tively short periods of time after training, but more intense amnesic treatments will be effective for longer periods of time after training. We do not know the asymptote of the effective training-treatment interval, nor do we know whether there is an asymptote. Is it possible—at least in theory—to disrupt memory at any time after training if a treatment of sufficient amnesic intensity is administered? Such thinking raises the possibility of continuity between ECS-produced RA gradients (up to several hours) and some drug treatments that may be disruptive if administered a day or more after training (*7*).

The electrocorticographic recordings made after the stimulation revealed that whereas no animals had brain seizures following 1-ma stimulation of either frontal or posterior cortex, all animals that received 2-ma or more stimulation of either brain site had brain seizures. The precise brain seizure pattern varied with intensity and locus of stimulation; however, the seizure patterns for any one type of stimulation did not vary significantly at different training-treatment intervals.

Thus, although the brain seizure thresholds and patterns did not vary significantly with different training-treatment intervals, the RA threshold increased with time after training. Under the conditions of the present experiment, brain seizures represent a necessary but not always sufficient condition for RA (*8*).

Experimental results have suggested several biological correlates for RA produced by ECS and brain stimulation; among these correlates are brain seizures, postictal depression, long-term changes in brain electrical activity, neurochemical changes, and behavioral convulsions (*6, 9, 10*). It now seems clear that there will indeed be many correlates of RA as a direct consequence of the increase in the RA threshold with time after training. Since both RA thresholds and RA gradients are influenced by a host of factors—including prior experience, the measure of retention, many task variables, and the method of ECS administration (*2, 3, 10*)—reports of many different neural correlates of memory disruption can be anticipated.

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Directionality of Rewarding Impulses within the Medial Forebrain Bundle Self-Stimulation System of the Rat

Abstract. *Self-stimulation performance of rats was tested with conditioning pulses to the anterior preoptic area of the medial forebrain bundle followed at various intervals by test pulses to the contralateral posterior hypothalamic area of this bundle. Alternatively, conditioning pulses were delivered through the posterior electrode and test pulses were sent through the anterior electrode. The animals' performance in these two test sequences was indicative of (i) synaptic facilitation and (ii) a posterior convergence site of "self-stimulation impulses" in the medial forebrain bundle.*

Facilitation of synaptic effects can be demonstrated by applying conditioning (C) and test (T) stimuli to different presynaptic neurons and recording the electrophysiological response from the postsynaptic neurons onto which they converge. To study this phenomenon in heteronymous synergistic motoneurons, for example, Lloyd (*1*) stimulated two afferent branches of the biceps femoris muscle in the cat. The C pulse to one nerve was insufficient to elicit a motoneuronal discharge, while the T pulse to the other nerve did produce a motoneuronal discharge. Stimulating both nerves simultaneously produced a maximal motoneuronal response that was considerably greater in magnitude than that produced by the T pulse alone. As the interval between C and T stimuli (C-T interval) was increased, the magnitude of the response decreased until there was no facilitation with an interval of 14 msec.

In an analogous fashion, Ungerleider and Coons (*2*) demonstrated facilitation of the rewarding effects produced by bilateral stimulation of the medial forebrain bundle (MFB). Rats were taught to press a lever for a train of C-T pulse pairs (*3*) delivered to the MFB. The C pulses were sent through one MFB electrode, and T pulses were sent through the contralateral homologous MFB electrode. The self-stimulation behavior of rats was maximal for pulse pairs with a 0.1-msec C-T interval and was considerably greater in magnitude than for C pulses alone. As the C-T interval was increased, the self-stimulation performance decreased. Thus, these behavioral data suggest that impulses from opposite sides of the brain converge upon a common neuronal system whose output mediates the rewarding effects of MFB electrical self-stimulation. The MFB pathways are represented bilaterally in the brain, contain both ascending and descending fibers, and converge in a number of areas (*4, 5*). For example, some ascending fibers converge in the forebrain (for instance, septal area) and some descending fibers converge in the midbrain (for instance, ventral tegmental area). Because electrodes in the above study (*2*) were bilaterally placed in homologous MFB sites and self-stimulation performance increased as the length of the C-T interval was decreased, the site of convergence seemed to be equidistant from the two stimulating electrodes.

Therefore, clear differentiation between possible convergence sites was not possible.

The purpose of the present experiment was to differentiate between anterior versus posterior MFB self-stimulation convergence. Accordingly, electrodes were implanted in MFB-related anterior and contralateral posterior areas. We postulated that by varying the C-T interval with the C pulses delivered through the anterior electrode and T pulses through the posterior electrode (Ca-Tp), and by varying the C-T interval with electrodes for the C and T pulses reversed (Cp-Ta), different stimulus-response functions would result depending on whether the self-stimulation impulses ascend or descend within the MFB. More specifically, maximal facilitation should occur at the convergence neurons when the C-T interval results in the simultaneous arrival of action potentials (AP's). For example, if the convergence neurons are located posterior to the MFB and the sequence Cp-Ta is employed, self-stimulation performance should progressively increase as the C-T interval is decreased, because the posterior conditioning electrode is closer to the convergence site than is the anterior test electrode. Under this condition, simultaneous arrival of AP's will only be approached but never reached. When the sequence Ca-Tp is employed, however, simultaneity of AP's should not occur at very brief C-T intervals since the AP's for C pulses will arrive at the convergence site after those for T pulses. At some slightly longer C-T interval, the AP's should arrive simultaneously. The opposite results for the Ca-Tp and Cp-Ta conditions would suggest an anterior convergence site.

Adult male albino rats were bilaterally implanted with indwelling monopolar electrodes (size 00 stainless steel insect pins insulated to within 0.5 mm of the tip). One electrode was placed in the anterior preoptic area of the MFB and the other was placed in the contralateral posterior hypothalamic MFB. The average difference in anterior-posterior electrode coordinates was 3 mm (*6*). An electrode pin placed rostrally in the animal's skull served as the indifferent electrode for brain stimulation. A week after recovery from surgery, animals were screened for self-stimulation behavior in a sound-attenuated operant conditioning box with a retractable lever. During screening,

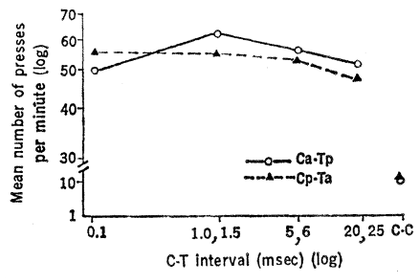

Fig. 1. Mean number of lever presses per minute for bilateral stimulation as a function of the C-T interval. Sequence Ca-Tp represents conditioning pulses sent through the anterior preoptic MFB electrode and test pulses sent through the contralateral posterior hypothalamic MFB electrode. Sequence Cp-Ta represents the opposite pulse-electrode condition. The C-C interval, which was held constant, was 40.0 msec for five rats and 50.0 msec for one rat.

each lever press resulted in the delivery of a 0.5-second train of 0.1-msec negative-going C pulses with an intensity not greater than 200 μa and a C-C interval of 5 msec. Brain stimulation parameters were continuously monitored on an oscilloscope as the animal pressed the lever. To be included in the experiment, an animal had to press the lever at least 30 times per minute for each electrode. The six animals that qualified as bilateral self-stimulators were then trained for two 1-hour sessions to adapt them to some of the succeeding test procedures. These included the priming procedure that preceded each trial, the method of initiating and terminating trials by inserting and retracting the lever, and certain changes in the duration of both the pulse train and the C-C interval.

In bilateral stimulation, C and T pulses were administered to separate electrodes on opposite sides of the brain in either sequence Ca-Tp or Cp-Ta. Each animal was tested for 4 consecutive days for each bilateral sequence. Trials lasted for 1 minute and were separated by 1 minute of rest with the lever absent. Each daily session consisted of five trials for each C-T interval and for C stimulation alone (that is, C-C stimulation). Half of the animals were tested with one set of C-T intervals (0.1, 0.5, 0.8, 1.5, 5.0, and 20.0 msec), and half were tested with a different set (0.1, 1.0, 3.0, 6.0, and 20.0 or 25.0 msec). The order of test intervals (C-C and C-T) were varied from trial to trial according to a 7 by 7 or a 6 by 6 Latin square design depending upon the number of intervals tested. The duration of the train of C-T pulse pairs was 0.6 second per lever press (0.5 second for two animals); the C-C interval, which was held constant, was 40.0 msec for five rats and 50.0 msec for one rat. Half of the animals were tested first under sequence Ca-Tp and then under sequence Cp-Ta, and the other half were tested with sequences in the opposite order.

Rats were primed, just before the lever was inserted, with four trains of pulses at the same interval as those they could self-administer once the lever was inserted into the box. The number of lever presses was recorded for each 1-minute trial. The current for a given electrode was that for which the animal would press the lever approximately 10 times per minute for C stimulation. The average current was 245 μa for the electrodes in the anterior preoptic area of the MFB and 218 μa for those in the posterior hypothalamic MFB.

Figure 1 presents the mean number of lever presses per minute as a function of the C-T interval for both bilateral stimulation conditions. Since previous data suggest that power function curves describe facilitation of behavior (*2, 7*), the data are presented on logarithmic scales. The graphing procedure transforms power curves into straight lines, providing a visual check on the expected behavior. Also, since the self-stimulation performance was quite similar under the two sets of C-T intervals, all six rats were combined for group analysis for the C-T intervals of 0.1 msec, 1.0 or 1.5 msec, 5 or 6 msec, 20 or 25 msec, and for the C-C condition. Because of the sample size and the within-subjects design of the experiment, correlated mean *t*-tests (two-tailed; d.f. = 5) were used to compare lever pressing rates at various C-T intervals.

Under sequence Ca-Tp, lever pressing rates were higher at C-T intervals of 1.0 or 1.5 msec than at those of either 20 or 25 msec ($t = 2.81$, $P < .05$) or 0.1 msec ($t = 2.56$, $P < .06$). Under condition Cp-Ta, however, lever pressing increased in a linear fashion as C-T intervals were reduced from 20 or 25 msec to 0.1 msec ($t = 4.66$, $P < .01$), with a slight but nonsignificant increase when the interval was reduced from 1.0 or 1.5 msec to 0.1 msec. Furthermore, self-stimulation rates did not differ significantly between the Ca-Tp and Cp-Ta sequences at C-T intervals of 0.1 msec, 5 or 6 msec, or 20 or 25

msec. However, at the C-T interval of 1.0 or 1.5 msec, self-stimulation rates under sequence Ca-Tp were significantly higher than those under sequence Cp-Ta ($t = 2.57$, $P < .05$). As an independent test, average rank order correlations (*8*) were performed to compare differences in C-T response curves for the Ca-Tp and Cp-Ta sequences with two model curves. The monotonic model described an increase in self-stimulation rate with decreases in the C-T interval. The inverted-U model was a self-stimulation curve with a maximum at a C-T interval of 1.0 or 1.5 msec. The curve for the Ca-Tp sequence showed a significant correlation with the inverted-U curve ($P < .03$) but a nonsignificant correlation with the monotonic curve. Conversely, the Cp-Ta data correlated significantly ($P < .01$) with the monotonic curve but nonsignificantly with the inverted-U curve. These results suggest that self-stimulation impulses converge from nonhomologous sites on opposite sides of the brain, and this convergence seems to occur posterior to the MFB.

The existence of facilitation is suggested by two major findings. (i) Although the animals would press approximately 10 times per minute for anterior or posterior stimulation alone (that is, C-C stimulation), response rates were many times higher when both areas were stimulated (that is, C-T stimulation). (ii) As the C-T interval was decreased, the self-stimulation rate increased. This latter effect was clear with sequence Cp-Ta at all C-T intervals, and was also seen with sequence Ca-Tp from the longest to a shorter C-T interval (1.0 or 1.5 msec). The fact that there was still significant facilitation at the C-T interval of 20 or 25 msec suggests prolonged synaptic effects on the convergence neurons.

The present data also support the hypothesis of a posterior convergence of MFB self-stimulation impulses. Under sequence Cp-Ta, an increase in self-stimulation occurred as the C-T interval was decreased, indicating that impulses were converging more closely in time. Under sequence Ca-Tp, however, the self-stimulation rate increased as the C-T interval was shortened, until maximal convergence was reached. As the C-T interval was shortened further, self-stimulation rates declined because of the decreased contiguity of AP's at the convergence site.

Our evidence for facilitation from the activation of nonhomologous MFB sites is consistent with the data of Ungerleider and Coons (*2*), who stimulated homologous MFB sites. Taken together, these studies suggest that impulses initiated from various bilateral MFB areas converge from opposite sides of the brain onto a common neuronal area whose output mediates the rewarding effects of MFB electrical self-stimulation. Furthermore, the present data suggest that this convergence area is posterior to the MFB. The most prominent posterior area of MFB degeneration after lateral hypothalamic lesions are made is the "limbic midbrain area" (*4*), which encompasses the ventral tegmental area, the ventral half of the periaqueductal gray substance, and the reticular cell groups of Bechterew and Gudden. Although the ventral tegmental area receives degenerated fibers bilaterally from the MFB (*4*), bilateral convergence could occur at a number of brain stem nuclei, because there is no consensus concerning the posterior termination of the MFB (*9*). While the present data do not exclude the possibility of anterior convergence of impulses from our electrodes, the convergence most relevant to self-stimulation seems to be at a posterior site.

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