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Selective Modification of Spontaneous ECoG Rhythms of the Cat Somesthetic Cortex by Psychoactive Drugs: Behavioral Correlates

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Abstract. Three psychoactive drugs with known central effects were administered to the freely moving cat in order to study their action on spontaneous rhythmic activities recorded from the primary somesthetic cortex, which are analogous to the rolandic mu rhyhm in man. The ECoG patterns obtained are qualitatively identical to those of the normal subject, but their temporal organization is profoundly disturbed by the action of the drugs. The normal ECoG consists of three rhythmic systems with distinct frequencies and displays a considerable time variability. In contrast, psychoactive drugs induce a stabilized pattern with only one type (or at most two types) of rhythm prevailing for one or several hours, which never occurs under normal conditions. These ECoG rhythms underlie various behavioral states. Under *d*-amphetamine, correspondence remains excellent between behavior and ECoG; under Ditran, complete dissociation occurs; finally, LSD represents a borderline case in which ECoG and behavior are partially correlated and partially dissociated.

Key words: *d*-Amphetamine – LSD-25 – Ditran – Motor behavior – Rolandic mu rhythms – Somatic area I – Quantitative ECoG – Alertness level

Among the psychoactive drugs, psychomimetic substances and *d*-amphetamine have long been known to elicit the electrocortical activities that normally underlie specific levels of alertness. Hence it was shown that after anticholinergic drugs (atropine, Ditran, etc.), cats develop sustained spindles and slow waves that last for several hours, which thereby mimick slow-sleep ECoG (Funderburk and Case, 1951; Wikler, 1952; Rinaldi and Himwich, 1955; Longo, 1956, 1966; Bradley and Elkes, 1957; Rougeul et al., 1965; Montplaisir, 1975). On the other hand, indolalkylamine-type substances, in particular LSD-25, produce abundant rhythms typical of a drowsiness ECoG (Rougeul et al., 1965, 1966, 1969; Rougeul and Verdeaux, 1972). Finally, *d*-amphetamine is usually believed to elicit strongly desynchronized cortical activity (Bradley and Elkes, 1953).

These studies (including our own on LSD) were usually performed without any particular attention to the precise location of the activities recorded. Recent studies (Bouyer et al., 1974; Rougeul-Buser et al., 1975) have shown that in the normal cat spontaneous rhythmic activities recorded from somesthetic area I (SI) consistently indicate the level of awakeness and even attentiveness. Like the rolandic 'mu' wicket rhythms recorded in human subjects (Gastaut et al., 1952, 1957; Chatrian et al., 1959), these rhythms can be observed only when the animal is immobile, and disappear with the least body movement. Since these activities proved to be spatially restricted, while at the same time underlying specific behavioral states, it was thought that reexamination of the ECoG effects of these three psychoactive drugs (the action of which is otherwise well known) was called for in order to follow quantitatively the temporal course of their effects. Our aim was also to demonstrate a possible dissociation between SI ECoG and behavior similar to that noticed with anticholinergic drugs.

MATERIALS AND METHODS

Thirty adult cats were used in these experiments. Cortical epidural electrodes were implanted in the following areas:

1. The lateral part of area SI (these electrodes were specially designed to record mu rhythms). Since the latter are often focalized within a very restricted cortical area, about 10 electrodes were implanted about 2 mm apart, permitting selection of those electrodes that displayed the maximum amplitude for mu-type rhythms during the first postoperative sessions.

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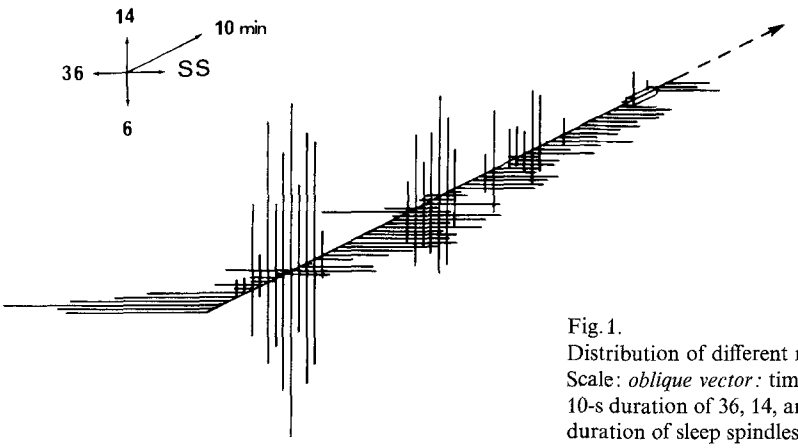

Fig. 1.
Distribution of different rhythms in normal cat during 1-h recording. Scale: *oblique vector:* time of recording = 10 min. $-x$, $+y$, $-y$ *Vectors:* 10-s duration of 36, 14, and 6 c/s rhythms respectively. $+x$ *(SS) Vector:* 10-s duration of sleep spindles (= 10 spindles)

2. The frontal area next to the midline for recording fast spindles (12–18 c/s), which are one of the typical patterns of slow sleep.

3. The visual area (these electrodes recorded the characteristic events of paradoxical REM sleep–posterior theta rhythm and ponto-geniculo-occipital PGO spikes) and the orbital zone (electrodes recorded rapid eye movements during the same REM episodes).

These implantations were carried out under general anesthesia (Nembutal 30 mg/kg i.p.) and the animal was allowed to recover for about 1 week before experimentation.

During recording sessions, the cat was placed in a large dimly lit cage that was not soundproof but was isolated from both experimenters and recording devices. A closed TV circuit allowed permanent observation of the animal's behavior. Three recordings (each 1 h long) were performed before drug administration in order to obtain a typical normal record characteristic of each animal tested.

All substances were injected i.p. at the following dosages: *d*-amphetamine 2 mg/kg; LSD-25 0.1 mg/kg; Ditran[1] 1 mg/kg. Each was tested under the same conditions on at least four animals. Three other control recordings had been performed for another purpose with the essence of eucalyptus (administered i.p.), considered a neutral substance with regard to the central nervous system, and were used here as controls.

The ECoG was quantified over the first hour after drug injection and compared to the 1-h ECoG recorded from the same animal in control sessions after the same period within the recording cage. Quantification was performed in the following way: for each minute recorded, the duration of each type of rhythm (36, 14, and 6 c/s) was calculated as well as the number of sleep spindles/min. Since the mean duration of a spindle was relatively constant (1 s) in both natural sleep and under Ditran, the number of spindles was roughly equivalent to the total duration of spindle activity/min. The values obtained were then plotted on a 5-directional vector system in the following procedure (Fig. 1): time was counted from left to right on an oblique vector; for each minute on the time axis, the duration of each rhythmic pattern in the preceding minute was represented by a vector, 6 c/s as $-y$, 14 c/s as $+y$, 36 c/s as $-x$, where $+x$ stood for the number of sleep spindles.

[1] JB 329. This drug was manufactured by Lakeside Laboratories and consists of a mixture of N-ethyl-3-piperidyl phenylcyclopentylglycolate hydrochloride (30%) and N-ethyl-2 pyrrolidylmethyl phenylcyclopentylglycolate hydrochloride (70%)

RESULTS

A. Patterns of SI Rhythms in the Normal Animal Under Test Conditions

The different types of rhythms that can be recorded from the SI area in a normal cat in distinct behavioral situations and a description of the chronology of wakefulness and sleep are briefly mentioned below.

1. Types of Rhythms. A first situation is that of 'exploration-vigilance'. While exploring a novel environment, the animal sometimes stops moving as if it were paying attention to a visual or acoustic stimulus. At such moments, an abundant hippocampal theta rhythm develops (Kemp and Kaada, 1975), and at the same time brief sequences (1–3 s) of rhythms with a frequency of about 36 c/s alternate with periods of desynchronized activity. These rhythmic sequences are observed simultaneously at SI and in the posterior thalamic group (PO of Poggio and Mountcastle, 1960), suggesting the existence of a rhythmic thalamocortical system PO–SI whose activity is indicated by horizontal bars ($-x$) to the left of the time axis in Figure 1.

In other situations, the animal is awake and immobile, without signs of hypervigilance, but rather of quiet expectancy (e.g., waiting for a conditional signal in operant learning). Rhythms then develop in area SI as well as in a limited zone of the ventral posterior thalamic nucleus (VP) in sequences of varying duration (1–20 s) and of rather constant frequency (12–18 c/s, $\bar{m}$ = 14 c/s). Consequently this activity is due to a rhythmic thalamocortical system VP–SI (Bouyer et al., 1974; Rougeul-Buser et al., 1975); in our diagram of the data it is represented by the vertical bars ($+y$) above the time axis (Fig. 1).

Finally, when the animal becomes drowsy, undergoing the transitional stage between quiet wakefulness

and slow sleep, the thalamocortical VP−SI system maintains its activity of 14 c/s ($+y$ bars). In addition, another slower system (4−7 c/s, $\bar{m}$ = 6 c/s) elicits simultaneous rhythmic activities. This last system seems to originate in the centrum medianum-parafascicularis complex (CM-Pf) of the medial thalamus; its activity is indicated by vertical bars below the time axis ($-y$). The complex activities of variable frequency (4−18 c/s, Rougeul et al., 1974) observed during drowsiness in the SI area are likely to be due to the convergence of systems VP−SI and CM-Pf−SI in the same cortical zone; the overall extent of both activities is more or less the same, as indicated by the almost identical lengths of $+y$ and $-y$.

After some time, the animal falls into typical slow sleep which is, as commonly known, characterized by sleep spindles (horizontal bars to the right of the time axis: $+x$) and slow waves.

2. Chronology of Wakefulness and Sleep. The chronology of states of wakefulness and sleep of the normal cat in the test chamber will now be described by means of an example. When the animal was placed in the recording space for 1 h, it first developed an exploratory behavior (Fig. 1) with episodes of 36 c/s rhythms during the first 6 min. This stage was followed by brief, alternating periods of quiet wakefulness and drowsiness. Quiet wakefulness is signaled on our graphs by either $+y$ bars (14 c/s) without any corresponding activity in the $-y$ domain, or a dominance of the $+y$'s as compared to the $-y$'s (Fig. 1). This stage was followed by an alternation of slow sleep and drowsiness periods; later, slow-sleep periods were interspersed with REM-sleep stages (empty blocks along the time axis).

The pattern illustrated by Figure 1 is, of course, an individual case: interindividual variations were indeed observed, but the complex pattern described above was generally the same. In all subjects, each stage was relatively short and large fluctuations of the extent of each rhythmic activity per minute were always observed.

B. Effects of Psychoactive Drugs

Each of the three drugs tested elicited a characteristic alteration of rhythmic patterns in SI, suppressing some features and enhancing others, for one to several hours.

1. d-Amphetamine. After injection of 2 mg/kg of *d*-amphetamine (i.p.), the animal displayed periods of immobility interrupted by stereotyped movements (turning the head to one side and then to the other).

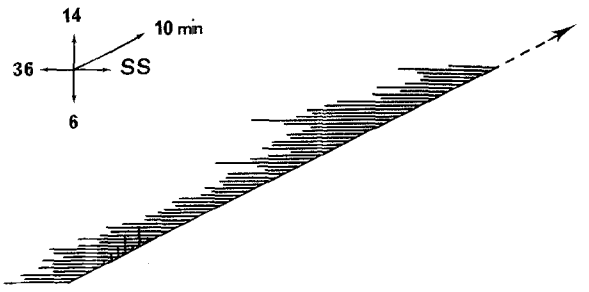

Fig. 2. Time distribution of cortical rhythms after *d*-amphetamine. Drug administered at time 0 (beginning of diagram)

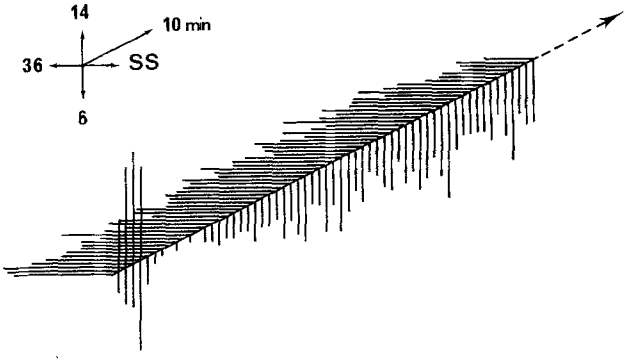

Fig. 3. Time distribution of cortical rhythms after LSD-25. Drug administered at time 0

Over periods of immobility, the ECoG consisted of fast 36 c/s rhythms (Fig. 2) similar to those of the normal animal in the exploratory phase. Except for some early short bursts of 14 c/s rhythms, neither slower rhythms nor sleep spindles could be noticed. The amount of fast rhythms per minute was similar to that of normal subjects in full wakefulness. These fast activities were maintained throughout the hour. This clearly contrasts with the ECoG patterns of the same animal under normal test conditions, where it never had such fast rhythms beyond a maximum of 15 min.

2. LSD-25. Under LSD, administered in a 0.1 mg/kg dose, wakeful but fairly abnormal behavior was observed: the animal was cramped into a corner and startled at the slightest stimulus. Various autonomic signs were observed, such as mydriasis and pilo-erection as previously described (Adey et al., 1962).

Somesthetic rhythms were observed on the ECoG; as in the normal cat, they developed only during immobility and disappeared as soon as the animal moved. However, the qualitative organization of these rhythms was abnormal. The 14 c/s rhythms that normally correspond to quiet wakefulness disappeared

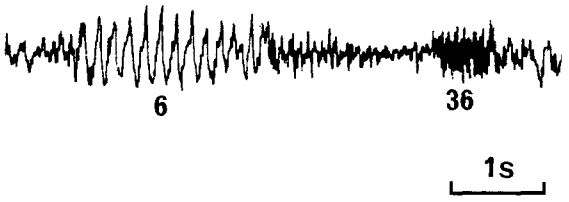

Fig. 4. ECoG recorded from SI after LSD-25. Note coexistence of 6 and 36 c/s rhythms, which does not occur in a normal cat

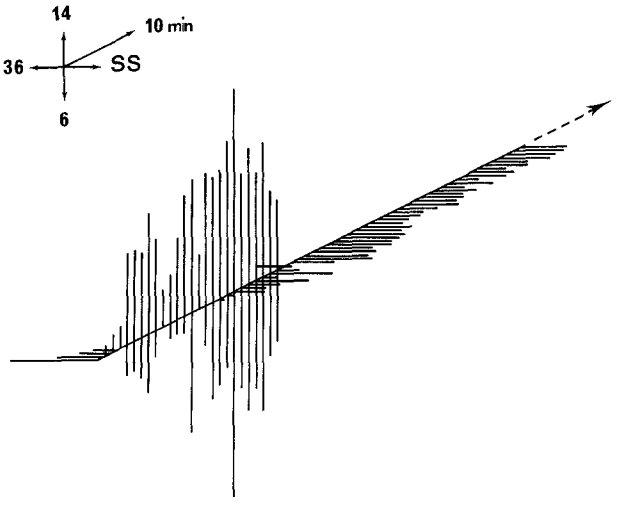

Fig. 5. Time distribution of cortical rhythms after Ditran. Drug administered at time 0

(Fig. 3), while those of 36 c/s were very abundant. Moreover, in contrast to the effect of *d*-amphetamine, these fast rhythms were now alternated by 6 c/s rhythms, indicating that the CM-Pf–SI system was activated independently from the fast rhythm system (Fig. 4). This pattern of alternation was prolonged without interruption, a configuration that had never developed in the normal animal under the present test conditions. A normal pattern was first observed after 3 h.

3. Ditran – A Central Anticholinergic Drug. Following a 1 mg/kg dose i.p., a very peculiar behavior was observed (Rougeul et al., 1965), where the cat restlessly explored the test cage for several hours.

The ECoG displayed a drowsiness pattern for about the first 20 min, then traced out spindles and irregular slow waves which perfectly resembled the animal's normal sleep pattern, with the same probability of occurrence (Fig. 5). Unlike the normal sleep pattern, however, this activity was pursued in a monotonous way with no change for a number of hours. Furthermore, it was *not* interrupted by locomotor activity, contrasting with the effect of the two other drugs under which all synchronized patterns were abolished at the least movement of the body.

DISCUSSION

The psychoactive drugs tested here strongly modify the temporal development of the somesthetic rhythmic activities of the cat. Following each type of drug studied, a different ECoG pattern could be observed, even though its constitutive elements did not differ from those of the normal subject.

1. Rhythms observed after drug administration all belong to the normal ECoG repertory recorded from the same cortical focus. Fast rhythms under *d*-amphetamine (Borenstein et al., 1976) and LSD were thus identical to those of the normal exploring animal. After Ditran, slow waves and spindles also closely resembled those of the normal animal under slow sleep. On the other hand, the slow rhythms (6 c/s) observed after LSD (a fact already noticed by Bradley and Elkes, 1953; Evarts et al., 1955; Schwarz et al., 1956; Adey et al., 1962; Lindsley et al., 1968) never develop alone in the normal animal. In fact, these slow rhythms exist in the normal ECoG during natural drowsiness, but they are masked by the simultaneous occurrence of 14 c/s rhythms in the same part of area SI. After suppression of these latter rhythms by LSD, the 6 c/s rhythms occur in isolation. Under these conditions, they correspond identically to the 6 c/s activities of the medial thalamus, which can be observed as well during natural drowsiness since they are never mixed with 14 c/s rhythms in this structure.

2. Hence the drugs studied mainly appear to modify the normal balance between the different thalamocortical systems underlying the rhythms. Natural drowsiness is characterized by simultaneous development of 6 *and* 14 c/s rhythms. LSD brings about two modifications: (1) rhythms of 6 c/s developing in isolation and (2) 36 c/s rhythms developing in alternation with these last. These modifications were never observed in normal subjects, and the only case where they did occur was after bilateral lesion of the VP area, which is the pacemaker of the 14 c/s rhythms (Rougeul-Buser et al., 1975).

3. Under the effect of drugs, the rate of appearance of these rhythms per minute also did not differ from that of the normal subject in any given state of alertness. On the other hand, their temporal organization was altered: under *d*-amphetamine or LSD, the same rhythmic pattern developed in a monotonous fashion for 3–4 h and, after Ditran, for several days. The variability and alternation of rhythms that are char-

acteristic of the normal animal's ECoG were thus disrupted by these drugs. Under normal conditions, no episode characterized by dominant SI rhythms of 36, 14, or 14 *and* 6 c/s exceeded 15 min, while SWS episodes were usually interrupted by phases of REM sleep or by a return to drowsiness or even to quiet vigilance.

4. Remarks may also be made regarding 'dissociations' between ECoG and behavior, i.e., when a given ECoG pattern develops that does not fit the corresponding behavioral state or, more radically, when a synchronized ECoG pattern persists in spite of body movement.

Under *d*-amphetamine, apparently no dissociation took place. The animal remained in a state of intense alertness and had an ECoG that fit this behavioral state well: 36 c/s rhythms developed when the cat was motionless and disappeared whenever it moved. The abnormality consisted of the fact that such a state extended over several hours, with stages of immobility alternating with ones of stereotyped behavior, as described by others (Randrup and Munkvad, 1967).

Under LSD, the problem is more complex. As far as motor behavior is concerned, no dissociation could be noticed; desynchronized activity took place during movement, while synchronized rhythms developed only during immobility. On the other hand, dissociation between the dominant category of rhythms and the apparent level of alertness occurred. Judging from its posture and autonomic signs, the animal behaved as if it were awake (Adey et al., 1962) while its rhythms jumped from the 'intense alertness' type to the 'drowsy' type without any apparent corresponding variation in behavior.

Under Ditran, the commonly known dissociation between motor activity and ECoG occurred, as already described for atropine and other anticholinergic drugs (Funderburk and Case, 1951; Wikler, 1952; Rinaldi and Himwich, 1955; Longo, 1956, 1966; Bradley and Elkes, 1957; Rougeul et al., 1965; Montplaisir, 1975). The animal went about exploring, although it had an ECoG that not only mimicked but was also practically identical to the sleep pattern recorded in the same animal with the same electrodes in a control situation.

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