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INFLUENCE OF THE CEREBRAL CORTEX ON HABITUATION

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If sensory stimuli are repeatedly applied to intact animals or to people at intervals of minutes, hours, or days, then the responses to those stimuli gradually diminish or disappear. This is a result of habituation, and there is reason to believe that it is a fundamental physiological mechanism of adaptation (Glaser & Whittow, 1953) but it has been known to psychologists for a long time (see Humphrey, 1933; Davis, 1934). The problem has been previously discussed (Glaser & Whittow, 1957; Glaser, Hall & Whittow, 1959) and reviewed (Glaser, 1958; Scholander, 1961).

A number of experiments had shown that the intensity of responses could be altered by impulses originating in the brain (Hagbarth & Kerr, 1954; Galambos, 1956; Hernandez-Peon, Scherrer & Velasco, 1956; Sharpless & Jasper, 1956; Hagbarth & Kugelberg, 1958; Glaser *et al.* 1959; Scholander, 1960) and there was also some specific evidence that the cerebral hemispheres might influence habituation (Glaser & Whittow, 1957; Glaser, 1958), but the part played by the cerebral cortex was by no means clear. The present experiments were designed to investigate this further.

In studies of habituation there must be a precise and reproducible stimulus which gives rise to a response that can be quantitatively assessed. It was known that rats could become habituated to a cold stimulus, and a technique for measuring the heart rate of conscious animals without trauma was available (Glaser & Yap, 1959; Glaser, Griffin & Knight, 1960). It was known also that the rat's tail served temperature regulation in the same way as the human hand (Knoppers, 1942), and preliminary tests had shown that immersions of rats' tails in water at 4° C were accompanied by an increase of the heart rate which resembled that observed during cooling of a hand in a previous experiment on habituation (Glaser & Whittow, 1957). This meant that the cooling of rats' tails could provide a suitable stimulus, while measurements of the heart rate would provide a suitable response. Some of the results have already been briefly reported (Glaser & Griffin, 1961).

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METHODS

Procedure. Female Wistar rats with initial weights of 120–130 g were used. Throughout the experiment the rats lived in the room in which the tests were carried out and which was kept at a temperature of 20–22·5° C (dry bulb) and 16·5–18·5° C (wet bulb). In all experiments each rat was held vertically without much restraint in a copper-wire tube from which its tail protruded through a rubber stopper to a constant level; the top of the tube was open and lined with rubber, comfortably supporting the animal's head and neck, so that its eyes and nose were outside the tube. Platinum-wire electrodes of 26 s.w.g. were inserted into the skin of the animal's backs under light ether anaesthesia, or while the animals were under pentobarbitone anaesthesia for operations on the brain, and screened electrocardiogram (e.c.g.) leads were clipped to these electrodes before each test. The electrodes remained there throughout the experiment, and they rarely needed replacing, as the animals took no notice of them.

Previous experiments had shown that placing rats in the vertical position caused a rise of their heart rates even after 30 min were allowed for immediate postural adjustments, but when the rats were put into that position every day for several days the rise of their heart rate became gradually less, which suggested that habituation to the vertical position had taken place (Glaser & Yap, 1959). It has also been observed in man that experimental procedures produced responses which diminished with habituation (Glaser, 1953; Glaser & Whittow, 1954). The rats were therefore placed vertically in the copper wire tubes for 2½ hr daily on 14 consecutive days while their tails were immersed to a constant level in water at 31° C, and every rat was trained to the basic experimental conditions in this way. Operations on the brain were done 7 days before this habituation to the experimental conditions was begun.

Immersions of the tails at 4° C were only carried out after training the rats to the experiment over 14 days. Base-line readings of the heart rate were taken each day before the tail was cooled and after the rats had been under the basic experimental conditions for 45 min with the tails at 31° C. All immersions of the tail at 4° C lasted for 10 min and they were always repeated six times daily with intervals of 10 min during which the tails were at 31° C.

Measurements. The heart rate was counted by decade scalers into which the amplified and discriminated R spike of the e.c.g. signal was fed. An automatic time switch gave readings over 15 sec, which meant that there was no subjective elements in these counts. Signals were monitored on cathode-ray tubes and on the scalers (Glaser *et al.* 1960).

The oxygen consumption of conscious rats was measured in a respirometer, as described by Davis & Van Dyke (1932), and the readings were taken by someone otherwise unconnected with the experiment who did not know what operations had been carried out on any particular animal.

The skin temperature was measured by copper-constantan thermocouples looped around the tail at a constant distance from its tip and closely adhering to the skin. The temperature was read on a calibrated potentiometer to 0·1° C and the reference junction was in melting ice.

Operations. Pentobarbitone anaesthesia was used. The fronto-parietal suture was located on the skull, and the site of operations was related to this. Lesions were produced by undercutting the cerebral cortex with a mounted sharpened needle inserted through burr holes, after which the separated brain tissue was removed by gentle suction. Stimulation of the brain surface was done by concentric stainless-steel electrodes, as described by Galambos (1956). Burr holes were made 7 days in advance under general anaesthesia and the electrodes inserted on the day of the experiment with local anaesthesia of the skin. The resistance of the electrodes in open circuit was 20–50 MΩ. After recovery from the immediate effects of operation, the operated rats ate, drank, gained weight, and cleaned themselves in the same way as the unoperated controls.

Histological studies. All operated brains were removed, fixed in formol-saline, and mounted in paraffin; serial sections were stained either by haematoxylin and orange G or by luxol fast blue and cresyl violet (Klüver & Barrera, 1953). Every section was independently checked by a neuropathologist who was specially interested in the rat's brain but otherwise unconnected with the experiment, and rats were allocated to different groups according to his assessment based on the presence of changes during the animal's lifetime, such as pigment phagocytosis, gliosis, and demyelination.

RESULTS

Habituation to the experimental conditions

When the rats were first placed vertically in the copper-wire tubes with their tails at 31° C, a steady state of the heart rate was achieved after 45 min in the tubes. On successive days the heart rate became gradually lower. This is shown in Fig. 1, which gives the results from a batch of eight

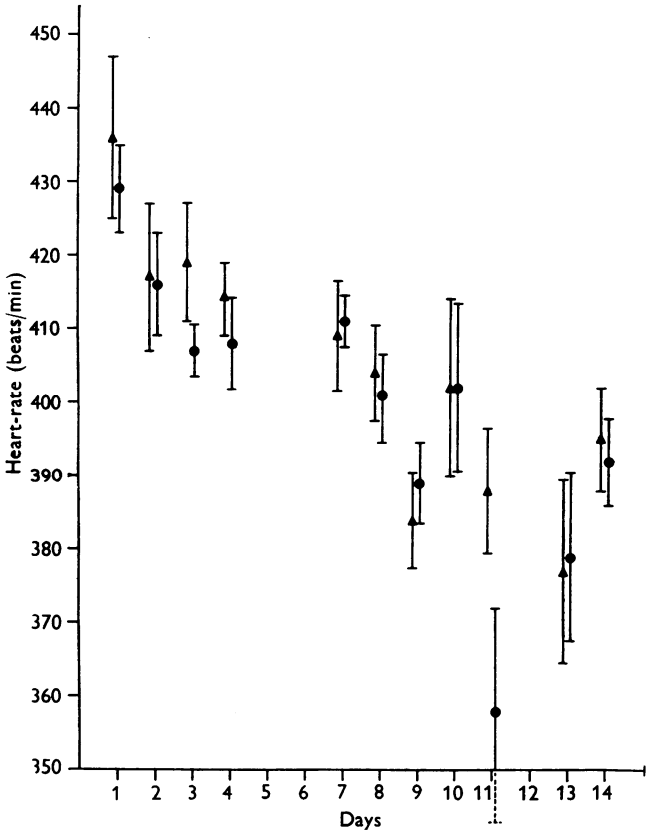

Fig. 1. Habituation to the basic experimental conditions. Mean heart rates, with standard deviations, of eight rats on 14 successive days, after 45 min and 2½ hr in vertical, rubber-lined tubes, with the tails at 31° C. ▲ 45 min, ● 2½ hr.

normal rats placed in the vertical position for 2½ hr daily over 14 consecutive days while their tails were at 31° C. On the 1st day the mean heart rate was 437 beats/min after 45 min and 429 beats/min after 2½ hr; on the 14th day it was 398 beats/min after 45 min and 396 beats/min after 2½ hr. The gradual fall of the heart rate over 14 days followed the same pattern as habituations previously observed (Glaser & Whittow, 1957; Glaser *et al.* 1959; Glaser & Lee, 1959). The finding that the heart rates were similar at 45 min and at 2½ hr also meant that base-line readings obtained at 45 min were relevant to experiments lasting for another 1½ hr.

Figure 2 shows the basic heart rates of rats with and without different lesions of the brain surface after 14 days' training to the experimental conditions, and it also shows that once habituation had taken place to the experimental conditions the basic heart rate was not affected to any relevant extent by immersions of the tails at 4° C on preceding days. Before the first immersion of the tails at 4° C (after 14 days' habituation to the experimental conditions), the mean basic heart rates of normal control rats, of animals with unilateral lesions of the frontal area, and of animals with lesions of the occipito-parietal region were within the mean range of 380–410 beats/min, and there was no further fall during the next 10 days, though there were some day-to-day fluctuations. In nine rats with superficial bilateral lesions of the frontal areas the mean basic heart rate was 461 beats/min after 14 days' training to the experimental conditions and 458 beats/min 10 days later.

Oxygen consumptions of normal rats and of rats with bilateral frontal cortical lesions. In order to find out whether the higher heart rates of rats with bilateral frontal cortical lesions were caused by some metabolic change or by an inability to adjust to the basic experimental conditions, the oxygen consumptions were measured in a respirometer, with the rats either unrestrained or held vertically in the tubes. Errors from habituation to the respirometer were avoided by comparing operated and unoperated rats of the same weight which had and which had not been trained to the experimental conditions.

When unoperated rats and rats with bilateral frontal cortical lesions were not under the basic experimental conditions their mean oxygen consumption was 2–2·16 l./kg/hr both before and after training to the experiment. Under the experimental conditions the mean oxygen consumption of all untrained rats increased by 40–44 %, but after 14 days' training this increase was only 11 % in control rats, whereas in rats with bilateral frontal lesions it remained at 45 % (Table 1).

TABLE 1. Oxygen consumption of rats with bilateral frontal cortical lesions and of normal controls (Standard errors of means are given in brackets)

	No.	Mean weight (g.)	Mean O_2 consumption (l./kg/hr)		
			Outside tubes	Inside tubes	Difference (%)
Without training to experiment					
Operated rats	6	134 (±3·5)	2·16	3·09	44 (±5·1)
Controls	6	136 (±2·0)	2·12	2·93	40 (±5·3)
After 14 days' training to experiment					
Operated rats	5	142	2·13	3·13	45
Controls	6	137 (±4·4)	2·00	2·13	11 (±8·7)

Habituation to repeated immersions of the tail at 4° C

Figure 2 shows the mean increases of the heart rate observed in rats with and without lesions of the cerebral cortex while their tails were being immersed at 4° C six times daily for 10 min at a time on 10 consecutive days, and it shows that the heart rate of all operated and unoperated animals increased when their tails were being cooled; this increase became gradually less if the frontal cortex was intact at least on one side of the brain, but it remained about the same during 10 days if the frontal cortex was bilaterally damaged.

The animals were tested in ten batches, each of which contained two operated rats and one normal control. The mean heart rate of ten normal control rats rose by 79 beats/min over its basic level on the 1st day of cooling at 4° C, and this increase became gradually less, until it was only 28 beats/min on the 10th day, the difference between the means on the 1st and 10th day being significant ($t = 9{\cdot}888$; $P < 0{\cdot}001$). Rats with lesions of the occipito-parietal cortex gave results which were indistinguishable from the normal controls, the mean increase of the heart rate being 77 beats/min on the 1st day and 34 beats/min on the 10th day of immersion of the tail at 4° C ($t = 9{\cdot}225$; $P < 0{\cdot}001$). Rats with one-sided lesions of the frontal area gave results which resembled those obtained in normal controls, showing a mean increase of 64 beats/min on the 1st day and 30 beats/min on the 10th ($t = 5{\cdot}605$; $P < 0{\cdot}001$). In all these three groups of rats the actual heart rates while the tail was being cooled were 455–480 beats/min on the 1st day and 410–430 beats/min on the 10th day.

Rats with bilateral lesions of the frontal areas had higher initial heart rates under the basic experimental conditions (see above) and they showed a smaller relative response to cooling of their tails than other rats, the mean increase of the heart rate being 42 beats/min on the 1st day, but the actual heart rate was 20–30 beats/min higher in these than in other rats. Subsequently neither the absolute heart rate nor the relative increase above the

base level showed any tendency to diminish while the tail was being cooled, and the absolute heart rate remained in the vicinity of 500 beats/min.

There were some superimposed irregular variations of the responses, which resembled daily variations of the heart rate under the basic experimental conditions, but analysis of variance showed that the results were not influenced by any variations of technique or of environment. Analysis of variance showed also that there were no significant interactions of any variables with different immersions of the tail at 4° C on the same day.

Measurements of the skin temperature of the tail showed that equilibrium was always reached after 5 min at 4° C and that the tail temperature

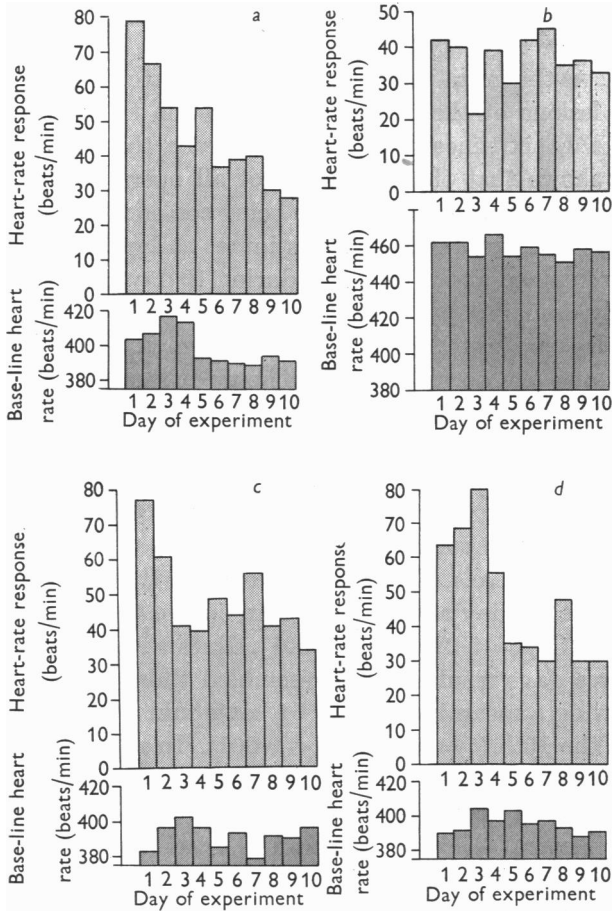

Fig. 2. Responses of the heart rate to immersions of the tails at 4° C. *a*, mean of ten normal control rats; *b*, mean of nine rats with bilateral frontal cortical lesions; *c*, mean of six rats with occipito-parietal lesions; *d*, mean of five rats with unilateral frontal lesions.

during and before immersions at 4° C did not change over 10 days, which conforms with similar observations made on the human hand (Glaser & Whittow, 1957). Histological examination of the tails at the end of the experiment showed no evidence of tissue damage through cold injury.

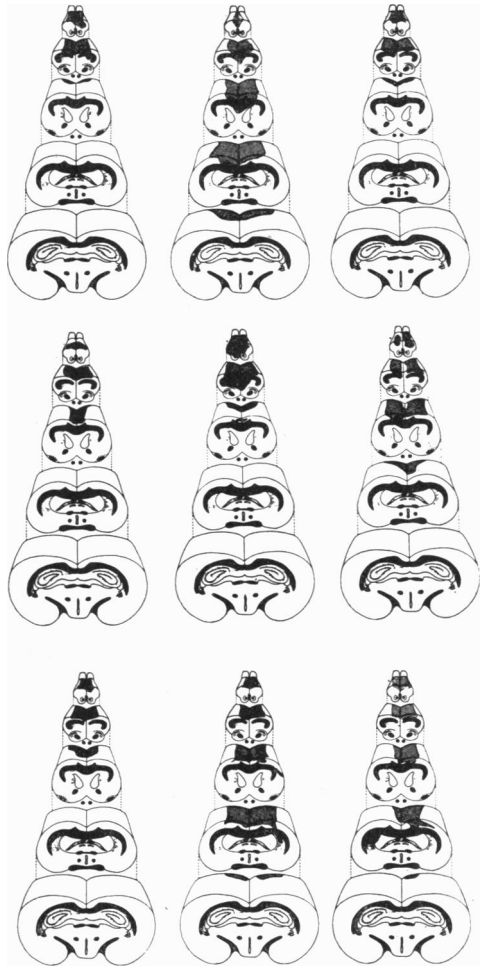

Fig. 3. Sites of bilateral frontal lesions drawn from serial sections of the brain.

Sites of lesions. Figures 3–5 show the extent of lesions in the twenty operated rats. The amount of brain tissue removed from the occipito-parietal area in some of the rats which did habituate to cooling of their tails was greater than the amount removed from both sides of the frontal area in some of those rats which showed no diminution of their responses after repeated immersions of the tail at 4° C, and the absence or presence

of habituation was in no way related to the amount of cortical tissue removed, but only to the site of the lesions. It should be noted, however, that none of the lesions were large.

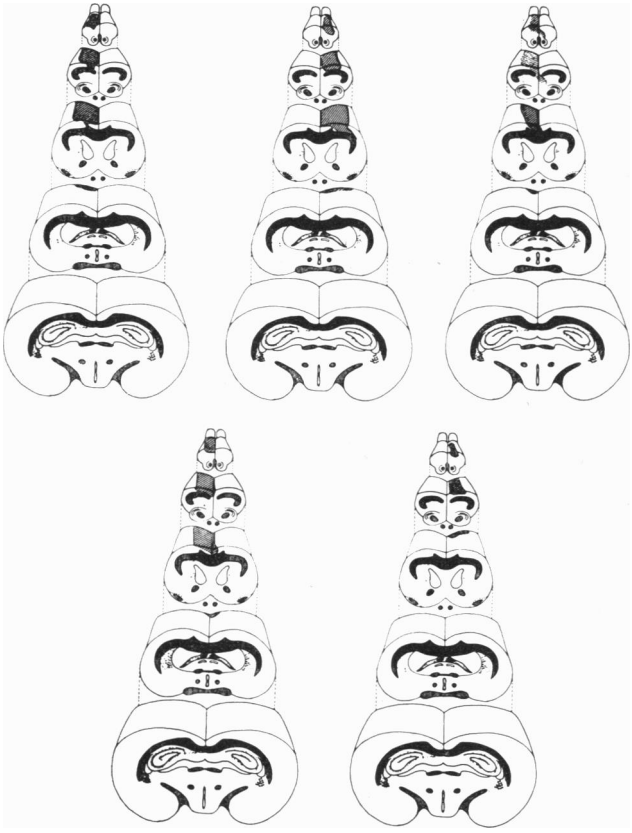

Fig. 4

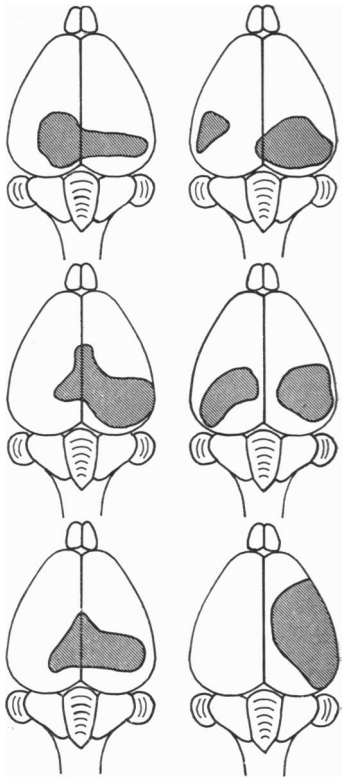

Fig. 5

Fig. 4. Sites of unilateral frontal lesions, drawn from serial sections.

Fig. 5. Sites of occipito-parietal lesions drawn from serial sections.

Effects of lesions upon established habituation

After training to the experimental conditions over 14 days eight normal rats had their tails immersed six times daily for 10 min at a time in water at 4° C as in the experiments described above, but bilateral frontal lobe lesions were made immediately after the 10th series of such cold immersions. During the following 6 days the rats were placed vertically in the tubes with their tails at 31° C, as for preliminary training to the experimental conditions but without any cooling of their tails. On the 7th day after the

operation the rats were again tested six times for 10 min with their tails at 4° C, and it was found that the heart-rate response of two rats had returned to the same level as when the tail was first cooled, but in the other six the response remained low, which suggested that habituation had been lost in only two out of eight animals. The main results are given in Fig. 6. Under

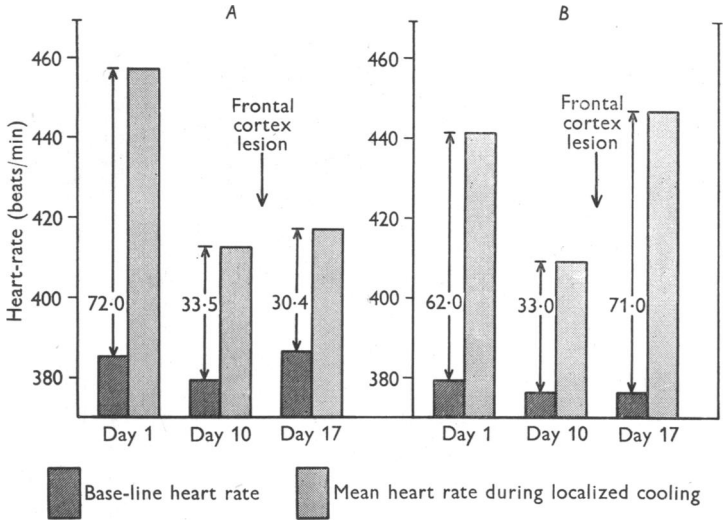

Fig. 6. Effects of bilateral frontal cortical lesions applied after habituation to localized cooling. *A*, mean results from six rats in which lesions did not alter the response of the heart rate to cooling of the tails. *B*, mean of two rats in which 7 days after operation the response returned to its original level.

the basic experimental conditions the heart rate did not increase significantly 7 days after bilateral frontal lobe lesions in any of these eight rats. Subsequent histological examination of the brains showed that the lesions were in the same regions and of a similar extent as bilateral frontal lesions shown in Fig. 3.

Eight control rats were tested in the same way but without any operations. Habituation to immersions of the tails at 4° C closely resembled that shown in Fig. 2*a*. Reduced responses of the heart rate to cooling of the tail were still observed 7 days or 14 days later, even though the tails had only been immersed at 31° C on the intervening days, there being only small and apparently random differences between the responses on the 10th day of daily immersions and after intervals of 7 or 14 days. This conformed with similar observations made on man (Glaser *et al.* 1959).

After habituation to the basic experimental conditions and to cooling of the tail, large lesions were applied to the cerebral cortex of two rats,

without involving the frontal areas, but causing more extensive damage than any lesions shown in Figs. 3–5. Seven days after such operations the heart rates were raised both under the basic experimental conditions and with the tails at 4° C, which conformed with findings by Lashley & Wiley (1933) that large lesions of the brain can cause a loss of stored information, irrespective of the site of lesion.

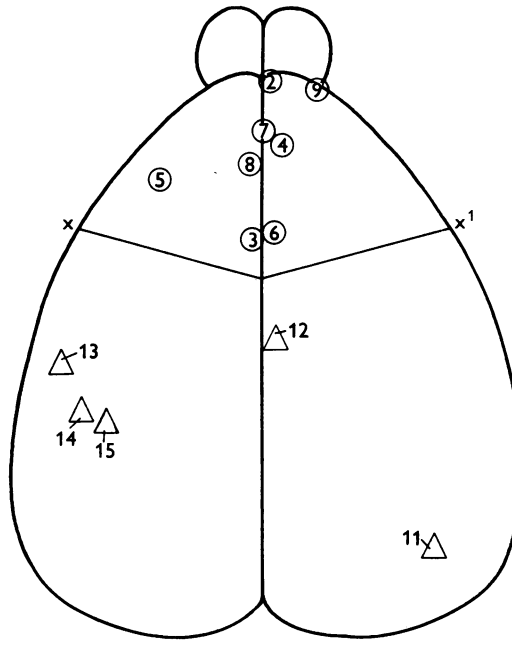

Fig. 7. Sites of stimulating electrodes on the brain surface. $x-x^1$ shows the position of the fronto-parietal suture.

Stimulation of the brain

Figure 7 shows the points at which stimulating electrodes were applied to the cerebral cortex. After habituation had been carried out over 14 days, as in Fig. 1, the tail was cooled six times at intervals of 10 min as in all other rats, but throughout the 2nd, 4th, and 6th immersions the brain was stimulated by square waves of 24 μA at frequencies of 0·5–30 impulses/sec with a duration of 0·9 m-sec. Figure 8 shows the mean results from eight rats in which electrical stimuli were applied to the frontal areas of the cerebral cortex (numbers 2–9 on Fig. 7), and in all these rats the responses to cooling were greatly reduced or abolished, both while the stimuli were applied and thereafter. While electrical stimuli were not being applied, the mean increase of the heart rate during cooling of the tail was 63 beats/min;

with stimulation it fell to 5 beats/min. Twenty-four hours after electrical stimulation of the brain the responses to immersion of the tail were still very much smaller than on the 2nd day of immersions in control rats (Fig. 2*a*) or in the same rats without stimulation, the differences being so large and consistent that statistical assessment of their significance was not appropriate (Fig. 8). For the next 5 days these animals were put vertically into the tubes with their tails at 31° C for $2\frac{1}{2}$ hr daily, and 7 days after the electrical stimuli had been applied to the brain the responses of the heart rate to cooling of the tails were still almost as low as they had been during electrical stimulation.

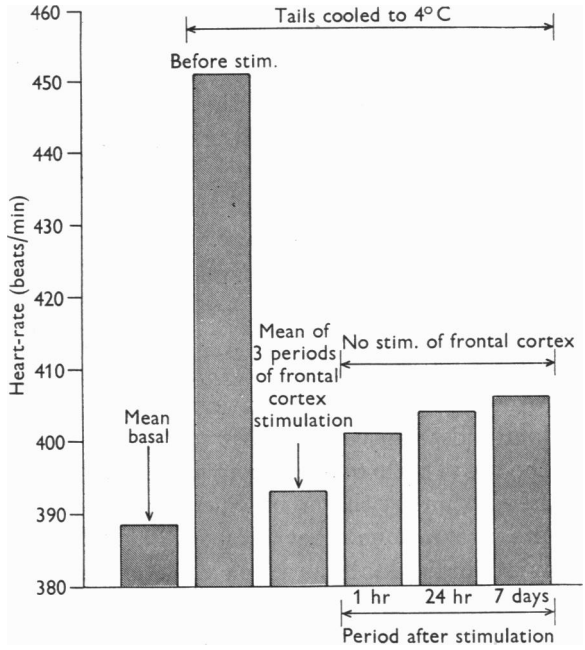

Fig. 8. Effects of stimulation of the frontal cortex upon responses of the heart rate to cooling of the tail. Mean result of eight rats (numbers 2–9 in Fig. 7).

Stimulation of the brain surface in the occipito-parietal region (Fig. 7, numbers 11–15) had no effect on the responses of the heart rate to cooling of the tail, either during stimulation or thereafter, and, if anything, stimulation was accompanied by a greater response of the heart rate to cooling.

Stimulation of the frontal areas at up to 30 impulses/sec under the basic experimental conditions while the tails were at 31° C did not alter the heart rate to any relevant extent. When the frontal cortex was stimulated

during immersions of the tail at 4° C at 100 impulses/sec, no effect on the heart rate was observed either during stimulation or subsequently, which might have been due to a Wedensky inhibition.

DISCUSSION

Validity of the results

In the present experiment there were two habituations, one to the experimental conditions, the other to cooling of the rats' tails at 4° C. The former depended on a complex stimulus which consisted of the rats being placed in the vertical position inside tubes with their tails immersed to a constant level at a neutral temperature and with leads clipped to indwelling electrodes, and it included a small amount of constant noise from apparatus. The second was to a single precise stimulus caused by cooling of the tail. Responses of the heart rate to cooling of the tail were related to base-line readings obtained under identical conditions on the same day (Fig. 2, 6, 8) but habituation to the experimental conditions was expressed in terms of the actual heart rates observed (Fig. 1), as in rats any attempt to measure the heart rate will inevitably alter it. The normal heart rate of rats is not known. It was given as 328 beats/min with a range of 261–600 (*Handbook*, 1956*a*) and as 460 beats/min at a body temperature of 37–39° C (*Handbook*, 1956*b*).

Oestrus, which takes place every 4–5 days, was an uncontrolled variable and it may have contributed to fluctuations of the heart rate, but its effects were randomly distributed, so that it could not have invalidated the results, whereas the use of male rats could have introduced errors because of mild trauma to the scrotum by the tubes. Since analysis of variance showed that there were no interactions other than irregular daily fluctuations of the basic heart rates of individual rats which influenced the results, and since the design of the experiment ensured that all possible causes of error should either be excluded or randomly distributed, significant changes of the responses could only have been due to previous applications of the stimuli.

The fact that removal or stimulation of the cerebral cortex in the frontal areas had any effect on habituation must have been due to those particular procedures, since the removal or stimulation of other cortical areas had no such effect. Immediate post-operative disabilities could not have played any part, because these would have been the same in all operations on adjacent parts of the brain and because at least 7 days were allowed to elapse before any data were collected after any operation. However, the loss of habituation observed in two rats after large lesions not involving the frontal areas shows that conclusions based on extensive damage to the brain could be misleading in the context of the present experiment.

The question was considered whether it could be concluded that rats with bilateral frontal lesions did not become habituated to immersions of their tails at 4° C because these rats had higher initial heart rates under the basic experimental conditions and smaller responses to localized cooling than other rats. However, the actual heart rates during cooling of the tails were higher in rats with bilateral frontal lesions at the end of the experiment than in other animals at the beginning, and presumably baroreceptor reflexes had come into play while the tails were being immersed at 4° C; these reflexes would have prevented as great a relative increase of the heart rate as if the initial heart rate had been lower. The results can only mean that rats with bilateral frontal lesions responded to localized cooling and that they showed no signs of habituation.

The possibility that the diminution of responses to localized cooling of the tail might have been due to some adaptation of peripheral receptors seemed a remote one, because successive immersions at 4° C on the same day produced no consistent change of response, not even by analysis of variance, and this possibility has been eliminated in a separate investigation of nerve fibres in the rat's tail (J. P. Griffin and Ingrid Witt, unpublished). It is unlikely that the diminution of response observed after repeated cooling (Fig. 2*a*, *c*, *d*) was related to a change of blood flow through the skin of the tail, because the skin temperature did not change nor were there any obvious histological changes in the tails. The normal resting oxygen consumption of rats with bilateral frontal lesions (Table 1), and their normal growth and intake of water, make it seem unlikely that the gradual diminution of responses was due to some primary changes of the endocrine system, and it seems even more unlikely that such endocrine changes should have been prevented or abolished by bilateral frontal lesions and accelerated by stimulation of the frontal areas.

The frontal areas

It is evident from these findings that in rats the frontal areas of the cerebral cortex play a specific part in controlling the intensity of responses, both by immediate effects and by habituation. The fact that rats with bilateral frontal lesions failed to become habituated either to the experimental conditions or to immersions of the tails at 4° C, although unoperated controls and operated rats in which at least one side of the frontal area was intact showed normal habituations, suggests that the relationship between the frontal areas and habituation is not limited to localized nociceptive stimuli but includes the complex adjustments to the experimental conditions (Table 1, Fig. 2). The specific influence of the frontal cortex on the level of responses was further shown by the findings that stimulation of this area, but not of other parts of the brain surface, depressed the re-

sponses to localized cooling and accelerated habituation. The present results have thus confirmed and expanded earlier circumstantial evidence that 'not only the responses but also habituation of these responses can be modified by the cerebral cortex' (Glaser, 1958). These findings are also in good agreement with those obtained in a different context by Brutkowski, Konorski, Lawicka, Stepien & Stepien (1956) and Lawicka (1957), who observed a loss of inhibitory conditioned reflexes in dogs after bilateral frontal lobectomies.

Previous experiments in which one hand was habituated to cold (Glaser & Whittow, 1957) or to heat and cold (Glaser *et al.* 1959) and in which responses of the heart rate were studied, suggested the possibility that habituation may have some functional localization in the brain, and the present experiments have shown that comparatively small areas of the frontal cortex can have an important influence upon habituation; but it does not follow that the frontal areas of the brain contain a kind of 'habituation centre'.

The nature of habituation

Habituation undoubtedly adjusts the level of responses in intact higher organisms according to previous experience of the appropriate stimuli, but the intensity of responses does not depend on habituation alone. Even if the stimulus is constant and the state of habituation unchanging, the magnitude of the appropriate responses can be modified by arousal from other stimuli arriving at about the same time (Glaser *et al.* 1959). It is known that arousal depends both on the brain-stem reticular formation and on the cerebral cortex (Hagbarth & Kerr, 1954; Galambos, 1956; Hernandez-Peon *et al.* 1956; Dawson, 1958), and the present experiments have shown that habituation depends on the frontal areas of the brain. It would seem, therefore, that the cerebral cortex and the brain-stem reticular formation act together in adjusting the level of responses according to the intensity of present stimuli and according to stored information about previous stimuli. Habituation would appear to be that part of this mechanism which depends on stored information, but the fact that habituation was not necessarily lost after bilateral damage to the frontal areas (Fig. 6) probably means that the frontal areas are needed only to establish a change of response, not to maintain habituation.

It has been suggested that the processes which bring about habituation may take place at the central nervous synapses (Glaser & Whittow, 1957; Glaser, 1958). Learning in *Octopus* may depend on the fact that distinct sets of neurones 'become so connected as to produce response in different directions' (Young, 1960), and it seems reasonable to assume that this could also happen in conditioning (Konorski, 1948). Changes of synaptic

conduction are thus common to learning, conditioning and habituation (Glaser, 1958), but these three phenomena are not identical. In physiological terms, learning is the acquisition of a new response, or a qualitative change of an existing response, or an inhibition or facilitation of an existing response by a new stimulus; conditioning is the transfer of an existing response to a new stimulus; and habituation is a gradual quantitative change of response which may lead to a loss of response but excludes any change of stimulus and any qualitative change of response. Thus learning and conditioning imply mainly the forming of fresh neuronal circuits, whereas habituation involves mainly the inhibition of existing pathways. Inhibition in the central nervous system may arise from two distinct processes, post-synaptic inhibition due to a specific chemical transmitter and presynaptic inhibition due to a diminution in the size and number of afferent impulses (Eccles, 1961), but the evidence does not allow a definite conclusion whether habituation is a post-synaptic inhibition gradually taking place at the internuncial neurones.

SUMMARY

1. A method was developed for studying habituation in conscious rats. This involved first the habituation of rats to the experimental conditions and then electronic counting of their heart rates while a uniform cold stimulus was repeatedly applied to their tails.

2. Cooling of the tail was accompanied by an increase of the heart rate in normal rats and in rats with various lesions of the cerebral cortex.

3. In normal rats this increase became gradually and significantly smaller after repeated cooling over a period of 10 days, which was taken as evidence of habituation.

4. Small bilateral frontal lesions of the cerebral cortex prevented habituation to the experimental conditions and to cooling of the tail in each of 9 rats so treated, but an established habituation was abolished by such operations in only two out of eight rats.

5. Eleven rats with unilateral frontal lesions or with occipito-parietal lesions of the cerebral cortex showed normal habituation to the experimental conditions and to cooling of their tails.

6. Electrical stimulation of the frontal areas depressed the responses to cooling of the tails and accelerated habituation, but stimulation of other areas of the cortex had no such effect.

7. It was concluded that the frontal areas of the cerebral cortex are necessary for the achievement but not the maintenance of habituation and that these areas are part of an integrated system which adjusts the level of responses in intact animals.

Assessment of the sites of lesions and helpful advice by Dr K. Weinbren, help and advice over histological techniques by Dr A. Howe, help with the measurements of the oxygen consumption and investigations of tail tissue by Mr P. D. Lewis, and much technical help by Mr J. Rawlings, are gratefully acknowledged.

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