Kindling With Stimulation of the Dorsal and Ventral Striatum

by

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ABSTRACT

The characteristics of the kindling of seizures produced by electrical stimulation of the nucleus accumbens (ventral striatum) or of the head, middle region, or tail of the caudate-putamen (dorsal striatum) were investigated in rats. Kindling in the accumbens group was characterized by high thresholds for afterdischarge (AD), forced movements during stimulation, slow progression from nonconvulsive to convulsive seizures, and large increases in the duration of the behavioral seizures. Kindling in the caudate groups was characterized by high AD thresholds, forced movements during stimulation, rapid progression from nonconvulsive to convulsive seizures, and small increases in the duration of the behavioral seizures. The similarities of striatal kindling to limbic and neocortical kindling are discussed, as are the relations of the present findings to previous evidence of striatal involvement in seizures.

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Dedication

I dedicate this thesis to my grandparents, Helen and Charles, for all the help and support over the last 2 years.

This thesis is concerned with the susceptibility of the neostriatum, a portion of the basal ganglia, to the kindling of seizures. In the thesis I describe the epileptiform effects of repeated electrical stimulation of the caudate-putamen, a major component of the neostriatum, and of the nearby nucleus accumbens.

Kindling involves the progressive development of seizures and an enduring increase in seizure susceptibility in response to intermittent electrical stimulation of certain structures in the forebrain. This phenomenon has its basis in the observation that epileptiform afterdischarges (ADs) can be triggered when low intensity current of brief duration is passed through the uninsulated tip of electrodes within certain areas of the brain. Initially the ADs have a short duration, and there are few or no behavioral effects observed in conjunction with the AD. The initial stimulations result in low amplitude AD spikes, and there is limited propagation to other sites in the brain. Repetition of the stimulation at a fixed interval (usually 24 hours) and a given magnitude of intensity (usually at the AD threshold, arbitrarily defined as the lowest intensity of stimulation that evokes an AD at the stimulation site) will lead to an increase in epileptiform activity manifested by typical behavioral responses and EEG patterns (Racine, 1978). Kindling is a long-lasting effect, with no remission of the phenomenon observed, at least at limbic sites (Goddard, McIntyre, & Leech, 1969). Kindled animals can demonstrate spontaneous seizures (Pinel, Mucha, & Phillips, 1975; Wada, Sato, & Corcoran, 1974).

Kindling does not appear to result from focal tissue damage (Goddard et al., 1969). In fact, lesions at the tip of the implanted electrode interfered with the kindling process (Goddard et al., 1969).

At the ultrastructural level, Goddard and Douglas (1975) failed to observe any evidence of degeneration following kindling.

Kindling therefore affords researchers excellent parametric control in studies of focal epilepsy and epileptogenesis while avoiding possible confounding toxic effects associated with exogenous administration of convulsant chemicals. Kindling also provides a model of neuroplasticity in the mature and immature nervous system that is permanent and apparently does not involve tissue damage.

Brain sites are differentially susceptible to kindling. Goddard et al. (1969) found that sites varied in the number of stimulations required to produce behavioral seizures. In order of decreasing susceptibility to kindling, the following pattern was found: amygdala, globus pallidus, pyriform cortex, olfactory bulb, septal area, preoptic area, caudate putamen, and the hippocampus. Also, most brainstem and several neocortical and caudate sites did not show any kindling effect, even following up to 200 stimulations. Goddard et al. (1969) used a fixed current intensity and did not record the number of ADs evoked during the stimulation procedures.

Racine (1972a, 1972b) demonstrated that the threshold required to trigger AD is variable (threshold decreases as a function of the number of stimulations) and that it is the triggering of ADs that is the important causal element in seizure development. When the intensity was adjusted to trigger an AD with each stimulation, Racine (1972a, 1972b) observed that the pyriform cortex and the olfactory bulb were the structures most susceptible to kindling. Furthermore, he found that several of the structures that Goddard et al. (1969) found difficult to

kindle have high thresholds for AD but kindle readily when these thresholds are exceeded.

Not only do various areas of the brain differ in responsiveness to stimulation, they also differ in the patterns of AD and seizure development observed. In rats, Burnham (1978) has described 2 principal patterns, "limbic" kindling and "anterior neocortical" kindling. Limbic kindling occurs with stimulation of the amygdala, olfactory bulbs, hippocampus, pyriform cortex, and the entorhinal and sulcal prefrontal cortices (Corcoran, 1988). Limbic sites typically have low AD-threshold with no behavioral (clinical) seizures associated with initial ADs. Repeated triggering of ADs produces increased AD duration; and, with amygdaloid stimulation, generalized behavioral seizures develop over a time course of 10-15 ADs (Corcoran, 1988). Racine (1972b) has described the typical pattern of limbic kindling as comprising 5 distinct stages: stage 1, mouth movements; stage 2, head nodding; stage 3, clonus of the contralateral forelimb; stage 4, bilateral clonus with rearing; and stage 5, rearing with falling. Other investigators (Pinel & Rovner, 1978) have described 3 additional stages of limbic kindling that develop after many seizures have been triggered: stage 6, multiple episodes of rearing and falling; stage 7, running fits; and stage 8, running fits with episodes of tonus. Anterior neocortical kindling occurs with stimulation of the motor cortex, medial prefrontal cortex, and the parietal cortex. AD thresholds are typically higher than in limbic sites, and neocortical ADs are short in duration and from the outset are accompanied by a brief clonic seizure of a similar duration (Burnham, 1978). Forelimb tonus develops over the course of approximately 10 ADs,

typically without increased AD durations (Burnham, 1978). Unlike limbic seizures, generalized neocortical seizures are somewhat unstable, as previously effective stimulation either may fail to elicit a generalized seizure (Seidel & Corcoran, 1986) or may elicit a partial seizure (Burnham, 1978).

As mentioned previously, some sites in the caudate nucleus support electrical kindling (Goddard et al., 1969), while others do not. The caudate is particularly interesting because, as I shall discuss below, it is not clear whether the caudate kindles in a limbic or anterior neocortical fashion. In addition, numerous investigators have reported both proconvulsant and anticonvulsant effects of stimulating the caudate nucleus. These contradictory results may relate to the diverse anatomical projections to the caudate and the projections of the caudate itself. Because kindling of the striatum is the focus of the present thesis, I review the anatomy of the area in detail below.

Anatomy of the caudate

In this section I review the neuroanatomy of the caudate nucleus and related structures. The review demonstrates the complexity of this region of the nervous system, and it lays the groundwork for several specific hypotheses the present thesis is designed to test.

The caudate is part of a larger system of associated nuclei known as the basal ganglia. The basal ganglia are also known as the corpus striatum due to their characteristic striped appearance. The basal ganglia comprise the striatum (the caudate nucleus and the putamen), the globus pallidus, and the amygdaloid complex.

In the rat brain there is no clear differentiation between the putamen and the caudate nucleus, which in the primate brain are separated by the internal capsule (Zeman & Innes, 1963). As well, in the rat the caudate nucleus does not extend back on the medial and dorsal aspects of the internal capsule as it does in primates. The caudate-putamen complex is referred to as the striatum or the neostriatum. The globus pallidus is referred to as the pallidum or the paleostriatum, and the amygdala is referred to as the archistriatum.

The inclusion of the nucleus accumbens in the striatum is debatable. The nucleus accumbens and the olfactory tubercle are sometimes included in the striatum, due to their proximity to the striatum and the similarity of their innervation and cell morphology (Heimer, Alheid, & Zaborsky, 1985). Heimer et al. (1985) proposed that the caudate and the putamen should be referred to as the dorsal striatum and the nucleus accumbens and lateral structures be referred to as the ventral striatum. In this scheme, the putamen is referred to as the dorsolateral striatum.

In general, the basal ganglia are connected to the rhinencephalon (limbic structures), the diencephalon (including the subthalamic nuclei), the mesencephalon (including the red nucleus and the substantia nigra), and the rhombencephalon (including the pons and medulla) (Noback & Demarest, 1977). Taken as a whole, these connections form a significant part of the extrapyramidal motor system.

A major afferent fibre system to the striatum comes from the centromedial (CE) thalamic nucleus, which sends small afferent fibres that run caudorostrally through the entire striatum. The CE thalamic

nucleus itself receives afferent fibres through the superior cerebellar peduncle from the cerebellum and the reticular formation (Zeman & Innes, 1963).

The efferent pathways of the basal ganglia form the striatopallidoreticular, striatopallidocortical, and striatonigral systems. Originating in the striatum, fibres of the striatopallidoreticular system terminate in the pallidum, making connections with neurons from the intralaminar nuclei of the thalamus. These in turn send their axons to the red nucleus and to the reticular formation, where the rubrospinal and reticulospinal tracts originate (Zeman & Innes, 1963).

The striatopallidocortical system provides a link between the basal ganglia and the neocortex. The pallidum receives strong afferent inputs from the striatum and projects via the ventrolateral (VL) thalamic nuclei to the neocortex, particularly to the regions of the neocortex that give rise to the corticofugal motor pathways.

The striatonigral system consists of pathways using the neurotransmitter gamma-aminobutyrate (GABA) and projecting from the cerebral cortex to the striatum, and from the striatum to the substantia nigra (SN). The striatonigral fibres project to both the pars reticulata and the pars compacta of the SN. The pars reticulata is rich in iron and lacking in melanin, whereas the pars compacta is rich in dopamine (DA) and melanin.

Projections from the SN are directed rostrally via the nigrostriatal fibres to the striatum or the nigrothalamic fibres to the VL thalamic nuclei, which project to the motor and premotor cortical

areas (Noback & Demarest, 1977). The nigrostriatal fibres are part of the DA neuronal system and provide the sole source of the DA found in the striatum.

The role of the basal ganglia is to modulate motor activities through circuits that directly and indirectly feed back to the cerebral cortex. Lesions in this system may lead to disorders of posture and movements, such as dyskinesia, Parkinson's disease, or Huntington's chorea (Noback & Demarest, 1977). Dyskinesia is thought to be a result of malfunction of the dopaminergic neuronal loop between the SN that project to the striatum, the cholinergic interneurons of the striatum, and the neostriatal neurons projecting back to the SN (Noback & Demarest, 1977). Degenerative changes in the SN and the pallidum and depletion of DA in the SN and striatum are the primary neuronal changes associated with Parkinson's disease (Bjorklund, Stenevi, Dunnett, & Iversen, 1981). Huntington's chorea involves damage to the neostriatum and cerebral cortex, and there is a decrease in GABA concentrations in the striatonigral pathways (Coyle & Schwartz, 1976).

The striatum is not a homogeneous area; it comprises 2 separate compartments, most commonly referred to as the patch (or striosome) and matrix (Graybiel & Ragsdale, 1978). These compartments differ in spatial distribution, biochemistry, and innervation. The patch compartment has dense patches of opiate receptor binding and is enriched in enkephalin (Herkenham & Pert, 1981) and substance-P immunoreactivity (Gerfen, 1984). The patches were first found in tissue sections that were stained for acetylcholinesterase (AChE); patches of tissue that did not stain were observed in areas of high staining (Graybiel & Ragsdale,

1978). Patches are more numerous in the dorsomedial and ventral striatum (Herkenham & Pert, 1981), although in the ventral striatum they are less distinct than in the dorsomedial striatum. The matrix compartment is characterized by dense AChE and choline acetyltranferase (ChAT) staining (Graybiel, Baughman, & Eckenstein, 1986) and consists of the area surrounding the patches. Enkephalin-rich patches are surrounded by areas of high AChE staining (Herkenham & Pert, 1981), and in the rat immunoreactivity to substance P occurs primarily in the patches (Gerfen, 1984). Somatostatin immunoreactive neurons are present in both the patches and the matrices (Gerfen, 1984). Dendrites from the matrix-labelled neurons extend into the patches and may prove to be the method of communication between the patches and the matrices.

Using anterograde markers (Phaseolus vulgaris leucocoaglutin, PHA-L) the dopaminergic afferents to the striatum were mapped (Gerfen, Herkenheim, & Thibault, 1987). Neurons originating in the ventral tegmental area project to the matrix of the ventral striatum. Fibres originating in the ventral part of the pars compacta of the SN project to the matrix in the dorsolateral striatum (Gerfen, 1984). Fibres originating in the ventral part of the pars compacta of the SN project to the patches in the ventral and dorsomedial striatum. A cluster of dopaminergic neurons originating in the pars reticulata of the SN projects to the patches in the dorsolateral striatum (Gerfen, 1984). Striatal cells labelled by retrograde staining of the pars reticulata were located primarily in the matrix of the anterior and middle caudate (Gerfen, 1985). Posterior levels of the striatum showed some patch cells labelled when the injections were in the lateral pars reticulata.

Both patch and matrix labelling occurred in the ventral striatum (Gerfen, 1985). These results were confirmed with anterograde staining of matrix cells in the ventral striatum that revealed a topographically organized projection to the pars reticulata (Gerfen, 1985).

Injections of tritiated leucine, an anterograde neuronal tracer, into the rat amygdala indicated that there are substantial connections in the caudal half of the striatum, especially the mediodorsal and medioventral quarters of the striatum. A large number of labelled fibres crossed the anterior commissure to the contralateral striatum, where they were less densely distributed than in the ipsilateral striatum (Kelley, Domesick, & Nauta, 1982). Conversely, a large number of cells in the basolateral amygdala were marked when retrograde cell markers were injected into several striatal locations (Kelley et al., 1982). These cells were labelled in a topographical correspondence with the injections in the striatum. Dorsal to ventral injection sites corresponded to medial to lateral cell marking in the basolateral amygdala, although the distribution of the amygdalostriatal fibres were confined to the most ventral region of the striatum.

Using anterograde markers, Ragsdale and Graybiel (1988) traced the connections from the amygdala to the striatum of the cat. They found that labelling was highest in the ventral striatum, but that it was also observed in the dorsomedial striatum. There was an absence of labelling in the dorsal and lateral parts of the striatum, specifically the striatal region that is targeted by fibres from the motor cortex. The amygdalostriatal fibres innervate the AChE-poor patches in the dorsal striatum and the matrix in the ventral striatum (the dorsal nucleus

accumbens).

Using the PHA-L anterograde marking technique, Gerfen (1989) found that the patches receive inputs from the prelimbic cortex. The prelimbic cortex is a medial frontal cortical area that has direct limbic inputs from the amygdala and the hippocampus (Gerfen, 1989). The anterior cingulate and the agranular motor areas primarily project to the matrix. The picture is complicated, however, by the observation that the labelling of either the patches or the matrices depends upon the level of the injection site. Deep cortical injections resulted in labelling primarily in the patches, whereas more superficial injections resulted in labelling primarily in the matrix. The projections of the prelimbic cortex to the striatal patches and the neocortical areas to the matrix only reflect the most dominant pattern of labelling. It is important to remember that the differences in the projections from different cortical areas to the 2 compartments are relative, as each area provides inputs to both striatal patch and matrix compartments.

In summary, the patches have large numbers of opiate receptors, and high numbers of binding sites for enkephalin and substance P. The matrix is rich in AChE and ChAT. Both the patches and the matrix contain somatostatin immunoreactive neurons, and this may be a communication network between the two areas. The matrix consists of the area surround in the patches, which are more numerous in the dorsomedial and ventral striatum.

The SN, ventral tegmental area, and amygdala selectively innervate the patch or matrix areas of the striatum. Neurons in the ventral pars compacta of the SN project to the patches of the ventral and dorsomedial

striatum and to the matrices of the dorsolateral striatum. The matrices in the ventral striatum receive fibres from the ventral tegmental area. Neurons in the pars compacta of the SN project primarily to the matrices in the anterior and middle striatum, specifically the caudate, although there is an innervation by dopaminergic fibres from the lateral pars compacta of the SN in the patches of the dorsal striatum. The amygdala receives fibres from the patches in the dorsal striatum and the matrices in the ventral striatum. Cortical projections are found in both the patches and the matrices, depending on the depth of the injections of the markers. With this confounding variable in mind, the prelimbic cortex projects primarily to the patches; and the neocortex projects primarily to the matrices.

Finally, the anatomy of the nucleus accumbens and the olfactory tubercle suggests that these structures are integral parts of the striatum. This is suggested by the interweaving of connections of the basal ganglia and cortex between the ventral and dorsal striatum.

Anticonvulsant role of the caudate

Given the complexity of striatal anatomy, as reviewed above, it perhaps comes as no surprise that studies have pointed to a mixed role for the striatum in experimental epilepsy, with some results suggesting that striatal activity antagonizes seizures and other results suggesting that striatal activity promotes seizures. In the present section I review the evidence for an anticonvulsant role for the striatum.

Many experiments have provided evidence that striatal activity antagonizes seizures. For example, destruction of the dorsal tail of

caudate increased susceptibility to seizures induced by pentylenetetrazol (PTZ) in rats (Kirkby, 1977). This was reflected in longer episodes of generalized seizures and higher incidence of myoclonic status epilepticus and postseizure mortality. A positive relation between lesion size and the duration of the evoked seizures was observed. Similarly, Pisa, Sanberg, Corcoran, and Fibiger (1980) injected kainic acid into the striatum. The infusions produced a lesion in the striatum, as a consequence of the drug's excitotoxic action, and they also produced a subsequent potentiation of seizures induced by PTZ. Pisa et al. (1980) found that spontaneous seizures developed in 7 of 10 rats receiving kainic acid. The infusions of kainic acid produced lesions in the head and body of the striatum (including the caudate). Kainic acid is a potent epileptogenic agent itself (Zackzek, Nelson, and Coyle, 1981), and thus the potentiation of PTZ-induced seizures may have been due to the kindling effect of kainic acid and not the lesions in the striatum. Reservations aside, these 2 studies support to the hypothesis that the intact caudate inhibits epileptic activity, in that both reported heightened susceptibility to the seizure-producing effects of PTZ when the caudate was lesioned.

LaGrutta, Sabatino, Ferraro, Liberti, & LaGrutta (1986) found that there is primarily an inhibitory action of the caudate on hippocampal AD. Unilateral caudate destruction facilitated the duration of electrically induced hippocampal AD and decreased the AD threshold. Kusske (1979) showed that direct stimulation of the caudate in rats increases the threshold required to trigger hippocampal AD. Thus these results suggest that activity in the caudate has an inhibitory influence

on hippocampal AD, and there is a disinhibition following caudate lesions. Low-frequency stimulation of caudate sites after unilateral destruction of the internal membrane of the globus pallidus no longer resulted in an inhibition of hippocampal AD (LaGrutta et al., 1986). When the medial septal region was destroyed, stimulation of the caudate no longer had any effect on hippocampal AD. This suggests that there is a pathway involving the caudate, globus pallidus, and medial septal region whose activity inhibits hippocampal AD.

LaGrutta and Sabatino (1988) infused penicillin unilaterally into the CA1 region of the rat hippocampus. Low-frequency electrical stimulation of the caudate reduced hippocampal spike frequency and amplitude. These effects were not seen when the septum was lesioned or when atropine was administered systemically. LaGrutta and Sabatino concluded that caudate activity in this situation is inhibitory and may exert its influences through a septal pathway or a pathway relying on acetylcholine as the neurotransmitter.

Low-frequency electrical stimulation of the head of the caudate in cats resulted in high-voltage slow activity (HVS) in the caudate (Mutani, 1969). HVS was also provoked when AD spread from a rhinencephalic focus (the hippocampus or the amygdala) to either the caudate or the neocortex, suggesting that the HVS is a nonspecific reaction of the caudate to stimuli of a certain intensity. During the HVS the excitability of the rhinencephalic focus decreased. Mutani (1969) suggested that the HVS is responsible for the unresponsiveness of the rhinencephalic structures to repeated triggering of seizures. He concluded that the caudate only modulates rhinencephalic activity when

the activity rises above a certain threshold, and that it is HVS that is responsible for the inhibitory influence of the caudate.

Fariello (1976) initiated amygdaloid focal seizures followed by stimulation in the caudate or the nucleus accumbens. In contrast to the investigators discussed above, he found that low-frequency stimulation of the head of the caudate in rats had no effect on amygdaloid AD, even when the caudate was exhibiting spindles. High-frequency stimulation of the head of the caudate exerted a prolonged inhibitory effect on interictal epileptiform activity. Stimulation of the nucleus accumbens at either high or low frequencies did not result in any change in amygdaloid AD.

Oakely and Ojemann (1982) found that continuous chronic caudate stimulation in monkeys resulted in a decrease in the frequency of alumina-induced behavioral seizures in 4 of 6 monkeys. All 4 of these monkeys had the stimulating electrodes in the head of the caudate, while the other 2 monkeys had stimulating electrodes in the middle caudate. This finding suggests that activity from the head of the caudate may be critical in the inhibitory effects exerted by the caudate. This also gives evidence for a topographical specificity of the inhibitory effects.

Infusions of bicuculline into the middle caudate of rats blocked the seizures induced by injections of pilocarpine, a muscarinic agonist (Turski, Cavalheiro, Calderazzo-Filho, Bortolotto, Klockgether, Iknonmidou, & Turski, 1989) and amygdala-kindled seizures (Cavalheiro, Bortolotto, & Turski, 1987). Bicuculline is an antagonist of GABA and a powerful convulsant when administered systemically or focally into the

amygdala, cortex, thalamus, or the CA3 region of the hippocampus. Cavalheiro and Turski (1986) showed that bilateral microinfusions of picomolar quantities of N-methyl-D-aspartate (NMDA) into similar sites in the caudate prevented amygdala-kindled seizures in rats. NMDA is a powerful convulsant when injected into the rat hippocampus, amygdala, cortex, or cerebral ventricles. It thus is surprising that injections of convulsants into the middle caudate resulted in an inhibition of kindled seizures.

Proconvulsive role of the caudate

In contrast to the results reviewed in the previous section, many other studies have shown that manipulations of the caudate can facilitate ictal activity. For example, decreases in the threshold required to trigger myoclonic jerking and a facilitation of sharp wave activity induced by subconvulsive doses of PTZ were observed following low-frequency stimulation of the head of the caudate in cats (Arushian & Avakian, 1978). Bilateral lesions of the caudate had the opposite effect: there was an increase in the threshold required to induce myoclonic jerking and a blockade of sharp wave EEG discharges in the cortex, as induced by subconvulsive doses of PTZ (Arushian & Avakian, 1978). This result suggests that the caudate plays an excitatory role in seizure development.

Mutani (1969) found that when electrical stimulation of the caudate did not result in HVS, there was an excitatory effect of caudate stimulation on seizures induced by focal injection of cobalt into the rhinencephalon. Subthreshold stimulation of the caudate (below that

required to trigger HVS) during an amygdaloid or hippocampal seizure increased the duration and severity of the seizure. Mutani (1969) hypothesized that the excitatory effect of the caudate on the rhinencephalon was due to current spread from the caudate to the internal capsule. Thus, Mutani suggested that the internal capsule is responsible for the excitatory influence, which is negated by HVS when stimulation is above the threshold. This hypothesis is contradicted by the results of LaGrutta and Sabatino (1988), who found that stimulation of the internal capsule had no effect on hippocampal seizures in rats. Thus, some studies (Mutani, 1969; Arushian & Avakian, 1976) suggest that low frequency or subthreshold stimulation of the caudate has an excitatory effect on ictal activity elsewhere in the brain.

The endogenous opiate system in the caudate may be involved in restricting the evolution of carbachol-induced seizures. Stach, Przewlocki, and Kacz (1983) gave rats injections of naloxone (an opioid antagonist) systemically, and then 30 min later they infused carbachol into the caudate. The injection of naloxone resulted in a marked prolongation of the duration of AD and a spread of AD to the contralateral hemisphere. An infusion of opiates into the caudate resulted in an inhibition of spontaneous and induced AD in striatal neurons (Stach et al., 1983). Naloxone enhanced caudate seizures, suggesting that there is an inhibitory opiate mechanism involved in seizure development in the caudate.

The evidence for kindling in the caudate has typically come from experiments designed to test the effect of other treatments. Corcoran and Wada (1979) kindled seizures with stimulation of the head of the

caudate in rats and found that the threshold for AD was significantly higher than in the amygdala. Differences between seizures kindled by stimulation of the caudate and of the amygdala were observed. For example, no behavioral response occurred during the train of amygdaloid stimulation, whereas during caudate stimulation an immediate ipsiversive loss of balance occurred due to ipsilateral flexion, contralateral extension, or both. This loss of balance was followed by AD, which was accompanied by contralateral clonus that developed into bilateral clonus (stage 4) with repeated triggering of caudate AD. Rats rapidly developed stage 4 seizures of short duration, but seizure development did not progress reliably beyond this stage of seizure. In contrast, amygdaloid kindling involved the development of generalized stage 5 seizures with significantly longer durations. Timofeeva (1990) kindled using electrical stimulation in the rostral caudate of the rabbit and observed the development of generalized clonic/tonic convulsions in half of the rabbits. Timofeeva could not elicit any seizure more severe than head nodding and rotation of the trunk in the other rabbits. There was no histological difference between the electrode placement of the 2 groups, and the incongruities were attributed to individual differences.

Pinel and Rovner (1978) stimulated the head of the caudate in rats and noted that the stimulation itself produced a forced motor response, followed by AD and a behavioral seizure. They found that seizures characterized by unilateral forelimb clonus (stage 3) or more severe symptoms were often elicited during the first AD. Unlike limbic kindling, however, caudate kindling did not progress to stages 7 or 8, characterized by running fits or running fits with periods of tonus,

respectively. Spontaneous interictal discharges were not observed in the caudate, even though the rats exhibited spontaneous behavioral seizures. There was no significant difference in the length of time required for spontaneous seizures to develop between the hippocampus, caudate, entorhinal cortex, or the amygdala. The behavioral forms of the seizures were indistinguishable between the groups. Similarly, Pinel, Treit, and Rovner (1979) found that seizures induced by stimulation of the caudate in rats were similar in number, form, and duration to those induced by amygdaloid or hippocampal stimulation. The rats in Pinel's experiments were electrically stimulated up to 3 times a day for 6 to 8 weeks. Within the last 6 weeks of testing, bilateral clonus of the jaw, head, and forelimbs were reliably elicited in all 3 groups of rats.

In summary, the few studies of kindling of the caudate in rats suggest that it involves an immediate loss of postural control and rapid development of behavioral seizures to a stage of bilateral clonus (Corcoran & Wada, 1979; Pinel & Rovner, 1978). Corcoran and Wada (1979) could not reliably trigger limbic-type generalized seizures, and Pinel and Rovner (1978) could not elicit generalized seizures beyond stage 6. A similar result was obtained in rabbits by Timofeeva (1990), who reported that there was also a large role played by individual differences in the development of generalized seizures with stimulation of the caudate.

Rationale

Previous studies have produced contradictory results concerning

the role of the striatum in experimentally induced seizures. The few studies of kindling with striatal stimulation have been unclear as to the kind of seizure, limbic or neocortical, that can be induced. The results of these studies are inconclusive, however, because the experiments typically examined kindling from a limited number of sites in the head of the caudate. I therefore attempted to provide a more extensive examination of the dorsal and ventral striatum's susceptibility to kindling than has previously been reported. In recognition of the complex anatomy of the striatum, I hypothesized that kindling with stimulation of the various regions of the striatum would differ in rate, pattern, or both.

As noted above, previous studies of kindling used stimulation sites primarily in the head of the caudate. I have tried to replicate kindling with stimulation at sites in the head of the caudate. I have also examined kindling at 2 additional sites in the caudate: the tail of the caudate, where kindling has not been studied previously; and the middle caudate. The latter site was chosen because it is the region in which infusions of the convulsants bicuculline and NMDA had an anticonvulsant effect (Turski et al., 1989; Cavalheiro et al., 1987). I also examined kindling in the nucleus accumbens, as kindling in this part of the ventral striatum has not been described previously. The accumbens has direct connections with the amygdala, and I therefore hypothesized that accumbens kindling would more closely resemble limbic kindling than kindling at other sites in the striatum.

METHODS

Subjects

Male Long Evans hooded rats (Charles River) weighing 350-450 g were individually housed in stainless steel cages under a constant 12 hr light-dark schedule. Food and water were available ad libitum.

Surgery

Under anaesthesia with sodium pentobarbital (60 mg/kg, ip), rats received implantation of bipolar stimulating/recording electrodes made up twisted nichrome wire (127 µm diameter) and insulated except at the cut ends. Electrodes were implanted bilaterally and aimed at homotopic sites in the 2 hemispheres. Table 1 summarizes the stereotaxic coordinates. A stainless steel wire (36 gauge) connected to the frontal bone with a dental screw served as ground reference for electroencephalographic (EEG) recording. Electrode wires were soldered into gold plated pins (Amphenol 220-S02) and secured in a plastic pedestal, which was affixed to the skull with dental acrylic.

Determination of AD threshold

Electrical stimulation for kindling consisted of a 1 sec train of constant current biphasic square wave pulses with a pulse width of 1 msec and a frequency of 60 pulses per sec (pps), generated by a Grass S88 stimulator and Grass PSIU-15 stimulus isolation units. Stimulation was applied to the electrode in one hemisphere only. EEG was recorded on a Grass model 79 EEG machine for at least 10 sec before and 40 sec after stimulation.

Ten days after surgery, thresholds for AD were determined.

Table 1

List of target placements of electrodes.

Group	A/P*	L	V
Accumbens group	1.2	1.2	6.5
	2.2	1.6	6.8
Head of the caudate group	1.2	2.8	6.1
	1.2	2.0	5.0
Middle caudate group	0.2	3.0	7.0
Tail of the caudate group	-1.8	5.0	7.0
	-1.8	4.7	5.0

*(A/P: mm anterior/posterior to bregma; L: mm lateral to bregma; V: mm ventral to the skull; incisor bar setting: -3.3mm; coordinates from Paxinos and Watson, 1982)

Stimulation was delivered at an intensity of 20 μA (base to peak). At 60 sec intervals, current intensity was increased first to 60 μA, then to 100 μA and then in steps of 50 μA to a maximum of 300 μA until AD was produced. If no AD was produced by stimulation up to 300 μA, threshold determination resumed 24 hr later with an initial intensity of 300 μA, and this was increased in 100 μA steps, delivered at 60 sec intervals, to a maximum intensity of 1000 μA. Again, failure to observe AD resulted in suspension of testing for 24 hrs. Testing resumed at 1000 μA, and this was increased in 500 μA steps to a maximum of 2500 μA. Threshold was arbitrarily defined as the lowest intensity of stimulation that elicited AD, and kindling stimulation was subsequently administered at threshold intensity. Two rats failing to display AD received a one week holiday from stimulation. They then received a single stimulation of 2500 μA. One rat did not exhibit AD at this point and was dropped from the study.

Kindling

Rats received stimulation at their threshold intensity once daily at approximately the same time each day. Once behavioral seizures occurred, they were classified following the system defined by Racine (1972b): mouth and facial movements (stage 1), head nodding (stage 2), unilateral forelimb clonus (stage 3), bilateral forelimb clonus and rearing (stage 4), and rearing and falling (stage 5). I included an extra category, stage 4+, to characterize generalized seizures that did not include rearing and falling. Specifically, the rats fell during stimulation and did not recover their balance until after the seizure

was finished. After 3 consecutive stage 4+/5 seizures had been triggered, stimulation was suspended. To assess the persistence of the kindled state, I resumed stimulation (rekindling) 1 week after the last stage 4+/5 seizure. Rekindling proceeded until 3 consecutive stage 4+/5 seizures had been triggered.

The intensity of stimulation remained constant for the entire experiment, unless the rat failed to exhibit AD for 3 consecutive days. If this occurred, on the third day the intensity was increased until AD was elicited and stimulation was maintained at this new intensity for the rest of the experiment.

Transfer

One week after the final primary-site seizure, transfer to the contralateral hemisphere was examined in some rats (n=7). Threshold testing at the secondary site followed the same procedure outlined above, and the rats were subsequently stimulated at the secondary site once daily until 3 consecutive stage 4+/5 seizures occurred.

Histology

At the end of the experiment the rats were killed with an overdose of sodium pentobarbital. Once deep anaesthesia was achieved, the rats were intracardially perfused with a 0.9% saline solution and the brain was removed and placed in a 10% formalin solution for a minimum of 3 days. Frozen sections 80 µm thick were taken and stained with thionine for confirmation of placements.

Rats were assigned to 1 of 4 groups on the basis of their

electrode placements, as determined histologically. Rats with electrodes placed in the nucleus accumbens were grouped together (accumbens group, n=7). Rats with electrodes placed in the caudate-putamen were divided into 3 groups on the basis of the placement of the electrode on the anterior-posterior axis. The head of the caudate group consisted of rats whose electrodes were were found to be placed in the caudate-putamen between 1.7 mm and 0.7 mm anterior to bregma (n=4). The middle caudate group consisted of rats whose electrodes were found to be placed between 0.2 mm anterior and 0.3 mm posterior to bregma (n=6). The tail of the caudate group consisted of rats whose electrodes were found to be placed between 1.3 mm and 2.3 mm posterior to bregma (n=9).

Analysis of data

A multiple analysis of variance (MANOVA, Pillais test, alpha=0.05) was performed on six measures of seizures, with the Neumann-Keuls test being used for post hoc comparisons. The 6 dependent measures were:

1. the threshold required to produce AD;
2. the AD that the first behavioral seizure was observed in;
3. the AD that the first stage 5 seizure was observed in;
4. the AD that the rat completed the study in, as measured by the first of three consecutive stage 4+/5 seizures;
5. the total number of ADs that were not accompanied by behavioral seizures;
6. the highest number of consecutive ADs that were not accompanied by behavioral seizures.

The maximum frequency, duration, and amplitude of the AD at the stimulated site was measured for each rat in each group. These three measures were taken at three episodes of AD: the first AD, the middle AD, and the last AD. These data were analyzed using a doubly multivariate analysis of variance (Norusis, 1986), and the significant effects were subjected to post-hoc tests (Neumann-Keuls, alpha=0.05). Differences in the severity of the first behavioral seizure stage observed were analyzed among the 4 groups using a Kruskal-Wallis 1-way analysis of variance ($p<0.05$).

The results obtained from the rats that underwent secondary-site kindling were not analyzed statistically because of the small number of rats used. For secondary-site kindling a savings score was computed by subtracting the rate of secondary-site kindling (expressed as the number of ADs to the first stage 4+/5 seizure) from the rate of primary-site kindling.

RESULTS

Histology

Twenty-six rats reached the criterion of 3 consecutive generalized seizures (greater than stage 4). Seventeen other rats failed to meet the criterion of 3 consecutive generalized seizures, either because they dislodged their electrodes or because they became too agitated to test. The data of these rats were not included in the analysis. The placements of the electrodes are shown in Figures 1 to 4.

Figure 1. The placements of electrodes in the rats in the accumbens group, on sections taken from the atlas of Paxinos and Watson (1982). The number of ADs required for development of the first stage 5 seizure is indicated by the following symbols: 1 - 10 ADs, ●; 11 - 20, ■; >21, ▾. The number to the left of each section indicates mm anterior or posterior to bregma. Abbreviations: Acb, nucleus accumbens; CPu, nucleus caudate-putamen; other abbreviations are found in Paxinos and Watson (1982).

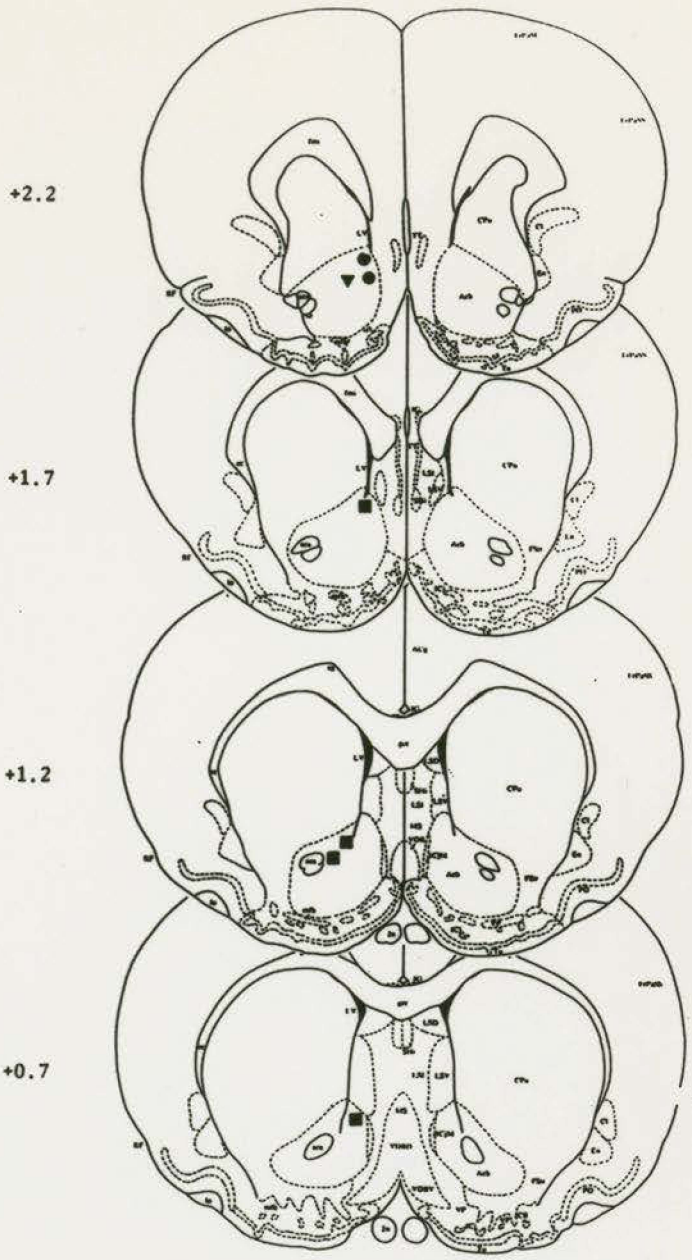
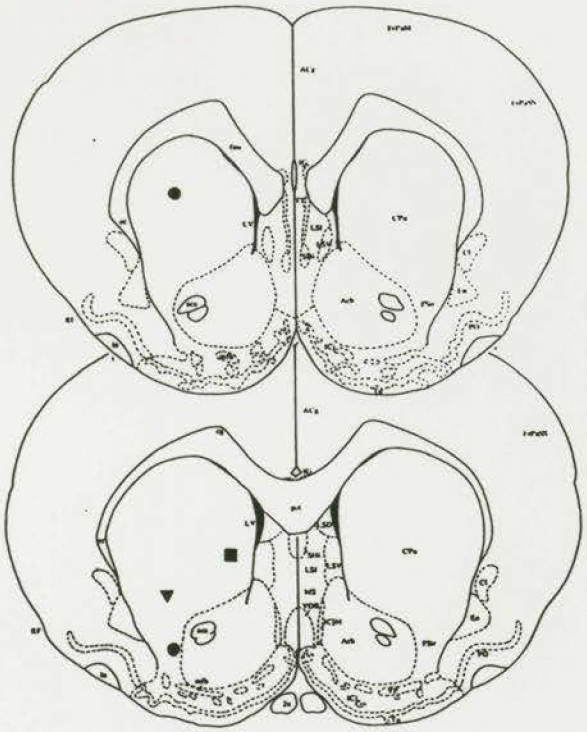

+2.2
+1.7
+1.2
+0.7

Figure 2. The placements of electrodes in the rats in the head of the caudate group. Symbols and abbreviations as in Figure 1.

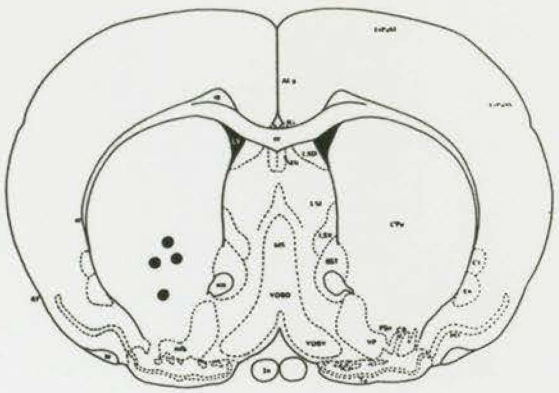
+1.7



+1.2

Figure 3. The placements of electrodes in the rats in the middle caudate group. Symbols and abbreviations as in Figure 1.

+0.7



+0.2

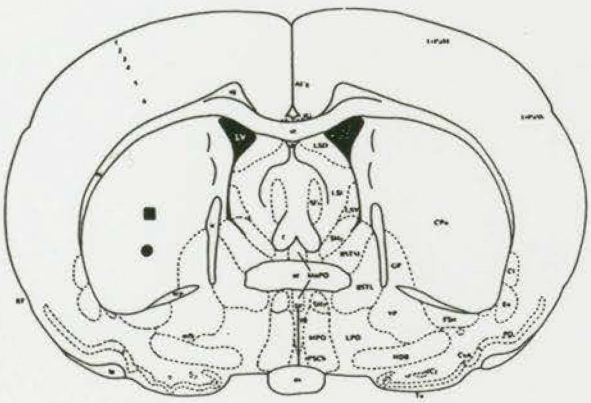
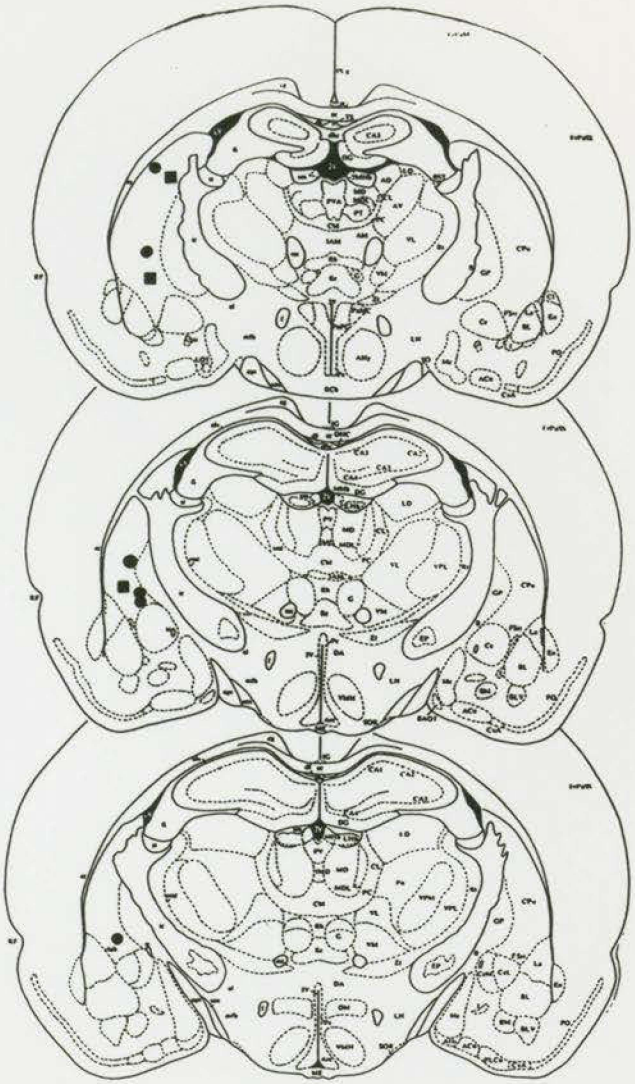


Figure 4. The placements of electrodes in the rats in the tail of the caudate group. Symbols and abbreviations as in Figure 1.


-1.8
-2.3
-2.8

Stimulation-bound behaviors

A number of behaviors were observed during the 1-sec trains of stimulation. The behaviors noted most often in all groups were contralateral turning of the head and torso, shaking of the head from side-to-side, and ipsilateral forelimb clonus. Certain rats in all groups occasionally exhibited more violent behaviors, such as rearing, falling, and rolling around the longitudinal axis of the body. These behaviors would then be followed by AD and behavioral seizures occurring during AD, which I considered to be ictal behaviors. Every rat in the middle caudate group displayed stimulation-bound behaviors in almost every testing session. This did not occur in the other 3 groups, where many rats did not exhibit stimulation-bound behaviors. If rats in the other groups did exhibit stimulation-bound behaviors, these behaviors were present intermittently throughout the testing sessions.

AD thresholds

As shown in Table 2, the tail of the caudate group had the lowest AD threshold (mean [±SEM] = 608.9 [162.7] μA) and the head of the caudate group had the highest (1212.5 [460.2] μA), with the thresholds of the other 2 groups falling in between (accumbens group = 985.7 [291.5] μA; middle caudate group = 883.3 [282.2] μA). However, these differences failed to reach statistical significance, perhaps because of the large degree of variability in each group.

Table 2

F values and means (± SEM) of measures of seizure development and AD threshold by groups.

	F value DF(3,22)	Sig. of F	Means of the 4 groups (± SEM) Accumbens group	Head of the caudate group	Middle caudate group	Tail of the caudate group
AD threshold intensity (in µA)	0.830	0.492	985.71 [291.49]	1212.50 [490.24]	883.33 [282.15]	608.89 [162.65]
Number of ADs required for the development of the first behavioral seizure	11.426	0.0001	11.57 [2.14]	1.0 [0]	2.33 [0.84]	5.22 [1.24]
Number of ADs required for the development of the first stage 5 seizure	3.451	0.034	16.14 [2.38]	11.25 [2.95]	6.17 [2.12]	11.11 [1.70]
Number of ADs required to reach completion criterion	3.931	0.022	19.29 [2.69]	13.25 [2.10]	6.5 [2.14]	16.56 [2.90]
Largest number of consecutive ADs without a behavioral seizure	8.119	0.001	12.71 [2.07]	2.0 [0.71]	2.67 [0.84]	4.11 [1.33]
Total number of ADs without a behavioral seizure	4.468	0.014	12.57 [2.48]	4.50 [1.55]	2.67 [1.02]	7.67 [1.92]
Total number of ADs between the first behavioral seizure and the first stage 4+/5 seizure	2.450	0.090	4.29 [1.04]	11.25 [2.95]	3.83 [1.68]	8.11 [2.16]

Rate and patterns of kindling

A MANOVA of the dependent variables was significant (Pillais test, $F(21,54) = 3.075$, $p=0.0001$). As shown in Table 2, the groups differed significantly in the number of ADs required to trigger the first behavioral seizure, with the head of the caudate group being the fastest (mean [$\pm$ SEM] = 1.0 [0] ADs) and the accumbens group being the slowest (12.7 [2.1] ADs) on this measure. Post hoc analysis (Table 3) revealed that the accumbens group was significantly slower than the other three groups, which did not differ among themselves. A Kruskal-Wallis 1-way analysis of variance showed that there was no significant difference among the groups in the severity of the first behavioral seizure (Table 4).

The groups also differed significantly in the number of ADs required for the development of the first stage 5 seizure, as shown in Table 2. The middle caudate group displayed the fastest rate of kindling (mean [$\pm$ SEM] = 6.2 [2.1] ADs), and the accumbens group displayed the slowest (16.1 [2.4] ADs). Post hoc analysis (Table 3) showed that the only significant group-by-group difference was between the accumbens group and the middle caudate group ($p<0.05$); the head of the caudate group and the tail of the caudate group did not differ from each other or from either of the other 2 groups (each $p>0.05$). As shown in Table 2, there were no significant differences among the groups in the number of ADs that occurred between the first behavioral seizure and the first stage 4+/5 seizure. Thus the rate of kindling of generalized seizures was slower in the accumbens group than in the other groups because more ADs were required for nonconvulsive seizures to develop

Table 3

Post hoc comparisons of the groups on the significant dependent variables.

Dependent variable	Significant Comparison(s)	q	P	sig. of q
Number of ADs required for the development of the first behavioral seizure	Middle caudate group vs. the accumbens group	5.89	4	<0.01
	Tail of the caudate group vs. the accumbens group	6.96	3	<0.001
	Head of the caudate group vs. the accumbens group	6.65	2	<0.001
Number of ADs required for the development of the first stage 5 seizure	Middle caudate group vs. the accumbens group	4.03	4	<0.05
Number of ADs required to reach the completion criterion	Middle caudate group vs. the accumbens group	4.08	4	<0.05
Largest number of consecutive ADs without a behavioral seizure	Head of the caudate group vs. the accumbens group	5.57	4	<0.01
	Middle caudate group vs. the accumbens group	6.06	3	<0.01
Total number of ADs without a behavioral seizure	Middle caudate group vs. the accumbens group	4.88	4	<0.05

Table 4

Means (± SEM) of the first seizure stage displayed by the 4 groups*.

	Mean Seizure Stage (+ SEM)
Accumbens group	1.7 (2.7)
Head of the caudate group	3.0 (0.7)
Middle caudate group	3.3 (0.6)
Tail of the caudate group	2.2 (2.9)

* tested using a Kruskal-Wallis 1-way analysis of variance, adjusted chi-square=5.1896, p=0.1584.

into convulsive seizures in the accumbens group.

The groups differed in the number of ADs required for the groups to reach the criterion of 3 consecutive stage 5 seizures (measured from the first seizure). As shown in Table 2, the middle caudate group required the smallest number of ADs to meet the criterion (6.5 [2.14] ADs), whereas the accumbens group required the largest number (19.3 [2.7] ADs). Post hoc analysis indicated that once again the middle caudate group met the criterion significantly more quickly than the accumbens group ($p<0.05$). There were no differences among the caudate groups.

While conducting the experiment I observed that many rats tended to omit behavioral signs or show regressions during the course of kindling. To quantify this form of ictal instability, I computed 2 additional measures: consecutive ommissions, the largest number of consecutive ADs unaccompanied by a behavioral seizure that each rat displayed; and total omissions, the total number of ADs unaccompanied by a behavioral seizure for each rat. Typically the ADs that occurred without behavioral seizures were early in kindling, before the development of the first behavioral seizure, and hence both measures are closely related to the rate of kindling displayed by each group. As shown in Table 2, there was significant variation among the groups on both measures, with the middle caudate group again having the lowest scores and the accumbens group having the highest. Post hoc analysis (Table 3) showed that the accumbens group displayed a higher number of ADs unaccompanied by behavioral seizures, both consecutive and total, than either the head of the caudate group or the middle of the caudate

group ($p<0.05$). There were no other differences among the groups. Thus the accumbens group displayed significantly slower kindling and significantly more omissions than the other groups. The groups with placements in the caudate did not differ significantly from each other on the dependent measures, although the middle caudate group consistently displayed the fastest kindling and fewest omissions of all groups tested.

Morphology of kindled seizures

The morphology of kindled seizures triggered by striatal stimulation was similar to that described for seizures triggered by limbic stimulation (Racine, 1972b). In particular, the first 4 stages were indistinguishable from limbic-type seizures. However, stages beyond stage 4 (bilateral forelimb clonus) differed from generalized seizures of the limbic type. That is, stage 4+ consisted of a generalized seizure wherein there was an immediate loss of balance during stimulation that the rat often did not recover from for the rest of the seizure. The rats typically were supine and displayed bilateral forelimb clonus and unilateral or bilateral hindlimb tonic extension. Opisthotonus frequently was observed, and the rats almost appeared to be balancing on their nose during the seizure. Stage 5 (bilateral forelimb clonus with rearing and falling) was observed with the following additional components. Frequent unilateral or bilateral tonic extension of the hindlimbs occurred. This was often accompanied by tonic retraction of the forelimbs and hypersensitivity to auditory stimulation. The latter features of striatal-kindled seizures resemble

the features of seizures triggered by stimulation of the anterior neocortex (Burnham, 1978; Buterbaugh, 1989; Seidel & Corcoran, 1986).

The groups differed in the durations of the behavioral seizures. As shown in Table 5, the first behavioral seizure in the accumbens group was significantly longer, in sec, than that of each of the caudate groups, which did not differ among themselves. Similarly, the accumbens group's first stage 5 seizure was significantly longer than that of each of the caudate groups, which did not differ among themselves (Table 6). Finally, as might be expected from the above, the absolute differences in the durations of the first behavioral seizure and first stage 5 seizure also varied significantly among the groups. As shown in Table 6, the accumbens groups showed a significantly larger increase than each of the caudate groups, which did not differ among themselves. To illustrate this point, I have shown, in figure 5, the durations of convulsive seizures (from the first behavioral seizure to the first stage 5 seizure) for a representative rat from each group. Because the group means were strongly influenced by outliers, I chose the rat that most closely matched the modal response for its group. Tables 5 and 6 and Figure 5 demonstrate that the caudate groups had relatively brief seizures that did not change much during kindling, similar to what is observed in anterior neocortical kindling (Burnham, 1978; Buterbaugh, 1989; Seidel & Corcoran, 1986). In contrast, the accumbens group displayed initially brief seizures that dramatically increased in duration during kindling, similar to what is observed in limbic kindling (Racine, 1972b).

Table 5

The F values and means (± SEM) of the duration (in sec) of the first behavioral seizure, the first stage 5, and the difference between them, by group.

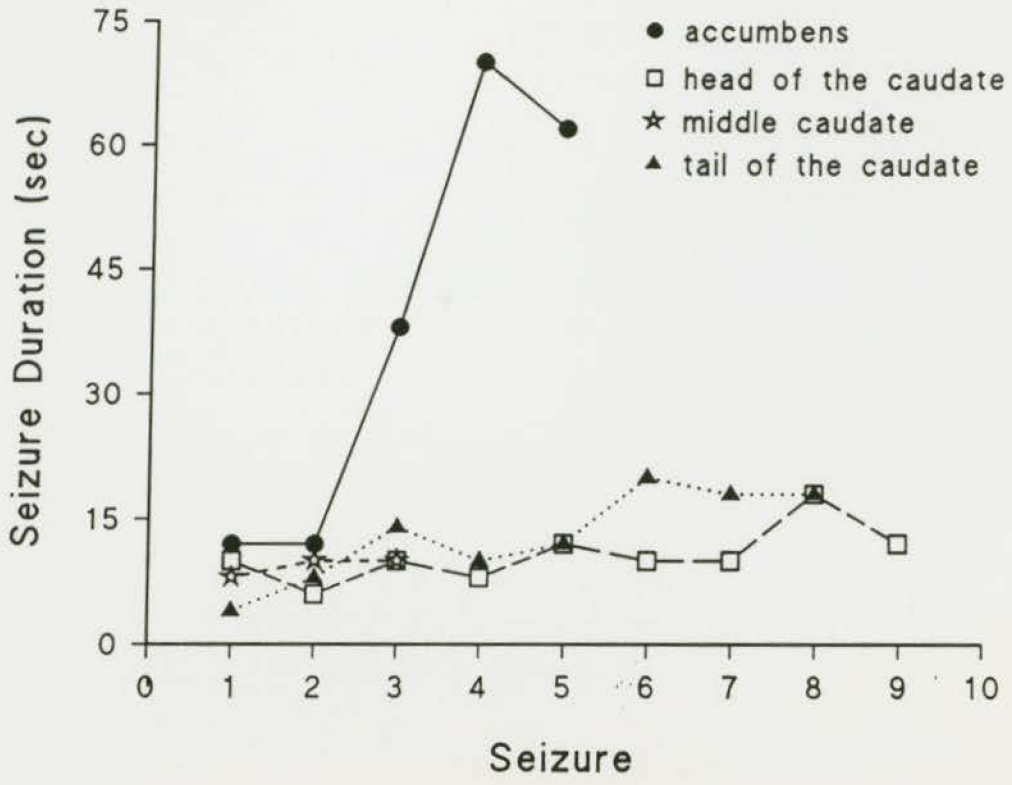
	F DF(21,54)	Sig. of F	Means (+ SEM) of the groups: Accumbens Group	Head of the Caudate Group	Middle Caudate Group	Tail of the Caudate Group
Duration of the first behavioral seizure	3.833	0.024	20.1 (6.1)	8.0 (1.4)	7.7 (2.9)	6.2 (1.8)
Duration of the first stage 5	9.122	0.0001	48.6 (9.3)	18.5 (2.3)	15.0 (3.2)	16.7 (1.9)
Difference between the 2 scores	*	*	28.5 (9.3)	10.5 (2.6)	7.3 (2.4)	10.5 (1.5)

* This was not analysed, because it is linearly dependent on the other 2 variables.

Table 6
Post hoc comparisons of the groups on the duration of the first behavioral seizure and the duration of the first stage 5.

Dependent variable	Significant comparison(s)	q	F	sig. of q
Duration of the first behavioral seizure	Accumbens group vs. the head of the caudate group	4.4	4	$p<0.05$
	Accumbens group vs. the middle caudate group	3.6	3	$p<0.05$
	Accumbens group vs. the tail of the caudate group	3.1	2	$p<0.05$
Duration of the first stage 5 seizure	Accumbens group vs the head of the caudate group	6.1	4	$p<0.01$
	Accumbens group vs. the middle caudate group	6.4	3	$p<0.001$
	Accumbens group vs. the head of the caudate group	4.9	2	$p<0.01$

Figure 5. The durations of convulsive seizures, from the first behavioral seizure to the last stage 5 seizure, for a representative rat from each group.


75
60
45
30
15
0
Seizure Duration (sec)
0
1
2
3
4
5
6
7
8
9
10
Seizure
accumbens
head of the caudate
middle caudate
tail of the caudate

Morphology of AD

The maximal frequency, amplitude, and duration of AD in each episode of kindling were quantified for each rat; and the data were analyzed using a doubly multivariate analysis of variance. There was significant variation by episodes (Pillais test, $F(6,86)=6.820$, $p=0.0001$) on each of the three measures of AD, but there was no significant groups effect or interaction.

Episode effects: As shown in Table 7 and figures 6, 7, and 8, there was significant variation in frequency, amplitude and duration of AD across the 3 episodes. There were no significant differences among the groups across the episodes; for clarity, however, I have displayed the data of the individual groups in Figures 6, 7, & 8. Post hoc analysis Neumann-Keuls) showed a similar pattern for the three measures: The final AD episode was significantly larger in amplitude, frequency, and duration than the middle and first episodes (each $p=0.0001$); and there was no significant difference between the middle and first episodes. To summarize, analysis of the morphology of AD indicated that there were no differences among the groups in measures of AD; that AD had grown significantly by the time generalized seizures had been kindled; and that the groups did not differ in the pattern of growth.

Postictal behaviours

A number of characteristic behaviors appeared after the end of the AD and seizure that I shall call postictal behaviors. These included stereotyped grooming and rearing, circling the stimulation cage, and licking and chewing the walls and floor.

Table 7

The F values and means (± SEM) of AD amplitude, frequency, and duration by episode measured, collapsed across groups.

	F DF(2,44)	Sig. of F	Means (+ SEM) of the episodes First AD episode	Middle AD episode	Last AD episode
Frequency (spikes/sec)	11.53	0.0001	2.9 (0.2)	3.3 (0.5)	5.6 (0.4)
Amplitude (μV)	14.69	0.0001	1528 (163)	1514 (210)	2586 (142)
Duration (sec)	32.23	0.0001	7.8 (1.0)	12.9 (2.0)	43.8 (5.6)

Figure 6. Mean duration of evoked AD in the first, middle, and last episode of AD for the 4 groups.

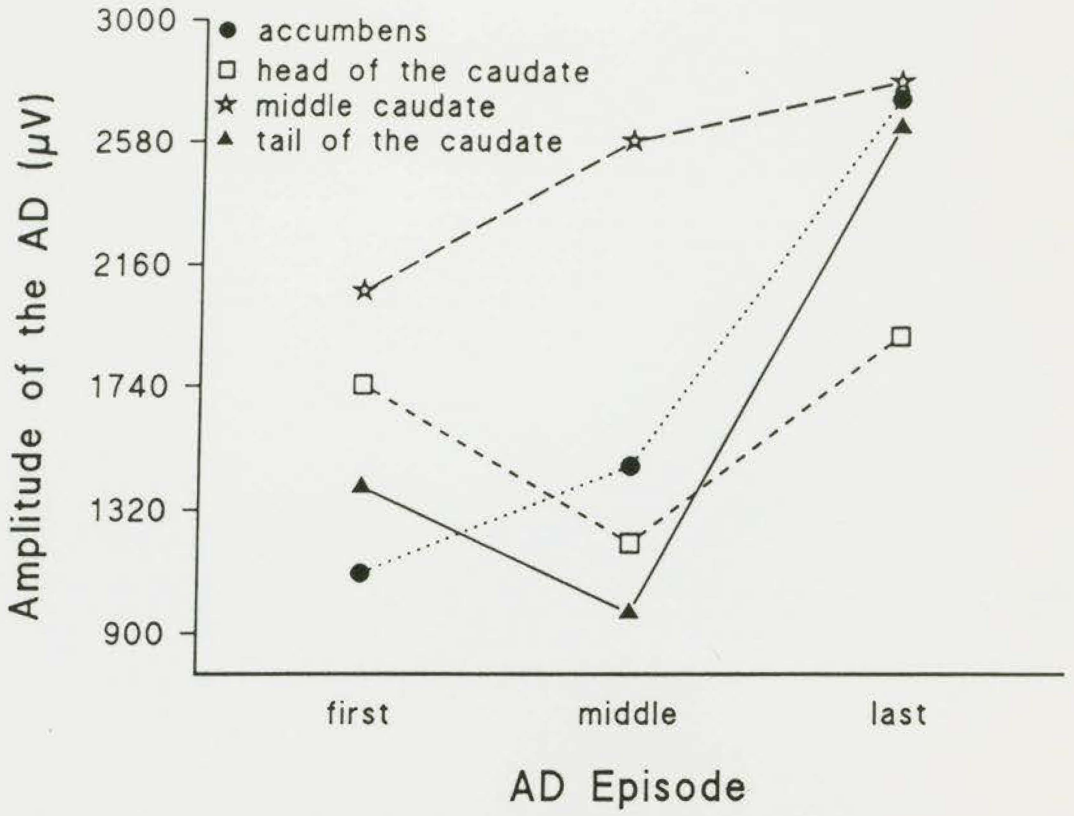

3000
2580
2160
1740
1320
900
Amplitude of the AD (μV)
accumbens
head of the caudate
middle caudate
tail of the caudate
first
middle
last
AD Episode

Figure 7. Mean amplitude of evoked AD in the first, middle, and last episode of AD for the 4 groups.

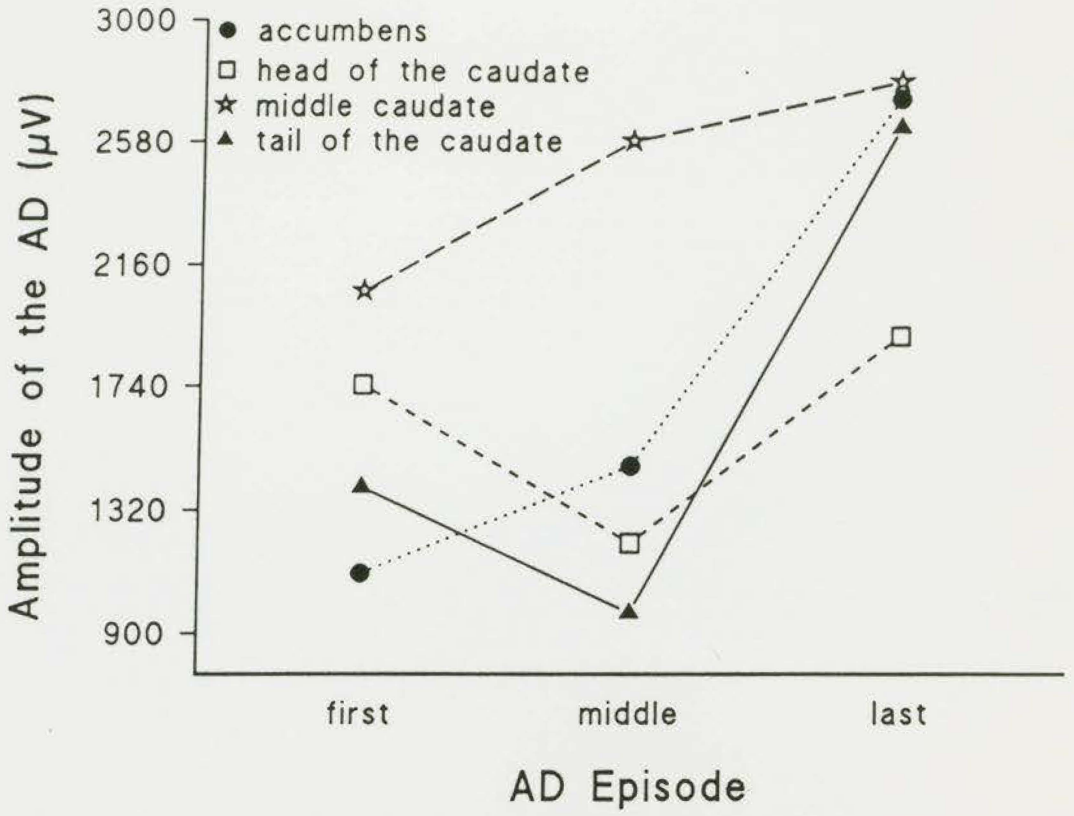
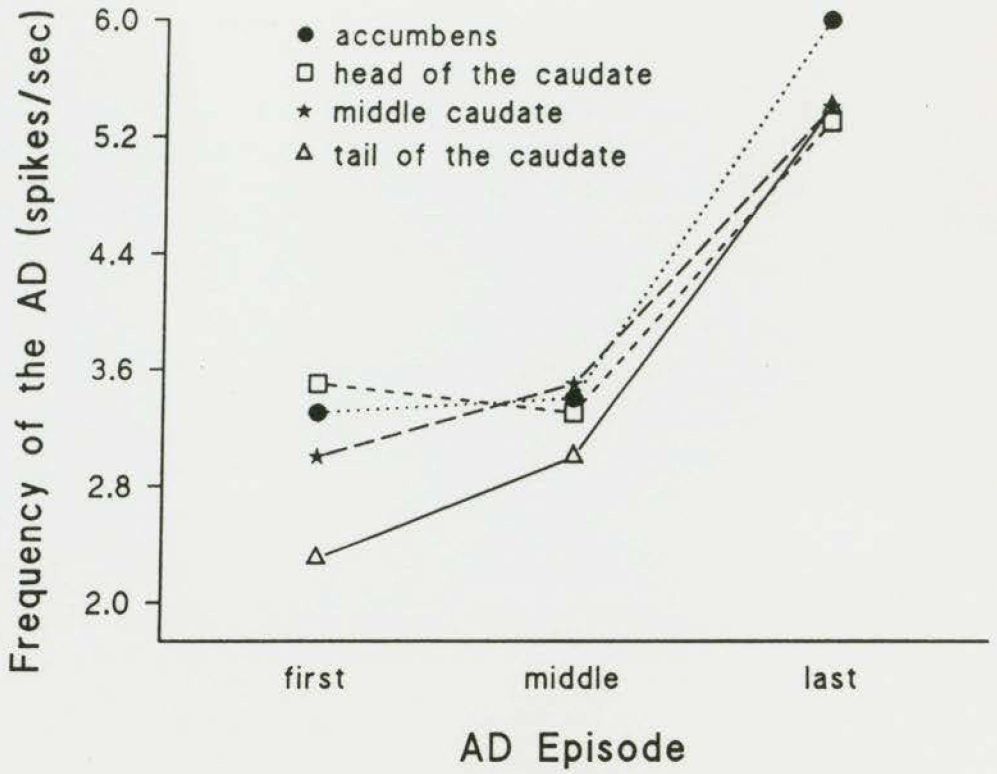

3000
2580
2160
1740
1320
900
Amplitude of the AD (μV)
accumbens
head of the caudate
middle caudate
tail of the caudate
first
middle
last
AD Episode

Figure 8. Mean frequency of evoked AD in the first, middle, and last episode of AD for the 4 groups.


Frequency of the AD (spikes/sec)
6.0
5.2
4.4
3.6
2.8
2.0
accumbens
head of the caudate
middle caudate
tail of the caudate
first
middle
last
AD Episode

The most common postictal behavior in the accumbens group was ataxia, defined as uncoordinated and irregular movements, which was seen in 4 of 7 rats. The accumbens group also displayed hyperreactivity to auditory stimulation (4 of 7 rats) resulting in jumping. I also observed stereotyped grooming and licking the floor (2 of 7 and 3 of 7 rats, respectively). Three rats showed an increase in locomotion, involving general movement around the cage in no particular pattern. Sniffing, rearing, and Straub tail were also observed in one rat.

Wet dog shakes (4 of 4 rats) and agitation (4 of 4 rats) were the most common postictal observations in the head of the caudate group. Agitation was indicated by vocalizations and teeth chattering, as well as by resistance to touching that included the biting of a probe and hyperreactivity to auditory stimulation. One rat repeatedly displayed ataxia and stereotyped movements that were incorporated into grooming.

Ataxia was the most common component of postictal movements (4 of 6 rats) in the middle caudate group. Ataxia was displayed in sniffing, chewing, rearing, grooming, and walking around the cage in a contraversive direction. One rat that displayed ataxia also exhibited opisthotonus and tail movements that were like a windmill, over several sessions.

Hyperreactivity to auditory stimuli (4 of 9 rats) and ataxia (6 of 9 rats), as evidenced during walking and grooming, were the most common postictal behaviors in the tail of the caudate group. Drooling (1 of 9 rats) and wet dog shakes (1 of 9 rats) were also observed intermittently. One rat exhibited myoclonic jerking accompanied by postictal spikes and opisthotonus only after the development of

generalized seizures.

Transfer

Of the 7 rats tested, 3 were in the accumbens group, 3 were in the tail of the caudate group, and 1 was in the middle caudate group. Secondary site kindling in the middle caudate rat occurred with a savings of 7 ADs, with the rat having a stage 5 seizure on the first AD in the contralateral hemisphere (Table 8). As shown in Table 8, the 3 rats in the accumbens group developed secondary-site stage 5 seizures very quickly, in 1, 3, and 6 ADs. This represents a savings of 23, 23, and 15 ADs, respectively. The third animal in the accumbens group did not achieve 3 consecutive stage 5 seizures, although 9 stage 5 seizures were recorded in the 23 times the rat was stimulated (Table 8). Stimulation of this rat was suspended, as I could no longer be connect it to its leads. The other 2 rats in this group achieved 3 consecutive stage 5 seizures. Two of the rats in the tail of the caudate group experienced a large savings in the number of ADs required for secondary site kindling and developed stage 5 seizures in 5 and 6 ADs, a savings of 13 and 22 days, respectively (Table 8). As shown in Table 8, the rate of secondary-site kindling in the third rat was the same as in the primary site, 8 ADs.

Persistence of kindled seizures

After a holiday of 7 days almost every rat had the first of 3 consecutive stage 5 seizures during the first or second AD triggered (16 of 17 rats tested; 9 other rats did not complete this phase of the

Table 8

Primary and secondary site kindling compared for each animal in each group tested.

	Number of ADs to completion Criterion		
	Primary Site*	Secondary Site**	Savings Score
Accumbens group			
Rat #1	24	1	23
Rat #2	26	3	23
Rat #3	21	6	15
Middle caudate group			
Rat #1	8	1	7
Tail of the caudate group			
Rat #1	8	8	0
Rat #2	18	5	13
Rat #3	28	6	22

*measured from the first of 3 consecutive stage 4+/5 seizures
**measured from the first stage 4+/5 seizure

experiment for reasons outlined above). Seven ADs without a stage 5 seizure were triggered in one rat from the middle caudate group. This rat was then withdrawn from the experiment as I could no longer connect it to its leads. Histology revealed that the placement of the secondary-site electrode in this rat was in relatively the same place as the primary-site electrode, which kindled in 5 ADs.

DISCUSSION

The present results support several conclusions about the susceptibility of the striatum to kindling. First, repeated stimulation of both the dorsal and the ventral striatum results in kindling of seizures, as has been suggested by previous experiments. Striatal kindling is genuine kindling, in that the following criteria were met: At most sites evoked AD initially failed to induce seizures, which appeared only after multiple ADs had been triggered; the intensity of the behavioral seizures and the AD increased with repeated stimulations; transfer of susceptibility to a secondary site was observed; and the increased susceptibility to seizures persisted over a rest period without stimulation. Second, as I hypothesized in the Introduction, the rate and pattern of kindling are influenced by the location of the electrodes within the striatum. Thus seizures developed significantly more slowly with stimulation of the nucleus accumbens than with stimulation of sites in the caudate nucleus. There were no significant differences in rate and pattern of kindling produced by stimulation at different sites in the caudate itself, although the middle caudate group showed a consistent tendency to develop generalized seizures more rapidly than the other caudate groups. Third, the pattern of kindling and the morphology of seizures evoked by stimulation at most placements in the striatum are not readily characterized as being either limbic or neocortical, but rather resemble a blending of these two prototypical forms of kindling. However, a neocortical pattern was seen with stimulation of the head of the caudate, as will be discussed below.

Characteristics of caudate kindling

Kindling with stimulation of the caudate exhibited features characteristic of both limbic and neocortical kindling. On the one hand, stimulation of sites in the caudate caused forced motor movements followed by AD, although motor responses were observed consistently only in the middle caudate group. Furthermore, AD could be evoked in the caudate only at high intensities of stimulation. These features are similar to the responses to neocortical stimulation (Burnham, 1978; Seidel & Corcoran, 1986); but they differ from the responses to stimulation at most limbic sites, wherein forced motor responses do not occur and AD thresholds are much lower (e.g., Racine, 1972b). In addition, the head of the caudate group displayed behavioral seizures in response to the first AD, and first-trial behavioral seizures are a cardinal characteristic of anterior neocortical kindling. Furthermore, the 3 caudate groups showed only small increases in the duration of the behavioral seizures during kindling; and neocortical kindling is also characterized by the triggering of brief seizures that increase only slightly in duration. On the other hand, the middle caudate and tail of the caudate groups did not display behavioral seizures during the first evoked AD, but instead required means of 2.7 and 4.1 ADs, respectively, before the first behavioral seizure appeared. Stimulation at limbic sites typically is also associated with the gradual emergence of behavioral seizures out of the early stages of nonconvulsive responses. Thus the present results suggest that the head of the caudate supports a form of neocortical-type kinding whereas the other sites support a form of kindling that seems to combine elements of limbic and neocortical

kindling. It may be significant that in previous studies of caudate kindling, stimulation was restricted to the head of the caudate and a neocortical pattern of kindling was observed, at least in response to the early ADs (Corcoran & Wada, 1979; Pinel & Rovner, 1978).

The unusual nature of caudate kindling is also suggested by the morphology of the kindled seizures themselves. Through the appearance of stage 4, seizures kindled by caudate stimulation closely resembled seizures triggered at most limbic sites, as described by Racine (1972b) and many other investigators (but see Grace, Corcoran, & Skelton [1990] for a description of atypical seizures triggered by stimulation of the dentate gyrus, a limbic site). When caudate-kindled seizures developed beyond stage 4, however, differences from limbic-type seizures became apparent. That is, the rats typically lost their balance at the outset of AD and remained supine during the seizure. These seizures were associated with opisthotonus, with the rats seemingly balancing on their noses, and often included unilateral or bilateral tonic extension of the hindlimbs and retraction of the forelimbs. The latter features of caudate-kindled seizures are similar to the features of neocortical-kindled seizures (Burnham, 1978; Buterbaugh, 1989; Seidel & Corcoran, 1986).

Characteristics of accumbens kindling

Kindling with stimulation of the nucleus accumbens also showed features of both limbic and neocortical kindling. For example, accumbens stimulation intermittently produced forced motor responses, and the threshold for AD was much higher than at limbic sites. These

features are reminiscent of the responses to both neocortical and caudate stimulation. However, the slow development of seizures in response to accumbens stimulation was even more pronounced than in the caudate groups. The accumbens group required a mean of 12.7 ADs before the first behavioral seizure was evoked, and each measure of the rate of kindling was significantly slower in the accumbens group than in each of the caudate groups. This slow progression of nonconvulsive seizures into convulsive seizures is reminiscent of kindling at limbic sites. Throughout kindling, the accumbens group also displayed significantly more omissions, ADs unaccompanied by behavioral seizure, than did the caudate groups. Omissions of this type are characteristic of both anterior neocortical kindling (e.g., Burnham, 1978; Seidel & Corcoran, 1986) and kindling at some limbic sites (e.g., Grace et al., 1990; Maru & Goddard, 1987). Finally, the duration of the behavioral seizures in the accumbens group increased dramatically during the course of kindling, a change that is similar to what occurs with kindling at most limbic sites (e.g., Racine, 1972b).

As with caudate-kindled seizures, the morphology of the seizures kindled by accumbens stimulation had features of both limbic and neocortical seizures. Seizures through stages 4 or 5 closely resembled limbic-type seizures, but differences from limbic seizures were also apparent in stage 4+. In the latter, the rats typically lost their balance at the outset of AD, remained supine during the seizures, and displayed opisthotonus.

Collectively the characteristics of both dorsal and ventral striatal kindling suggest that they cannot be easily assigned to either

of the two prototypical categories of kindling, limbic and neocortical. Rather than neatly fitting into one or the other category, striatal kindling instead seems to exhibit a unique mixture of features of both types of kindling. Thus striatal kindling represents a form of atypical kindling; and the striatum is one of several sites supporting atypical patterns of kindling, sites such as the brainstem reticular formation (Burnham, Albright, Schneiderman, Chiu, & Ninchoji, 1981), sensory relay nuclei in the thalamus (Cain, 1979), and posterior neocortex (Cain, 1982).

Relations to the anatomy of the striatum

It is difficult to relate the observed patterns of striatal kindling to the anatomy of the striatum in any but the most superficial fashion. The limbic-like pattern of kindling with stimulation of the nucleus accumbens (ventral striatum) is perhaps not surprising in view of the strong anatomical projection from the accumbens to the amygdala (Ragsdale & Graybiel, 1988) and from the amygdala to the accumbens (Kelley et al., 1982), pathways that presumably would be activated by stimulation of the accumbens. The motor responses intermittently evoked by accumbens stimulation and the atypical behavioral seizures evoked might have been due to activation of the anatomical connections between the accumbens and subcortical motor structures (Heimer et al., 1985). Although portions of the caudate also are interconnected with the amygdala, its primary anatomical interconnections are with other subcortical and cortical motor structures (Heimer et al., 1985). Thus the mixed nature of kindling at dorsal striatal sites may be broadly

understood in light of the gross anatomy of the region.

Unfortunately the present results cannot readily be interpreted in terms of the fine anatomy of the caudate nucleus. In particular, the results do not address the question of whether there is a relation between patterns of caudate kindling and the patch-matrix pattern of striatal organization that has received so much attention in recent neuroanatomical investigations (e.g., Gerfen, 1984, 1985, 1989; Graybiel et al., 1985; Graybiel & Ragsdale, 1978). My results do not address this issue in part because of the imprecision with which the anatomical studies have identified the exact location of the areas under investigation. For example, the anatomical studies are usually vague as to the location, on the anterior/posterior axis, of the areas receiving specific afferent innervations; and this vagueness makes it difficult to be certain that the electrode placements in the present study corresponded to appropriate anatomical subdivisions. To increase the anatomical resolution of striatal kindling, future studies might be designed to provide the appropriate labelling or staining procedures (e.g., Gerfen, 1984; Graybiel et al., 1986) in the very rats receiving kindling stimulation, so that electrode placements might be unequivocally related to patch-matrix fields.

Another potential reason why my results do not address the relation of function and anatomy may be that the technique of electrical stimulation, and the AD it induces, is simply not fine enough to permit the detection of subtle anatomical distinctions. Recall that AD could be induced only with very high intensities of stimulation, which might work against the kind of finely grained mapping that would be desirable.

It is also likely that the tips of the bipolar electrodes were large enough to extend into multiple patches and matrices, also offsetting precise anatomical localization. Perhaps the problem could be addressed in future studies by use of finer electrodes, which might result in more restricted fields of current and higher current density.

Relations to previous evidence of striatal involvement in seizures

As noted above, several other investigators have reported that stimulation of the head of the caudate produces neocortical-like kindling (Corcoran & Wada, 1979; Pinel & Rovner, 1978), an observation I was able to replicate. However, other investigators have observed both much slower kindling and a number of ineffective placements when stimulating the caudate (Goddard et al., 1969). In the present sample, only 2 negative placements were obtained, at which stimulation failed to evoke AD even at the highest intensities. The vast majority of my placements supported triggering of AD, although with very high thresholds, and the subsequent kindling of seizures. Thus my results suggest that failure to observe striatal kindling can usually be attributed to use of low intensities of stimulation, below the threshold for AD. Goddard et al. did not record EEG activity after kindling stimulations, and hence they would have been unaware of this possibility.

In contrast to successful attempts to kindle seizures with striatal stimulation (Corcoran & Wada, 1979; Pinel & Rovner, 1978; the present investigation), some studies have reported that striatal stimulation has anticonvulsant effects (reviewed in the Introduction).

I did not observe anticonvulsant effects in the present investigation, but of course I did not test for them. In other words, to detect anticonvulsant effects one would have to examine the effects of striatal stimulation superimposed on seizures evoked by other means. Thus it is possible that, in the present investigation, mixed effects of striatal stimulation occurred but only the proconvulsant effects were detected. It is also possible that anticonvulsant effects are a function of the frequency of stimulation, with low-frequency stimulation being most effective (Mutani, 1969). If the effects of striatal stimulation are frequency-dependent, then one might predict that the caudate would not be susceptible to low-frequency kindling, in contrast to limbic sites such as the amygdala and hippocampus (Cain & Corcoran, 1981; Corcoran & Cain, 1980). This hypothesis could readily be tested experimentally.

An unexpected observation in the present study was the rapid kindling observed with stimulation of the middle caudate, an area that Turski and colleagues have described as exerting anticonvulsant effects on amygdaloid-kindled seizures (Turski et al., 1987, 1989). Turski found that amygdaloid seizures were suppressed after infusions of bicuculline, a convulsant GABA antagonist, or NMDA, a convulsant amino acid agonist, into the middle caudate. I found that stimulation of the middle caudate resulted in rapid development of generalized seizures, in a pattern combining features of both limbic and anterior neocortical kindling. It is not immediately clear why an "anticonvulsant area" of the caudate should be so susceptible to electrical kindling. Possibly kindling at this site is due to activation of fibres of passage, whereas the anticonvulsant effects are due to activation of intrinsic neurons.

Another possible explanation is that the caudate infusions trigger AD that spreads to the amygdala, thereby rendering the amygdala refractory to further epileptiform activity. These and other possibilities can be tested experimentally.

APPENDIX 1: A sample of the raw data.

This appendix gives an example of the raw data that were used in the analyses in this thesis. The first object of this appendix is give an example of typical EEG to illustrate the maximal amplitude, frequency, and duration (see Figure 9). The maximal amplitude in this figure is 2800 uV, as taken from the first and largest spike. The maximal frequency is taken as an average over a 2 sec period, 8 secs after stimulation, and the maximal frequency is 3 spikes/sec. The duration of the AD is 20 secs. The duration is taken from the first AD spike on the stimulated side (the top trace) to the last AD spike. The second object of this appendix is to give typical examples of histology for each group (see Figures 10-14).

Figure 9. A typical example of EEG from an experimental rat.

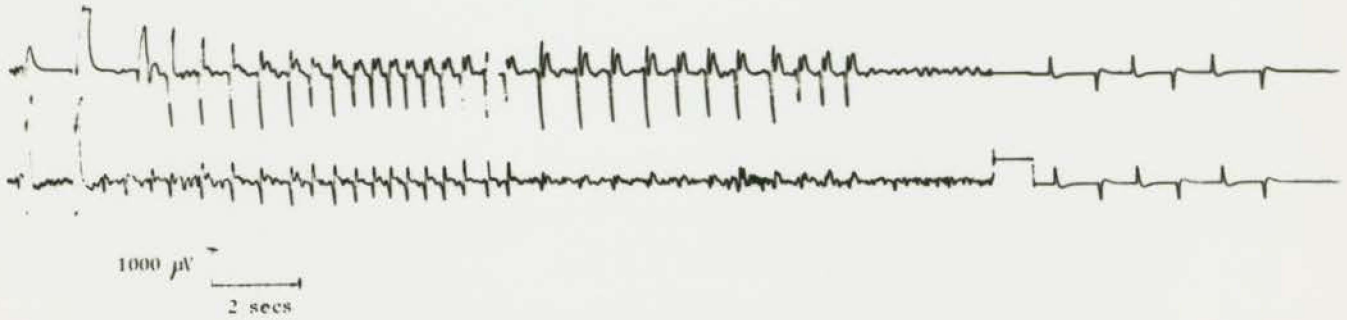

1000 μV
2 secs

Figure 10. A photomicrograph of a typical placement of an electrode in the nucleus accumbens. The arrow indicates the tip of the electrode; magnification: 100x.

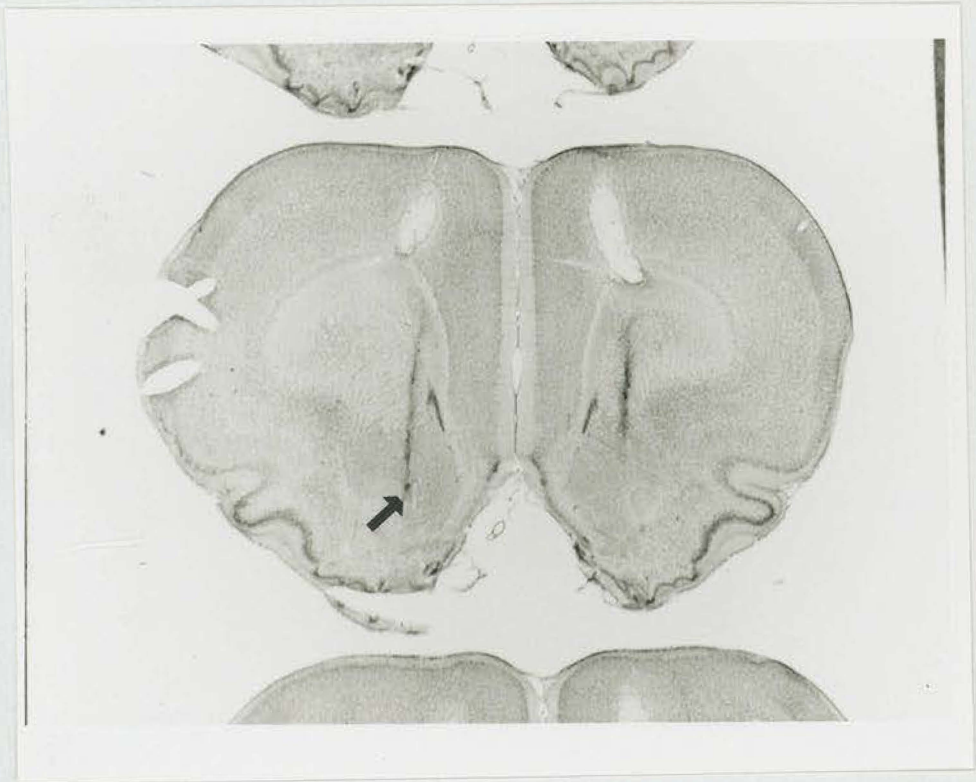


Figure 11. A photomicrograph of a typical placement of an electrode in the head of the caudate. The arrow indicates the tip of the electrode; magnification: 100x.

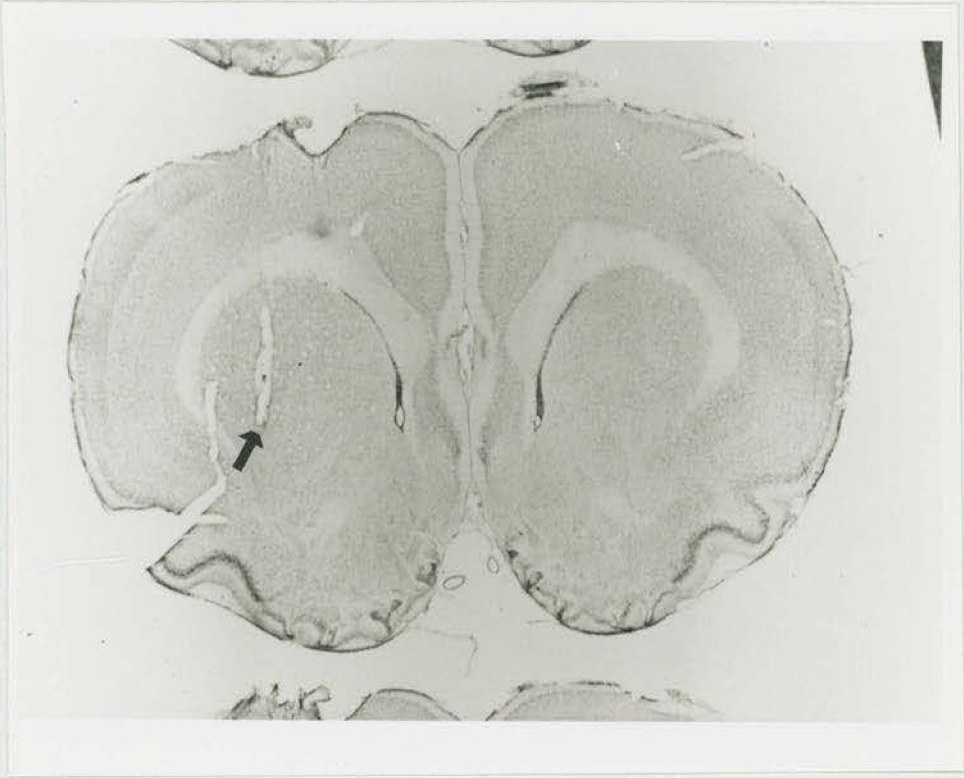


Figure 12. A photomicrograph of a typical placement of an electrode in the middle of the caudate. The arrow indicates the tip of the electrode; magnification: 100x.

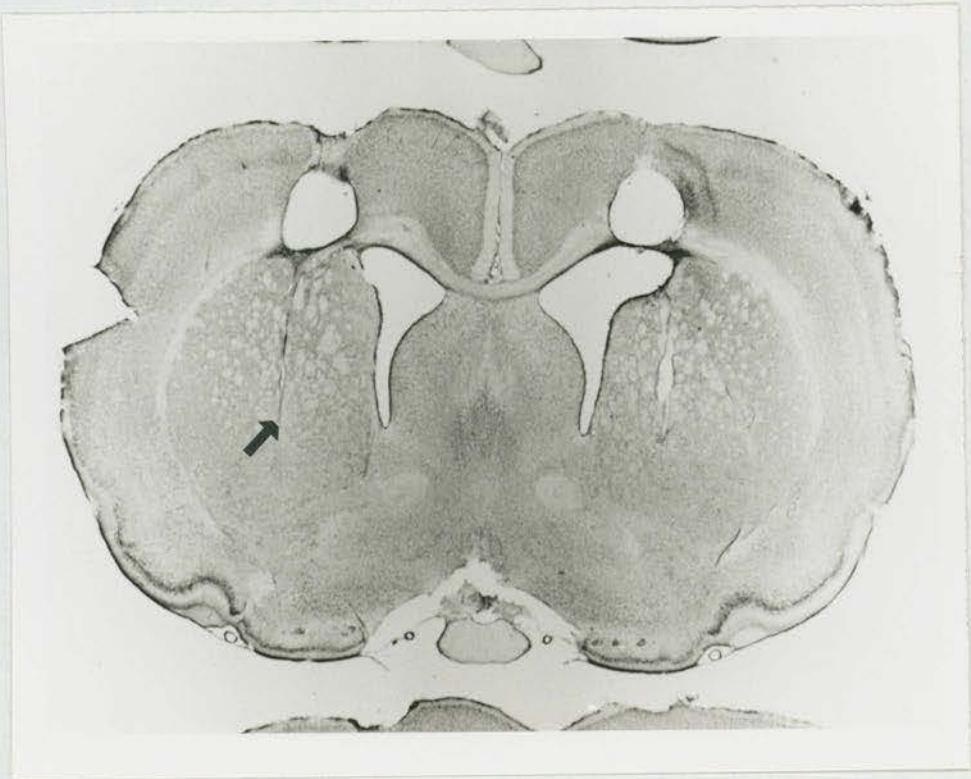
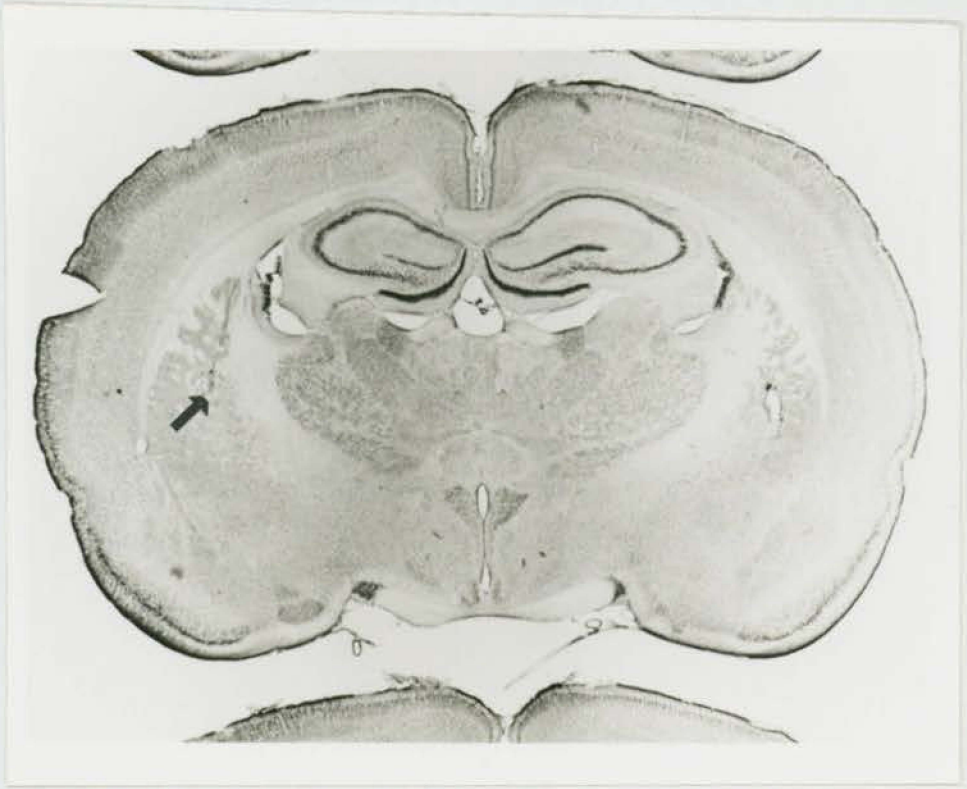


Figure 13. A photomicrograph of a typical placement of an electrode in the tail of the caudate. The arrow indicates the tip of the electrode; magnification: 100x.



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