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SPINDLE OSCILLATIONS DURING CORTICAL SPREADING DEPRESSION IN NATURALLY SLEEPING CATS

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Spindling activity characterizes the EEG of animals and humans in the early stages of resting sleep. Spindles are defined as waxing and waning rhythmic waves at 7–14 Hz that recur periodically every 3–10 s. Spindling originates in the thalamus,[7] but a role for the cerebral cortex in triggering and synchronizing thalamic spindles was shown by stimulation of the contralateral cortex avoiding antidromic activation of thalamocortical axons[11] and by diminished coherency of thalamic spindles after hemidecortication.[2] Spontaneous spindles under barbiturate anesthesia are waxing and waning[1] but under ketamine–xylazine anesthesia or when evoked by strong stimuli spindle waves are almost exclusively waning,[4] i.e. they start with maximum amplitude and then decrease progressively. Waxing and waning of spindles has been ascribed to progressive entrainment of units into the oscillation followed by a progressive desynchronization.[1,4] Therefore, exclusively waning spindles would be produced by an initial high synchrony in the corticothalamic network. Such a situation is observable upon strong stimulation or, spontaneously, when spindles are paced by the slow cortical oscillation and preceded by a strong corticothalamic drive.[3,9] We have conducted experiments in naturally sleeping cats to verify the occurrence of two patterns of spindle oscillations and to test the role of the cortex in synchronizing and shaping spindles. We have found that indeed two types of spindles (waxing and waning or mostly waning) occur in naturally sleeping animals. We also demonstrate that during cortical spreading depression[6] spindles are less synchronous and only of the waxing and waning type. As cortical activity recovers, waning spindles reappear and are preceded by electroencephalogram deflections which are related to corticothalamic depolarizing inputs. Our results strongly support the hypothesis of the role of the cerebral cortex in shaping and synchronizing thalamically generated spindles. © 1997 IBRO. Published by Elsevier Science Ltd.

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In order to present spindling in the EEG of the unanesthetized naturally sleeping cats, it is useful to describe first the patterns of spindles under ketamine–xylazine anesthesia, in which spontaneous activity in corticothalamic network is high,[3] and under barbiturate anesthesia, in which the background activity is considerably lower.

Under ketamine–xylazine anesthesia (10–15 mg/kg; 2–3 mg/kg, i.m.), spindles are preceded by a depth-positive cortical EEG wave that ends with a sharp negative wave followed by a waning spindle sequence, usually at the upper frequency limit of spindling (13–14 Hz) (Fig. 1, Ketamine). Under barbiturate anesthesia (25–35 mg/kg), spindling is waxing and waning, and its frequency is lower with increasing the barbiturate doses (Fig. 1, Barbiturate).

During natural slow wave sleep, two types of spindle pattern were observed, one with a characteristic waxing and waning pattern (Fig. 1, Natural sleep, right panel), while in the other spindles were preceded by an EEG biphasic complex (depth-positive, depth-negative) followed by a spindle sequence lacking the initial waxing feature (Fig. 1, Natural sleep, left panel).

To test the hypothesis that the sharp depth-negative EEG deflections of the cortical slow oscillation trigger and synchronize spindle sequences in the thalamus thus changing their shape, cortical depression was induced by placing a drop of concentrated potassium acetate (3 M) in the vicinity of recording electrode 1 (n=6). The potassium solution induced a complete flattening of the local EEG that spread slowly (12 mm/min) towards electrode 8 (Fig. 2, top panel, spreading depression). The progressive spread of cortical depression was reflected as a complete flattening of the EEG trace recorded by the corresponding tungsten electrode, with a progression from the middle to the posterior suprasylvian gyrus (Fig. 2, a–d). After a short period (50–80 s) of almost complete absence of cortical activity (Fig. 2, d), spindling activity reappeared, and it was first visible

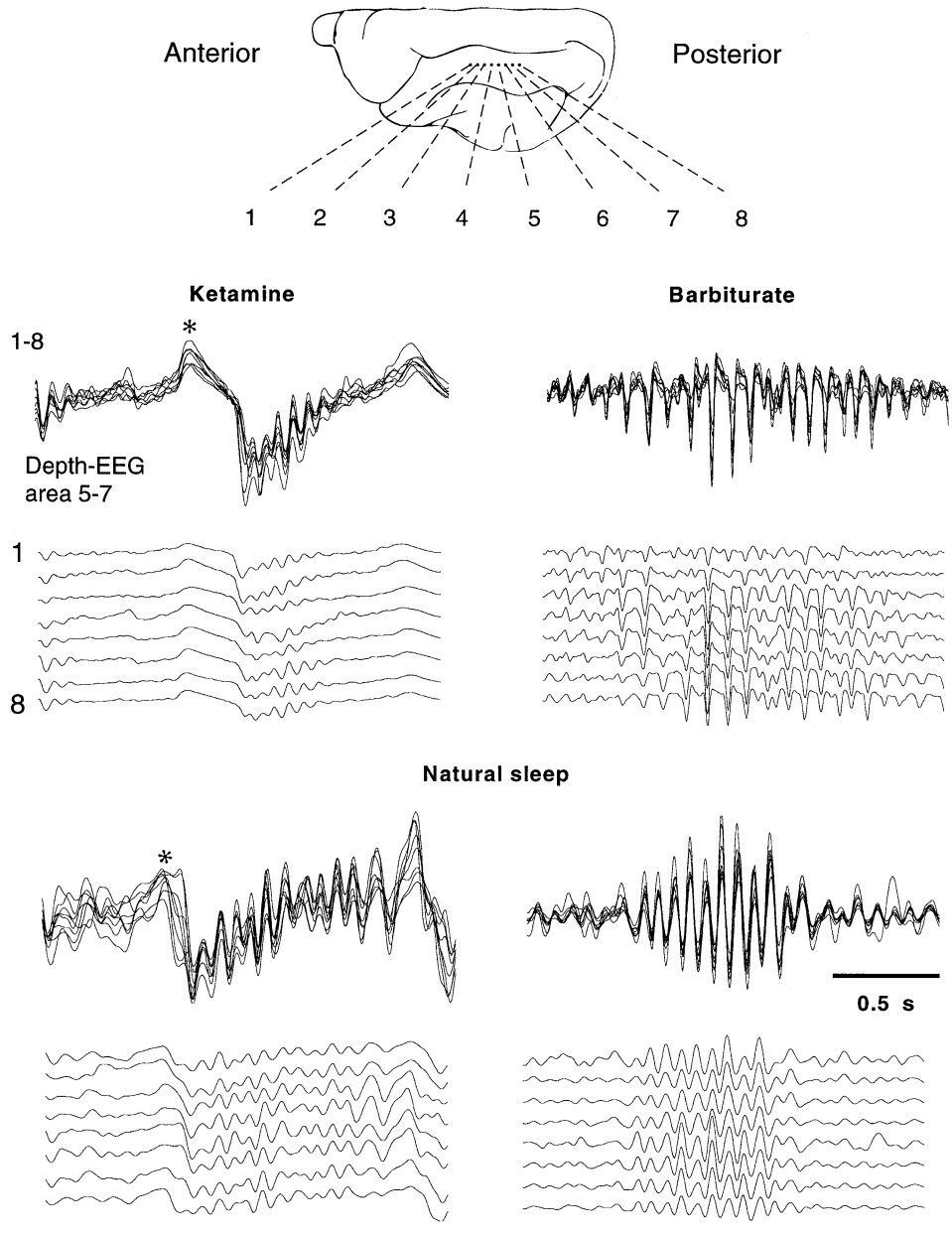

Fig. 1. Different types of spindling under various types of anesthesia and in naturally sleeping cats. Top panel shows a view from above of the left hemisphere of the cat brain. Electrodes numbered 1–8 (dots) separated by 1 mm, were inserted in the depth of the suprasylvian gyrus. Examples of spindles recorded with the eight electrodes under anesthesia (ketamine–xylazine or barbiturate) are compared to spindling recorded in unanesthetized, naturally sleeping animals. In each panel, top trace is a superposition (1–8) of the eight traces displayed below. Experiments were performed in four adult cats, chronically implanted with electrodes for distinguishing different states of the sleep–wake cycle. All surgical procedures and data analysis have been described previously.[8] Eight tungsten electrodes for recording of local field potentials were inserted, with 1 mm interelectrode distance, over the suprasylvian gyrus (top panel), at a depth of 1 mm from the surface. Electrodes were numbered 1–8 from anterior to posterior. Data were recorded on tape and posteriorly digitized at 250 Hz for computer analysis. All traces were filtered between 3 and 20 Hz.

in the leads where the depression started, to then be observed in the others, indicating that recovery started at the same electrode level as the depression (Fig. 2, e–h). Importantly, spindling activity during the initial period of recovery after cortical EEG depression was much less synchronized than that occurring with normal cortical activity (Fig. 2, compare e, f with g, h) and occasionally displayed propagation.[5] That the loss of synchrony was not due to the disruption of horizontal intracortical interactions by the spreading depression, was shown by unaffected synchrony of spindles after deep cuts in

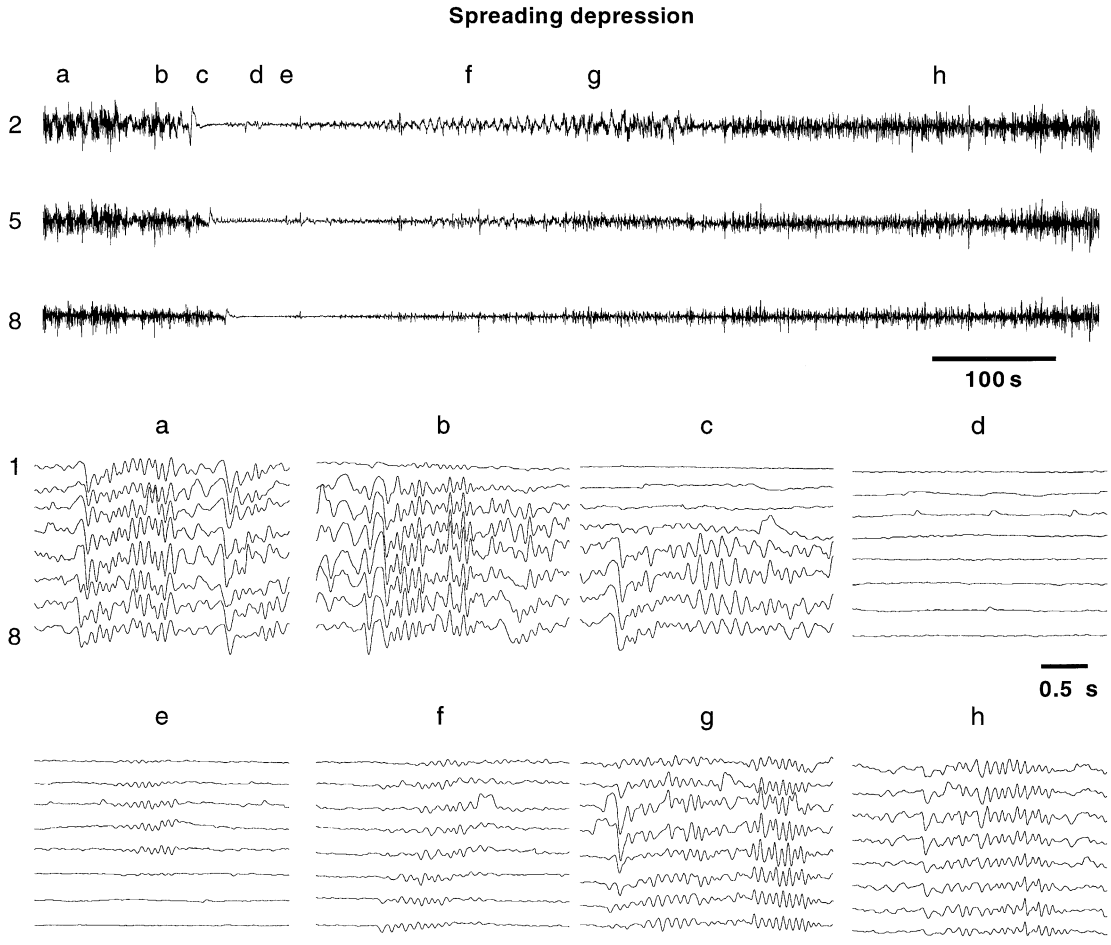

Fig. 2. Effect of spreading depression on spindling pattern and synchrony. Upper three traces are spontaneous activity at electrodes 2, 5 and 8 during the spreading depression. Letters (a–h) mark expanded recordings at the points shown in top panel. Depression spread through the cortex until all leads show a flat trace (a–d). Spindling was less synchronized, occasionally displaying propagating patterns, during early recovery from cortical depression (e and f). As the EEG comes back waning spindles reappear and became more synchronized (g and h).

the suprasylvian cortex.[2] The return of normal cortical activity was marked by the appearance of depth-EEG positive waves, followed by sharp negative deflections characteristic of the slow cortical oscillation (Fig. 2, g; electrodes 3 and 4). Once the cortex recovered, EEG complexes characteristic of the slow oscillation appeared synchronized in all leads, and so did spindling (Fig. 2, h).

In order to quantify the effect of the cortical depression on the spatial distribution of spindle oscillations, we measured the spatial correlation of spindle sequences before, during, and after the spreading depression. Spatial correlation was computed by averaging the values at time zero of all cross-correlations between electrodes. The signals were normalized by subtraction of their average value and division by their standard deviation. This procedure permits the correlation to be evaluated independently of the amplitude and offset of each channel. The spatial correlations were evaluated for several windows of 3 s each, delimiting a spindle sequence, and showed no significant difference with windows of 30 s provided the signal was stationary within them.

During natural sleep, spindle oscillations showed a remarkably high correlation across distances up to 7 mm (Fig. 3, Control). During cortical spreading depression, the spatial correlation showed a significant decrease with distance (200–300%; Fig. 3, Spreading depression). As the activity in the cortex recovered, the values of spatial correlation of spindling returned to the control range (Fig. 3, Recovery).

The main finding of the present study is that cortical activity strongly increases the synchrony of thalamically generated spindles and may change their shape (Fig. 2, compare f and g). Our results show that graphoelements similar to those characterizing the slow oscillation under anesthesia[3] also occur in the condition of natural sleep.[8] The present data strongly support the idea that the depth-EEG positive wave followed by a negative sharp deflection

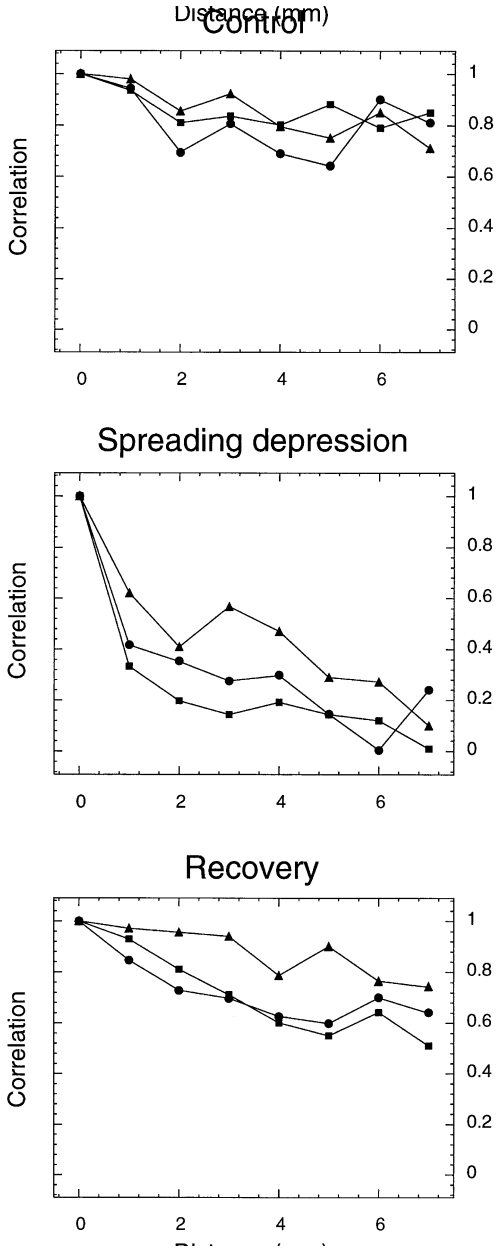

Fig. 3. Spatial correlation of spindling is reduced during spreading depression. Each graph is the mean correlation as a function of distance in the cortex. Abscissae indicate electrode number. Ordinates give the correlation value between 0 and 1 for three spindle sequences (circles, triangles and squares), before (Control), during (Spreading depression), and after (Recovery) the spreading depression. First of the three sequences used for the period during the spreading depression is shown in Fig. 2, f.

and triggering waning spindles is of cortical origin. Indeed, while the slow cortical oscillation survives extensive thalamic lesions,[10] it does not appear in thalamic recordings after decortication.[12]

In conclusion, our results strongly support the hypothesis of the role of the cerebral cortex in shaping and synchronizing thalamically generated spindles.[4,11]

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