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Synaptic integration fields and associative plasticity of visual cortical cells *in vivo*

Y Frégnac, V Bringuier, F Chavane

Équipe Cognisciences, Institut Alfred Fessard, CNRS, 1, ave de la Terrasse, 91198 Gif-sur-Yvette, France

Summary — Two major constraints in connectivity decide the spatial extent of visual cortical receptive fields, both during development and adult functioning: 1) feedforward input, extrinsic to visual cortex, is organized in an orderly projection to form a point-to-point mapping of the retina onto the cortical mantle and constitutes the core of the minimal discharge field (MDF) after amplification by local intracortical circuits; and 2) a second type of connectivity consists of long distance horizontal intracortical connections which are thought to favor the binding of local visual operations occurring simultaneously in different parts of the visual field. We review here possible factors, intrinsic to the considered cortical cell, that may control the effectiveness of post-synaptic integration. Their expression during sensory recognition could depend on the spatio-temporal distribution of active inputs onto the target cell dendrite and on their interplay with non-linearities of the membrane properties. On the basis of intracellular recordings in cat area 17, we have observed that peripheral responses (excitatory and inhibitory) could be boosted by coincident postsynaptic depolarization. This effect is lost if the response and the postsynaptic depolarization are mismatched by 1000 ms, suggesting that temporal correlation of central and peripheral responses could regulate in a non-linear manner the gain of center-surround interactions. This temporal selectivity is compatible with up-regulation of composite potentials by the transient voltage-dependent activation of slowly inactivating conductances in visual cortical neurons. A direct consequence of these different considerations is that the receptive field (RF) of neurons in visual pathways should not be considered as a static hardwired window probing the outer environment, but as an active filter which may continuously adapt and be updated as a function of global context and past experience.

graph matching theory / horizontal connectivity / center/surround / receptive field / intracellular recording *in vivo* / slowly inactivating conductances / synchrony

Introduction

Milner was probably the first theoretician to propose explicit rules for the compositionality of cortical assemblies (Milner, 1974). One of his postulates was that repeated coactivity patterns arising in a closed circuit of cells would reinforce the synaptic links between them, and in addition 'prime' a certain number of connections, as yet subthreshold, for further recruitment. The latent 'tagged' synapses would remain transiently eligible for further potentiation by the contiguous firing of other assemblies. Repeated sequential activation would thus reinforce the primed connections so that they become an integrative part of the next active assembly, therefore resulting in the recall of the learned set of associations.

The prediction that Milner made in 1974 was that temporal correlation might be used by cortical networks to bind elementary representations into a cognitive 'whole', on a much faster time scale than initially proposed by Hebb: "*if adjacent, or nearly adjacent, cells interact when excited, in such a way as to synchronize and perhaps intensify each other's activity, this could provide the unifying characteristics that tie the elements of a figure together. At subsequent levels of the pathway, impulses from the cells fired by one whole would arrive as synchronous volleys, whereas impulses from different figures would have a random temporal relationship to each other*" (Milner, 1974).

A related formalism was revived 7 years later which postulated fast binding processes during visual shape recognition depending on the temporal correlation of firing between co-stimulated cells (Von der Malsburg, 1981, 1986). The hypothesis of 'fast Hebbian synapses' made by Von der Malsburg (Bienenstock and Von der Malsburg, 1987; Von der Malsburg and Bienenstock, 1987; Von der Malsburg and Singer, 1988) offered a new field of validation for Hebbian associative theory, in the millisecond time scale (see also Softky, 1994) rather than the classical developmental scale which is supposed to take place over hours or days. Theoretical studies of graph matching assume the temporal propagation of synchronous activation events across distributed cell ensembles ('synfire chains') (Abeles, 1982, 1991), where binding would be promoted between polysynaptic circuits that satisfy transitivity rules in transmission delays (Bienenstock and Doursat, 1991).

What neurobiological substrates could explain the waxing and waning of functional coupling? Some may be characteristic of fast redistribution of synaptic efficacy since it is well known that the evoked response in cortical cells elicited by presynaptic spikes activating the same synapse less than 50 ms apart undergo fast up- and down-regulations in amplitude. It is indeed well established that two successive stimulations of the same presynaptic fiber induce paired-pulse depression or potentiation of the test response and the amplitude of this effect is related non-linearly to the past interval

since the presynaptic cell has last fired (review in Magleby, 1987; Thomson, *et al*, 1993a). Recent evidence obtained in identified synapses between pairs of neurons recorded intracellularly suggests that the sign of the change might be dependent on the initial synaptic efficacy (Debanne *et al*, 1996), the weaker the synapse, the more readily it will be susceptible to potentiation, and thus play the role of the latent 'tagged' connections that were imagined by Milner to participate to the growth of the chain of synchronous activity. The alteration in synaptic gain also depends on the nature of the postsynaptic cell if not of the type of connection, since excitatory synapses onto an excitatory cell become readily depressed (Markram and Tsodyks, 1996) whereas their efficacy of transmission may be potentiated if the target cell is an inhibitory interneuron (Thomson *et al*, 1993b). Such fast changes in synaptic gain are thought to be predominantly of presynaptic origin, and linked to free calcium accumulation or depletion and alterations in vesicular recruitment which will affect subsequent liberation of neurotransmitter (Zucker, 1989). Nevertheless the implication of postsynaptic regulatory mechanisms cannot be excluded at both excitatory and inhibitory synapses and might involve receptor desensitization or fast-acting regulation of second messengers (reviewed in Marty and Llano, 1995).

Rationale of the experimental plan

In spite of a declared quest for 'fast' Hebbian synapses, reversible modulation of functional links, if it exists, does not require a recapitulation of the elementary subcellular processes responsible for Hebbian associative LTP and heterosynaptic LTD, in order to share a similar phenomenology accelerated on a 10^3 to 10^5 faster timescale. Another class of regulatory processes which cause strong non-linearities in the final summation and integration of synaptic events carried out by the postsynaptic neuron, is linked to the activation of voltage-dependent and temporally gated conductances allowing the cell to boost or damp the response to a test synaptic input during a fixed temporal window. For instance the work of Deisz *et al* (1991) in somatosensory cortex *in vitro* shows a strong APV-resistant voltage-dependency of synaptic potentials evoked by white matter activation. These authors demonstrated that a low threshold calcium current is responsible for the increase in size and duration of the initial EPSP appearing for more depolarized membrane potential values (fig 1a). The most remarkable feature of this process is that the amplification gain depends on the past history of the membrane potential, and acts over a critical temporal window, in the order of 100 to 200 ms following the onset of depolarization, during which the boosting of the postsynaptic response can be expressed independently of an actual change in synaptic transmission. When the cell has been kept depolarized for a longer period, the arrival of synaptic input, out of phase with the onset of the change in membrane potential, no longer benefits from the calcium inward current which is now inactivated (fig 1b).

How general is this process in cortical cells? It is now well established, at least in the pyramidal neurons of CA1, that apical dendrites possess voltage sensitive calcium conductances (Magee and Johnston, 1995a, 1995b). The currents are mainly of the T type (Christie *et al*, 1995), as found by Deisz *et al* in neocortical neurons (Deisz *et al*, 1991). At the level of dendritic spines, and shafts, retro-propagating action potentials elicit intracellular calcium transients that can cooperatively enhance the calcium accumulation resulting from synaptic activity (Yuste *et al*, 1994; Yuste and Denk, 1995). These have even been implicated in the induction of LTP following repeated activation of the same afferent pathway in the presence of APV (Komatsu *et al*, 1991). Other mechanisms of fast regulation of EPSPs may also be considered. In principle, a major source of voltage dependent amplification should be observed following NMDA receptor activation (Thomson, 1986; Stern *et al*, 1992), and visual responses elicited at rest have been shown to contain an APV-sensitive component (Miller *et al*, 1989). Another type of conductance which might prolong the depolarization evoked by an excitatory input is that linked to persistent sodium channels and has been described *in vitro* in somatosensory and visual cortical neurons (Stafström *et al*, 1984; Hirsch and Gilbert, 1991). Recent work on neocortical slices supports the hypothesis that very distal dendrites may have enough sodium channels to significantly amplify local synaptic inputs (Schwindt and Crill, 1995).

However, the diversity of conductances participating in the postsynaptic machinery offers symmetrical associative ways of damping afferent input, thus providing a normalization of synaptic weights, certain synapses being boosted whereas others might be transiently weakened. An example of this latter process can be found in non-cortical networks, such as the solitary complex (fig 1c, d). In this structure, which is a caudal bulbar relay of the brainstem involved in respiratory activity (Bianchi *et al*, 1988; Ezuré, 1990), Fortin and colleagues have shown that low threshold calcium currents present before birth (which in neocortical neurons are responsible for the associative boosting) are replaced during the first postnatal week of life by potassium currents at the same time that GABA-ergic

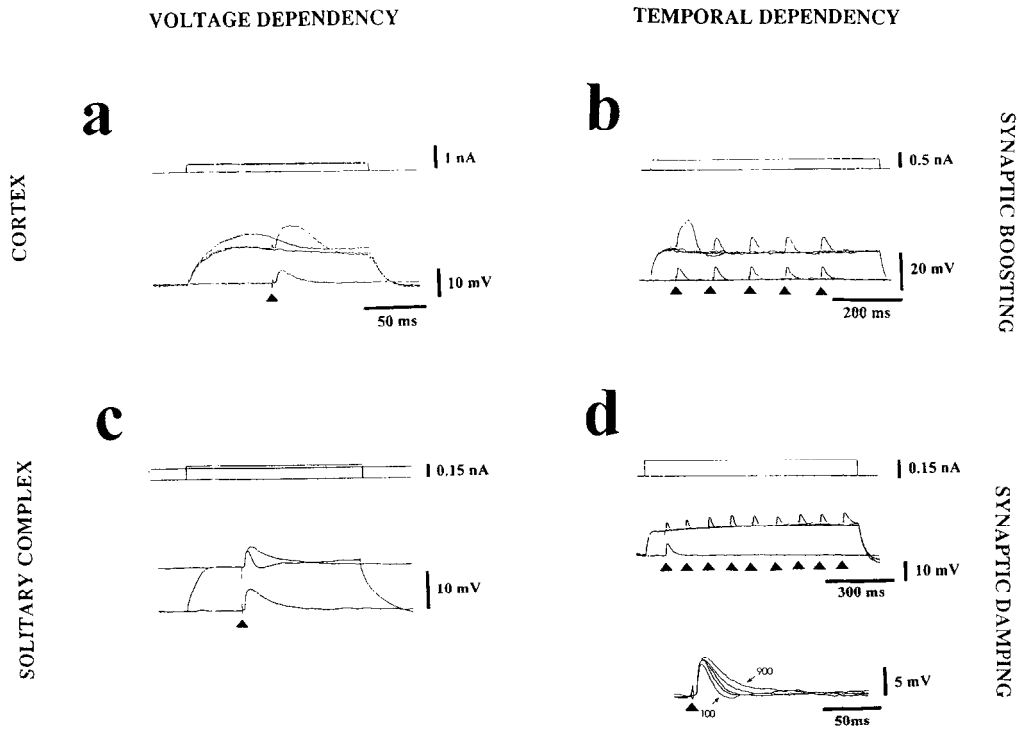

Fig 1. Role of slowly inactivating conductances in the modulation of the effective synaptic gain *in vitro*. **a, b.** Data adapted from Deisz *et al* (1991), with permission. **c, d.** Data adapted from Fortin (1993), with permission. **a.** Voltage dependency of EPSPs recorded in a rat sensorimotor cortex layer 2–3 cell and evoked by stimulation of white matter. The superimposed traces correspond to recordings with and without orthodromic stimulation at different levels of depolarization. EPSPs evoked at a depolarized level, 50 to 100 ms after the current onset are markedly larger than control EPSPs evoked at resting potential or evoked when the cell has been kept depolarized for a long time. The current step value is chosen just below the level of activation of the low threshold calcium current. **b.** Superimposed traces of EPSPs evoked in independent trials and positioned at different delays after the onset of the depolarizing current pulse. A selective enhancement of the EPSP is observed only for that evoked at a short delay after the onset of the current pulse. **c.** Voltage dependency of EPSPs recorded in a cell of the solitary complex evoked by stimulation of the solitary tract. The superimposed traces correspond to recordings with and without orthodromic stimulation at different levels of depolarization. EPSPs evoked at a depolarized level, 50 to 100 ms after the current onset are markedly shorter in duration than control EPSPs evoked at resting potential or evoked when the cell has been kept depolarized for a long time. **d.** Superimposed traces of EPSPs evoked in independent trials and positioned at different delays after the onset of the depolarizing current pulse. The comparison of the shape of all recorded EPSPs, shown in the lower inset, demonstrates the selective shortening of the falling phase of the EPSP, due to a potassium current (see text) activable only for a short period following the onset of the current pulse.

innervation appears (Schweitzer *et al*, 1992). Associative protocols similar to those applied in neocortical neurons reveal a transient damping of synaptic input at that age (Fortin, 1993). This opposite change in the modulation of the apparent synaptic gain is due to a potassium outward current, probably of the I_A type, which shortens the time course of EPSP if the depolarization has been applied within the last 100 ms, but is inactivated for longer delay periods (fig 1d).

Materials and methods

In order to test for the existence of boosting or damping of subthreshold inputs in visual cortical neurons, we decided to replay the protocol devised by Deisz *et al* in a more functional framework, presenting the same visual stimulus twice, one second apart, and to pair the onset of the first presentation with a maintained intracellular subthreshold current step injection (Bringuier *et al*, 1995). The aim of this work was several fold: i) to study the spatial and voltage depend-

ency properties of subthreshold responses in the periphery of the MDF; and ii) to determine how synchronization of one input with somatic current depolarization, or of different sources of subthreshold activity, could facilitate their postsynaptic integration.

Kittens, aged from 6 to 14 weeks (within the critical period), and adult cats were anesthetized with Althesin (synthetic steroid), and paralyzed with Flaxedil (gallamine triethiodide). Two technical approaches were used to record intracellularly from area 17 cells, using either: 1) sharp electrodes (50–100 MΩ glass micropipettes filled with potassium methyl sulfate (2 M) + KCl (4 mM) and in some cases QX314 (100 mM)) or patch pipettes using whole cell configuration (2–5 MΩ glass micropipettes, filled with standard K-gluconate solution: 140 mM K gluconate, 10 mM Hepes, 4 mM ATP, 2 mM $MgCl_2$, 0.4 mM GTP, 0.5 mM EGTA).

Once the intracellular recording had been stabilized and the basic membrane parameters of the cell were established using standard I/V procedures, the minimal discharge field (MDF) was characterized using hand-held stimuli. Then, the visual field was partitioned arbitrarily into three zones cocentered on the geometrical center of the MDF: the classical central zone of the receptive field (120% of the plotted MDF), the Near periphery (nine times larger than MDF), and the Far periphery (the extent of which was limited by the borders of the 21′ screen positioned at a distance of 57 cm). Visually evoked postsynaptic potentials and firing activity were measured in response to static or drifting bars and gratings (of optimal speed, spatial and temporal frequency) shown in the center and/or the peripheral regions surrounding the RF.

A 'current-vision association' protocol was devised, which consisted of randomly interleaved pairings of dual sequential visual stimulations in different parts of the visual field (MDF, Near, Far) with an intracellular current pulse. The value of current was subthreshold, *ie* a fraction of the threshold intensity required to reach spike initiation. Both polarities of current and spatial locations of the test stimuli were chosen randomly in order to avoid long-lasting effects of the pairing procedure. The onset of the current pulse was matched in phase with the ON response to the first visual stimulus such that the membrane potential depolarization starts concomitantly with the first evoked visual response, *ie* is applied at a delay precisely adjusted to compensate for the latency of visual cortical responses. The second visual stimulus was presented out of phase with respect to the pulse onset, *ie* 1 s later, at a delay where temporal interaction no longer occurs between successive stimuli (Nelson, 1991), but when the current step is still applied.

Results

For this study, 20 cells of cat area 17 were recorded intracellularly for a duration ranging from 50 to 243 min. The 'current-vision association' protocol was run for 13 cells (recorded for more than 1 h) and fully completed for seven cells. Three types of effects were observed: i) one concerned the firing frequency of the neuron: in certain cells the response of the cell to the first stimulus became larger and more tightly tuned temporally than the response to the second stimulus. This observation might appear surprising since increases in the duration of the postsynaptic potential under the influence of calcium conductances do not predict an improvement in the synchronization of temporally overlapping inputs; ii) a second finding was that in some of the cells, peripheral input leads to synaptic potentials whose amplitude and duration was favored by the concomitant depolarization during the first visual stimulus presentation (fig 2), thus reproducing in a functional context the observations made by Deisz and collaborators (1991); and iii) a third observation was that occasionally IPSPs could also benefit from such boosting.

Our preliminary results indicate that cells in visual cortex seem to possess the non-linear conductances needed to selectively boost either excitatory or inhibitory synaptic input. A particular prediction can be applied to the filtering ability of cells in response to (normally subliminal) contextual input presented in the periphery at the same time as they are depolarized for instance by the presentation of the sensory stimulus in a central part of the receptive field. Our data can be compared to the recent observations of 'pop-out' effects in visual cortical receptive fields by Knierim and Van Essen (1992) who varied the orientation of the texture of the background while stimulating the MDF with a fixed orientation, and those of Sillito and colleagues when peripheral presentation of a luminance grating annulus had an orientation orthogonal to an inner disk grating (bipartite stimuli) presented in the center of the receptive field (Sillito *et al*, 1995). This latter group observed that the level of firing of the recorded cell became selectively enhanced when the two orientations (central and peripheral) differed by 90° independently of their absolute values, suggesting that an optimal activation of the cell was achieved when central and surround parts of the classical receptive field were detecting an orientation contrast.

A plausible regulatory mechanism derived from our experiments could be that the transmission of the peripheral input which is by itself mainly excitatory (when remaining within the tuning subthreshold preference of the cell) benefits from the sudden concomitant onset of the presentation of the stimulus in the central part of the receptive field, especially when the latter is cross-oriented or distinct from the preferred orientation of the cell, *ie* when it evokes only *per se* a subliminal depolarization equivalent in our case to somatic current injection. In contrast, the co-alignment across the visual field observed when the central input takes the same (preferred) orientation as that of the

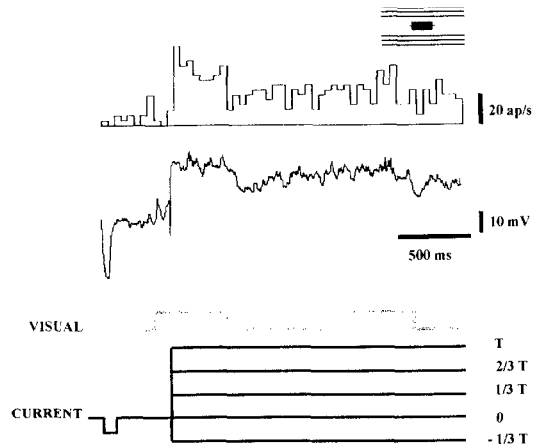

Fig 2. Boosting of visually evoked lateral EPSPs by temporal coincidence with post-synaptic depolarization. Complex cell, recorded in area 17 of an adult cat at a resting potential of –73 mV. The association protocol is schematized in the lower part of the figure: an identical visual stimulus was shown twice in the same trial, each time for a duration of 400 ms, separated by a 600-ms delay. Meanwhile, a step of current was injected so that its onset coincided with the beginning of the visual response (which required an initial measurement of its latency). The two successive presentations of the stimuli differed only by their delay with respect to the current pulse. From trial to trial, the parameters which were varied were the amount of current injected (five levels, expressed as a fraction of the intensity (T) needed to elicit a significant change in the spontaneous level of spiking) and the retinal location of the visual stimulus (MDF, Near, Far, see text). The two upper graphs represent the response to the association of the largest intracellular current (+ 0.27 nA) with a Near stimulation, using a moving grating restricted to the side bands of the MDF. The top histogram is the PSTH averaged over 16 trials and the lower trace corresponds to the averaged membrane potential after spike filtering. The second presentation of the test grating evoked almost no response, whereas the first one elicited a large membrane depolarization and a significant two-fold increase in firing, the duration of which lasted for that of the stimulation.

stimulus shown concomitantly in the periphery, might trigger (as we have observed) a non-linear suppressive interaction, responsible for hypercomplexity. This reduction in postsynaptic firing, which is an 'interaction' component, could be expressed when the excitatory drive exceeds the threshold needed to fire inhibitory interneurons (which are assumed to require a higher level of convergence than excitatory cells). These two simple mechanisms, which were in part already suggested by Sillito (1977), would result in a differential increase in the response, thus allowing a cell to detect local orientation contrast between its own preferred orientation and that shown in the peripheral field.

Discussion

Our data suggest that visual cortical receptive fields should not be considered as a fixed entity but more as a dynamic field of integration whose extent could vary depending on the past history of the membrane potential of the cell. Associative properties of central information and of input coming from the reputed unresponsive regions surrounding the receptive fields are strongly non-linear and can be in certain cases suppressive, and in other cases able to boost hidden responses.

Several types of interaction might be dominant in revealing responses to the periphery. Synchronization processes due to the simultaneous presentation of co-linear stimuli or stimuli sharing the same direction preference or orientation preference might increase the gain of horizontal excitatory connectivity, and may oppose in certain ranges of contrast the suppressive effects of length summation at the retinal and thalamic levels. A second type of cortical non-linearity might help to selectively amplify lateral input when the feedforward activation resulting from the presentation of the stimulus in the central part of the receptive field differs strongly from that presented in the periphery (pop out effect) and evokes already a subthreshold change in the membrane potential of the neuron. The gain of the response to the global center/surround stimulus configuration would depend on the activation of slowly inactivating postsynaptic conductances, boosting the convergence and the synchronization of the various sources of synaptic inputs (feedforward, lateral, etc) during a time window of 100 to 200 ms.

As far as a graded control of functional coupling is concerned, the conductance inactivation scheme presents a definite advantage over a scenario based on pure synaptic plasticity: it does not require reversibility of the established changes, whereas fast Hebbian schemes have to be accompanied by complementary depression rules to reset connectivity back to its initial state (before the start of the recognition process).

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