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CHANGES IN BEHAVIOR THROUGH STIMULATION OF THE RETICULAR FORMATION OF THE MONKEY

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This presentation is a sequel to two prior publications[1,2] in which the resulting behavior on stimulating various areas of the reticular formation of the Macaca mulatta was described. Further areas of the reticular formation have been explored by stimulation and the behavioral changes are the basis for this present report.

Technique and Observations: Macro-electrodes, consisting of two #50 stainless steel wires coated with #13 Tygon paint (baked on at 300°F for 30 minutes) were made to adhere together by placing them approximately 0.5 mms. apart, and applying a further coat of Tygon paint (and again baking at 300°F for 30 minutes). The wires were so placed that the tip of one extended 5-6 mms. beyond the other and after the final baking the tips were bared by scraping to expose approximately 1 mm. of each wire tip. The longer wire was bent acutely to form a hook (Figure 1) and to separate the two bared electrode tips by 2-3 mms. The electrodes were placed using the Horsley-Clarke stereotaxic instrument, the hook of the bipolar electrode hooking into the opening at the tip of a #20 lumbar puncture needle shaft which served as a carrier for the electrode into the brain substance (Figure 2). On reaching

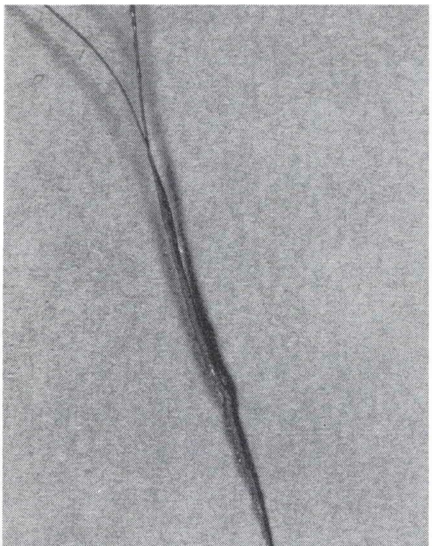

Figure 1

The bipolar "hooked" electrode

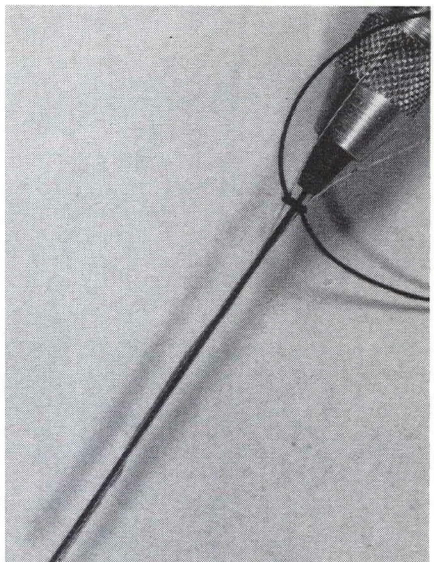

Figure 2

The bipolar "hooked" electrode attached to needle shaft carrier of Horsley-Clarke sterotaxic instrument.

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the intended area in the brain, the lumbar puncture needle shaft was merely withdrawn, the electrode remaining "hooked" in the brain at the intended point.

The two leads of this bipolar electrode were passed through a small nylon button screwed into the animal's skull and securely held within this button by a nylon plug screwed down on the leads through the center of the button — this reduced to a minimum any movement of the electrode within the brain after its placement. The two leads were then led under the scalp to a larger nylon button, also screwed into the skull and having metal jacks fixed into its substance. The leads made contact with these jacks and stimulation or recordings were effected by "hearing aid" type of plugs connected to these jacks and to the Type s4 Grass stimulator or the input of an Offner Transistor type E.E.G. unit.

In earlier experiments macro-electrodes of the Jasper-Delgado type (twisted #50 stainless steel wire coated with plastic paint until rigid enough for placement or wound about a central fine glass core and painted) were utilized.[1]

Prior to electrode placement, the monkeys were brought to a plateau of performance as measured by psychological testing. The oddity test of Harlow[3] was used, the animals having to choose the odd object of three to obtain a food reward. The animals performed consistently for 3-6 weeks at approximately 80 percent efficiency before electrode placements were made. This performance was again checked 48 hours after electrode placement and all animals used in this report were shown to have maintained their pre-electrode placement performance at approximately 80 percent efficiency.

We had previously determined[1,2] that the parameters of stimulation were an important factor in determining the type of response obtained. This applied to other parameters as well as the voltage. The frequency of the stimulating impulse used varied from 350-500/sec., the duration of each train of impulses used varied from 0.10-0.20 msec., and the delay between each train of impulse was 0.01-0.05 msec. These parameters with voltages 0.4-12.0 V (depending on the portion of the reticular formation stimulated) produced stimulations which resulted in little, if any, "Jacksonian like" motor responses. Increasing voltage, decreasing frequency or increasing delay between trains of stimulating impulses resulted in the appearance of the above-mentioned motor responses. Monophasic square top impulses were used in all experiments and the stimulus was continuous throughout the behavioural changes except in the case of post-stimulus hemiballismus to be reported.

In our previous publications[1,2], it was shown that stimulation by bipolar electrodes 2-4 mms. apart placed in a variety of areas of the reticular formation, extending from the anterior hypothalamic nucleus area to the reticular cell mass in the median raphe of the pons produced changes in consciousness that significantly reduced or eliminated the monkey's ability to perform a learned task so that the animal obtained a food reward. In a subsequent publication, changes in behavior were described which resulted from stimulation through more widely separated bipolar electrodes (at least 10-20 mms. apart) with at least one electrode placed within the reticular formation of the monkey.

Stimulation through one electrode in the right subthalamic body and the other in the reticular formation in the contralateral anterior hypothalamus resulted in a gereralized convulsion followed by approximately 90 minutes of hemiballismic movements of the right arm and leg (Figure 3).

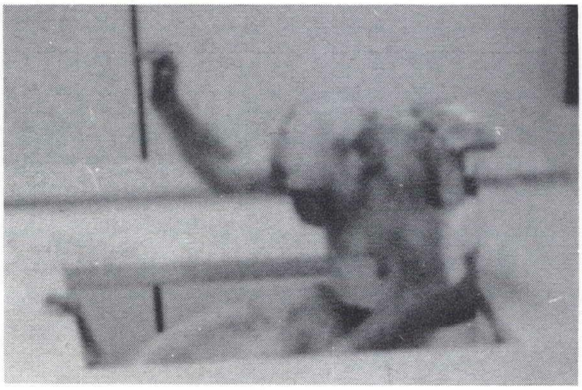

Figure 3
Hemiballismic Responses: Movement of right arm and leg.

Stimulation through one electrode in the nucleus reticularis of the thalamus and the other electrode in the ipsilateral aggregation of cells (reticular formation) at the mesocephalopontine junction produced a "genital response" (priapism and handling of genitals) (Figure 4). Of course, this latter response could have been due to a purely sensory phenomenon through involvement of the medial lemniscus.

Figure 4
Genital response

Since the above investigations, we have made three separate placements of our "hook" bipolar electrode (electrode points seperated 2-3 mms. in the vertical plane).

The first placement was in the region of the head of the right caudate nucleus, the lower electrode being implanted medial to this nucleus in the root of the choroid plexus adjacent to the stria terminalis, and the upper electrode 2 mms above was in the body of the corpus callosum. The inter-electrode resistance in situ was 40,000 ohms (approximately).

On stimulating through this bipolar electrode (monkey #12 using voltages 4.0-5.2, frequencies 400-410/sec., duration of train of impulses 0.20 msec., and delay between trains of impulses 0.015 msec., a typical yawning occurred 4-5 sec after stimulation commenced. This response occurred with this placement of electrodes on approximately 15 out of 20 trials. Any unusual visual or auditory stimuli appeared to inhibit it and if the animal's foot was touched by the experimenter during the atypical yawn, the monkey flew into a rage. The atypical aspect of the yawn was marked protrusion of the tongue. Immediately after the yawn was completed and with the stimulus continuing, there did not appear to be any significant impairment of the monkey's ability to perform the oddity test.

A second bipolar electrode was placed with the tip in the reticular formation lateral to the red nucleus and dorso-medial to the substantia nigra, and the upper electrode 3 mms. above this region (Figure 5). The inter-electrode resistance was

Figure 5

Bipolar electrode in situ in mesencephalic reticular formation (lateral to red nucleus). At the end of the tract is the tip electrode and the upper electrode is situated 3 mms. directly above it.

25,000 ohms. Using voltages 0.60-0.80, frequency of 400/sec., duration of train of impulses 0.1 to 0.2 msec., and delay between trains of impulses 0.010-0.015 msec., yawning occurred 2-3 secs after commencement of stimulation. With this placement it was more difficult to inhibit the yawn by visual or auditory stimuli, and, in spite of such stimuli, yawning would occur by increasing the voltage to 0.90-1.10 V. Some 30-40 yawning responses were obtained and most of them did not show the atypical feature of protrusion of the tongue, (Figure 6). Touching the monkey's foot while yawning brought about a rage reaction, (Figure 7) not as marked as that noted when the yawn was obtained by stimulating through the electrodes in the caudate nucleus and stria terminalis area.

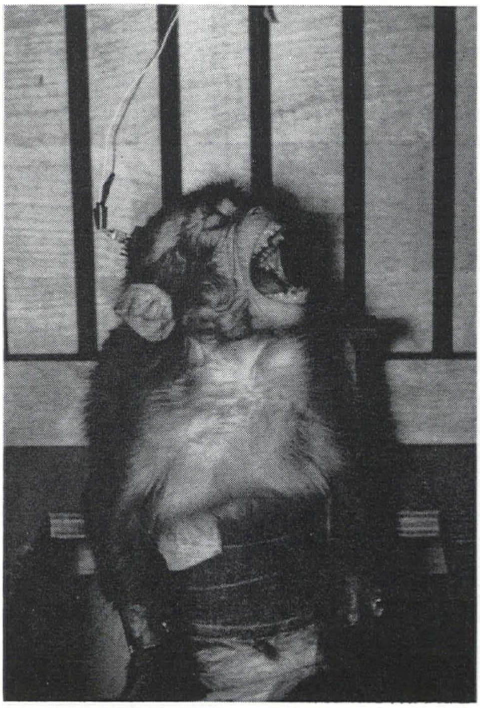

Figure 6
The yawning response.

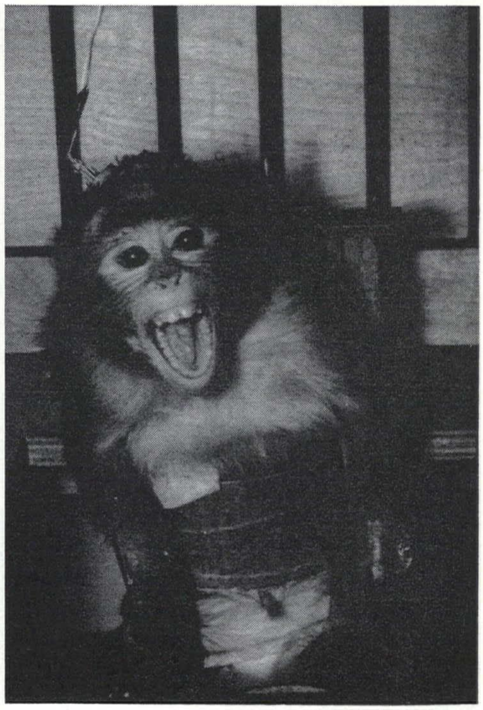

Figure 7
Rage response.

Following the yawn, continuation of the stimulation did not impair significantly the animal's ability to perform the psychometric test (oddity test). He maintained the pre-stimulus efficiency of 75-85 percent correct choices.

A third bipolar electrode was placed to the left side of the mid-line with the tip resting in the subcallosal region (cerebral fissure medial portion), and the upper electrode approximately 2 mms. above in the corpus callosum. The inter-electrode resistance was 22,000 ohms. Using frequencies of 400/sec., duration of train of impulses 0.10 msec., delay between train of impulses of 0.015 msec., and voltages above 0.80, stimulation produced an adverse motor response with the head and eyes turning to the right, and the right upper limb flexing at the elbow and wrist. This adverse head turning response may be the result of involving the cingulate gyrus in the stimulus field. No yawning response occurred and with voltages below 0.80 no motor response occurred. The animal's ability to perform the oddity test was not impaired significantly (still made correct choice 10 of 12 trials). Ten to twelve separate stimulations confirmed the above observations.

The electrode placements were confirmed 10 days following perfusion of the animal's brain with 10% formalin by examination of gross and miscroscopic sections of the brain.

Discussion: We first observed the yawning response on stimulating with bipolar electrodes placed in the reticular formation just lateral to the red nucleus of a monkey in 1957[1] (monkey #6). However, this animal was suffering from acute enteritis and died the following day so we were unable to convince ourselves that the morbid state did not contribute to this yawning response. It would now appear this acute enteritis was not a significant contributing factor in view of the many yawning responses obtained on stimulating the same area of a healthy monkey. In this first animal, (monkey #6), sleep followed the yawning, but an increase of 0.20 V in the stimulus awakened the animal, and the monkey would again be made to yawn and fall asleep on reducing the voltage to the previous voltage.

A similar emotional reaction to that obtained on touching the animal, during a yawn produced by electrical stimulation was noted on stimulation by bipolar electrodes (3-4 mms. apart) placed just ventral to red nucleus in 1957[1] (monkey #5). The reaction was brought about by slowly increasing the voltage up to 0.60 V, and if the voltage was increased to 0.90 V extreme panic occurred. French[4] reports panic reactions on stimulating in the mesencephalic reticular formation in monkeys.

The investigations reported in the literature as to the mechanism of yawning are few and provide little, if any, scientific evidence to localize the area of the central nervous system primarily involved in its production. A good review of the literature to 1946 is given by Heusner[5]. Penfield[6] described a case in which lesions involving the third and fourth ventricle produced abnormal yawning and Yakovlev[7] describes yawning as a sign related to disorders involving the basal nuclei. Excessive yawning is frequently seen in cerebellar abscess or tumors[8,9,10,11,12], and its occurrence in an alert patient suggests a search be made for signs of hypothalamic dysfunction. It is interesting that paroxysmal yawning is one of the sequalae of epidemic encephalitis which frequently produces mesencephalic lesions.

One of us (Robert S. Knighton) has observed that while performing a chemopallidolysis (alcohol) the patient frequently yawns on injection of the alcohol into the basal nuclei area. The area of injection is, of course, variable in extent but the injection is directed to the globus pallidus. No doubt, it often involves the ansa lenticularis which has ramifications in the tegmental reticular formation (nucleus mesencephalicus profundus).

Ingram et al[13] have reported contraction of facial muscles on tegmental stimulation of the anaesthetized cat.

It would appear that on stimulating in the reticular formation in the region of the red nucleus, the stimulus is able to bring about the yawn response more consistently and with a shorter period of stimulation than when stimulation took place in the region of the caudate nucleus and stria terminalis. This may be explained by the stimulus having to use a circuitous route to arrive at the more specific centers responsible for the yawning response, and it is interesting to note that the stria terminalis has ramifications in the amygdaloid nucleus and through the hypothalamus to the mesencephalic tegmentum.

The above evidence points to a rather diffuse system that contributes to the yawning phenomenon.

As to the rage reactions that have been noticed on touching the yawning animal (under stimulation): it would appear that the electrical stimulus probable reached hypothalamic centers by descending fibers via stria terminalis or ascending fibers from the mesencephalic reticular formation, to produce an extremely "alert" state so that a slight tactile stimulus could produce the rage or "fight" response noted.

This would offer an explanation as to how stimulation either in the stria terminalis or in the reticular formation of the tegmentum produced a similar rage phenomena. At the present time we are arranging to record electrographically from the amygdala and hypothalamic areas during yawning produced by stimulation of the caudate nucleus and stria terminalis, and by stimulation of the mesencephalic reticular formation.

Summary: Changes in behavior on stimulating the reticular formation in the Macaca mulatta have been described. These include changes in "consciousness", "genital" responses, hemiballismus, rage responses and finally yawning. The yawning may be typical or include the forcible protrusion of the tongue.

The yawning response has been observed in two animals with electrodes placed in the mesencephalic reticular formation or in the region of the caudate nucleus and stria terminalis. A rage response occurred if the animal was touched during this yawn response. A control bipolar electrode placed in the corpus callosum above the mesencephalic reticular formation failed to produce the yawn response or rage reaction on stimulation.

Stimulation of the reticular formation produces a most varied behavior response depending upon the location of the electrode and the area included in the stimulus field. A more thorough investigation of the behavioral responses possible on stimulation of the various areas of this ill-defined system should provide ample scope for extensive research in the future.

This presentation is only intended to show the results of a very gross examination of the possible behavioral changes on stimulating several areas of the reticular formation in the Macaca mulatta.

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