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# TWO SEPARATE SYNCHRONIZING MECHANISMS IN THE BASAL FOREBRAIN: STUDY OF THE SYNCHRONIZING EFFECTS OF THE ROSTRAL HYPOTHALAMUS, PREOPTIC REGION AND OLFACTORY TUBERCLE

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# TWO SEPARATE SYNCHRONIZING MECHANISMS IN THE BASAL FOREBRAIN: STUDY OF THE SYNCHRONIZING EFFECTS OF THE ROSTRAL HYPOTHALAMUS, PREOPTIC REGION AND OLFACTORY TUBERCLE [1]

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## INTRODUCTION

The existence of a powerful synchronizing system in the basal forebrain has been proved by several experiments (31, 25). Although the dimension of this area decreases in the course of phylogenesis (18), nevertheless, it was considered to be of great importance in generating sleep even in mammals (30). It has been suggested that various parts of the basal forebrain have a synchronizing influence. In studying the effect of high and low frequency stimulations, Sterman and Clemente (43, 44) located the synchronizing area in the ventral part of the preoptic region and the diagonal band of Broca. Bremer (4, 5) suggested the existence of a synchronizing strip extending from the basal part of the lateral hypothalamus to an undefined rostral region. Using the method of warming circumscribed areas, it was found, however, that cortical synchronization and sleep was elicited most effectively from the medial preoptic region (3, 35). Both synchronization and sleep were brought about by cholinergic stimulation of various parts of the basal forebrain; the pyriform cortex, preoptic region, olfactory tubercle and the hypothalamus (15). An adynamic state (16) and

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cortical synchronization (7) was reported resulting from the stimulation of the anterior hypothalamus. Since the stimulation of the orbital cortex also brings about sleep (21, 41), and inhibits both somatic reflexes (37) and hypothalamically induced attack behaviour (40), a widespread area of the basal forebrain, from the anterior hypothalamus to the orbital cortex, may be supposed to play a part in behavioural and electrophysiological inhibition.

The purpose of the present experiment was to map the synchronizing structures by systematically stimulating the area between the anterior hypothalamus and the olfactory tubercle. Two distinct synchronizing areas and a purely desynchronizing area in the basal forebrain were distinguished in a study of the effects of both low and high frequency stimulations on the cortical and hippocampal electrical activity. Since the basal forebrain structures have been reported to be sensitive to anaesthetics (8, 13), unanaesthetized immobilized cats were used. By avoiding painful stimuli as far as possible, fairly controllable conditions could be obtained.

## Methods

Experiments were carried out on 62 male or female cats weighing between 2.5 and 4 kg. Under ether anaesthesia, the trachea and the vena femoralis were cannulated and the animals were fixed in a stereotaxic instrument. Removing the calvaria, the left eyeball and the dura, the convexity and the orbital surface of the brain were exposed. All pressure points and wound edges were infiltrated with 1% procaine. The local anaesthetic procedure was repeated hourly during the experiments. When surgery was completed, other anaesthesia was discontinued. Gallamine triethiodide (Flaxedyl) was administered intravenously and artificial respiration was introduced. Body temperature was kept at 37° C by placing the animal in a thermostate box. Blood pH and $pCO_2$ were also controlled (Astrup method). Polyglukin and glucose solutions were administred repeatedly throughout the experiments.

For unipolar recording, silver ball electrodes were placed over the gyrus coronarius (C), gyrus sigmoideus anterior (SA), gyrus suprasylvius medius (SSM) and a silver electrode was introduced into the dorsal hippocampus (Hipp), (Fr, 3.0; L, 6.0; V, 7.0). An indifferent electrode was placed on the tongue of the cats.

Electrical stimulation was applied ipsilaterally by means of bipolar concentric electrodes of 0.5 mm tip-barrel distance. Square wave pulses (frequency: lo cps and loo cps, pulse duration: 0.5 msec, amplitude: 250 $\mu$A) were applied through an isolation unit in trains of 10 sec. The stimulated points were located between the frontal 12 and 18 planes, in a region between the vertical zero plane and the basal brain surface, with a lateral width of six mm. The frontal 18.5 plane of the stereotaxic atlas (17) was used to illustrate the results of stimulating the olfactory tubercle (Fr, 18.0), since according to histological examinations, it corresponded to the stimulated area.

At the end of each experiment, the brain was perfused with isotonic saline and 10% formalin. After embedding the brain in parafine, serial sect-

ions of 10 $\mu$ were stained by means of the Klüver-Barrera technique. Results obtained with electrodes showing a deviation of 0.5 mm or more from the aimed coordinates were excluded on the basis of histological examination of the electrode tracks.

Every synchronization evoked was scored visually on an arbitrary scale of zero to three degrees for purposes of statistical evaluation. The results obtained at each coordinate point in 4-23 individual experiments are summarized in Table I to III, as well as in Fig. 1 and Fig. 2 in columns indicating the synchronizing effects. The percentage values corresponding to the various degrees of the subjective scale were calculated, and the synchronizing effect (S) was expressed as the weighted sum of the percentage values. In Figs. 1 and 2 only sites yielding a sum over 60 were marked by columns. The EEG changes characterized by an increase in amplitude or the appearance of slow waves were considered to be synchronizations. The standard deviation (C and SA) and integrated values (SSM, Hipp) of 10 sec EEG epochs determined by a computer (CII 1010/B) were used to quantitatively evaluate the EEG changes in 16 cats during and after stimulation. The preamplified EEG epochs sampled at a rate of 200/s were fed into the computer through a four channel AD converter. To analyse the effect of a single stimulation, five 10 sec long EEG epochs were processed; one before, one during and three after the stimulation. The prestimulus values were taken to be 100% and the percentage deviations obtained in the subsequent epochs were used in the statistical evaluations. Findings from 6-14 tests obtained at each coordinate point were averaged and the standard error of mean (S.E.M.) was calculated (Figs. 3 and 4), Table I to III.

## Results

Various distinct structures in several planes of the basal forebrain were stimulated. The area included the hypothalamus at the rostral pole of the nucl. ventromedialis, the preoptic region, olfactory tubercle, anterior commissure, the ventral part of the thalamus, the medial edge of the internal capsule and certain parts of the striopallidal system. The low frequency stimulation of most of the structures resulted in cortical synchronization. However, we also observed regions in which low frequency stimulation did not produce cortical synchronization. Several synchronizing areas were found which varied as to type, cortical distribution and aftereffect of the stimulation, in their response to high frequency stimulations and changes induced in hippocampal activity. The visually estimated responses to low frequency stimulation are illustrated in Fig. 1 as well as in Table I-III. The heights of columns at the stimulated points correspond to the synchronizing effects. Since specific evoked responses following the frequency of stimulation, like the appearence of the recruiting-type EEG activity or spindles, were regarded as synchronizations, the internal capsule was depicted as a synchronizing structure like the thalamus or other parts of the

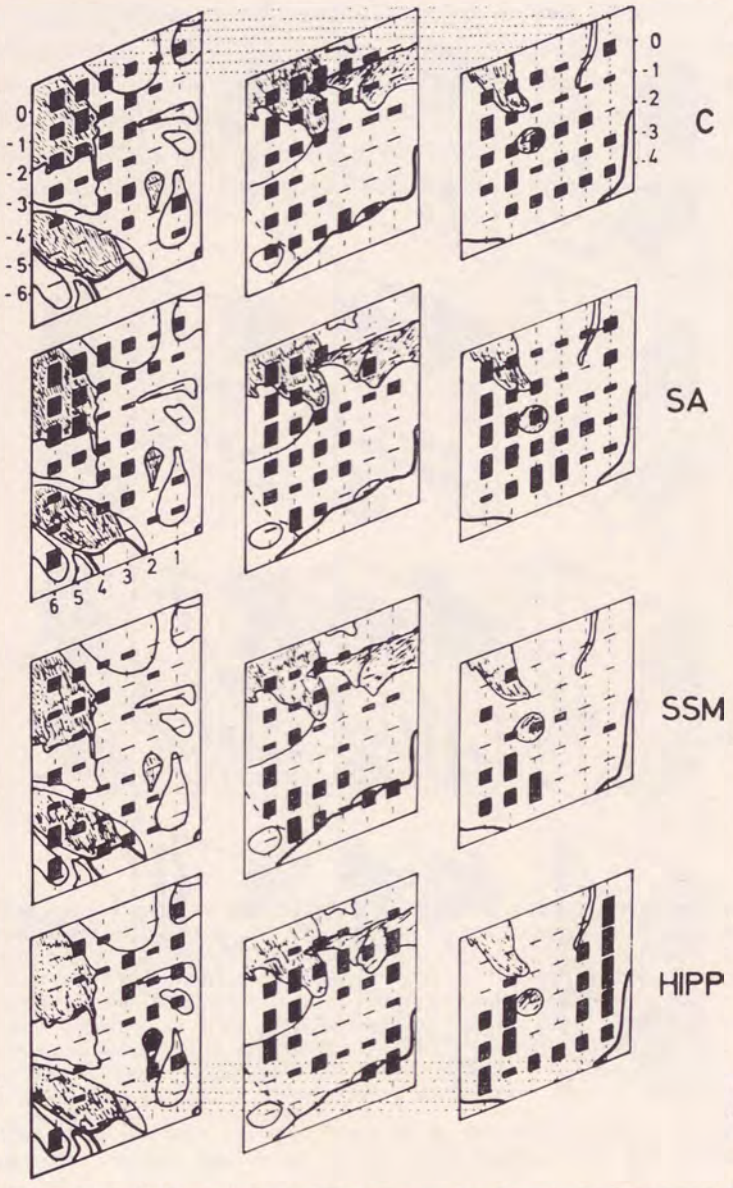


Fig. 1. – *Stimulation sites in the basal forebrain resulting in cortical and hippocampal synchronization upon low frequency stimulation.*

The frontal diagrams at the level of the rostral hypothalamus (Fr, 12), preoptic region (Fr, 15) and olfactory tubercle (Fr, 18) were taken from the Jasper, Ajmone-Marsan stereotaxic atlas. The height of the columns in the stimulation sites corresponds to the mean degree of synchronization estimated visually. Ineffective points are indicated by minus signs. Each row of diagrams indicates the effect of the stimulations on different derivations; C: gyrus coronarius; SA: gyrus sigmoideus anterior; SSM: gyrus suprasylvius medius; Hipp: dorsal hippocampus.

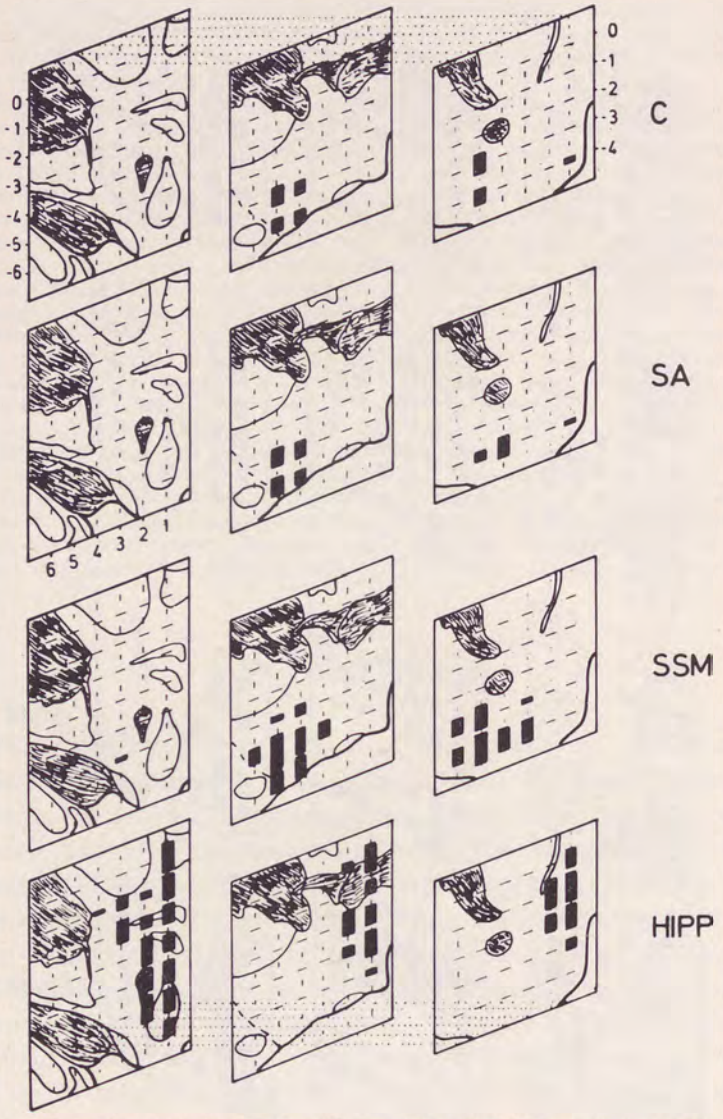


Fig. 2. – *Stimulation sites in the basal forebrain resulting in cortical synchronization and hippocampal theta activity upon high frequency stimulation.*

For abbreviations and explanations see Fig. 1.

bašal forebrain. At the level of the rostral hypothalamus, the synchronizing area was confined mainly to the lateral part of the plane, but it progressively increased in width rostrally. This phenomenon can be primarily observed in the maps of C and SA (Figs. 1 and 3).

SSM synchronizing points were restricted to the laterobasal areas in every plane studied (Figs. 1 and 4). Low frequency stimulations of the medial parts proved to be most effective in synchronizing the hippocampal activity. The areas synchronizing the cortex and the hippocampus were found to be distinct; this separation was most conspicuous at the level of the rostral hypothalamus.

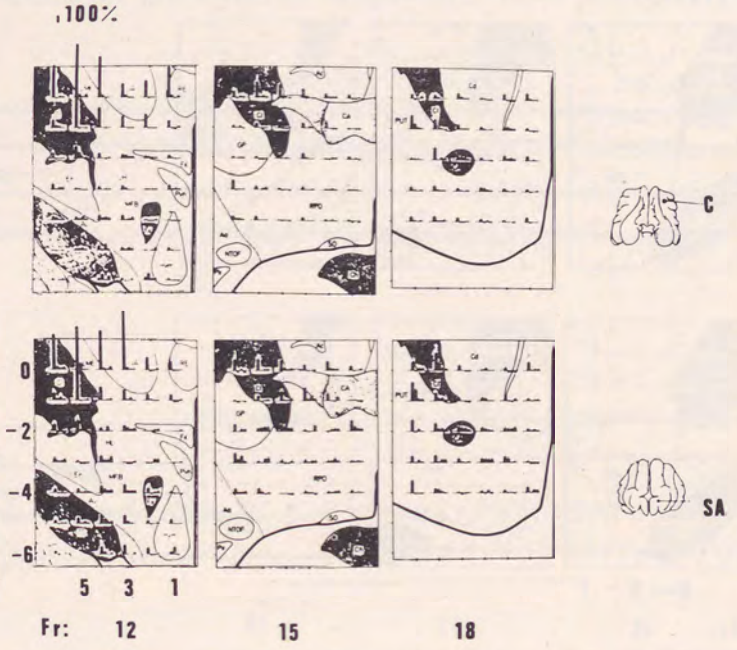


Fig. 3. – Computer evaluated synchronizing effects and aftereffects of low frequency stimulations in the rostral hypothalamus (Fr, 12), preoptic region (Fr, 15) and olfactory tubercle (Fr, 18) on C and SA.

10 sec EEG epochs were characterized by standard deviation values. The height of the columns indicates the percentage deviation from the baseline value obtained in a 10 sec epoch prior to stimulation. The first column at each stimulation point represents the effect of the stimulation, the three subsequent columns correspond to the aftereffects. Outline diagrams were taken from the Jasper, Ajmone-Marsan stereotaxic atlas. The recording sites are indicated on the right.

The distribution of cortical and hippocampal synchronizing points obtained by high frequency stimulations reveals a completely different pattern (Fig. 2). In contrast to the medio-dorsal distribution of the synchronizing sites obtained by low frequency stimulation, a narrow strip-like area inducing cortical synchronization was found in the laterobasal part of the preoptic region and

olfactory tubercle. The most pronounced response produced from this area was observed over the SSM. In evaluating the hippocampal effects, we disregarded the high voltage irregular synchronized activity accompanying the cortical synchronization elicited from the ventral synchronizing area and illustrated only theta induc-

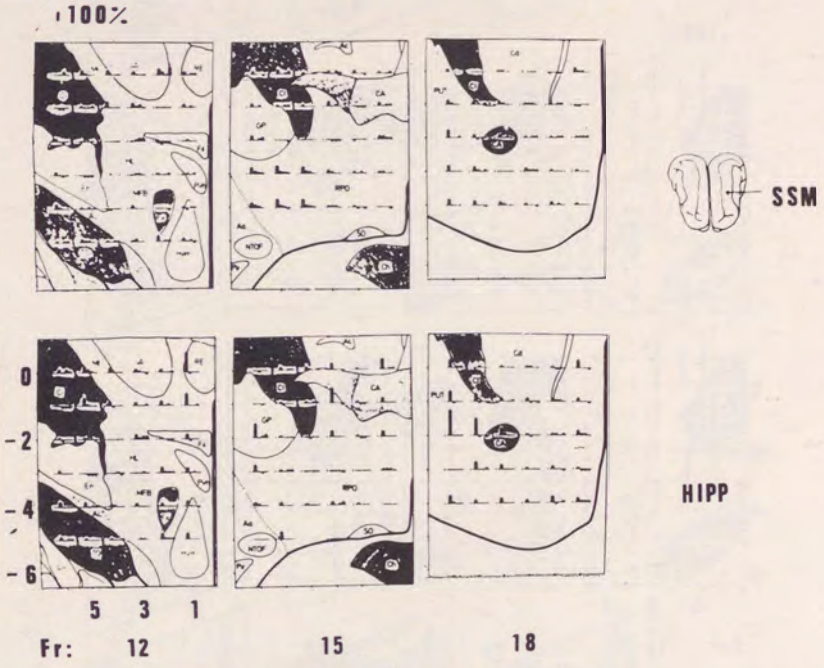


Fig. 4. – Computer evaluated synchronizing effects and aftereffects of low frequency stimulations in the rostral hypothalamus (Fr, 12), preoptic region (Fr, 15) and olfactory tubercle (Fr, 18) on SSM and Hipp. Ten sec long epochs were characterized by integrated values.

ing points (Fig. 2). Theta activity could be obtained by stimulating both the medial parts of the regions investigated and the dorsal part of the lateral hypothalamus.

At the level of the rostral hypothalamus (Fr, 12) synchronizing effects were consistently obtained by low frequency stimulations of the lateral hypothalamus. The most pronounced effect was observed over the motor cortex. The synchronizing effect gradually increased as the electrode was advanced in a dorsoventral direction, and the stimulation of the ventral part of the lateral hypothalamus resulted in synchronization over the SSM as well. Synchronized

aftereffects over C and SA, particularly on stimulating the ventral parts, followed the stimulations (Fig. 3). The synchronization was similar to the recruiting responses obtained by the stimulation of the nonspecific thalamic nuclei (Fig. 5). The high frequency stimulation of the area resulted in cortical and hippocampal desynchronization, while stimulation the dorsal part of the lateral hypothalamus often elicited hippocampal theta activity.

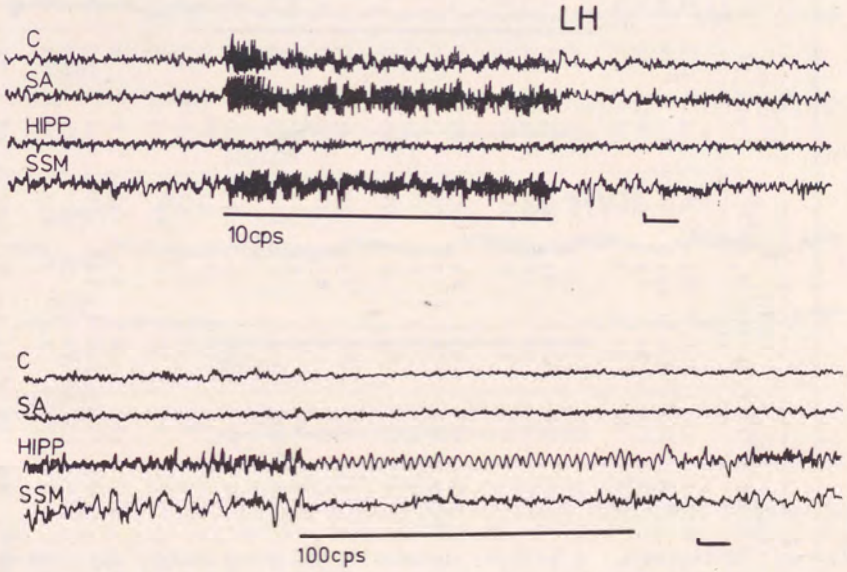


Fig. 5. – Top: Cortical synchronization induced by low frequency stimulation of the lateral hypothalamus (LH). Bottom: Cortical desynchronization and hippocampal theta activity induced by high frequency stimulation of the lateral hypothalamus. Calibration: 100 $\mu$V and 1 sec.

Low frequency stimulation of the medial hypothalamus failed to induce cortical synchronization (Figs. 1-4 and Table I), apart from the slight effect on C, and sometimes even resulted in desynchronization (Fig. 6). At the same time, a high voltage synchronization following stimulation frequency appeared in the hippocampus. Characteristic theta activity accompanied by cortical desynchronization was observed by stimulating the medial hypothalamus with 100 cps. Both low and high frequency stimulations were often followed by theta aftereffects.

Slight cortical and considerable hippocampal synchronizations

TABLE I. – *Comparison of the subjective (visual) and computer assessment of the synchronizations over the gyrus coronarius (C), gyrus sigmoideus anterior (SA), gyrus suprasylvius medius (SSM) and in the hippocampus (Hipp) upon the stimulations in the frontal 12 plane of cats (Jasper, Ajmone-Marsan atlas). The ventral and lateral coordinates are presented on the top and right side of the table.* Subj.: values (S) expressing the summed effect of the stimulations, obtained by visual scoring of the effect of the stimulations in different experiments. Comp.: percentage increase of the amplitude values during stimulations from the prestimulus values calculated by the computer. S is defined by the formula $S = 100/n\ (n_1 + 2n_2 + 3n_3)$, where n is the total number of experiments considered, $n_1$, $n_2$, and $n_3$ are the numbers of stimulations resulted in a synchronization of one, two and three degrees, respectively.

Fr, 12

| Lat. | 6 | | 5 | | 4 | | 3 | | 2 | | 1 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Subj. | Comp. $\bar{x}$ S.E.M. | Subj. | Comp. $\bar{x}$ S.E.M. | Subj. | Comp. $\bar{x}$ S.E.M. | Subj. | Comp. $\bar{x}$ S.E.M. | Subj. | Comp. $\bar{x}$ S.E.M. | Subj | Comp. $\bar{x}$ S.E.M. | |
| C | 198 | 486 193 | 246 | 821 185 | 246 | 660 211 | 239 | 196 24 | 96 | 244 118 | 134 | 450 145 | |
| SA | 219 | 514 175 | 271 | 631 221 | 256 | 574 152 | 151 | 859 142 | 126 | 189 72 | 120 | 124 42 | |
| SSM | 136 | 4 14 | 131 | 60 12 | 108 | 58 12 | 111 | 44 13 | 54 | 76 25 | 75 | 42 40 | |
| Hipp | 39 | 39 9 | 118 | 84 21 | 110 | 61 10 | 50 | 41 9 | 33 | 37 4 | 186 | 230 84 | 0 |
| C | 143 | 115 46 | 202 | 421 62 | 165 | 292 72 | 152 | 156 72 | 204 | 186 65 | 55 | 112 81 | |
| SA | 200 | 99 47 | 236 | 446 62 | 150 | 189 55 | 150 | 153 34 | 174 | 92 35 | 106 | 84 56 | |
| SSM | 82 | —1 19 | 138 | 18 2 | 99 | 75 29 | 52 | 60 6 | 107 | —4 3 | 29 | 39 3 | |
| Hipp | 55 | 2 12 | 100 | 98 27 | 84 | 64 7 | 102 | 44 6 | 85 | 58 12 | 159 | 157 64 | —1 |
| C | 159 | 68 27 | 133 | 169 56 | 147 | 75 24 | 116 | 47 14 | 35 | 25 9 | 38 | 39 12 | |
| SA | 177 | 102 56 | 191 | 149 46 | 133 | 39 25 | 132 | 86 15 | 30 | —3 26 | 54 | —4 5 | |
| SSM | 27 | 41 4 | 135 | —3 17 | 32 | —4 1 | 105 | —3 6 | 28 | —34 2 | 23 | —4 1 | |
| Hipp | 44 | 24 13 | 36 | 17 4 | 46 | —3 2 | 135 | 62 9 | 92 | 15 3 | 93 | 69 5 | —2 |
| C | 121 | 84 32 | 68 | 24 5 | 123 | 49 13 | 67 | 69 15 | 30 | 5 9 | 23 | 58 42 | |
| SA | 124 | 64 23 | 106 | 18 15 | 111 | 89 15 | 118 | 4 12 | 36 | —18 2 | 19 | —3 2 | |
| SSM | 119 | 44 11 | 105 | 1 18 | 43 | —3 1 | 49 | —1 4 | 35 | 16 7 | 44 | —3 7 | |
| Hipp | 60 | 49 13 | 45 | —4 2 | 53 | —2 2 | 100 | —3 1 | 122 | 85 4 | 75 | 67 8 | —3 |
| C | 107 | 45 4 | 43 | 46 13 | 10 | 92 22 | 125 | 86 4 | 25 | 10 14 | 19 | —2 8 | |
| SA | 84 | 53 21 | 81 | 64 24 | 86 | 103 25 | 138 | 126 22 | 37 | 68 45 | 31 | 21 15 | |
| SSM | 97 | 85 10 | 160 | 18 6 | 67 | —1 14 | 81 | 38 21 | 37 | —2 13 | 56 | 23 8 | |
| Hipp | 27 | 80 12 | 81 | 57 12 | 41 | 16 9 | 57 | 36 12 | 148 | 45 2 | 33 | 58 22 | —4 |
| C | 50 | 1 18 | 38 | 19 3 | 38 | 63 41 | 110 | 46 12 | 44 | 6 2 | 140 | 24 9 | |
| SA | 88 | 39 25 | 36 | 82 13 | 114 | 126 34 | 143 | 120 34 | 66 | 42 15 | 110 | 86 21 | |
| SSM | 150 | 23 7 | 130 | 45 3 | 55 | 11 5 | 132 | 22 3 | 77 | 79 32 | 12 | 39 6 | |
| Hipp | 42 | 36 3 | 129 | 10 4 | 42 | 14 5 | 76 | 1 3 | 115 | 79 11 | 132 | 81 12 | —5 |
| C | 50 | 23 7 | | | 60 | 39 8 | 33 | 34 5 | 25 | 43 25 | 87 | 14 7 | |
| SA | 200 | 40 15 | 16 | | 67 | 110 42 | 51 | 135 23 | 75 | 97 15 | 124 | 36 12 | |
| SSM | 150 | | 33 | | 160 | | 140 | | 75 | | 16 | | |
| Hipp | 150 | | 65 | | 100 | | 42 | | 69 | | 39 | | —6 |
| | | | | | | | | | | | | | Ventr. |

were brought about by low frequency stimulations of the rostral part of the ventromedial nucleus.

Low frequency stimulations in the dorsal part of the preoptic region (Fr, 15) resulted in a synchronization in SA similar in every

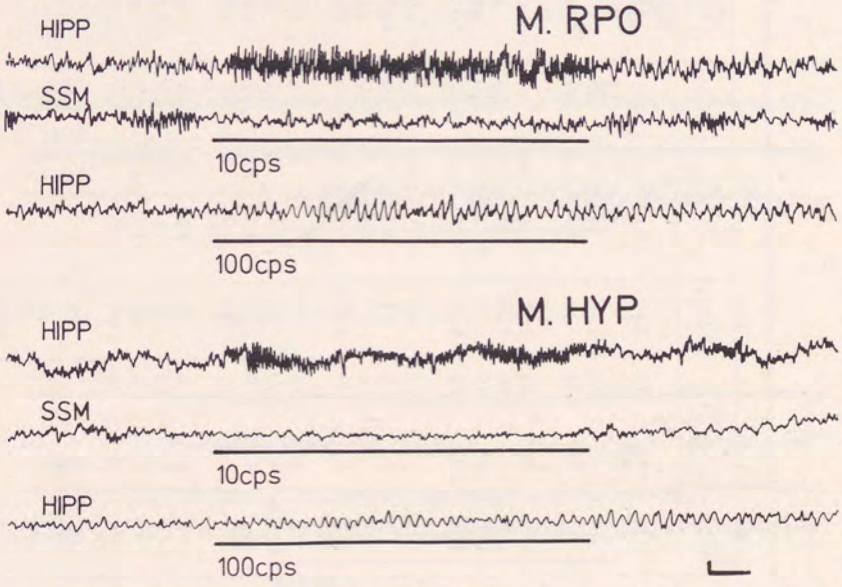


Fig. 6. – Top: Effects of low and high frequency stimulation of the medial preoptic region (M.RPO). Bottom: Effects of low and high frequency stimulation of the medial hypothalamus (M.HYP.). Calibration: 100 $\mu$V and 1 sec.

respect to the synchronization induced from the lateral hypothalamus. High frequency stimulations desynchronized the EEG in every derivation.

A pronounced synchronized activity, that appeared over the SSM, was induced by stimulating the laterobasal part of the preoptic region (Figs. 1 and 4, Table II). The synchronization was characterized by an activity similar to physiological sleep spindles (Fig. 7). Waves following stimulation frequency were observed between the spindles at the beginning of stimulation. They were replaced by slow waves during the course of the stimulation. Synchronization was maintained for some minutes after switching off the stimulation. Recruiting synchronization was observed over the anterior cortical areas. Sometimes spindles which were of longer

TABLE II. – *Comparison of the subjective (visual) and computer assessment of the synchronizations over the gyrus coronarius (C), gyrus sigmoideus anterior (SA), gyrus suprasylvius medius (SSM) and in the hippocampus (Hipp) elicited by stimulating systematically the frontal 15 plane of cats.*

Fr, 15

| Lat. | 6 | | | 5 | | | 4 | | | 3 | | | 2 | | | 1 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Subj. | Comp. $\bar{x}$ | S.E.M. | Subj. | Comp. $\bar{x}$ | S.E.M. | Subj. | Comp. $\bar{x}$ | S.E.M. | Subj. | Comp. $\bar{x}$ | S.E.M. | Subj. | Comp. $\bar{x}$ | S.E.M. | Subj. | Comp. $\bar{x}$ | S.E.M. | |
| C | 162 | 92 | 15 | 152 | 225 | 88 | 160 | 185 | 20 | 134 | 120 | 12 | 110 | 61 | 15 | 63 | 51 | 23 | |
| SA | 180 | 159 | 96 | 144 | 165 | 54 | 110 | 204 | 32 | 55 | 84 | 25 | 67 | 132 | 53 | 53 | 59 | 32 | |
| SSM | 140 | 40 | 15 | 88 | 63 | 12 | 145 | 16 | 5 | 45 | 40 | 13 | 55 | 30 | 13 | 58 | 16 | 12 | |
| Hipp | 61 | 0 | 25 | 87 | 33 | 15 | 113 | 31 | 27 | 86 | 88 | 31 | 42 | 16 | 7 | 96 | 132 | 84 | 0 |
| C | 140 | 30 | 7 | 124 | 59 | 25 | 135 | 79 | 16 | 122 | 69 | 24 | 101 | 94 | 34 | 49 | —10 | 2 | |
| SA | 150 | 9 | 18 | 120 | 72 | 16 | 36 | 132 | 26 | 21 | 193 | 60 | 129 | 99 | 54 | 75 | 4 | 7 | |
| SSM | 110 | 49 | 13 | 100 | 20 | 7 | 130 | 17 | 6 | 90 | 58 | 26 | 8 | —1 | 12 | 30 | 44 | 12 | |
| Hipp | 98 | 4 | 37 | 113 | 18 | 15 | 96 | 17 | 16 | 200 | 204 | 87 | 143 | 21 | 5 | 132 | 63 | 21 | —1 |
| C | 110 | 24 | 7 | 109 | 20 | 12 | 109 | 54 | 23 | 82 | 72 | 25 | 93 | —3 | 24 | 87 | 28 | 15 | |
| SA | 176 | 103 | 54 | 126 | 44 | 5 | 143 | 93 | 24 | 82 | 24 | 6 | 92 | 14 | 25 | 39 | 148 | 95 | |
| SSM | 110 | 61 | 10 | 121 | 2 | 3 | 90 | —1 | 16 | 40 | —3 | 14 | 70 | —23 | 5 | 99 | 45 | 26 | |
| Hipp | 131 | 175 | 143 | 141 | 18 | 5 | 90 | 1 | 23 | 112 | 81 | 32 | 121 | 15 | 4 | 150 | 70 | 8 | —2 |
| C | 135 | 128 | 45 | 99 | 44 | 20 | 58 | 24 | 6 | 43 | 36 | 12 | 49 | 5 | 9 | 14 | 12 | 14 | |
| SA | 165 | 135 | 42 | 108 | 21 | 3 | 134 | 38 | 5 | 133 | 27 | 30 | 54 | 25 | 10 | 43 | 3 | 5 | |
| SSM | 170 | 83 | 12 | 108 | 115 | 7 | 62 | 94 | 5 | 85 | 43 | 6 | 36 | 15 | 12 | 47 | 22 | 6 | |
| Hipp | 182 | 77 | 46 | 143 | 20 | 4 | 55 | 1 | 23 | 58 | 2 | 23 | 60 | 0 | 11 | 81 | 19 | 5 | —3 |
| C | 137 | 64 | 15 | 95 | 55 | 11 | 92 | 1 | 9 | 78 | 44 | 4 | 42 | 12 | 22 | 32 | 5 | 7 | |
| SA | 135 | 76 | 11 | 110 | 75 | 11 | 130 | 0 | 5 | 113 | 34 | 12 | 51 | 22 | 36 | 43 | 33 | 14 | |
| SSM | 118 | 74 | 13 | 171 | 124 | 5 | 138 | 103 | 3 | 128 | 15 | 9 | 29 | 17 | 14 | 78 | —4 | 2 | |
| Hipp | 63 | 43 | 3 | 82 | 43 | 2 | 90 | 21 | 4 | 91 | 39 | 4 | 90 | 18 | 4 | 96 | 4 | 8 | —4 |
| C | 104 | | | 115 | | | 120 | | | 162 | | | 88 | | | 49 | | | |
| SA | 22 | | | 144 | | | 126 | | | 7 | | | 40 | | | 15 | | | |
| SSM | 11 | | | 171 | | | 81 | | | 32 | | | 48 | | | 99 | | | |
| Hipp | 12 | | | 36 | 98 | 4 | 12 | | | 20 | | | 120 | | | 165 | | | —5 Ventr. |

latency than those over the SSM appeared over the SA. Hippocampal activity was characterized by high amplitude waves.

High frequency stimulation of this area also resulted in cortical synchronization primarily over the SSM (Figs. 2 and 7). Slow wave

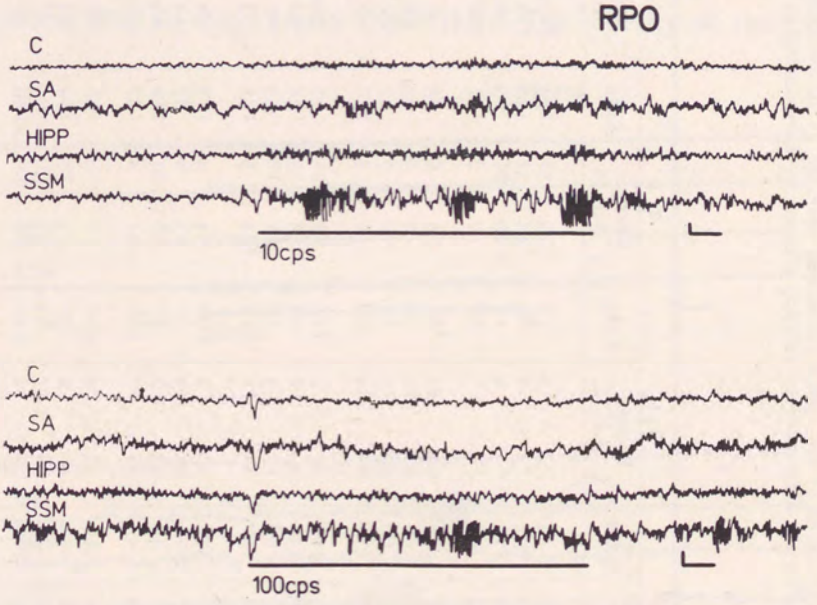


Fig. 7. – Top: Cortical and hippocampal synchronization induced by low frequency stimulation of the laterobasal preoptic region (RPO). Bottom: Cortical and hippocampal synchronization induced by high frequency stimulation of the same point. Calibration: 100 $\mu$V and 1 sec.

activity and spindles were observed even after stimulation was terminated. High amplitude irregular activity appeared in the hippocampus.

The area from which low frequency stimulations elicited synchronization formed a strip in the basal part of the preoptic region. The more laterally stimulation was applied within this strip the more pronounced was the synchronizing effect. Points responding to high frequency stimulations were found in the lateral part of the strip.

The low frequency stimulation of the medial preoptic region brought about a response similar to that obtained from the medial hypothalamus (Fig. 6). Desynchronization was observed over the cortical areas, while the hippocampal activity was characterized

TABLE III. – *Comparison of the subjective (visual) and computer assessment of the synchronizations over the gyrus coronarius (C), gyrus sigmoideus anterior (SA), gyrus suprasylvius medius (SSM) and in the hippocampus (Hipp) elicited by stimulating systematically the frontal 18 plane of cats.*

Fr, 18

| Lat. | 6 | | | 5 | | | 4 | | | 3 | | | 2 | | | 1 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Subj. | Comp. $\bar{x}$ | S.E.M. | Subj. | Comp. $\bar{x}$ | S.E.M. | Subj. | Comp. $\bar{x}$ | S.E.M. | Subj. | Comp. $\bar{x}$ | S.E.M. | Subj. | Comp. $\bar{x}$ | S.E.M. | Subj. | Comp. $\bar{x}$ | S.E.M. | |
| C | 133 | 59 | 12 | 151 | 50 | 10 | 126 | 85 | 21 | 33 | 22 | 3 | 77 | 79 | 51 | 114 | 103 | 24 | |
| SA | 165 | 118 | 27 | 133 | 250 | 101 | 110 | 73 | 15 | 105 | 7 | 4 | 88 | 42 | 31 | 145 | 125 | 45 | |
| SSM | 81 | 43 | 2 | 143 | 0 | 17 | 50 | 15 | 10 | 72 | —1 | 4 | 11 | —20 | 16 | 63 | 59 | 9 | |
| Hipp | 57 | 104 | 12 | 70 | 3 | 8 | 17 | 19 | 23 | 42 | 17 | 8 | 56 | 19 | 3 | 117 | 96 | 25 | 0 |
| C | 159 | 201 | 185 | 123 | 143 | 46 | 107 | 79 | 23 | 74 | 43 | 2 | 84 | 33 | 6 | 85 | 31 | 22 | |
| SA | 182 | 273 | 98 | 163 | 109 | 20 | 126 | 41 | 7 | 96 | 38 | 12 | 70 | 40 | 9 | 93 | 26 | 7 | |
| SSM | 135 | 63 | 26 | 90 | 35 | 4 | 81 | 41 | 3 | 69 | 18 | 15 | 24 | 16 | 7 | 37 | —24 | 5 | |
| Hipp | 50 | 135 | 101 | 99 | 101 | 20 | 44 | 37 | 13 | 30 | 42 | 34 | 99 | 20 | 3 | 150 | 38 | 4 | —1 |
| C | 158 | 18 | 9 | 156 | 159 | 52 | 120 | 44 | 5 | 106 | 27 | 4 | 121 | 61 | 21 | 78 | 59 | 4 | |
| SA | 173 | 159 | 56 | 189 | 116 | 27 | 129 | 73 | 4 | 130 | 49 | 2 | 98 | 43 | 25 | 78 | 51 | 6 | |
| SSM | 40 | 101 | 25 | 117 | 40 | 10 | 140 | 37 | 8 | 98 | 17 | 3 | 40 | 21 | 18 | 53 | 17 | 13 | |
| Hipp | 154 | 237 | 83 | 140 | 215 | 107 | 36 | 93 | 22 | 40 | 21 | 81 | 16 | 24 | 5 | 175 | 73 | 14 | —2 |
| C | 105 | 55 | 9 | 145 | 75 | 3 | 99 | 45 | 6 | 123 | 53 | 4 | 100 | 44 | 4 | 113 | 34 | 7 | |
| SA | 152 | 84 | 16 | 160 | 87 | 2 | 119 | 49 | 7 | 101 | 52 | 3 | 90 | 75 | 6 | 87 | 14 | 23 | |
| SSM | 144 | 80 | 20 | 193 | 64 | 5 | 35 | —2 | 6 | 42 | 43 | 7 | 37 | 18 | 21 | 112 | 19 | 20 | |
| Hipp | 134 | 2 | 20 | 163 | 103 | 24 | 27 | 62 | 13 | 45 | 19 | 17 | 166 | 41 | 2 | 137 | 21 | 3 | —3 |
| C | 30 | 63 | 12 | 135 | 70 | 11 | 110 | 49 | 11 | 116 | 39 | 4 | 101 | 18 | 9 | 96 | 67 | 14 | |
| SA | 139 | 187 | 16 | 162 | 64 | 5 | 156 | 6 | 2 | 144 | 17 | 4 | 90 | 29 | 13 | 114 | 75 | 27 | |
| SSM | 161 | 95 | 3 | 159 | 62 | 2 | 156 | 43 | 2 | 76 | 23 | 7 | 63 | 37 | 9 | 64 | 22 | 17 | |
| Hipp | 141 | 104 | 16 | 117 | 37 | 4 | 129 | 59 | 25 | 160 | 27 | 4 | 122 | 82 | 26 | 120 | 58 | 16 | —4 Ventr. |

by high voltage synchronization. The high frequency stimulation of the same points resulted in hippocampal theta activity accompanied by cortical desynchronization.

A synchronization over C was induced by low frequency stimulations of almost every point on the plane of the olfactory tubercle (Fr, 18, Fig. 1 and Table III). The activity of the SA,

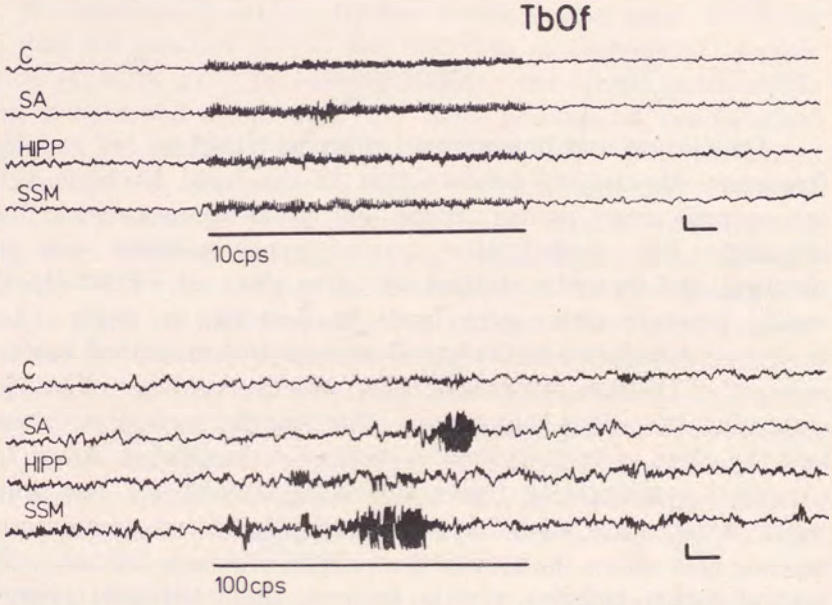


Fig. 8. – Top: Frequency following cortical and hippocampal synchronization induced by low frequency stimulation of the cortical part of the olfactory tubercle (TbOf). Bottom: Cortical and hippocampal synchronization induced by high frequency stimulation of the same point. Calibration: 100 $\mu$V and 1 sec.

was also synchronized by stimulating the same area, while the most medial sites failed to synchronize. The type of synchronization and aftereffects were similar to those described on stimulating the lateral hypothalamus and the dorsal part of the preoptic region.

The same type of synchronization, sustained negativ-positive evoked responses following stimulation frequency, were obtained in every derivation by stimulating the laterobasal part of the olfactory tubercle (Fig. 8). The stimulation produced no aftereffects. High frequency stimulation of this area, *i.e.*, the cortical part of the olfactory tubercle, evoked cortical synchronization (Figs. 2 and 8)

which was characterized by slow waves and spindles, especially over the SSM. Sometimes the synchronized activity persisted even after stimulation was switched off. High amplitude irregular waves were brought about in the hippocampus. Low frequency stimulation of the medial part of the olfactory tubercle induced synchronization following the stimulation frequency in the hippocampus, while high frequency stimulations resulted in theta activity.

## Discussion

The cortical and hippocampal effects obtained by low and high frequency stimulations indicate that in the basal forebrain there are several areas having diverse functional characteristics. On stimulating the medial sites, cortical synchronization was not obtained, and desynchronization was often observed. Rostrally, the medial desynchronizing area tends to decrease in width. Low frequency stimulation in the lateral sites resulted in cortical synchronization. The synchronizing region widens rostrally. The synchronizing area is not homogenous. Keeping the cortical projections and the effect of high frequency stimulation in mind, a dorsal and a ventral synchronizing region can be distinguished. The dorsal region includes the lateral hypothalamus, the dorsal preoptic area and the area above the cortical part of the olfactory tubercle. The ventral region includes a strip between the laterobasal preoptic area and the cortical part of the olfactory tubercle. According to Bremer (5, 6) the ventral region extends into the laterobasal part of the rostral hypothalamus, however, no evidence of this was found in our experiments. Synchronization was produced by stimulating the rostral pole of the ventromedial nucleus but the phenomenon was not studied thoroughly. Similar findings were reported by Morgane (29).

Stimulations in the ventral strip have the following common features: *i*) high frequency stimulation resulting in cortical synchronization with a latency of some seconds; *ii*) the most pronounced synchronizations consisting of spindles and slow waves produced over the SSM; *iii*) synchronizations sustained after switching off the stimulation; *iv*) cortical synchronization accompanied by hippocampal synchronization characterized by high amplitude irregular activity.

The type and cortical distribution of synchronization induced by ventral preoptic stimulations are in agreement with the findings described by Sterman and Clemente (43). The synchronizing effect of the ventral preoptic region was supported by the results of several electrophysiological studies but the synchronization elicited by high frequency stimulation of the olfactory tubercle has not yet been reported.

A considerably wide strip-like synchronizing area, involving the diagonal band of Broca, was described in the ventral preoptic region (5, 6, 8, 43). In our experiments, the lateral parts of the strip were found to produce the most pronounced synchronized response. As more lateral points were not tested the question as to whether the synchronizing region extends into the substantia innominata remains to be decided. The ventral synchronizing strip seems to extend rostrally into the cortical layers of the olfactory tubercle. The type and cortical distribution of the synchronizations brought about by high frequency stimulation of the ventral preoptic area and the olfactory tubercle were quite similar, however, synchronizations induced by low frequency stimulations differed to a great extent. A type of activity similar to physiological synchronization was elicited by preoptic stimulation. In every derivation stimulation of the olfactory tubercle resulted in a synchronization consisting of sustained evoked potentials. By stimulating the preoptic region, we observed a synchronized aftereffect which was absent on stimulating the olfactory tubercle. It seems that diverse mechanisms are put into action by the low and high frequency stimulations of the olfactory tubercle. The mechanism activated by high frequency stimulation may be similar to the synchronizing mechanism of the ventral preoptic region.

The question arises as to whether there are possible interactions between the two structures. Hernández Peón (15) pointed out that synchronization and sleep can be brought about by cholinergic stimulation of both the preoptic region and the olfactory tubercle. Large cholinergic cells were described in the preoptic region (39), and high concentration of choline acetyltransferase was reported in the olfactory tubercle (33). Between the olfactory tubercle and the preoptic region abundant neural connections were found (26, 32). Mizuno *et al.* (27) suggested that impulses descending from the orbital cortex are relayed in the olfactory tubercle. Both the entorhinal (34) and the dopaminergic entopeduncular afferents (19)

to the olfactory tubercle traverse the preoptic area from which synchronization could be elicited. Thus the interaction of the two structures was found to have a morphological basis. The suppressor effect of olfactory stimulations was also reported (4). Some of these morphological connections can provide support for the existence of a common mechanism in the preoptic region and in the olfactory tubercle responsible for the synchronizing effect of high frequency stimulations in both structures. Further experiments are needed to determine the similarities and differences between the mechanisms of these two areas.

The dorsal synchronizing area has the following characteristics: *i*) low frequency stimulation resulting in recruiting-type cortical synchronization; *ii*) the most pronounced effect over the anterior cortical areas, primarily over the motor cortex; *iii*) increase in recruiting-type synchronization over the SSM, as the electrode is advanced in a dorsoventral direction; *iv*) cortical synchronization accompanied by fast wave activity in the hippocampus; *v*) high frequency stimulation resulting in cortical and hippocampal desynchronization; *vi*) effects that persist after termination of the stimulation.

Much data concerning the cortical and behavioural effects of high frequency stimulations in this region is available. Cortical desynchronization (46) and the activation of various types of behaviours have been reported. Relatively little data, however, have been published concerning the effect of low frequency stimulations. On stimulating the lateral hypothalamus, the most prominent evoked potentials were obtained in the motor cortex (2). Since spindle activity over the motor cortex is associated with behavioural inhibition (36, 45), similar behavioural changes can be anticipated on stimulations of the lateral hypothalamus in chronic animals. The adynamic effect elicited by the stimulation of the anterior hypothalamus has already been observed by Hess (16). Caspers and Winkel (7) reported a similar adynamic state accompanied by cortical synchronization elicited by low frequency stimulation in rats, while the opposite effect was obtained in applying high frequency stimulation in the same area.

The opposite effect of low and high frequency stimulations of the lateral hypothalamus and the dorsal preoptic region is similar to the results obtained by stimulating the nonspecific nuclei of the thalamus. Findings of the existence of two distinct mechanisms

bringing about these opposite cortical effects were reported by Schlag and Chaillet (38). They suggested that the ascending activating system is necessary only in the case of the desynchronization evoked by the high frequency stimulation of the nonspecific system. The structure of the hypothalamus meets the morphological criteria of the nonspecific systems (32). Some experiments demonstrate the increase of unit activity in the reticular formation of the brain stem resulting from stimulation of the lateral hypothalamus (24, 28), therefore, it was suggested that the brain stem mediates the activating effect of the lateral hypothalamus (24). On the other hand, Skinner and Linsdley (42) found that a cryogenic blockade or a lesion in the rostral part of the lateral hypothalamus eliminated the spontaneous spindle activity, and recruiting responses could no longer be evoked. These effects were attributed to the elimination of the orbitothalamic connections along the inferior thalamic peduncle. Both the preoptic region and the rostral hypothalamus are connected, through the stria medullaris and the inferior thalamic peduncle, to the nonspecific thalamic system, primarily to the dorsomedial nucleus (26, 32). With these facts in mind, diverse pathways either to the reticular formation or the thalamus can explain the contrasting effect of the low and high frequency stimulation of the lateral hypothalamus.

Cortical synchronization can be elicited by low frequency stimulation of various sites of the brain. The synchronization induced by stimulating the nonspecific thalamic nuclei (9) has been subjected to extensive investigation, however, the synchronizing effect of the nucleus of the solitary tract (23), the nucleus fastigii (11), and even the reticular formation (12) are also well known. High frequency stimulation, however, could elicit cortical synchronization only from the orbital cortex, ventral preoptic region and the diagonal band of Broca. It seems that low frequency synchronizing areas produce their effect through the thalamus, whereas, the high frequency synchronizing areas are connected directly to distant cortical and subcortical structures (10, 20, 24, 41). Further experiments are required to clarify the interaction of these two mechanisms.

Several experiments demonstrate that high frequency stimulation of the medial hypothalamus results in hippocampal theta activity, while stimulation of the lateral hypothalamus evoked desynchronization (1, 22, 47); however, theta activity elicited by stimulation of the lateral hypothalamus was also occasionally re-

ported (14). The present results including the theta activity evoked by stimulating the lateral hypothalamus agree with previous findings. However, theta activity was elicited only in the dorsal part of the lateral hypothalamus. The low frequency stimulation of the theta-inducing points resulted in high voltage frequency following hippocampal synchronization. These stimulations either produced no cortical synchronization or a desynchronization. The cortical desynchronization induced by low frequency stimulation is an unusual phenomenon, although a similar finding was obtained by Magnes, Moruzzi and Pompeiano (23) by stimulating the region around the nucleus tractus solitarius. These results suggest that there are structures capable of producing only a desynchronized response regardless of stimulation frequency.

## Summary

1. Systematic mapping of the region between the rostral hypothalamus and the olfactory tubercle by means of low and high frequency stimulations revealed a dorsal and a ventral synchronizing area having diverse functional characteristics.

2. The ventral region included the laterobasal preoptic area and the cortical part of the olfactory tubercle. Although differences were found in the type of synchronization elicited by low frequency stimulation of the two areas, the cortical and hippocampal synchronizing effect of high frequency stimulation showed a common feature.

3. The dorsal region extended from the lateral hypothalamus through the dorsal preoptic area to the olfactory tubercle. Its characteristics were similar to those of the nonspecific thalamic system, *i.e.* low frequency stimulations resulted in recruiting type cortical synchronization, while high frequency stimulations desynchronized cortical and hippocampal activity.

4. The regions in the vicinity of the midline were of a powerful desynchronizing nature. High frequency stimulation resulted in cortical desynchronization as well as hippocampal theta activity, and sometimes cortical desynchronization was induced even by low frequency stimulation. This activity was accompanied by high voltage hippocampal synchronization.

5. It is suggested that direct cortical pathways to the ventral synchronizing area and the participation of the thalamus in producing the synchronizing effect of the dorsal area are the cause of the diverse activities associated with these two regions. Pathways from the dorsal area to the brain stem reticular formation may be responsible for the desynchronization obtained by high frequency stimulation of the dorsal area.

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