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ELECTRICAL STIMULATION OF CORTICAL-CAUDATE PAIRS DURING DELAYED SUCCESSIVE VISUAL DISCRIMINATION IN MONKEYS

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Abstract. The anterodorsal head of the caudate nucleus is the recipient of efferent projections from the dorsolateral prefrontal cortex while the tail of the caudate receives fibers originating in inferotemporal cortex. In order to investigate whether anatomically related members of these two systems are also functionally related, monkeys were trained on a delayed successive visual discrimination task. Electrical stimulation was administered during varied portions of individual trials to determine when in each trial performance was most disturbed as a function of the structure stimulated. Comparisons of stimulation effects allowed for examination of both functional dissociation and functional equivalence. Performance was maximally impaired when a 2 sec train of stimulation was applied to the principal sulcus region of dorsolateral prefrontal cortex or to the anterodorsal head of the caudate nucleus early during the delay or was delivered to posterior inferotemporal cortex or the tail of the caudate during cue presentation. No significant differences were seen between stimulation performance curves drawn for two members of each anatomically related system. Thus it appears that the anatomical systems may be functionally dissociated while the anatomically related structures within these systems show a functional equivalence; however the nature of this equivalence is uncertain. The theoretical functional relationship of the cortical-caudate pairs is also considered.

INTRODUCTION

A double dissociation of function (Teuber 1955) between prefrontal and inferotemporal cortex has long been recognized. Monkeys having sustained lesions of the prefrontal cortex are severely impaired in the acquisition and retention of delayed response and delayed alternation performance (Jacobsen 1936, Jacobsen and Nissen 1937); however, these

*S*s are unimpaired on visual discrimination tasks (Jacobsen 1936, Oscar and Wilson 1966). Studies utilizing the technique of focal electrical stimulation of prefrontal cortex have yielded similar results (Stamm 1961, 1969, Weiskrantz et al. 1962).

The results of lesions of inferotemporal cortex, however, present a different picture. Injury to this area leads to marked impairment of performance specific to visual discrimination tasks, but performance on delayed response and alternation tasks is unaffected; hence, the double dissociation.

Recently, the functional areas of prefrontal and inferotemporal cortex have been fractionated, such that lesions of the ventral portion of dorsolateral prefrontal cortex result in the perseveration of central sets, while lesions of the principalis region of dorsolateral prefrontal cortex produce performance decrements upon tasks involving spatially related behavior (Mishkin et al. 1969). Lesions of the orbitofrontal cortex produce motivational changes which are interpreted as being caused by the disinhibition of drives (Brutkowski 1965). Lesions placed in various portions of the inferotemporal cortex have similarly led to the conclusion that this cortical area is not homogeneous in function but that the anterior region is related to the *S*'s ability to make associations between cue and reinforcement, in visual discrimination tasks, while the posterior region is related to the perception of the cue itself (Iwai and Mishkin 1967).

With regard to a subcortical system, it has been demonstrated that the dorsolateral prefrontal cortex has efferent projections to the anterodorsal head of the caudate nucleus (Mettler 1947, De Vito and Smith 1964, Johnson et al. 1968) and that inferotemporal cortex projects to the tail of the caudate (Whitlock and Nauta 1956). Thus it is not surprising that both lesions and stimulation within the head of the caudate nucleus have been demonstrated to yield impaired performance on delayed response and delayed alternation tasks (Rosvold and Delegado 1956, Rosvold at al. 1958, Batting at al. 1960, 1962, Cianci 1965, Divac 1968*a*).

Seeking to further investigate the functional relationship between caudate and cortical areas, Divac, Rosvold and Szwarcbart (1967) observed that lesions within regions of the caudate to which a given cortical area projects result in performance decrements on only those tasks on which performance is impaired following cortical damage alone. Of particular relevance here are the findings that lesions of the anterodorsal head of the caudate resulted in impairment only on delayed alternation while lesions of the caudate tail produced performance decrements limited to visual discrimination. These findings present a striking parallel to the double dissociation of function of cortical areas outlined above.

Those observations raise the possibility that anatomically related areas of the caudate and cortex are equivalent in function. Although individual areas within a given anatomically related system seem to subserve behavior necessary for performance on identical tasks, this does not necessarily indicate that these areas are functioning in a strictly identical fashion. Divac (1968*b*), in a review treating the question of functional equivalence, points out that the behavior of decorticate animals is less efficient than that of normals, but that these "striatal" *S*s are capable of more elaborate behavior than *S*s with both cortex and striatum removed ("thalamic" preparations). He goes on to conclude that the functions of anatomically associated regions of the caudate and cortex may be related to a hierarchy of complexity of behavior, with the cortex subserving the more complex behavior patterns within the hierarchy. This is consistent with Jackson's (1958) levels of organization.

It is the purpose of this paper to examine the question of functional equivalence between the anterodorsal head of the caudate nucleus and the principalis region of dorsolateral prefrontal cortex as well as equivalence between the tail of the caudate and inferotemporal cortex by employing both an experimental technique and a behavioral task which may avoid the limitations inherent in previous studies. Stamm (1969) has recently employed a technique of electrical brain stimulation such that stimulation is delivered only during discrete portions of trials in a delayed response task. The main advantage of the stimulation technique is that it is reversible, i.e., the function of the stimulated structure is not disrupted permanently as in lesion experiments but, under certain conditions, only for the duration of the stimulation itself. This fact allows comparison of performance under conditions of stimulation occurring within a specific portion of individual trials with performance related to stimulation administered during other portions of the trials. Furthemore, because of the reversible nature of the stimulation technique, each *S* may serve as its own control, thereby allowing a comparison of behavior associated with the disruption of the normal ongoing activity of the stimulated structure with performance under nonstimulation conditions. It is this technique of application of electrical stimulation during discrete segments of individual trials which was employed in the present experiment.

With regard to the experimental task, previous studies involving double dissociation of function have relied upon separate behavioral tasks. It seemed that application of the stimulation technique outlined above would allow for functional dissociation of the structures to be stimulated within the same task if this taks employed elements common to both visual discrimination and delayed response problems. Thus task

designed for the present experiment was a delayed successive visual discrimination.

The present experiment therefore employed electrical stimulation as a probe along the temporal dimension in an attempt to allow comparisons of performance as a function of both the locus and time of stimulation. By examination of not only what structures must function, but, more importantly, when they must function during individual trials in the performance of this task, it was felt that two questions might be answered: (i) using the present approach, can one distinguish the two cortical-subcortical systems, and (ii) can one differentiate the two members of a given system. Thus it was hoped that the issues of heterogeneity of function within the caudate nucleus as well as functional equivalence between anatomically related structures might be clarified.

METHOD

Subjects

The *S*s were six experimentally naive, preadolescent, male rhesus monkeys (*Macaca mulatta*) weighing 2.7–3.8 kg. These animals were housed in individual cages and maintained on a standard laboratory diet.

Electrodes

Plate electrodes used for stimulation of prefrontal cortex consisted of a polyethylene sheet through which were inserted four leads of 0.127 mm Formvar-coated stainless steel wire. The ends of each lead had been fused to form a spherical contact approximately 0.5 mm in diameter. The array of contacts formed a square 8 mm on a side. The wires from the electrode points were led through a polyetylene tube to form a cable and soldered to a female Amphenol connector. One connector pin was available for grounding purposes. The depth electrodes were constructed from 22 gauge Formvar-coated stainless steel hypodermic needles. The twin parallel leads, also 0.127 mm Formvar-coated stainless steel wire, were inserted into the shaft and emerged 4 mm beyond the lower edge of the shaft. Electrodes intended for inferotemporal cortex and caudate tail employed leads which were cut flush with each other, whereas electrodes intended for the caudate head utilized leads with 0.5 mm uninsulated tips which were vertically separated by 0.5 mm.

Surgery

All *S*s were implanted bilaterally with chronic electrodes in two of the four areas to be stimulated: mid-principalis region of dorsolateral prefrontal cortex, middle to posterior inferotemporal cortex, anterodorsal

head of the caudate nucleus, and anterior tail of the caudate. Each of the six *S*s was implanted according to one of the six unique, non-identical pair combinations of these loci. Surgery was performed under aseptic conditions. *S*s were anesthetized with Nembutal and placed in a stereotaxic instrument. A longitudinal incision was made in the scalp and the scalp, fascia, and muscle were reflected. In the case of principalis electrode placements, the skull overlying the prefrontal area was rongeured away, thus exposing the dura which was cut and reflected. The plate electrodes were placed on the pial surface under visual guidance so as to straddle the middle third of the principal sulcus. The dura was sutured over the electrodes and surgical stainless steel screening placed over the bone defect. When depth electrodes were used, the anterior and lateral stereotaxic coordinates were marked on the skull and holes sufficiently large to accommodate the electrodes were drilled at these points with an electric dental drill. The electrodes were inserted into the brain through the dura which had been previously slit and lowered to the desired depth. In the case of ventral placements, a calibrated probe (22 gauge stainless steel hypodermic needle) was first lowered through the brain to determine the vertical coordinate of the inferior skull surface which was used as the vertical reference. The electrode shafts were held in place by dental acrylic cement which was poured around the shaft and a nearby screw threaded into the skull. The leads were connected to a female Amphenol connector. The connectors were tied by wires to skull screws and a mound of dental acrylic built up around them. The muscle fascia, and scalp were then sutured in anatomical layers around the acrylic mound. The stereotaxic coordinates for the depth electrodes were the following: caudate head — A: 23.0, A: 19.0, L: 5.0, V: 15.0 mm ventral to dural surface; caudate tail — A: 11.5, A: 9.5, L: 14.0, V: 10.0 mm dorsal to inferior skull surface; inferotemporal cortex — A: 8.0, A: 0.0, L. 16.0, V: 2.5 mm dorsal to inferior skull surface. Electrode placements in each *S* are shown in Table I.

Stimulation and recording apparatus

The implanted electrodes were connected to a relay panel which allowed switching between an electroencephalograph and a stimulator. A Grass S4 square wave stimulator, stimulus isolation unit, and constant current regulator provided bipolar stimulation across pairs of electrode points. Stimulation duration was regulated by a timer which was activated by another timer that was set for a latency period following the *S*'s response. Stimulation consisted of 2 sec trains of 1 msec pulses. 50 pulses/sec, at selected constant current settings. Current and voltage were monitored on a Tektronix 502 A dual beam oscilloscope. EEG activity was recorded by a 12 channel Grass Model 4 EEG machine.

Testing apparatus

The *S*, while seated in a restraining chair with the non-dominant hand restrained by a wrist cuff chained to a platform above his lap, faced an automated panel housing two round display windows 3.5 cm in diameter which could be illuminated from behind by variable pattern projectors (one plane digital display unit, Model 10D83; Industrial Electronic Engineers). These windows were mounted at eye level with a center separation of 6.5 cm. The manipulanda, clear lucite buttons covering the display windows, when depressed activated a microswitch which provided an input signal to the behavioral programming apparatus. Located below the manipulanda were two food cups, 16 cm apart, into which the reward, a 45 mg dextrose pellet could be delivered. Reinforcement was accompanied by 3 sec of illumination of the appropriate food cup.

Procedure

Pre-operative training. *S*s were adapted to the laboratory surroundings, handling, sitting in the restraining chair used in testing, and finally to pressing levers and buttons in automated testing apparatus to obtain dextrose reward pellets. During this period the *S*'s handedness was determined by noting the percentage of responses *S*, while seated in the restraining chair, made with each hand in order to receive dextrose pellets offered by *E* in varied positions in the visual field. Similarly noted was the percentage of responses using the right or left hand to operate the manipulanda of the testing apparatus during the adaptation procedure.

Subsequent to adaptation procedures, *S*s were shaped to perform a delayed successive visual discrimination task. The *S*s were first given a preliminary successive red-green discrimination problem. In this case, both discriminanda were either red or green fields filling the display windows, red indicating a response to the left button was required, green indicating a right response was appropriate. The stimuli remained present until the response was executed. The response resulted in termination of stimulus presentation, delivery of reinforcement following correct responses, and initiation of an 8 sec intertrial interval during which the display windows remained dark. The order of presentation of stimuli was determined by a Gellermann (1933) sequence. This sequence placed the following constraints upon the pattern of responses required for reinforcement: (i) an equal number of right and left responses in a block of 10 trials, and (ii) no more than three consecutive rewarded responses to the same side. *S*s were given 100 trials per day until they met a criterion of 90% correct responses in a single session, followed by one

overtraining session. The problem was then changed from the preliminary to a 0 sec delay paradigm. Under this procedure, the red and green stimuli were presented for 3 sec and were replaced immediately, i.e., after an intratrial delay of 0 sec, by the response cues, white fields presented in both windows. Depression of the manipulanda only in the presence of the white response cues could lead to reinforcement; other responses were ineffective. The Gellermann sequence was again employed. *S*s were trained until the criterion defined above, including overtraining, was met. Subsequently the intratrial delay was increased in 1 sec steps from 0 sec delay to 7 sec delay with *S*s meeting the same criterion at each step. They were then trained with an 8 sec delay until they reached a performance criterion of 90% correct responses per session for 3 out of 4 days.

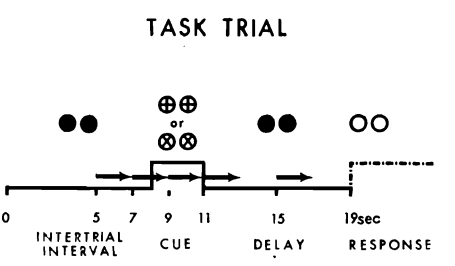

Fig. 1. Schematic representation of task trial. Circles illustrate appearance of display windows. These are illuminated by stimulus patterns and white fields during the cue and response periods, respectively. They remain dark during both the intertrial interval and delay. Arrows indicate portion of trial in which 2 sec stimulation was delivered.

The task was then changed to that used in the experiment proper, the only difference being that the red stimuli were replaced by white plus (+) patterns on a black background and the green by white Xs on a similar background (*see* Fig. 1). The total areas of the plus and X patterns were identical. The training procedure as outlined above was repeated until the *S* met criterion at the 8 sec intratrial delay level. Transfer from the color to pattern stimuli was rapid. A temporary constraint added to the task was a DRL (differential reinforcement of low response rates) schedule employed during the delay such that any intradelay response reset the delay timer. Thus the actual delay was measured from termination of the stimulus display or from the last intradelay response if such a response has occurred. At the end of training, virtually all intradelay responses had been extinguished; consequently, the DRL schedule was no longer employed.

Post-operative stimulation. Following recovery from surgery, as

evidenced by absence of observable behavioral changes as well as by the absence of EEG injury potentials recorded from electrode locations, *S*s were retrained to criterion performance on the experimental task at the 8 sec delay. Subsequently, *S*s were tested under conditions of electrical stimulation of one anatomical locus per session, current being delivered unilaterally to the hemisphere contralateral to the dominant hand used in performing the response (the non-dominant hand being restrained). In the case of depth electrodes, tissue between two electrode shafts in a given structure were stimulated, rather than tissue beneath a single shaft. For principalis electrodes, best results were obtained if stimulation was applied to the anteromedial and posterolateral electrode points (*see* Fig. 2).

Electrical stimulation below threshold for motor responses (current level averages for the four structures varying from 1.0 to 3.6 ma) was delivered during blocks of 10 trials each, separated by similar blocks in which no stimulation was administered. Non-stimulation blocks also occurred at the beginning and end of each session. Stimulation was never administered unless and until the *S* made at least 8 correct responses during the preceding 10 non-stimulation trials. During a given block of stimulation trials, the stimulation was always delivered during the same discrete portion of each trial. There were five such stimulation blocks, one for each of the five trial portions under investigation. The onset of the 2 sec train of stimulation, in terms of latency from the previous response, occurred at the following times and encompassed the following trial segments: 5 sec, stimulation delivered during the sixth and seventh sec of the intertrial interval (hereafter referred to as the intertrial period); 7 sec, the last second of the intertrial interval and first second of cue presentation (early cue); 9 sec, the remaining 2 sec of the cue (late cue); 11 sec, the first 2 sec of the delay (early delay); and 15 sec, the third quarter of the delay (late delay). These periods of stimulation are indicated by the arrows in Fig. 1 which illustrates the task trial. The order of trial periods during which the stimulation was delivered was systematically varied across sessions as was the structure being stimulated. Once the current thresholds for performance decrements were determined, these remained fairly constant over testing sessions.

Data were gathered over 25 stimulation sessions (a total of 250 trials for each time period) per anatomical locus in each *S*, except in the case of the S178 which died after 12 sessions per locus. During the last five experimental sessions for each locus in each *S* (with the exception of S178), EEGs were recorded.

Histology. Subsequent to completion of behavioral testings, *S*s were anesthetized with Nembutal and their electrode points fulgurated. All

Ss, including S178, were perfused with isotonic saline and 10% formalin. The brains were removed and sectioned serially at 48 μ using a modification of the frozen section technique suggested by Sherer and Pribram (1962). Every fifth section through the electrode tracks were retained and stained according to the Klüver-Barrera (1953) method and examined for the location of electrode points.

RESULTS

Histology

Actual electrode locations as verified histologically are illustrated in Fig. 2 and 3. Figure 2 shows a lateral view of principalis electrode placements in *Ss* 178, 181, and 184. Figure 3 presents serial transverse sections showing electrode locations for each *S*. Briefly, all electrodes were located within the intended structures with the exception of one shaft intended for the tail of the caudate nucleus in S178 which was

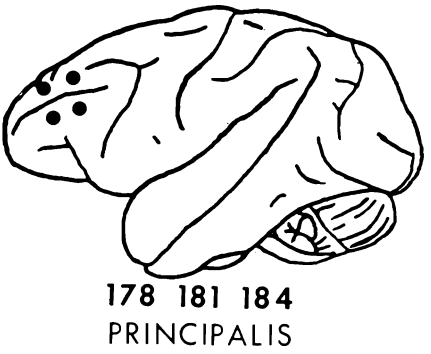

Fig. 2. Lateral view of the brain illustrating placement of principalis electrode points indicated by black spots. Points formed a square with 8 mm sides and straddled middle third of principal sulcus. *Ss* implanted with principalis electrodes are indicated.

placed in the substantia innominata. It should be noted, however, that like the tail of caudate, the substantia innominata is also a projection area of inferotemporal cortex (Whitlock and Nauta 1956). Note that none of the electrode placements encroached upon internal capsule, corpus callosum, optic radiations, or lateral geniculate. In the case of inferotemporal electrode locations, no fulgeration burns were observed on the dura underlying this area, indicating performance as a function of inferotemporal stimulation was not a result of stimulation of the dura.

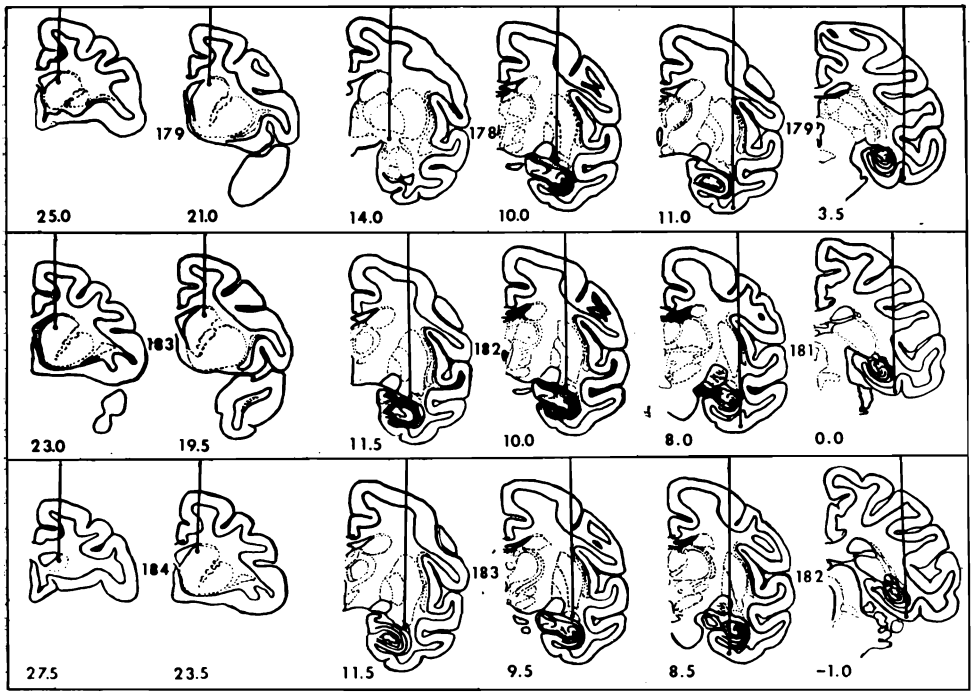

Fig. 3. Serial transverse sections showing histological verification of placement of depth electrodes in each *S*. *Ss'* numbers are indicated as are anterior-posterior stereotaxic coordinates of sections. For clarity, only locations of electrodes actually used for stimulation are shown and without regard to hemispheric location.

Task performance

Behavioral effects of stimulation are illustrated in Table I for each *S* and in Fig. 4. In Fig. 4, the 2 sec period of stimulation is indicated by its latency of onset from the previous response. Curves shown represent group mean performance in per cent correct responses as a function of latency of stimulation onset for each of the structures stimulated. Note that minima for these parallel curves occur at a latency of 7 sec (early cue) for both inferotemporal cortex and tail of the caudate and at 11 sec (early delay) for only principalis cortex and the head of the caudate nucleus.

For statistical purposes, the six *S*s were divided into three unique teams, the members of each team having between them all four anatomical structures under investigation. From this point of view, the analysis of variance reduced to a three factorial $\times$ team design. The factors were considered to be anatomical system (System), cortical vs. subcortical level (Level), and latency of stimulation onset (Latency). The

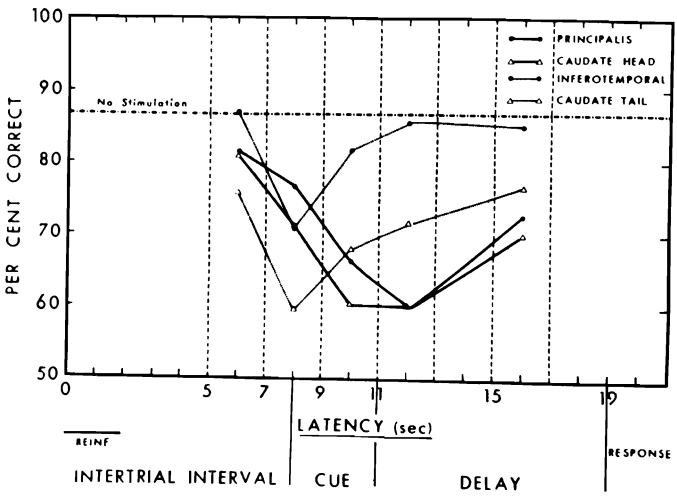

Fig. 4. Group mean performance in per cent correct as a function of latency of 2 sec stimulation onset. Stimulation occurred at 5 sec, 7 sec, 9 sec, 11 sec, and 15 sec. Performance under non-stimulation condition is indicated by horizontal line.

entries into each cell were the proportions of appropriate trials correct over the entire experiment, rather than the individual means of correct responses for each testing session. This was necessitated by the loss of data consequent to the unexpected demise of S178. The analysis of variance revealed that there was only one significant main effect, that of the Latency ($F = 23.00$, $df = 4/8$, $p < 0.001$) and that only one interaction, Latency $\times$ System, reached significance ($F = 36.87$, $df = 4/8$, $p < 0.001$). Of particular relevance here is the fact that neither the Latency $\times$ Level nor the Latency $\times$ Level $\times$ System interaction attained significance. These interaction results indicate that stimulation applied during different portions of the trial will produce performance decrements which vary as a function of which system is stimulated but that these decrements do not vary appreciably as a function of which structure within that system is stimulated. This conclusion is further supported by 2-tail t tests which demonstrate no significant differences between performance related to principalis stimulation and that related to caudate head stimulation for any given latency ($ts = 0.04$–0.88, $df = 2$, $ps > 0.05$). Similarly, performance related to stimulation of inferotemporal cortex and that related to stimulation of the caudate tail do not differ for any given latency ($ts = 1.42$–4.02, $df = 2$, $ps > 0.05$) with the exception of stimulation occurring during the late cue (9 sec) ($t = 6.11$, $df = 2$, $p < 0.05$). As is revealed below by 2-tail t test for related measures performed upon the individual data points, stimulation occurring at the following portions of each trial produced performance

TABLE I

Individual and group data for performance as a function of latency of electrical stimulation onset and non-stimulation condition[a]

Electrode location	Subject	Side stim.	No stimulation	Mean per cent correct responses Latency of stimulation 5 sec	7 sec	9 sec	11 sec	15 sec
Principalis cortex	178	Right	83.8	80.8	75.0	59.2	52.5	61.7
	181	Left	95.3	90.0	82.4	78.4	72.4	84.8
	184	Right	77.3	74.0	72.8	61.2	56.0	71.6
	Group mean		85.3	81.6	76.7	66.3	60.3**	72.7
Head of caudate	179	Left	86.0	84.0	76.4	66.0	64.8	78.4
	183	Right	89.6	83.6	64.4	56.8	57.2	64.8
	184	Right	84.1	75.2	72.8	58.0	58.8	68.4
	Group mean		86.5	80.9	71.2	60.3**	60.3***	70.5
Inferotemporal cortex	179	Left	86.1	88.4	72.0	76.8	88.8	86.0
	181	Left	90.7	81.6	66.4	83.2	83.2	81.2
	182	Left	87.7	91.2	74.4	85.2	85.2	88.0
	Group mean		88.2	87.1	70.9*	81.7	85.7	85.1
Tail of caudate	178	Right	82.8	76.7	59.2	66.7	62.5	65.8
	182	Left	89.4	76.8	58.8	72.0	83.2	84.8
	183	Right	89.9	73.6	60.4	65.2	69.2	78.8
	Group mean		87.3	75.7	59.5***	68.0**	71.6	76.5

a Hemisphere stimulated is contralateral to hand used in performing instrumental response.
* $p < 0.05$; ** $p < 0.02$; *** $p < 0.01$ in comparison of stimulation with no stimulation condition.

decrements which significantly differed from the no stimulation condition only for those structures noted: intertrial period — none; early cue — inferotemporal cortex and caudate tail; late cue — caudate tail, caudate head and principalis cortex; early delay — caudate head and principalis cortex; late delay — none.

Principalis. Performance subsequent to stimulation occurring during the early delay (11 sec) was significantly different from all other stimulation conditions for this structure ($ts = 4.55$–11.83, $df = 2$, $0.05 > ps > 0.005$) and differed significantly from the no stimulation condition ($t = 8.50$, $df = 2$, $p < 0.02$). Performance as a function of stimulation delivered during the late cue (9 sec) was also significantly different from the no stimulation condition ($t = 7.49$, $df = 2$, $p < 0.02$) as well as from all others ($ts = 4.41$-4.87, $df = 2$, $ps < 0.05$) with the exception of the late delay (15 sec) condition ($t = 2.82$, $df = 2$, $p > 0.05$),

but performance under this latter condition did not differ from the no stimulation condition ($t = 2.68$, $df = 2$, $p > 0.05$). These apparently contradictory results are viewed as related to high variability in these *S*s' performance under the late delay condition. No other conditions yielded statistically significant results.

Caudate head. Stimulation occurring during the late cue (9 sec) and the early delay (11 sec) were the only conditions which resulted in performance which differed significantly from the no stimulation condition ($ts = 9.19$–11.52, $df = 2$, $0.02 > ps > 0.005$). Performance under these conditions differed significantly from all other conditions ($ts = 5.36$–8.48, $df = 2$, $0.05 > ps > 0.01$). Furthermore, performance levels under these two conditions did not differ significantly from each other ($t = 0.0$).

Inferotemporal cortex. Stimulation occurring during the early cue presentation (7 sec) was the only condition which resulted in performance which differed from that under the no stimulation condition ($t = 6.71$, $df = 2$, $p < 0.05$). Performance under this condition also differed from performance under any other condition of stimulation of this structure ($ts = 4.87$–40.40, $df = 2$, $0.05 > p > 0.0005$).

Caudate tail. Performance levels as a consequence of stimulation occurring during any portion of the cue, early (7 sec) or late (9 sec), differed significantly from those observed under all other conditions ($ts = 4.67$–10.01, $df = 2$, $0.05 > ps > 0.005$), and were the only levels differing from those seen under the no stimulation condition ($ts = 7.33$–12.90, $df = 2$, $0.02 > ps > 0.005$). They, in turn, did not differ from each other ($t = 3.43$, $df = 2$, $p > 0.05$).

Electroencephalography

EEGs were recorded during the last five experimental sessions which together totaled 250 individual stimulations of each locus in each *S* (with the exception of S178). These were analyzed manually for afterdischarges, slow wave activity, and amplitude depressions. The time of occurrence during the trial and the duration of these effects were noted along with the *S*'s performance for each trial. Due to blockage of the EEG amplifier, however, it was not always possible to observe these patterns immediately after stimulation. Analysis of the data revealed no consistent relationship between that portion of the trial during which any afterdischarge was present and performance. The only critical factor was that period in which the stimulation itself was applied. Measures of the spread of stimulation effects were also recorded and are reported below. Note that with the exception of discussion concerning spread of stimulation effects to contralateral representations of the stimulated structure, distal effects were based upon observations of one *S* each, since only

one *S* was implanted according to each of the six unique, non-identical, pair combinations of anatomical loci.

Principalis. No distal effects were noted in inferotemporal cortex. In one *S* (S181), spread to the contralateral principalis region was rare (approximately 5% of the trials), whereas in another (S184), such spread was moderately common (31%). In this same *S*, stimulation effects were also observed bilaterally in the caudate head (15%).

Caudate head. Effects of stimulation were rarely seen to spread to the contralateral head (2%); never to the tail of caudate or inferotemporal cortex. Presumably antidromic spread was observed in S184 to the ipsilateral principalis region (10%).

Inferotemporal cortex. Distal effects were rarely observed in the contralateral inferotemporal cortex (10% in one *S* (S181) and never in the others). Excitation was not demonstrated in the head of caudate, tail of caudate, nor in the principalis region.

Caudate tail. Stimulation effects were rarely recorded from the contralateral tail (3%) although such effects were commonly observed ipsilaterally and bilaterally in the head of the caudate (57%). Stimulation occasionally (20%) produced slow wave activity in the ipsilateral inferotemporal region.

DISCUSSION

The findings reported here strongly indicate that the tail of the caudate nucleus and the posterior portion of inferotemporal cortex both play their greatest roles in the processing of perceptual information while that information is actually present in the environment, whereas the anterodorsal head of the caudate nucleus and principalis region of dorsolateral prefrontal cortex are involved in non-perceptual (in the classical sense) functions occurring during the early portion of the delay period. These findings are interpreted as support for the concept of functional heterogeneity of the caudate nucleus. However, although structures within a given anatomically related system are also functionally related in as much as they are maximally sensitive to disruption by stimulation occurring at identical times within the task trial and are not associated with significantly different degrees of behavioral impairment when disrupted at these times, this does not necessarily indicate that these structures are performing functions according to strictly identical mechanisms. That is, there may be hierarchical levels within anatomically related systems as has been suggested by Divac (1968*b*). What these levels may be remains the subject for further investigation; however, it is apparent that such levels may not be dissociated by probing along the temporal dimension.

Further interpretation of the data summarized in Fig. 4 revolves about a question addressed to the possibility of stimulation effects outlasting the stimulation application itself. With regard to the curves drawn for stimulation of the tail of caudate and posterior inferotemporal cortex, one may ask why it is that stimulation extending only 1 sec into the cue presentation causes a significant performance decrement. It seemed plausible that stimulation effects were outlasting the duration of the applied stimulation itself by at least 2 sec, although sufficient evidence of this was not recorded electroencephalographically due to frequent EEG amplifier blockage. The answer to this question was determined behaviorally. One *S* (S182) was given alternate blocks of 10 trials under the following conditions which yielded the performance levels noted: (i) no stimulation and a 3 sec cue presentation, 81.7% correct; (ii) 2 sec stimulation of inferotemporal cortex with a latency of 7 sec (early cue) and a cue duration of 3 sec (the stimulation condition normally employed) 56.0%; (iii) 2 sec stimulation of inferotemporal cortex occurring at 7 sec (early cue), but with a cue duration of 5 sec, 80.0%. Thus it appears that if the cue presentation is extended by 2 sec, the effects of stimulation are no longer present or are without consequence and the visual information is adequately processed. It may be possible to infer that stimulation effects lasting throughout the 3 sec cue presentation may be present in the case of stimulation of the caudate tail as well. Thus, if normal ongoing activity of inferotemporal cortex or the tail of the caudate is disrupted by stimulation or its effects throughout the cue presentation, behavior is maximally impaired relative to effects caused by stimulation occurring at any other point in the trial. It is apparent that if 1 sec of cue information is presented before the onset of stimulation of posterior inferotemporal cortex (late cue condition), this curtailed amount of information is sufficient to allow for unimpaired performance. This is not surprising in view of the fact that Fehmi, Adkins and Lindsley (1969) have demonstrated unimpaired performance in monkeys on a visual pattern discrimination task employing a backward masking technique utilizing an interstimulus interval as short as 30 msec. (In fact, knowledge of these results determined the use of early cue stimulation commencing 1 sec before the onset of cue presentation).

A second question which may be raised relates to the significant impairment observed when the onset of stimulation delivered to the tail of the caudate occurs after 1 sec of visual cue information is presented (late cue condition). In the one *S* with electrodes implanted in both head and tail of the caudate (S183), afterdischarges and amplitude depression of EEG potentials subsequent to stimulation delivered to the caudate tail were seen to spread to the head. Thus performance consequent to stimu-

lation of the tail may be in part a reflection of this distal effect and related to performance observed as a function of electrical stimulation applied to the caudate head. Furthermore, this spread of effect may account for the generally greater performance decrements observed following stimulation of the caudate tail with respect to stimulation applied to inferotemporal cortex, although the difference between the two curves in Fig. 4 drawn for these loci is not statistically significant.

As previously stated, analysis of the data relating performance on the experimental task under conditions of stimulation of the anterodorsal head of the caudate nucleus and the principalis region of prefrontal cortex reveals no significant difference between the respective curves as drawn in Fig. 4. One may speculate, however, as to the functional significance of the performance decrements noted following stimulation occurring during the late cue or early delay. With respect to the late cue stimulation effect, Stamm and Rosen (1970) have demonstrated in an analogous delayed response experiment that stimulation during the final 2 sec of cue presentation results in performance decrements even if the duration of presentation of the cue, a single white disc, is extended to 6 sec. These findings may be interpreted as the result of late cue stimulation effects outlasting the stimulation application itself and disrupting some critical functions taking place during the early delay. Alternatively, it may be possible that there is some ongoing activity in these structures which reaches a maximum during the early portion of the delay period. Evidence for this notion has been provided by Stamm and Rosen (1969) who described changes in steady (slow) cortical potentials during delayed response trials. Of special relevance here is the fact that they observed a shift in negativity of the cortical surface with respect to the depth of cortex in the region of the principal sulcus. This shift was seen to commence at the beginning of the trial (cue onset) and increase to a maximum during the first few seconds of the delay before falling to pretrial levels. Since increased negativity of steady potentials is interpreted as related to increased cortical activity as measured by EEG frequency, amplitude, and response threshold. (O'Leary and Goldring 1964, Rosen and Stamm 1966), it is logical that disruption of this activity by application of stimulation when such activity is at its maximum should produce a maximal performance decrement. Furthermore, should stimulation at *any* point during the trial prevent cortical activity from attaining maximum values, one would expect to observe an impairment. Thus the present behavioral data with respect to stimulation of the principalis region of prefrontal cortex occurring during the latter portion of the cue may be interpreted as related to disruption of maximal cortical activity occurring during the early portion of the delay period. Although

there are no analogous findings relating to steady potential shifts in the caudate during delayed response performance, it is felt that an interpretation along the lines of prevention of maximal caudate activity during the early delay by late cue stimulation is applicable.

The placement of the relative critical periods of function along the temporal dimension as in the cue and early delay portions of the trial for posterior inferotemporal and principalis cortex respectively, are consistent with the findings of several investigators. Iwai and Mishkin (1967) have demonstrated in a series of experiments using a surgical fractionation technique, that posterior inferotemporal cortex performs functions related to perception of the environment (anterior inferotemporal cortex being related to the establishment of cue–reinforcement associations). The present results are also consistent with those observed by Stamm and Rosen (1970) in an analogous experiment involving stimulation of principalis and inferotemporal cortex during trials on a delayed response task in which the relevant cue was the position of a disc of light (traditional indirect mothod). It is of interest to note that they also used unilateral inferotemporal stimulation to produce performance decrements, as was the case in the present experiment; however, Chow (1961) reported that he was unable to produce impairment on a visual go–no go discrimination task unless stimulation was bilaterally applied to inferotemporal cortex. The explanation of this discrepancy is uncertain.

Cianci (1965) has also demonstrated that stimulation of prefrontal cortex in monkeys performing a delayed response task in a Wisconsin General Testing Apparatus (WGTA) may lead to behavioral impairment if applied during the delay. He also observed impairment related to stimulation throughout the cue or association phase, but these latter effects may be interpreted as possibly being related to post-stimulation physiological changes. One may also question Cianci's operational definition of the onset of the delay, i.e., the interposition of the opaque barrier between the subject and the food cups. One may prefer to consider that the delay actually begins once the bait is covered in the food well; this event occurs before the end of the association phase and may itself be the point of demarcation between the association and retention phases. Thus stimulation occurring during the association phase may actually be overlapping with the retention stage. The importance of factors present during the delay in delayed response tasks and their relevance to performance by monkeys with frontal lobe damage has been outlined in a review by Fletcher (1965).

With respect to performance concomitants of stimulation applied to the head of the caudate nucleus, again, the results reported here are consistent with those described elsewhere. In Stamm's experiment (1969),

stimulation applied to the caudate resulted in maximal impairment if delivered during the early delay. Severe impairment was also seen under the late delay condition. In addition, performance decrements associated with stimulation during the late cue were not as marked as those described in the present experiment, but these differences may be due to the fact that the electrodes in that study were located in the posteroventral area of the caudate head. Lesions in that area also lead to delayed alternation deficits, but no fiber degeneration is seen there following ablation of dorsolateral prefrontal cortex (Divac et al. 1967). Cianci (1965) also has observed results following caudate head stimulation which parallel his observations of the effects of stimulation of dorsolateral prefrontal cortex.

The caudate head has also been stimulated in cats as they performed a position reversal task in a WGTA (Thompson 1958). In this task the subject received reinforcement for responding to the position of one of two identical cues until attaining four out of five correct responses or for a maximum of 12 trials. An interval of 30 sec separated individual trials. The position was then reversed; there were four such reversals in 1 day. Stimulation was applied before, during, or after the *S* was permitted to respond. Significant impairment was associated with stimulation occurring after the response. Note, however, that under this paradigm, the events occurring at the time of the response are the cues for the next trial. Thus stimulation before the response is analogous to the late delay condition in the present experiment; during, the cue condition; after, the early delay condition.

With regard to the exact nature of principalis-anterodorsal caudate head functions, the present experiment does not provide any definitive answer. The results reported here would be consonant, however, with the notion of these two areas acting together in a system which allows the monkey to adopt a spatial mnemonic plan based upon its ability to encode the spatial aspects or spatial meanings of the cues within an egocentric spatial coordinate system rather than a coordinate system having an external origin. The interoceptive basis of such a spatial mnemonic and egocentric coordinate system may rely upon the monkey's ability to utilize subtle, covert motoric responses which may provide either spatial-kinesthetic cues (inflow information) as Konorski (1967) has suggested, or corollary discharges (outflow) such as hypothesized by Teuber (1966).

It does appear that both the dorsolateral prefrontal cortex, or the middle third of the principal sulcus in that region (Butters at al. 1969, Stamm 1969), and the anterodorsal head of the caudate nucleus perform functions subserving performance on tasks requiring an ability to encode the spatial location of a cue, as in delayed response, or to plan the spatial

itinerary of a response as in delayed alternation. A brief analysis, however, brings with it some parsimony if one assumes that the spatial location of cue, and hence its meaning, is encoded by some covert movement or orientation towards it, and that the cue in delayed alternation is also a spatial movement, the previous response. Thus it appears that until recently, in being allured by first the mnemonic aspects of the delay tasks and then later the spatial characteristics of these tasks, many have overlooked the importance of motor movement analysis per se as the function of the principalis–anterodorsal caudate head system. (The use of the term system is prompted here not only by the functional similarities of the paired structures, the identity of times during which both are maximally sensitive to disruption, or the known anatomical relationships, but also in light of the data presented by T. J. Tucker (unpublished data) which indicate that functions of the prefrontal cortex in the adult monkey are similar to those mediated by the caudate in the neonate, at a time when the cortex is either functionally plastic or undifferentiated).

Although one may have difficulty in envisioning an ecologically significant analogue of delayed response behavior of monkeys performing in a WGTA (Warren et al., this Symposium), the ability to utilize motoric information, either spatial-kinesthetic inflow or corollary discharge outflow, is of obvious adaptive significance, for it is this information which is utilized as a basis of a spatial code. Specifically, these movements related stimuli form the elements of space-encoding according to a coordinate system which is egocentric in nature. Data has been presented by Mishkin and Pribram (1956), which may be interpreted as evidence indicating that monkeys with lesions of prefrontal cortex are capable of spatial delayed response performance if the cues are themselves not spatial (the subject was required to retain which cue was presented, not where the cue appeared). Since both cues always were displayed over the same food well, that food well may have served as the external origin of a spatial coordinate system with responses being made toward or away from that origin as opposed to being directed towards the left or right.

The inability of monkeys with dorsolateral prefrontal lesions to use motoric information, and hence the inability to egocentrically code space, in spite of their ability to perform a delayed go–no go task (Mishkin and Pribram 1955) indicates that prefrontal cortex functions are related to certain, but not all, types of motor information. Quite likely this analysis is related to active, self-produced movement. Bossom (1965) has shown that of 13 lesion groups of monkeys, only those subjects with either caudate lesions or prefrontal lobectomy were unable to adapt visuomotor coordination to visual rearrangements (primarily spatial displacement of the environment) as seen through refracting prisms. Such a mechanism

seems to follow an outflow model of motor control, possibly through a corollary discharge, since monkeys were observed to adapt to prism-induced rearrangements following deafferentation via dorsal rhizotomy; however, when the same subjects sustained caudate lesions, they failed to initiate reaching movements toward a visual target unless the reaching limb was in view (Bossom and Kommaya 1968). The implication of these observations is that the caudate head may mediate an efferent control system which subserves the subjects ability to perceive the external environment and localize objects within it relative to an egocentric spatial coordinate system. Such an implication is supported by the findings that rats with caudate lesions and humans with Huntington's Chorea both are impaired on egocentric localization tasks (Potegal 1969). In such a model, the caudate head may act as a comparator receiving input from principalis efferents (DeVito and Smith 1964), sparse efferents originating in motor cortex (Mettler 1947), and efferent polysensory information (Albe–Fessard et al. 1960*ab*).

The prefrontal cortex, however, may be processing motor information according to an inflow mechanism such as that proposed by Konorski (1967) in which this cortical area would act as a kinesthetic analyzer containing gnostic units receiving information from muscle spindles and tendons. As Nauta (this Symposium) points out, this area is also the recipient of polysensory information.

As to the relative importance of inflow vs. outflow mechanisms, outflow mechanisms may be sufficient in controlling gross movement, at least to the extent of reaching movements required in Bossom's (1965) experiment, without the benefit of fine coordination, whereas inflow or afferent information concerning movement is necessary for the execution of skilled motor patterns. Whereas important differences between active and passive movement have been considered in terms of outflow and inflow mechanisms respectively, Konorski (1970) has shown evidence for an inflow mechanism in which Purkinje cells of the cerebellum function as a filter allowing discrimination between active and passive movement. Information concerning self-produced movement is then relayed from the cerebellum to the "kinesthetic gnostic area" (presumably cortical) via the ventrolateral thalamus. In view of this last finding, one may conjecture that the analysis of active self-produced movement essential for egocentric spatial localization may follow an outflow mechanism at the level of the caudate nucleus and a parallel inflow mechanism at the cortical level.

In conclusion, it is the author's contention that principal sulcus region of dorsolateral prefrontal cortex and the anterodorsal head of the caudate nucleus perform functions related to analysis of active, self-produced

movement information, possibly via inflow (afferent) and outflow (efferent) mechanisms respectively, and that such information is the basis of an egocentric coordinate system according to which spatial information of the type required for delayed alternation and delayed response is encoded. Whereas posterior inferotemporal cortex and the anterior tail of the caudate process visual information while it is actually present in the environment, i.e., during cue presentation, the prefrontal cortex–head of caudate system appears to function critically during the early portion of the delay.

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