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DISRUPTION OF TEMPERATURE DISCRIMINATION DURING LIMBIC FOREBRAIN STIMULATION IN MONKEYS

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Abstract—Neural substrates that may participate in modulating the pain experience were investigated indirectly through the study of the effects of brain stimulation on gross temperature discrimination in Rhesus monkeys. Temperature discrimination performance was disrupted during stimulation of limbic structures (amygdala and orbital gyrus) as compared to somatosensory cortex. Performance errors decreased during repeated stimulation of amygdala but not of orbital gyrus. In contrast, visual discrimination performance was not affected during similar brain stimulation. These results and a review of the literature suggest that the limbic forebrain partakes of a protocritic system which deals with the intensive aspects of experience.

INTRODUCTION

STUDY of the cortical representation of the pain system is fraught with conceptual and practical difficulty. Pain as a somatosensory modality appears even in the periphery in two aspects: a discrete sensation giving rise to local signs mediated by type A afferents; and, a diffusely unpleasant feeling due to stimulation of small unmyelinated Group C nerve inputs. These aspects were studied extensively by HEAD [1] by means of experiments in which he severed his own peripheral nerves, allowed them to degenerate and regenerate while analyzing the sensations produced when the deafferated structures were stimulated. He was thus able to dissociate the discrete from the diffuse aspect of sensation, finding that the diffuse was correlated with the pathology of incomplete regeneration—which was later shown [2] to depend on the fact that initially only fine fibers are present in the regenerating nerve. Head coined the term *epicritic* for the discrete sensory systems and, because of their initial manifestation in pathological states, the term *protopathic* for the diffuse sensations.

At the spinal and lower brain stem level another peculiarity of the pain system becomes clearly manifest. The clinical syndrome of syringomyelia and the neurosurgical procedure of chordotomy have thoroughly established on clinical grounds that the pain system is intermingled with or closely adjacent to another, the temperature sensory system [3–5]. Electrophysiological laboratory experiments have amply confirmed these clinical studies (see [6] and [7]). This relationship between the pain and temperature neural systems has now

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been extended to the peripheral afferent systems: both pain and thermal sensations are mediated by unmyelinated and the small myelinated A-delta fibers [8].

The upper brain stem level brings its own set of surprises to the study of pain. Here the pain system becomes intermingled with, or closely adjacent to, yet another system, that from which the self-stimulation effect is obtained [9–11]. The effects of self-stimulation have been interpreted as producing reinforcement [12] and pleasure [13]. One is therefore faced with the possibility that in the upper brain stem (mesencephalon and diencephalon) there is a neural representation of hedonic–anhedonic functions [14].

Another difference characterizes studies of the pain system at the upper brain stem level. Here destruction has as yet been found to have little effect on pain sensitivity, while electrical or chemical stimulation [15] appears to "gate out" the appreciation of pain. MELZACK and WALL [16] have suggested a possible mechanism for the gating effect which depends on the structuring of input by the touch and pressure receptivities of the somatosensory system. The active suppression of pain by electrical and chemical stimulation appears, however, to occur even more directly through a separate medially lying neural system (periaqueductal grey and midline thalamus) terminating on lamina V of the dorsal horn of the spinal cord [17]. This medially lying system may be anatomically indistinguishable from the pain system itself, since electrical stimulation with slow frequencies (10–20 Hz) produces analgesia while higher frequency stimulation (60–100 Hz) produces pain [18].

The final curiosity to be noted concerns the locus of representation of the positive and aversive self-stimulation systems in the forebrain. The major effects are obtained from limbic structures [19]. The limbic forebrain was at one time called the rhinencephalon because it serves as the terminus of olfactory afferents [20].

We are thus faced with a situation in which at the lower brain stem, spinal and peripheral levels the pain system is closely related to temperature sensitivity, while at the upper brain stem level the pain system becomes part of an hedonic–anhedonic mechanism only to merge at the forebrain level with the olfactory sense. Conceptually, the problem of studying the pain system would therefore be markedly simplified if some relationship could be demonstrated between temperature sensitivity, hedonic self-stimulation and the olfactory sense, the three intimates of the pain system. These three, apparently disparate, functional systems are each, at their own level, so difficult to disentangle anatomically from the pain system that it seems reasonable to search for some other commonality that distinguishes them from alternate modes of sensory experience.

In this search, the relationship between olfaction and temperature sensitivity provides a reasonable beginning. Faraday first noted that many odorous materials strongly absorb radiation in the infrared region. BECK and MILES [21] and BECK [22] developed a comprehensive theory to the effect that monomolecular films of odorous chemicals are adsorbed on the olfactory membrane and that the nose acts as an infrared radiator and thus produces differential cooling of the chemically altered membrane. PFAFFMAN [23] reviews these and related theories for the *Handbook of Experimental Psychology* within the framework of olfaction as a chemical sense. Yet, as he points out, olfaction tends to resemble an auditory analogue where complex tones can be subjected to analysis by a multiplicity of tuned receptor units, rather than the relatively simpler chemical sensitivities found in the taste modality.

The conception of olfaction as a chemically dependent development of the temperature system much as audition is a development of the lateral line system's vibratory sensitivity is, however, far from being well established. There is good evidence that stereochemical

binding sites in the olfactory mucosa account for a good deal of the variations in sensitivity to olfactants. Yet a similar set of stereospecific binding properties characterizes the pain/pain suppression (analgesic) system described above [24]. Such specific binding sites have been found in the periaqueductal grey, the medial thalamus and the amygdala. Interestingly, when these same sites are stimulated electrically with low frequency pulses in man, not only is analgesia produced, but also a feeling of cooling and sometimes even of cold [18]. Thus relationships between the olfactory, pain and temperature senses continue to crop up and need to be seriously investigated.

There is further evidence that the anterior portions of the limbic forebrain [25] and even the olfactory bulb [26] are involved in temperature regulation, as is, of course, the preoptic area of the diencephalon [27]. The relationship between sensitivity to body temperature as reflected in the diencephalic blood circulation, and the relationship of these to other metabolic processes has been well documented [28]. Again, there is anatomical juxtaposition and intermingling of these effects on temperature regulation with those of self-stimulation [13] both at the limbic, rhinencephalic, level and at the diencephalic level.

Finally, thermal sensitivity has been directly related to comfort. In the mid 1930's WINSLOW, HERRINGTON and GAGGE [29] introduced the dimension of "pleasantness" into the study of temperature sensitivity. This work has been brought up to date by a further series of experiments reviewed by GAGGE and STEVENS [30]. On the basis of this work, two power functions are discerned, one for warmth and one for cold which together form an operative index of perceived comfort with respect to physical temperature.

In short, the view that emerges is of an as yet only loosely discerned system that extends from periphery to cortex, a neural system or closely linked set of systems which deals with deterrence and reinforcement, with discomfort and comfort, with anhedonic and hedonic experience, and with olfaction, all based on the intensive dimensions of somesthesis, especially the senses of pain and temperature. According to Head's and subsequent analyses, the epicritic aspects of these sensations form separate systems that deal with local sign, their extensive properties. The intensive aspects form a modality which Head termed protopathic but which, in the light of the current knowledge detailed above, is functional in normal as well as in pathological states. It is therefore more appropriately referred to as *protocritic*.

The protocritic system thus defined includes the intensive aspects of pain and temperature sensitivities, the deterrent and reinforcing properties of brain self-stimulation, and the olfactory system, the rhinencephalon or limbic forebrain. It is conceived to serve basic and phylogenetically ancient *discriminative* functions, thus *protocritic*, in the intensive mode of experience.

Practically, this view leads to the hypothesis that the cortical representation of intensive pain and temperature should be found in the limbic forebrain and that tests could be made of the hypothesis by the use of pain or temperature *discrimination* tasks. Tests of threshold would not be expected to be affected at the forebrain level and pain threshold is not [31].

But a serious problem of interpretation arises when pain discrimination is tested. Experimental situations such as active avoidance involve a memory component and others, such as passive avoidance, involve conflict. Some years ago, therefore, one of us (Pribram) performed an unpublished pilot study in which anterior limbic resections (orbital surface of the frontal lobe, anterior insular cortex, temporal pole and amygdala) were made and, on the basis of the reasoning presented above, the effects on temperature discrimination were assayed. Disturbances of discrimination were obtained but they were not uniformly severe in all monkeys; they lasted a variable period of time and opportunity for control

lesions or control discrimination testing was prevented by a move of the laboratory.

Meanwhile a number of studies have shown that discrimination of large differences in temperature (10°C) remains unaffected when bilateral resections of somatosensory cortex are made in rats [32] although finer discriminations (3°C) may be variably impaired by such lesions [33].

The present experiments were therefore undertaken to study the cortical representation of protocritic functions by comparing the effects of interfering with the mechanism of operation of the limbic forebrain areas (orbital frontal cortex and amygdala) with those of the parietal cortical areas, somatosensory I and II. Because, as noted above, electrical stimulation has been found to be a more reliable technique than resection for obtaining changes in function in the protocritic system, this method of interfering with normal function was chosen. Discriminations in the visual modality were tailored to control for the complexities necessary to test even the temperature aspects of protocritic mode. Definite and interesting results were obtained and make up the substance of this report.

METHODS

Preliminary pretraining

Eight naive Rhesus monkeys were used in this study. The animals were initially pretrained in transport cages to press lighted panels in the automated, computer controlled, Discrimination Apparatus for Discrete Trial Analysis (DADTA) as described by PRIBRAM [34]. Subsequently the animals were given several simple visual discriminations in preparation for two difficult visual problems. The visual tasks used the paradigm originally proposed to be used in a computer controlled temperature discrimination problem. In the difficult color discrimination problem the monkey was first required to initiate the trial by pressing both a red and a green panel located adjacent to each other after which two zeroes appeared directly above the colored panels. A correct response consisted of hitting the zero directly above the green panel after which the animal was rewarded by a banana pellet. In the corresponding pattern discrimination problem the numbers 2 and 6 were substituted for red and green. A correct response consisted of hitting the zero directly above the 2.

Temperature discrimination

A temperature discrimination problem was first presented to the monkeys in a Wisconsin General Testing Apparatus. Two capped tubes containing water with maximal temperature differences of 25, 14 or 9°C were attached with spring clips to sliding covers above two food wells. The monkey was first required to touch both tubes while the covers to the food wells were kept closed by back pressure and then push the warmer or colder of the tubes to obtain the food reward. Between each trial, when the screen separated subject from experimenter, the tubes were wiped to remove moisture and finger prints. Tubes were replaced by those from the baths at least every five minutes during the testing period.

The monkeys were then shifted to an enclosed chamber (5 ft × 2 ft × 2 ft) with a one-way window containing another apparatus in which the temperature could be controlled by a PDP-8 computer. Two thermoelectric units (Genalex 16 RBI, 1¼ in. square) connected to a d.c. power source (Electro Products, Model H) were used as the source of temperature differences. Heat sinks cemented (Wakefield Delta Bond 152) to the units were cooled by a large fan. A copper plate directly above but electrically insulated (Wakefield Thermal Compound No. 122) from each thermoelectric unit was connected to a capacitor-operated "touch" switch (Eicocraft EC-1800) which sensed when the units were touched. The temperature of each unit was determined from a calibrated thermoresistor (Veco 35A1) attached to each of the copper plates. The output of each thermoresister converted to voltage was read into two channels of an analogue to digitial (A → D) converter so that the temperature was maintained through activation of relays which turned the current of the appropriate polarity either off or on. One thermoelectric unit was maintained at 15°C and the other at 30°C in a predetermined random sequence such that the temperature difference between the two units was 15°C. A 30 sec intertrial interval was needed for the same unit to change from 30° to 15°C. The thermoelectric units were 2 in. apart and were completely surrounded by translucent Plexiglass to transmit light signals. The appearance of a steady light indicated the beginning of a trial. In the original paradigm both thermoelectric units had to be touched before two buttons above them were lit. Pressing the button above the unit of the rewarded temperature activated the feeder which delivered banana pellets as food rewards to the animals.

In the present paradigm the monkey was required first to touch each thermoelectric unit when a steady light appeared on the panel around the units. After the monkey's hand was momentarily removed from the units, the steady light around them began to flash to indicate to the animal that a choice was to be made. A

correct response consisted of touching the thermoelectric unit being rewarded, after which the flashing lights disappeared. Each animal was presented the same temperature difference of 15°. The warmer (30°C) of the two units was rewarded in 4 monkeys and the colder (15°C) unit in the other 4 animals. Gross behavior was observed through the one-way window. The latency of the response was defined as the time between the onset of the steady light at the beginning of a trial and the final pressing of the appropriate panel when the animal made its choice during the period of flashing light. If the animal had not completed the response within 191 sec from the beginning of the trial, the trial was automatically terminated and counted as a "no response". The correctness of each trial and its latency were automatically tabulated by the computer. Five of eight animals reached criterion performance of 68 correct responses in 80 trials (85%). During control sessions of 20 trials the latency of the response varied among the animals and ranged from a mean of 0·502 ± 0·069 (S.D.) sec to 4·254 ± 0·766 (S.D.) sec.

Brain stimulation

The 5 animals that reached criterion performance were implanted under general anaesthesia with 8 to 12 bipolar electrodes. Electrodes were made from 300 μm insulated nichrome wire with tip separation of 1·5 to 2 mm. Electrodes were connected to a 25 pin Microdot plug. In all 5 monkeys 8 bipolar electrodes were implanted bilaterally in amygdala, orbital gyrus and somatosensory cortical areas SI and SII (see Fig. 1).

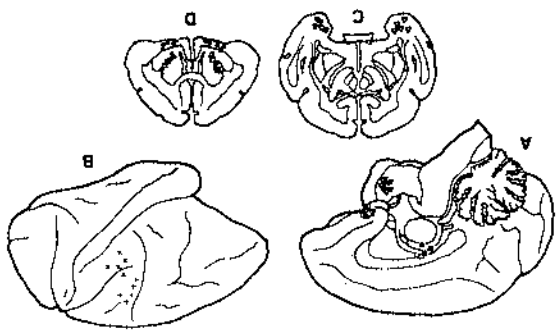

FIG. 1. Brain sites stimulated in the limbic forebrain structures, amygdala (△), orbital gyrus (○) and stria terminalis (□) (A); and somatosensory cortical areas SI (+) and SII (×) (B). A cross-sectional view of the sites stimulated in the amygdala (C) and orbital gyrus (D) are also shown. The solid symbols indicate stimulation on the right and open symbols stimulation on the left. In one monkey nucleus parafascicularis (▲, A) was stimulated.

In three of the monkeys, electrodes were also aimed for various subcortical sites. Histological analysis indicated the placements to be in and around stria terminalis (near fornix and corpus callosum) and in one subject in nucleus parafascicularis (Fig. 1A). All of these have been designated "stria terminalis" area throughout this paper since no differences between them in terms of behavioral results were observed from stimulation.

After a minimum of 2 weeks following surgery each animal was placed in a monkey chair and retested for retention of the temperature discrimination. Each brain site was stimulated bilaterally (when possible) through two isolated stimulators (American Electronic Laboratories). Biphasic pulses ranging from 0·1 to 1·5 mA, 0·5 to 1·0 msec duration were delivered at a rate of 20 to 100 c/s. Current and voltage were monitored continuously on a Tektronix oscilloscope so that the resistance of the stimulated areas could be determined.

The effects on performance of continuous brain stimulation during blocks of 20 trials were compared to the previous control performance on the same day. For each block of 20 trials mean latencies of correct, incorrect and all responses were also compared.

If two consecutive no responses occurred during brain stimulation, the stimulator was turned off. The animal was then required to have a minimum of 17 correct responses out of 20 trials before stimulation was resumed. Those parameters of stimulation found effective in disrupting temperature discrimination were usually repeated for 6 days or until no deficits were observed. These effects were retested 2 to 16 weeks later.

Visual discrimination

A visual discrimination task using the same paradigm, apparatus and environment as the temperature problem was also given to the monkeys. A "+" was substituted for the warmer (30°C) thermoelectric unit while a "÷" replaced the cooler (15°C) of the units. The monkeys were required to touch both symbols when the steady light appeared. The visual symbols then disappeared during the flashing light, and the

animals had to hit the same panel on which the rewarded symbol had been presented. The long intertrial time of 30 sec was also used. The various brain sites were stimulated with the same parameters effective during the temperature discrimination.

RESULTS

Preliminary pretraining

In an attempt to accelerate the learning of a computer controlled temperature discrimination problem requiring the panel above the correct response to be pressed, eight rhesus monkeys were pretrained on several tasks. To introduce the paradigm, the monkeys were given two relatively difficult visual problems in the automated, computer controlled, discrimination apparatus (DADTA). Subsequently they were trained to discriminate temperature differences of 25, 14 and 9°C in a Wisconsin General Testing Apparatus.

The first visual problem required the monkey to initiate the trial by pressing both a red and a green panel and then hit the zero directly above the green panel. In 8 monkeys the average number of trials needed to reach the criterion of 85 correct responses in 100 trials for this difficult color discrimination task was 2160 $\pm$ 1244 (S.D.). In the second visual task the numbers 2 and 6 were substituted for the colors red and green respectively. Five of the eight monkeys learned this pattern discrimination in fewer trials than the color problem. The mean number of trials required for criterion in the eight monkeys was 1868 $\pm$ 1336 (S.D.). No differences in performance between males and females were observed in either of the visual discrimination problems (Table 1).

Table 1. Sex differences in number of trials to criterion performance during preliminary pretraining

TEST	FEMALES Mean ± S.D.	MALES Mean ± S.D.	SIGNIFICANCE OF DIFFERENCE
Visual Discrimination (DADTA machine)			
Color (red, green)	2547 ± 1165	1747 ± 1362	n.s.
Pattern (2,6)	1834 ± 1076	1903 ± 1595	n.s.
Temperature Discrimination (Wisconsin box) Temperature differences			
25° C.	1720 ± 710	3339 ± 698	**
14° C.	1963 ± 717	3875 ± 702	**
9° C.	2200 ± 582	4188 ± 282	***

Criterion performance = 85 correct in 100 trials

Level of significance, 2-tailed test

** $p \leqq 0.025$

*** $p \leqq 0.01$

n.s. not significant

All 8 monkeys learned to discriminate differences of 25, 14 and 9°C in the Wisconsin General Testing Apparatus in an average of 2873 trials. The number of trials required to reach the criterion of 85 correct responses in 100 trials was subjected to a two-way analysis of variance. For the grouped data, the analysis indicated large animal differences ($F = 44{\cdot}79$, 7, 14 *df*, $P \leq 0{\cdot}001$) and increasing number of trials required for increasing difficulty of the temperature discrimination ($F = 10{\cdot}42$, 2, 4 *df*, $P \leq 0{\cdot}05$). Subdivision of the data showed differences in performance depending upon the sex of the monkey. As indicated in Table 1, the 4 females required approximately one-half the number of trials to learn the three temperature discriminations as did the males. No differences were obtained as to whether the warmer or the cooler of the two tubes was rewarded.

Acquisition of automated temperature discrimination

In order to eliminate experimenter–subject interaction that may have been inadvertently present during testing in the Wisconsin box, the monkeys were presented with a temperature discrimination which was completely automated by the computer. The original paradigm of having the animal touch both thermoelectric units and then press the lighted panel above the correct response was extremely difficult. All eight monkeys were only at chance level of performance after a mean of 2251 $\pm$ 154 (S.D.) trials. The paradigm finally used in the remainder of the study required the monkey initially to touch both thermoelectric units during the appearance of a steady light around the units, and then touch either the warmer or the colder of the two thermoelectric units when the lights began to flash. Only 5 of the 8 monkeys learned the paradigm for this difficult temperature discrimination task controlled by the computer. The 3 males dropped from this study were only at chance performance after 5613 (mean) $\pm$ 1036 (S.D.) trials; they were usually hyperactive during the long 30 sec intertrial intervals. The remaining 5 animals used in the brain stimulation studies were required to complete 68 correct responses (85%) in 80 consecutive trials. The number of trials needed to reach this criterion ranged from 2737 to 15,226 with a mean of 7372 $\pm$ 5497 (S.D.) (see Table 2). The high individual variation was attributed to the animals' techniques in performing the problem: the 3 monkeys pressing the thermoelectric units with their palms required less than one-third the number of trials to reach criterion compared to the 2 animals using mainly their finger tips. Comparison of the number of trials to criterion for the temperature discrimination in the Wisconsin box to that in the computer controlled apparatus showed savings in only 1 (Daimon) of the 5 monkeys (see Table 2).

Gross behavioral changes during brain stimulation

The gross behavioral manifestations during brain stimulation varied with the site and the intensity of the stimulus. The effects during stimulation of a specific site were characteristic for each animal but differed among animals. During amygdala stimulation the animals were generally quieter but less "attentive" to the stimulus panels than in control sessions, decreased intertrial pressing, responded more slowly as confirmed by longer latencies, and often stared at the top of the observation chamber. One monkey bit his fingers and nails while another fought to avoid the amygdala stimulation. In all 5 animals increasing the intensity of amygdala stimulation led to periods of no responding on the panels.

During orbital stimulation the latency of the response was increased as during amygdala stimulation but the behavioral signs differed and ranged from searching the environment, getting generally restless, to no change from control. Some of the errors made during orbital stimulation were attributed to the incorrect sequence of events in completing

Table 2. Trials to criterion performance in individual monkeys during temperature and visual discrimination before brain stimulation

ANIMAL	Sex	Temperature Discrimination			Visual Discrimination	
		Correct Response	Wisconsin Box	Computer-controlled Apparatus	Correct Response	Computer-controlled Apparatus
Prudence	(F)	cold	1075	4518	$\frac{\cdot}{\cdot}$	450
Daimon	(M)	cold	4498	3349	$\frac{\cdot}{\cdot}$	825
Shalom	(F)	cold	2551	15226	$\frac{\cdot}{\cdot}$	491
Charity	(F)	warm	2359	2737	+	184
Vanessa	(F)	warm	1688	11031	+	300
Mean ± S.D.			2434 ± 1293	7372 ± 5497		450 ± 243

a response. When the current was raised maximally, 2 of the monkeys worked as they usually did during the lower level of stimulation, 2 stopped working, and the fifth animal exhibited striking behavioral changes such as picking at her forehead, shaking her head and grimacing.

During stimulation of stria terminalis area the monkeys appeared to be searching for the source of the stimulus, and sometimes tried to get out of the restraining chair to avoid stimulation. Random hits on the response panels appeared to account for most of the performance errors in these hyperactive animals. When the increased behavioral activity was confined to the intertrial period, the animal performed at criterion level.

No particular behavioral changes were observed concommitant with stimulation of somatosensory areas except that the animal often looked up to the ceiling of the chamber. Two of the animals appeared to fall asleep during stimulation of SI but these effects were not consistently observed.

Performance deficits on temperature discrimination during brain stimulation

Initial 3 days. The initial magnitude and persistence of the performance deficits in the temperature task during brain stimulation are reflected in the bar graphs of the averaged data for 3 days in Fig. 2A. Temperature discrimination performance was disrupted during electrical stimulation of the limbic forebrain structures (Fig. 1A), amygdala (Fig. 1C), orbital gyrus (Fig. 1D) and stria terminalis (Fig. 1A). The performance deficits in these areas were not significantly different from one another. In contrast, performance was unchanged or was only transiently reduced during stimulation of sensory cortical areas SI and SII (Fig. 1B). In 4 of 5 animals there was no performance deficit in temperature discrimination until SI was stimulated at intensities that caused gross motor incoordination or evoked petit mal or grand mal convulsions. In 3 of 5 monkeys performance was decreased 20–30% only on the first day of stimulation of SII. The mean performance deficits of 16·1–18·3% for 3 days during limbic forebrain stimulation were significantly greater than the 2·3–6·3% decrements during stimulation of the cortical somatosensory areas (Fig. 2A).

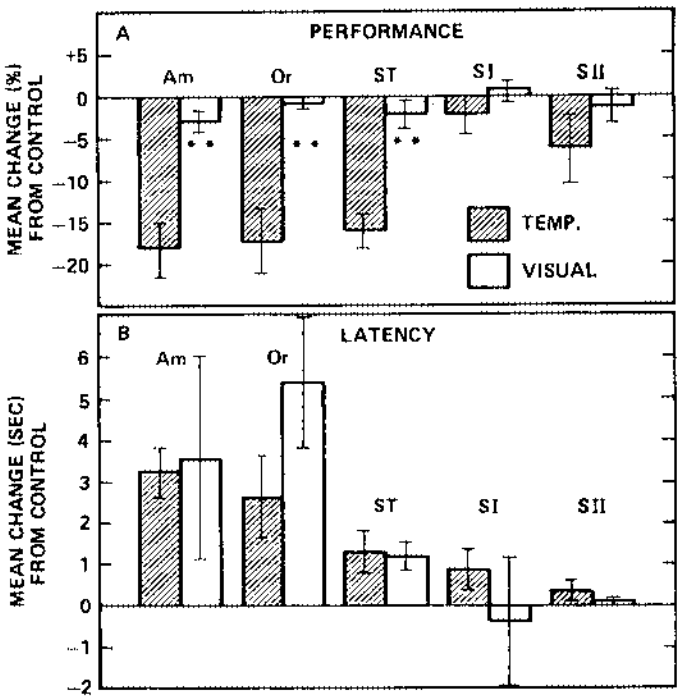

FIG. 2. Mean changes in performance (A) and latency (B) during the first three days of brain stimulation in temperature and visual discrimination. Brain areas stimulated: limbic forebrain structures – – – amygdala (Am), orbital (Or), and stria terminalis area (ST) compared to somatosensory cortical areas I (SI) and II (SII). The standard errors of the means represent the variability across animals. In the temperature task (cross-hatched bars) performance deficits were significantly greater during stimulation of limbic forebrain structures than during stimulation of somatosensory areas (A). ** indicates significant difference between temperature and visual performance, $P \leq 0{\cdot}025$, A, but the latency of the response was increased in both discrimination problems (B).

In 3 of the 5 monkeys performance deficits of 15% or more were also observed in the post-stimulus period 20 to 40 trials after termination of the stimulus. The original decreases in performance during limbic forebrain stimulation were repeatable in these monkeys after 3 to 14 weeks.

Repeated stimulation. Performance deficits during stimulation of the various brain areas could be further differentiated when the effects of repeated stimulation for six days were assessed (Fig. 3). Habituation to the effects of stimulation in amygdala (Fig. 3A, solid line, $r = 0{\cdot}494$, $P \leq 0{\cdot}01$, 2-tailed test), and stria terminalis area (Fig. 3C, solid line, $r = 0{\cdot}47$, $P \leq 0{\cdot}02$, 2-tailed test) was observed as the animals made progressively fewer errors in the temperature discrimination task during daily stimulation. The effects of orbital stimulation differed from the above areas in that the increased errors in performance did not habituate during repeated testing (Fig. 3B). These differences in the trends of the performance deficits during repeated stimulation of the amygdala-stria terminalis complex, as compared to orbital gyrus, were confirmed by the significant differences ($P \leq 0{\cdot}05$, 1-tailed test) of the slopes of the respective regression lines (Figs. 3A–C). The positive slope of the corresponding regression line for the combined somatosensory areas (Fig. 3D,

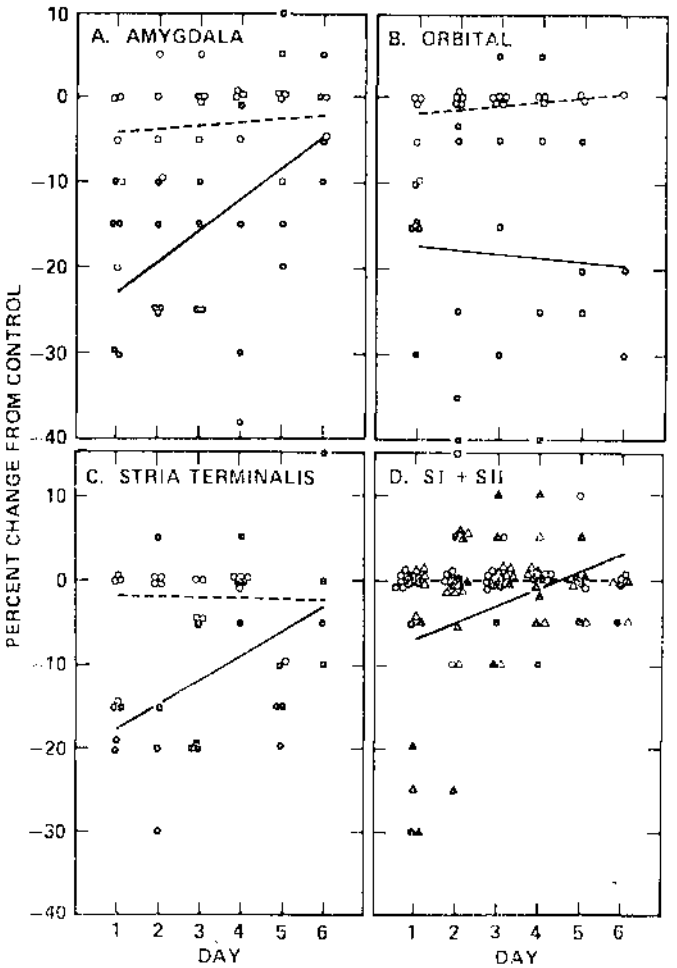

FIG. 3. Performance change during repetition of brain stimulation for six days in temperature (solid lines) and visual (dashed lines) discriminations. The solid (O—temperature) and open (○—visual) circles represent the individual data points from which the regression line was calculated by the least squares method. In D, SI is represented by circles and SII by triangles. The correlation coefficient indicated smaller performance deficits in the temperature task with repeated stimulation of the amygdala (A, $r = 0{\cdot}494$, $P \leq 0{\cdot}01$), and stria terminalis areas (C, $r = 0{\cdot}472$, $P \leqq 0{\cdot}02$). The slopes of these two lines were significantly different from the corresponding lines during visual discrimination (A and C) and from those during orbital stimulation (B).

solid line) reflects primarily the performance errors made on the first day of brain stimulation but most of the individual data points for the subsequent days are centered around the control base line indicating no change in performance.

Latency changes on temperature discrimination during brain stimulation

Initial 3 days. The corresponding latency of the responses during the first 3 days of stimulation was longer during limbic forebrain stimulation than for the control period (Fig. 2B) irrespective of whether the performance was correct or incorrect. The increase in latency was largest during amygdala and orbital stimulation.

Repeated stimulation. The latency data were further analyzed for all of the days of stimulation across animals to determine the persistence of the initial effects (Fig. 2B) and the influence of errors upon this measure (Table 3). The variability of the latency of the response

Table 3. Mean latency changes in temperature discrimination during all days of brain stimulation

Brain Area Stimulated	No. of Sessions	Latency change from control in sec. (Mean ± S.E.) All Responses (A)	Correct Responses (B)	Incorrect Responses (C)	Difference (C-B)
Amygdala	39[a]	3.196 ± 1.222	2.411 ± 1.040	4.344 ± 1.604	1.933 ± 0.637
"	42[b]	8.524 ± 5.412	7.751 ± 5.401	4.054 ± 1.276	-3.697 ± 5.65
Orbital	35	1.545 ± 1.455	1.026 ± 1.687	5.552 ± 3.087	4.526 ± 3.240
Stria Terminalis	28	1.132 ± 0.798	0.945 ± 0.674	1.670 ± 1.036	0.725 ± 0.366
SI	12	0.715 ± 0.376	0.693 ± 0.367	1.312 ± 0.601	0.619 ± 0.312
SII	15	0.425 ± 0.211	0.357 ± 0.173	0.159 ± 0.085	-0.198 ± 0.191

a only 4 monkeys
b all 5 monkeys

was usually greater during brain stimulation than in the control session, both within the same animal and across animals. For the grouped data the mean latency of all responses was longer during stimulation of the amygdala and orbital gyrus than of the somatosensory areas (Table 3) similar to that observed during the first 3 days of stimulation. The latency of incorrect responses tended to be longer than correct responses for all areas stimulated except SII, but the effects were observed most consistently during orbital (all 5 monkeys) and amygdala (4 of the 5 monkeys) stimulation. The mean increase in latency of the incorrect trials across animals was 4·526 ± 3·240 sec (S.E.) longer than the correct responses during orbital stimulation and 1·933 ± 0·637 (S.E.) sec during amygdala stimulation (Table 3).

Acquisition of visual discrimination

To test whether the discrimination deficits observed during limbic forebrain stimulation were specific for the temperature modality or were a generalized phenomena irrespective of the sensory input, a plus (+) and a divide (÷) sign were substituted for the warm and cold thermoelectric units. All other parameters in this visual discrimination task were identical to those in the temperature paradigm. The mean number of trials required by these sophisticated monkeys to reach criterion performance of 72 correct responses in 80

trials (90%) was 450 ± 243 (S.D.) (see Table 2). The mean number of trials to learn this visual task may be somewhat inflated since 4 of the 5 monkeys did not look at the symbols during the initial trials. Although the monkey Daimon was the only animal that appeared to be looking at the symbols and to be aware that a visual problem was being presented during the initial 100 trials, he nevertheless required the largest number (825) of trials to reach criterion performance (see Table 2).

Effects of brain stimulation on visual discrimination

Performance deficits. In the visual discrimination task mean performance was essentially unchanged during stimulation of all the same brain sites used in the temperature problem, either during the initial three days of stimulation (Fig. 2A) or during repeated daily stimulation (Fig. 3). For the grouped data the mean performance in the visual task was significantly better than that in the temperature discrimination task during limbic forebrain stimulation (Fig. 2A; Figs. 3A–C). Only one of the 5 animals performed poorly on the first day of limbic forebrain stimulation.

Latency changes. The latency of the responses were variable across animals but were increased during brain stimulation similarly to that observed during temperature discrimination (Fig. 2B; Table 4). Although there were very few errors in the grouped data

Table 4. Mean latency changes in visual discrimination during all days of brain stimulation

Brain Area Stimulated	No. of Sessions	Latency change from control in sec. (Mean ± S.E.) All Responses (A)	Correct Responses (B)	Incorrect Responses (C)	Difference (C-B)
Amygdala	44	4.438 ± 2.209	3.702 ± 1.644	11.925 ± 5.936	8.223 ± 3.705
Orbital	22	3.457 ± 1.631	2.824 ± 0.987	16.810	13.986
Stria Terminalis	22	0.823 ± 0.369	0.746 ± 0.305	1.917 ± 0.589	1.171 ± 0.154
SI	15	0.620 ± 1.066	0.603 ± 1.069	-------	-------
SII	22	-0.042 ± 0.076	-0.042 ± 0.076	-------	-------

for the visual problem, latency of incorrect responses, when present, tended to be greater than those for correct responses (Table 4).

DISCUSSION

The results of the present experiment show that a gross temperature discrimination can be disrupted by electrical stimulation of limbic structures: orbitofrontal cortex, amygdala and stria terminalis. No such disruption occurred in a visual discrimination designed to be

comparable to the temperature task in every way except modality. Nor did electrical stimulation of somatosensory cortex (SI and SII) have similar effects on temperature discrimination, although minimal fleeting effects of stimulation in this location were occasionally observed.

There were differences between the effects of stimulation of the orbital cortex and those of the amygdala. Orbital cortex stimulations caused persistent erroneous performance of considerable magnitude producing a great change in reaction time. By contrast, stimulation of the amygdala and of the stria terminalis caused prolonged reaction times and the effects of stimulation, when repeated over many days, gradually habituated.

The question arises whether such an increase in reaction time would in itself be a sufficient explanation for erroneous performance during amygdala and stria terminalis stimulations. We cannot answer this question definitively, though we designed the visual discrimination to control for this possibility. Amygdala and stria terminalis stimulation increased response latency in the visual as well as in the temperature task, yet visual discrimination remained intact. Still, the argument can be made that short-term memory is more readily disrupted in the somatosensory than in the visual mode [35–37], and that therefore the effects of amygdala system stimulation influence primarily short-term memory rather than temperature discrimination. We consider this explanation unlikely since the measured increase in reaction time was to a large extent, if not exclusively, due to delays in starting a trial and in touching the temperature panels during the sampling period. Only a small part of the increase can be attributed to a delay involving short-term memory: i.e. in making the final decision of selecting the correct panel.

The differences between the effects of orbital cortex stimulation and those of the amygdala system are more likely due to a difference in primary localization of temperature discrimination. The orbital cortex lies just anterior to the rostral hypothalamic region known to be the prime center for temperature regulation [27], see recent review [38]. Further, orbital cortex stimulation is known to produce changes in peripheral vascularity and temperature [39–41].

The amygdala system, on the other hand, is known to modulate primary physiological regulatory mechanisms, not to participate in them directly (see reviews in [42] and [43]). The results of the present experiment on temperature discrimination are therefore consonant with those reported earlier. However, temperature is usually considered to be a somatosensory modality, not just an internal physiological regulatory mechanism. The interest of the results of the present experiment derives from this juxtaposition in a brain system of an exteroceptive with an interoceptive function.

The monkeys used in this study were initially introduced to the concept of temperature as the modality being discriminated in a Wisconsin General Testing Apparatus. As expected, the number of trials for acquisition of the temperature discrimination increased with difficulty of the task as the temperature differences became smaller. However, it was an unexpected finding that the 4 female monkeys learned all the temperature discriminations in about one-half the number of trials required by the males. Sex differences in normal temperature sensitivities attributed to progesterone release have been described in humans [44]. No sex differences were observed in acquisition of two difficult visual discriminations involving color and pattern. It is thus possible that the male monkeys in this study performed poorly since they had greater difficulty than the females in the temperature testing situation. This possibility is supported by the observed hyperactivity of the male monkeys in the Wisconsin General Testing Apparatus and the fact that 3 of the 4 males had to be

dropped from the automated study since they were performing at the chance level after 5600 trials (140 days of testing).

Since we were interested in the qualitative detection of temperature for its intensive aspect rather than in its finer discrimination, we chose to study temperature differences of 15°C in the computer-controlled situation. This difference is quite large compared to the known capacity of man [45] and monkey [46] to detect differences of less than 1°C. In spite of the supposedly easy temperature discrimination and the extensive preliminary training of the animals, this study has been extremely difficult and lengthy since thousands of trials (mean of 7372) spread over hundreds of days were required before the monkeys reached criterion performance. The three major test factors that contributed to the difficulty of the temperature task were the complexity of the paradigm, the long intertrial interval of 30 sec needed for the thermoelectric units to change temperature combined with associated restlessness of the animals, and the varied techniques used by the individual animals in pressing the response panels. The two monkeys that required up to 15,000 trials to learn the temperature discrimination touched the panels only lightly with their fingertips, while the other animals pressed them firmly with their palms. Additional force in pressing the temperature discriminanda also improved the performance of the monkeys used in the study of CRAGG and DOWNER [46].

Except for occasional, minimal, transient, one-day effects, stimulation of cortical sensory areas SI and SII were ineffective in disrupting gross temperature discrimination in the monkeys compared to the larger effects of the limbic forebrain areas. Only 1 of 5 monkeys showed such a minimal effect during SI stimulation but 3 of 5 showed it during stimulation of SII. CRAGG and DOWNER [46] found unilateral lesions of SI and SII in monkeys did not affect temperature discrimination greater than a difference of 2°C in the contralateral hand, but the transfer of this discrimination to the untrained hand was impaired after lesions of precentral and postcentral gyri. In rats, bilateral lesions of somatosensory cortex (SI) had no effect on discrimination of temperature differences of 10°C [32] but variably impaired finer discrimination of 3°C [33]. Rats with combined lesions of SI and SII showed no temperature deficits [33]. Our stimulation results for sensory cortex are thus in agreement with the lesion studies since in our experiments only large temperature differences of 15°C were routinely studied.

The effects of orbital cortex and amygdala system stimulation are of course not limited to the temperature modality. The effect of prolonging the reaction time and reducing intertrial responses and general reactivity confirms similar effects previously reported in [47] and [48]. Habituation to repeated electrical stimulation has also been routinely found: of an alerting response evoked by amygdala stimulation [49], of an amnestic response [50]. Yet, in contrast to the specific effects obtained in these and in the present study, chronic stimulation of the amygdala at intensities sufficient to evoke after discharges bilaterally does not modify ordinary lever pressing in positive and negative reinforcing situations in which food, electric shock or brain stimulation are used [48]. This, as well as experiments using the split brain technique [51–53], in which the effects of unilateral amygdalectomy were shown to be ipsilaterally restricted, suggest that attentional rather than performance factors are involved. The involvement is considered to be attentional rather than sensory because threshold (to electric shock) in amygdalectomized monkeys is unaltered when measured by the galvanic skin response [31]. Still, such attentional influences appear to operate via an efferent control mechanism which is to a large extent inhibitory. Several types of studies using stimulation have assigned an inhibitory function to orbital cortex.

KAADA, PRIBRAM and EPSTEIN [40] and KAADA [47] found slowing of heart rate, temporary arrest of respiration and fall in blood pressure as well as somatomotor inhibition induced in cats, monkeys and humans during stimulation of the posterior orbital areas, the insula and temporal pole. In chloralosed cats, electrophysiological studies showed that stimulation of orbital cortex reduced various reflexes [54–57], and both spontaneous and evoked unit firing in lumbar dorsal horn interneurons of laminae IV and V [58]. Of major interest to the thesis which motivated the current research is the fact that these very lamina of the dorsal horn receive cutaneous input from small myelinated fibers [59] and [60] and are involved in transmission of painful stimuli. These inhibitory effects of orbital cortex on reflexes and the dorsal interneurons are thought to be presynaptic and mediated through the brainstem [58], similar to those found in trigeminal afferents [61].

Further support of the thesis that the anterior limbic forebrain serves the intensive aspects of interoceptive and a variety of exteroceptive modalities comes from changes in electrical activity evoked in the limbic areas. The recordings of electrical responses in orbital cortex indicate it is an area of convergence of visceral [62] and [63], thermal [64] and [65], somatosensory (excluding light touch or hair movement), visual, and auditory inputs [66] and [67]. From such data ALBE-FESSARD [68] has proposed that the orbital cortex in the cat receives the projection of discriminative pain. We add, on the basis of the results of the experiment reported here, that the orbital cortex is also involved in the discriminative aspects of temperature and perhaps of the intensive dimension of other sensory modalities.

When discrimination involves intensity, parietal cortex resections (which alter localization, the extensive dimension) fail to produce any change. Thus removal of the parietal lobes did not affect pain tolerance of monkeys trained to press a lever to lower the intensity of shocks delivered to the gasserian ganglion [69]. Following limited resections of the postcentral gyrus in man, pain may be somewhat reduced, but is not blocked [70] and even these effects are often only temporary (WHITE and SWEET). By contrast, amygdala stimulation has been reported to relieve pain for from 12 to 36 hr after termination of the stimulation [5], and following bilateral amygdalectomy, 2 of 4 cases of trigeminal neuralgia have reported complete relief, the other two obtaining a partial effect [71].

In summary, the current study has shown that temperature discrimination can be grossly interfered with by electrical stimulation of orbital cortex and the amygdala system and only minimally, if at all, with parietal cortex stimulation. However, the effects of amygdala system stimulations (but not those of orbital cortex) habituate, and are thus most likely to be due to attentional factors. The effects on temperature discrimination are in any case not considered to be unique. Evidence from other studies is reviewed to show that orbital cortex and amygdala serve other modalities, as well. The effects on pain are of special interest because of the association at the spinal level of pain and temperature. On the basis of these data the hypothesis is tendered that pain and temperature tracts form the core of a protocritic neural system engaged in the processing of the intensive dimension of sensory experience. Experiments are now under way to test further this hypothesis.

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Résumé :

On a procédé à une investigation indirecte des substrats nerveux susceptibles de participer à la modulation de l'expérience douloureuse en étudiant les effets de la stimulation cérébrale sur la discrimination de température chez les singes rhésus. Par comparaison avec la stimulation du cortex somatosensitif, la stimulation des structures limbiques (amygdale et gyrus orbitaire) perturbait la performance de discrimination de température. Les erreurs de discrimination diminuaient avec des stimulations répétées de l'amygdale mais non du gyrus orbitaire. En revanche, la performance de discrimination visuelle n'était pas affectée par des stimulations cérébrales similaires. Ces résultats de même qu'une revue de la littérature suggèrent que les structures limbiques font partie d'un système protocritique qui s'occupe des aspects intensifs de l'expérience.

Deutschsprachige Zusammenfassung:

Während der Untersuchung von Reizeffekten am Gehirn bezüglich grober Temperaturunterscheidung bei Affen wurden indirekt neurale Substrate entdeckt, die möglicherweise an der Regulierung von Schmerzerlebnissen beteiligt sind. Die Temperaturunterscheidungsfähigkeit wurde während einer Reizung limbischer Strukturen unterbrochen (Amygdala und orbitaler Gyrus) und zwar im Vergleich zum sensomotorischen Cortex. Die Fehler gingen bei wiederholter Reizung der Amygdala zurück, nicht aber bei Reizung des orbitalen Gyrus. Im Gegensatz dazu wurde die optische Unterscheidungsfähigkeit während einer ähnlichen cerebralen Reizung nicht beeinflußt. Diese Ergebnisse und Berichte in der Literatur sprechen dafür, daß der limbische Hirnbereich an einem protokritischen System teilhat, das sich mit Intensitätsaspekten von Erfahrungen befaßt.