The dendritic tree: a mathematical integrator

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1. ABSTRACT

Neurons in the primary visual cortex (V1) are sensitive to simple features of the visual scene such as contrast, spatial frequency or orientations. In higher mammals, they are organized into columns of orientation-preference, whereas such organization is absent in rodents. However, in both types of organization, neurons can be highly selective or poorly selective for a particular stimulus. In mouse V1, it has been shown that all stimuli are represented on the dendritic tree of single neurons. To what extent this concept is applicable in higher mammals? In this review, we discuss possible models of integrating visual information from visual cortical neurons. In particular, how the modulation of the number of inputs and/or the frequency firing can explain the orientation selectivity in V1. Based on our findings and literature, we propose three different hypotheses namely the spatial summation, the temporal summation and the excitation-inhibition. In addition, we discuss the possible interactions between excitatory pyramidal neurons and inhibitory interneurons during stimulus processing.

2. INTRODUCTION

Modern technology in neuroscience has revealed a large amount of informative clues on how neural computations are performed in response to sensory stimulation. In particular, visual cortical neurons have been largely used as a model to investigate those computations. Optogenetic techniques, two-photon calcium imaging and electrophysiology shed light on the neuronal integration up to single cellular levels.

In this opinion, we use the orientation selectivity as a paradigm to explain the synaptic integration of oriented inputs and their processing within the dendritic tree of visual neurons. Indeed, in relation to previous research work and results from electrophysiology, we discuss possible models of the integration of information between cells using the convergence-divergence concept.

Orientation selectivity is an inherent property of visual cortical neurons. It is highly structured during the post-natal period and is malleable mostly during the critical period. Numerous animal models have been used to study the anatomical and physiological characteristics of orientation-selective neurons ranging from rodents, ferrets, cats and monkeys. In fact, two major structures have been described, namely columnar organized cortices and random-orientation distribution called "salt and pepper". This latter is associated to mice which lack the columnar segregation of similarly tuned neurons clustered in orientation domains or columns.

At a cellular level where hundreds of inputs converge, a study by Jia *et al.* (1) has provided extensive information about stimulus computations where every input (preferred orientation) is represented on the dendritic tree. They captured the dynamic of calcium entrance to the cell via N-methyl-d-aspartate (NMDA)-type glutamate receptors. This concept raises the question: to what extent this model could be applicable to columnar-organized cortices such as cats or monkeys?

This question becomes important considering that neurons in the primary visual cortex of such animals are not strictly tuned to a specific oriented stimulus although a dominant stimulus emerges from the computations of orientation preference at single neuron level. Moreover, some neurons are tuned to a broad spectrum of orientations (see next section). Yet these cortices show a proximity-based preference for oriented stimuli.

Due to these divergences in neuronal selectivity, different cells could be implicated in stimulus processing, and in the changes in orientation selectivity during
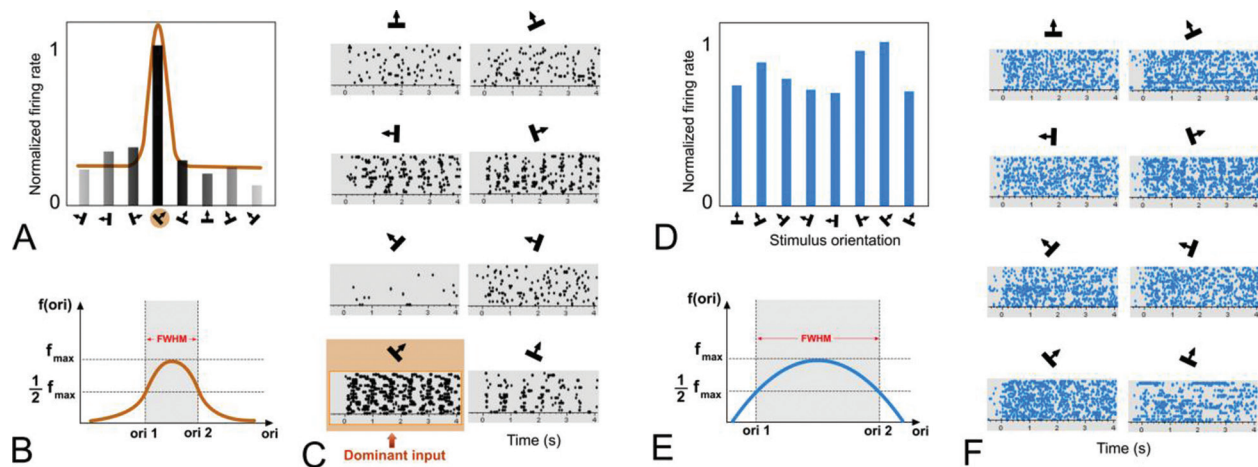
Figure 1. Orientation selectivity profile of two V1 neurons. (A) Orientation tuning curve of the responses of a neuron at different stimulus presentations. The optimal orientation in this case is 135 degrees (higher response, narrowly tuned neuron). (B) Tuning bandwidth of the same neuron. The computation is generated using the full width at half maximum (FWHM). (C) Raster plot showing the raw responses at all stimulus presentations. A dominant preferred orientation emerges. (D-F) Same as (A-C) for a broadly tuned neuron (or poorly tuned). The large spectrum of responses to all stimuli confers a low selectivity to this cell.

plasticity. As a matter of fact, broadly tuned inhibitory interneurons may play a key role in shaping the stimulus selectivity of excitatory pyramidal cells and consequently, the balance excitation-inhibition is modulated during induced-plasticity. The possible mechanisms and a review of previous findings are summarized and discussed.

3. NON-ABSENCE OF NEURONAL RESPONSE TO NON-OPTIMAL STIMULUS

Depending on the position of the neuron within the orientation map (in iso-orientation domain, between two orientation domains, or within a pinwheel where all orientations converge), the typical tuning response of the neuron presents distinct profiles ranging from highly selective profile to more broadly tuned shape. Two examples are shown in Figure 1. A highly selective neuron (black) exhibits an orientation tuning curve with a dominant preferred stimulus (Figure 1A) and a narrow tuning bandwidth (Figure 1B). These calculations were generated from the raw responses of the neuron when all the stimuli were presented. The raster plots of these responses are shown in Figure 1C. On the other hand, a poorly selective neuron (blue) exhibits the opposite trend (Figures 1D-F) with an absence of a dominant preferred stimulus and an equal spectrum of all orientations in the response profile.

These two types of neuronal selectivity could be explained by the degree of convergence and/or divergence of neurons. The afferent inputs to a neuron confer its degree of convergence. On the other hand, when the neuron fires, its output is propagated to other neurons through its axon terminals. It is thus not surprising that inhibitory interneurons in mouse for instance are tuned to a broad spectrum of orientations so as to modulate the local activity.

Moreover, neuron type-specific distinctions in orientation selectivity such as the relationship between the firing rate levels (burst-spiking or regular-spiking) and the degree of orientation selectivity could distinguish biophysical features orchestrating the dynamics of stimulus integration (2). The coupling strength of neurons with the neighboring population could also play a key role in information processing within a neuronal assembly (3, 4).

In cats and monkeys, it has been shown that the global profile of the neuronal selectivity, i.e., the wideness of the response curve to different orientations depends on the position of the neuron in the orientation map (5). For instance, in pinwheels where a large range of orientations are represented, the neuronal tuning response has a larger bandwidth, i.e., when fitted with a Gaussian function, the full width at half maximum (FWHM) is higher (for example in Figure 1E). The non-absence of firing response at non-preferred stimuli leads to the hypothesis that a neuron in V1 receives a multitude of oriented inputs within its dendritic tree. One could imagine that broadly tuned neurons have a higher degree of divergence in order to modulate the activity of sharply tuned neurons.

4. WINNER-TAKES-ALL MODELS

From the above arguments, we propose three different models that could shape the orientation selectivity with a predominance of one input. This "winner input" triggers the cell to fire giving that its spiking threshold is reached.

It was proposed that due to small changes in the membrane potential, if multiple inputs are summed
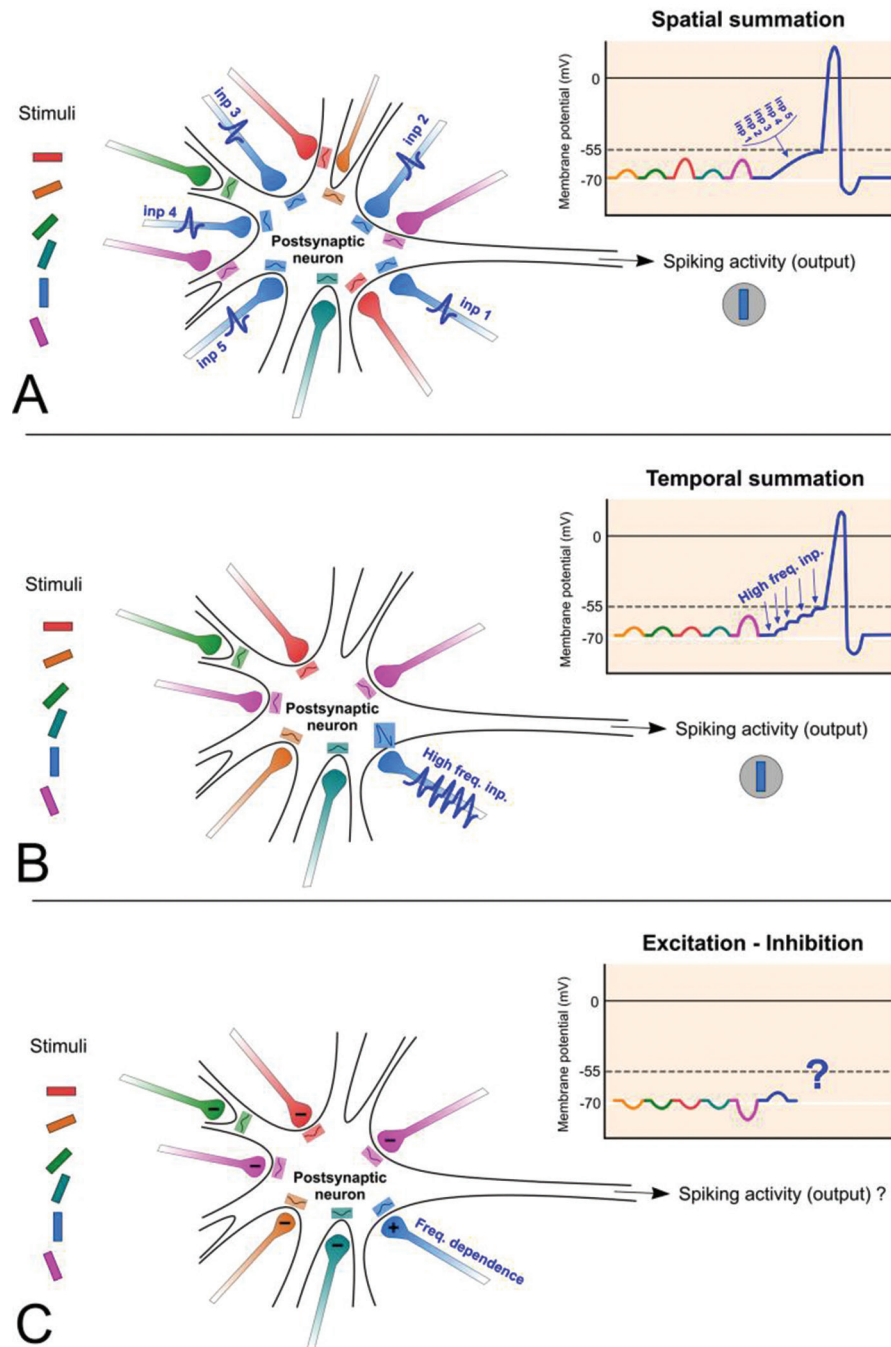
Figure 2. Proposed models for the integration of information. (A) The spatial summation model where an overrepresentation of the dominant orientation within the dendritic tree leads to the synchronous afferences to the post-synaptic neuron and its selectivity for that stimulus (in this case the blue). (B) The temporal summation model: all the inputs are represented equally on the dendritic tree. However, the high frequency firing of one dominant input leads to the selectivity of the post-synaptic neuron to it. (C) The E-I model: the emergence of EPSP's and IPSP's within the dendritic tree leads to complex calculations between the summation of excitatory and inhibitory inputs. The response of the post-synaptic neuron will depend on the frequency firing of the excitatory pre-synaptic neuron.

in a sufficiently brief period of time through spiking synchronization, the spiking threshold of the postsynaptic cell will be reached (6). Figure 2A schematizes this concept. Within the dendritic tree of the post-synaptic neuron, distinct oriented inputs are propagated through pre-synaptic contacts. However, one input is dominant due to a higher number of synaptic contacts. Consequently, the synchronous firing of the pre-synaptic
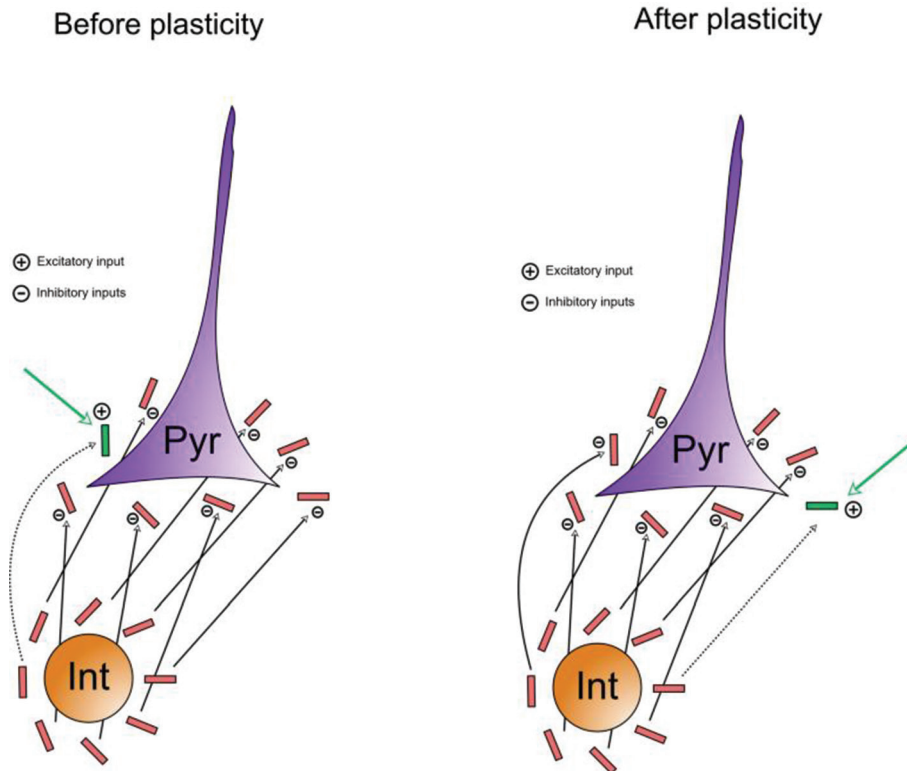
Figure 3. Interaction between an interneuron and a pyramidal cell. The interneuron shapes the selectivity of the pyramidal cell by sending inhibitory projections to the dendritic tree of the pyramidal cell. Less inhibition is exerted on the synapse corresponding to the vertical orientation which receives also excitatory input from another origin. On the right is shown the modulation of inhibition during plasticity where the balance changes in favor to the new acquired stimulus.

neurons coding for the dominant stimulus will trigger the post-synaptic cell to spike and the preferred orientation emerges.

For the temporal summation model (Figure 2B), all the presynaptic inputs (i.e., all the orientations) are equally represented in the dendritic tree as proposed by Priebe and Ferster (7). The dominant input in this case exhibits the highest frequency of firing triggering the postsynaptic neuron to reach the depolarization threshold. Priebe and Ferster proposed that synaptic inputs corresponding to all the orientations are also present on neuronal dendrites of higher vertebrates (cats). However, each orientation in the synapses is co-localized in clusters on the neuronal dendrites. This may eventually fit into the columnar organization of higher vertebrates as such co-localization facilitates the communication between similarly selective dendrites on other neurons. This cascades eventually explain the structure of the pinwheels.

A third important concept has to be discussed. The interplay between excitatory and inhibitory inputs plays a determinant role in regulating the cortical activity (Figure 2C). A highly possible scenario is that the emergence of both EPSP's and IPSP's within the dendritic tree gives rise to complex computations between the

summation of excitatory and inhibitory inputs. Indeed, due to the diversity of the nature of neurotransmitters on one hand, and the wide range of postsynaptic membrane receptors on the other hand, the generation of spikes depends on the fine balance between the relative contributions of both excitation and inhibition. The response of the post-synaptic neuron will depend on the frequency firing of the excitatory pre-synaptic neuron.

Here again, the broadly tuned inhibitory interneurons may improve the neuronal performance by sharpening the pyramidal cells' activity. In fact, the neuronal selectivity to different stimulus properties can be suppressed if inhibition is absent (8).

All these models explain a major concept raised by Busse *et al.* (9) where two simultaneous stimuli with distinct contrasts were presented. The neuronal responses ranged from a regime of summation when both contrasts were similar to a regime of competition when one contrast was dominant.

Orientation selectivity is a well-defined tool used in neural circuitries and plastic phenomenon. We believe that during plasticity, the modulation of the inputs and the consequent outputs leads to the changes of neuronal
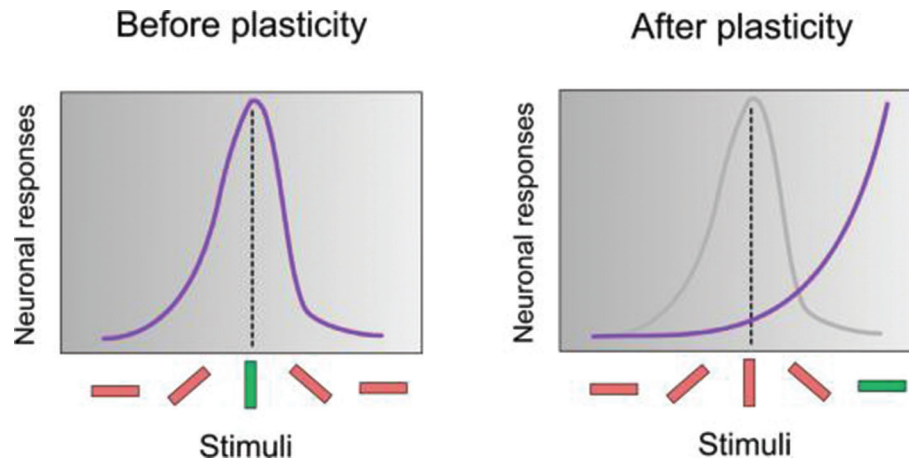
Figure 4. Response profile of a pyramidal neuron pre- and post-plasticity. The dominant input as shown in Figure 3 is due to the inhibition of other orientations by the interneuron. The best neuronal response shifts towards a new acquired stimulus after plasticity (right) and the equilibrium E-I is recalibrated.

Table 1. Effects of inhibition on neural anatomy and cortical processing

Method	Effect	References
Augmentation of serotonin and noradrenaline	Suppression of inhibition	(21)
Reduction of GABA	Recovery of ocular dominance plasticity	(19, 20, 24)
Administration of fluoxetine	Decrease of GABAergic inhibition	(23)
Reduction of GABA	Reduction of dendritic spines loss	(25)
Pharmacological reduction of inhibition	Facilitation of ocular dominance plasticity	(22)

selectivity and, as a result, reframe the orientation-preference organization.

5. PLASTICITY AND INHIBITION

The balance between excitatory and inhibitory inputs is crucial in cortical processing. In the primary visual cortex, these interactions have been examined due to the major role of inhibitory interneurons. Indeed, it has been shown that the suppression of paravalbumin interneurons enhances the spiking activity of pyramidal neurons whereas their activation drastically diminishes the neuronal responses of the pyramidal cells (10). Numerous studies point to the fact that inhibitory interneurons in the visual cortex are tuned to a large spectrum of preferred stimuli, the pyramidal neurons tend to be tuned to a specific optimal stimulus and strongly connect cells sharing similar properties (10-14). Inhibition seems to be highly implicated in the modulation of cortical responses and shapes the activity of the pyramidal neurons. Figure 3 illustrates the interaction between a pyramidal neuron which receives inhibitory inputs within its dendritic tree from an interneuron. This latter exert less inhibition on the synapse corresponding to the vertical oriented stimulus. In addition to the excitatory afferences from other neurons, this equilibrium confers to the pyramidal neuron its preference for the vertical orientation (Figure 3, left). Neurons in the primary visual cortex can change their selectivity for orientation (15-18) by rebalancing the inputs. This plasticity is induced by different procedures such as perceptual learning, stimulus exposure or environment enrichment that lead to the emergence of a novel preferred stimulus for the neuron. The removal of inhibition enhances the neuronal responses at the new acquired stimulus. On the other hand, the interneuron exerts strong inhibition on the synapse of the initial optimal stimulus (Figure 3, right). In many reports, it has been demonstrated that the reduction of inhibition could play a key role in enhancing cortical plasticity (19-24).

6. NEURONAL RESPONSE PROFILE AFTER PLASTICITY

Within the dendritic tree, the "winner" input confers to the neuron its preference for orientation. These scaled computations could, at a larger scale, frame the well-known orientation maps in the primary visual cortex. At a cellular level, the neuronal response profile is represented by the spiking activity of the neuron at every presented stimulus. As described above, the response bandwidth reflects the high or low tuning of the cells

for a specific orientation. When an induced-plasticity is applied to a neuronal population, the dendritic trees have to play a major "mathematical integrator role" in order to rebalance the excitatory and inhibitory interactions. This leads to the emergence of a new acquired stimulus. Figure 4 shows a typical response profile after plasticity; the initial response declines and the combination of the removal of inhibition and new excitatory afferences as shown in Figure 3 changes the selectivity of the neuron, as shown by many studies (3, 15, 18).

Inhibition seems to be the key factor that modulates the cortical activity within local populations. Several reports support the fact that the reduction of GABAergic inhibition enhances brain plasticity. These results are summarized in Table 1. Taken together, these findings give new insights on how at a neuronal level, fine scale computations change the optimal properties of neuronal populations during learning and memory.

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