Brain function in epilepsy: midbrain, medullary, and cerebellar interaction with the rostral forebrain

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SYNOPSIS Against the background of previous findings in epileptic patients, in whom electroencephalographic recordings were obtained from numerous deep and surface brain sites during seizures, rhesus monkeys with electrodes implanted into specific brain sites were used to demonstrate anatomical connections by evoked potential techniques and to serve as models of experimental epilepsy. In the animals, many monosynaptic connections were revealed between forebrain sites consistently involved in seizures in patients and more caudal brain sites subserving functions of sensory perception, eye movement, synaptic chemical transmission, and motor coordination. Further, the participation of these interrelated sites during seizures was demonstrated. The findings provide an anatomical-physiological explanation for many of the clinical phenomena observed in epileptic patients and a rationale for the use of cerebellar stimulation as a treatment.

That epileptic seizures are associated with distinct and characteristic electroencephalographic (EEG) changes in the cerebral cortex has been well established. In our programme at Tulane, data from epileptic patients prepared with brain electrodes for treatment of intractable neurological disorders revealed pathologial recordings from specific deep brain structures when cortical and scalp recordings were normal. These recording aberrations occurred during interictal periods. Moreover, before the appearance of characteristic seizure EEG activity in the cortical recordings at the onset of the clinical seizure, chronological spread of seizureal activity was consistently noted from the hippocampus and amygdala to the septal region (Mickle and Heath, 1957; Heath, 1962, 1963). Because the functional involvement of these subcortical structures is so consistent in the genesis of the seizure, we group them together as forebrain seizureal transmission sites.

For several years, investigators have been accumulating data that suggest the influence of the cerebellum on epileptic seizures (Snider and Magoun, 1949). Recently, electrical stimulation of the surface of the anterior lobe of the cerebellum has been used to control certain types of epilepsy (Cooper et al., 1973; Cooper and Snider, 1974). Anatomical and physiological studies in our laboratories indicate that forebrain seizureal transmission sites (hippocampus-amygdala-septal region) have monosynaptic anatomical connections with the cerebellum as well as with many other specific subcortical nuclei through the midbrain and lower brain stem. We have reported some of these connections (Heath, 1972, 1973, 1976; Harper and Heath, 1973; Paul et al., 1973; Harper and Heath, 1974; Heath and Harper, 1974, 1976); but many others have not been described previously. In most instances, the connections are two-way, the more caudal structures projecting rostrally to the forebrain seizureal transmission sites.

In the present report of findings obtained in monkeys made epileptic by several experimental methods, principal caudal connections are grouped roughly according to function under the following headings: sensory relay nuclei, chemical transmitter sites, sites for facial expression and eye movement, nuclei involved in motor coordination, and non-specific sites. Recordings from these numerous deep brain sites of animals made epileptic indicate the anatomical connections that are significant in epilepsy. The recordings show the manner in which the more caudal functional sites are interrelated with the forebrain seizureal transmission sites in the genesis of a seizure.

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METHODS

Young adult rhesus monkeys with electrodes implanted into specific brain sites were used to demonstrate anatomical connections by evoked potential techniques and to serve as models of experimental epilepsy. The findings presented in the current report are from 50 monkeys in which electrode sites were confirmed histologically and from which evoked potential data were gathered. Twenty-four of the animals were also used to determine the spread of epileptic seizures.

ELECTRODE IMPLANTATION PROCEDURE

By previously described methods (Heath et al., 1968, 1976) and with the Atlas of Snider and Lee (1961) as a guide, each monkey had electrodes implanted into the anterior septal region (Heath, 1954), mid-septal region, fastigial nucleus of the cerebellum, hippocampus, amygdala, and bilaterally on the temporal cortex. In addition, electrodes were implanted into at least one of the following brain sites of several monkeys in the group: ventroposterior lateral thalamus, medial and lateral geniculate nuclei, hypothalamus, mesencephalic reticulum, substantia nigra, locus coeruleus, raphe nuclei, nucleus cuneiformis, red nucleus, dentate nucleus of the cerebellum, inferior olive, superior colliculus, caudate nucleus, and over the frontal and occipital cortices. The subcortical bipolar silver-ball electrodes, each 0.5 mm in diameter, were each separated by 2.0 mm. Cortical implants were single silver-ball electrodes, each 0.5 mm in diameter, and scalp electrodes were silver discs. The implantation procedure was accompanied by radiological visualisation with air in the ventricular system to ensure accuracy of placement. At the end of the studies, the monkeys were killed, and the brains were fixed in 10% formalin for histological study and confirmation of electrode placements.

Each monkey was allowed to rest for two to three weeks after implantation to allow all postoperative recording artefacts to disappear.

ELECTROENCEPHALOGRAMS

Electroencephalograms (EEGs) were obtained on a 16-channel Grass Model 6 electroencephalograph. Sometimes, in order to obtain additional channels of recordings, an 8-channel Grass Model electroencephalograph was also used, the two machines synchronised by a time code generator.

EVOKE POTENTIALS

To demonstrate anatomical-physiological connections between various specific sites, we evoked potentials in the monkeys by applying a stimulus between the two leads of an implanted electrode while bipolar recordings were made between the pairs of an electrode at one of the other implanted sites. The stimulus consisted of a rectangular bidirectional pulse of 0.1 to 0.25 ms duration at currents varying from 2 to 5 mA. All studies were conducted with the monkeys awake. Evoked responses were recorded on a Tektronix dual-channel 502A oscilloscope, with Tektronix low-level preamplifiers to which a Polaroid C-12 camera was mounted to obtain permanent photographic records. For each study, recordings were obtained of a single response, a superimposition of 30 responses delivered at one-second intervals (which will be used in the current report to demonstrate connections), and a high-frequency stimulation between 50 and 145 Hz.

MODELS OF EXPERIMENTAL EPILEPSY

Three methods were used to induce experimental epilepsy in monkeys: focal electrical stimulation, implantation of cobalt, and administration of convulsant drugs.

Focal electrical stimulation To induce an after-discharge, we delivered an electrical stimulus (0.5 ms biphasic pulse, 60 Hz, at 2 mA for two seconds) to the hippocampus of the monkey. Recordings from all deep sites were bipolar, between the two leads of a subcortical electrode. Cortical recordings were also bipolar between combinations of single-ball leads under the bone. Scalp leads were bipolar between silver disc leads fixed to the scalp.

Subcortical implantation of cobalt Introduction of an irritant into a specific brain site of an animal has proved effective in studying functional relations among various brain sites. For this study, metallic cobalt was introduced, by a procedure previously described, into deep nuclear brain sites into which electrodes had previously been implanted (Guerrero-Figueroa et al., 1963). Recordings were obtained one hour after cobalt implantation and at intervals thereafter for days or weeks, depending on responses and developing foci.

Use of convulsant drugs Three drugs, d-LSD, phencyclidine, and leptazol (Metrazol), were used for this study. The d-LSD was given intravenously at a dose of 100 μg/kg, whereas phencyclidine was given intramuscularly at a dose of 0.25 mg/kg. Metrazol was administered intravenously in one ml (10 mg) increments at 30-second intervals until epileptiform activity appeared in the monkey’s recordings.
RESULTS

ANATOMICAL CONNECTIONS REVEALED BY EVOKED POTENTIALS

In monkeys, monosynaptic connections in the brain were denoted by short delay time between stimulus and response. Responses evoked at various brain sites by electrical stimulation of the rostral septal region are shown in Fig. 1.  The short delay times suggest monosynaptic connections from the septal region to these sites. In Tables 1–5 direct connections among brain sites, demonstrated by evoked responses in the monkeys, are grouped according to functions considered relevant in epilepsy. Responses evoked in various sites with stimulation of forebrain transmission sites are listed in Table 1. Table 2 lists the delay responses obtained in numerous sites with stimulation of sensory relay nuclei, and Table 3 lists those obtained when stimuli were applied to various transmitter chemical reservoir nuclei. Responses obtained with stimulation to nuclei influencing motor coordination and expression (facial and eyes) are shown in Table 4, and those obtained with stimulation of non-specific brain sites are listed in Table 5.

FUNCTIONAL RELATIONSHIPS REVEALED BY ‘MODEL EPILEPSY’ TECHNIQUES

Cobalt-induced experimental epilepsy After implantation of cobalt into certain specific subcortical nuclei presumed to be implicated in epilepsy, epileptiform activity usually developed at the implanted site within a few hours. Spreading from the primary focus (site of implantation) to directly-connected nuclei (that can be functionally grouped together as previously described), the activity gradually intensified over the next 12 to 24 hours. Regardless of the nuclear site implanted with cobalt, the directly-connected sites were also implicated. In Fig. 4, serial recordings from a monkey with cobalt implanted into the right anterior septal region demonstrate this phenomenon. As the hours passed, epileptiform activity was transmitted from the right anterior septal region to the contralateral septal region, amygdala, and hippocampus. Before long, the spread involved the substantia nigra and inferior olive. By 18 hours after cobalt implantation, the sensory relay nuclei (ventro-posterior lateral thalamus and deep cerebellar nuclei) were also involved with the seizural activity which continued in the amygdala, hippocampus, and septal region. At this point, the continuous discharge migrating among forebrain structures and sensory relay nuclei also involved nuclei controlling the eyes (superior colliculus), and structures controlling coordination (inferior olive and dentate nucleus of the cerebellum), as well as a transmitter chemical site (substantia nigra containing dopaminergic neurons). By 24 hours after cobalt implantation, midbrain and hindbrain structures showed intermittent seizural activity. Clinical manifestations of the seizure occurred, however, only after the forebrain transmission sites (hippocampus, amygdala, septal region) and then the cortex had developed continuous rhythmical seizural activity.

Recordings from another monkey show the seizural activity induced with cobalt implanted into the fastigial nucleus of the cerebellum (Fig. 5). In this example, intermittent spiking activity first involved the contralateral dentate nucleus of the cerebellum, the hippocampus, and the temporal cortex. Seizural activity then encompassed the hippocampus, septal region, and temporal cortex concomitant with slow activity in the ventro-posterior lateral thalamus. (As previously described, the fastigial nucleus of the cerebellum projects monosynaptically to all these structures.) Only after seizural activity spread to the septal region did the cortical mantle become completely involved and the animal develop a grand mal seizure.

When cobalt was implanted into the hippocampus, epileptiform activity spread similarly to implicate interconnected subcortical sites. In the recordings shown in Fig. 6, epileptiform activity appeared first at the primary site and then spread to the septal region.
Four hours after cobalt implantation, the substantia nigra and dentate nucleus of the cerebellum were also involved. By six hours after implantation, epileptiform activity had increased at these sites and also had encompassed the ventroposterior lateral thalamus and the amygdala.

**Drug-induced seizure activity** Figure 7 shows EEGs obtained from a monkey before (baseline) and after intravenous administration of d-LSD. Because the rhesus monkey has a high threshold for d-LSD, it requires a dose equal to that given to a man to induce a response. Thirty seconds after the injection, initial changes were noted in forebrain structures (septal region, hippocampus, and caudate nucleus), and then soon implicated the substantia nigra. By four minutes after the injection, epileptiform activity had intensified and spread to involve other more caudal, interconnected structures (superior colliculus and deep cerebellar nuclei).

The effects of phencyclidine were somewhat different. As shown in Fig. 8, not only did EEG changes develop promptly in forebrain structures (hippocampus, amygdala, septal region), but significant changes also rapidly appeared in cortical structures and sensory relay nuclei (medial geniculate and ventroposterior lateral thalamus). Likewise, as evidenced by the EEGs, the fastigial nucleus of the...
Sensory Relay Nuclei Sites

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<tr>
<th>Site of stimulation</th>
<th>Sensory relay nuclei</th>
<th>Forebrain transmission sites</th>
<th>Transmitter chemical reservoirs</th>
<th>Motor coordination and expression</th>
<th>Non-specific sites</th>
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*Local evoked response recorded from other leads at this site.

Tables 1–5 summarise evoked potential data in monkeys. The latency response listed is the shortest one obtained for the site in the series of monkeys that were studied. I: Ipsilateral. C: Contralateral. NR: No response obtained. NT: Site not tested.
Although significant graphic changes in finishing, through these activity injection muscular cerebellum and the substantia nigra were quickly involved. For as long as one hour after the intramuscular injection of phencyclidine, epileptiform activity continued to migrate, intensifying and diminishing, through these brain structures.

Clinical seizures did not occur with use of d-LSD or phencyclidine. Although significant cortical electrographic changes developed after administration of phencyclidine, they were different in form, and seizural activity did not spread subsequently through the septal region to encompass the cortex, as occurred consistently with the clinical seizure.

Intravenous use of Metrazol invariably induced grand mal seizures in the monkeys (Fig. 9). Consistent with the EEGs we have obtained from epileptic patients during clinical seizures, and from monkeys.
**TABLE 5**

<table>
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<tr>
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**FIG. 2** Baseline electroencephalograms from a rhesus monkey.

**FIG. 3** Electroencephalograms from the same monkey after stimulation of the hippocampus.

(Figures 2 and 3 are considerably reduced in order that they may easily be compared. Markers—both Figures: 50 μV, 1s.)
FIG. 4  Electroencephalograms from a rhesus monkey before (baseline) and after implantation of cobalt into the right anterior septal region. The electrocardiogram (ECG) with a slightly different frequency establishes that the rhythmical brain discharges do not represent heart beat.

FIG. 5  Electroencephalograms from a rhesus monkey before (baseline) and 24 hours after implantation of cobalt into the left fastigial nucleus of the cerebellum. Migration of seizural activity.
in which seizural activity was induced by other techniques, epileptiform activity migrated through forebrain transmission sites (hippocampus, amygdala, septal region) and encompassed the cortex as the clinical seizure began. These recordings from a monkey with electrodes in several deep sites in addition to the forebrain nuclei, and at surface sites as well, further demonstrated the way in which seizural activity encompasses other nuclei associated with specific neural functions. In this example, the hypothalamus and cuneiform nucleus were implicated early, along with the hippocampus. Epileptiform activity, after appearing in septal leads, spread to involve the raphe nuclei and fastigial nucleus of the cerebellum. Metrazol created so much agitation in the

monkeys that artefacts from the consequent movement made surface recordings worthless.

A phenomenon we have observed consistently in the epileptic monkeys during seizures and during postictal periods is illustrated in the recordings from the fastigial nucleus of the cerebellum of the monkey that received Metrazol (Fig. 9). After the seizure has passed its peak, high-amplitude cerebellar activity appears. It continues rhythmical as the seizure ends and it persists well into the postictal period. (In the epileptic monkeys, this phenomenon has been observed in both the fastigial and dentate nuclei.) This recording pattern indicates that activation of the deep cerebellar nuclei correlates with cessation of the seizure (Figs. 5 and 9).
FIG. 7  Electroencephalograms from a rhesus monkey before (baseline) and after intravenous administration of d-LSD (100 µg/kg).

FIG. 8  Electroencephalograms from a rhesus monkey before (baseline) and after intramuscular administration of phencyclidine (0.25 mg/kg).
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DISCUSSION

These studies in monkeys extend observations made in patients concerning the organisation of the brain in epileptic patients. In addition to altered consciousness and motor manifestations, both consistent features of seizures, other functions are often affected. For example, variable signs and symptoms occur with aura. Some of the most common are changes in emotional state, alterations in sensory perception, changes in facial expression and eyes, and impairment of motor coordination. The brief delay times in evoked potentials suggested direct anatomical connections among nuclei subserving these functions. Even when electrode placements are verified histologically, the evoked potential technique for demonstrating anatomical pathways lacks precision, as the eliciting stimulus can activate nearby structures and the recorded response can be from a site near the recording electrode. The technique serves as a satisfactory, quick screening method, but it is desirable further to establish the connections by histological methods. Many of the principal connections revealed by evoked potentials have been verified by Fink-Heimer axonal degeneration studies and horseradish peroxidase methods for demonstrating afferent connections to a given site (Heath, 1972, 1973, 1974; Paul et al., 1973; Heath and Harper, 1974, 1976; Clark, Ellison, and Heath, in preparation).

In our patients with depth electrodes, the forebrain transmission sites were always involved, in a uniform chronology, during interictal periods and seizures (Figs. 10 and 11). Not only are these sites interconnected, but each is connected, back-and-forth, with caudal sites (grouped together arbitrarily by virtue of subserving special functions). In the monkeys in which experimental epilepsy was induced, electrodes were implanted into these caudal sites. The recordings show that seizural EEG activity not only occurred at forebrain sites (where it had been recorded in epileptic patients), but spread to more caudal sites, migrating among these sites interictally. Before a clinical seizure, build-up of epileptiform activity occurred at these various sites, but immediately before a seizure, the same chronological dispersion that we have observed in patients spread through the hippocampus and amygdala, then to the septal region, and finally to the cortex.

In epileptic patients with depth electrodes, we have previously observed that intensified epileptiform activity in forebrain transmission sites correlated with altered emotionality (Heath, 1962, 1975, 1976; Heath

**FIG. 9** Electroencephalograms from a rhesus monkey before (baseline) and after intravenous administration of Metrazol. Generalised seizure.
and Gallant, 1964). The same sites and complex pathways have been shown to be basic to emotional expression, and they are thus significantly involved in healthy and pathological behaviour (Heath, 1964, 1966, 1972, 1975, 1976; Heath et al., 1974). In epileptic patients, behavioural concomitants ranging from mildly inappropriate emotionality (usually adverse, rarely pleasurable) to irrational psychotic behaviour, which sometimes occur interictally and frequently occur as part of an aura, have been correlated with the aberrant EEG activity in forebrain transmission sites. This finding that the same interconnected neural structures are involved in behavioural phenomena and seizures also provides an anatomical-physiological basis for the observation that aberrant behaviour can be ameliorated by the induction of seizures, as in electroconvulsive or Metrazol therapy. These treatments evolved from clinical observations of an occasional inverse relationship between epilepsy and psychosis. Electroencephalographic activity recorded from the involved brain sites of epileptic patients during seizures is different from that recorded in patients with profound behavioural pathology who are seizure-free. In the epileptic patients with depth electrodes, who had psychotic episodes as well as seizures, both kinds of EEG recordings were obtained depending on clinical state. During their psychotic behaviour, recordings often closely resembled those of other psychotic patients—for example, schizophrenic patients—whereas, during seizures, recordings were characteristic of the epileptic.

The animal data reported herein demonstrate that the rostral forebrain structures, where recordings in patients correlated with the clinical phenomena of seizures and emotionality, are directly connected with several brain sites subserving other functions. Further, the animal data reveal the involvement of these
FIG. 11  Deep and surface recordings from an epileptic patient during a psychomotor seizure. The three 16-channel recordings (sample) show different sequences in the onset of the seizure.
remote sites in clinical seizures. In the experimental epileptic animals, recordings show that electrical seizures could spread over direct pathways to involve other interconnected sites, the sequence varying from one seizure to the next. This finding could account for the variability in aura and sequelae of seizures.

Involvement of the sensory relay nuclei (medial and lateral geniculates, ventroposterior lateral thalamus, and fastigial nucleus of the cerebellum) in the seizure spread could explain the disturbances in sensory perception that often occur during aura of the seizure and could also account for the observation that sensory stimuli sometimes precipitate a seizure.

Ocular involvement in seizures, such as the blank stare during a psychomotor attack and the gross aberrations associated with a grand mal seizure, is probably due in part to involvement of the superior colliculus and third nerve nuclei. The consistent input from the inferior olive and dentate nucleus in perpetuating the seizure discharge provides an explanation for changes in coordination during seizures (Llinas et al., 1975).

The functional role of various putative neurotransmitters in epilepsy is by no means clear. Underscoring the complexity of this phenomenon is the finding that cell reservoirs for several transmitters are involved in the interconnected pathways implicated in the development of an epileptic seizure. The chemical synaptic transmitters involved are probably the basic determinants of whether activity at these neural structures results in seizures or pathological behaviour.

Participation of the deep cerebellum in the course of a seizure appears unique. Although epileptiform activity in the deep cerebellar nuclei occurred during build-up to seizure, rhythmic high-amplitude epileptiform activity did not begin there until the clinical seizure had passed its peak. High-amplitude rhythmic cerebellar discharges then continued for some time postictally while recordings from other sites were virtually isoelectric, suggesting that enhanced activity of the deep cerebellar nuclei correlated with cessation of the seizure. One can only speculate on the relation between this finding and the beneficial results that have been obtained with use of surface cerebellar stimulation for control of seizures (Grabow et al., 1974). Since the Purkinje cells of the cerebellar cortex inhibit activity in the deep nuclei, the assumption that cerebellar stimulation is beneficial by virtue of activating Purkinje cells would be irreconcilable with our findings. An alternative explanation might be more feasible. Conceivably, the slow-frequency stimulation may inhibit Purkinje cells or a mechanism not involving the Purkinje cells may facilitate activity in the deep nuclei to control the seizure.

Many of these same brain structures and pathways—the septal region, hippocampus, and amygdala of the rostral forebrain; the thalamic nuclei; the relay nuclei for sensory perception; the midbrain nuclei for various chemical transmitters and for eye movement—all interrelated with the hind-brain through the cerebellar-inferior olive system, have been shown to be implicated in dyskinesia. Physiological intervention at some of these sites (by different treatment methods) has proved effective in alleviating signs and symptoms of dyskinesia (Cooper, 1969). Drugs beneficial in treating behavioural disorders often induce dyskinesia. On the other hand, drugs used for treating dyskinesia sometimes induce or aggravate pathological behaviour. The complicated anatomical-functional relationship among systems subserving these different functions offers a basis for understanding clinical observations and may ultimately open the way for other therapeutic procedures.

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