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THE ROLE OF FRONTAL CORTEX–RETICULAR INTERACTIONS IN PERFORMANCE AND EXTINCTION OF THE CLASSICALLY CONDITIONED NICTITATING MEMBRANE RESPONSE IN THE RABBIT

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SUMMARY

In order to investigate the behavioral role of interactions between frontal cortex and reticular nuclei, we examined the effects of single and combined lesions of these structures on the classically conditioned nictitating membrane response (NMR) of rabbits. Lesions of frontal cortex decreased latencies of the conditioned NMRs in reacquisition and retarded extinction of the conditioned response. Lesions of nucleus reticularis pontis oralis (NRPO) produced similar effects. In contrast, lesions of nucleus reticularis tegmenti (NRT) increased NMR latencies during reacquisition. The opposite effects of frontal cortex and NRT lesions were abolished when the two lesions were combined, indicating that the two lesion effects summed. In contrast, the deficits due to frontal and NRPO lesions did not sum; combined frontal–NRPO lesions produced deficits very similar in magnitude and time course to those of the NRPO lesions alone. These findings suggest that frontal cortex may exert its inhibitory effects on behavior not by directly interacting with NRT, but by facilitating NRPO, which in turn may inhibit the nucleus of the VIth nerve, the final common pathway to the NMR.

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NRT may facilitate the motor pathway by modulating the inhibitory effect of NRPO on the VIth nerve nucleus.

INTRODUCTION

Lesions of frontal cortex disinhibit the suppression of strong response tendencies in many mammalian species, including rats, rabbits, cats, dogs, monkeys and humans, tested in a variety of behavioral tasks [36]. Anatomical and electrophysiological findings suggest that frontal cortex may suppress response tendencies via its connections with the reticular nuclei of the brain stem. Thus, frontal cortex projects to the mesencephalic reticular formation in monkeys [19, 24] and in rats [3, 20]; frontal projections to the medullary and pontine reticular formation have been described in cats [18, 31]. Evidence that frontal cortex modulates these reticular structures is provided by findings that electrical stimulation of frontal cortex in cats inhibits spontaneous unit activity in the mesencephalic reticular formation [21] and suppresses reflexes [32] via frontal projections to the inhibitory bulbar reticular area of Magoun and Rhines [22].

In the present study, we examined the role of frontal–reticular interactions in inhibition of the classically-conditioned nictitating membrane response (NMR). We chose the NMR to study because of evidence that it is disinhibited following frontal lesions in rabbits; that is, rabbits with frontal lesions are impaired in withholding the NMR in differentiation and extinction tests and show abnormally short-latency NMRs [8].

One of the reticular regions we studied, nucleus reticularis tegmenti (NRT) [33], also referred to as nucleus cuneiformis [9], constitutes a major portion of the mesencephalic reticular formation. This structure plays a role in activating the cortical EEG [23], and in facilitating reflexes [15, 29] and learned behaviors in rats [35] and monkeys [11]. The results of a pilot study, showing that conditioned NMR latencies increase following NRT lesions in rabbits, support the view that this reticular nucleus may also be involved in facilitation of CRs in rabbits. The assumption that conditioned NMR latencies provide a measure of the strength of facilitatory processes underlying CR performance is supported by the finding that latencies of conditioned NMRs gradually decrease as the number of training trials increase [12].

The results of additional pilot tests suggest that another reticular zone – nucleus reticularis pontis oralis (NRPO) – may have inhibitory control over the conditioned NMR in rabbits. Lesions of this nucleus in rabbits, like frontal cortex lesions [8], reduced the NMR latency during acquisition and disinhibited the NMR during extinction.

In the present experiment, lesions of each of these two reticular nuclei, NRT and NRPO, were made singly and in combination with frontal lesions. If frontal cortex exerts inhibitory control solely by its projections to one of these nuclei, then

the disinhibitory behavioral effects of lesions of both that reticular nucleus and frontal cortex would be no different from the effects of lesions of the reticular nucleus alone. Conversely, if frontal cortex and one of these reticular nuclei exert their behavioral control via independent routes, one might expect that the behavioral effects of making lesions in both structures would not be different from the sum of the effects of making lesions in each structure alone.

METHODS

Subjects. The subjects were 76 male New Zealand white rabbits (*Oryctolagus cuniculus*), obtained from Johnson's Rabbitry in Coldwater, MI. They were fed Purina Lab Chow throughout the experiment.

Apparatus and Procedures. The NMR was recorded by a photocell-transducer mechanically linked to a nylon loop through the nictitating membrane of the right eye. The transducer was fixed to the rabbit's head by a yoke over its ears. The output of the photocell was led to a polygraph (Beckman Dynograph Model 2), which amplified and recorded movements of the nictitating membrane. The apparatus and procedures of training and testing are described in detail in a prior publication [8]. In acquisition, the CS, a 500 msec burst of white noise, 90 dB SPL, was paired with the UCS, a 1.0 mA 60 cps transcorneal shock, which elicited the unconditioned movement of the nictitating membrane across the rabbit's eye. Training was continued until the subjects performed conditioned NMRs to the CS on 9 out of 10 consecutive trials. Following acquisition of the conditioned response (CR), the subjects were tested daily for reacquisition and extinction of the CR. Extinction trials, in which only the CS was presented, were administered immediately after the rabbits reacquired the CR to a criterion of 27 CRs in 30 consecutive trials. The extinction procedure continued until no CRs were performed in 9 out of 10 consecutive trials, or until 100 extinction trials were presented. Daily sessions in which reacquisition was followed by extinction were continued until the subjects met the extinction criterion within 25 trials in five consecutive sessions. This procedure was followed in order to insure consistent and stable extinction. Nineteen rabbits did not achieve stable extinction performance by the 25th day and were consequently eliminated from the experiment. One additional rabbit was eliminated during preoperative training due to otitis interna.

The remaining 56 subjects were then assigned to 8 groups, 7 of which received surgery, and one of which was an unoperated control group. We attempted to match the groups for number of sessions to reach stable extinction, as well as for CR latencies on the final 5 preoperative sessions.

Seven days following surgery, and 9 days after the unoperated control subjects completed preoperative testing, the subjects were retested for reacquisition and extinction. The procedures were the same as those used preoperatively,

except that: (1) a maximum of 150 extinction trials was administered to subjects that did not attain the extinction criterion in fewer trials, and (2) all subjects were tested for 10 sessions.

Surgery. Surgical lesions of the following structures were performed: (1) frontal cortex (FR); (2) motor cortex, lesions of which served as a cortical control (CC) operation; (3) NRPO; (4) NRT; (5) FR and NRPO; (6) FR and NRT; and (7) CC and NRT. All the lesions were bilateral and performed in one stage. Of the 51 operated rabbits, 5 died from causes associated with surgery, and 11 were eliminated from the study because of inappropriate lesions. Consequently, 35 subjects, 5 in each of the 8 groups, were tested postoperatively.

Lesions of frontal cortex, defined as the cortical projection field of the dorsomedial thalamic nucleus [30], were intended to remove the cortex on the dorsolateral and medial surfaces of the frontal poles, sparing the olfactory bulbs and tracts. The lesions were performed with a narrow-gauge aspirator. Motor cortex lesions were intended to destroy motor area I [37]; they were made by cauterizing the pial surface in order to limit their surface extent and to spare the underlying white matter. Reticular lesions were performed by passing radiofrequency current (30 μA for 20 sec) through a stainless steel electrode, 0.4 mm in diameter and with an exposed tip of 1.0 mm. Coordinates used for positioning the electrode were derived from the brain atlases of Sawyer et al. [33] and of Fifkova and Marsala [9]. The coordinates for the NRT were: 8.5 mm posterior to bregma, 2.5 mm lateral to the midline and 3.5 mm below the surface of the cortex. The coordinates for the NRPO lesions were: 11.5 mm posterior to bregma, 2.0 mm lateral to the midline and 8.5 mm below the surface of the cortex. Other details of the surgical procedures may be found elsewhere [8].

Histology. After postoperative testing was completed, the operated subjects were injected with an overdose of sodium pentobarbital and perfused through the heart with 0.9% saline followed by 10% formalin. Segments of the brains containing the lesions were then cut in the vertical stereotaxic plane, placed in 10% formalin and then in 30% sucrose–formalin until they sank. Brain segments with cortical lesions were then embedded in albumin–gelatin. Frozen sections 40 μm thick were cut, and every 10th section through the cortical lesions and every 5th section through the reticular lesions were stained with thionin. Cortical lesions were plotted on enlarged tracings of cross sections, from which the lesions were reconstructed on standard sagittal and lateral outlines of the rabbit brain. Reticular lesions were directly plotted on reproductions of cross sections of the brain taken from the atlases cited above.

RESULTS

Histological findings

As seen in Fig. 1, the frontal cortex lesions in the FR, FR–NRP and

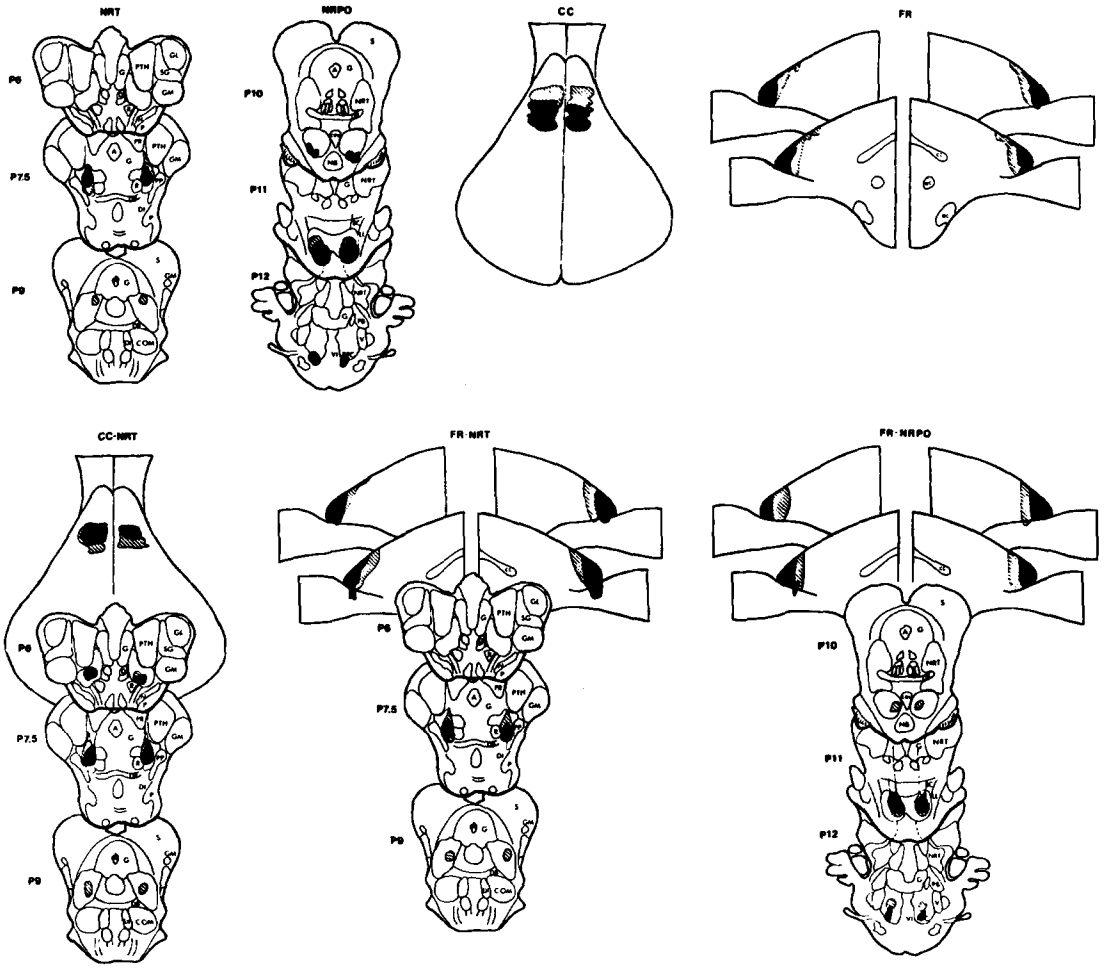

Fig. 1. Reconstructions of lesions in experimental groups described in the text. Blackened areas and hatched areas indicate extent of smallest and largest lesions, respectively. A, cerebral aqueduct; AC, anterior commissure; BC, brachium conjunctivum; CES, n. centralis superior; COM, n. compactus pedunculopontini tegmenti; D, n. Darkschewitsch; DBC, decussation of BC; DI, n. dissipatus pedunculopontini tegmenti; G, central gray; GL, lateral geniculate nucleus; GM, medial geniculate nucleus; I, n. interstitialis; LL, lateral lemniscus; N, substantia nigra; NB, n. Bechterewi; NRT, n. reticularis tegmenti; P, cerebral peduncle; PB, n. parabrachialis; PP, n. peripeduncularis; PR, pretectum; PTH, n. posterior thalami; R, n. ruber; S, superior colliculus; SG, n. suprageniculatus; VI, n. abducens.

FR–NRPO groups were very similar to each other in size and locus. They consistently involved bilateral removal of all, or almost all, the anterior frontal cortex on the medial and lateral surfaces, as defined by Rose and Woolsey [30]. However, most of the frontal lesions did not include the most posterior portion of the cortex, which receives a dorsomedial thalamic projection according to a more recent anatomical study [4]. Damage to the adjacent olfactory bulbs, which occurred in some frontal operations, was minor and unrelated to the severity of

the deficits in postoperative tests. The cortical control lesions, shown in Fig. 1, were limited to motor area I, as defined by Woolsey [37]. Unlike the aspiration-produced frontal lesions, the motor cortex lesions, which were made by cauterizing the pial surface, involved primarily the superficial cortical layers and were smaller and more variable in size than the frontal lesions.

The lesions of the reticular nuclei were, as intended, relatively small, symmetrical and for the most part limited to the target nucleus (see Fig. 1). The NRT lesions were subtotal and similar in size and locus in the NRT, FR–NRT and CC–NRT groups. The lesions in the NRT group were somewhat more anterior than those in the other two groups. Several of the NRT lesions encroached slightly on the medial lemniscus, crus cerebri or red nucleus. The passage of the electrode produced slight bilateral damage to the optic tract and posterior nucleus of the thalamus. Like the NRT lesions, the NRPO lesions were all subtotal and similar in locus and size, with the exception of two cases (one in the NRPO group, the other in the FR–NRPO group) in which NRPO was only slightly damaged. Damage to other structures in rabbits with NRPO lesions was slight and variable. Three rabbits in the FR group incurred unilateral damage to the trapezoid body. In the FR–NRPO group, the trapezoid body was partially damaged in two subjects and the brachium pontis was slightly damaged in 4 subjects. Electrode passage produced slight damage in the superior colliculus, central gray and brachium conjunctivum. No relationship was found between the size or locus of the reticular lesions and the severity of behavioral deficits in postoperative tests.

Preoperative behavioral findings

The rabbits acquired the conditioned response rapidly, meeting the criterion of acquisition in only 51 trials on the average. They also achieved the criterion of extinction quickly (overall mean = 7.0 trials) in the last 5 reacquisition–extinction sessions. Furthermore, the groups were well matched preoperatively for rate of acquisition and extinction of the NMR. However, the mean NMR latencies of two groups (CC–NRT and FR–NRPO) differed significantly from each other in the last 5 reacquisition sessions ($t = 3.46$; df = 8; $P < 0.01$). There were no other significant group differences in this measure.

Postoperative behavioral findings

Postoperatively, 4 measures were used to compare the groups to each other: trials to criterion and NMR latencies in reacquisition, and trials to extinction criterion and number of NMRs in extinction. All the performance measures, except NMR latencies, were expressed as absolute scores. Because they varied considerably among subjects, the NMR latencies of each subject in each reacquisition session were divided by the mean NMR latency of that subject in the last 5 preoperative sessions.

Subjects in all of the groups reacquired the CR rapidly; the modal number

of reacquisition trials was zero. Hence, there were no significant group differences in this measure. However, analyses of variance of the other 3 measures disclosed significant group effects (for NMR latencies: $F = 11.76$; df = 7/32; $P < 0.0005$; for trials to extinction: $F = 20.08$; df = 7/32; $P < 0.0005$; for NMRs in extinction: $F = 9.46$; df = 7/32; $P < 0.005$). In addition, the group × session interactions were significant for NMR latencies ($F = 1.34$; df = 63/288; $P < 0.05$) and for trials to extinction ($F = 2.73$; df = 63/288; $P < 0.0005$). The Sheffé post-hoc test was used to analyze these significant effects; the results of these tests are presented in the following sections. Since the performance of subjects with motor cortex lesions was identical to that of the normal controls, the scores of the latter group were used to evaluate the effects of single lesions.

NRT lesions

The response latencies of the rabbits with NRT lesions were significantly longer ($P < 0.05$) than those of the normal rabbits (see Fig. 2A). The rabbits with NRT lesions, compared to the control rabbits, also tended to extinguish more rapidly and perform fewer NMRs, especially in early extinction sessions (see Fig. 2B, C); however, neither of these effects was statistically reliable.

NRPO lesions

Lesions of NRPO produced behavioral effects opposite to those of NRT lesions. Thus, the response latencies of the rabbits with NRT lesions were significantly shorter than those of the control rabbits ($P < 0.05$) and those of the rabbits with NRT lesions ($P < 0.01$; Fig. 2A). Response latencies following NRPO lesions were reduced in all acquisition sessions except for the first two; hence the groups × sessions interaction with respect to this measure was significant ($P < 0.05$). Furthermore, the rabbits with NRPO lesions perseverated the NMR in extinction, as shown by two measures – number of NMRs in extinction (see Fig. 2B) and trials to extinction (see Fig. 2C). Both of these effects of NRPO lesions were statistically reliable; the rabbits with NRPO lesions performed more NMRs in extinction and required more trials to extinguish the response than did the normal rabbits or those with NRT lesions ($P < 0.01$, for all comparisons). As seen in Fig. 2B, the NRPO rabbits' perseveration of responding in extinction was greatest in the initial 3 sessions. In these sessions, the extinction scores of the NRPO group were significantly higher than those of the unoperated group (trials to extinction: $P < 0.01$; NMRs in extinction: $P < 0.01$), and those of the NRT group (trials to extinction: $P < 0.01$; NMRs in extinction: $P < 0.01$). However, with continued testing, the extinction scores of the NRPO rabbits tended to decline. Consequently, in the final 3 extinction sessions, the NRPO rabbits' extinction scores were significantly lower than they were in the first 3 sessions

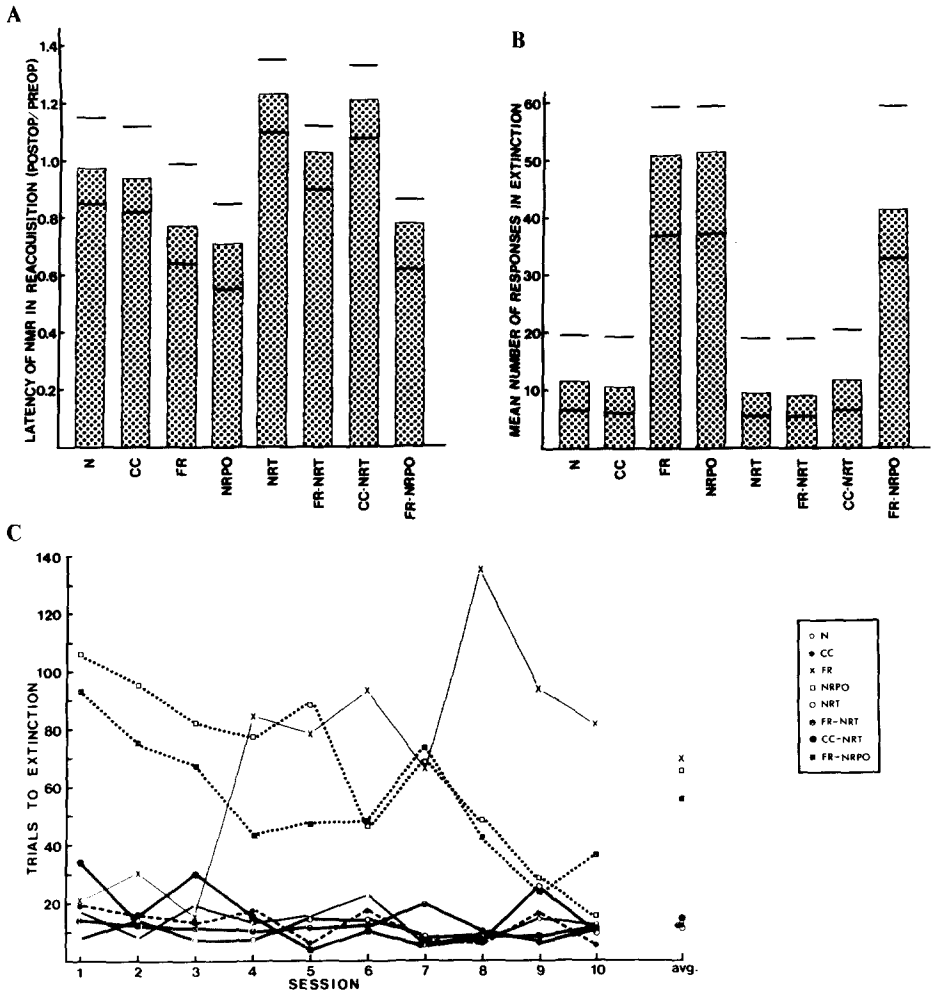

Fig. 2. Postoperative performance of rabbits in each of the 8 groups tested. Horizontal bars indicate cut-off values for significant differences ($P = 0.05$) between group means. A: mean preoperative/postoperative ratios of NMR latency in reacquisition. B: mean number of NMRs in extinction. C: mean trials to extinction criterion in each postoperative testing session and the overall mean trials to extinction (avg.).

(trials to extinction and NMRs in extinction: $P < 0.01$) and did not differ significantly from the scores of the control rabbits or those of the NRT rabbits.

FR cortex lesions

The rabbits with FR lesions, like those with NRPO lesions, required more trials to extinguish and made more NMRs during extinction than did the unoperated rabbits or those with NRT lesions (see Fig. 2B, C). All of these effects were highly significant ($P < 0.005$, for all comparisons). However, as seen in Fig. 2C, the extinction impairments of the FR rabbits, in contrast to those of the NRPO

rabbits, were not evident in the first 3 sessions, but appeared only with further testing. The FR rabbits' extinction scores were significantly larger in the final 3 sessions than they were in the first 3 sessions (trials to extinction and number of NMRs: $P < 0.05$). The FR rabbits also required significantly more trials to extinguish and made more NMRs than did the control rabbits ($P < 0.01$, for both comparisons) or the NRT rabbits ($P < 0.05$, for both comparisons) in the final 3 sessions. Furthermore, the FR rabbits' extinction scores in the final 3 sessions were also significantly higher than those of the NPRO rabbits (trials to extinction and NMRs in extinction: $P < 0.05$), whose scores decreased markedly during these sessions. In addition, the NMR latencies of the rabbits with frontal lesions were significantly shorter than those of the unoperated control animals ($P < 0.05$); this effect was consistent across test sessions. However the FR rabbits' latencies were not significantly shorter than those of the cortical control rabbits.

FR cortex–NRT lesions

Combined lesions of NRT and frontal cortex cancelled the behavioral effects of each of the single lesions. Thus, as seen in Fig. 2A, the NMR latencies of the FR–NRT group, like those of the unoperated rabbits, were not altered following surgery. Furthermore, group comparisons revealed that the NMR latencies of the FR–NRT group were significantly longer than those of the FR group ($P < 0.05$) and significantly shorter than those of the NRT group ($P < 0.05$). This pattern of effects was not found when NRT lesions were combined with cortical control lesions: the NMR latencies of the CC–NRT group were not different from those of the NRT group (see Fig. 2A). Combined NRT–frontal cortex lesions also abolished the perseverative effects of frontal cortex lesions in extinction. Thus, the FR–NRT group, unlike the FR group, did not differ from the unoperated group in trials to extinction or number of NMRs in extinction (see Fig. 2B and C). Furthermore, like the unoperated group, the FR–NRT group required fewer trials to extinction ($P < 0.01$) and made fewer responses in extinction ($P < 0.01$) than did the FR group.

FR cortex–NRPO lesions

Combined lesions of FR cortex and NRPO resulted in behavioral alterations very similar to those found after NRPO lesions. Thus, the rabbits with FR–NRPO lesions showed reduced response latencies following surgery, required more trials to extinguish the NMR, and made more NMRs in extinction compared to the control rabbits (see Fig. 2). These effects of FR–NRPO lesions were statistically reliable when evaluated relative to the unoperated controls (response latencies: $P < 0.05$; trials to extinction: $P < 0.01$; number of NMRs in

extinction: $P < 0.01$). None of the behavioral scores of the FR–NRPO rabbits differed reliably from those of the NRPO group.

Furthermore, the extinction scores of the rabbits with FR–NPRO lesions showed trends over sessions very similar to those shown by the rabbits with NRPO lesions alone and opposite to those of the FR rabbits (see Fig. 2C); the FR–NRPO group's retardation in attaining the extinction criterion was most severe in the first 3 extinction sessions relative to the unoperated controls ($P < 0.05$) and to the frontal rabbits ($P < 0.05$). With continued testing, the extinction impairment of the FR–NRPO group, like that of the NRPO group, became less pronounced, and was no longer present in the final extinction session. The number of NMRs of the FR–NRPO group showed a similar decreasing trend across extinction sessions.

DISCUSSION

None of the 3 kinds of lesions affected reacquisition of the conditioned NMR, suggesting that frontal cortex, NRT and NRPO do not play a significant role in the relearning of this response. However, it is possible that NRT or NRPO lesions larger than those made in this study might alter NMR reacquisition.

Following frontal lesions, the rabbits showed symptoms of behavioral disinhibition similar to those described in a prior study [8] – reduced NMR latencies and retardation of NMR extinction. However, the extinction impairment of the frontal rabbits in the present study appeared only after several sessions, whereas the extinction impairment found in the prior study was initially severe and declined with subsequent testing. This discrepancy may be accounted for by the degree of medial cortex damage, which was greater in the present study than in the prior one. This conclusion is supported by the finding that over successive extinction tests, impairments similar to those found here gradually increase after medial cortex lesions but decrease after lateral frontal cortex lesions in rabbits [1].

NMR latencies of the rabbits with frontal lesions were significantly shorter than those of unoperated control rabbits, but not those of the rabbits with motor cortex lesions. This finding might be due to the larger size of the frontal lesions compared to the motor cortex lesions. This conclusion, however, is inconsistent with findings that conditioned NMR latencies of rabbits are not reduced, but rather are increased, after very large cortical lesions that include all of the motor cortex [25–28].

The finding that discrete NRPO lesions have disinhibitory effects on response latencies and on extinction is consistent with Hammond's report [14] that selective NRPO lesions in rats produce disinhibition of the startle response (i.e. increased response amplitude). However, the present findings appear to contradict results showing that NRPO stimulation facilitates reflexes in cats [32]. These conflicting results may be due to differences in species, lesion size, response

measures, or in some combination of these factors. It should also be pointed out that the disinhibitory effects of NRPO lesions found in the present experiments were not identical to those of frontal cortex lesions: the time course of the extinction impairments following the two lesions were opposite, for reasons that are not clear.

In contrast to NPRO and frontal cortex lesions, selective lesions of NRT increased the latencies of conditioned NMRs, an effect that may reflect an impairment in facilitation of the NMR. It was not possible to determine whether NRT lesions accelerate extinction, as might be expected if these lesions interfere with NMR facilitation, for the control animals showed rapid extinction following surgery.

Whereas NRT damage alone did not significantly alter extinction, it did eliminate the heightened resistance to extinction associated with frontal cortex lesions. Likewise, combined frontal cortex and NRT damage also abolished the effects of single frontal cortex lesions and the effects of single NRT lesions on response latencies. Indeed, the opposite effects of frontal cortex and NRT lesions on response latencies appeared to summate: the mean latency change of the FR–NRT group (1.02) was very close to the average of the mean latency change of the FR and NRT groups (0.99). The finding that frontal cortex and NRT lesions had summative effects strongly implies that frontal cortex exerts inhibitory control over the conditioned NMR not via its projections to NRT, but rather via a different efferent pathway.

In contrast to the effects of combined frontal–NRT lesions, the effects of combined frontal cortex and NRPO lesions did not summate. Rather, these two lesions together produced disinhibitory effects which were no greater than those of NRPO lesions alone. Moreover, the time course of the extinction deficit following combined frontal–NRPO lesions was quite similar to the time course of the NRPO rabbits' deficit. These findings strongly suggest that inhibition of the conditioned NMR by frontal cortex is mediated in large part by NRPO. Alternatively, it is possible that the behavioral effects of NRPO lesions (as well as those of NRT lesions) were due to destruction of fibers of passage rather than to destruction of the cell groups in these nuclei.

The functional interrelationships between frontal cortex, NRT and NRPO suggested by our findings are illustrated diagrammatically in Fig. 3. The main

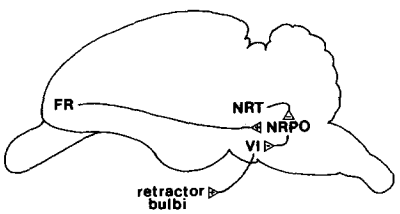

Fig. 3. Model of frontal–reticular interactions based on results obtained in the present study. See text for explanation.

features of this diagram are: (a) frontal cortex directly or indirectly facilitates NRPO, which in turn inhibits the nucleus of the VIth nerve, the origin of the final common pathway to muscles controlling the NMR [5, 6]; and (b) NRT facilitates the motor pathway directly by disinhibiting the effect of NRPO on the VIth nerve nucleus or indirectly, perhaps by activating the forebrain [23]. The finding that NRT lesions by themselves do not affect extinction, but do eliminate the extinction impairment associated with frontal lesions, suggests that NRT facilitates the motor process by modulating the NRPO pathway to the VIth nerve nucleus as shown in Fig. 3.

This proposed model of frontal–reticular interactions is supported by several anatomical findings. Frontal cortex projects directly to mesencephalic and pontine reticular nuclei, including NRT and NRPO, in the rat [2, 20]. In addition, frontal cortex might influence NRT and NRPO via several anatomical pathways that have recently been demonstrated in cats: frontal cortex projects to the midline tegmentum, which in turn projects to NRT and NRPO. Furthermore, NRT and NRPO are reciprocally interconnected and NRPO, but not NRT, projects via direct and indirect pathways to the abducens nucleus [13]. Each of these findings is consistent with the above described model.

It should be pointed out, however, that the proposed model does not incorporate all known frontal–reticular interactions. Thus, by its projections to Magoun and Rhine's [22] medullary inhibitory area of the reticular formation [18, 31], frontal cortex apparently mediates inhibitory control of reflexes in cats [32]. Whether the proposed model is also limited to particular kinds of responses can be determined by applying the combined lesion method employed here to other responses altered by frontal cortex lesions.

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