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ANALYSIS OF EXTRACELLULAR FIRING PATTERNS OF DEEP TEMPORAL LOBE STRUCTURES IN MAN[1]

T. L. BABB, E. CARR AND P. H. CRANDALL

Division of Neurological Surgery, UCLA Center for the Health Sciences, Los Angeles, Calif. 90024 (U.S.A.)

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A number of studies have reported recording extracellular action potentials from humans in an attempt to characterize the activity of certain thalamic nuclei (Albe-Fessard *et al.* 1963; Jasper and Bertrand 1966) or of epileptogenic tissue (Ward and Schmidt 1961; Rayport and Waller 1967; Verzeano *et al.* 1971). For example, Ward (1969) has reported that high frequency burst patterns are characteristic of neuronal activity in human epileptogenic cortex even during inter-ictal periods. Verzeano *et al.* (1971) have reported changes in amygdala neuronal activity minutes prior to a clinical seizure. Such findings support the idea that analysis of neuronal activity may provide useful diagnostic information such as the location of abnormal nervous tissue, as well as provide basic knowledge about the functional anatomy of the human brain.

The micro-electrode techniques employed in human recordings have traditionally been acute procedures limited to the operating room (Ward and Schmidt 1961; Albe-Fessard *et al.* 1963; Rayport and Waller 1967; Goldring and Ratcheson 1972) or to a single depth penetration in a sterile environment (Verzeano *et al.* 1971). Chronically implanted devices have involved flexible wires (Marg *et al.* 1970), or movable stiff wires (Heuser *et al.* 1969) which are repositioned to sample new neurons at each session.

Chronic recordings of single neuron activity have been achieved in animals for many years (Strumwasser 1958). This flexible, fine-wire bundle technique has been ably described and the quality of the recordings demonstrated (Harper and McGinty 1972). We have modified this technique for surgical implantation in 8 patients with recording electrodes bilaterally placed in temporal lobe structures for the electrographic identification of epileptogenic foci.

At the Brain Research Institute and Neuropsychiatric Institute at UCLA, we have used arrays of macro-electrodes distributed through the limbic system structures medial to the temporal lobe for depth EEG analysis of patients with uncontrolled psychomotor epilepsy scheduled for therapeutic surgery. The safety of blunt-tipped, bipolar macro-electrodes (0.5 mm diameter) has been demonstrated from clinical evaluations and histological verification in anterior temporal lobe resections which were used as the mode of definitive surgical treatment following localization of the seizure focus in more than 40 patients since 1961. These coaxial macro-electrodes were modified to permit the stainless-steel tubing to be used as a conduit for micro-electrodes. Two advantages were achieved. The macro-electrodes provided rigidity and X-ray verification relative to the anatomical target. The fine, flexible micro-electrodes provided greater safety as it is highly unlikely that any blood vessel of significant size can be torn in the vicinity of the target.

Stable extracellular recordings from the same single neuron appear to have been maintained for several days. Neuronal discharges were recorded for over a period of 3 weeks postoperatively in order that the analysis of unit activity may provide information important to the patient's diagnosis. This report will detail the micro-electrode technique used and an analysis

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of firing patterns of "normal" neurons in deep temporal lobe structures *contralateral* to the identified side of primary pathology.

METHOD

The stereotaxic technique for electrode implantation into the human temporal lobe structures has been previously described (Crandall *et al.* 1963). Fig. 1 shows a composite drawing of the components of the micro-electrode insertion technique. A stainless-steel cannula, which serves as an EEG macro-electrode, is used as a conduit for the introduction of a bundle of 7 fine wires. After the cannula is implanted into the desired structure and locked to a skull screw guide (*A*), the stylet is removed. The seven fine wires are then cut bluntly to a length 5 mm beyond the implanted end of the cannula and dipped in sterile water so that all wires adhere to each other in a single strand. This strand is then threaded into the cannula by laying its tip on the trough of the cannula mouth (*B*) and pushing it down the cannula and into the brain. The wires are affixed to the cannula and hermetically sealed by a delrin[1] cap (*C*) and acrylic cement.

X-rays indicated that, by using this technique, all the wires remained together in a bundle and did not diverge from one another when entering the brain (Fig. 1, *D*). This probably results in more trauma near the recording tips than if each wire spreads out from the bundle to its own neuronal territory. The wires will enter the brain in non-parallel paths (Fig. 1, *E*) if, after cutting, the ends are bent approximately 45°. A short pre-threaded tube (3 mm of PE number 10) may be brought down over the bent ends to bring them together for insertion into the mouth of the implanted cannula (Fig. 1, *F*). The construction of the funnel-shaped delrin mouth of the cannula (Fig. 1, *G*) eliminates the sharp edges of the cannula which may damage the insulation on the wires as they pass into the cannula. An X-ray (Fig. 2) shows the final location of the fine wires, which "spray" out from the cannula end. To date, our findings using the two different insertion techniques indicate that the less traumatic "spray" insertion results in successful unit recordings on *more* micro-electrodes and for longer periods than when the wires remain in a bundle. Also, the wider spatial distribution of tip ends has resulted in more successful recordings from non-nuclear structures such as Ammon's horn or the hippocampal gyrus. It should be noted that the fine wires were calculated to extend no more than 5 mm in any radial direction from the cannula end. The placement of the cannulas in the desired structures is known to be as accurate as is possible from radiological measurements at the time of implantation. In a previous study of 13 anterior temporal lobectomy specimens done in serial sections, 88% of the 51 placements localized radiographically were verified histologically (Crandall 1973).

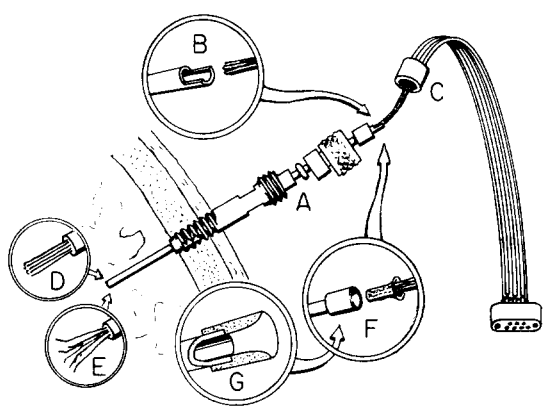

Fig. 1. Components for the micro-electrode implantation, showing insertion techniques. Bundle insertion (*B*) results in wires implanted as in *D*. Spray insertion (*F*) results in wires implanted as in *E*. Components: *A*: Skull screw guide and lock-fitting cap. *B*: trough mouth of implanted cannula. *C*: Delrin friction-fitting cap. *D*: Implanted bundle of fine wires. *E*: Implanted spray of fine wires. *F*: Delrin funnel mouth on implanted cannula. *G*: Cut-away view of *F*.

[1] E. I. Dupont de Nemours and Company.

Only certain pure metals (*e.g.*, tungsten) and alloys (*e.g.*, Pt 79%–Rh 15%–Ru 6%) are recommended for use as a chronic micro-electrode. These metals have a high elastic modulus and retain the stiffness to penetrate the brain when drawn into a small caliber wire. Nevertheless, when implanted, such wires are flexible enough to move with the brain movements. These wires may be obtained in diameters small enough (30–62.5 μ) that, when cut perpendicular to the axis of the wire, the tip exposure is small enough to detect large extracellular discharges. Fig. 3, *A*

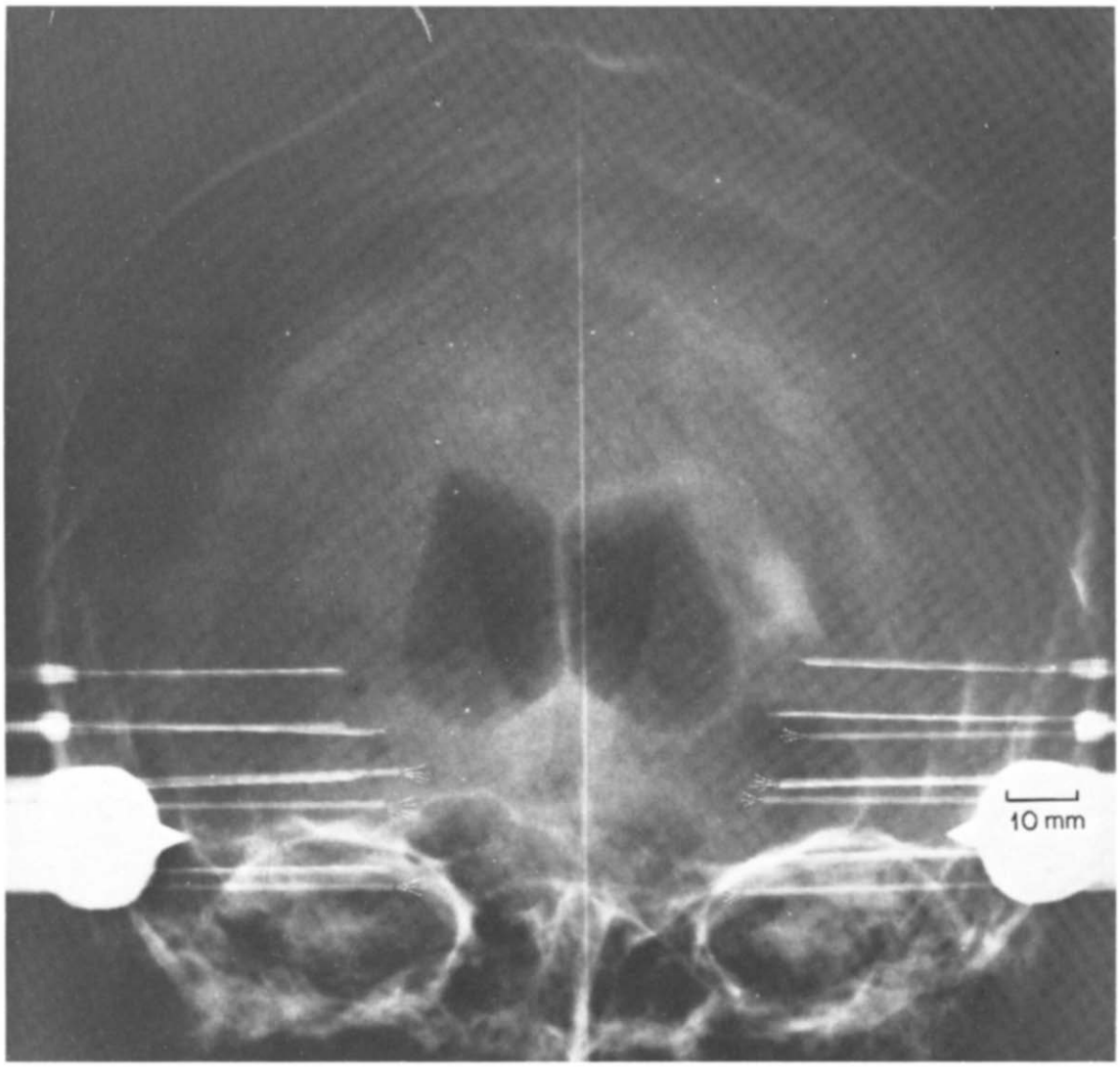

Fig. 2. A–P X-ray showing the locations of "sprays" of seven fine wires bilaterally placed, from top to bottom, in Ammon's horn (not seen in patient's right side), hippocampal gyrus, and approximately 3 cm anterior in amygdala and uncus. The fine wires, clearly visible in the negative, have been retouched for photographic reproduction.

is a view of the exposed ends of three Pt 79%–Rh 15%–Ru 6% wires with cross-sectional cuts made by sharp scissors. The tip exposure is greatly increased if the wire is cut at an angle or cut with blunt scissors (Fig. 3, *B*). Such improper cutting will lower the impedance at the tip of the electrode and result in inferior recording properties. Typically, fine wire impedances in brain tissue range between 100 and 300 kΩ but after a slanted cut may drop below 60 kΩ, an impedance we have found to be generally too low for detection of spikes with a signal-to-noise ratio greater than 2.

Recordings were taken by passing signals from the fine wires through battery-powered source followers (input impedances approximately 60 MΩ) and into Grass 7P511 differential amplifiers which were referred to the outer table of the vertex. The signals, with half-amplitude frequencies 1 c/sec and 10 kc/sec, were stored on an oscillograph (bandpass 1–90 c/sec) and on direct-recording magnetic tape (bandpass

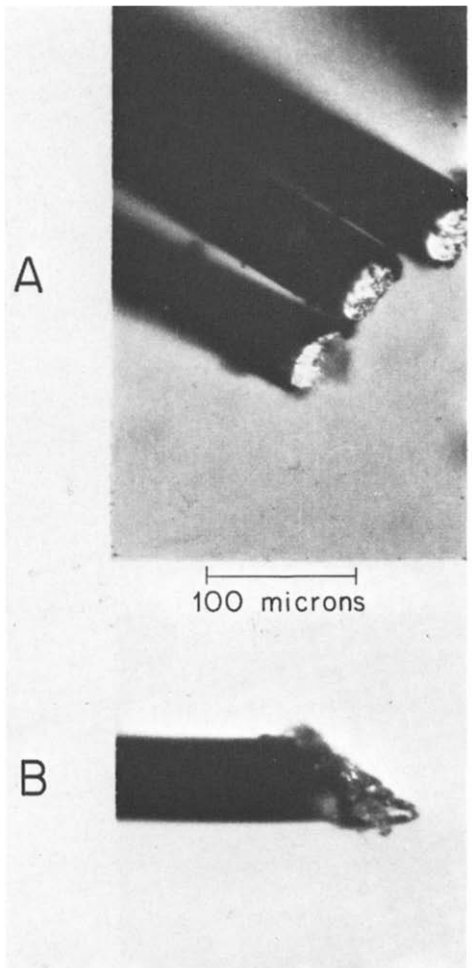

Fig. 3. Photomicrographs of the tips of fine wires showing different tip configurations and exposures after cutting with sharp (*A*) or dull (*B*) scissors.

50 c/sec–10 kc/sec). On many occasions, high-speed FM tape recordings were made in order to preserve low frequency field potentials (band-pass 0–2.5 kc/sec).

The neuronal activity was monitored on an oscilloscope throughout the recording sessions and facts such as movement artifacts or the alertness of the patient were noted on the voice track of the tape recorder. Off-line computation of firing rates and interval histograms were performed on a PDP-12 digital computer using a program which permitted separation of spikes of similar amplitude from smaller amplitude (multi-unit) activity (Wyss and Handwerker 1971). The spike wave forms shown in Fig. 4 and 6 were plotted after the analog signals from the tape recorder were digitized every 50 μsec and stored on the PDP-12 magnetic disk. Due to the incremental plotter, steps can be seen on the rising and falling phases of certain wave forms.

RESULTS

Spontaneous activity

The spike amplitudes recorded from the fine wires do not generally exceed 300 μV, are usually electrically negative and monophasic with a small after-positivity. These characteristics indicate that the wires are probably detecting action potentials from the soma, rather than fiber action potentials (Amassian 1961). In some cases, initially positive, continuous multiple spikes have been recorded which were predominantly biphasic and small in amplitude, usually less than 60 μV. These spikes were probably recorded from white matter (Amassian 1961).

Extracellular spikes have been recorded for several hours from neurons in the amygdala (N = 32), uncus (N = 32), Ammon's horn (N = 17) and hippocampal gyrus (N = 22). Fig. 4 shows firing patterns typical of each structure. These data are presented as an approximation of "normal" spontaneous discharge of neurons in the human rhinencephalon. They represent periods of inter-ictal spontaneous activity (*i.e.*, activity in the absence of intentional stimulation or movements) and have been selected from the electrographically determined non-pathological side of 5 patients who were in bed, relaxed but fully awake. All the data computed and presented here were collected within the first 6 days post-operatively, before any seizures had occurred, and while the patients were on full anti-convulsant medication. At these times, no typical epileptiform waves were recorded from "normal" sides and few occurred on the focal sides. Nevertheless, inter-hemispheric influences through the anterior commissure and psalterium may be important enough for projection of "pathological" firing patterns from neurons in the focal side to contralateral structures. However, inter-hemispheric influences are probably less important than synaptic input from ipsilateral structures, as indicated by failure to find contralateral responses to electrical stimulation of

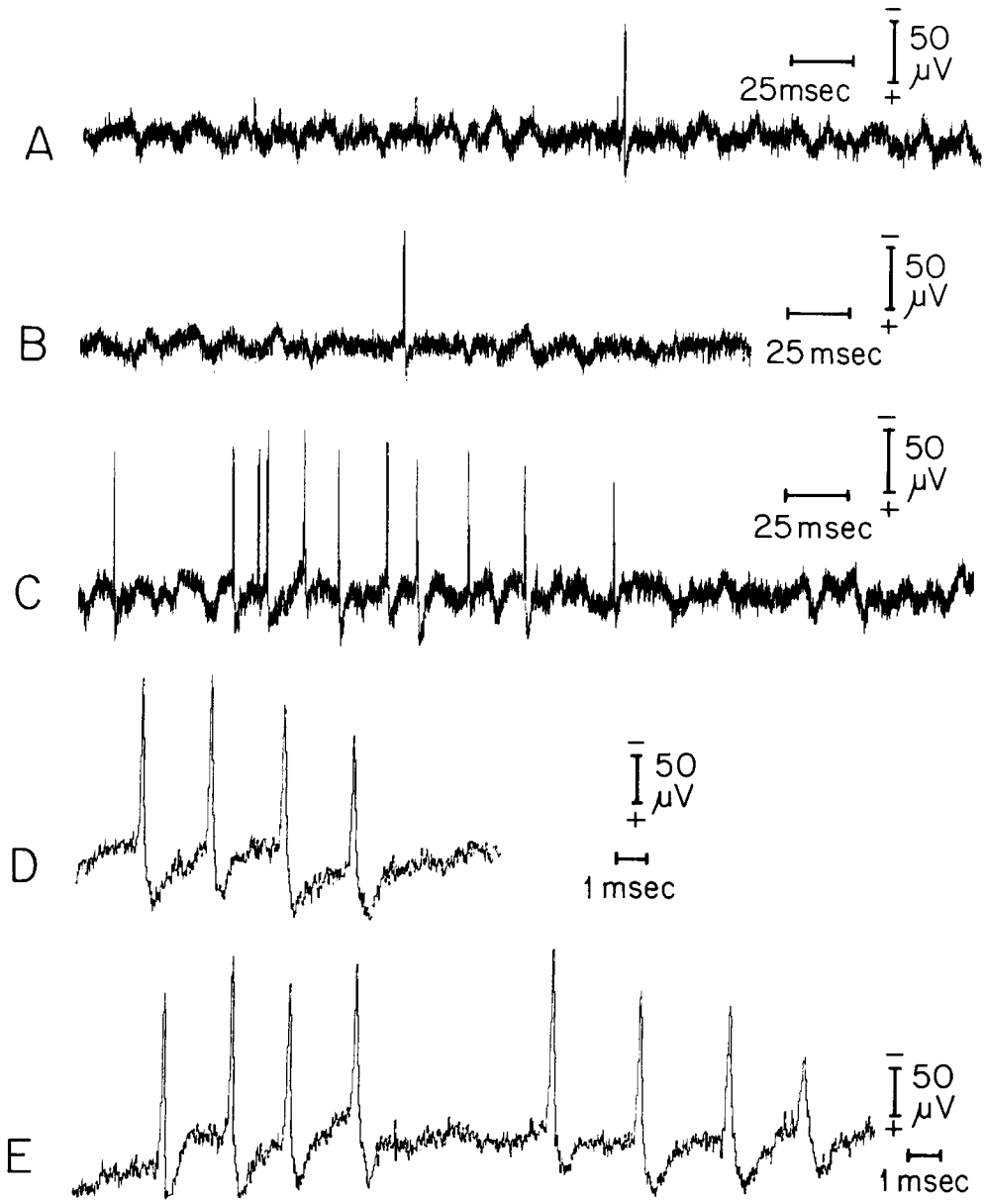

Fig. 4. Recordings from awake patients. Single neuron discharge patterns typical of amygdala (*A*), uncus (*B*) and hippocampal gyrus (*C*). Burst patterns commonly found in neurons of Ammon's horn are shown in *D* and *E*. Note the decreasing spike amplitudes in *D* and at the end of the strip in *E*. Recording band-pass 50 c/sec–10 kc/sec. Due to this high pass filtering the true spike wave form is slightly differentiated.

either Ammon's horn or amygdala while ipsilateral responses between the two structures were commonly found (Brazier 1973). It is not known to what extent the neuronal activity may have been affected by the anticonvulsant medication taken by the patients.

Neurons in the amygdala predominantly fired with a single discharge, sometimes two, but rarely in a burst pattern of multiple spikes. The rate of discharge was low (median rate 15.8/min, N = 15) and inter-spike intervals were usually long (see Fig. 5, *A*). In these histograms

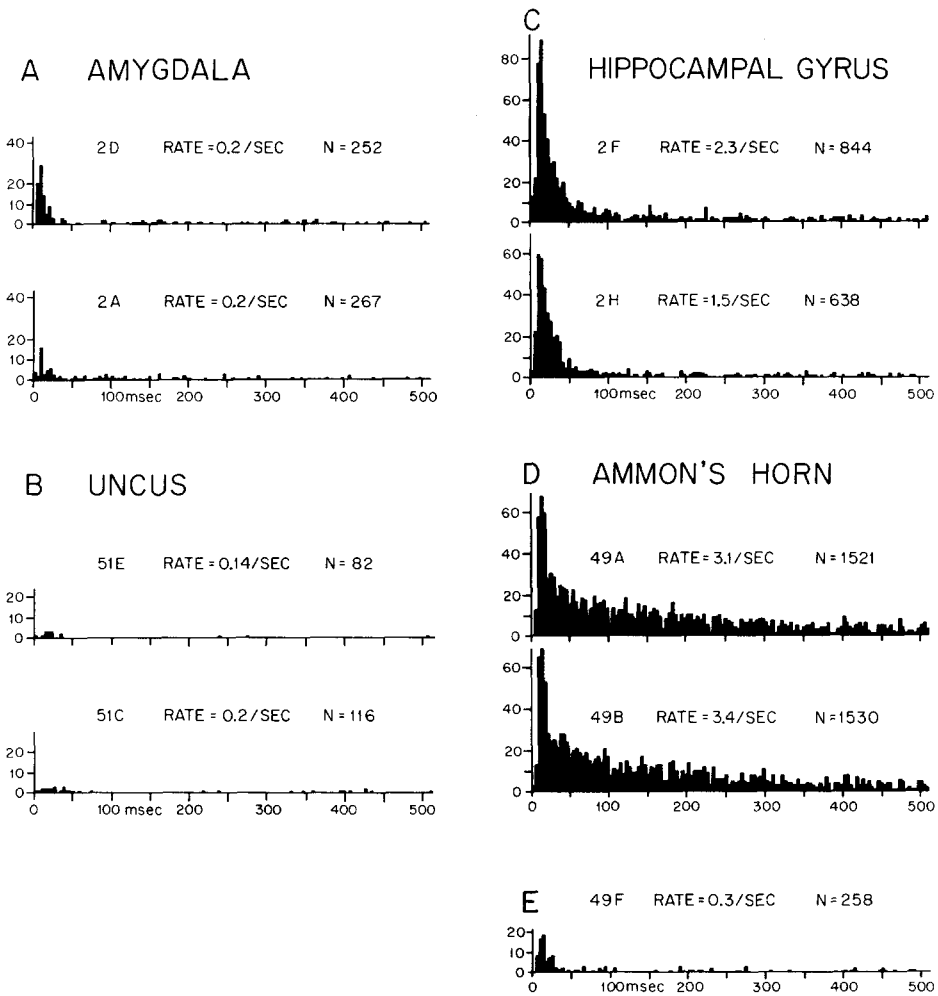

Fig. 5. Inter-spike interval histograms for two different single neurons in each structure characterizing firing patterns typical of amygdala (*A*), uncus (*B*), hippocampal gyrus (*C*) and Ammon's horn (*D*). A pattern atypical for Ammon's horn neurons is shown in the interval histogram of *E*. The intervals between successive spikes were plotted on the abscissa and their recurrences were added to the ordinate. The resolution or bin width in each histogram is 4 msec. The longest interval plotted in the histograms is 512 msec; however, all intervals in the sample period, no matter how long, were counted and are represented as N. The average firing rate for the sample period is given as the Rate.

over half the intervals were longer than 512 msec and are not shown in the histogram. Similar firing patterns were observed for neurons in the uncus, except that the firing rates were much lower (median rate 5.8/min, N = 7). Fig. 5, *B* indicates how disorganized and infrequent were the firing patterns of uncal neurons.

Contrary to the uncus, neurons in the hippocampal gyrus commonly fired in bursts of repetitive discharge (see Fig. 4, *C*). Rates of firing were generally higher (median rate 136.2/min, N = 7). This pattern is clearly indicated by the predominance of short intervals around a modal interval of 16 msec (Fig. 5, *C*).

Neurons in Ammon's horn also fired in a burst pattern, but their activity could usually be distinguished from the bursts of gyral neurons due to the fact that certain bursts from Ammon's horn neurons were characterized by repetitive spikes of markedly decreasing amplitude (Fig. 4, *D*). Intracellular recordings from cat pyramidal cells during similar bursts indicate that

the amplitudes of succeeding spikes decrease due to depolarizing after-potentials which may build up to produce an effective cathodal block terminating the burst (Kandel and Spencer 1961). Long inter-burst intervals, then, would probably be found following bursts ending with a small spike. Fig. 4, *E* shows a four-spike burst without decreasing amplitudes. A *short* inter-burst interval followed this burst and lead to another burst with decreasing spike amplitudes,

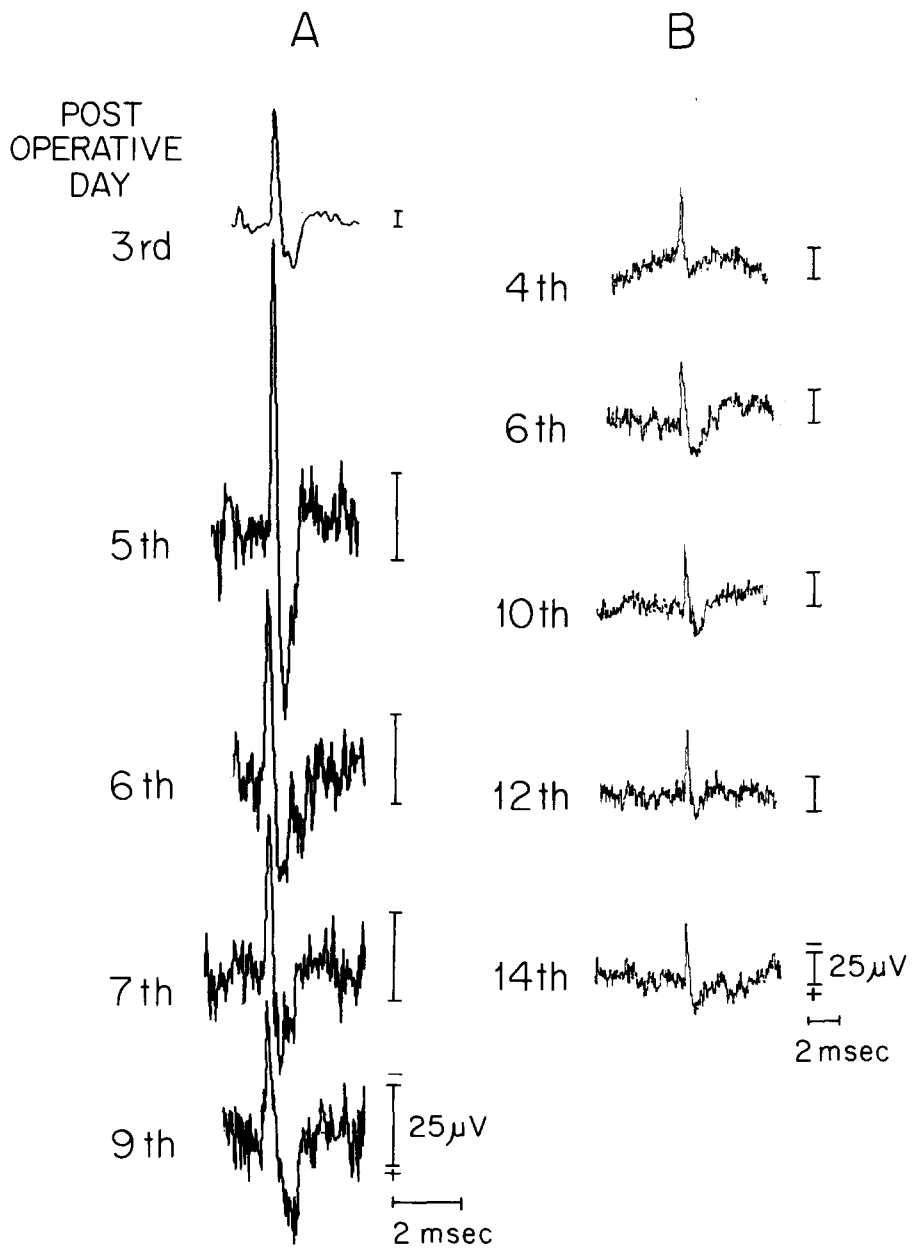

Fig. 6. Post-operative recordings of extracellular spikes from the same amygdala micro-electrode (*A*) and uncal micro-electrode (*B*). Note the wave form and amplitude changes in *A*; only the wave forms of 6th and 7th can be considered similar. These alterations were probably due to electrode displacement because some wave form changes were associated with amplitude changes. In *B*, amplitude loss did not occur for 10 days. The micro-electrode used in *B* was constructed of noble metals and tissue reaction may have been less than that for *A*, which was recorded with a Ni–Cr–Fe alloy.

which was followed by a *long* inter-burst interval. It should be noted that the last spikes in gyral bursts were often smaller than the first ones (*e.g.*, Fig. 4, *C*); however, the difference between first and last spikes was never as great as occasionally observed in bursts from Ammon's horn neurons, where the last spike may be only 25% of the first spike (*e.g.*, the second burst of Fig. 4, *E*). Burst patterns and high rates of firing (median rate 186.0/min, N = 11) are indicated in Fig. 5, *D*. However, isolated single discharges occurred in all Ammon's horn neurons, and one neuron was found to fire slowly (19.4/min), very similarly to amygdala neuron activity (see Fig. 5, *E*).

Chronic recordings

Recordings from a single neuron were easily maintained for several hours despite procedures which might acutely change intracranial pressure or cause brain movement, *e.g.*, seizure movements, postural adjustments and hyperventilation. This fact can likely be explained by the relative flexibility of the fine wires, since under similar conditions a rigid micro-electrode will usually lose contact with the cell.

Recordings from the same neuron for several days may be possible, although to do so would be fortuitous, and unequivocal verification would be impossible without constant monitoring of each discharge over the days. Fig. 6, *A* shows a chronic recording from a micro-electrode which is possibly detecting the same neuron's discharge on subsequent days. The firing rate did not vary by more than 50% from day to day. However, note that the amplitude decreased over days, possibly due to tissue reaction near the recording tip. Since the wave form also changed, this transition is probably due to gradual movement between the neuron and the wire. Another chronic recording (Fig. 6, *B*) did not show a gradual decrease in amplitude over the days, possibly due to less tissue reaction to the Pt 79%–Rh 15%–Ru 6% tip than present with the Ni 61%–Cr 15%–Fe 24% tip used to obtain the recordings in Fig. 6, *A*. It was also noted that some electrodes which initially did not record unit activity would, days or weeks later, detect large action potentials. This clearly indicated movement of the wires closer to neurons. However, electrode displacement was not a problem. It was more common for an electrode to detect neuronal activity for weeks than it was for activity to disappear or for activity to appear on an electrode which had previously detected no activity.

DISCUSSION

Extracellular recordings from flexible micro-electrodes chronically implanted along the rhinencephalon have provided the first extensive studies of the spontaneous activity patterns of neurons in limbic structures of man. It has been proposed that analysis of spontaneous firing patterns may help to make deductions about inputs to certain structures as well as indicate characteristic properties of neurons and their interconnections (Moore *et al.* 1966). In general, spontaneous activity patterns of neurons in the rhinencephalon of man are similar to extracellular discharge patterns recorded from homologous structures in lower animals. This suggests that despite some morphological changes in man, the basic input systems and output transfer functions of each structure may have remained phyletically similar.

Neurons in both the amygdala and the uncus tended to fire slowly, usually with isolated discharges. Similar low rates have been recorded in the cat amygdala using chronic (O'Keefe and Bouma 1969; Jacobs and McGinty 1971) and acute micro-electrodes (Creutzfeldt *et al.* 1963). Creutzfeldt *et al.* (1963) also reported a resting discharge rate of 1–5/sec for units in periamygdaloid areas which are homologous with the uncus in man. However, spontaneous rates of firing for different amygdala neurons in the cat have been reported to range from 1 to 50/sec (Machne and Segundo 1956) or between 4 and 15 spikes/sec (Ben-Ari and Le Gal La Salle 1971). These studies were designed to investigate evoked unit activity and perhaps for this reason neurons were selected on the basis of a reliable baseline firing rate. Immovable micro-electrodes (O'Keefe and Bouma 1969; Jacobs and McGinty 1971) would be less susceptible to such a bias. Nevertheless, the fact that we have not as yet found fast firing amygdala or uncal neurons in man may be related to the decreased role of olfaction in man. Alternately, regional differences

within the amygdala complex may account for differences in firing rate. For example, Rayport (1968) has reported recording slow and fast firing, including burst patterns, from "... the lower third of the "surgical" nucleus" (Rayport 1968, p. 304) of the amygdala. Perhaps our micro-electrodes have not been in this area, and our sample is too small to draw any final conclusion about such a heterogenous structure as the amygdala. It is tempting to speculate that our electrodes were repeatedly put in regions of the amygdala which have a closer functional relationship with the basal ganglia than with the hippocampus. Slow firing rates have been reported for certain neurons in the caudate nucleus (Purpura and Malliani 1967) and globus pallidus (Noda *et al.* 1968) of the cat. Close structural relations between amygdala and the basal ganglia (Gloor 1955; Adey and Dunlop 1960; Nauta 1961; Russell *et al.* 1968; Hall 1972) have led anatomists to classify the amygdaloid complex of man together with these deep extrapyramidal nuclei (Crosby *et al.* 1962; Ford and Schadé 1971).

Neurons in the parahippocampal gyrus of the cat commonly fire in burst patterns of relatively high rates (Coyle 1970). These patterns are somewhat similar to the rate and pattern of discharge of hippocampal pyramidal neurons (Noda *et al.* 1969). Of special interest is the finding in the hippocampus of man of neurons which burst with decreasing spike amplitudes (see Fig. 4, *D* and *E*). This behavior has been noted as a special property of pyramidal neurons in the hippocampus of the rabbit (Von Euler and Green 1960) and cat (Kandel and Spencer 1961). This finding, then, is another indication that the known synaptic organization of the hippocampus of lower mammals may be applied to man.

A second generality from these results is the finding of a dichotomy of firing patterns in anterior (amygdala, uncus) *versus* posterior (hippocampal gyrus and Ammon's horn) structures. This striking result supports an anatomical model of relatively distinct synaptic input systems. A model of functionally different anterior and posterior rhinencephalic systems has been proposed on the basis of anatomico-physiologic data from animals (Pribam and Kruger 1954). Brazier (1964) has reported that, in man, sensory-evoked potentials may be recorded from along the hippocampal axes but not from the amygdala. This finding agrees with our conclusion, based on analysis of spontaneous neuronal discharge, that hippocampal and amygdala sectors probably have discontinuous synaptic inputs. In the present series of patients, our micro-electrodes have consistently been placed in the middle hippocampal gyrus and Ammon's horn. It will be interesting to note whether this dichotomy persists when the micro-electrodes are placed more anteriorly, near the uncal extremity of the hippocampus, where McLardy (1963) has shown that CA3 pyramids of the hippocampus are continuous with the amygdaloid complex.

SUMMARY

The spontaneous activity of "normal" neurons in four different limbic structures of man has been recorded from flexible micro-electrodes in the unaffected side of psychomotor epileptics who were bilaterally implanted for diagnostic EEG analysis. Neurons in amygdala and uncus fired slowly, usually with isolated discharges. Neurons in middle hippocampal gyrus and Ammon's horn fired faster and with burst patterns. These different neuronal output patterns indicated an anatomical arrangement of separate input systems and different synaptic organizations for anterior *versus* posterior limbic structures in man. These patterns were so similar to those recorded from homologous structures in lower mammals that is was suggested that the synaptic organizations of each limbic structure in man evolved with few functional changes. Using flexible micro-electrodes, extracellular action potentials from single neurons were easily maintained for several hours, despite movements, and may be maintained for over 3 weeks post-operatively. It is suggested that recording from the same neuron from day to day is possible.

RESUME

ANALYSE DES PATTERNS DE DECHARGES EXTRACELLULAIRES DES STRUCTURES PROFONDES DU LOBE TEMPORAL CHEZ L'HOMME

L'activité spontanée de neurones "normaux" de quatre structures limbiques différentes a été enregistrée du côté sain chez des malades atteints d'épilepsie psychomotrice et porteurs de micro-électrodes flexibles bilatérales implantées à fin d'analyse EEG diagnostique. Les neurones de l'amygdale et de l'uncus présentent une activité lente, associée habituellement à des décharges isolées. Les neurones du gyrus hippocampique médian et de la corne d'Ammon ont une activité plus rapide associée à des décharges en bouffées. Ces patterns neuroniques différents indiquent l'existence de systèmes anatomiques récepteurs distincts et d'organisations synaptiques différentes pour les structures limbiques antérieure et postérieure chez l'homme. Ces patterns sont tellement semblables à ceux qui sont enregistrés au niveau de structures homologues chez des mammifères inférieurs que l'on peut supposer que l'évolution des organisations synaptiques de chaque structure limbique chez l'homme ne subit que peu de modifications fonctionnelles. A l'aide de micro-électrodes flexibles, les enregistrements des potentiels d'action intra-cellulaires de neurones isolés peuvent être aisément poursuivis pendant plusieurs heures malgré les mouvements, et peuvent être maintenus pendant une période dépassant trois semaines après l'opération.

Les auteurs suggèrent qu'il est possible d'enregistrer le même neurone jour après jour.

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