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Time Course of Interictal EEG Patterns Induced by a Penicillin Injection Into the Olfactory Cortex

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HORN, E., K. ESSELING AND R. WAGNER. *Time course of interictal EEG patterns induced by a penicillin injection into the olfactory cortex.* PHARMACOL BIOCHEM BEHAV **40**(2) 351–357, 1991.—In awake rats, the time courses of behavioural and cortical interictal hyperactivity patterns were investigated following an injection of the GABA antagonist Na-penicillin (PCN) (125 IU/0.5 μl) into the olfactory or motor cortex. The cortical EEG was recorded by means of 6 AgAgCl-electrodes, behaviour was videotaped simultaneously. Behavioural hyperactivity developed immediately after PCN injection. It lasted longer than 2.5 to 4 h in the olfactory but less than 30 min in the motor cortex group of rats. The interictal EEG pattern of the olfactory group was characterized by a slow establishing of three centers of high cortical activity. They were located in the ipsilateral central and the contralateral frontal and occipital cortex. In the motor cortex group, however, a cortical center of high activity developed immediately after the PCN injection near the injection site only, or additionally, over the homotopic area of the contralateral hemisphere. The results indicate different susceptibility properties in the underlying neuronal networks. Ongoing epileptiform activity obviously modifies this susceptibility in a site-specific manner. Moreover, the time-correlated occurrence of high activity in the frontal motor and occipital cortex evoked by a PCN injection into the olfactory cortex suggests a close coupling of these three areas. A coupling between the frontal motor, occipital and focal area could not be shown, if PCN was injected into the motor cortex.

Penicillin Olfactory cortex Motor cortex EEG Focal interictal activity Mapping

INVESTIGATIONS on the neuropharmacology of the olfactory cortex have given some insight in neurotransmitters involved in the control of activity of this area. Excitatory transmission from olfactory tract fibres to cortical neurons and in the association fibre system is mainly based on glutamate, aspartate and/or the dipeptide N-acetylaspartate (4), while di- and polysynaptic excitation in the olfactory cortex is mediated by N-methyl-di-aspartate (NMDA) receptors (5). Inhibition within the olfactory cortex depends on adenosine (6, 15, 29), the activation of presynaptic M1-type muscarinic receptors (1), or gamma-aminobutyric acid (GABA) (18,21). Slice preparations have revealed the participation of GABA-B receptors in neurotransmission at synapses of association fibres (5). This multiple transmitter system points to complex influences of this area on general brain function. In fact, the olfactory cortex projects to many cerebral structures (31) including the limbic system (20), it helps to maintain normal adaptive behaviour (35), and is also a site at which generalized epileptiform activity can easily be elicited as revealed by local injections of glutamate, kainic acid, carbachol or bicuculline (23).

The highly divergent projection of the olfactory cortex output (2, 10, 20, 25, 28, 31) raised the question how epileptiform activity induced at this site [cf. (23)] acts on other cortical centers to create a multifocal pattern. Therefore, epileptiform activity was elicited by a local injection of the GABA antagonist penicillin (PCN) [cf. (17, 24, 33)], and its time course was followed by recording the EEG and general motor activity simultaneously. To consider site-specific effects, epileptiform activity was also induced by a local PCN injection into the motor cortex of other rats. It was followed by using the same methods.

METHOD

Animals

Experiments were performed with 16 male and female Wistar rats (age 7 to 9 months) from the stock of the Centre for Experimental Animals of the University of Ulm (FRG). Rats were maintained on a 12–12-h light-dark cycle. Under pentobarbital (Nembutal) anaesthesia (75 mg/kg body weight IP), a guiding tube for the PCN injection and 6 AgAgCl-electrodes were fastened to the skull. The electrodes were placed 0.4 mm above the dura at the stereotaxic coordinates A4.5 (bregma) and R/L2; P1 and R/L2.5; and P6 and R/L2.5. A recovery period of two to four weeks was allowed before the experiments were performed. Meanwhile, all rats were handled daily.

Procedure

Na-penicillin G (PCN) was diluted in sterile saline at a concentration of 250 IU/μl. From this solution, 0.5 μl were injected from dorsally into the olfactory cortical area of the right hemisphere (5 rats) at the stereotaxic coordinates A1.7 (bregma), R4, H−8 [coordinates according to (22)]. In 8 other rats, the same amount of PCN was injected into the motor cortex of the right

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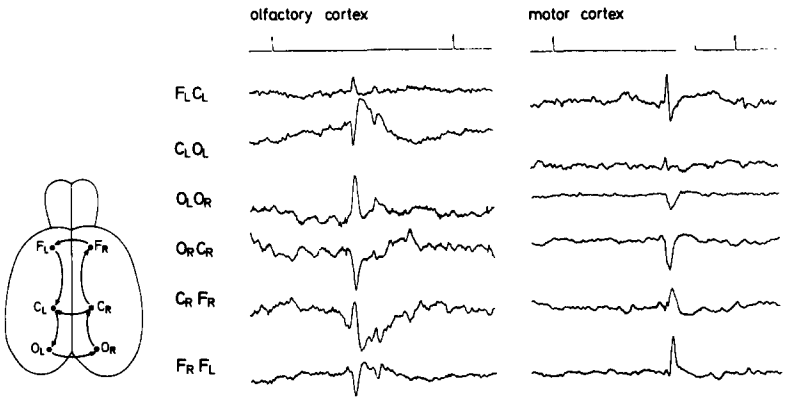

FIG. 1. Spikes recorded after a local application of Na-penicillin into the olfactory (left) or motor cortex (right). The location of the centers with high activity can be derived from the orientation of these spikes in adjacent channels. These spikes point to the common electrode of the adjacent traces. Recording sites and types of differential recordings are indicated on the left margin of the traces and in the inset figure. $F_{R,L}$, frontal; $C_{R,L}$, central; $O_{R,L}$, occipital electrodes of the right or left hemisphere, respectively. Upper trace: space between the two time marks indicates 1 s.

TABLE 1

EFFECTS OF A LOCAL INJECTION OF PENICILLIN INTO THE OLFACTORY OR MOTOR CORTEX ON PARAMETERS CHARACTERISTIC FOR THE INDUCED EPILEPTIFORM ACTIVITY

Animal	Seizures Latency (min)	Period (min)	Duration (s)	Number (n)	Frequency (n/h)	Potentials Frequency (n/min)	Period (min)
				Olfactory Cortex			
354m	15.7	>279	23.6	119	26	42.5	>280
355m	27.8	>251	21.9	156	37	49.5	>252
400f	21.4	204	45.2	11	3	14.6	229
401f	20.9	82	19.5	8	6	14.5	225
402f	25.6	82	16.9	146	46	40.0	209
Median	21.4	204	21.9	119	26	40.0	229
				Motor Cortex			
418m	15.2	90	17.2	13	9	21.9	151
419m	4.4	190	8.9	277	87	16.4	315
420m	9.9	234	11.0	97	25	21.9	406
422m	8.8	182	10.9	106	35	18.2	380
026f	7.8	152	25.9	20	8	20.2	227
027f	4.0	195	11.7	154	47	14.7	195
031f	12.7	110	13.0	54	29	17.2	133
032f	16.5	121	11.3	42	21	17.2	247
Median	9.4	167	11.5	76	27	17.7	237
p	<0.01	n.s.	<0.05	n.s.	n.s.	n.s.	n.s.

Values for individual animals are given in this table as well as the median values for the sample.

Latency: time between the PCN injection and the first seizure; Period: time between the PCN injection and the last seizure or epileptiform potential, respectively; Duration: mean duration of all recorded seizures of the animal; Number: number of seizures during the observation period; Frequency: number of seizures per hour and number of potentials per minute, respectively.

m and f: male and female, respectively.

p: level of significance between the olfactory and motor group.

n.s.: not significant ($p>0.1$).

Significant levels were calculated by means of the U-test.

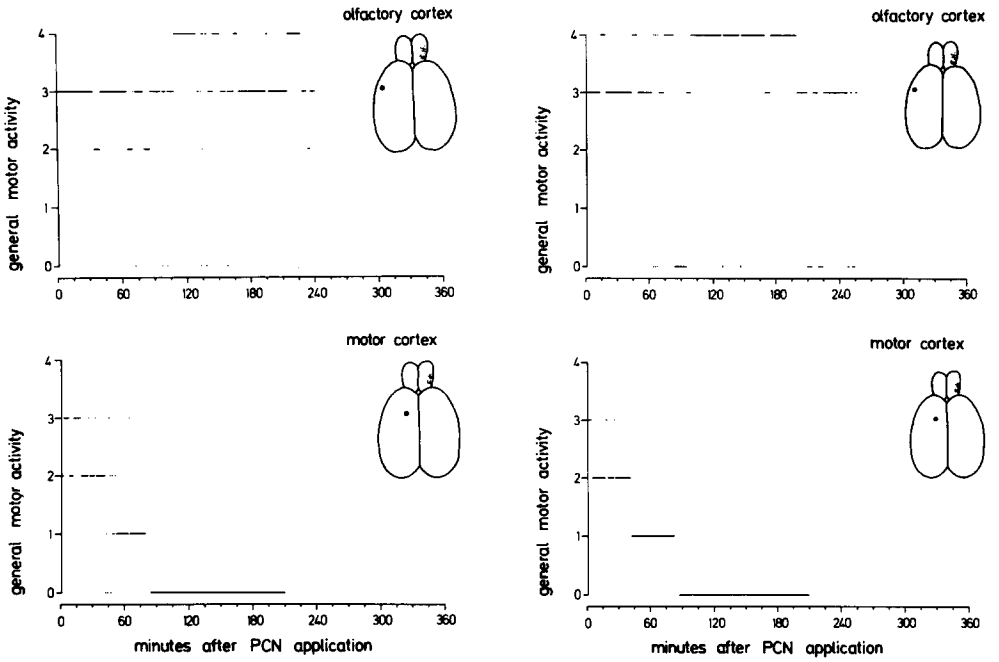

FIG. 2. General motor activity of 4 rats following local application of PCN into the olfactory or motor cortex of the right side (cf. inset figure, black dot). Classification of locomotor activity: 0, rest; 1, sniffing activity but no locomotor activity; 2, slow walking, rearing; 3, long periods of walking with periods of resting; 4, only running. PCN was injected at time zero. These representative examples were chosen to demonstrate the high degree of similarity in the activity pattern in rats with the PCN-focus in the same cortical area.

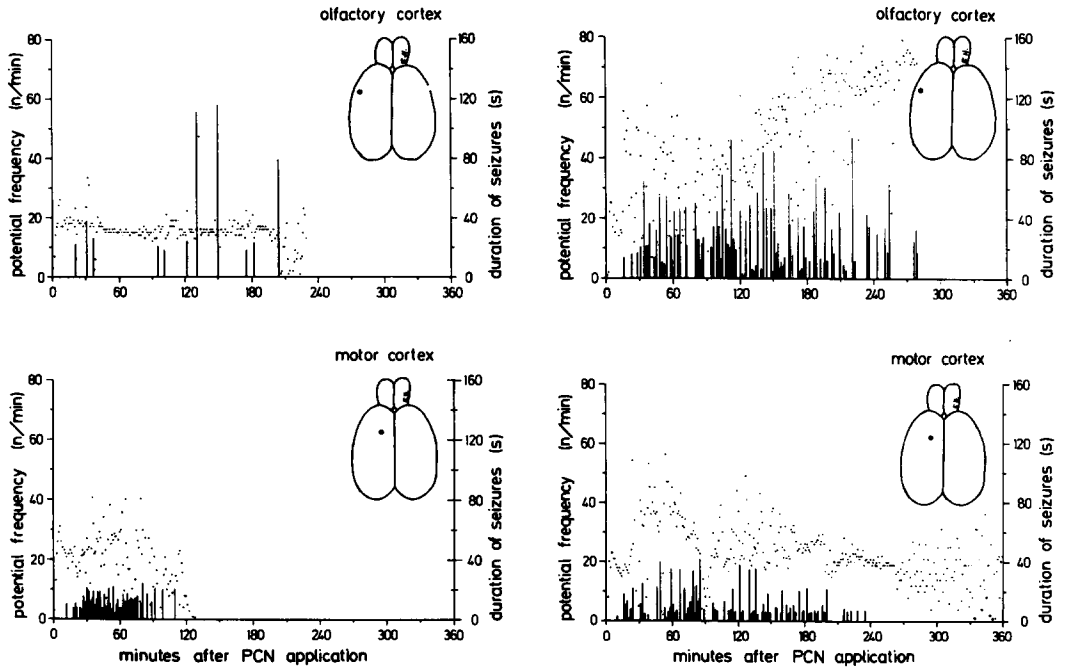

FIG. 3. Time courses of interictal and ictal activity of 4 rats induced by a local application of PCN into the olfactory or motor cortex of the right side. Interictal activity is described by the number of potentials per min (left ordinate: dots), ictal episodes by their onset and duration (right ordinate: vertical bars). PCN was injected at time zero. These representative examples were chosen to show 1) the span of time courses and 2) the regular initiation of seizures throughout the experiment.

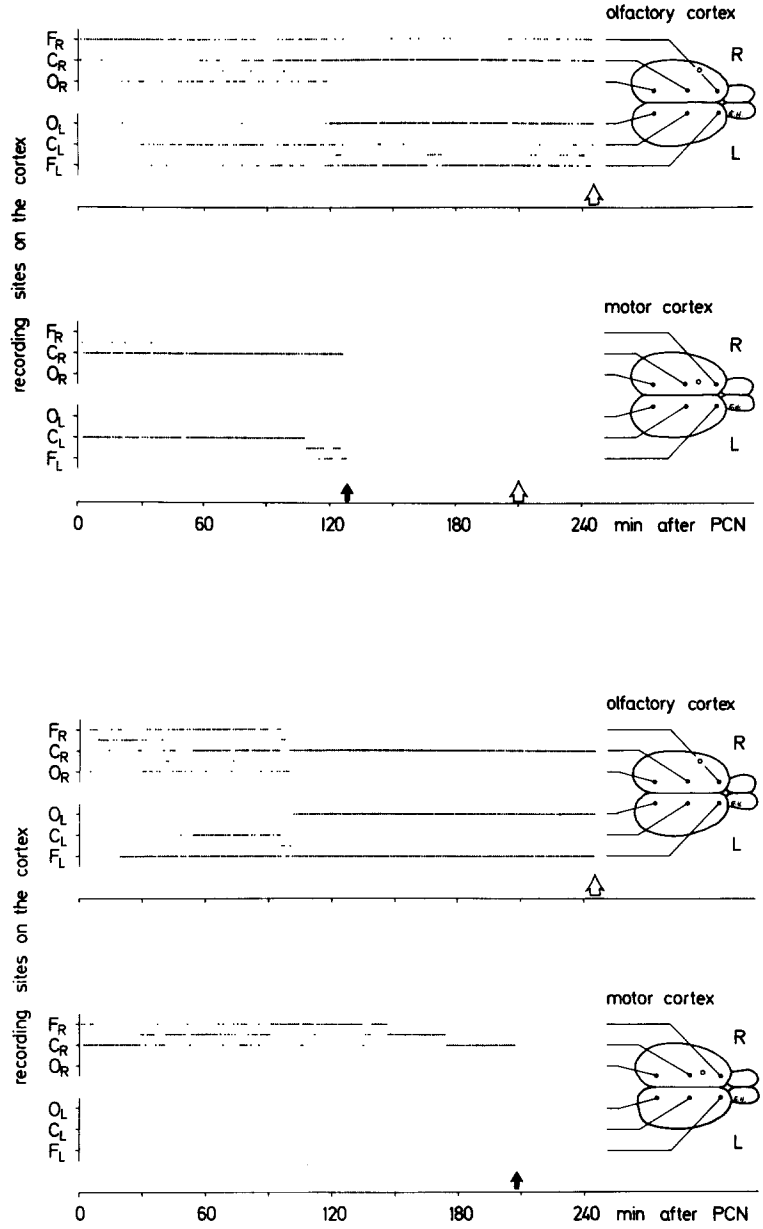

FIG. 4. Location of the cortical activation centers after a local injection of PCN into the olfactory or motor cortex of the right hemisphere (circle in inset figures). Each dot indicates the location of the main activation center recorded every minute throughout the experiment. $F_{R,L}$, frontal; $C_{R,L}$, central; $O_{R,L}$, occipital electrodes over the right or left hemisphere, respectively. Black arrows: end of epileptiform activity; white arrows: end of recordings.

hemisphere at the stereotaxic coordinates A1.7, R2 and H − 1.3. Control rats received equal volumes of the solvent either in the olfactory (n = 1) or motor (n = 2) cortex. Injections were performed without anesthetization. Carefully handled rats never showed avoidance behaviour during this treatment.

During the recordings the rats could move freely in a chamber of $25 \times 25 \times 40$ cm^3. Differential recordings were taken between neighbouring electrodes (cf. Fig. 1, inset). The derivations were arranged in a circular manner so that adjacent channels had a cortical electrode in common. One of these recordings was used to determine the frequency of interictal activity and the number, duration and frequency of generalized seizures. All channels were used to determine "centers of cortical activation" (= cortical foci) during the interictal activity. These centers were defined as areas with high cortical activity. They were identified by the interictal potentials pointing to the focus (cf. Fig. 1) [cf. (32)]. Behavioural activity was analysed minute by minute on the basis of video recordings using the following scores irrespective of superimposed epileptiform movements: 0, rest; 1, sniffing activity but no locomotor activity; 2, slow walking, rearing;

3, long periods of walking with periods of resting; 4, only running.

Statistics were based on the nonparametric U-test from Wilcoxon, Mann and Whitney (34).

RESULTS

After injection of PCN into the olfactory cortex rats became immediately hyperactive and exhibited intense sniffing and running activity. This behavioural hyperactivity persisted for at least 2.5 h at a mean score level of 3.3 ± 0.2 (mean $\pm$ SD; $n = 5$) (control level of these rats before the injection: 0.8 ± 0.2) interrupted only by short episodes of inactivity lasting less than 1 min (Fig. 2, upper plots). In contrast, rats of the motor cortex group increased locomotor activation only for a period of less than 30 min from 0.9 ± 0.2 before to 2.3 ± 0.2 ($n = 8$) after the injection of PCN (Fig. 2, lower plots). Intracortical injections of the solvent induced only transiently a slight tremor of eye and facial muscles in all three rats.

The EEG of PCN-treated rats was characterized by spike-like (interictal) potentials lasting up to 100 ms (Fig. 1). They developed one to two minutes after the injection and could be recorded for several hours. In the motor but not in the olfactory cortex group, they correlated with jerks of the forelimb and/or the head. The period of their occurrence (229 min vs. 237 min) as well as their median frequency (40.0/min vs. 17.7/min) did not differ significantly ($p > 0.1$; U-test) between both the olfactory and the motor cortex group, respectively (Table 1).

Generalized seizures interrupted the interictal activity. They were characterized by high-frequent fluctuations of the EEG baseline up to 16/s and were always accompanied by abnormal behavioural responses. In the olfactory group, elements of limbic seizures like chewing, tonic body torsions, wet-dog shaking, body tremor or salivation occurred. In the motor cortex group, tonic and clonic leg and head movements were the main elements of the generalized seizures with focal origin. These observations agreed with those described by other authors (7, 12, 23). The ratio between these behavioural components varied even for the sequence of seizures observed in individual rats, but time-related changes were never observed during the period of the epileptiform activity.

The first ictal activity appeared significantly later in the olfactory than in the motor group (21.4 min vs. 9.4 min after PCN injection; $p < 0.01$), while the period of their occurrence was similar (204 min vs. 167 min; $p > 0.1$). Seizures always occurred regularly during this period no matter whether the number of seizures was high or low in both the olfactory or the motor cortex group (Fig. 3). The median duration of single seizures was significantly longer in the olfactory than in the motor group (21.9 vs. 11.5 s), while differences concerning their absolute number (119 vs. 76; $p > 0.1$) and their frequency (26/h vs. 27/h; $p > 0.1$) were insignificant (Table 1).

Striking differences became obvious in the time course of the interictal activity. As noted before, the local injection of PCN exhibited spike-like potentials (Fig. 1) which clearly defined centers of cortical activation. In the rats with a PCN focus within the olfactory cortex, the spikes recorded during the initial period from the motor area were larger (up to 2 mV) than those recorded from the occipital area. This period was characterized by a single center of cortical activation located over the ipsilateral frontal hemisphere. After 15 to 30 min, however, the potentials recorded from the ipsi- and contralateral occipital area became larger (Fig. 1, left). At the same time, other cortical areas were activated. This period lasted about 60 to 75 min and was followed by the formation of a supplementary center over the occipital, sensory area which was simultaneously active with the others. Two of the 5 rats finally developed three stable centers located over the contralateral frontal, ipsilateral central and contralateral occipital cortex (Fig. 4, first and third plot). In the other three rats, a similar three-center pattern was observed for 60 min before it changed to a two-center pattern over the right and left motor cortex, but with cortical foci which were never located in homotopic areas.

In rats with a PCN focus within the motor cortex, the interictal activity pattern was organized more simply. Spike amplitudes up to 2 mV were only recorded from the frontal hemisphere, either occurring ipsilaterally (3 rats) or bilaterally (5 rats). Spikes recorded from the occipital cortex were significantly lower throughout the experiment (Fig. 1, right). The centers of high cortical activity were located only on the frontal cortex. In 3 rats, a single center developed on the injection side shifting within the motor field (Fig. 4, lower-most plot). In the remaining 5 rats, a second focus developed at the homotopic region. This pattern appeared 2 min after the PCN injection and was stable throughout the experiment (Fig. 4, second plot). The interictal spikes always occurred simultaneously until this activity faded away.

DISCUSSION

The motor or olfactory cortex are sites from which epileptiform activity of different behavioural representation can be elicited by a local injection of the GABA antagonist penicillin (PCN) (7, 12, 23). The present experiments confirmed these observations but, in addition, demonstrated that also the temporal pattern of the cortical interictal activity depended on the location of the PCN-focus (Fig. 4). Cortical activity determined by EEG recordings reflects cortical events near the recording site, and simultaneous activity of distant activation centers means functional coupling between these areas. Therefore, in addition to unit recordings [cf. (8,30)] or neurochemical approaches [cf. (36)], an analysis of functional connections between specific foci and cortical areas and their time-related activation by means of the analysis of the temporal pattern of the cortical interictal EEG will give more insight in the understanding of multifocal cortical activity.

A PCN focus in the olfactory cortex induces long-lasting behavioural hyperactivity paralleled by a slowly developing multifocal interictal EEG pattern covering the motor as well as the sensory cortex. In contrast, rats with a PCN focus in the motor cortex exhibit a short-lasting behavioural hyperactivity and a unilateral or bilateral, symmetric pattern of cortical activation immediately after injection of this GABA antagonist which is restricted only to the motor areas (Figs. 2 and 4). These differences cannot be related to the density of GABAergic neurons or terminals because it is quite similar within the focus regions (18). It is also unlikely that the spread of PCN within the cortical tissue differs markedly because diffusion properties of different brain regions are quite similar (11, 14, 19, 27). The influence of new-established epileptic foci characterized by independent, self-sustaining discharges [cf. (9)] cannot be estimated for several reasons. They may come under the control of the primary focus, or vice versa, may trigger its activity. In fact, in all experiments, interictal activity was synchronized at all recording sites (cf. Fig. 1) Synchronous or time-correlated discharges, however, indicate functional coupling.

The data in Table 1 also show no significant differences for the frequency of interictal potentials and seizures between both the motor and olfactory group. Therefore, general mechanisms of seizure initiation cannot account for different temporal pat-

terns of interictal activity (cf. Fig. 4). It is more likely that the differences can be related to the epileptogenic susceptibility of those cerebral networks which include the focal area, and to a site-specific modification of this susceptibility by the ongoing ictal and interictal activity. In fact, the bifocal symmetric patterns of the motor group started immediately with the occurrence of the early interictal potentials, 7 min before the first seizure (cf. Fig. 4 and Table 1) and showed no modification throughout the experiment. On the other hand, the multifocal and asymmetrical pattern in the olfactory group occurred after the initiation of the first seizure while before this event, only unilateral focal cortical activity was visible.

Distant effects of a primary focal epileptogenic process are well-known in epilepsy research (16), especially in homotopic areas (8, 26, 30, 36). The long delay for the development of multifocal cortical interictal activity indicates that primarily unaffected areas were sensitized by the repetitive stimulation originating from the primary PCN focus. Transfer experiments revealed that the more seizures were evoked in a primary focus, the lower was the threshold in a secondary focus (26). The olfactory cortex has close connections to the limbic system (2, 20, 28, 31) which is a rather epileptogenic and neuroplastic site. It cannot be excluded that these hippocampal or amygdala components could account for the late formation of this multifocal cortical activity, especially for those centers located in the occipital cortex.

The motor cortex, on the other hand, is closely connected to the basal ganglia [cf. (3)], a structure subserving motor programming (13), i.e., more rigidity of activity patterns. Therefore, it can take on more rapidly a stable pattern of cortical activity. Bilateral symmetrical foci may be formed by commissural fibres connecting homotopic regions in the two hemispheres [cf. (3)] leading to the bilateral activity even in the early phase of epileptiform activity (7).

In conclusion, the time course of synchronized cortical interictal hyperactivity reveals site-specific differences between PCN-foci within the motor or olfactory cortex which cannot be due to different GABAergic receptor site densities. It is more likely that specific epileptogenic and neuroplastic properties of the neuronal networks which include the primary PCN-focus influence the development of the temporal pattern of the interictal cortical activity. Moreover, the time-correlated occurrence of high activity in the frontal motor and occipital cortex evoked by a PCN injection into the olfactory cortex suggests a close coupling of these three areas. A coupling between the frontal motor, occipital and focal area could not be shown, if PCN was injected into the motor cortex.

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