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Role of Ipsilateral Forebrain in Lateral Hypothalamic Stimulation Reward in Rats

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STELLAR, J. R., J. ILLES AND L. E. MILLS. *Role of ipsilateral forebrain in lateral hypothalamic stimulation reward in rats.* PHYSIOL. BEHAV. 29(6) 1089–1097, 1982.—The forebrain was ablated unilaterally to a level dorsal to the thalamus and anterior commissure. Ipsilateral lateral hypothalamic electrodes were then implanted and the animal was tested for self-stimulation behavior. Tests included an initial test for behavioral reactivity to changes in reward level and then two estimates of the quantitative relationships between stimulation parameters: the number-current and charge-duration relationships. Comparison between these findings and those known for intact rats suggest that the substrate for unilateral hypothalamic stimulation reward is not impaired by removal of the ipsilateral tissue.

Self-stimulation Hemiforebrain ablation Lateral hypothalamus Quantitative reward measures

EVER since the original discovery that rats would work to obtain bursts of electrical stimulation of the brain [21], researchers have been interested in the underlying neuroanatomy. A major clue to the anatomy of this self-stimulation phenomenon was first suggested by the locations of the effective electrode sites which seemed to track, in part, the catecholamine pathways as they were revealed by histofluorescence [5,12]. Recently, pharmacological evidence [8, 29, 30] and movable electrode mapping studies [3,4] have focused attention on the ascending midbrain dopamine systems and their terminal fields in the forebrain as a likely anatomical substrate of self-stimulation reward. In addition, descending projections from forebrain sites such as the medial prefrontal cortex to the medial forebrain bundle may underlie at least part of the reward of hypothalamic stimulation [5, 6, 23].

This forebrain-hypothalamic hypothesis is somewhat complicated by the finding that rats with bilateral destruction of most forebrain tissue rostral, lateral, and superior to the thalamus have been shown to be able to learn to rear or to elevate their tails to obtain electrical stimulation of the lateral hypothalamus [15,16]. Rats with this lesion are termed "thalamic rats" after the highest unlesioned structure remaining in the brain. Given that sites within the brainstem [3, 23, 24] will support self-stimulation in intact rats, it is possible that the self-stimulating thalamic rat is now operating on these brainstem circuits. However, the original studies [15,16] do not provide enough information as to the extent of change in the properties of hypothalamic reward following the ablation to estimate what has been subtracted by the ablation, much less to support the notion of a shift to "lower systems." In addition it should be noted that thalamic rats show little or no extinction when the brain stimulation is discontinued and that they have profound general behavioral limitations [16]. Therefore, it is difficult to make careful comparison to intact self-stimulating animals.

This report attempts to investigate the extent of change in the properties of hypothalamic reward following forebrain ablation by applying the quantitative measurement techniques developed by Gallistel [9]. These techniques permit estimation of various parameters of the neural mechanisms underlying brain-stimulation reward and thereby allow comparison between lesioned and intact animals. However, they require that animals show behavioral sensitivity to changes in the level of stimulation (e.g., intensity, frequency, etc.) delivered as a reward. Therefore, hemithalamic rats with unilateral forebrain ablations and ipsilateral hypothalamic electrodes were prepared in hopes of bypassing most of the behavioral limitations of the thalamic rat but still permitting an analysis of the role of at least the ipsilateral forebrain in hypothalamic reward.

Two experiments are reported. In the first experiment, behavioral sensitivity to variation in the level of brain stimulation is established for hemithalamic rats in the runway. This finding specifically permits the use of this paradigm in the second experiment in which two aspects of the reward substrate are assessed. These two aspects are discussed in the second experiment.

EXPERIMENT 1

METHOD

Subjects

Subjects were five male albino rats of the Sprague-Dawley strain weighing between 420–455 g at the time of first

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surgery. Throughout the experiment all rats were housed in standard hanging wire cages in a 12 hr light 12 hr dark, day-night reversed colony with continuous access to laboratory chow and water.

Surgery

Rats were first anesthetized with Chloropent anesthesia (3 cc/kg) and placed in the stereotaxic device. They were then given a left side craniotomy and an unilateral forebrain ablation by aspiration. The targets for aspiration were all structures superior and lateral to the thalamus and anterior to the anterior commissure. These targets included neocortex, hippocampus, striatum, cingulate and pyriform cortex, septum and most amygdala, accumbens, and olfactory bulb. During surgery, hemostasis was practiced by elevating the animal's head 10–12 cm above its feet, flushing the area of aspiration with saline and packing it with Gelfoam. Following the aspiration, the Gelfoam packing was completed, the wound closed and the animal given a 0.2 cc intramuscular injection of Crystycillin and a 10–15 cc subcutaneous injection of saline. Postoperatively, rats were maintained by two daily intragastric intubations of H_2O powdered Enfamil, and egg yolk as necessary.

Once animals were feeding normally and body weight had recovered to preoperative levels, rats were reanesthetized with Chloropent and chronically implanted with a preconstructed bilateral array of 4 monopolar stainless steel stimulating electrodes constructed from size "00" insect pins insulated to within 0.25–0.5 mm of the tip with Formvar enamal. The bregma-based, level-skull coordinates for the electrodes were: AP −2.0, ML +1.8, DV −8.5; AP −4.0, ML +1.4 and −1.4, DV −9.0. The implant was anchored by dental cement to 4 skull screws placed in the remaining bone tissue. These skull screws also served to complete the circuit between the electrodes and the stimulator. Other details of the electrode construction and the implantation method are given in a previous report [11].

General Procedure and Apparatus

Following recovery from the second surgery, rats were pretested for self-stimulation by being trained to lever press for 1/2 second bursts of brain stimulation in the goal end of a straight runway. In this experiment, bursts of brain stimulation always consisted of a preset number of square wave, cathodal pulses of 0.1 milliseconds duration that were delivered from a constant voltage source. In the pretest, the frequency of pulses was 100 pulses per second and current was varied to produce vigorous self-stimulation. All animals which self-stimulated vigorously in the lateral hypothalamus/medial forebrain bundle area on the ablated side were employed in the experiment.

Rats were trained to run the runway for medial forebrain bundle stimulation of the ablated side of the brain. Each trial began with an intertrial interval of 20 seconds. This was followed by 10 bursts of pretrial priming stimulation [11] delivered at the rate of 1 burst/second and each burst contained 60 pulses. Priming stimulation current was set for each rat so as to produce clear arousal without signs of aversiveness, e.g., freezing, defecation and attempts to escape the priming box. After the priming stimulation, the animal was transferred to the start box of the runway. Following a 6 second delay, the door opened giving the rat access to the 1 meter straight alley with a lever at the goal end. Pressing the goal lever initiated a single burst of brain stimulation pulses, the frequency, current, and number of which were preset. Data was collected as the elapsed time from the door drop to the lever press and converted into an overall speed score which is given in centimeters per second. After pressing the lever, a new trial was automatically initiated with the beginning of the intertrial interval. Trials were run in groups of 11 with no change in stimulation parameters. On any trial in which the rat did not run the runway and press the lever within 20 seconds, the rat was picked up by the experimenter, placed on the lever (thereby delivering the stimulation), and given a running speed score of zero.

Reward Variation Procedure

In order to test the rats' behavioral sensitivity to variation in the amount of the brain stimulation reward, the following procedure was employed. Rats were first trained to run the runway for 1 burst of 100 pulses of brain stimulation with the pulse frequency being set at 100 pulses/second. The stimulating current was set so as to produce vigorous running. Priming stimulation was fixed as described above. Number of reward pulses was then varied in an alternating fashion from 100 pulses (high reward) to 1 pulse (low or no reward) every 11 trials and animal's running speed was recorded for each trial. This alternation procedure was repeated 3 or 4 times until the animal's behavior was stabilized. Then, data were collected until 7 alternations of high and low reward had been completed. The first high reward condition was discarded since it was not preceeded by the alternate condition. On a trial by trial basis, medians were then constructed to show the changes in running speed following a change of condition.

RESULTS AND DISCUSSION

Recovery from the hemiforebrain ablation operation took about 2 weeks while 3–4 days were allowed for recovery from the implant operation. Five rats ultimately received both surgeries and self-stimulated well enough on electrodes on the ablated side of the brain to be included in the study. One rat, JI 20, had two good electrodes on the ablated side and both were included in the study.

In the reward variation part of this experiment, all rats showed sensitivity to changes in the reward level. When the reward level was decreased from 100 pulses to 1 pulse, all animals began running at nearly the same speed as the prior condition and then decreased their median running speeds to asymptotically low levels within 3–6 trials. When reward was increased from 1 pulse to 100 pulses, all animals again began running at a speed appropriate to the prior condition and then increased their median running speed to asymptotically high levels within 2–5 trials. These data are given in Fig. 1. Statistical analysis, presented in Table 1, shows that in all cases significant differences exist between the first and last trial of a session but no statistical difference exists between the first trial of a condition and the last trial of the prior condition for any animal. This type of variation in running speed is similar to that observed in intact rats in a runway paradigm [11]. Recently, hemithalamic rats, even with additional contralateral damage, were shown to exhibit extinction when the reward was discontinued in a free lever-pressing paradigm [17]. These findings suggest that hemithalamic rats, in general, do not have the extinction problems of bilateral thalamic rats [15], even though they are stimulated in the hypothalamus on the ablated side. In particular, our results permit the standard use of the runway as a

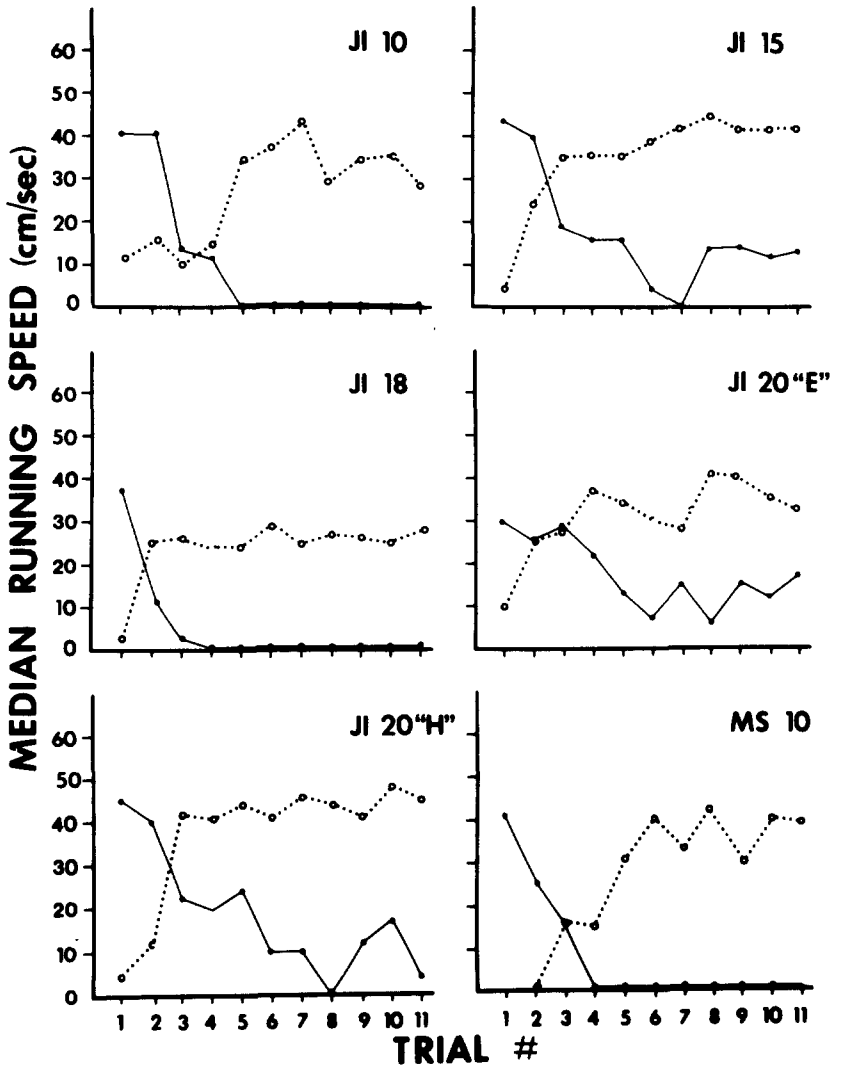

FIG. 1. Median trial by trial changes in running speed as reward stimulation was alternated between high (100 pulses) and low (1 pulse). The high reward condition is indicated in open circles and dashed lines, while the low reward condition is indicated in filled circles and solid lines. Statistical analysis of the changes in running speed with each condition is given in Table 1.

tool for making more quantitative assessments of the reward substrate [9, 10, 11].

EXPERIMENT 2

In this experiment, two parametric measurements were made of the neural substrate of self-stimulation in hemithalamic rats. They were the number-current and the charge-duration trade-off relationships required to keep behavior (e.g., self-stimulation) constant. These measures were developed by Gallistel [9] with implanted but intact rats and provide a partial characterization of the substrate mediating hypothalamic reward. It is hoped that by comparing this characterization for hemithalamic and intact rats some understanding might be developed of how the ipsilateral forebrain contributes to hypothalamic reward.

The first measure, the number-current relationship, takes advantage of the fact that changing either the number or current of the discrete pulses delivered in a reward burst will change the reward and thereby change the rat's behavior. Within some range, if one increases the number of pulses the rat will run the runway faster to collect its larger reward. Decreases in current intensity of these pulses will cause corresponding decreases in running speed and, if adjusted properly, will exactly compensate for increases in numbers of pulses. By applying this procedure one can end up with pairs of number and current values which make up sets of stimuli for which the rat will perform equally. In intact rats, Gallistel has found the relationship between number and current to be one of reciprocity [9].

The second measure employs the above technique of equivalent stimuli but it focuses on the relationship between the total charge delivered to the brain in a reward burst and the duration over which this charge is applied. Frequency is held constant. In intact rats, Gallistel found that the charge-duration relationship was linear with a particular slope and

TABLE 1
ANALYSIS OF REWARD VARIATION EXPERIMENT

Condition	Group Mean (cm/sec)	Standard error
First Trial Low Reward (FTLR)	42.0	3.4
Last Trial Low Reward (LTLR)	7.7	3.0
First Trial High Reward (FTHR)	6.7	2.8
Last Trial High Reward (LTHR)	39.8	3.4

Individual Statistical Differences*

	Within Condition		Between Condition	
Animal	FTLR vs LTLR	FTHR vs LTHR	LTLR vs FTHR	LTHR vs FTLR
JI 10	$p<0.002$	$p<0.047$	ns	ns
JI 15	$p<0.004$	$p<0.001$	ns	ns
JI 18	$p<0.001$	$p<0.002$	ns	ns
JI 20 E	$p<0.001$	$p<0.008$	ns	ns
JI 20 H	$p<0.001$	$p<0.008$	ns	ns
MS 10	$p<0.001$	$p<0.001$	ns	ns

*Mann-Whitney U Test $n_1=7$ $n_2=7$.

intercept; which also means that the relationship between current intensity and burst duration is hyperbolic with a particular chronaxie [9].

METHOD

Subjects and Apparatus

The subjects were the same rats as employed in Experiment 1, and they were tested in the same runway apparatus.

General Procedure

Data collection was conducted as before. However, in this experiment, stimulation intensity was varied as follows. At the start of a session, a high level of current was given for 11 trials to provide a large reward and insure the rat was running briskly. Then current was lowered to a value for which the rat would not run and running speed was extinguished to a criterion of 4 consecutive no runs. Following this, the stimulation current intensity was increased every 11 trials typically in 50 μA steps, until the rat was running at asymptotically high speed. In this way, a running speed vs current intensity curve was generated with all other stimulation parameters held constant. After one curve was determined, a stimulation parameter (e.g., number of pulses) was changed and a new speed-intensity curve was found.

Number-Current

To measure this relationship, a family of speed-intensity curves was generated by varying from curve to curve the number of pulses in a reward burst while holding the duration of the burst at 1 second. Values of 200, 100, 50, and 25 pulses per burst were tested with additional values selected if necessary. Actual number-current pairs were determined by selecting a fixed level of behavior, about $^1/_2$ of asymptotic running speed, and calculating from the speed-intensity curves the current to reach that running speed for each number curve (e.g., Fig. 2). This calculation was made by interpolating between the two points of the speed-intensity curve which bracket the desired running speed value. See Fig. 2 for an example of this procedure. Data were analyzed by preparing graphs with log current on the abscissa and log number on the ordinate, and calculating the best fitting regression line through these points according to the method of least squares. If the relationship between number and current is one of reciprocity, then the best fitting line should have a slope of -1.0.

Charge-Duration

The charge-duration relationship was obtained in a similar fashion to the number current relationship with the difference being that pulse frequency was fixed at 100 pulses per second and duration of the reward burst was varied to generate the family of speed-intensity curves. Again, current required to sustain $^1/_2$ asymptotic running speed for each duration was calculated by interpolation from points in the speed-intensity curves. Because pulse width was always fixed at 0.1 msec and number of pulses could be determined by multiplying frequency and the chosen duration, this determination of required current permitted calculation of the overall charge content in a given burst.

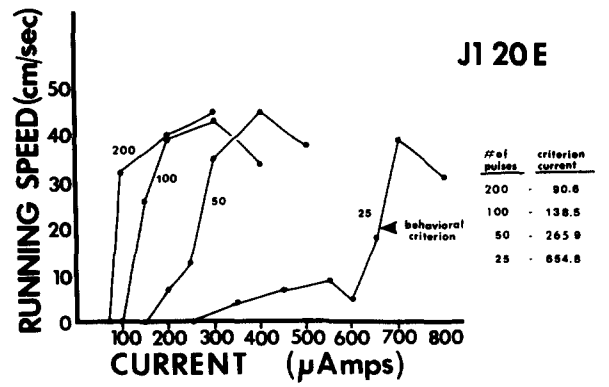

FIG. 2. Median changes in running speed as stimulating current is varied for animal JI 20 E. For each curve a different value of number of pulses is indicated. These values for number of pulses and the corresponding stimulating current required to reach a behavioral criterion of 20 cm/sec running speed are given at the right of the figure.

Data was analyzed by constructing graphs with duration on the abscissa and total charge on the ordinate, and calculating the best fitting line through these points according to the method of least squares linear regression. The slope and y intercept of these lines were found and compared to similar calculation made by Gallistel [9]. The chronaxie was calculated for each animal by dividing the intercept of the linear charge-duration function by its slope [9].

These procedures are straightforward adaptations of techniques developed previously [9,10].

Histology

Following this experiment all animals were sacrificed with an overdose of chloropent anesthetic and perfused through the heart with saline followed by 10% Formalin. Brains were then removed, soaked in 20% sucrose for two days, frozen and sectioned at 40 μm on a microtome with a freezing stage. Tissue was stained with cresyl violet and read with both a tissue projector and a microscope. The extent of the hemiforebrain ablation and the electrode tip location was reconstructed on plates from the atlas of König and Klippel [18].

RESULTS AND DISCUSSION

Number-Current

Figure 3 presents graphs of the data from six electrode locations in five animals relating log current to log number of pulses required to keep behavior and therefore reward at a constant level. From this figure it can be seen that the best fitting line through these points ranges from a slope of −0.861 to −1.41. Listed in the order (left to right, top to bottom) as they appear in Fig. 3 the r^2 values for the proportion of the variance accounted for by each of these lines are respectively: .969, .953, .921, .971, .872, and .790. These r^2 values are all statistically significant and the associated levels are $p<0.01$, 0.025, 0.005, 0.01, 0.005, and 0.025, respectively. The mean of the observed slope of these lines is −1.07, with the standard error of the mean being 0.088, and is not significantly different from the expected mean slope of −1.0 ($t=0.80$, $df=5$). Thus, it seems quite clear that over the range tested the number-current relationship in hemithalamic rats stimulated in the hypothalamus on the ablated side approximates one of reciprocity, as it does in intact rats.

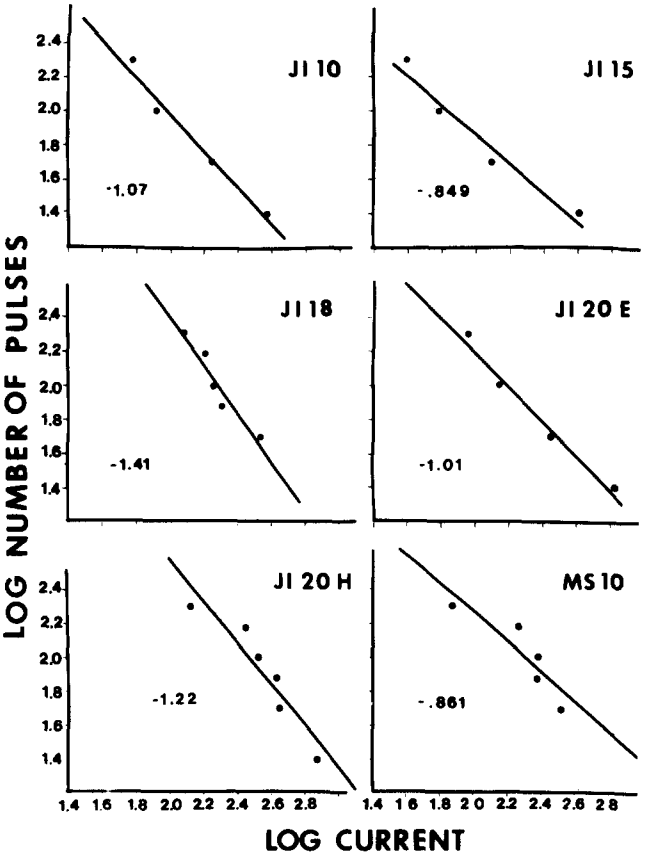

FIG. 3. Relationship between log number of pulses of reward stimulation and log current required to reach behavioral criterion plotted for all animals. Slope of best fitting line is calculated by the method of least squares and is indicated for each animal.

Further Analysis of the Number-Current Relationship

Recently, a new way of analyzing the number-current reciprocity was proposed by Shizgal and colleagues [10]. If current is plotted against the reciprocal of number, a linear regression line can be calculated, the slope of which represents the way current must be increased to keep pace with decreasing number. An example of this is presented in Fig. 4 for animal JI 18 "H." The slope gives evidence as to how many additional reward relevant neurons are recruited into firing each time the stimulation field is expanded by increasing the current. The intercept may signify the theoretical minimum current required to reach any or enough neurons to get the animal to perform the task given that there was no limit on the number of effective pulses those axons could carry in a fixed duration [10]. If the medial forebrain bundle was appreciably thinned of reward relevant axons by the hemiforebrain ablation, then the slope of this line should be steeper and/or the intercept greater, representing the increased requirement for current to offset decreased number of axons available for stimulation.

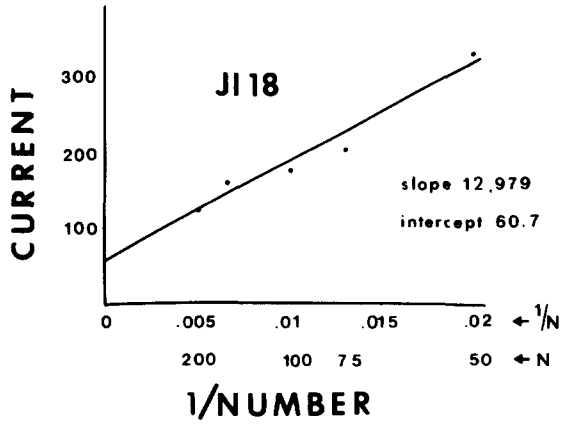

FIG. 4. Relationship between current and number of pulses of reward stimulation plotted for animal JI 18 with number given as its reciprocal. Slope and intercept of the best fitting line calculated by the method of least squares are given.

In order to make this comparison, raw data on number-current relationships in intact rats were obtained from Gallistel and were transformed to show the reciprocal of number vs current, as described above. Linear regressions were then calculated for both our data and Gallistel's data. From here, weighted linear regression lines were calculated, and the resulting slopes and intercepts for each subject are presented in Table 2. The differences between the hemithalamic and intact groups were not statistically significant and, if anything, the intact groups had the greater slope and intercept. These data provide no evidence for a thinning of reward relevant fibers under the electrodes.

Charge-Duration

Only four rats were tested in the charge-duration phase of this experiment and their data are presented as graphs in Fig. 5. The slopes and intercepts of the best fitting regression lines are given for each animal in Fig. 5. Listed in order (left to right, top to bottom), the r^2 values for the proportion of the variance accounted for by those best fitting lines are .994, .997, .997, and .971. All of these values are statistically significant ($p<0.001$). Because Gallistel [9] expressed his results as slopes and intercepts of weighted linear regressions, we so analyzed our data (see [9] for further discussion of weighted linear regressions). Our values are not significantly different from those observed by Gallistel [9] for intact rats. This comparison is made to means of raw data taken from Table 1 of Gallistel's report [9] and is presented in this report in Table 3. Also presented in Table 3, is the chronaxie of the current-duration function. This statistic can be calculated by dividing the intercept of the charge-duration function by its slope [9]. When this was done for our data, the mean result, as expected, was insignificantly different from the mean of the chronaxies reported by Gallistel for intact rats [9]. These findings do not support the idea that ipsilateral hemiforebrain ablations impair the integration processes whereby discrete pulses of lateral hypothalamic stimulation are summed to produce reward.

Histology

Reconstructions of the hemiforebrain ablation and the electrode tip location are plotted for each rat in Fig. 6 with

TABLE 2

RECIPROCAL OF NUMBER-CURRENT RELATIONSHIP WEIGHTED LINEAR REGRESSION

Animal number	Slope	Intercept
Hemiforebrain Ablated:		
JI 10	8,162	58.8
JI 15	7,932	15.5
JI 18	13,368	4.5
JI 20 "E"	14,022	15.0
JI 20 "H"	19,292	99.8
MS 10	18,507	13.4
Mean	13,547	32.8
SEM	1,986	15.8
Intact*:		
1	13,715	43.3
2	19,426	31.3
3	22,155	40.4
4	12,199	77.3
5	16,148	26.1
Mean	16,728	43.7
SEM	1,825	9.0
Comparison		
t Value	0.697	0.570
Significance	none	none

*Raw data were given to us by Gallistel for this analysis.

the exception of MS 10 whose brain was damaged in sectioning. For all rats, nearly complete destruction of ipsilateral neocortex and hippocampus was achieved. In the case of other targets, particularly the septum and nucleus accumbens, the results varied. Typically, the amygdala was largely spared. In JI 10, most of the accumbens, septum and caudate-putamen were ablated unilaterally with damage to the septum occurring bilaterally. In JI 15, the septum received minor damage while the nucleus accumbens, globus pallidus, and ventral medial portions of the caudate-putamen were spared. Results from the other two animals are intermediate, with greater damage to the caudate than in JI 15 but without major damage to the nucleus accumbens, and only some damage to the septum.

It should be noted that despite sparing of primary damage, many structures underwent secondary degeneration. For example, ipsilateral degeneration was readily observed in some thalamic nuclei, septum, and fiber tracts such as the fornix and internal capsule. The corpus callosum was smaller on the contralateral side. Less obvious but still present was secondary ipsilateral degeneration in the amygdala and medial forebrain bundle, particularly in JI 10.

These lesions are nearly, but not quite as extensive unilaterally as the bilateral ablations discussed previously [15,16].

GENERAL DISCUSSION

The clear conclusion of this study is that despite substantial loss of forebrain tissue rostral to the lateral hypothalamic electrode site, the neural process which translates the elec-

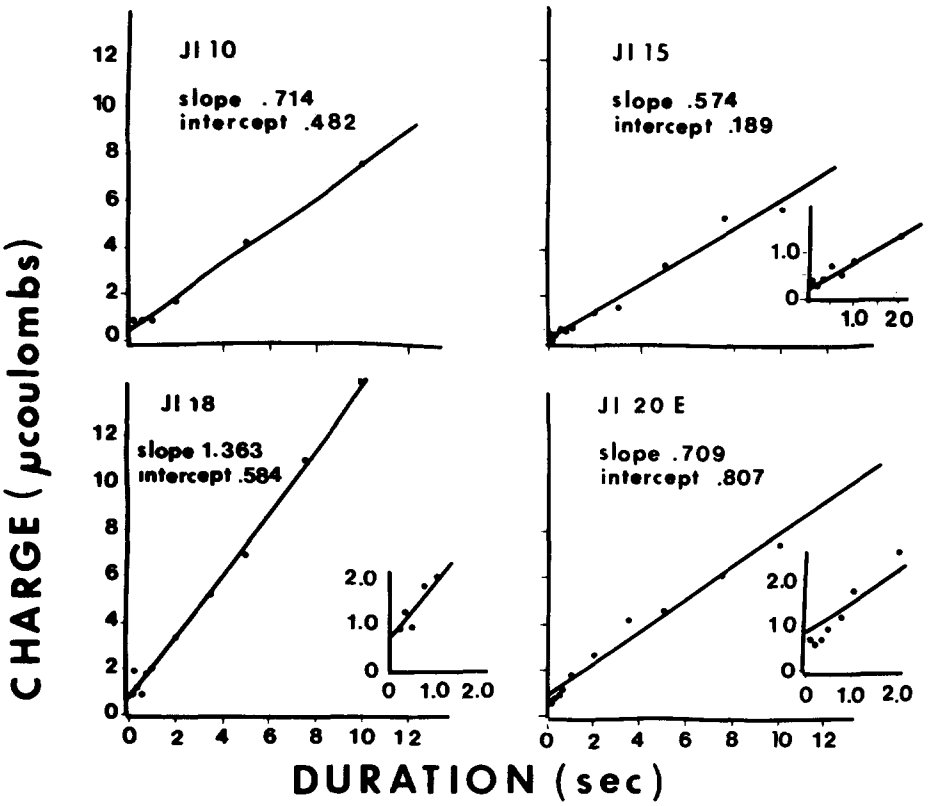

FIG. 5. Relationship between overall charge and duration of reward stimulation is plotted for four animals. Inset shows expansion of the origin of the axis. Slope and intercept of the best fitting lines calculated by the method of least squares are given.

trical stimulation into reward is not impaired. Such a conclusion was suggested by the results of the first experiment where rats were able to be trained to perform normally in the runway for lateral hypothalamic reward and by similar findings by Huston *et al.* [17]. However, the real strength of the conclusion rests on the two fundamentally different measurements of the reward process made in the second experiment.

The first experiment examines how increases in current recruit into firing additional neurons at the fringe of the stimulation field. It determines how much the current must be increased to offset a decrease in the number of pulses within one stimulation burst, and it gives information on the arrangement of directly excited axons in the medial forebrain bundle [10]. If neurons which originate in the ipsilateral frontal cortex and descend through the medial forebrain bundle actually do contribute substantially to the reward of hypothalamic stimulation [24,25], then they should be lost following the forebrain ablation. Greater increases in current would then be required to offset the same decreases in number and a greater slope in the current vs reciprocal of the number plot would be observed. We did not observe this; hence, we find no support for the idea that ipsilateral frontal cortex contributes to the reward of lateral hypothalamic stimulation in this fashion. This agrees with other research showing that frontal cortex self-stimulation does not involve the medial forebrain bundle [2].

The second measurement concerns the integration of rewarding pulses over time, which presumably takes place at some distance from the hypothalamic site [10]. Here, total excitation, as signified by total charge given to the brain, is traded off against the duration over which that charge is applied. Since the integrator "leaks," the charge required to keep reward constant increases as duration is extended and this leak is reflected in the slope of the charge-duration function [9]. If the rate of leak was increased by the forebrain damage, the slope of this function should be steeper, indicating more charge was required for each additional second of duration. The intercept of the charge-duration function represents the theoretical charge required to generate the chosen level of reward if it could be delivered over an infinitesimal duration [7]. If forebrain damage reduced the effectiveness of charge in activating reward, then the intercept of the charge duration function should be elevated over that of intact rats. Since neither of these outcomes was observed, no support can be given to the specific hypotheses that either the ipsilateral sulcal [1] or medial prefrontal cortex [6, 22, 23, 25] play a large role in hypothalamic brain stimulation reward. This conclusion is stronger in the latter case since the prefrontal cortex was always removed while the sulcal region was severely damaged only in some cases. Additionally, this conclusion can be generalized to any structure within the ablated region.

These findings are also interesting in light of the hypothesis that hypothalamic stimulation reward depends on the activation of the ascending midbrain dopamine systems [1, 4, 8, 29, 30] because it focuses attention on the extent to which unilateral hypothalamic stimulation can have contralateral as

TABLE 3

CHARGE-DURATION RELATIONSHIP WEIGHTED LINEAR REGRESSION

Animal number	Slope	Intercept	Chronaxie
Hemiforebrain Ablated:			
JI 10	0.622	0.649	1.043
JI 15	0.536	0.243	0.437
JI 18	1.346	0.621	0.461
JI 20 "E"	0.859	0.535	0.623
Mean	0.841	0.510	0.140
SEM	0.182	0.095	0.140
N	4	4	4
Intact*:			
Mean	1.217	0.566	0.453
SEM	0.128	0.301	0.140
N	12	12	12
Comparison			
t Value	1.52	0.347	1.98
Significance	none	none	none

*Taken from [9] Table 1.

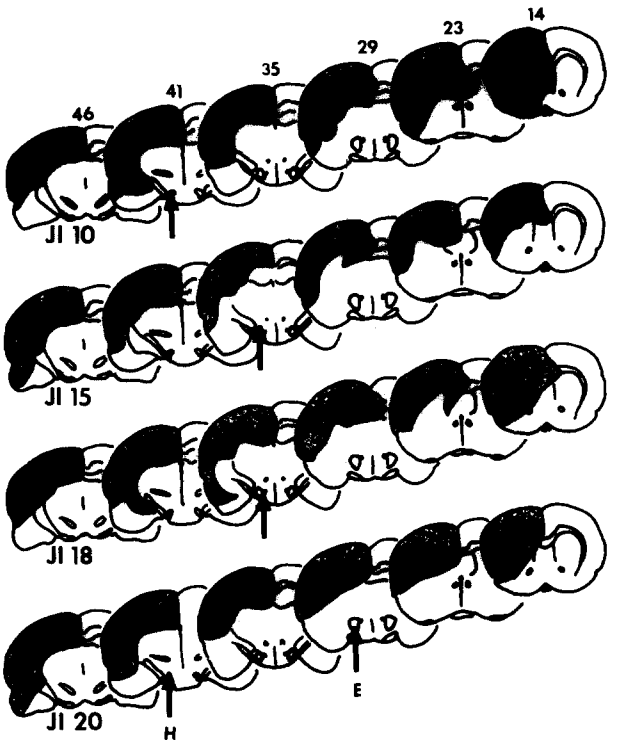

FIG. 6. Reconstructions of forebrain ablations for four animals plotted on plates of the atlas of König and Klippel [18]. Only primary tissue loss is plotted. Corresponding secondary degeneration in related structures (e.g., thalamus) is not shown. Plate numbers are given above the array and the animal is indicated at the lower left for each row. Electrode tip locations are indicated by the tip of the vertical arrows. JI 20 carries two electrodes as shown. The electrode tip for JI 10 shown on plate 41 was actually best plotted on plate 40, while JI 15's electrode tip shown on plate 35 was actually at plate 38. Dorsal-ventral and medial-lateral relationships were preserved when collapsing these two electrode tip locations onto the plates of this figure.

well as ipsilateral effects. Anatomically, the midbrain dopamine systems have been thought to project primarily ipsilaterally [20] but some crossed projections do occur [7], and these might sustain function in this preparation through direct connections to contralateral structures that were ablated ipsilaterally. However, these contralateral projections are weaker than the ipsilateral ones [7], and a shift to such a diminished substrate would be expected to show up in the behavioral measures [9].

On other grounds, the hypothesis of direct dopamine activation by the self-stimulation electrode has been called into question. Recent quantitative work characterizing the reward substrate has shown that the behaviorally measured velocity of action potential conduction is much too high [10] to be compatible with the conduction velocity of the small unmyelinated neurons of the midbrain dopamine systems [13,14]. In addition, the current required to fire the dopamine axons as measured by recordings from the cell body region is much higher than needed to induce vigorous self-stimulation [9, 10, 31]. However, this quantitative work does suggest that the fibers subserving lateral hypothalamic self-stimulation run through the midbrain tegmental area [26], and some are believed to be descending [27]. This provides for a possible descending pathway leading to indirect activation of the dopamine neurons which could then participate as a second stage in the elaboration of the self-stimulation reward process [30]. At least two recent studies [19,28] in addition to the present report, agree with the notion of a descending pathway. Neurons belonging to such a pathway might escape the hemiforebrain ablation and provide strong direct connections to the contralateral dopamine cells which could then function to convey the reward signal on the intact side of the brain. Major descending fibers of the medial forebrain bundle are known to originate from the septal and lateral preotpic-hypothalamic area [20], and some of these fibers were missed in our hemiforebrain ablations.

Finally, it should be noted that other possibilities exist outside the descending-path hypothesis, as discussed above. For example, non-dopamine targets of the numerous brainstem connections of the medial forebrain bundle [25], direct forebrain commissures [17], and remaining ipsilateral forebrain tissue which may still receive dopaminergic input [20,29] could be acting to serve as part of this reward substrate. However, whatever pathway remains in our subjects, it must be able to sustain normal or quite nearly normal function. Further research in this area will be required to continue to narrow the possibilities. If lesions, ablation, or transections are used to disrupt the pathway(s), then quantitative behavioral measurement techniques should be employed to assess the extent of the disruption of hypothalamic reward.

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