

WE have recorded from extrastriate area V4 in monkeys performing a visual search task. When animals became tired or drowsy, responses to visual stimulation were often reduced or even completely blocked, and background activity changed to the burst-pause pattern typically seen in sleep. In spite of such neuronal sleep observed in V4, animals continued to perform the visual task, indicating that at least the primary visual cortex was still working. This observation shows that sleep does not develop simultaneously in all cortical areas but may affect some areas earlier than others. In particular conditions, local sleep of certain areas may be a stable and long-lasting phenomenon.

**Key words:** Area V4; Development of sleep; Monkey; Neuronal activity; Sleep; Visual cortex

## Evidence for asynchronous development of sleep in cortical areas

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### Introduction

It is generally assumed that sleep develops synchronously in all areas of the mammalian cortex. The only exception has been reported for dolphins,<sup>1</sup> whose EEG show periods of deep slow wave sleep in either the right or left hemisphere alone. Such periods of unilateral sleep may last for > 2 h. Even in dolphins, however, EEG activity in different areas of one hemisphere was always found to be synchronized or desynchronized simultaneously. This led to the conclusion that sleep developed synchronously over each hemisphere.<sup>1</sup>

During sleep the propagation of external sensory signals to the cortex is blocked,<sup>2,3</sup> and neurons in the visual cortex stop responding to visual stimulation.<sup>4</sup> It is reasonable to assume, therefore, that, given a synchronous development of sleep in the cortex, all visual areas will lose responsiveness to external stimulation simultaneously. During an investigation of neuronal responses in two behaving monkeys, we noticed that responses of different visual areas did not always disappear synchronously with developing sleep. Rather, neurons in extrastriate cortical area V4 could stop firing to visual stimuli while animals still performed the task, often long before they closed their eyes and fell asleep. A brief account of these observations was made elsewhere.<sup>5</sup>

### Materials and Methods

Recordings were made in two juvenile (2.5–4.5 years) male monkeys (*Macaca fascicularis*). All procedures conformed to the local laws and were carried out under institutionally approved protocols designed in accordance with the NIH Guidelines for the Care and Use of Animals. From MRI scans, individual maps of cortical topography were reconstructed and recording sites were localized. For painless head fixation during recording sessions, eight posts were fixed to the skull and stabilized by a frame around the animal's head. Precise DC eye movement recordings were made with a magnetic search coil implanted in one eye. This technique not only provided exact control of gaze direction and fixation. The recorded eye movement patterns could also be used as a highly sensitive indicator of the animal's level of wakefulness. As was shown earlier,<sup>6</sup> spontaneous drifts of the open eyes indicate drowsiness of the animal, and during slow wave sleep the closed eyes are strongly inclined.

The face of the animal and its posture in the chair were continuously recorded with two videocameras. For extracellular recording of neuronal activity, a recording tube was installed above area V4 in the prelunate gyrus. Single-cell activity was recorded with varnished tungsten electrodes inserted through

small (1.5 mm) holes in the skull. All major surgeries were done under general pentobarbital anesthesia (Nembutal i.v.) in aseptic conditions; bone holes were drilled under ketamine.

All observations presented here were obtained while animals performed a delayed match-to-sample visual search task. Stimuli were presented on a computer monitor which covered about  $30 \times 40^\circ$  of the animal's central visual field. Each trial started with a 'sample stimulus', a single line shown in the center of gaze. After a pause of 0.5–1.5 s the 'test stimulus' with several lines was presented, in which the previous sample stimulus was or was not contained. Lines were arranged in such a way that one element of the test stimulus was always shown within the receptive field of the neuron under study. Animals had to fixate a small light point in the center of the screen and to indicate the presence or absence of the sample line among the test lines by pressing one of two pedals. Correct responses were rewarded by a small quantity of milk baby food. After a break of 5–8 s, the next trial started.

Animals were neither food nor water deprived, and no punishment was administered for incorrect responses. They received the milk mash only as a reward in experiments; fruits were given as an additional reward at the end of each session. After every experiment animals had free access to food pellets until the end of the day. Experiments were run on 3–6 days a week, and animals were fed normally on days without experiment.

Sometimes, during the course of an experiment, animals became drowsy, particularly when they had eaten a considerable amount of baby mash, and one of the monkeys could even fall asleep completely when the task was interrupted. After a short nap he usually became alert again and continued performing the task.

## Results

Most neurons in area V4 responded well to visual stimulation, with stable responses over long recording times when the animal was awake. Sometimes, however, neurons with previously stable responses suddenly became less responsive or neuronal responses were even completely blocked. Then we often noticed slow eye drifts between normal saccadic eye movements, which indicated that the animal was drowsy. Any attempts to find another responsive neuron within a distance of 500  $\mu\text{m}$  were not successful in such cases. In spite of this dramatic change in the excitability of neurons in area V4, the animal continued to perform the visual search task and hence must have been able to discriminate visual stimuli. This suggests that propagation of sensory

signals was not yet blocked in the primary visual cortex (area V1).

Figure 1 illustrates this effect. Horizontal lines plot the activity of one single cell to the same visual stimulus as it was repeatedly shown in the course of the experiment. Each spike is marked by a dot. During the first 40 min (see time marks on the left) the neuron produced strong and stable responses to each presentation of the stimulus. During the next 10 min responses became smaller, and their latencies appear to be slightly increased. In the subsequent 20 min responses diminished dramatically, and finally disappeared completely, although the monkey continued to perform the task.

When neuronal responses had disappeared the program was stopped and execution of the task was interrupted. The monkey was given a break, and soon after he fell asleep. After 10 minutes he woke up again and the task was continued, with partially restored neuronal responsiveness. However, 15 min later the responses disappeared again. Despite the lack of responses to visual stimulation in this neuron, the monkey continued to work in the behavioral task for another 15 min, until the end of experiment.

During 2 years of recording from this animal we observed similar episodes of local unresponsiveness in 43 neurons from 287 studied. In a second animal, who never slept during experiments but occasionally became drowsy, such effects were observed in only six of 143 neurons studied.

Disappearance of visual responses was usually accompanied by changes in background activity. In some neurons there was a general suppression of firing rate (Fig. 1). In other neurons, spontaneous firing transformed into a burst-pause activity pattern. Similar transformations of background activity have been described for cortical neurons during sleep.<sup>7</sup> In all cases, firing patterns of background activity during episodes of local unresponsiveness in the performing animal were similar to those obtained when the animal later closed the eyes and fell asleep.

Analysis of receptive field properties revealed that episodes of local unresponsiveness were more frequently observed in neurons with more peripheral receptive fields than in neurons with receptive fields close to the fovea. This is shown, for one monkey, in Fig. 2. We subdivided neurons according to size and eccentricity of their receptive fields in three groups. Neurons of the first group (left column in Fig. 2) had small receptive fields (less than  $5^\circ$  diameter) which were located within  $5^\circ$  from the fovea. Receptive fields of the second group (middle column) were larger ( $5\text{--}12^\circ$ ) with centers more towards the periphery ( $5\text{--}10^\circ$  from the fovea). Neurons of the third group (right column) had large bilateral receptive fields, the centers of

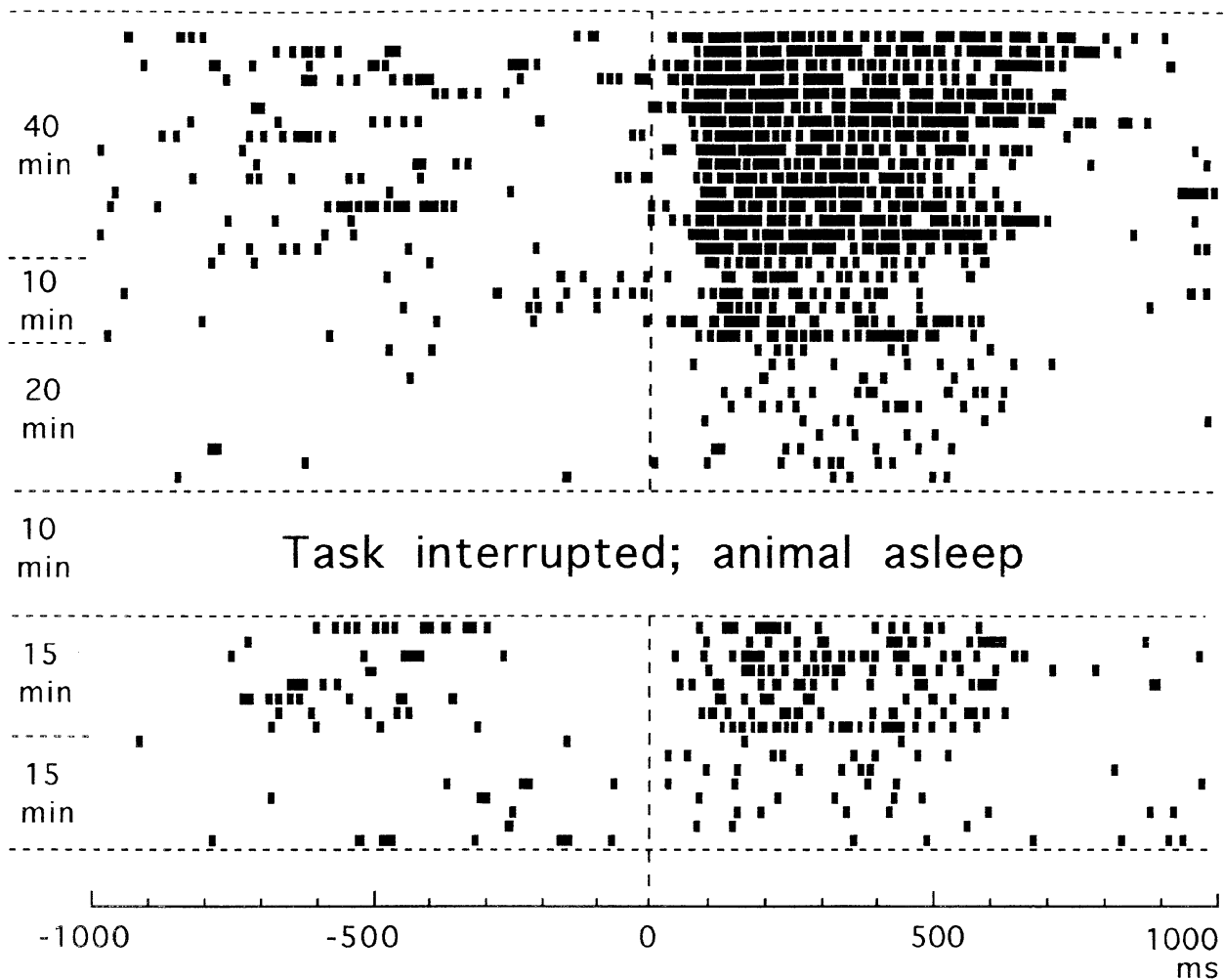


FIG. 1. Responses of a single neuron in area V4 to a vertical bar in the receptive field; stimulus onset at  $t=0$  (vertical dashed line). Each dot represents a single spike. Different lines are drawn from repeated presentations of the same stimulus in the course of a longer experiment in which the animal had to identify and discriminate visual stimuli. Trials with different stimuli were tested in between and are not shown. Segments of the record with distinct patterns of response are separated by short horizontal dashed lines (for details see text).

which occurred at eccentricities of more than  $10^\circ$ . Receptive field sketches are shown for each group in Figure 2A.

Figure 2B shows the fraction of neurons which demonstrated episodes of local unresponsiveness (markedly reduced responses while the monkey was still performing the task) from the total number of neurons in every group. More often such episodes were recorded in neurons with peripheral receptive fields, whereas only few neurons near the fovea revealed such a property. In the second animal, neuronal activity was only recorded in the central part of area V4, within representation of neurons of the first (86 neurons) and second (57 neurons) group. In each group we recorded three neurons revealing episodes of local unresponsiveness. One of us has seen such episodes before in chronic experiments on cats. In drowsy but behaviorally still active animals, responses to external stimulation were seen to be

diminished or completely blocked in extrastriate cortical areas in the suprasylvian gyrus, and also in the associative somatosensory area 5.

## Discussion

Our observations reveal that in drowsy animals visual responses in the extrastriate cortex may be reduced or even completely blocked while the animals continue to perform in a visual task. This decrease in neuronal responsiveness can hardly be regarded as an effect of habituation which is known to exist in extrastriate areas. Habituation effects develop over a much shorter time (seconds). Response attenuation usually disappears after a short pause, and simply the elongation of interstimulus time intervals or a change of the shape of the stimulus is sufficient to restore the full response. In our task, the stimuli over the receptive field varied from trial to trial, and intervals

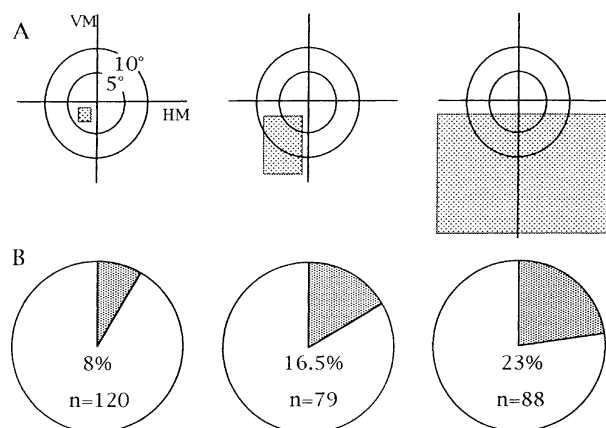


FIG. 2. Non-homogeneous development of local unresponsiveness within V4. (A) Schematic drawing of receptive fields of three groups of neurons with different receptive field locations. VM, vertical meridian; HM, horizontal meridian. (B) Fraction of neurons which demonstrated episodes of local unresponsiveness, from the total number of neurons in the corresponding group.

between subsequent presentations ( $\geq 7$  s) were long enough to exclude habituation. The lack of habituation effects can also be seen from Fig. 1. Responses were stable during the first 30 minutes of the experiment and then diminished for all subsequent stimulus presentations.

One could argue that local unresponsiveness of neurons in V4 was due to satiety or to the possibility that the animals lost their interest in the visual stimuli. We do not think that such an assumption could explain our observations. The animals were never forced to perform the task and could stop working in the experiment at any time. Instead, however, they continued to perform the task even in periods when neurons in V4 were found to be unresponsive, with hit rates well above chance level (though performance during such periods was sometimes slightly reduced compared with that of the fully alert animal). If, on the other hand, animals did lose their interest in the task and stopped working for some time, without signs of drowsiness, a reduction of responses in V4 was rarely seen. Finally, although episodes of local unresponsiveness were often seen in the second half of a recording session, in some experiments such episodes were seen quite early and disappeared later. Neuronal responses then remained strong until the end of the session.

We think that, rather than habituation or potential disinterest, the observed changes in neuronal firing resemble properties of sleep. The reduction of neuronal excitability was very similar to that

described for cortical neurons during sleep,<sup>4</sup> and background activity during periods of reduced responsiveness appeared to be the same as in periods when the animal slept completely. Episodes of local sleep were only seen in drowsy animals and they were much more frequent in the animal which apparently experienced stronger sleep pressure and fell asleep during recording sessions. On the other hand, when sleep pressure was reduced after a short nap, neuronal excitability was usually restored. We therefore conclude that the described effects indeed reflect processes of sleep. This sleep, however, remained local because the animals could still perform the task indicating that the primary visual cortex was still involved in visual processing.

## Conclusion

The observations presented here suggest that sleep does not necessarily develop simultaneously in all cortical areas but may spread from associative cortical areas towards primary sensory representations which fall asleep last. In area V4, episodes of local sleep were more often observed in the representation of the periphery of the visual field than in that of the center, which suggests that even within one cortical area sleep may develop dynamically from periphery to the center of the visual field.

In normal life, development of sleep may be a fast process and onset asynchrony may be difficult to observe. But in cases when behavioral requirements, as in our experiments, counteract the sleep pressure, local sleep of some but not all cortical areas may be a stable and long-lasting phenomenon. This partial inactivation of cortical areas could be the neuronal basis of diminished cognitive abilities and attention deficits in drowsiness or after sleep deprivation.<sup>8</sup>

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