D-60

REPRINTED FROM

BRAIN RESEARCH

ELSEVIER PUBLISHING COMPANY

AMSTERDAM

CORTICOFUGAL INFLUENCE AT COCHLEAR NUCLEUS OF THE CAT: SOME EFFECTS OF ABLATION OF INSULAR-TEMPORAL CORTEX

JAMES H. DEWSON, III, KENNETH W. NOBEL AND KARL H. PRIBRAM

Department of Psychiatry, Stanford University School of Medicine, Palo Alto, Calif. (U.S.A.)

(Received February 10th, 1966)

INTRODUCTION

A recent study by Dewson[9] showed that bilateral removal of the insular-temporal cortex of cats impairs the discrimination of vowel sounds while leaving intact the discriminative response to differences in frequency and intensity. The present report deals with an initial attempt to uncover the mechanism by which this impairment is produced. As a general working hypothesis, we assumed that the insular-temporal as well as other so-called cortical association areas might exert their influence via modality specific efferent fibers that operate on various stations of the afferent systems. Both Desmedt[3] and Pribram[16] have previously suggested these possibilities. Clues to the presence of such centrifugal influences were sought in the present investigation in which responses evoked by paired acoustic clicks were recorded from the cochlear nuclei of cats prior to and after ablations of insular-temporal cortex.

METHODS

Subjects and implanting procedures

Eight healthy adult cats were anesthetized (Nembutal) and had bipolar enamel-insulated nichrome wire electrodes (300 μ diam.) implanted stereotaxically in the cochlear nuclei. Aseptic precautions were observed. The electrodes were twisted wire pairs and had tip separations and uninsulated tip exposures of 1 mm or less. Neural activity was monitored through the electrodes during placement, and tip depth was determined by the location which yielded evoked responses of maximum amplitude to various acoustic stimuli. The electrodes were affixed to the skull at their point of entrance with dental cement. The exposed portions were then threaded through short lengths of polyethylene tubing and the wire ends soldered to a sub-miniature plug. A reference lead was routinely placed in the bone overlying the frontal sinus. The entire assembly was cemented to the skull, and the muscle and cutaneous layers approximated and sutured.

Stimulation and recording

Paired acoustic clicks, generated by leading 20 V, 0.1 msec pulses through a power amplifier and into a 6 inch loudspeaker, were delivered once per second to the restrained *awake* cat. The clicks thus produced were 72 dB above normal human threshold at the location occupied by the cat's head. The animal's restraining box was located in a radio-frequency shielded cage and positioned in a standard orientation to the loudspeaker which was suspended 11 inches from the top of the animal's exposed head and located outside the screened enclosure.

Time separation within each pair of clicks was controlled by selectively delaying the second member of the pair of pulses; continuous calibration of pulse amplitudes and intervals was effected by viewing both pulses on one beam of a dual-beam oscilloscope. One-hundred pairs of clicks at desired interstimulus intervals (25–300 msec) were presented and the evoked neuroelectric activity was amplified in two stages (gain adjustable from 10,000 to 1,000,000 ×) and led to the input of a CAT 400A (Mnemotron Corp.) where it was cumulated and algebraically summed. The resulting waveform was written out by a strip-chart recorder for measurement and analysis. To recapitulate: 100 click-pairs with interstimulus intervals of 25, 50, 75, 100, 125, 150, 175, 200, 250, and 300 msec were delivered once per second. This procedure was carried out in its entirety for each electrode placement at least three times prior to (and three times following) the surgical interventions described below.

Surgery

Uni- or bilateral cortical ablations of insular-temporal cortex (5 cats), primary auditory cortex (2 cats), or primary visual cortex (1 cat) were made by subpial aspiration under deep barbiturate anesthesia. Single-stage bilateral ablations were performed on 2 cats; single-stage unilateral ablations were preformed on the remain-

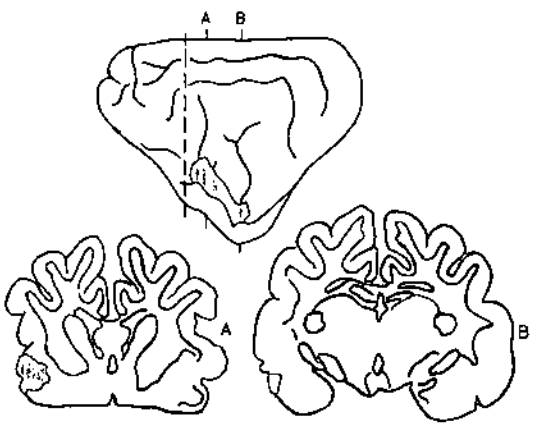

Fig. 1. Reconstructed unilateral (left) ablation of insular-temporal cortex. The two representative cross sections show the depth of cortical removal.

ing 6 animals of the group, and of these, 2 were subsequently reoperated upon thus becoming two-stage bilateral preparations. Extreme care was exercised during surgery to ensure that the electrodes and their chronic mountings were left undisturbed. The procedures taken to control for electrode movement will be discussed in a later section of this paper. At least two weeks was allowed for postoperative recovery; all animals recovered well.

When postoperative testing procedures had been completed, a direct current was passed through the recording electrodes. The animals were then killed, perfused with saline followed by 10% formalin, and the brains and brain stems sectioned at 50 μ and stained with thionine. Operative lesions were delineated by serial reconstructions (see Fig. 1), and electrode tip placements verified by noting the location of the electrolytic lesion made at the time of sacrifice.

Data processing

The data are presented as computer-averaged recovery functions which show the ratio of amplitudes of the two responses evoked by the pair of clicks expressed as a percent (Response No. 2 of Response No. 1). Each function was determined at least 4 times for each electrode placement. Postoperative changes in both shape and/or range of values of the function were evaluated. If, following the ablation, no change in the shape of the recovery function was noted (during three successive determinations), three more complete functions were obtained, and these last compared with the three preoperative assessments. If, however, a function shape change was apparent in the first postoperative determinations, no further runs were made. In every case possible, recovery functions were derived from peak-to-peak measurements of the initial, relatively fast portion of the response complex evoked by the stimulus. In any event, all measurements pre- and postoperative were taken on identical portions of the waveform complex.

RESULTS

Effects of bilateral ablations

Four animals were studied in this experiment. Two were operated on in a single-stage bilateral procedure, and 2 (from the group of 6 unilateral experimental subjects) underwent a second stage insular-temporal cortex ablation 4 months following the initial removal. After either the one- or two-stage bilateral ablation, changes in the shape of the recovery function became apparent almost immediately. These changes were most marked at the shorter interstimulus intervals, *viz.* 25, 50, and 75 msec, where recovery was speeded.

Fig. 2 presents the averaged recovery functions derived from the 3 cats with bilateral lesions of insular-temporal cortex. Function N is a mean recovery function derived from preoperative measurements taken from 10 individual electrode placements at cochlear nucleus prior to any surgical intervention. It is used, in this and the

succeeding figure, as the 'normal' recovery cycle for cochlear nucleus; functions labeled L have thus been derived from percentage values expressing their deviation

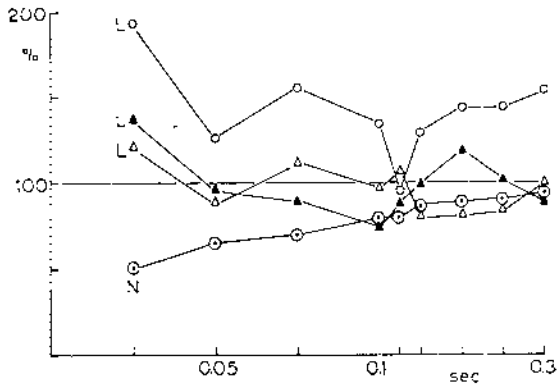

Fig. 2. Recovery cycles at cochlear nucleus. N = normal; L = after bilateral ablation of insular-temporal cortex. Functions labeled L are plotted as deviations from function N.

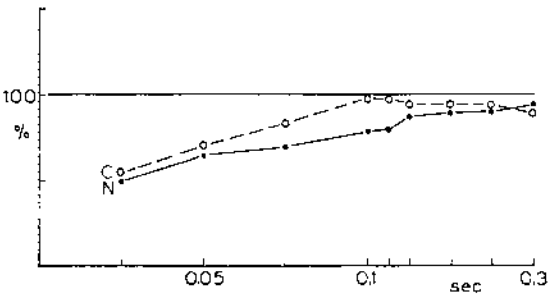

Fig. 3. Recovery cycles at cochlear nucleus. N = normal; C = after bilateral cortical ablation of primary auditory projection areas. Function C has been plotted as deviation from function N.

from N. Fig. 3 shows the recovery cycle of a control cat with a bilateral lesion of primary auditory cortex.

Effects of unilateral ablations

Recovery functions measured up to 3 months after unilateral insular-temporal cortex ablation show no essential changes in shape from those recorded preoperatively. There is, however, a marked change in the range of values at a given interstimulus interval over which an average of 100 stimulus pairs may fall. Fig. 4 illustrates the changes of mean range (computed over each interstimulus interval) between pre- and postoperative determinations for 6 subjects. Each of the two change functions shown in Fig. 4 differ from 'no change' at the 0.01 level of significance. Five of the 6 subjects contributing to these data were implanted bilaterally, thus providing even further control. The changes illustrated were noted only after 6 weeks had elapsed since surgery. The initial postoperative runs showed neither a change in function shape nor in average range.

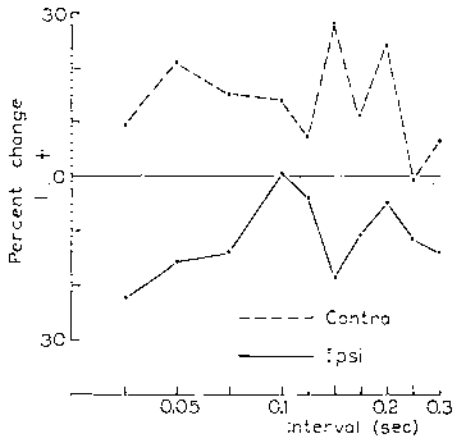

Fig. 4. Recovery cycles at cochlear nucleus; percent change of mean range as a function of interstimulus interval. Unilateral insular-temporal cortex ablations only. Eleven electrode placements in 6 animals are represented; the parameter is location of electrode with regard to location of lesion.

In unilaterally operated insular-temporal subjects, then, the range of cumulated values *decreases* at the *ipsilateral* cochlear nucleus and simultaneously *increases* at the cochlear nucleus *contralateral* to the ablation. Such range changes do not occur in control subjects. One control cat had a unilateral lesion made in primary visual cortex and the range of averages at the cochlear nuclei of this subject increased slightly but insignificantly both ipsilaterally and contralaterally to the lesion. Another control animal, with an ablation of primary auditory projection cortex (A1) and an ipsilateral recording electrode, also showed only slightly increased average ranges; an increase ipsilateral to the lesion was never noted in any of the experimental group of animals. Neither of the control cats showed any change in the shape of the recovery function throughout the 3-month postoperative testing period.

Effects of control procedures

Though extreme caution was exercised during surgery in order that the electrodes be left undisturbed, the possibility remained that changes in either the range or shape of a recovery function might be due to electrode tip displacement. The differential nature of the effects due to the locus of lesion suggests that electrode displacement is not responsible. Further, the differential nature of the effects due to the locus of electrode placement, and the fact that these effects were always consistent *within* each animal, argues against the occurrence of electrode movement having occurred. To additionally rule out the possibility of electrode displacement, a quadripolar electrode (interelectrode tip separation approximately 500 μ) was implanted and simultaneous records taken from each pair of leads. Fig. 5 illustrates the different waveforms of the responses evoked by a click-pair at each electrode tip. The recovery functions derived simultaneously from activity evoked at each electrode are shown. Note especially that the 2 bipolar pairs of macroelectrodes record distinctive

evoked potential waveforms. Note also that adjacent cell populations yield dissimilar recovery functions to identical click-pairs. By way of further example, the data presented in Fig. 6 show recovery functions derived from a bipolar electrode in the cochlear nucleus of one of our experimental animals. The data for each function were taken at intervals of 3 months; between the first and second derivation, a unilateral ablation of insular-temporal cortex was made, and between the second and third derivations, the opposite insular-temporal cortex was ablated. Note here the essential constancy of the responses evoked by identical click-pairs over 6 months recording time despite the two intervening surgical procedures. In no case do any of our present findings arise from an instance in which electrode movement might have occurred; at only 3 placements were changes in the waveform of individual evoked responses recorded and the use of these electrodes was discontinued.

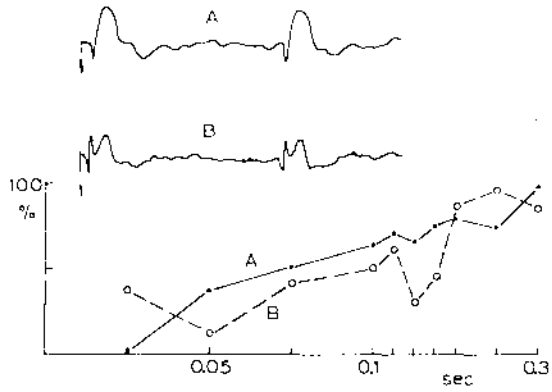

Fig. 5. Two recovery cycles derived simultaneously from a quadripolar recording electrode. Retouched strips at top of figure show responses recorded at each bipolar electrode; the neural activity was evoked by clicks separated by 300 msec.

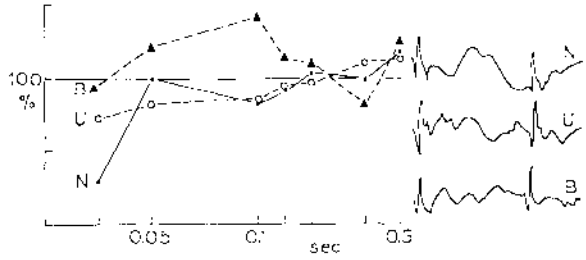

Fig. 6. Recovery cycles at cochlear nucleus. N — preoperative; U = following unilateral ablation of insular-temporal cortex; B following ablation of second side insular-temporal cortex. One animal. Retouched strips on right show activity evoked by click-pairs at 100 msec separation.

Simmons[18] and Carmel and Starr[2] have shown that contraction of the middle ear muscles to both acoustic and non-acoustic stimuli can cause significant attenuation of auditory input at the cochlea. Removal of insular-temporal cortex might act upon the normal mode of action of this reflex system and thus alter recovery function

shape and/or range. To control for this possibility, one of our experimental animals had both sets of middle ear muscles severed prior to the initial implantation of electrodes. This animal eventually became a two-stage bilateral 'operate', and the data derived showed *no* essential differences when compared with data from animals whose middle ear muscles were intact. Further, direct electromyographic recordings from the tensor tympani muscle of a normal cat have shown that contraction-induced effects upon click-pair stimuli identical to those of the present experiments are occasional, small and rarely apparent after the initial 3 or 4 stimuli (Dewson, unpublished observations). Similar adaptive phenomena have been obtained by Simmons and Beattie[19] through recordings made from the stapedius muscle. We thus conclude that middle ear muscle contraction-induced effects are of negligible importance to the present findings where click-pairs of only moderate intensity were repeated so often.

The range changes in the present study refer to changes in averages rather than to variability of individual evoked responses. It is just this 'evoked response variability' due to the waking state of the subject which is circumvented through response accumulation. The inclusive washing-out of individual evoked response differences which occurs as the computer processes the data makes it most likely that, statistically at least, a highly reliable consequence of insular-temporal cortex ablation has been uncovered.

DISCUSSION

The present study demonstrates the existence of corticofugal influence at the level of the first synapse of the ascending auditory system. Although the anatomical picture is by no means complete, ample evidence demonstrating necessary descending pathways has been presented by Rasmussen[17], Walther and Rasmussen[20], Desmedt and Mechelse[7], Al'tman and Iontov[1], and Massopust and Ordy[15]. Indeed, Desmedt and his co-workers[4-6] have, on the basis of their data, postulated a centrifugal extrareticular auditory control system (CERACS) which is presumed to originate at the same cortical locus as that involved in the present study.

The results of the bilateral ablations of insular-temporal cortex strongly suggest that the corticofugal influence ordinarily inhibits recovery of cells in the ascending sensory system. Thus, segments of a given neural aggregate could become decoupled from one another, leaving only a portion of the units available to the input at any moment. When this descending influence is removed, *e.g.* by bilateral cortical ablation, recovery is speeded and the system becomes more synchronously activated by successive stimuli. A similar mechanism involving desynchronization of the input system has been suggested by Lindsley[14].

The unilateral lesions reflect a less dramatic interference with function, and one whose effect occurs more slowly. The differential nature of the effect suggests involvement of both homolateral and heterolateral projections, and the time course indicates neuronal degeneration. The equal magnitudes of average range change at ipsi- and contralateral cochlear nuclei might well represent the compensations taking place in a bilaterally symmetrical and almost totally crossed fiber system such as the auditory.

Since the mean recovery functions are found unchanged, the essential descending influence is apparently still present, but the fractionation of a given cell population (over time) is not as controlled as in the normally-operating system. This hints that in the undisrupted state, the patterning of desynchronization of the local aggregate may also be under central, insular-temporal cortical influence.

An important finding of the present study is that the facilitated recovery cycles were produced by increased amplitudes of the responses evoked by the *second* member of the pair of stimuli; the amplitudes of the responses evoked by either single clicks or the initial member of the stimulus pair remained essentially unchanged. Involvement of descending tonic inhibitory influences often ascribed to the brain stem reticular system by, for example, Hernandez-Peon and co-workers[12,13], does not appear to be a primary correlate to the bilateral lesion. By the same reasoning, effects on the receptor *per se*, as conceivably mediated via the descending olivocochlear bundle (see *e.g.* Ref. 8, 10, 11), seem equally unlikely.

Although the corticofugal influence could operate directly on the cochlear nucleus, our findings do not force this conclusion. The involvement of both homolateral and heterolateral projections by the unilateral lesion is, in fact, better accounted for anatomically if the locus of the centrifugal effect is cephalad to the cochlear nucleus. The exact site remains to be established. In sum, the results of this study strongly indicate that understanding of the function of so-called association cortex will be gained as much from studies of corticofugal effects upon sensory input as on analyses of cortico-cortical relationships.

SUMMARY

Recovery functions were derived from neuroelectric activity evoked by paired acoustic clicks in awake cats and recorded through electrodes chronically implanted in the cochlear nuclei. Bilateral ablations of the ventral insular-temporal cortex gave rise to speeded recovery, while unilateral ablations of the same cortical area caused specific changes in the range of values obtained for the various interstimulus intervals. These effects are due to the specific cortical area ablated; further, they cannot be accounted for by activity of the middle ear muscles. Tonic inhibitory influence such as might be mediated by the brain stem reticular formation has been ascertained unlikely as a factor in these results. The present study, then, conclusively demonstrates the influence of a non-primary cortical area upon ascending neurosensory activity.

ACKNOWLEDGEMENT

This research was supported in part by a research grant (GB-3370) from the National Science Foundation.

REFERENCES

1 AL'TMAN, YA. A., AND IONTOV, A. S., Connections between zones AI and AIV of the auditory cortex, *Fed. Proc.*, 23 (1964) T96.

2 CARMEL, P. W., AND STARR, A., Acoustical and nonacoustical factors modifying middle-ear muscle activity in waking cats, *J. Neurophysiol.*, 26 (1963) 598–616.
3 DESMEDT, J. E., Neurophysiological mechanisms controlling acoustic input. In G. L. RASMUSSEN AND W. WINDLE (Eds.), *Neural Mechanisms of the Auditory and Vestibular Systems*, Thomas, Springfield, 1960, pp. 152–164.
4 DESMEDT, J. E., Auditory-evoked potentials from cochlea to cortex as influenced by activation of the efferent olivo-cochlear bundle, *J. acoust. Soc. Amer.*, 34 (1962) 1478–1496.
5 DESMEDT, J. E., AND MECHELSE, K., Sur un phénomène d'inhibition centrifuge dans la voie acoustique centrale chez le chat, *C. R. Soc. Biol. (Paris)*, 151 (1957) 2209–2212.
6 DESMEDT, J. E., AND MECHELSE, K., Suppression of acoustic input by thalamic stimulation, *Proc. Soc. exp. Biol. (N.Y.)*, 99 (1958) 772–775.
7 DESMEDT, J. E., AND MECHELSE, K., Corticofugal projections from temporal lobe in cat and their possible role in acoustic discrimination, *J. Physiol. (Lond.)*, 147 (1959) 17–18.
8 DESMEDT, J. E., AND MONACO, P., Mode of action of the efferent olivocochlear bundle of the inner ear, *Nature*, 192 (1961) 1263–1265.
9 DEWSON, J. H., III, Speech sound discrimination by cats, *Science*, 144 (1964) 555–556.
10 FEX, J., Auditory activity in centrifugal and centripetal cochlear fibers in the cat, *Acta physiol. scand.*, Suppl. 189, 55 (1962) 1–68.
11 GALAMBOS, R., Suppression of the auditory nerve activity by stimulation of efferent fibers to the cochlea, *J. Neurophysiol.*, 19 (1956) 424–437.
12 HERNANDEZ-PEON, R., JOUVET, M., AND SCHERRER, H., Auditory potentials at cochlear nucleus during acoustic habituation, *Acta neurol. lat.-amer.*, 3 (1957) 144–157.
13 HERNANDEZ-PEON, R., SCHERRER, H., AND VELASCO, M., Central influences on afferent conduction in the somatic and visual pathways, *Acta neurol. lat.-amer.*, 2 (1956) 8–22.
14 LINDSLEY, D. B., The reticular activating system and perceptual integration. In D. E. SHEER (Ed.), *Electrical Stimulation of the Brain*, Univ. of Texas Press, Austin (Texas), 1961, pp. 331–349.
15 MASSOPUST, L. C., JR., AND ORDY, J. M., Auditory organization of the inferior colliculli in the cat, *Exp. Neurol.*, 6 (1962) 465–477.
16 PRIBRAM, K. H., Neocortical function in behavior. In H. F. HARLOW AND C. N. WOOLSEY (Eds.), *Biological and Biochemical Bases of Behavior*, Univ. of Wisc. Press, Madison (Wisc.), 1958, pp. 151–172.
17 RASMUSSEN, G. L., Efferent fibers of the cochlear nerve and cochlear nucleus. In G. L. RASMUSSEN AND W. WINDLE (Eds.), *Neural Mechanisms of the Auditory and Vestibular Systems*, Thomas, Springfield, 1960, pp. 105–115.
18 SIMMONS, F. B., Middle ear muscle activity at moderate sound levels, *Ann. Otol. (St. Louis)*, 72 (1959) 1126–1144.
19 SIMMONS, F. B., AND BEATTIE, D. L., Habituation (adaptation) in the middle ear muscle reflexes of the cat, *Acta oto-laryng.*, 57 (1964) 89–96.
20 WALTHER, J. B., AND RASMUSSEN, G. L., Descending connections of auditory cortex and thalamus of the cat, *Fed. Proc.*, 19 (1960) 241.