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Context, state and the receptive fields of striatal cortex cells

Florentin Wörgötter and Ulf T. Eysel

Visual cortical cells are commonly characterized by their receptive-field structure. Originally, a visual receptive field was defined in a purely spatial way as that retinal area from which a change in spiking response of the regarded cell could be elicited by visual stimulation. The first attempts to understand receptive-field structure were based entirely on the anatomical connectivity of the primary visual pathway. More recently, however, it has been discovered that the spatial and temporal context in which a stimulus is presented to a cell can strongly influence its receptive field, and this in turn is dependent on the state of arousal and attention. Accordingly, new concepts recognize that cortical receptive fields are highly dynamic entities embracing more than the sum of the full spatial and temporal response properties of a cell.

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INFORMATION PROCESSING in the brain relies on the coordinated activity of its individual single neurons. This led to the traditional physiological approach of recording from single cells, in order to decode functional mechanisms from their responses. To this end, a sensor organ (for example, the retina) is stimulated and its primary (or higher order) afferents are monitored. In this framework, cells were regarded as passive input–output systems that perform some kind of transformation. Accordingly, a visual receptive field was thought to be a spatially defined retinal area that reacted in a rather static way such that the same stimulus led to identical responses differing only because of stochastic variations (noise).

However, the visual world at the level of a single cortical cell (outside an electrophysiology laboratory) is anything but predictable. Receptive fields of cortical cells often encounter new stimulus situations, owing to fast (saccadic) eye movements, which occur at an average rate of 3/s, or to object motion in the viewed scene, or both. Even during fixation or smooth pursuit, retinal positioning errors induce target shifts that lead to a fast changing stimulation of the cortical cells. These effects can be interpreted as a constantly changing flow of information that enters the visual system. The cortical network has to react to these changes in order to create a reliable visual perception. As a direct consequence of the fast changing signals that arrive at any given cortical cell, a strongly varying activity pattern is observed as its output. Through lateral and feedback connectivity this activity re-enters the cortical network at all levels and is able to influence even those cells (and especially their receptive field structure) from which it initially originated. It now seems clear, therefore, that the (anatomical) structure of the connectivity, together with the ongoing activity in the network, defines the actual response of a cortical cell to a specific stimulus (and thereby its receptive field) at any given point in time. In this article, the gradual shift of paradigm of the concept of a visual cortical receptive field is described, covering a multitude of spatial and temporal observations on different scales. First, it will be demonstrated that visual perception is influenced at the cellular level by visual context. Second, how the dynamics of cortical

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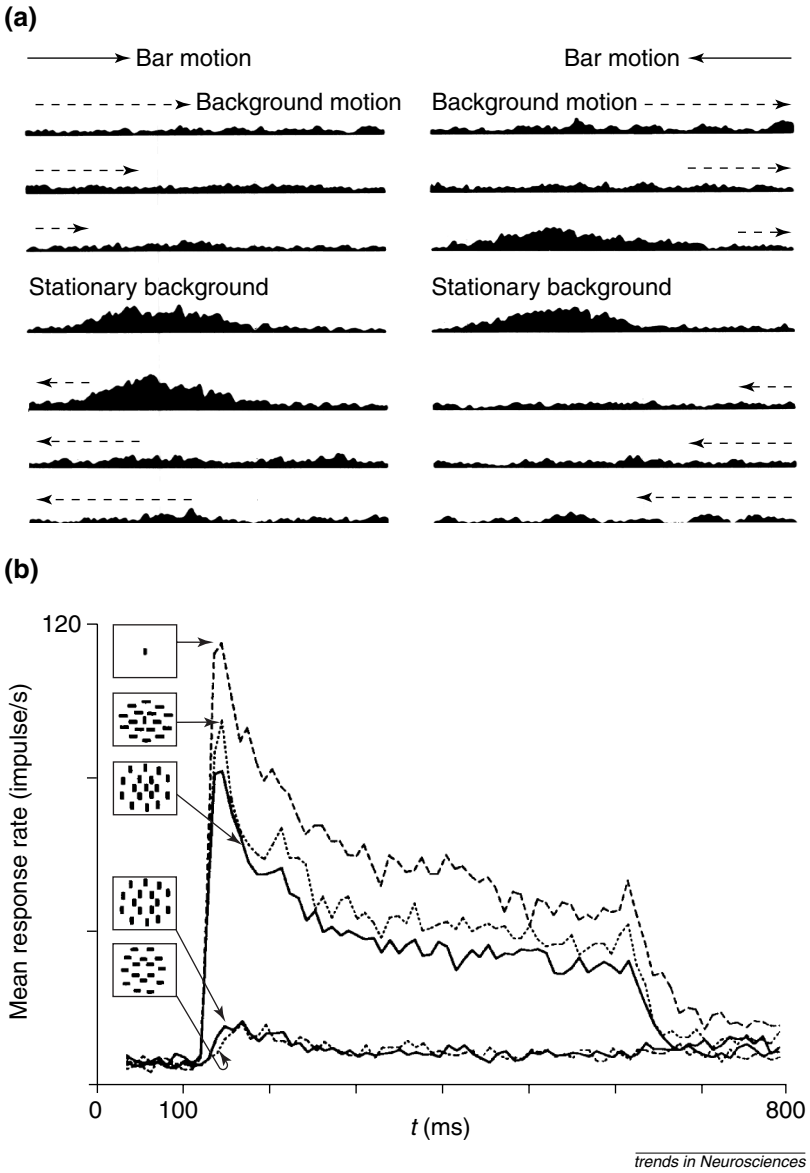

Fig. 1. ***Spatial stimulation context influences cortical responses.*** **(a)** *Differential effects of bar and texture background motion on the response of an area 17 cell in the cat. In these experiments, a bar (direction and velocity of motion is depicted by the solid arrows above) was presented together with a background (texture) pattern (direction and velocity of motion shown by broken arrows below); it was generally found that simultaneous motion of bar and background reduced the cell responses, regardless of the direction of bar motion. However, in many cells the direction selectivity can be enhanced when bar and background motion are opposite (right). In most cases background motion depresses the cell response, only slow background motion opposite to the direction of the bar motion leads to an overall facilitation as judged by the total spike count. This leads to strongly enhanced direction selectivity in this cell. The lower traces show the responses when the bar was moved on a stationary background. Both movement directions lead to similar responses and, thus, no direction selectivity is observed* **(b)** *Context-dependent response changes in monkey. A field of surrounding stimuli influences the temporal characteristic of the cell response to a bar stimulus with optimal orientation inside its receptive field. The small insets depict the different contextual situations. (a)* Reproduced, with permission, from Ref. 24, and (b) reproduced, with permission, from Ref. 26.

cell responses change as a consequence of the ongoing network activity will be shown. And finally it will be demonstrated that even the general state of arousal–attention changes the characteristics of the cortical receptive fields. Given the repetitive structure of the cortex in general, it seems reasonable to assume that similar properties also govern other (sensory) cortices.

Foundations – the traditional view

Receptive fields in the striate visual cortex (V1) were first described by Hubel and Wiesel[1,2]. Using moving or flashing bar stimuli, they discovered that simple-cell receptive fields in the cortex consist of elongated (ON- and OFF-) subfields, from which responses can be directly elicited by bright or dark stimuli, and described their specificity to the orientation of the stimulus and its direction of motion[2]. They also discovered other cell classes (complex and hyper-complex cells), which have an even more complicated basic spatial receptive-field structure (for example, overlapping subfields and end-inhibition). However, contextual effects, which are one of the key topics in this article, are already observed in rather an exemplary way in simple cells of the cortex. All the early-observed cortical-cell properties were initially explained by feed-forward, excitatory, afferent convergence from visual thalamic cells [lateral geniculate nucleus, LGN (Refs 2,3)]. However, inhibitory responses were found between antagonistic subfields (mutual inhibition[4]) and, in particular, inhibition could also be elicited from regions adjacent to the subfields (for example, end-inhibition at the long end of a subfield[5–7] or inhibitory side-bands that flank the subfields[8,9]). Consequently, cortical receptive-field models had to be extended to include intracortical feed-forward lateral inhibition, because direct inhibitory afferent connections do not exist. This led to the subdivision of a cortical receptive field in the spatial domain into the classical receptive-field center, defined by excitatory (ON- and OFF-) regions, and a spatially adjacent surround[10,11], which mainly exerts modulatory[12] or inhibitory influences[13], or both. (For a review of these older studies of cortical receptive fields see Orban[14].)

Stimulation context changes cortical responses – influences on visual perception

Special stimulus protocols were designed to investigate the interactions between central and more-distant, peripheral parts of the receptive field[11,13,15–17]. Of particular relevance for visual information processing were those studies that showed how cortical cells change their responses in a context-dependent way.

Direction selectivity is influenced by stimulation context

Experiments performed in cats, mainly by Hammond and Orban *et al.*[18–24], and later in monkeys by Sillito and co-workers[25], showed that the perception of relative motion and also certain motion after-effects could have their origin in context-dependent receptive-field effects (Fig. 1a). Essentially, it was found that relative motion was enhanced at the cellular level, which could underlie the similar enhancement effect observed at the perceptual level. Large field, unidirectional background motion can also lead to an adaptation of those cells, which are selective for this particular direction. This effect could be the basis of the so-called 'waterfall' motion after-effect[26]: that is, when concentrating for some time on a wide-motion field with constant velocity and direction (like falling water in a waterfall), the observer will perceive motion in the opposite direction as soon as he looks away. An imbalance between the spontaneous firing of the adapted downward selective cells, versus the non-adapted upward selective cells, could be the source of this percept.

Orientation selectivity is influenced by stimulation context

A different group of experiments demonstrated that the orientation tuning of cortical cells is also affected by the stimulation context. In general, a wide variety

of effects are observed[27–34]. Two are particularly relevant to visual perception.

(1) Presenting a stimulus with preferred orientation in the receptive field center together with many orthogonally oriented surround stimuli will enhance the response, whereas similar orientations in the surround will suppress it[28,31] (Fig. 1b). This effect is further augmented by the relative contrast between center and surround stimuli[35].

(2) Cells also adapt to stimulus orientation in a way that is similar to motion adaptation (see 'waterfall effect', above). After prolonged presentation of a sinusoidal grating, the orientation preference of the cells will shift away from the orientation of the grating stimulus[36]. Recently, it was found that such adaptation effects could be rather fast, such that even short successive representations of similar images could influence the cell responses[37].

Both of the above could contribute to the perception of 'orientation pop-out'. (In a field of similarly oriented lines any group of lines that has a significantly different orientation will immediately 'pop-out', without having to be found by a serial visual search[29,38,39].)

Receptive field size is influenced by stimulation context

In addition, the phenomenon of perceptual filling-in could have a direct neuronal correlate at the level of receptive fields in striate cortex. To demonstrate this, the 'artificial scotoma' was introduced as an experimental paradigm by Gilbert *et al.*[40–42]. An artificial scotoma is a gray area centered on the receptive field of a cell within a surrounding pattern of moving lines or twinkling dots. After prolonged presentation of this stimulus it was shown that the receptive fields inside the artificial scotoma were significantly expanded[40–42]. The robustness of this effect, however, was questioned by other groups[43,44], although this might have been a consequence of a different interpretation of the data[44]. It is well established that a true (for example, lesion-induced) scotoma is to a large degree compensated for by fast perceptional filling-in[45]. However, it is not entirely clear that this situation can be unequivocally mimicked by an 'artificial scotoma', which is only another type of visual stimulus. This could, for example, lead to adaptation[46], and thus will not produce identical effects to those of a real scotoma.

The observations described in the previous section have demonstrated that significant spatial influences arise from regions that are distant from the classical receptive field, and can in some instances be interpreted in terms of visual perception. Several of the described findings (for example, adaptation effects), however, indicate that the temporal stimulation history is particularly important in shaping the actual response.

Stimulation history influences the cortical responses – the dynamics of cell behavior

Temporal changes caused by synaptic processes

One way to explain the relatively slow adaptation effects is to assume a gradually changing level of synaptic sensitivity that, after a while, leads to a significant reduction of the response to the adaptation stimulus. Indeed, short-term, synaptic changes have been reported by several groups[47–49]. They found that the synaptic response to a single stimulating current pulse could be larger or smaller than the response to the second or to subsequent pulses, depending on the type of synapse and on the experimental situation.

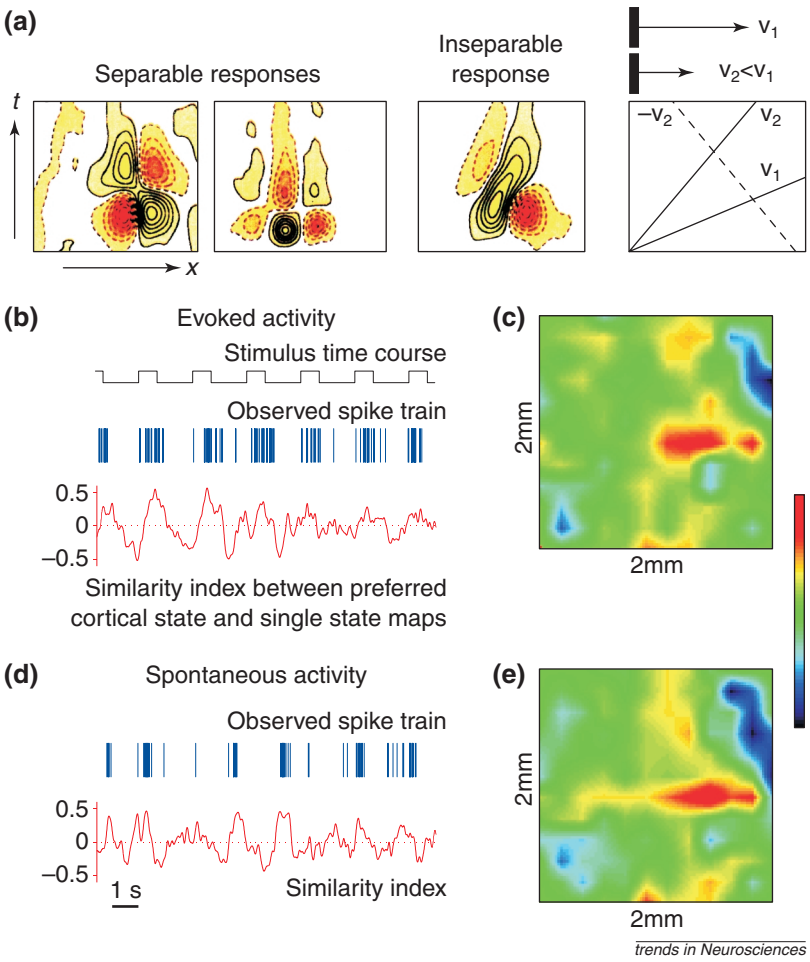

Fig. 2. Temporal *stimulation history influences cortical responses.* (a) *Spatiotemporal receptive field plots recorded with the reverse correlation technique showing how simple-cell ON- and OFF-subfields develop with time in the cat. The x-axis represents the axis that cuts across the preferred orientation of the cell. Only some simple cells ON- (unbroken altitude lines) and OFF-subfields (broken lines) can be separated from each other by vertical and horizontal lines. These cells have spatiotemporally separable receptive fields (left). These studies are also of major relevance in explaining direction and velocity sensitivity. Two stimulus situations of a moving bar with different velocities are depicted on the right ($v_2<v_1$), which result in a different slope in the x–t profile. Only the trajectory of the slower stimulus (v_2) matches the oblique ON-subfield of the inseparable simple cell profile shown on the left. Thus, an optimal response will be obtained only if the temporal structure of stimulus follows the temporal structure of the receptive-field dynamics. Obviously, a stimulus moving in the opposite direction ($-v_2$, broken line) will never lead to a good match. Thus, this simple cell is also direction selective.* **(b)** *Correlation between spike firing and the 'preferred cortical state' map. In a first set of experiments Tsodyks and co-workers[56] measured cortical maps with optical imaging at high resolution, together with the activity of a single neuron. These maps were averaged whenever the cell fired a spike in response to an optimally oriented stimulus (grating). The resulting average map is called the 'preferred cortical state' map of this neuron* **(c)**. *In a second experimental test, a continuous cross-correlation was computed between single frame maps and the preferred cortical state map* (b). *It demonstrates that this cell prefers to fire (see spike train) whenever the activity of the patch that surrounds it resembles the preferred cortical state map (see peaks in the red curve). The same is true for spontaneous activity* **(d)**. *When those states that belong to a spontaneously fired spike are averaged, the resulting map is similar to the preferred cortical state map* **(e)**. (a) Reproduced, with permission, from Ref. 55, and (b)–(e) reproduced, with permission, from Ref. 56.

Often, however, a reduction of slope and amplitude of the second EPSP at a cortical pyramidal cell was observed and interpreted as momentary synaptic depletion. These effects take place within milliseconds and do not necessarily persist, whereas adaptation usually has an influence over several minutes on visual perception. Therefore, short-term synaptic changes can only be the starting point and additional longer term mechanisms (like short- and long-term depression and potentiation – STP, STD, LTP and LTD) are also necessary.

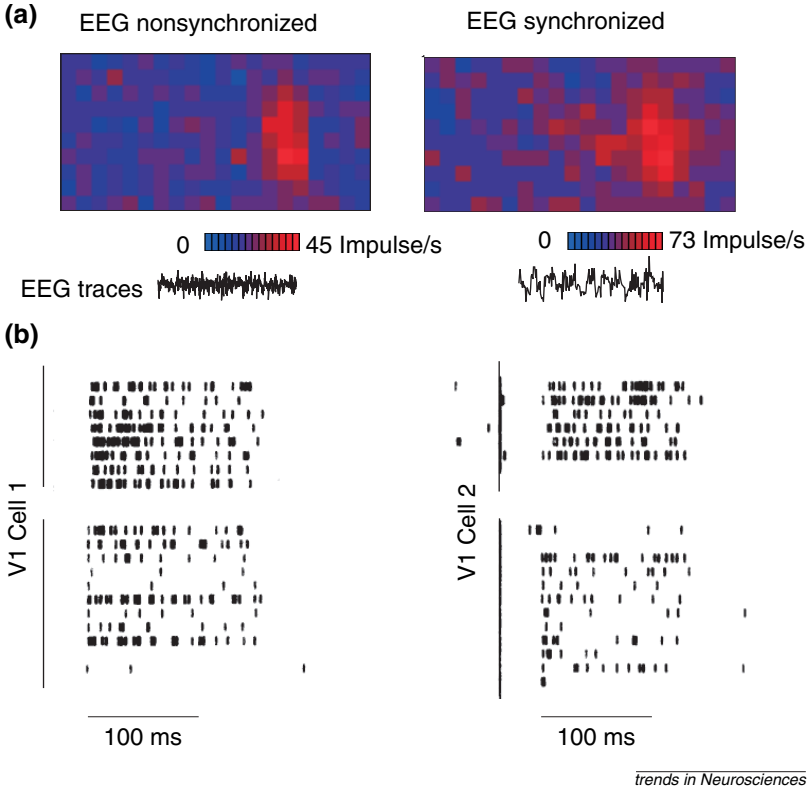

Fig. 3. State of vigilance influences cortical responses. **(a)** *State-dependent receptive-field size change in a simple cell OFF-response in the cat. Receptive fields are wider during a synchronized EEG than during a nonsynchronized EEG. EEG traces are shown at the bottom.* **(b)** *Raster displays of the responses of two V1 cells (monkey) during a fixation task. Before stimulus presentation, attention was either directed towards (top) or away (bottom) from the receptive-field location of the recorded cell without moving the eyes. The vertical line depicts the stimulus onset. Attention towards the receptive-field location enhances the response.* (a) Reproduced, with permission, from Ref. 73 and (b) reproduced, with permission, from Ref. 74.

All these observations require synaptic modifications and strongly bear the characteristics of a feed-forward effect taking place between a source cell and its target. By contrast, the following studies show that the structure of a receptive field can undergo complex changes on very short timescales, which also need dynamic feedback.

Recurrent network effects - the concept of 'effective connectivity'

In order to obtain a more detailed picture of the spatiotemporal structure of a receptive field, 2D field maps were measured in multiple, subsequent, short time-windows following stimulation ('reverse correlation technique'[50–55]). If viewed one after the other, these windows create a movie of the waxing and waning cortical responses and, thus, of the changing structure of a receptive field in time. To concentrate on the temporal changes the spatial dimension parallel to the preferred orientation of the receptive field in this movie is collapsed and a single *x–t* profile is generated that depicts the temporal development of the receptive field (Fig. 2a).

As expected, these time-resolved receptive-field profiles reproduced the general ON–OFF substructure known from older studies of cortical simple cells. In addition, however, for many cells it was observed that their orientation tuning develops within the first 40–80 ms of the response[57], and that the ON and OFF subfields are tilted in time[55] (Fig. 2a). This indicates that the spatial and temporal response components of such a cell cannot be dissociated: their receptive fields are directionally tuned and spatiotemporally inseparable. Quantitative estimates of the degree of directional tuning, however, are not possible with these receptive-field profiles, probably because of additional nonlinear effects that enhance direction selectivity (for example, nonlinear feed-forward inhibition in the nonpreferred direction[58,59] or nonlinear temporal summation in the preferred direction[55,60], or both). Indeed, strong evidence exists that inhibition shapes cortical receptive fields, for example, by keeping receptive fields small and subfields separated[61,62].

The speed of all such receptive field changes requires very fast mechanisms. The complexity of these changes (for example, tilted profiles), in addition, argues in favor of a mechanism that generates a rich dynamic behavior. Feedback loops are therefore the only true candidates. Feedback, however, leads to the effect that the neuronal activity of a given cortical cell can, in principle, modify itself through re-entry. What are the consequences for a single synaptic connection?

In general, one way to define the synaptic strength is by quantifying the efficiency of signal throughput at the considered connection. The re-entry of network activity, however, strongly influences the momentary membrane depolarization level of a cell, which, in turn, will determine the efficiency of signal throughput at every synapse connecting to it. Thus, it must seem that the strength of a given synaptic connection (measured by its throughput) is continuously varying. In order to account for this phenomenon, the term 'effective connectivity' has been coined by Aertsen *et al.*[63,64]. It points to the fact that the actual synaptic efficiency of a connection can be judged only in conjunction with the history of the membrane potential of the cell, which in itself is a reflection of the past network activation. Short-term synaptic changes[47,48] could have their origin here. Direct evidence for the strong influence of the membrane potential history was provided by Azouz and Gray, who showed in intracellular recordings that the probability for spiking depends on it[65]. For example, spikes are elicited at a given threshold level much more reliably when the slope of the membrane potential depolarization is steep. This is probably due to the kinetics of the Na^+ channels, which desensitize when depolarized too slowly. In a series of experiments Arieli and co-workers used optical imaging with voltage-sensitive dyes and recorded 2D signals that are similar to a local 2D field potential recorded with a very high spatial and temporal resolution[56,66,67]. These studies impressively demonstrated how strongly the activation history of the patch affects its current responsiveness. They showed that, for a given cell, spikes are preferably elicited when the cortical patch, within which the cell is contained, displays a specific activation pattern, which they called the preferred state of that cell[56] (Fig. 2b). Although the studies of Gray remain spatially restricted, the work of Arieli shows that really the activation history of a spatially rather extended region needs to be taken into account when trying to predict the momentary cell response and, thus, the dynamically changing shape of its receptive field.

These results demonstrate that receptive fields are not only spatially but also temporally determined entities. Their dynamically changing structure cannot be simply understood in terms of rigid feed-forward connectivity. In addition, synaptic changes in the mil-

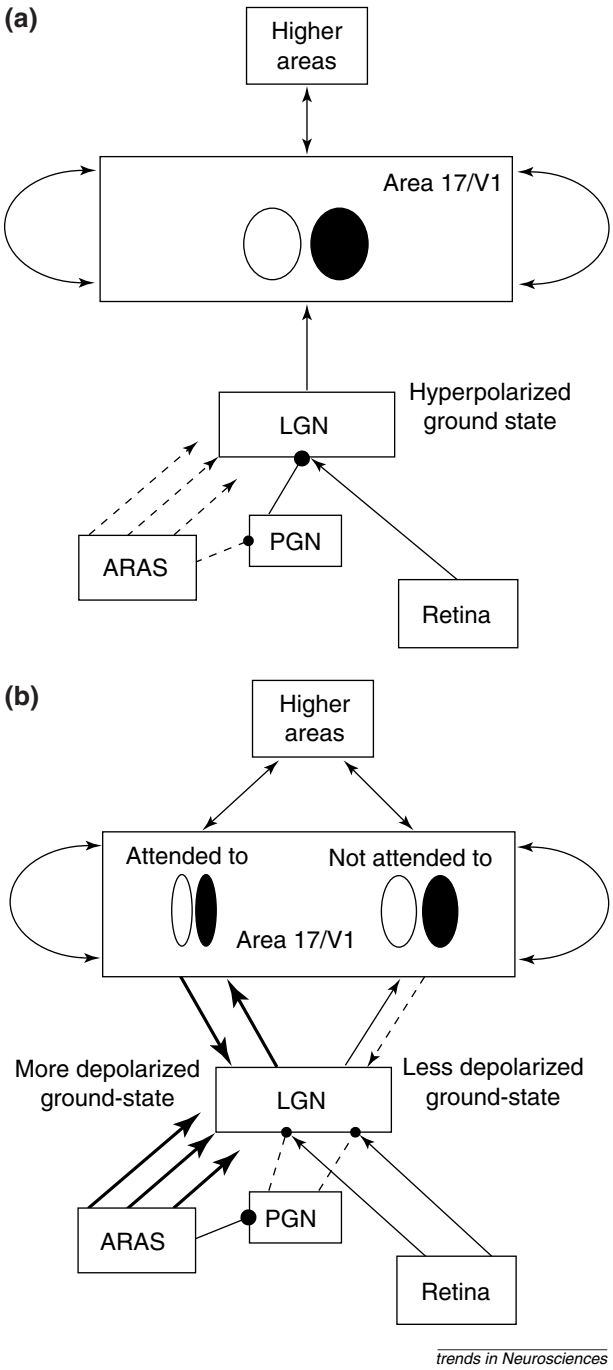

Fig. 4. ***Functional speculation about the spatial changes of cortical receptive fields observed in parallel to an EEG transition from a non-synchronized to a synchronized EEG.*** *During a synchronized EEG* **(a)**, *the ascending reticular arousal system (ARAS) exerts little influence on the thalamus [lateral geniculate nucleus (LGN), perigeniculate nucleus (PGN)]. PGN inhibition is efficient*[89] *and LGN cells are in a hyperpolarized ground state and fire in burst mode leading to wide cortical receptive fields. During a nonsynchronized EEG* **(b)**, *the ARAS is active and PGN inhibition is low. LGN cells are in a depolarized ground state firing in tonic mode, and cortical receptive fields are smaller than during synchronized EEG. The momentary size of cortical receptive fields in this situation might be strongly influenced by the corticofugal feedback loop*[90]*. This speculation rests on the assumption that feedback is stronger in those patches of cortex where the focus of attention is currently active. Accordingly, LGN cells that receive this feedback are in a more-depolarized ground state, whereas adjacent zones of the LGN remain in a less depolarized state. This could lead to relatively smaller receptive fields under the focus of attention (and, accordingly, to an enhanced spatial resolution) than everywhere else. Currently, evidence exists that cells in the primary visual area (V1) change their activity in an attention-dependent way*[74,82–86]*. Whether this leads to the proposed size change of their receptive fields will require more-detailed experimental analysis. Lines ending in arrowheads indicate excitation, lines ending in solid circles indicate inhibition. The width of the lines indicates the amount of activity, broken lines indicate the lowest activity.*

lisecond range, as well as feedback-driven modifications of the network history, which can affect the effective connectivity of a synapse, need to be taken into account. By employing this framework, more-concise explanations were found for some long-known features of cortical receptive fields, such as their adaptation and direction selectivity.

Vigilance influences cortical responses – state-dependent information processing

States of arousal

Apart from the processes that rely on the fast intrinsic dynamics of the visual network in the millisecond range, recent observations have shown that cortical receptive fields can also change on a timescale in the range of several tens of seconds. For example, the degree of synchronization of visual cortical responses as reflected in the EEG can be influenced in a longer lasting way by electrical stimulation of the brainstem[68], which induces experimentally an aroused state in the animal.

The frequency content in the EEG is normally used to distinguish between sleepy and aroused states. During drowsiness α waves (~8–13 Hz) interspersed with θ waves (4–7 Hz) prevail, whereas deep sleep is characterized by δ waves (~0.5–4.0 Hz). The EEG during drowsiness and sleep is called synchronized EEG. During alert, wakefulness β waves (~13–30 Hz) are mainly observed in a so-called nonsynchronized EEG. During rapid eye movement sleep, β waves also dominate. Spontaneous state transitions occur even in the anesthetized preparation. These spontaneous transitions are strongly correlated with dramatically changed response characteristics of the cortical afferents: the thalamic relay cells[69]. During synchronized EEG ('drowsiness, sleep') thalamic cells are hyperpolarized[70] and respond in the so-called 'burst-mode': spontaneous activity is low and responses to stimulation are dominated by brief high-frequency bursts (for a review, see Ref. 71). Intriguingly, the temporal behavior of cortical cells upstream of the thalamus is much less affected by EEG state changes[72]. The spatial structure of the receptive fields, however, is, and cortical receptive fields decrease in size when the EEG switches from the synchronized to the nonsynchronized EEG state[73] (Fig. 3a). This effect can be attributed to a changing effective connectivity of the thalamocortical synapses during different EEG states. Bursts in the LGN, which occur during synchronized EEG, will result in a much higher effective connectivity, lead to a large point-spread of activity and, thus, to wider receptive fields. This effect can be understood in terms of strong temporal summation. The opposite is true for the weaker, more-tonic thalamic activity during nonsynchronized EEG. It needs, however, to be emphasized that this feed-forward component probably serves only as an initial trigger to elicit other more-complex intracortical processes[42,75]. These processes can amplify the initial receptive field differences on a spatial scale that exceeds the afferent arborization. In addition, inhibitory influences driven by the basal forebrain[76] could be involved in the sharpening of receptive fields during arousal.

Attention

Attention effects on cortical cell responses were first reported for higher visual cortical areas[77,78]. In Fig. 3b, however, two recordings are shown, which demonstrate that responses in V1 can also change significantly when the focus of attention is changed[74]. Many groups initially did not confirm these findings and failed to show attentional response modulation in V1 (Refs 79–81). More recently, however, new evidence has accumulated that V1 is also actively involved in attention effects[82–86]. In V1, and even at the level of the thalamus, it has been observed that attention suppresses the activity in a retinotopic band peripheral to the representation of the stimulus[87]. In general, studies in V1 have mainly found that attention modulates firing rate. So far, spatial receptive-field changes have not been reported. This, however, could be due to the small size of V1 fields. In an awake experimental animal, attention-induced spatial changes of a receptive field would fall easily within the range of remaining eye movements during fixation, which would efficiently prevent the measurement of attention effect[88].

In the last section, it has been shown that receptive fields can change their appearance as a result of intrinsic control mechanisms, involving either voluntary attention or general states of arousal. One can speculate that the resizing of receptive fields serves to adjust the visual resolution: that is, during drowsiness or sleep, a fast (burst) but coarse (wide receptive field) wake-up stimulus would suffice, whereas during attentive wakefulness detailed visual analysis requires smaller receptive fields (Fig. 4). The concept of effective connectivity has proven useful at this stage in explaining how changes in thalamic temporal firing patterns can translate into spatial receptive field changes at the level of the cortex.

Concluding remarks

The receptive field of a cell can intuitively be regarded as the aperture through which it receives its input; and movements of either the eye or the stimulus will lead to fast changing luminance patterns inside this aperture. Thus, at a first glance, individual V1 cells have a spatially and temporally very restricted 'view of the world'. At the small scale of such a receptive field, very similar luminance patterns will occur rather often in a normal viewing environment; many times, one and the same luminance pattern can be part of entirely different objects and situations. Only the spatial and temporal visual context can help to decide to which situation this pattern actually belongs. As a further complication, stimulation with the same pattern can nonetheless require very different reactions, depending on the state of vigilance of the individual[91]. Thus, information about the external visual context, both spatial and temporal, as well as information about the state of the individual have to be integrated for adequate analysis of a scene and to elicit the right behavior eventually (for a review see Ref. 92). This article has summarized evidence that already at the level of cortical receptive fields in V1 (and in some cases even in the thalamus) significant aspects of the required contextual information are collected and used to modify the responses in a context-dependent manner. A number of perceptual phenomena can be explained this way. More importantly, by taking advantage of context and state, the response of a cortical cell can adapt rapidly to the changing demands for information processing in the visual world. As a consequence, visual perception is actively shaped already within the primary visual pathway, which can lead to very different responses to the same objects if they are seen in different contexts. Conversely, receptive-field aspects reveal themselves always in a context- and state-dependent way, and a receptive field can no longer be regarded as passive input–output transformation device, instead it needs to be seen and analyzed as a highly dynamic and active structure.

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