillator and detector having an output of about 70 volts for about 0.5 micro-micro-farad change of capacitance.[7]

If a nongrounded or grounded monkey touches a metallic contact connected through a 500 micro-micro-farad condenser with this circuit, the output shifts 70 volts and holds this value as long as the monkey maintains his contact. If he now releases his contact, the output falls to zero and the stimulation is caused either to be started or to be stopped (Figs. 4–2, 3), depending on other appropriate control circuits connected to this trigger. These touches and the releases are recorded on an inkwriter (Fig. 4–2). In using this trigger the monkey's effort is minimized; he moves against only gravity plus the resisting forces within his own body.

If the zone is a "start" one, the triggering release is arranged to *start a train* whose length is controlled by a preset type of electronic counter (Berkeley). This counter shuts off the train after a predetermined number of pulse-pairs (from 1–1 million) irrespective of the pulse-pair repetition rate up to 4000 per second; we use from 2 to 600 pulse-pairs in a train for exploratory work, usually at 50 pulse-pairs per second.

If the zone is a "stop" one, an electronic timer is arranged to start the train and to shut it off after a fixed interval and repeat the sequence periodically. If the animal touches and releases his metallic contact, the triggering release is used so as to *shut off the train* at any time between its beginning and its timed end.

The monkey is restrained in a two-table chair used by us since 1949, at which time we had modified a single-table model devised by William W. Chambers and William F. Windle; Dr. John Mason further modified our model of this chair and has published drawings.[11] Dr. Joseph Brady also uses it. We have some feedback here; we now use a new model modified after Mason's modifications.

Results

Figure 4–1 illustrates some results along a single electrode track and shows the method of finding the "start" and the "stop" zones (Table 4–1). As the electrode is thrust into cortex, in 1-mm. steps, the threshold for movement is easily determined for 1–2 second trains at 50 pulse-pairs per second.[8,9] We have found that the "cortical" type of evoked movement is a good guide to loci within cortex.[10] An inspection of Fig. 4–1 shows the variation of threshold with the distance of the track from the stimulated

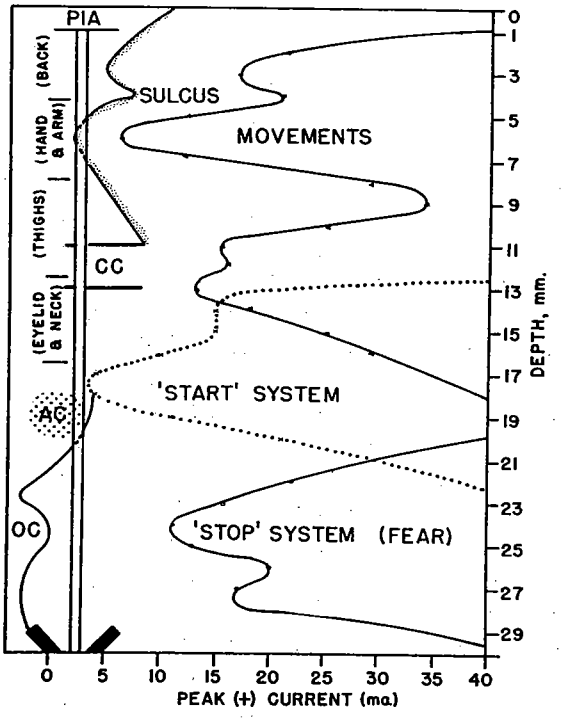

FIG. 4–1. Thresholds along a single electrode track at 1-mm. intervals. *CC* is corpus callosum; *AC,* anterior commissure; *OC,* optic chiasma. The stalk of the pituitary is shown at the bottom of the track between 29 and 35 mm. down. The section is rotated 90° from frontal to sagittal just below the corpus callosum. The track was in the midsagittal plane and went down the stalk of the pituitary. The cortical thresholds show the effect of distance of the electrode from the cortex. The "start" effect was accompanied by "hallucinatory" or "searching" behavior. At levels of current greater than these thresholds in the "stop" region, a "fear" syndrome is seen. Below 29 mm. only peripheral nerve responses were detected.

cell layers. This type of movement disappears as the electrode leaves cortex with increasing depth, and other phenomena appear at about the same range of values of stimulating current.

TABLE 4–1. TABLE OF DEFINITIONS AND REACTIONS

	Kind of zone in CNS	
	Start	*Stop*
A. Synonyms	1. "Rewarding" 2. "Positively reinforcing" 3. "Positive" 4. "Enamoring"	1. "Punishing" 2. "Negatively reinforcing" 3. "Negative" 4. "Alienating"
B. Stimulated behavior, without training, clinical syndromes	"Contentment," increased "interest," reduction of "anxiety," improved cooperation with observer, improved appetite, "want more" types of reaction	At least 3 related but distinct syndromes: 1. Localized "pain" signs 2. "Fear" to "panic" 3. "Malaise" to "shocklike" In general, escape and avoidance behavior
C. Stimulated learned behavior	In general, "start the stimulus" reactions and this kind of "capture" pattern	In general, "stop the stimulus" reactions and this kind of "capture" pattern, and loss of ability to operate a release at high current levels
D. Size of CNS regions	Large	Much smaller

Further down at 17 mm. and 3.8 ma. (Fig. 4–1), the monkey looks around his environment during each train, ignoring the observer, as if seeing something moving in the air in irregular paths not seen by the observer or as if searching in a space not containing the observer. A long train (10 seconds) is then started by the observer, and the monkey is tested for the presence or absence of "angry" attack responses elicited by painful pulling of hair on the belly or chest. If the monkey does not attack during the train, shows a facial expression of preoccupied "relaxation," rather than "anger" or "pain," and suddenly attacks after the end of the train with appropriate changes in facial expression, it is usually found that a "start" zone has been entered. The trigger contact is given to the monkey and the train is shortened to 10 pulse-pairs; either his spontaneous "play" is allowed to start trains of stimuli by accidental contacts, or his hand is moved by the observer up and down on the triggering metallic connector.

If the zone is a powerful one, a few trains (100–500) start the monkey

making touches and releases. The train is then shortened to 3 to 5 pulse-pairs to obtain his fastest rate. Figure 4–2 is a segment of a record after training to such behavior.

At 24 mm. and 3 ma. (Fig. 4–1), the monkey not only will no longer touch and release but will make obvious efforts to prevent touches and releases by the observer. At higher currents, he appears to be "frightened" (in other "stop" regions, he appears to be in "pain"). His pupils dilate,

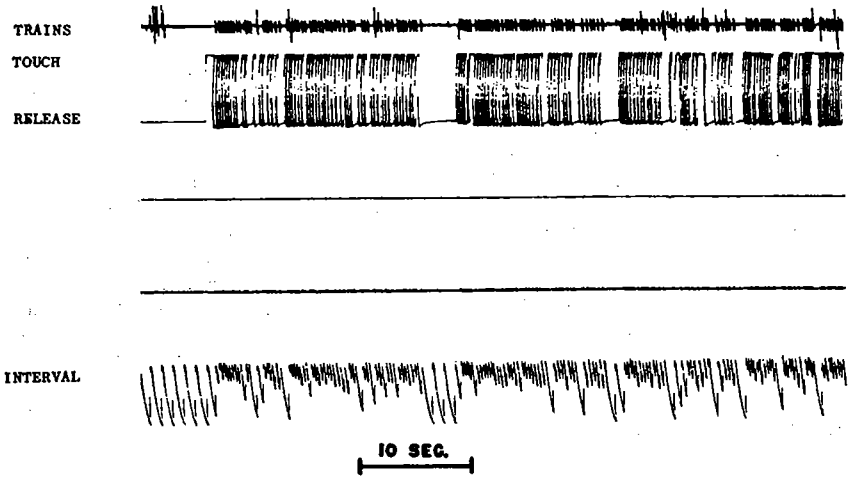

FIG. 4–2. Portion of a record showing the "start-capture" pattern. The interval recorder shows the persistent constant rate during bursts of triggering, interspersed with pauses of varying length. Anatomic locus: putamen.

palpebral fissures widen, nares move with the now hyperventilating respiration, the hair erects all over the body, he defecates, the whole body shakes incoordinately and asynchronously, he holds on tightly to any object placed near his hands or pushes such objects away, makes violent escape movements, and bites and tears any nonfood object placed within his visual field near the mouth, even to the extent of breaking teeth out of his jaw. This "fright" syndrome is one of the varieties of reaction to stimulation in the "stop" regions.

With an electrode in such a region we have found that he can be trained to shut off the train of stimuli presented as described below. He can also be similarily trained in regions which show localized "pain" reactions.

The 2 patterns of behavior, "start" and "stop," are discussed in more

detail below. In general, I wish to say that between these lowest threshold points (Fig. 4–1), interaction between the systems may raise the threshold to the values shown in each of the 2 types of systems, thus generating the curves shown here; i.e., the 2 curves may reflect not purely a distance effect but either or also a mutual neuronal or behavioral antagonistic effect.

"START" PATTERNS AND REGIONS

1. General Pattern for Most Regions (Head of Caudate, for Example). Once the first "start" zone is found and the monkey is thoroughly trained, stimuli in other "start" zones can cause him to touch and release without further training; i.e., a "free" train given by the observer or by a timer can start the pattern. The fully developed, learned pattern we call "start-capture" of the monkey—he becomes a part of the cyclical feedback system from which it is difficult to extricate him as long as the circuits are available to him (Fig. 4–2). These specific physical operational terms are preferred to "positive" and "negative" reinforcement, which tend to interpret the pattern in learning theory terms (Table 4–1).

With a trained animal, the pattern of "start-capture" can be initiated by a free train and by keeping the circuits in the triggerable state. The pattern is stopped rapidly by shutting off the supply of trains. The monkey then "tests" his trigger at a decreasing rate every minute or so and finally gives up his testing after a few hours or days. After being off the capture circuit for days or weeks, from 1 to several trains will restart the pattern.

If a very long train, several seconds to several minutes long, is introduced during a capture sequence, the monkey may stop triggering or at least slow down, and will start again immediately at the end of the train. If each of the trains is given a longer duration, he tends to slow his rate to maintain continuous stimulation. The shortest trains (down to 3 pulse-pairs at 50 pulse-pairs per second) tend to give the highest triggering rates for the longest periods (from 18,000 per 24-hour day for several weeks to 200,000 in a 20-hour period, terminated by exhaustion).

Distributions of the time courses of some "start-capture" sequences are shown for one monkey in Fig. 4–3 and for another in Fig. 4–4. This latter figure illustrates the change in distribution of the intervals between touches with training: initially the intervals cover a wide range; later they peak sharply at about 0.32 seconds, i.e., at a rate of about 3 touches and releases per second. The trained monkey tends to touch and release at a constant rate when he is active and stops for varying lengths of time depending on other circumstances. The record of Fig. 4–2 illustrates the

3. Hierarchy of Different Muscle Groups. The monkey's output mode is not important as long as it is a trainable one. We have trained 2 monkeys to trigger with fingers, hand, foot, or tongue in many loci—the hierarchy of the ease of training and rate of training were hand and fingers, tongue, and finally, foot—but we have not been able to train either to "coo" or to "bark" to a capture level. However, we are not yet fully satisfied that we cannot train a Macaca to vocalize for this stimulation in *all* zones; we have not yet tried the most powerful one. The approximate trained rates were hand, 3 per second; tongue, 2 per second; and foot, about 1 per 2 seconds.

4. Relations to Sleep. Runs for several days (24 hours per day) show that no matter what region is stimulated, the monkey sleeps at least 8 hours out of the 24. Either he takes his normal time out, or he is so active to exhaustion that he is forced to sleep. This effect seems to be a function of some fundamental metabolic limitation.

5. Tests of Motivation. This stimulus apparently acts as a "reward" analagous to that of food. Using this stimulus as a reward, we have trained monkeys to trigger to sounds as clues, to a cyclical time period with a free train as the clue, to alternation between 2 triggers, to delayed alternation, and to quasi-counting with 2 triggers alternately up to 10 releases on each trigger.

6. Relations to Eating When Hungry. The "little pig" effect dominates; he does both, alternately or simultaneously.

7. Effects on "Negative," "Painful," "Fearful," "Alarming," and Similar Emotional States. He triggers faster when "threatened" and touches and releases even when he cannot obtain trains when threatened. Long trains attenuate and even can eliminate "fright," "anger," and even "pain-like" behavior. Simultaneous stimulation in a negative area increases the average, long-term triggering rate. Such "start" triggering also seems to increase the threshold for "fear" or "pain" in the "stop" systems (see below).

8. Transfer of Learning Between CNS Zones and Between Output Modes. Only 1 to 50 trials are needed to transfer the learned pattern to a novel and never before tried zone or to a new output muscle group. These effects can be demonstrated in one 3–4 hour training period. The ubiquity of the learned response is startling.

9. Longer-Term Effects. In general, an animal working and being stimulated in these regions is easy to work and live with. Few, if any, bite or scratch during and after such periods. The animal is less jittery,

more tractable, more "interested" in the observer's activities, and develops a more "affectionate" attitude to the observer, such as grooming the observer's hand instead of scratching it.

Stimualtion here reverses the "bad" aftereffects of stimulating the "stop" regions (see below). It can also eliminate the "depressed" behavior characteristic of a monkey left alone for a long period; his liveliness and "interest" are increased by stimulation or by start-capture sessions.

"STOP" PATTERNS AND REGIONS

We failed to obtain the "stop" pattern using trains of constant amplitude and external warning signals for trials every 10 seconds, 6 hours per

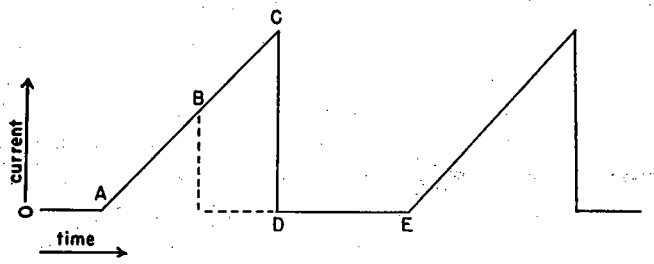

FIG. 4–5. Form of the envelope of trains for use in "stop-capture" training. *A* is the onset of crescendo number 1. *B* is a sample, elective "stop" point caused by the animal triggering the circuits. *C* is the point at which timer turns off crescendo at a peak chosen by the observer. *D* is the beginning of a stimulus-free period. *E* is the beginning of crescendo number 2.

day for 5 days in 2 cases. We devised finally a successful technic to obtain (in about 50 trials at 13-second intervals) the "stop" behavior pattern without external clues and, simultaneously, to obtain various kinds of thresholds. The procedure can be carried out with or without external clues, and, we think, demonstrates that internal clues ("subjective feelings") are evoked by these stimuli in these animals.

Figure 4–5 illustrates our procedure, a so-called *crescendo* stimulation. An electronic timer starts a modulated train of stimuli which is repeated at regular intervals. If the monkey does nothing, each train runs its course and is shut off at regular intervals. If during the train the monkey releases the trigger contact, the train goes off. The successful training was obtained

with a modulation envelope, which is a triangular wave, with linearly increasing pulse-pair amplitude with time; this "crescendo envelope" allows the observation of the peak current at the time of interruption (and/or the number of pulse-pairs in the train to that instant).

Figure 4–6 shows a series of such interruptions with the value of current at each interruption; this series was early in the training period. Figure 4–7 shows a later stage in the learning—he is more efficient and more accurate. Figure 4–8 shows an analysis of the distributions of the currents

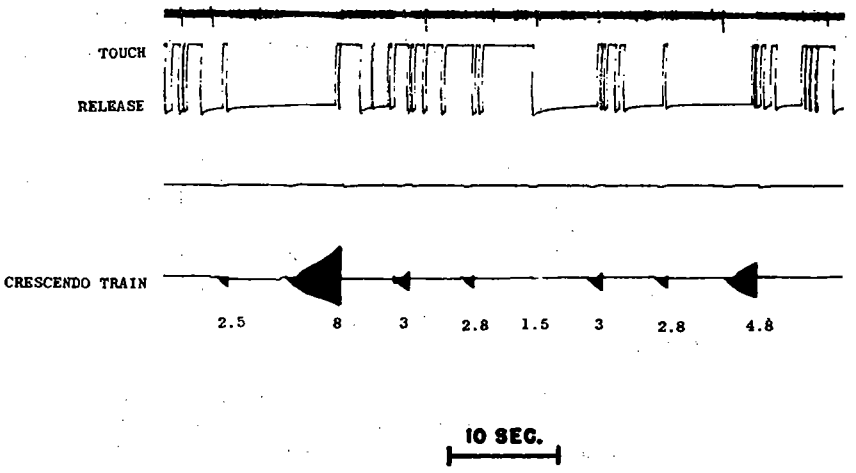

FIG. 4–6. Stop-capture development (during learning). The currents (ma.) at each interruption are given below each crescendo. The scatter of these values is great. Anatomic locus: supra-hypophyseal 3rd ventricle.

for a series of interruptions like those in Fig. 4–7 in a continuous sequence with 339 hits, 339 runs, no misses, and no errors.

In general he tends to shut off the current at a level lower than that at which clinical signs of a disturbed state (here "fright") appear. At the bar and arrow (Fig. 4–7) is our threshold for detection of a "fearlike" reaction; at currents well above this value, he could be said to be in "panic," with all gradations down to zero visible effect at lower values. No visible signs occurred at the current values at which he interrupted the crescendos.

In another animal we have had an opportunity to examine the development and the operations of this stop-capture pattern in more detail. Gratuitously we were given at least 2 new kinds of thresholds.

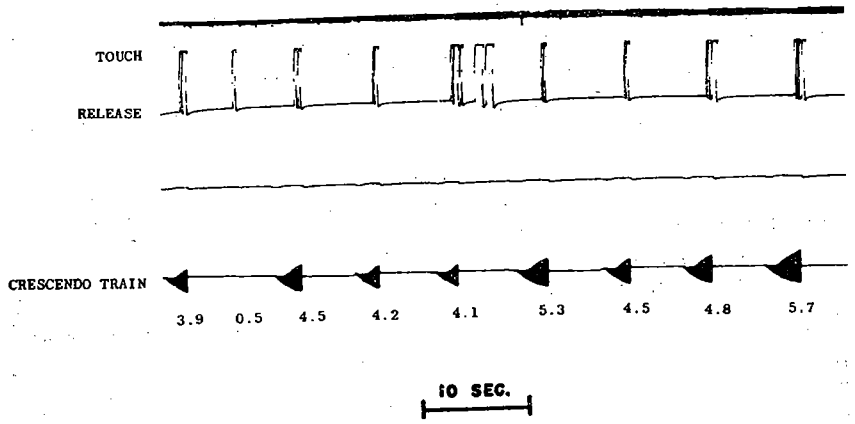

FIG. 4–7. Stop-capture developed (after learning). The scatter of the currents at interruption is now smaller (see Fig. 4–8). Anatomic locus: supra-hypophyseal 3rd ventricle.

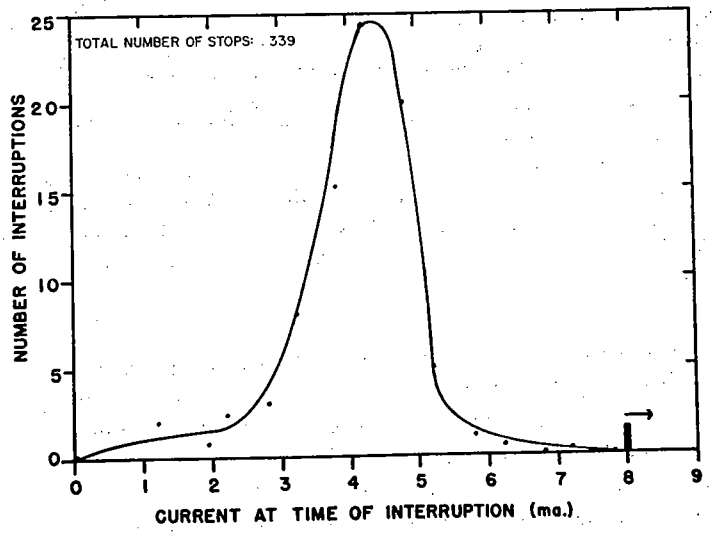

FIG. 4–8. Stop-capture: distribution of values of current at the time of interruption. The figure shows the threshold for "urgent" interruption (compare Fig. 4–9). Anatomic locus: supra-hypophyseal 3rd ventricle.

1. Thresholds. Figure 4–9 shows an analysis of about 650 crescendo triggerings. The triangular envelope is shown as curve A; it begins suddenly at zero (at about 1 ma.) and ends at 520 pulse-pairs (15.0 ma.). Curve C shows the distribution of touches just preceding the triggering releases, whose distribution is shown in curve B. It is to be noted that there

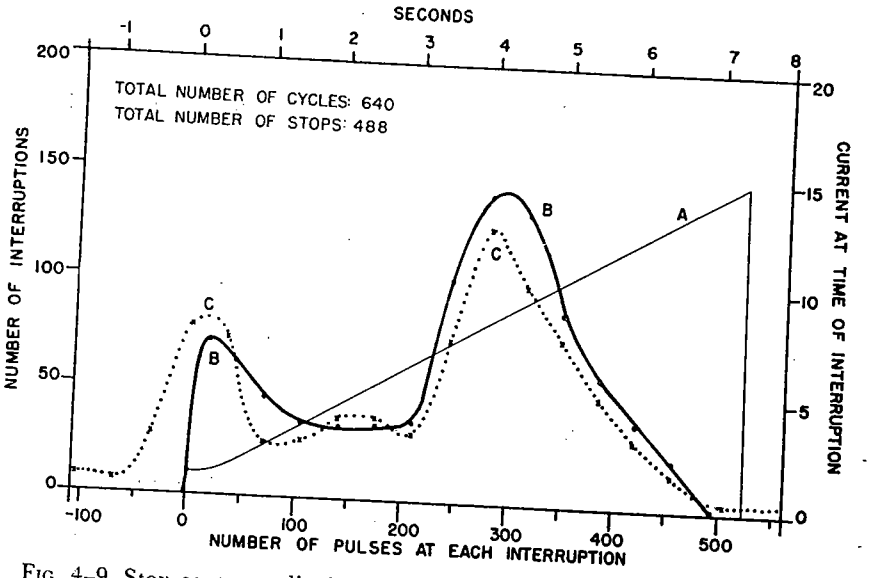

FIG. 4–9. Stop-capture: distribution of 750 crescendo interruptions. Curve *A* is the trace of the crescendo starting at zero pulses, zero seconds, and at about 1.0 ma., and ending at 520 pulses, 15 ma., and 12.8 seconds, if not interrupted by the animal. *C* is the distribution of the touches preceding the effective triggering releases which are plotted as curve *B*. Touches occur all the way through the whole cycle: releases only from 0 to about 490 pulses (at values less than the peak).

are 2 peaks in each curve, 1 near the beginning of the crescendo, the other about halfway up the crescendo. The touch curve is continuous through the cycle; the release curve begins at the crescendo's beginning and ends *before* the peak (520 pulse-pairs or 15.0 ma.) at about 490 pulse-pairs. The clinical signs of "fright" appear at about 350–400 pulse-pairs (8–10 ma.), and obvious "panic" at about 450–520 pulse-pairs (10–15 ma.).

Thus we see at least 3 thresholds: 1 at the beginning of the crescendo, 1 near the middle, and 1 near the peak. The lowest threshold is apparently

partly a "sensation" (releases and touches after cycle begins) and partly conditioning to a time interval (touches and releases before cycle begins); the second is apparently that for urgent avoidance; and the third, "that which is to be avoided," with violent "escape" behavior being stimulated. In the latter phase, he can touch the contact and hold on to it, but he cannot release it; it's as if he "froze on the controls" at this level.

2. Aftereffects. If a monkey is left on this stop-capture circuit in the anterior midline hypothalamic zone for about 3 hours, there are very deleterious aftereffects which persist (unless actively reversed by the observer) up to 24 to 48 hours. He becomes irritable—biting or scratching when approached. He refuses to eat. Food already in the stomach is held there and vomited during the night. His skin and mucous membranes become gray and pallid; his heart rate goes up. He may be dehydrated (because of the repeated bowel movements?); he does drink water despite his refusal to eat. Eventually he becomes apathetic and relatively nonresponsive.

3. Reversibility. If one does not wait too long, this whole picture can be reversed rapidly by placing him in a start-capture circuit; he revives in a few minutes; his appetite returns, and he works with us again. This rather startling revival emphasizes the peculiar persistence of the "bad" aftereffects; it is almost as if the destruction, once started, carries its own mechanisms for further destruction unless actively opposed. Concerning this point we have some other kinds of evidence as to what may be going on.

4. Controllable Time Course. If one uses short trains of constant amplitude (rectangular envelope) and stimulates this zone, one can turn on, maintain, and turn off the clinical appearance of "fear." But if one either raises the current strength or prolongs the train, the state starts, is maintained, and continues after the train is off for periods up to many minutes. We hypothesize that the "turned on, maintained, turned off" state is probably purely "neuronal processes," whereas the persisting one is "neuronal with hormonal feedback."

Comment

The only speculations I have to offer are some articles of neurophysiologic faith. In extreme emergencies subcortex has priority over cortex—built-in escape, attack, or "freeze" behavior must take place ahead of "wait and see." But in *most* of life's activities, cortex and subcortex function smoothly together. The 40,000 cells per cu. mm. of the many cubic centimeters of

cortex exert at least a comparable if not a much greater influence in behavioral sequences than the much fewer cubic centimeters of similar numbers of cells per cu. mm. in diencephalon-mesencephalon-medulla. These latter cells cure or kill when hyperactive or missing; but in the intact brain, cortex and its diversified and differentiated inputs modulate their activities up or down just the appropriate amount in relation to present environment, past learned relations, and future, computed, anticipated, "intuited" situations. We are constantly marveling at the differences between an untrained animal and the same animal after training; the differences may be mainly feedback circuitry changes within cortex and between cortex and brainstem.

Does the animal feel any emotion with these stimuli? My guess, which is fast becoming a contention, is that of course he does. In agreement with Sherrington's 1904 definition,[17] we say that any "sham" or "pseudaffective" terminology is nonsense when applied to a nontruncated, intact animal. When an intact monkey grimaces, shrieks, and obviously tries to escape, one *knows* he is fearful or in pain or both; when one lives day in and day out for weeks with one of these monkeys, hurting him and feeding him and caring for him, his experience of pain or fear is so obvious that it is hardly worth mentioning. I have spent a very large fraction of my working time for the last 8 years with unanesthetized monkeys with implanted electrodes, and I agree with Professor Hess when he calls a certain pattern elicited by stimulating (in one "stop" region) from a cat "affective-defensive;"[4] the affect *is* present. The results presented above on the "stop" zones demonstrate that the subjective, danger-signaling feelings are probably present. The monkey detects and terminates them at levels below those at which we can see any external effects.

We must study these states, as well as the rewarding ones, even though it is uncomfortable for us, for our colleagues, for administrators, and for laymen. If we can show the necessity for such study, to some day reduce in men and women the intensities of such destructive internal events, I am sure that all reasonable persons will agree with our aims. I, for one, would not recommend neurosurgeons or others to stimulate any patient or other human being anywhere in the systems we label "stop the stimulus" or "negative" or "punishing." These are dangerous systems, not only psychologically dangerous, and socially dangerous, but biologically dangerous to the animal. Here is where the basic seeds of destruction of the organism itself reside; our monkeys become basically ill—so sick that we feel the absolute necessity of switching to the "start" systems to prevent the develop-

ment of a clinically irreversible downhill course. In the knowledge of the brain, of the diencephalon, of the mesencephalon, some of these ideas are old, but we have never been so close to trying it on patients. If anyone does try it, let's hope he knows enough about these and other findings to recognize at least the *known* dangers and the definite probability of *unknown* dangers.

The "start" or "positive" or "rewarding" systems are intriguing; but let us be cautious here also. We do not yet know enough about these systems (and how to stimulate them safely) to know what are hopeful fantasies of the "elixir of youth by push-button control" and what are the basic limits of any and all biological rewards, in monkeys and in men. We have failed to make a monkey vocalize for this reward; likewise, sick men may be stubborn enough to refuse to use good feelings, even when forced to feel them by electrical stimulation, and healthy men already know how to maintain good feelings without such forcing. One can drive and force learning by employing "stop the stimulus" zones and "start the stimulus" zones combined sequentially in monkeys, but in the larger brains than those of monkeys, immediate release from pain and immediate gratification and pleasure have only periodic and temporary urgency. Somehow the larger cortex seems to be able to reduce the urgency and delay the gratification. Some men are strong enough to hold out for months against such short term gains pitted against longer term losses.[16]

One analogue we can offer of a monkey triggering stimuli in some of the "start" regions at 3 times per second is a man talking—same kind of activity, same kind of reward.

I leave you with one general "interdisciplinary" proposition to question: *the initiation and the repetition of all (motor) actions of themselves are either internally rewarding ("start" effect) and/or cause the termination of internal punishment ("stop" effect)*. This may sound "psychological," but by "internally" and "internal" I mean "within the brain," and I do mean specific basic neurophysiologic activities yet to be delineated when I talk about "reward and punishment"! The "start" and the "stop" patterns with and without true "capture" must permeate all of the animal's and all of the human's life to assure continuous and constant attention to that which leads to survival of the body, of the species, and even of institutions. The initiation of certain activities must be pleasurable or urgent, and the termination of others must be fast and compelled by activities within the brain.

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Appendix: Injury and Excitation of Brain by Electrical Currents

Our goal has been to find an electrical current waveform with which one would be able to stimulate animals through implanted electrodes for several hours per day for several months without causing irreversible changes in threshold by the passage of current through the tissue. We have found one waveform.[2,3] This discussion is designed to bring out certain ultimate limitations in the use of any electrical waveforms, including this one. The search for an ideal waveform is being continued—the ideal has only been approached, not reached.[2] In this paper we bring out the thermal energy limit and the electrolytic limit which are reached as one traces the neuronal threshold data through large systematic changes of waveform. We are discussing *only* chronic persistent stimulation: 1–3 trains per second for up to 18 hours per day, 5–7 days per week for 6 to 12 months, not acute stimulation at 1 session or stimulation for 1 hour per day for several weeks. Many waveforms, including 60 cps. sine wave current,[8] apparently can be used safely for these latter schedules of stimulation but, in our experience, cannot be used for the former schedule.

INJURY

Electrical current passed through the brain can cause at least 2 distinct types of injury, thermal and electrolytic. These types are separable by the proper choice of the electrical parameters and in the proper parametric regions can have thresholds less than those for excitatory processes. The technical problem in chronic brain stimulation is to stay above the excitatory threshold and below the injury threshold in the system of interest; this result can be achieved most easily by the proper choice of waveforms and their time courses, and less easily by the choice of the range of repetition frequencies and train durations.[1] As has been amply demonstrated by us[1] and by many others,[4,5,6] these parameters also influence excitatory thresholds and possibly determine which systems are excited in the vicinity of the electrode.[1,4] Our first emphasis is on avoidance of injury; we proceed on the basis of accepting as threshold excitation of any or all systems at the electrode tip the values of current which give a visually or tactually detectable response or change of behavior. (Of course other methods of detection can give *lower* threshold values, and other waveforms can excite

the energy (watts) per pulse is given as peak current (amperes) squared times the resistance (ohms) of the electrode. The amount of electricity (coulombs) passed per pulse is the product of the pulse duration (seconds) times the peak current (amperes). To illustrate the points involved some values have been calculated for a representative implanted electrode in a monkey, and the results shown in Figs. 4–10, 11, 12, 13. In

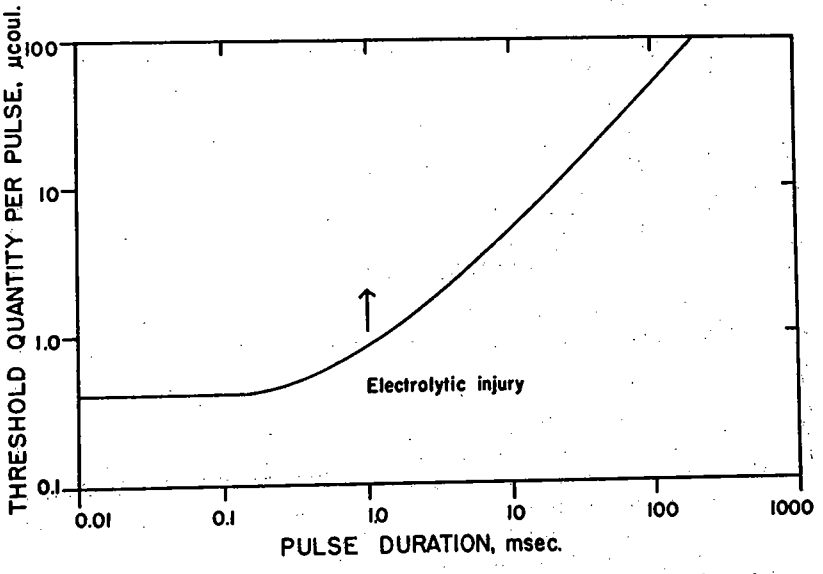

FIG. 4–12. Quantity of electricity per pulse versus pulse duration at threshold. For this electrode, waveform, and train parameters, the electrolytic injury threshold is at about 0.5 microcoulombs per pulse at about 1.0 milliseconds pulse duration.

all these figures, pulse repetition frequency and train duration are held constant at 60 pulses per second and 5 seconds.

Figure 4–10 shows the relation between the threshold current and the pulse duration. The classical rheobase is difficult to obtain because of the electrolytic injury which raises the threshold rapidly; the value here is an extrapolated estimate.

Figures 4–10, 11, 12 are calculated from the data of Fig. 4–10. Figure 4–11 gives the threshold peak energy per pulse, and Fig. 4–12 gives the threshold quantity of electricity per pulse, each plotted against the pulse

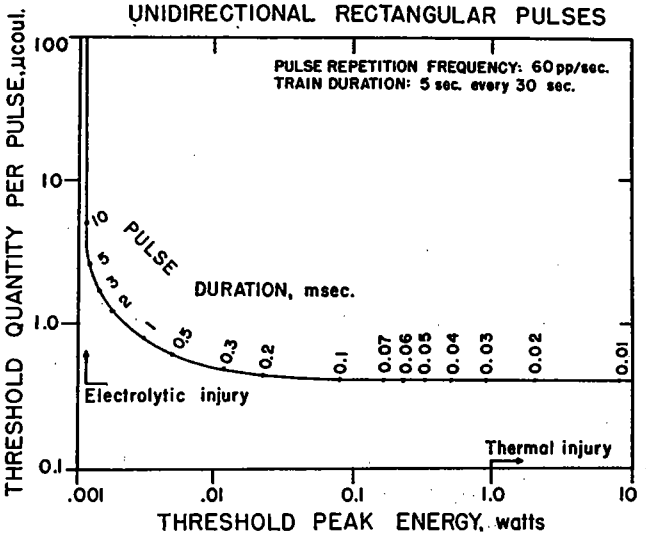

FIG. 4–13. A relatively minimal injury parametric region: quantity versus peak energy at threshold at various pulse durations. Data are combined from Figs. 4–11, 12. This figure shows both of the injury thresholds for the parameters previously given. The vertical straight line portion of the curve is "rheobase" and the horizontal is "constant quantity" on this plot. It is to be emphasized that for maximum safety the waveform of Fig. 4–10 is to be used; no region for this *unidirectional* waveform can be used longer than the times given (5 sec. every 30 sec.) without causing electrolytic injury. It is also to be emphasized that this waveform can be shortened or extended to give results like those in this and in previous figures; values of the injury thresholds very close to the ones of this figure are found for such shortened and extended forms for very long trains applied continuously for hours per day for several weeks. The bidirectional waveform in the proper parametric region extends the permissible total stimulation time of each session by many hours.

duration; Fig. 4–13 shows the energy plotted against the quantity. In each of these figures, an estimate is given of the threshold for the 2 types of injury, thermal in Fig. 4–11 and electrolytic in 4–12, both in 4–13. However, it is suspected that the electrolytic injury threshold is very much lower than this value—the lower limit is yet to be determined carefully

for stimulations lasting many days. The thermal injury threshold is an estimate based on the observation of the breakdown of water to steam for single pulses at a metallic electrode whose resistance was the same as the electrode chosen for these figures; the values for tissue damage are probably lower than this one. This threshold is a function of the area of metal exposed and the size and efficiency of the heat conduction path away from this electrode interface; however, this value is of the approximately correct order of magnitude for practical electrodes. As the area of the metal in contact goes down (smaller electrodes) and hence the resistance goes up, the threshold energy may reach such values that the local temperature reaches injurious levels at local threshold values of current.

We have found[2] that if a 120-microsecond rectangular pulse is quasi-differentiated (to a pulse duration of about 30 μ seconds) and the resulting pulse-pair used to stimulate, no detectable injury occurs over many weeks of stimulation. Apparently this short-term (within 200 μ seconds) reversal of current, with equal charge in each of the opposite pulses, reverses processes leading to "electrolytic" injury.

In some unpublished work we have found that if the pulse-pair interval is extended to 16 milliseconds (60 per second) and the duration of each condenser-discharge type of pulse extended to a time constant of 5 milliseconds, the threshold rose slowly in the first few hours of stimulation (deep, subcortical electrode). We then changed to the short pulse-pair: the threshold stayed at the final value for 6 months. Many experiments in several loci at many "dosages" demonstrated that "electrolytic" injury was being generated by this longer pulse-pair. In other experiments the duration of each member of the pulse-pair was shortened to 10 μ seconds; at threshold values of current the threshold rose rapidly until breakdown of water began to interrupt the current seen on an oscilloscope. The peak energy dissipated per pulse was of the order of 2 watts. The thermal injury level was exceeded by these very much shortened pulses. Thus for the matched opposite pulse-pairs there are 2 extremes, limiting the range applicable to brain stimulation without injury; the lower, low current, low energy, high quantity one causing electrolytic injury; the upper, high current, high energy, minimum quantity one, thermal injury.

In other experiments we have found that even in the presence of a 100 per cent rise in threshold resulting from electrolytic injury (maintained for 6 weeks), the damage was not detectable under the microscope; only very much larger increases in threshold were correlated with visible damage.

EXCITATION

In general, the threshold discussed is that for either demonstrable evoked movement or some change in what the monkey did in response to stimulation. The first threshold is definitely higher than for the minimum evokable local electrical activity, and the second can be of a magnitude comparable to that of the electrical response.

As can be seen from the figures, the short pulses (and pulse-pairs) have a constant quantity of electricity per pulse at threshold; these quantities are of the order of 0.2–0.5 microcoulombs per pulse at 60 pulses (or pulse-pairs) per second in 5-second trains for pial electrodes over cortex, and about 0.05 microcoulombs for some deeper placements. The long pulses have, temporarily, a constant current threshold (rheobase of the order of 0.2–1.0 milliamperes) but such pulses destroy tissue.

Hess[4] used a very long duration "balanced" waveform, in order to excite all elements near the electrode in equal amounts. We do not know how long he stimulated in each session (hours) nor for how many days or weeks he observed thresholds. If these times are comparable to ours and the thresholds remained constant, the facts in the 2 cases disagree, and further research is needed.

The shorter balanced pulses may possibly stimulate only short chronaxie elements, but this is doubtful. To obtain an observable effect on behavior requires firing several thousands of elements near the electrode. The local field strengths near the electrode at the currents observed are presumably very much above threshold for even small fibers. Apparently the shell within which small, long-chronaxie elements fire is smaller than the shell in which the larger, short-chronaxie elements respond. With the longer pulses (resembling Hess' case), the 2 shells may be more coincident in space. However, it is yet to be demonstrated that these differences do not average out in the mass of excited elements, rendering them undetectable by behavioral criteria; a point to point comparison should be done, in which, if possible, injury is avoided. There may be a different injury threshold for each of the different elements, analogous to but not identical with the differences in excitation thresholds.

At the present time, careful, quantitative data concerning the spatial factors in electrical excitation are conspicuously absent in the literature. Many more data and much more analysis are needed for evaluation of the results of stimulating closely packed systems like the hypothalamus, intralaminar nuclei, etc. At best, localization of function in the CNS at

present suffers from a lack of a truly quantitative theory based on what is done in the laboratory rather than on some neuroanatomic fantasy. Obviously the neuroanatomic findings are essential and contain the most quantitative data we have to date, but an understanding of function needs, in addition, a biophysical quantitation of the geometry of the relations between excitation and the field set up by the current.

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Discussion

DR. MACINTYRE: Dr. Bond's group at Western Reserve University has long been interested in the investigation of injury resulting from the passage of unidirectional currents through the brain. While this work was undertaken to quantitate several of the electrical variables and other related factors entailed in the production of electrolytic lesions of brain, one of the primary problems involved the differentiation of the effect of total ion flow (coulombs) from that of heat dissipated.

For each lesion, the total number of coulombs delivered was calculated as the product of the time of stimulation and the direct current amperage, as recorded by meter reading or by a calibrated cathode ray oscilloscope. Since the resistance (R) of the lesion was not constant during long stimulation, the heat was calculated as a product of the average voltage (V) multiplied by

the number of coulombs delivered (Q) rather than the usual expression of I^2Rt, where I represents the current and t the time of application. This was converted to and expressed in calories.

Provided the number of millicoulombs is kept constant, lesions of equal size have resulted, notwithstanding 120-fold variation in the duration of current flow, 20-fold variation in voltage, and 6-fold variation in calculated resistance. In isolated studies involving other parameters the foregoing ranges have been extended to 1000-fold in time and current flow and 70-fold in heat released with similar results. This is, of course, in reference to unidirectional currents and entirely apart from the thermal effects that Dr. Brady mentioned.

The dependence of lesion size upon the number of millicoulombs passed was investigated over the entire range from 0.25 millicoulomb to 200 millicoulombs. There is independence of lesion size with D.C. pulses within a range up to 500 pulses per second. The pulse duration of 50 milliseconds is still relatively short in reference to many of the effects previously discussed.

Platinum and silver electrodes have exhibited approximately the same volume of lesion as copper, with stainless steel giving the smallest electrolytic effects of any metallic electrode so far used.

We have some preliminary results on bidirectional currents which indicate that with current values in the range of 1 or 2 milliamperes, little damage is observed at frequencies higher than 20 cycles per second or durations less than 12.5 milliseconds. Below 20 cycles per second the damage progresses with increased pulse duration, while above this value lesion size is relatively small to well over 100,000 cycles per second.

Dr. Bickford: It is not necessary to pass a current to get these effects. Fisher did a series in our laboratory in which different metals were used without the passage of current, and copper is quite toxic under these conditions. If it is left in place for a couple of weeks there is diffusion apparently from the metal even without passing current. Silver is also toxic under these conditions, which surprised us somewhat. Stainless steel is without toxic effect.

Dr. Alberts: How soon after insertion do you get behavioral effects and what is the approximate range of voltages?

Dr. Lilly: Voltage and current have very little meaning unless you specify everything else. You have to describe at least 5 parameters for every stimulus. However, our electrodes by the substitution method, substituting an ideal resistance for the electrode circuit, usually run between 5000 and 10,000 ohms. The usual threshold, if you are in an active cell group and in a high density neurone population, such as cortex, with the electrode in the fifth layer, will be between 0.6 milliamperes and 3 milliamperes. The duration is of the order of 60 microseconds. If you specify this in terms of microcoulombs then you do not have to specify the duration because it is independent of duration. It comes out to be a tenth of a microcoulomb per pulse. This is in 5 second trains. In some regions it may be 20 second trains.

Dr. Mountcastle: In your work in the motor cortex you were able to differentiate gray matter and white matter by changing the parameters. This

is a crucial problem for all subcortical stimulation. Could one develop different stimulating parameters to stimulate cells at lower thresholds?

DR. LILLY: I don't think we are ready to answer that question yet. One general statement that can be made, based on the cortical work and subcortical work, is that 1 pulse by itself means practically nothing to the nervous system in terms of behavior. One pulse repeated once per second means very little, but as soon as these are of the order of a tenth of a second apart then they begin to have meaning and you get excitation.