Reprinted from JOURNAL OF NEUROPATHOLOGY AND EXPERIMENTAL NEUROLOGY
Vol. XII, No. 3, July, 1953
Printed in U.S.A.

CORTICAL AND SUBCORTICAL ELECTRICAL ACTIVITY IN EXPERIMENTAL SEIZURES INDUCED BY METRAZOL*

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The convulsant drug, metrazol, has long been known to produce experimental seizures of the grand mal type and, more recently, has been employed clinically, either in shock therapy for patients with mental disease (11) or as an aid in the diagnosis of suspected epilepsy (2, 3, 8, 12, 16). Administration of subconvulsive doses of metrazol has been used to provoke abnormal discharge in the electroencephalogram of epileptic patients during inter-seizure periods (2, 12, 16). In addition, similar doses of metrazol have been utilized in conjunction with photic stimulation (3) or direct stimulation of the brain (8) in the case of focal epilepsy, to induce controlled seizures.

This usefulness of metrazol in the study of seizures in man makes it desirable to learn more of its action upon the brain (1, 4, 5, 9). The present experiments have investigated the alterations in cerebral electrical activity during metrazol seizures in the cat. Because of growing interest in subcortical influences upon the activity of the cerebral cortex, special attention has been directed to the participation of deep brain structures and, in particular, that of thalamic nuclei in the metrazol fit.

METHODS

Cats were prepared under ether, immobilized with B-erythroidine and maintained with a Palmer respirator. Metrazol was diluted in sterile water so that 1 cc. contained 20 mg. and was administered intravenously. Electrical activity of the brain was recorded with an 8-channel, Grass Model III amplifier and ink-writer, the emergency all-channel de-amplifier being used when seizure amplitude became excessive. Cortical electrodes consisted of the balled tips of silver wires, oriented with the Grass multiple electrode holder. Deep electrodes were of the concentric bipolar type, oriented with a multiple electrode carrier and stereotaxic instrument; their placement being subsequently determined in microscopic sections. Click stimuli were delivered from a toy cricket, manually operated. Electrical stimuli to the brain consisted of condenser discharges with a falling phase of 1 m. sec. delivered from a Goodwin stimulator.

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[1] Visiting Fellow, Paris.

[2] Aided by a grant from the National Institute of Mental Health, U. S. Public Health Service.

[3] The help and supervision of Drs. J. D. French and H. W. Magoun are gratefully acknowledged.

RESULTS

In presenting the findings, attention may be devoted first to the cortical and subcortical events in fits produced by convulsive doses of metrazol, following which the induction of seizures by afferent or direct thalamic stimulation after the intravenous injection of subconvulsive doses of metrazol will be considered.

I. Metrazol Seizures

Electro-cortical events induced by metrazol in sufficient dose to produce a seizure (15 mgm./Kg.) characteristically began with sporadic discharge, of complex and variable pattern, which appeared synchronously in all areas of the cortex (fig. 1) though it might often be most pronounced in a specific region, as the auditory (fig. 1A) or sensory-motor (fig. 1B) area*. The repetition of these prodromal discharges at increasing frequencies ushered in a period of continuous firing, which comprised the main body of the fit (figs. 1–6). In all areas, this firing consisted initially of sharp, fast, spiking or irregular discharge at frequencies of 10–20/sec. (figs. 1–3), which often appeared first or was most pronounced in the region in which prodromal discharge was largest (fig. 1). As the amplitude of firing continued to increase, its frequency slowed to between 7 and 11/sec., and the discharge assumed the form of regularly recurring waves (figs. 2–5). During this stage, the somatic sensory and, less often, the motor regions of the cortex sometimes exhibited runs of extremely symmetrical spike-wave sequences at the same rate as the simple waves in other areas (fig. 2B, C; fig. 4A). After variable periods, the frequency of discharge slowed further still until, with a succession of almost individual beats, firing ceased abruptly and simultaneously in all areas and a period of iso-electricity ensued (figs. 2, 3, 6). After one dose of metrazol, this sequence of events was repeated many times.

Subcortical seizure activity was generalized in the prodromal phase of the fit, all deep sites, irrespective of their location in the thalamus or basal ganglia, exhibiting initial sporadic discharge synchronous with that in the cortex (fig. 1A, B). With the onset of the repetitive cortical seizure, however, regional subcortical specificity was exhibited, and the only general feature of this activity of deep regions was its subordination to events occurring in the cortex. Similarly, seizure activity in the brain stem did not, as a rule, outlast that in the cortex, but ended with the post-ictal cortical silence (fig. 3). Variations in the promptness of its appearance and in its intensity and form may be considered first with reference to the functional groups of thalamic nuclei.

Sensory relay nuclei. The sensory relay nuclei of the thalamus displayed the most marked seizure activity, from the point of view of promptness of onset and amplitude of discharge. In Figure 2A, a brief seizure is seen to commence, reach its maximum and diminish, with remarkable similarity, in the sensory area of the cortex and in the related nucleus ventralis posterior of the thalamus, major individual potential charges in these two regions usually being synchronous with one another. During periods when the sensory cortex exhibited spike-wave sequences, correlated spike discharges were seen in the ventral thalamic nucleus (fig. 2B). In the case of the medial geniculate nucleus, a similar close relationship to the activity of the related auditory cortex was seen, the deep seizure starting after the cortical fit was well advanced, but mirroring it closely during the tonic stage (fig. 2C). Of the relay nuclei, the lateral geniculate showed the poorest seizure activity, both in promptness of onset and amplitude of waves, the best correspondence with the activity of the visual cortex being seen in the regular waves in the repetitive part of the seizure (fig. 2D).

Other thalamic nuclei with specific projections were not essentially different in their par-

* Because of the important role which afferent stimuli may play in precipitating metrazol seizures (see Section II), their predominance in the somatic sensory and auditory areas of the cortex in these experiments may have resulted in part from the background of somatic and auditory stimulation inevitably present in the laboratory situation.

ticipation. The nucleus ventralis lateralis, related to the motor area of the cortex, manifested seizure discharge which paralleled that in the motor region, but was in general more wavelike, particularly in the terminal phase (fig. 3A). In the nucleus lateralis posterior, similar seizure activity occurred after the repetitive phase of the fit had become well established in the lateral or middle suprasylvian association cortices, to which this nucleus is related (fig. 3B), and was again predominantly of wave form.

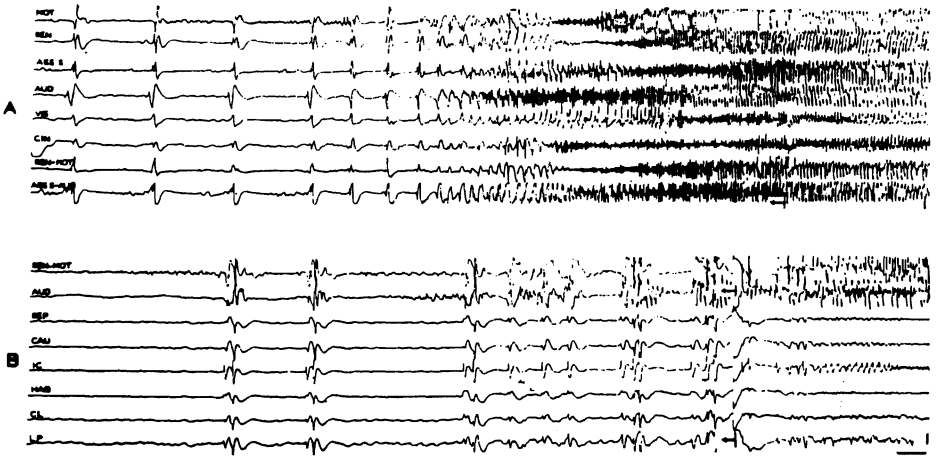

FIG. 1. Prodromal discharge generalized in cortical and subcortical regions in instances when the seizure induced by 15 mgm/kg. metrazol was generalized (A) or local (B). In all figures, the horizontal line at the lower right marks a second, while—unless noted—the vertical signal indicates 200 μv. Vertical signals with arrows mark the point at which amplification was reduced.

Abbreviations for all figures are as follows:

AD, anterodorsal n.; AM, anteromedial n. or amygdala; ASS L, lateral gyrus; ASS S, middle suprasylvian gyrus; AUD, auditory cortex; AV, anteroventral n.; BIC, brachium of inferior colliculus; BP, basis pedunculi; BRC, decussation of brachium conjunctivum; C or CAU, caudate nucleus; CE, centralis medialis n.; CG, central gray; CL, centralis lateralis n.; CLA, claustrum; CM, centre median n.; COR, coronal gyrus; EN, entopeduncular portion of globus pallidus; GP, globus pallidus; HAB, habenular n.; HIP, hippocampus; HP, habenulopeduncular tract; IAM, intermediate anteromedial n.; IC, internal capsule; IP, interpeduncular n.; LA, lateralis anterior n.; LG, lateral geniculate n.; LP, lateralis posterior n.; M, medial n.; MB, mammillary body; MG, medial geniculate n.; ML, medial lemniscus; MOT, motor cortex; OT, optic tract; PA, paraventricular n.; PL, pulvinar; PRE, pretectal region; PUT, putamen; RE, reuniens n.; RET, reticular n.; RF, midbrain tegmentum; RN, red nucleus; SC, superior colliculus; SEN, sensory cortex; SN, substantia nigra; ST, subthalamic n.; SUB, subthalamus; TEG, midbrain tegmentum; VA, ventralis anterior n.; VIS, visual cortex; VL, ventralis lateralis n.; VM, ventromedial n.; VMH, ventromedial hypothalamic n.; VP, ventralis posterior n.; VPL, ventroposterolateral n.; VPM, ventroposteromedial n.; ZI, zona incerta.

Nuclei of the diffuse projection system were the least typically affected of the thalamic nuclei. Abnormal potentials were late in appearing and differed considerably from those manifest in nuclei of the thalamus with specific relations to the cortex. In the diffusely projecting nuclei, activity was invariably wavelike and frequently exhibited a waxing and waning of amplitude which bore no relation to changes in seizure discharge elsewhere. Figure 2A shows the development of such wave activity in the centre median, beginning some six seconds after the commencement of the cortical seizure, gradually increasing in amplitude until it fell into phase with wave discharge (in the nucleus ventralis posterior) in the late phase of the fit.

A record from the centralis lateralis, in Fig. 4A, shows absence of any seizure activity corresponding to that in the cortex until the terminal stages were reached, when giant rolling 3/sec. waves in this part of the thalamus were coincident with spike and wave discharges

of the motor cortex. In the instance seen in Fig. 4B, the centralis lateralis displayed more activity which was initially irregular and then settled into a rhythmic series of large 7/sec. waves in phase with discharge in the somatic sensory cortex. Such waves were present also, but waxed and waned in the ventralis anterior. It is of interest to note that in intermediate

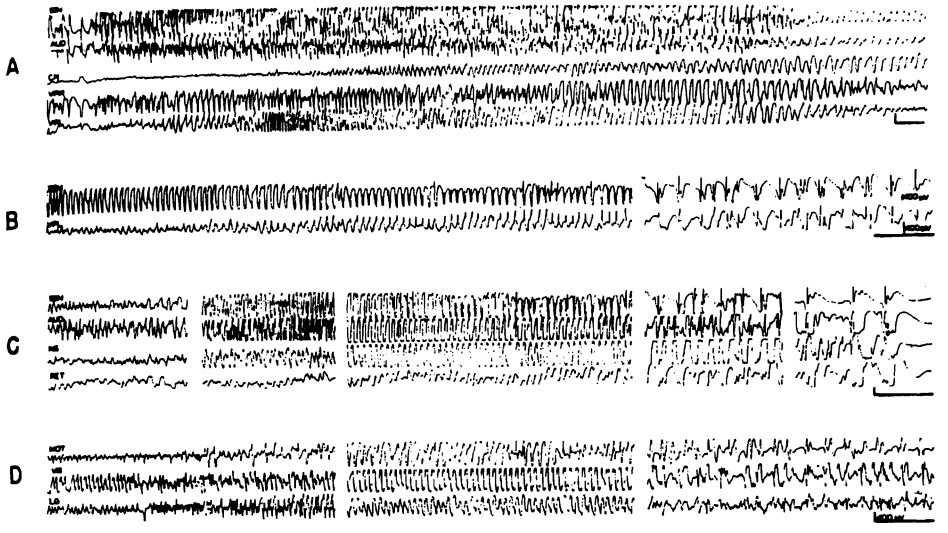

FIG. 2. Records from sensory areas of the cerebral cortex and thalamic relay nuclei related to them, showing seizure discharge induced by 15 mgm./kg. metrazol: A and B, somatic sensory cortex and nucleus ventralis posterior; C, auditory cortex and medial geniculate nucleus; D, visual cortex and lateral geniculate nucleus. Records are included from the centre median (A) and reticular nucleus (C). The continuity of the record is interrupted in B-D to show examples from different periods of the seizure.

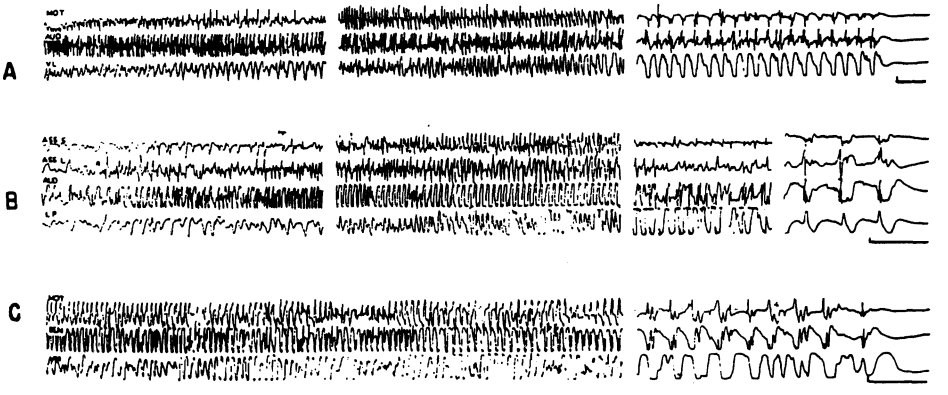

FIG. 3. Records from motor, associational and sensory areas of the cortex and thalamic relay nuclei related to them, showing seizure discharge induced by 15 mgm./kg. metrazol: A, motor cortex and nucleus ventralis lateralis; B, associational cortex and nucleus lateralis posterior; C, motor and sensory cortex and nucleus ventralis medialis.

stages of the cortical fit, when regular spike and wave discharge was often present for considerable periods in the sensory or motor region, and sometimes in the auditory area (figs. 2B, 3C, 4A), nothing resembling a spike-wave complex was ever recorded from the diffusely projecting nuclei.

The ventromedial thalamic nucleus exhibited seizure activity which closely resembled

that of the diffuse projection nuclei, as seen in Fig. 3C. Large waxing and waning waves, in phase with 9/sec. discharge in the sensory and motor cortex continued through the regular part of the fit and, in the terminal clonic phase, slowed to giant 2 or 3/sec. swings.

Thalamic localization. On the levels through the diencephalon, shown in Fig. 7, triangles mark the sites from which subcortical seizure activity was recorded. The size of the symbols indicates the amplitude and promptness of onset of the fit, and sites exhibiting low amplitude or extremely late alteration of activity are not included. Best effects were recorded, in the thalamus, from the nucleus ventralis posterior (B), medial geniculate body (C), and nucleus lateralis posterior (B, C). Generalizing, the thalamic nuclei having reciprocal connections with specific areas of the cortex were most profoundly affected during metrazol seizures, a greater or less correlation of activity being evident between discrete cortical areas and related subcortical structures. This relationship was most clear in the sensory relay nuclei of the thalamus, but was discernible also in the nuclei having connections with association cortex. The nuclei of the diffuse projection system, whose activity is wavelike (spindle-bursts) in the anesthetized animal, showed late seizure potentials which often grouped themselves into giant spindles, differing from those encountered normally only in their excessive amplitude. Their later participation tended to occur in association with the regular wave period of discharge in the cortex, and was in phase with it, but no closer relation was apparent. Spike-wave discharge was never encountered in the diffusely projecting

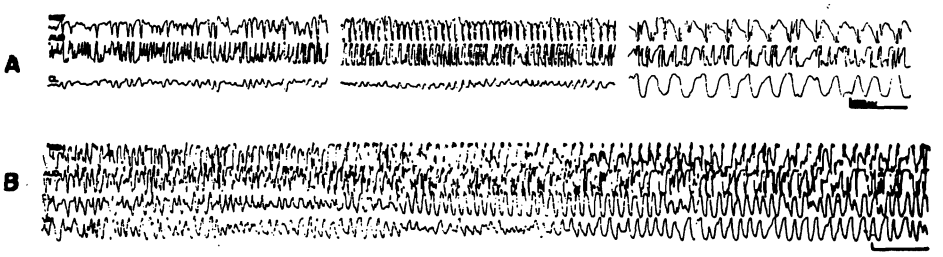

FIG. 4. Records from motor and sensory areas of cortex and nuclei of the diffuse thalamic projection system, showing seizure discharge induced by 15 mgm./kg. metrazol: A, nucleus centralis lateralis; B, nucleus centralis lateralis and ventralis anterior.

or any other thalamic nuclei, even when it was present regularly in the sensory or motor cortex. The ventromedial nucleus, which has reciprocal connections with the orbital cortex, closely resembled the diffusely projecting nuclei in its activity. In all cases, thalamic seizure activity was subordinate to that in the cortex, its rise and decline evidently being secondary to changes taking place at a cortical level.

Extrathalamic deep structures. In contrast to the internal capsule and basis pedunculi (fig. 7), the component nuclei of the corpus striatum did not participate markedly in metrazol seizures. An example of the slight alteration present in the globus pallidus, during a marked cortical fit, is shown in Fig. 5A. Conversely, the hippocampus showed marked seizure activity, which might consist predominantly of wave activity (fig. 5B), or of sharp spiky discharges resembling the 40–50/sec. high amplitude spikes frequently recorded in the normal animal (fig. 5C). A general feature of hippocampal seizure activity, which differed markedly from that in the thalamus, was its maintenance, often for many seconds, into the post-ictal silent period following the cessation of the cortical fit, either as rhythmic slow waves (fig. 5B) or spike-wave complexes (fig. 5C).

In the midbrain, abnormal discharge in the superior colliculus usually paralleled to some degree the fit in the visual cortex but again might continue into the post-ictal silent period, along with low-voltage discharge in the visual cortex (fig. 6A). In the mesencephalic tegmentum, a region normally characterized by fast activity, seizures could also be recorded, but here failed to block out the normal background discharge. In the instance illustrated (fig. 6B), fast activity continued, even during the height of the tonic phase of the fit, riding

along on the large potentials and giving the record a fuzzy appearance, while, with the onset of the clonic stage, high frequency discharge was as good as ever. Therefore, in these extrathalamic deep structures, seizure activity showed some independence from that in the cortex, either as persistence of discharge into the period of post-ictal cortical silence, as in the hippocampus and superior colliculus, or as failure of abnormal firing to blot out spontaneous activity, as in the tegmentum of the midbrain.

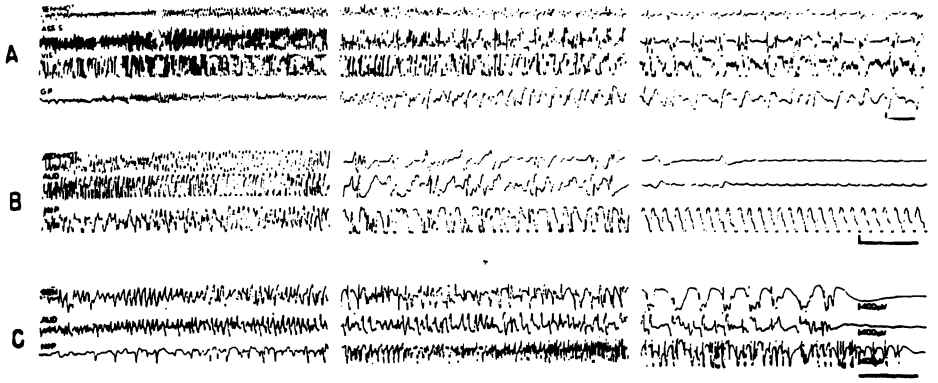

FIG. 5. Records from the cerebral cortex and extrathalamic subcortical structures, globus pallidus (A) and hippocampus (B and C), showing seizure discharge induced by 15 mgm./kg. metrazol.

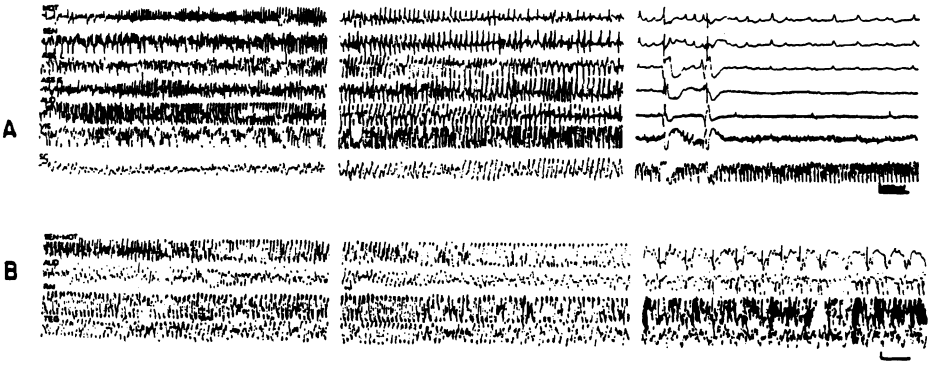

FIG. 6. Records from the cerebral cortex and extrathalamic subcortical structures, superior colliculus (A) and red nucleus and midbrain tegmentum (B), showing seizure discharge produced by 15 mgm./kg. metrazol.

II. Induced Seizures

The recent clinical usefulness of metrazol in the diagnosis and study of seizures rests upon the capacity of visual stimulation (3) or direct stimulation of the cerebral cortex (8) to induce seizure activity in patients to whom a subconvulsive dose of metrazol has been administered. The present investigation has explored the sequence of events involved in such seizure induction by auditory stimulation or by direct stimulation of the thalamus for any contribution the findings might make to the general principles of seizure inception and spread.

Seizures evoked by auditory stimulation. After a subconvulsive dose of metrazol, serially repeated click stimuli led to the development of a generalized seizure. With repetition, the potential evoked in the auditory cortex by each click gained progressively in amplitude and

complexity until it characteristically became a triphasic spike, followed by a diphasic wave (fig. 8). As Gastaut and Hunter (4) have pointed out, by disregarding deflections below the baseline, this resembles closely the classical, negative, spike-wave discharge of petit mal. The rapidity with which this response complex gained full amplitude depended upon the excitability of the preparation and the frequency of serial repetition of stimulation, rates of 2 or 3/sec. usually being effective.

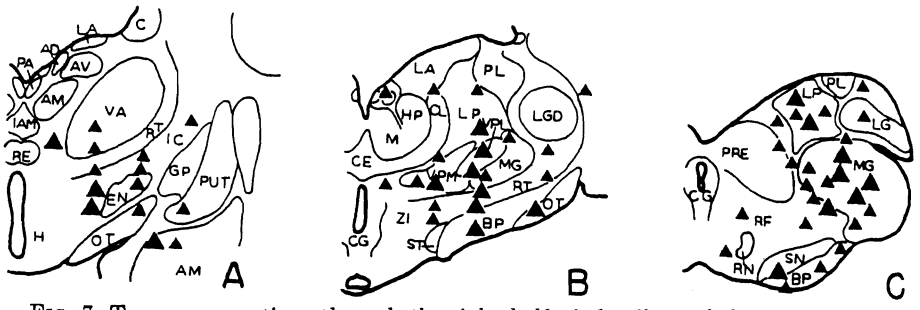

FIG. 7. Transverse sections through the right half of the diencephalon and midbrain. Triangles mark sites from which seizure discharge was recorded after convulsive doses of metrazol (15 mgm./kg.). The size of the triangle is a reflection of the intensity of the seizure.

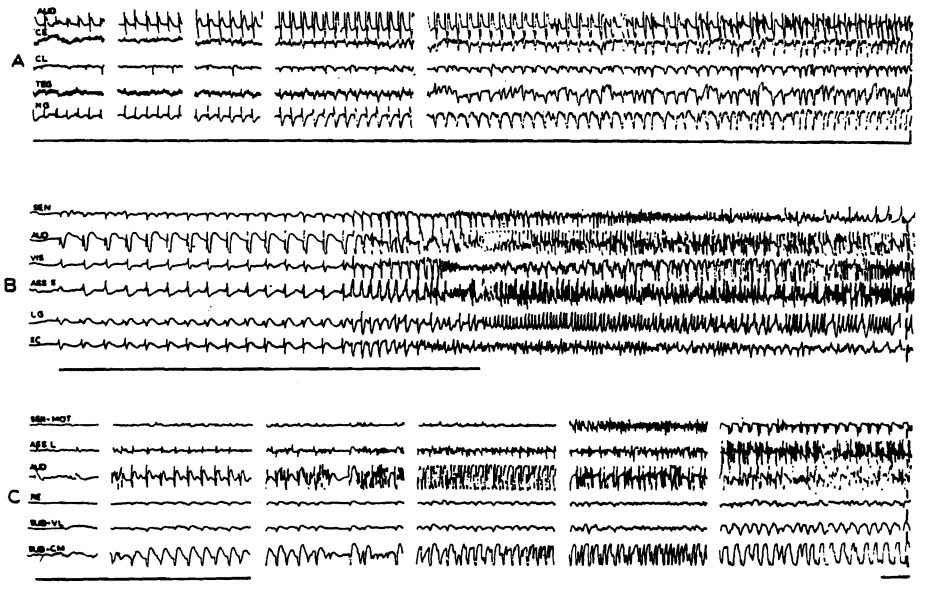

FIG. 8. Records from cortical and subcortical areas showing alteration and irradiation of evoked potentials and seizure discharge induced by repetitive click stimulation after a subconvulsive dose (8 mgm./kg.) of metrazol. The period of stimulation is marked below each record and frequency is indicated by evoked potentials in the auditory cortex.

A few seconds after the evoked spike-wave complex had reached its maximum, irregular repetitive discharge appeared upon the spikes, or in the intervals between them previously occupied by waves. This discharge rapidly gained in amplitude and constancy to become a full-fledged and self-promoting seizure running the course described above (fig. 8B). If click stimuli were delivered into the beginning of the fit, they might (fig. 8A) or might not (fig. 8B) continue to evoke auditory potentials.

Associated with the development of this response complex in the auditory receiving cortex was a spread of click-induced potentials to other cortical areas. This sometimes failed to occur, the fit either being localized to the auditory area or not involving other regions until long after. More commonly, extensive cortical spread of click-evoked potentials occurred, and the tonic seizure tended to start at about the same time over the whole cortex (fig. 8B), though the auditory area usually led slightly, and zones in which preliminary activity had developed poorly manifested commensurately small fits, as did the somatic sensory cortex in Figure 8B. In contrast to the progressive development of discharge in the auditory cortex, the serial growth of click-evoked potentials in distant cortical areas was but slight, so that seizure induction appeared to be impressed from outside them rather than to be the climax of their intrinsically developed activity. As in the auditory cortex, the seizures commenced as repetitive discharge upon and between the click-evoked potentials and, once generated, ran the typical course described above.

Subcortical participation in evoked seizures. In an attempt to study subcortical participation in the spread of evoked potentials in the cortex, the brain stem was explored during this provocation of seizures by click stimuli. Abnormal discharge of deep structures never became prominent until the spike-wave complex had developed in the auditory area, and the more widespread cortical participation became, the more ubiquitous were the subcortica

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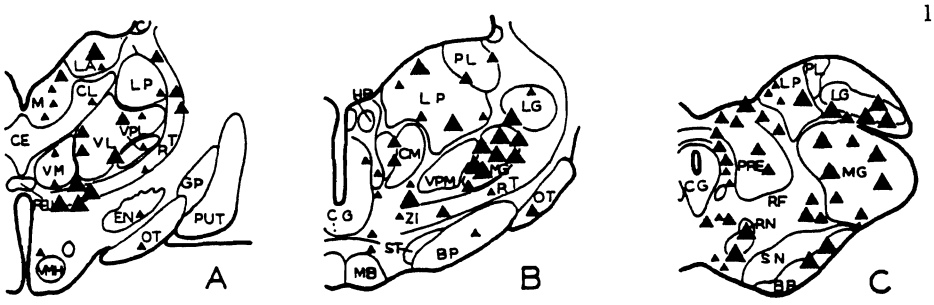

FIG. 9. Transverse sections through the right half of the diencephalon and midbrain; triangles mark the sites from which records were obtained of seizure discharge induced by repeated click stimulation after subconvulsive doses of metrazol (8 mgm./kg.). The size of the triangle is a measure of the intensity of the seizure.

effects. When alterations in electrical activity were confined to the auditory area of the cortex, subcortical effects were limited to the medial geniculate nucleus, as in Fig. 8A, where spike-wave, and later, wave changes mirrored the potential complexes evoked in the cortex. In this instance (fig. 8A), records from the medial and lateral parts of the intralaminar nuclei showed no related activity whatever during the initial period when spike-wave complexes were developing in the auditory cortex and medial geniculate nucleus. Subsequently, waves appeared with each auditory discharge, but were of smaller amplitude than those seen concurrently in the midbrain tegmentum. In the instance seen in Figure 8C, more marked irradiated potentials were recorded between the centre median and subthalamus.

When, in contrast, potentials evoked by click stimuli swept across the cortex generally, widespread effects were recorded from deep structures. An example is seen in Figure 8B, where abnormal discharge in the lateral geniculate nucleus and superior colliculus closely resembled that in the visual and adjacent association cortex. In all cases, abnormal alterations in subcortical electrical activity either developed concurrently with or followed changes in electrocortical activity, but were never primary.

The subcortical regions exhibiting such click-induced seizures are indicated in Fig. 9 by triangles, whose sizes are proportional to the intensity of discharge. The relay nuclei of the thalamus were again the most active of the functional groups, the medial and lateral genicu-

late bodies now being the most strikingly affected (fig. 9B, C), whereas previously the medial geniculate and ventralis posterior had been predominant (fig. 7). The nuclei of the diffuse thalamic projection system were not markedly involved, the centre median being the only component which participated (fig. 9B). The subthalamus and midbrain tegmentum displayed more seizure activity than before (fig. 9), as did the midbrain tectum (fig. 9C).

Seizures evoked by brain stem stimulation. Because of the marked effect of auditory stimulation in precipitating cortical seizures, direct excitation of the brain stem was tested after subconvulsive doses of metrazol. Under these conditions, 3–7/sec. stimulation of the thalamic relay nuclei was efficacious in provoking cortical seizures and, as with click stimuli, the seizures commenced in the projection cortex and commonly spread to distant areas.

In the instances shown in Figure 10, stimulation of the nucleus ventralis posterior led seriatim to progressive increment of the evoked spike in the somatic cortex, to the development of a succeeding wave complex and to the appearance of multiple discharges to each shock, which ushered in a self-propagating seizure. Early irradiation of evoked responses to

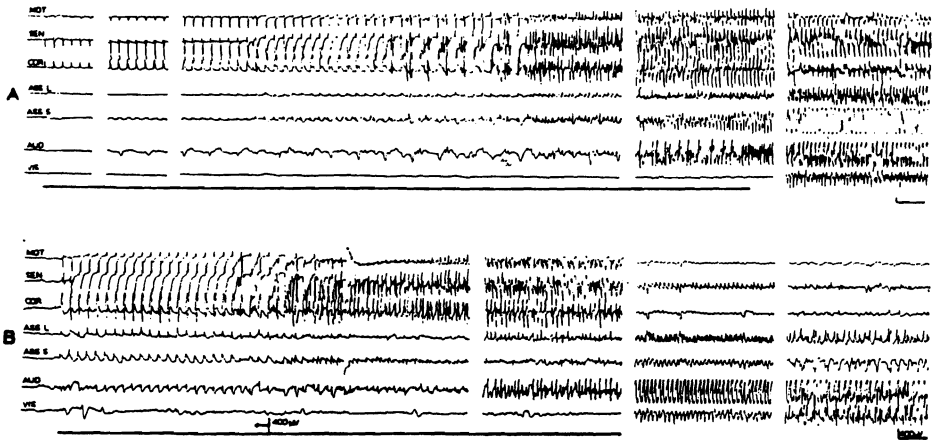

FIG. 10. Records from several areas of the cerebral cortex showing evoked potentials and seizure discharge induced by direct, low frequency stimulation of the thalamic nucleus ventralis posterior, after a subconvulsive dose of metrazol (8 mgm./kg.). The period of stimulation is marked by a line below the record and its frequency by evoked potentials in the somatic sensory cortex.

other cortical areas was similar to that seen with auditory stimuli, but the spread of the tonic seizure was more gradual, extending caudally over the cortex to involve the visual area last (fig. 10A). In the instances seen in Figure 10B, propagation of the seizure to the auditory and visual areas did not occur until abnormal discharge in the anterior part of the cortex was almost completed. Similar results were obtained on stimulating the medial or lateral geniculate bodies, but the augmentation of response and the development of a seizure occurred first in their respective cortical areas of projection. Once a seizure was induced, continued thalamic stimulation failed to evoke either local or irradiated cortical potentials (fig. 10).

Other areas of the diencephalon or midbrain were stimulated under the same conditions. Excitation of the nucleus lateralis posterior produced spikes in the middle suprasylvian cortex, but no seizure resulted. The ventralis anterior, intralaminar and centre median nuclei of the diffuse thalamic projection system were stimulated and, although recruiting responses were produced, seizures did not follow. Low frequency stimulation of the sub- or hypothalamus or of the midbrain tegmentum was similarly incapable of initiating such a cortical seizure. In each instance of negative result, control stimulation of one of the thalamic relay nuclei produced a seizure.

III. Lesions

To provide further information concerning seizures induced by auditory or thalamic stimulation after subconvulsive doses of metrazol, various structures were destroyed.

Complete destruction of the thalamus and upper midbrain except for the auditory pathway would insure that cortical propagation of seizure discharge, evoked by click stimulation, occurred in the cortex itself. After such a lesion, the evolution of an auditory-evoked seizure was essentially unchanged; progressive increment of evoked potentials, their radial migra-

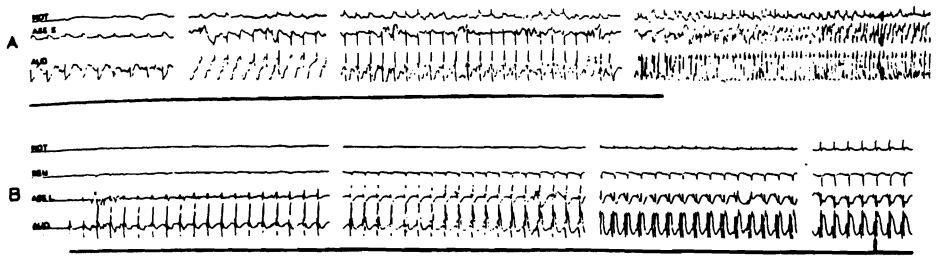

FIG. 11. Records from cortical areas after destruction of the thalamus and upper midbrain except for the ascending auditory pathway; i.e., the medial geniculate nucleus and auditory radiation to the cortex. *A*—Records showing alteration and irradiation of evoked potentials and the development of a seizure induced by repetitive click stimulation after a subconvulsive dose of metrazol (8 mgm./kg.). *B*—Records showing alteration and irradiation of potentials evoked by direct low frequency stimulation of the medial geniculate nucleus, in same animal.

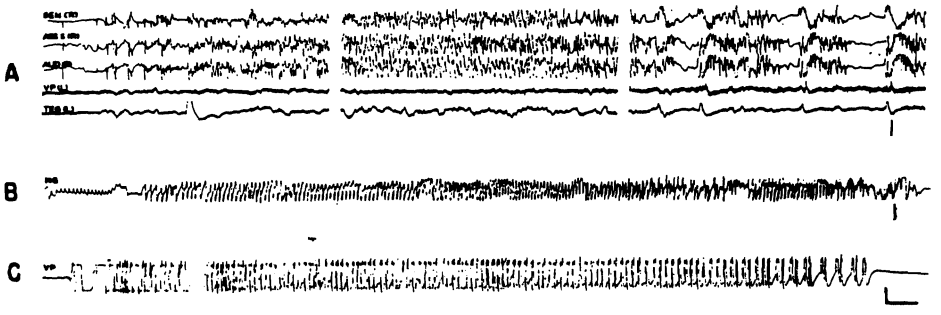

FIG. 12. *A*—Records from cortical areas, the thalamic nucleus ventralis posterior and midbrain tegmentum, after isolation of cortex from brain stem, showing seizure discharge produced by 15 mgm./kg. metrazol and limited to cerebral cortex. *B*—Record showing seizure discharge produced in thalamic medial geniculate nucleus after decortication. The dose of metrazol required was 120 mgm./kg. *C*—Record showing seizure discharge produced in thalamic nucleus ventralis posterior after decortication. The dose of metrazol required was 105 mgm./kg.

tion, and onset of the tonic seizure in the auditory cortex, with gradual involvement of more remote areas, occurred as in an intact animal (fig. 11A). Development of waves and duplication of potentials in the auditory cortex before the onset of self-sustaining discharge were also unaltered. Direct stimulation of the medial geniculate body had the same result, and the initial development of complex potentials in the auditory cortex and their irradiation to other cortical areas is seen in Figure 11B.

Bilateral extirpation of the auditory cortices, moreover, effectively prevented the appearance of evoked discharges in all other cortical regions upon click stimulation, although these regions still exhibited seizures with threshold doses of metrazol. After such cortical

ablation, click stimuli similarly failed to induce irradiated responses in the thalamus or midbrain.

Removal of the cerebellum was without significant result. Convulsive doses of metrazol caused cortical seizures as in the intact animal and, with subthreshold doses, click stimuli led to the same development and irradiation of evoked responses seen normally, and to the production of a generalized seizure.

Isolation of the cortex. The cerebral cortex was completely undercut to insure that any seizure activity occurring in it would have a cortical origin and not be attributable to the action of subcortical structures. The dose of metrazol required to provoke a cortical seizure under these circumstances was 15 mgm./kg., as in the intact cat, and the inception, rise and decline of abnormal cortical discharge was not different from before, although simultaneous records taken from the isolated thalamus revealed only the normal, fast activity of this region (fig. 12A).

Thalamic seizures. However, metrazol seizures could be produced in the thalamus deprived of its cortical connections, but the dose necessary for their production was 90–120 mgm./kg., many times that required for provoking a cortical seizure. Also, the discharge was different in nature from that observed either in the cortex or brain stem of intact animals, spikes being more prevalent and mixed with waves. In the decorticate medial geniculate body (fig. 12B), the onset of abnormal activity was sudden; only a few abnormal potentials preceded the tonic seizure, and many spikes occurred terminally. In the decorticate nucleus ventralis posterior of the thalamus (fig. 12C), the same general pattern was apparent, the sudden onset and sharp spike discharge mixed with waves being even more marked.

DISCUSSION

A comprehensive survey of experimental epilepsy by Moruzzi (13) indicates that two general features, a tendency to hypersynchrony and to repetitive high frequency firing, characterize neuronal discharge in seizures. The convulsive drug metrazol is capable of inducing both of these alterations in the activity of the nervous system and, when threshold doses are employed, it is clear both from the present experiments and from earlier ones that these alterations are primary and the seizure originates in the cerebral cortex (1).

In the present study, the electrocortical alterations commenced as sporadic discharges which, repeated at increasing frequency, gave way to continuous firing, initially composed of 10–20/sec. spikes and later of 7–11/sec. waves. After variable seizure periods, the frequency slowed still further until, with a succession of individual beats, discharge ceased abruptly and iso-electricity ensued. These findings are essentially the same as those of Goodwin, Kerr and Lawson (5) in the rabbit, in which animal the changes in electrocortical activity have been correlated with motor performance. The prodromal periods marked the initial clonic or excitatory stage. The main period of repetitive firing represented the tonic phase of the fit, while the lower frequency discharge near the end was associated again with clonic activity. Terminal post-ictal electrocortical silence was coincident with motor inactivity.

However, alterations in electrical activity in a metrazol seizure are by no means confined to the cerebral cortex. As expected, abnormal discharge was conspicuous in the long corticifugal fiber paths in the internal capsule and basis pedunculi. Although the components of the corpus striatum participated only slightly, more marked seizure activity in the subthalamus and midbrain teg-

mentum may have represented conduction in extrapyramidal corticifugal pathways descending to motor outflows. It need hardly be pointed out that at present only the vaguest sort of information exists as to how the motor manifestations of a seizure are managed by the nervous system (6).

However, subcortical participation in the fit was by no means limited to motor structures. Seizure activity was prominent in the thalamus, the sensory relay nuclei of which were most prominently affected and mirrored most closely the fit in their respective cortical projection areas. Other thalamic nuclei with specific relations to the cortex—as the ventralis lateralis and lateralis posterior—were next most conspicuously involved. Although the ventromedial thalamic nucleus has specific projections to the orbital cortex, its discharge differed from the rest and resembled that of the nuclei of the diffuse thalamic projection system.

In these diffusely projecting nuclei—the centre median, intralaminar, and ventralis anterior—abnormal potentials were late in appearing, were invariably wave-like and often exhibited waxing and waning of amplitude, unrelated to seizure discharges elsewhere, giving the activity the appearance of giant spindle bursts. Because of the correlation of such activity with loss of wakefulness (10), it is of interest to speculate upon the possibility that the appearance of such activity in the thalamic diffuse projection system may be associated with loss of consciousness in seizures. Because these thalamic nuclei have been implicated in the spike-wave discharge of petit mal (7), it is of interest to note that the spike-wave discharge exhibited by the sensory and motor cortex, in the intermediate portion of the metrazol seizure, was never associated with such activity in these or any other subcortical structures.

Participation in the metrazol seizure of each of the subcortical structures so far discussed was definitely secondary to events in the cerebral cortex. Seizure activity in the thalamus did not appear until the fit was established in the cortex and, in instances when the cortical fit was circumscribed, was present only in related thalamic nuclei. Similarly, seizure activity in the thalamus or basal ganglia did not outlast that in the cortex, but ended with the post-ictal cortical silence. Furthermore, in preparations in which the cortex and thalamus were isolated from one another, a threshold dose of metrazol induced a fairly typical fit in the cortex while thalamic activity was unaltered. These findings indicate that with threshold doses of metrazol, seizure discharge in subcortical structures depends principally upon corticifugal conduction, neither corticipetal transmission nor loop circuit activity between deep and cortical levels being essentially involved. In this respect, thalamic seizure discharge in these experiments resembled that encountered by Winokur, Trufant, King and O'Leary (15) during cortical paroxysms, spreading in front of a wave of spreading depression in the rabbit, and depending also upon corticothalamic linkages.

Two subcortical regions—the hippocampus and the superior colliculus—differed from others in the respect that seizure discharge in them continued for varying periods after the cortical fit had ceased. Except for the obvious indication that they thus possess independent capacities for displaying seizure activity, the significance of this observation is not apparent, though each of these regions

is structurally a primitive cortex. It should be pointed out that while the organizational features of a cortex appear to favor the capacity of a neural structure to display seizures, they are not essential, for, with greater concentrations of metrazol, seizures could be produced in the decorticate thalamus.

A second aspect of this study has been concerned with the capacity of serially repeated afferent stimuli to induce a cortical seizure after subconvulsive doses of metrazol. The prodromal features of such seizure induction consist of the progressive development of a complex spike-wave response in the receiving region of the cortex and of irradiation of evoked potentials to other cortical areas. Gastaut and Hunter (4) have recently analyzed such irradiation of the visual response with metrazol, and have found it to be abolished after ablating the cortical visual area but still present after circumscribing this region from the rest of the cortex. Irradiated responses were also recorded in the diffusely projecting and other nuclei of the thalamus, and intrathalamic injection of metrazol was some times sufficient, by itself, to lead to response irradiation. Gastaut and Hunter conclude that the irradiated photic response is elaborated in the diffuse projection system of the thalamus and is initiated there by impulses from visual pathways, an essential component being relayed from the visual cortex (4).

In the present study, response irradiation and seizure induction with auditory or somatic stimuli occurred exactly as with visual stimulation and could be abolished by ablating the respective receiving areas of the cortex as Gastaut and Hunter showed (4). In the present experiments generalized cortical irradiation of the auditory response could still be demonstrated after destruction of all of the thalamus except the medial geniculate body. Upon recording from the intact thalamus during repetitive auditory stimulation, the development of a spike-wave complex in the medial geniculate nucleus closely paralleled that in the auditory cortex, while the centre median was the only component of the diffuse projection system to display early and prominent irradiated potentials*. Upon direct repetitive stimulation of thalamic nuclei, response irradiation and seizures were readily induced in the cortex by excitation of the thalamic sensory relay nuclei—the medial geniculate or ventralis posterior—while excitation of the nuclei of the diffuse projection system led only to the usual recruiting responses and failed to provoke seizures. These findings do not provide support for the view that the diffuse thalamic projection system plays a prominent role in the formation of local or irradiated spike-wave responses or in seizure induction under metrazol. They emphasize instead the importance of afferent volleys conducted to the cortex by the specifically projecting sensory relay nuclei of the thalamus, and of intrinsically cortical events in such seizure induction.

SUMMARY

An electroencephalographic study has been made of both cortical and subcortical activity occurring in the brain of the cat during seizures produced by

* Further study is needed to explore the relationship of such "irradiated responses" to collateral potentials normally evoked in this part of the thalamus by afferent stimulation (14).

convulsive doses of metrazol and by auditory stimuli or direct stimulation of thalamic nuclei in the presence of subthreshold doses. The effect upon this activity of various lesions was also observed.

The seizure induced by threshold doses of metrazol appeared, by every test, to be primary in the cerebral cortex and to radiate from it to deep structures. Prominent activity in the internal capsule, basis pedunculi, subthalamus and midbrain tegmentum appeared to represent discharge descending to motor outflows. The basal ganglia did not display conspicuous seizure activity. The thalamus was prominently involved, its sensory relay nuclei exhibiting the most marked seizure discharge, paralleling that in related cortical areas. Associational thalamic nuclei were next most affected. The nuclei of the diffuse thalamic projection system were implicated later than their neighbors and manifested a markedly different type of activity, resembling giant spindle bursts. The possibility is suggested that this may be associated with loss of consciousness in seizures.

With subconvulsive doses of metrazol, repetitive afferent stimulation led to development of a complex evoked potential in the receiving cortex, to its irradiation to other cortical area and, finally, to seizure induction. This series of events could still be provoked after destruction of the thalamus, except for the relay nucleus of the sensory pathway involved. It could be reproduced by direct stimulation of the thalamic sensory relay nuclei, but not the nuclei of the diffuse thalamic projection system. It was abolished by ablating the sensory receiving area of the cortex. The ascending sensory pathway and the cerebral cortex itself seem to be the only structures essentially involved in such seizure induction.

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