Chapter 3

Are Sensory Neurons in the Cortex Committed to Original Trigger Features?

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Abstract

Sensory cortices are inherently dynamic and exhibit plasticity in response to a variety of stimuli. Few studies have revealed that depending upon the nature of stimuli, excitation of the corresponding sensory region also evokes a response from other neighboring connected areas. It is even more striking, when somatosensory areas undergo reorganization as a result of an intentional disturbance and further explored as a paradigm to understand neuroplasticity. In addition, it has also been proved that drugs too can be used as a model to explore potential plasticity in sensory systems. To this aim, through electrophysiology in cats, we explored that visual neurons, throughout the cortical column, have a tendency to alter their inherent properties even when presented a non-visual stimulus. Furthermore, it was explored in mice, how the application of drugs (serotonin and ketamine) modulates potential plasticity within the visual system. Indeed, we found a shift in orientation tuning of neurons indicated by Gaussian tuning fits in both scenarios. These results together suggest that sensory cortices are capable of adapting to intense experiences by going through a recalibration of corresponding or neighboring sensory area(s) to redirect the sensory function and exhibit remarkable extent of neuroplasticity within the brain.

Keywords: cortex, neuroplasticity, adaptation, orientation selectivity, tactile learning, cross-modal plasticity, ketamine, serotonin, reorganization, multisensory integration

1. Introduction

Brain's sensory systems translate raw elements of the external world into practical processable data adapted to sensory nervous system analyses. Forthcoming sensory stimuli trigger initial neural representations in the sensory structures that recurrently end in stimulus-specific

modifications. Through different ascending and descending physiological mechanisms, subsequent nerve impulses are enrooted toward appropriate regions of the cortex. The regularity of these processes devises an organized circuitry of neuronal connections elicited by a variety of stimuli [1–3]. Thus, it is the early sensory experience that guides the evolution of neural circuitry in the cortex.

2. Selectivity in critical period and inhibition

During development, the brain undergoes intense episodes of augmented plasticity known as a critical period. The advent of the critical period has been fundamental to understanding brain development. Critical periods are recognized as the epochs during which developing brains mature in a dynamic yet invariable way by anomalous experience. Considering, inhibition makes the postnatal brain undergo a permanent process of change; more often, brain is referred to as "plastic." The critical period is characterized by a heightened increase in excitation and inhibition right after birth, leading to a large restructuring of neuronal networks, and decreasing alternatively with age. It has also been acknowledged that there are multiple critical periods associated with various brain functions wherein early sensory processing have shorter critical periods than for higher complex functions or cognitive/executive functions. This maturation of cortical inhibition just after eye-opening is necessary for the establishment of experience-dependent ocular dominance plasticity in the visual cortex which relies on counteraction between two eyes to drive cortical responses. Moreover, it is presumed that critical period contributes to improving our ability to survive in the dynamic environment in later sensory experiences.

In general, sensory deprivation is associated with powerful cross-modal changes in the cortex which has been used as a paradigm to study neuroplasticity. Lack of sense of vision or hearing during early development may interfere with the calibration process that occurs during the critical period. It has been demonstrated by a number of studies in deaf and blind that cortex reorganizes itself as a result of the loss of sensory modality. This has also been found true in congenital blind and deaf.

2.1. Reorganization of the cortex following sensory deprivation or sensory loss

The most surprising yet striking phenomenon in the cortex takes place during the critical period. It was demonstrated that during the critical period, auditory cortex could develop finely tuned maps for different orientations of visual stimuli when a rerouting of visual input was enforced to an otherwise de-afferent auditory cortex [4]. Another study by Sharma et al. [5] examined and compared intrinsic connections in the rewired primary auditory cortex (A1) to normal A1 and normal primary visual cortex (V1). They found that diverting visual inputs to auditory cortex led to sharp orientation selectivity in rewired A1 and found that A1 maps were like V1 maps, but not as clean as V1. Further, it is also familiar now that during development, there is extensive and undefined emergence of connections that are particularly strong for cortical-cortical networks [6]. Despite having an individual skill associated to every recognized sensory area, nearby associative and auditory cortical areas respond to auditory motion stimuli, including the superior temporal sulcus cortex (STS), which is the sulcus separating

the superior temporal gyrus from the middle temporal gyrus in the temporal lobe of the brain. It could be possible that STS provides auditory input to the MT (middle temporal visual area or V5) during development. The STS in normal adult monkeys consists of pure auditory, pure visual, and multisensory neurons [7]. It seems likely that the auditory input within STS may spread to the nearby middle temporal visual area during development and the undefined contacts may align themselves during the visual deprivation period.

2.1.1. Disappearing of cortical borders in the barrel cortex by tactile learning

In monkeys, another type of tactile learning was used to show whether or not it was possible to change tactile receptive fields in the somatosensory cortex [8]. In this study, authors wanted to simultaneously stimulate two adjacent fingers and see if the somatosensory cortex displayed any kind of adaptation or reorganization (**Figure 1**). To increase their chances to achieve synchronized stimulation of two adjacent fingers, they surgically fused them by connecting the

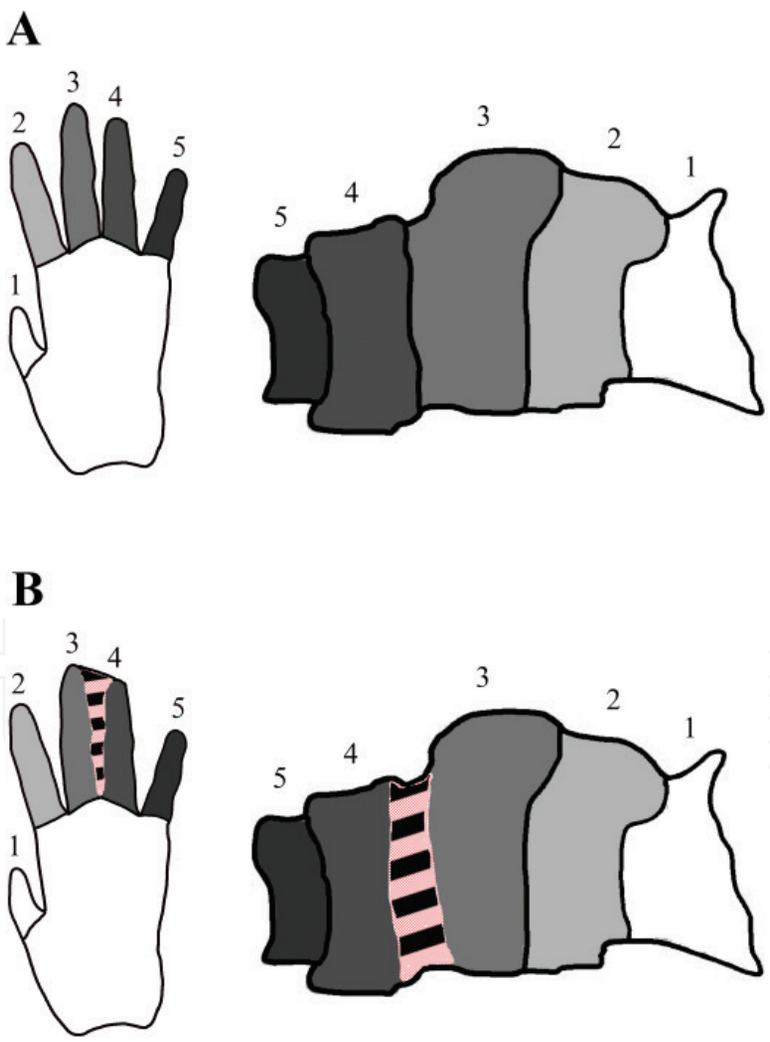

Figure 1. Model of cortical reorganization of area 3b following synchronous-stimulation of two fingers. (A) Normal monkey hand (left) with the associated cortical territory (right) in area 3b of the somatosensory cortex. (B) Fingers 3 and 4 were then surgically merged (left) to achieve synchronized stimulation of both fingers, conducting a reorganization of area 3b (right). Striped area represents overlapping between fingers 3 and 4 (model based on Clark et al. [8]).

skin, creating a syndactyly for digits 3 and 4 of owl adult monkeys. In [8], the strict separation between fingers receptive fields disappeared, allowing them to merge, forming a new single receptive field similar than that of a single unaltered finger. Stimulation of one of the two connected digits resulted not only in the activation of neurons in the previous finger receptive field, but also in the overlapping part of the newly formed cortical territory. Thus, these results suggest that the cortical map of specific body surface is linked to the temporal correlation of afferent stimuli. Tactile learning is then a useful procedure to help organize the somatosensory cortex and maintain tactile memory over long periods of time.

2.1.2. Typical example: reorganization of the barrel cortex following sensory loss by finger amputation

We now know that it is indeed possible to merge fingers' cortical receptive fields in the somatosensory cortex of the adult monkey, using synchronized stimulation of adjacent fingers. However, this experiment was conducted in a situation where no tactile receptors were eliminated. What would happen if the animal encountered some form of sensory loss on the tactile level? This was further explored by Merzenich and his colleagues [9], in an experiment which again involved adult owl monkeys. To test how the cortex would react to sensory loss, monkeys underwent surgical amputations of digit 3, or 2 and 3, and digital nerves were tied to counter their regeneration after the amputation (**Figure 2**). For digit 3 amputated monkeys, cortical mapping was realized before amputation, and 62 days post-surgery. Even though cortical territory for each finger was clearly defined before surgery, the area of the amputated digit was now used to represent adjacent fingers. Finger representations for finger 2 and 4 expended their territory inside the former digit 3 area, activating neurons when fingers were stimulated. As for digits 1 and 5 receptive fields, no changes were observed. As a rule for the brain, plasticity reduces with age, yet these results suggested that somatosensory cortex can reorganize its cortical territories to fully recover from the sensory loss, a beautiful proof of plasticity retained in adult monkeys. Furthermore, they mapped the cortical territories of remaining fingers for dual (digits 2 and 3) amputated monkeys. Just as digit 3 amputated specimens, the remaining fingers receptive fields expanded to the digit less cortical areas. However, in regions previously associated with fingers 2 and 3, it was found that some neurons were not activated by adjacent finger stimulation, rendering these cortical territories silent.

2.2. Congenital blindness

Reorganizing the somatosensory cortex was proved to be possible [8, 9], but only within itself and with sensory loss occurring during adult life. In the study of Kupers et al. [10], experiments were conducted on human late blinds (LB) and early blinds (EB). Human subjects were previously trained with a tongue display unit (TDU), which is a tactile vision sensory substitution system (TVSS) [11, 12], showing that activation of occipital cortex could be achieved and increased using sensory substitution. However, it was not proved that activation of either cortex could be achieved without using sensory substitution. Subjects were then prepared for transcranial magnetic stimulation of the occipital cortex [11], and were asked if they had any reaction. Some subjects affirmed to have experienced tactile sensations on the tongue, following stimulation of occipital cortex. Other regions of the occipital region were then stimulated, each

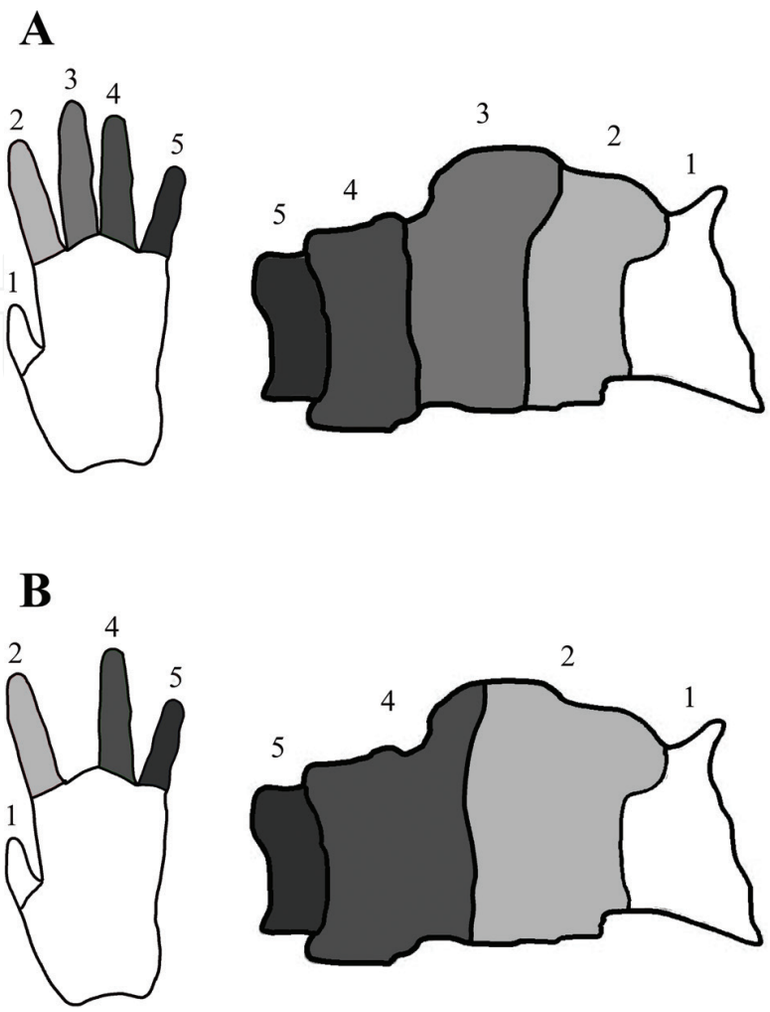

Figure 2. (A) Normal monkey hand (left) with associated cortical territory (right) in area 3b of the somatosensory cortex (B) after finger 3 was surgically amputated (left), area 3b of the somatosensory showed cortical reorganization (right) with fingers 2 and 4 territories expanding into the now deprived finger 3 territory (model based on Merzenich et al. [9]).

of them resulting in an evoked response on different areas of the tongue. Hence, these results proved that early sensory deprived cortices could be involved in cross-modal plasticity, following training with sensory substitution techniques.

2.3. Selectivity modified in adult visual and auditory cortices

For eons, it has been tested and verified that the structure and interneuronal connections of the central nervous system cannot be modified in adulthood. Yet, the past decade investigations carried out on invertebrates [13] and vertebrates [14–20] have revealed that neurons may change their response property or stimulus selectivity exhibited since after birth following an appropriate experimental protocol. To mention a few cases, monocular deprivation produces an amblyopic condition that results in a loss of vision in the affected eye due to unbalanced synaptic drive in the visual cortex. Reversing the deprivation by closing the unaffected eye and stimulating the initially closed eye switches the effect. In this process, the synaptic equilibrium is reversed because the initially deprived eye is strengthened and the companion eye is weakened. Ocular dominance can be shifted even in adult

brains, meaning that neuronal networks maintain potential plasticity from an infant into adulthood. In the auditory system, stimulating neurons with narrow band stimuli excluding the preferred frequency induces responses outside the preferred frequency range [21]. Similarly, cerebral cortex neurons belonging to somatosensory barrels whose whiskers have been cut respond to intact whiskers, suggesting an expansion of the latter's territory [22]. The somatosensory cortex homunculus may be altered with both increased and decreased stimulation [9]. Therefore, neurons in the adult cortex, following manipulation of inputs, display novel response properties that were not present after normal brain's maturation. Most of the investigations studying brain plasticity use a strategy based on the removal or weakening of sensory inputs, such as enucleating eyes, dark rearing, etc., in developing and immature animals. Conclusively, the neuronal plasticity is derived from an absence of excitation. Recording neuronal evoked action potentials in different regions of cortex have profited researchers to deeply explore and understand how separate sensory areas perform individually as well as part of the big sensory systems. It has been unveiled that cells in visual cortex (and elsewhere in cortex) respond to relatively narrow ranges of stimuli features such as the orientation of an elongated edge, direction of stimulus, a direction of whisker displacements, etc. For instance, a typical plot of the response magnitude versus function of orientation reveals a Gaussian type curve, the peak of which indicates the preferred orientation that generates the maximal number of action potentials. Consequently, cortical cells are exquisitely selective to restricted ranges of stimuli properties exhibiting the preferred or optimal stimulus, which usually are acquired during the critical period that follows the birth of the animal. More recently, a collection of published results showed that frequent or forced application of specific non-preferred trigger features, which evoke a feeble response, induces profound modifications of optimal properties exhibited since birth. Studies published in this direction have shown that adaptation diminished responses evoked by the initial optimal orientation, whereas responses evoked by the adapter were considerably augmented. Hence, the original optimal orientation evokes a much weaker response than the response produced by the adapting orientation [16, 23–27].

2.3.1. Cortical neurons exhibit neuroplasticity by acquiring new stimulus features following induction of non-preferred stimulus

Visual adaptation alters perception and tuning selectivity, and these modifications are quite selective suggesting a cortical reorganization of the primary sensory areas. Psychophysical studies revealed that adaptation permits isolating specific sensory channels responsible for eliciting responses induced by a narrow range of properties without affecting responses evoked by stimuli falling outside this range. For instance, adapting an observer to one particular spatial frequency results in a loss of sensitivity to that value of spatial frequency; for this reason, tuning curves present a dip corresponding to the particular band of the adapter [28]. In humans, frequent or prolonged exposure to one particular stimulus generally produces a change in the detectability of the target, because there is a reduced perception to the test stimulus, that is, the threshold becomes elevated due to a selective loss of particular characteristics of the adapter [29]. Prolonged adaptation changes fMRI responses in V1 in an orientation-specific manner [30].

However, in various mammals, adaptation induces more versatile trends. At the single cell level, the effect of adaptation was investigated for several properties in a number of areas and quite a few species. Frenkel et al. [15], showed that repeated presentation of gratings oriented at an orientation to mice induces a specific response potentiating (SRP) to the test orientation. Jin et al. [31], described response suppression resulting in shifts of the peaks of tuning curves away from the adapter, often referred as repulsive shifts. As cortical cells respond well to motion, this property was studied extensively. In primates, V4 adaptation confers a better directionality for cells normally poorly tuned to the direction [32]. In MT of macaque, Kohn and Movshon showed that adaptation causes direction tuning to shift toward the adapted direction; this effect is accompanied by a reduction of direction-tuning bandwidth [33, 34]. On the other hand, Yang and Lisberger [35], reported data demonstrating that adaptation globally reduces the magnitude and the width of direction- and speed-tuned curves. In the same direction, it has also been demonstrated that after monkeys learned to associate directions of motion with static shapes, the neurons of MT area exhibited unexpected selectivity for the static shape, suggesting acquisition of a novel visual property induced by the learning procedure [36]. In parallel, more studies in V1 showed that evoked discharges in response to the originally preferred stimuli are selectively reduced [37–39], but Krekelberg et al. showed that evoked discharges after adaptation are in a direction-dependent manner. Thus, the response enhancement to the adapter stands in contrast to earlier studies where it has been shown that when a neuron is adapted to a particular grating, its sensitivity to that grating is reduced [40–43].

A study [44] carried out on mouse visual cortex and employing the double photon technique disclosed that a single dendritic branch of a cortical cell possesses a collection of synaptic connections for several orientations. In the same cell, these different inputs are located in proximity to the dendritic tree. Repulsive shifts appear to be resulting from a differential weakening of synaptic drives activated by the adapter. The attractive shift required a different explanation. If one assumes that a limited, small area of a dendrite receives contacts from a broad spectrum of properties, one group of inputs will dominate, thus creating a bias that carries the membrane potential across the action potential threshold. The excessive afferent activity ensuing from the lengthened application of a non-preferred stimulus transfers the bias in favor of the adaptor [44]. This produces attractive shifts such as described in the visual and auditory systems. The shifts of tuning curves whether in repulsive or attractive directions are the result of very selective response modulations. The spontaneous activity is unaltered during tests, and responses evoked by stimuli characteristics at distant flanks of the tuning curve are weaker. The response modulations are constrained most closely to the adapter and original optimal property, ruling out a sudden surge of excitability [16, 24, 33, 45]. A second adaptation performed (many minutes sometimes up to 2 h) after the recovery from the first episode of adaptation, yields similar results [46]. Others showed that cortical cells discharge selectively to the null direction (classically, a direction failing to excite the cell), if an appropriate electrical pulse is delivered while the stimulating bar sweeps the cell's receptive field. This emergence of responses to the null direction may last several minutes and well after the conditioning electrical pulse is terminated, suggesting a substantial change of cellular property [47]. Another study in ferrets also explored the critical period for ocular dominance plasticity using intrinsic optical imaging. On comparing ferrets with cats, they found that ferret's critical period

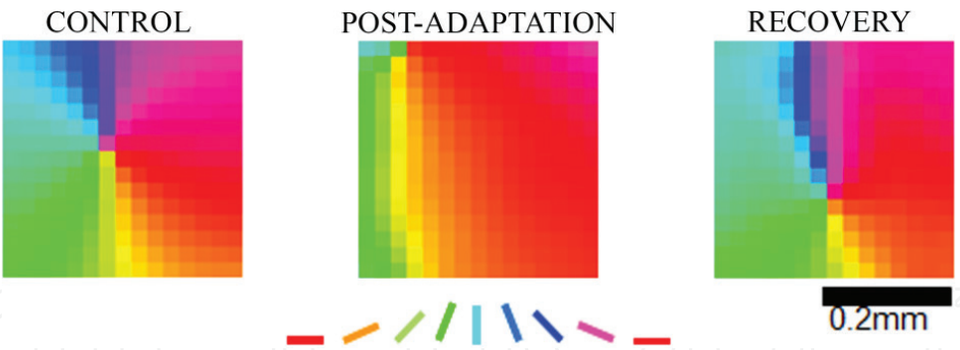

Figure 3. Reorganization of orientation columns in cat primary visual cortex shown by optical imaging.

begins ~75 d which is actually 6–7 days earlier than a cat on conception. Moreover, ferret's LGN becomes laminated and extends axons into visual cortex ~1 week before the cat's LGN does. However, overall, they found the critical period process to be quite similar, yet the development in ferrets appears to be slightly more rapid than cats.

In line with previous reports, few studies from our laboratory through electrophysiology showed that layer 2/3 neurons exhibit attraction and repulsion by changing their orientation selectivity toward or away from adapting orientation or retaining or refracting their orientation tuning in some cases [26, 46]. It was further confirmed by another study using optical imaging that following adaptation for 12 min, the orientation maps are modified in response to the adapter [27] (**Figure 3**). A similar result was obtained in mice by Jeyabalaratnam et al. [48]. Further, a significant study confirmed that a continuous adaptation on the recording site for 12 min yields attractive and repulsive shifts, wherein the shifts carry equivalent averages of a shift in orientation tuning to averages of tuning of neurons recorded from another site away from receptive fields of target neurons. Authors called this as "domino effect" as the reorientation observed after adaptation was found to be guided by the imposed adapter and initiated itself at the site of recording and was followed systematically as a marker by neurons in other columns [49]. Based on this observation and hypothesis, Chanauria et al. [50] demonstrated that the typical behavioral response of visual neurons persists and can be observed in layer 5/6 neurons too when recorded simultaneously with layer 2/3 neurons. Authors further stressed that domino effect does not only exists in layer 2/3 neurons, but also inherently prevails within the neurons throughout the cortical column [50].

At control, each orientation is evenly distributed in the camera-captured zone. However, the post-adaptation situation is no longer the case, as the adapting orientation took over the quasi-totality of the captured zone. After a recovery period, previously preferred orientation regains its control territory (S. Cattan unpublished material).

2.4. Organization of somatosensory cortex and trigger features

All sensory receptors input to the somatosensory cortex, and are then used by the brain to generate a response to the input stimuli by giving information about the environment or position of the body. However, sensory pathways do not only convey information to the somatosensory

cortex but instead, relay the information to specific parts of the cortex [51–53]. It has been shown that using somatotopic maps, a "Sensory Homunculus" can be created, which shows the uneven distribution of cortical areas to different parts of the body. For example, face and hands areas display a bigger area distribution than legs and feet [51]. This was first demonstrated by Penfield and Boldrey [53] using electrical stimulation of the brain during open surgery on consenting patients. Electrical stimulus was applied to a cortical region, and intensity was increased until a response was obtained. Even though this experiment was crucial to the understanding of somatotopic mapping in the brain, it was none the less an invasive and risky experiment. As technology evolved, new tools came into existence and hardware got developed that was now capable of recreating the same experiments, but noninvasively. Techniques like functional magnetic resonance imaging (fMRI) to display brain activity based on blood oxygenation difference became at disposal [51, 52, 54]. The fMRI technique brought a better resolution to the somatotopic maps, showing that each cortical area is dedicated only to a specific part of the body, similarly to receptive fields in the visual cortex [55–57]. The somatosensory cortex is organized in such a way that cortical territories are well-defined and region-specific with respect to body parts. However, some animals harbor some vibrissae, also called "whiskers." Since higher primates possess stimulus-specific cortical territories, it was hypothesized that lower vertebrates also embody the same somatotopic pattern. Indeed, studies conducted on mice proved that their somatosensory cortex is organized similarly to humans. For example cortical areas dedicated to forelimb or hindlimb [58] were found congruent in higher and lower vertebrates, An entire territory dedicated to whiskers inputs was also discovered [59]. These inputs regions with respect to whiskers were called "barrel cortex," because each column in this barrel cortex area of somatosensory cortex was found associated to only one whisker. The barrel cortex occupies an estimated 70% of the primary somatosensory cortex (S1) in mice [59]. Thus, it is no wonder that mice use their whiskers, before their vision, to locate and identify objects not only by their shape [60–64], but also by their texture [65, 66]. The somatosensory cortex is generally shaped to collect and analyze surround information from the environment, with specific structures depending on the species.

2.4.1. Whisking: adaptation and tactile learning

It is convenient to study somatosensory cortex in rodents via the barrel cortices because each whisker is linked to a cortical column, making it "effortless" to identify which neurons will respond to the stimulation of a specific whisker [67, 68]. In [69], the researchers investigated the correlation between spiking and whisking. In their study, neurons were recorded at different levels in the corresponding barrels of stimulated whiskers. It was found that during a whisking episode, neurons from supragranular layers (e.g., L2/3) had lower spiking frequencies than that of infragranular layers (e.g., L5), suggesting that infragranular neurons' spiking frequencies were correlated to whisker position. Once this direction was explored, de Kock and colleagues hypothesized that spiking episodes were correlated to the behavioral state of the rat. To test their hypothesis, they compared the spiking frequencies between three different "behaviors." Their results showed that spiking frequencies in non-whisking awake episodes were similar to whisking episodes under urethane anesthesia. However, when the rats were awake, spiking frequencies were independent between layers, with infragranular (L5) neurons spiking to higher frequencies than supragranular neurons. Moreover, infragranular

neurons (e.g., L6 neurons) did not display significant changes between different behavioral states. Thus, they concluded that behavioral state influenced principally spiking frequencies in L5 neurons. To further confirm their observations, de Kock and de Kock [70] tried to observe cell-type frequencies correlation to a specific behavior state. By analyzing frequencies from supragranular pyramids, slender-tufted and thick-tufted pyramids, L6 pyramids, and granular spiny neurons, it was shown that mainly slender and thick tufted pyramids neurons recorded at 1000–1500 μm, corresponding to L5, displayed significant changes in spiking frequencies for quiet (non-whisking) and whisking states.

2.4.2. Tactile learning

Rodents mainly use their whiskers to acquire information about their surrounding environment. Hence, their natural instinct is to explore new and unfamiliar components of their environment, to get better acquainted with their living space [71]. Wu et al. based their study on this natural instinct [71], used it to investigate the short-term memory of the somatosensory cortex in mice. Their results proved that mice spent more time "exploring" the new panel than that of "exploring" the familiar panel, shown in their arena-based experimental setup. These results suggested that the somatosensory cortex can retain short-term tactile memory by perceptual learning. To further investigate the mechanisms invoked in this tactile memory, they set up the experiments in a way that only tactile stimuli were used by the animal to discriminate the two different textures (suppression of olfactory components, textureless grooved panels for the second trial). In this case, mouse did not express memory in tactile less trial. Moreover, as whisker-less mice did not show the same exploring pattern, their results also demonstrated that this tactile memory was vibrissae-based. With this study, by Wu et al. [71] uncovering the short-term tactile memory of the mice, it was then hypothesized that the effect of perceptual learning can be maintained for a much longer period [72]. With the same kind of experimental setup, trials were separated by 24 h instead of 5 min. After analysis, it was shown that mice spent an average of 65.20% with the novel gratings [72], thus indicating that the perceptual-learning-acquired memory could be maintained for a 24-h period.

2.5. Multisensory integration and cross-modal plasticity

Multisensory stimulation can have a substantial impact on the basic visual perception. Non-visual input, such as auditory stimuli, can affect visual functioning in a myriad of ways. Numerous studies have demonstrated these alluring cross-modal relationships. For example, anatomical and electrophysiological approaches in non-human primates [73, 74] have provided evidence that multisensory interactions can be observed at early primary unimodal stages of sensory processing [1]. This body of evidence suggests that projections from the auditory cortex reach deeper layers of the visual cortex and vice versa. Another study by Muckli and Petro [75] highlights the existence and the importance of non-geniculate input to V1 by associated areas such as auditory cortex. Moreover, a fMRI report by Vetter et al. [76] displayed through task-based approaches in blindfolded healthy adults that, by solely performing an audio task, a response in the visual cortex could be observed. Therefore, primary areas, such as V1 and A1, showcase high multisensory interaction, predominantly a

modulatory influence in response to a complementary stimulus. In a recent study [77], authors have shown that auditory stimulus sharpens the selectivity of visual neurons. In the present investigation, through electrophysiological techniques, we examined the effect of sound on the simultaneously recorded visual cells from supra- and infragranular layers. An auditory stimulus was presented continuously and uninterruptedly for 12 min, and the recordings were performed in area 17 of the visual cortex in anesthetized cats. The effect of the sound stimulus was tested by comparing orientation tunings of neurons before and after the presentation of sound. Indeed, we noticed an intense modulation of response accompanied by a modification of orientation tuning of the neurons. Our data showed that after 12 min presentation of the auditory stimulus, a population of visual cortical neurons experienced modulation of excitation and inhibition and attained new orientation selectivity. In addition, few-layer II–III and V neurons lose their preference and become untuned. These results suggest that visual neurons in either layer change their properties on the application of an auditory stimulus which highlights the cross-modal interactions between visual and auditory systems and a robust reconfiguration of visual cortex induced by sound. An illustration is shown to explain the obtained result. **Figure 4** explains the effect of sound on visual neurons. Sound acts as a non-visual input to the primary visual cortex. Here, instead of a traditional pathway being implicated, a non-geniculate route has been activated. New orientation selectivity is attained by the L2/3 and L5/6 neuron pair recorded from the same site after 12 minutes. The upper curves are L2/3 neuron, whereas bottom curves are L5/6 neuron. Control curves are shown in bold and dotted curves are shown for post-adaptation with sound.

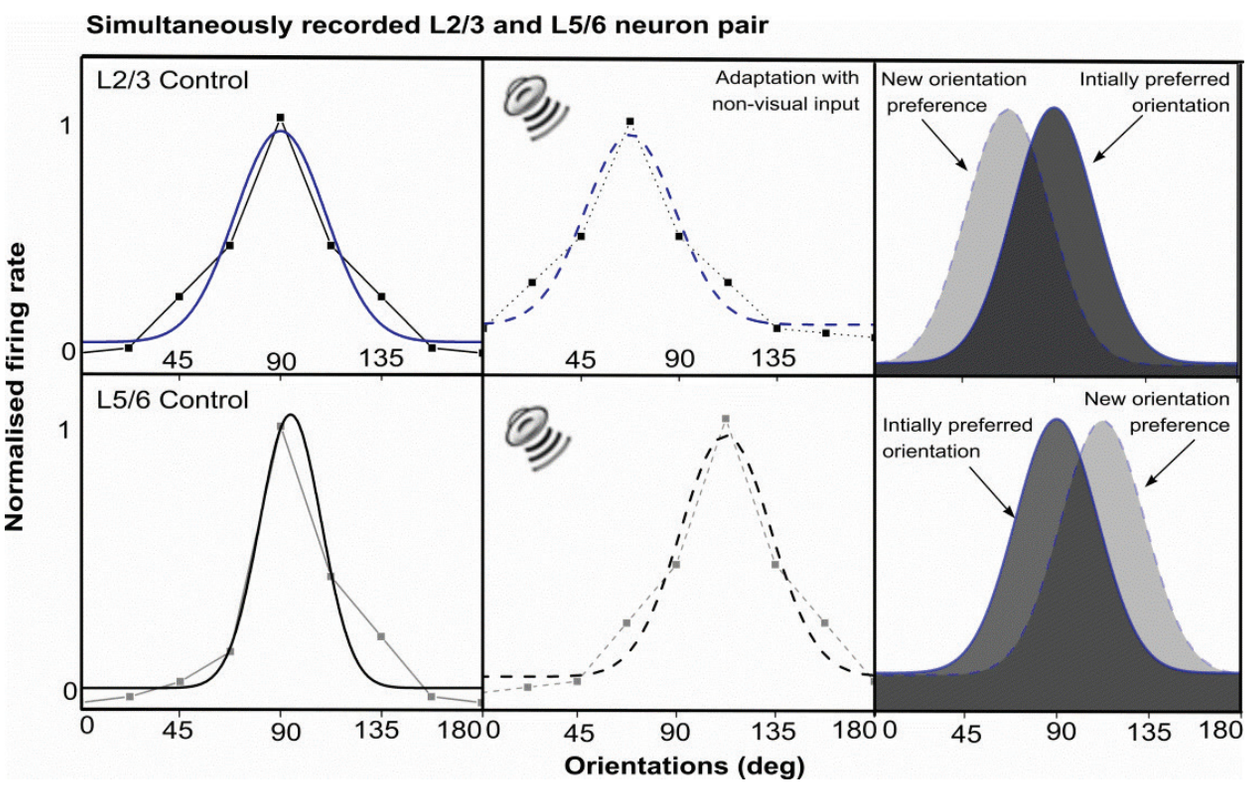

Figure 4. Illustration of effect of a sound stimulus on a pair of simultaneously recorded neurons from L2/3 and L5/6 from a recording site.

The possible explanation to these results could be simply attributed to direct anatomical connections between primary sensory areas within the cortex [73] or an indirect pathway involving arousal of a multisensory area as a mediator to facilitate the modulation of responses [74]. These mediator areas could be pulvinar, superior colliculus or other thalamic nuclei that act as ports of entry of information to primary areas.

The bold curves indicate control tuning curves with respect to raw firing rates, whereas the dotted curves represent raw firing rates. For clarity, raw fits have been fitted with Gauss functions. Curves in upper and lower rows attribute to L2/3 and L5/6 neuron, respectively. On the extreme right (above and below) are non-linear Gaussian fits plotted to infer the exact numerical values of orientation preferences. The superimposition clearly indicates that neuron pair that was similarly tuned initially attained a new selectivity after experience with sound stimulus for 12 min. Modulation of firing rate can be observed and accompanied by the alteration in selectivity. A similar response shift, yet in the opposite direction can be observed in the L5/6 neuron. This indicates that neurons in a column may choose to show a similar response, yet behave independently toward the same stimulus.

2.6. Possible mechanism underlying adaptation and plastic modifications

Recordings of electrical neuronal activity reveal modifications of neuronal properties following adaptation. Since response modifications come about rapidly within a time window of several minutes to a few hours, it seems reasonable to propose that the response alterations following adaptation are carried out by mechanistic processes directly available to neurons. Two-photon microscopy permits visualization of isolated dendritic branches with their spines in vivo. Jia et al. [44], described in V1 that single dendritic branches are divided into several short segments, each selective to one particular orientation. Accordingly, synaptic inputs of different orientation preferences contact a single branch of a dendritic tree. Orientation-tuned neurons, therefore, process their characteristic firing pattern by integrating spatially distributed synaptic inputs responding to multiple orientations. It follows then the most intensely stimulated dendritic segment that drives the neuron above the firing threshold which attributes a novel preferred orientation corresponding to the adapter. Other studies suggest that dendritic structural modifications may happen at a relatively rapid pace. Yang and Lisberger [35] have been able to follow identified dendritic spines over time while mice were submitted to new sensory experiences. The experiments revealed extensive spine remodeling that correlated with behavioral improvement after learning [78, 79]. Also, the remodeling of dendritic branches takes place within a few days following eye suture. Importantly, a small fraction of new spines produced by novel experience, together with most spines formed earlier during development and surviving experience-dependent elimination, are preserved and may provide a structural basis for holding on to memory during the entire life of an animal [35]. A recent [79] study showed that spines and matching axonal boutons of inhibitory neurons undergo rapid changes following retinal lesions. In fact, the same authors suggested that the loss of sensory inputs to inhibitory neurons triggers the plastic dendritic transformation of excitatory cells. The above experiments suggest that daily sensory experience and learning leave small but permanent marks on cortical connections, implying that enduring memories may be associated with the synaptic formation. It may be worth adding that in 1949,

Hebb wrote that "when one cell repeatedly assists in firing another, the axon of the first cell develops synaptic knobs." Nowadays, we may identify it as spine formation on dendrites following prolonged adaptation which produces a sustained, high firing rate in an afferent cell. Cortical orientation maps visualized with intrinsic optical imaging techniques revealed vanishing of pin-wheels without recovery. The prolonged return to preadaptation maps is attributed to structural modifications occurring in dendritic branches [80].

3. Understanding at population level/interareal explorations

In previous sections, we described changes of neuronal selectivity occurring at the single cell level brought about by adaptation. As cells acquire new optimal properties, it is reasonable to postulate that these changes are the consequences of a new equilibrium between excitatory and inhibitory relationships amid reciprocally connected neurons. In other words, adaptation affects a cell's population activity. Intrinsic optical imaging revealed that on the surface of the visual cortex, orientation preference forms parallel slabs [81–83]. These maps exhibit two fundamental features such as linear zones (with orientation remaining the same over these zones) or singularities and fractures (orientation preferences are changing abruptly over a short distance of cortical surface) [84]. Also, investigations have demonstrated that the layout of orientation preference maps is roughly scattered around pinwheel centers, rather than aligned in slabs [80, 85]. Within pinwheels, adjacent neurons at the center of pinwheels display large differences in orientation preference. For example, neurons with orthogonal orientations are in proximity [14, 85]. Such a display makes pinwheel areas particularly susceptible to adaptation since the convergence of a broad range of orientation preferences presents a large potential for reorganization, because there are numerous mutual connections between cells directly or through inhibitory interneurons.

4. Modulation of plasticity by application of drugs

In parallel with physiological processes inducing plasticity, drugs and other substances which operate as a neurotransmitter or selective neurotransmitter reuptake inhibitor and modulate visual plasticity [86]. Indeed, some of them, such as the protein Lynx1, decrease the level of plasticity and provoke stability by locking the cortical network [87].

4.1. Effect of serotonin and fluoxetine on cortical plasticity

Fluoxetine, which is antidepressant and reacts with selective serotonin reuptake inhibitor (SSRI), restores ocular-dominance plasticity in adult rats, when they are treated in a long-term protocol [88, 89]. In line with the previously published data, it has been shown that after the treatment of ischemic stroke patient with fluoxetine, there is facilitation of the motor recovery in comparison to placebo subjects [90]. Similar to the antidepressant fluoxetine, it has been shown that the neurotransmitter serotonin increase the attractive behavior (attractive shift is a shift of a peak of the orientation tuning curve), following adaptation in primary visual cortex V1 in anesthetized adult cats. Few neurons will serve as a reference for the other cells that lose their

stability during adaptation to achieve a new preferred selectivity in the direction of the adapter. Likewise, repulsive neurons shift their orientation tuning peaks away from the direction of forced orientation. In this study, it has been shown that the larger attractive shifts of the peak of the orientation tuning curve (attractive to attractive) are stronger in case of serotonin application if compared to fluoxetine. Hence, this result suggests that for the group of cells that increased the attractive effect during adaptation with drug administration, the effect is due to direct serotoninergic actions; however, the non-significant attractive amplified effect of fluoxetine (SSRI) could be explained by an indirect weaker process such as inhibition of serotonin reuptake. This indirect path is is reported to potentiate after long-term chronic administration in rats [88, 91]. In the same framework, Komlosi et al. [92] showed that the influence of fluoxetine on the polysynaptic transmission is relatively smaller than the serotonin action. In addition, it is shown that both drugs affect amplify the shift magnitude but not the firing magnitude of neurons post-drug administration and adaptation. In other words, serotonin and fluoxetine modulate the plasticity by acting on polysynaptic transmission which affects, for the most part, the selectivity range of a neuron rather than its evoked discharge rate. Thus, these differential effects of both drugs can be explained by the saturation of the firing rates; so, the strength of the evoked discharges remain relatively stable after application of drugs, while the increase in orientation-selectivity can be due to the ability of serotonin and fluoxetine to change the threshold of neurons. Therefore, neurons exhibit a higher firing rate with a new preferred orientation enhanced to the adapter. This explanation suggests that both drugs act at synapse level causing a drift (displacement) toward the adaptor. Based on the fact that spontaneous activity remained unmodified after administration of both drugs, the previous idea seems to be supported. Furthermore, serotonin, as well as fluoxetine, has a partial effect on evoked response magnitude. Indeed, both significantly affect the response amplitude evoked by the adapter and the original preferred orientations but not those that were evoked by flank orientations.

Molecular processes are further developed below:

Overall, fluoxetine (SSRI) and serotonin (neurotransmitter) promote sensitization of refractory cells (which maintain their preference after adaptation) by acting on synaptic components and lead them to learn an non-preferred stimulus, enhance the attractive effect of neurons, and contribute to increasing the plasticity for the repulsive cells. In the primary visual cortex, the ability of neurons to learn a non-preferred stimulus drives synaptic reorganization that serves as a scaffold and contribute to cerebral pharmacological treatments or cognitive mechanisms such as learning or memory.

4.2. Effect of ketamine on cortical plasticity

In a similar direction to previous reports from our laboratory, we sought to examine the effect of ketamine on the modulation of adaptation-induced orientation plasticity in the primary visual cortex of anesthetized mice. Ketamine is widely used in clinical medicine as a short-acting dissociative anesthetic. The preliminary results show that post-adaptation firing rate is lower than that of control. However, even when ketamine was applied on adapted neurons, post-adaptation firing rate did not significantly decrease in comparison with control. As

adaptation is a mechanism used to understand plasticity, we suggest that ketamine acts as a short-term blocker of the orientation plasticity post-adaptation by reducing the response rate following adaptation.

In the same framework, we aimed to investigate the effect of ketamine on the potential plasticity of neurons in V1 of anesthetized mice by comparing several parameters which were measured before and after the application of ketamine. Our data shows that following ketamine, a majority of cells shifted their optimal orientation. The comparison of mean of OSI between control and post-drug application revealed a significant decrease in the OSI post ketamine, which implies that application of ketamine weakened the initial orientation selectivity of neurons in V1. However, the bandwidth of orientation tuning curves did not display any significant modification between the two conditions (before and after ketamine application). The measure of the amplitude of the highest response displayed by the Gaussian-like function shows two populations of cells: one that initially (control condition) had weak amplitudes but increased after ketamine application and the other that initially had strong amplitudes but decreased after ketamine application (**Figure 5**). Thus, ketamine modulates the initial downward or upward amplitudes of Gaussian-like function. However, it was not known to what factor this modulation is correlated. To assess and describe the variability of neuronal response, a Fano factor (FF) was calculated for each neuron by dividing the variance of a neuron by the mean of firing rate of the same neuron. The larger the Fano factor is, the more significant is the variability of the neuronal response and vice versa. The comparison of evoked response variability before and after ketamine application shows that the value of the FF decreases significantly post ketamine, which meant that ketamine declines the cells' potential to respond variably to a large range of orientations. So, ketamine not only narrows the window of the variability of cells' response to stimuli, but also weakens their orientation selectivity. Moreover, it was revealed that following ketamine application, the FF value of spontaneous and evoked response remains similar while they were significantly different in the absence of ketamine. This suggests that ketamine decreases the orientation selectivity of cells and brings their evoked activities in response to stimuli closer to their spontaneous activities (**Figure 5**). The FF values of spontaneous responses calculated before and after ketamine application remained similar that suggests that ketamine does not affect the spontaneous response and its effect is not global but limited to evoked responses. In summary, ketamine causes orientation shifts, modulates the highest amplitude of Gaussian-like function, decreases the orientation selectivity, and narrows the variability range of evoked responses by acting at synaptic transmission while modifying the synaptic functional domain. Globally, ketamine features a sort of inhibitory effect on V1 potential plasticity. Molecular bases underlying cortex plasticity in general and how fluoxetine, serotonin, and ketamine can modulate the cortical plasticity, are discussed in the following section.

4.3. Molecular mechanism of cortical plasticity and pathways related to action of drugs

The studies on mammalian visual cortex have long been a field of discovery of mechanisms leading to plasticity during development and adulthood because of the ease of its handling and measuring results at physiological, anatomical, and molecular levels. Importantly, the experience-dependent plasticity derived from ancestral mechanisms occurs during development [4, 93, 94].

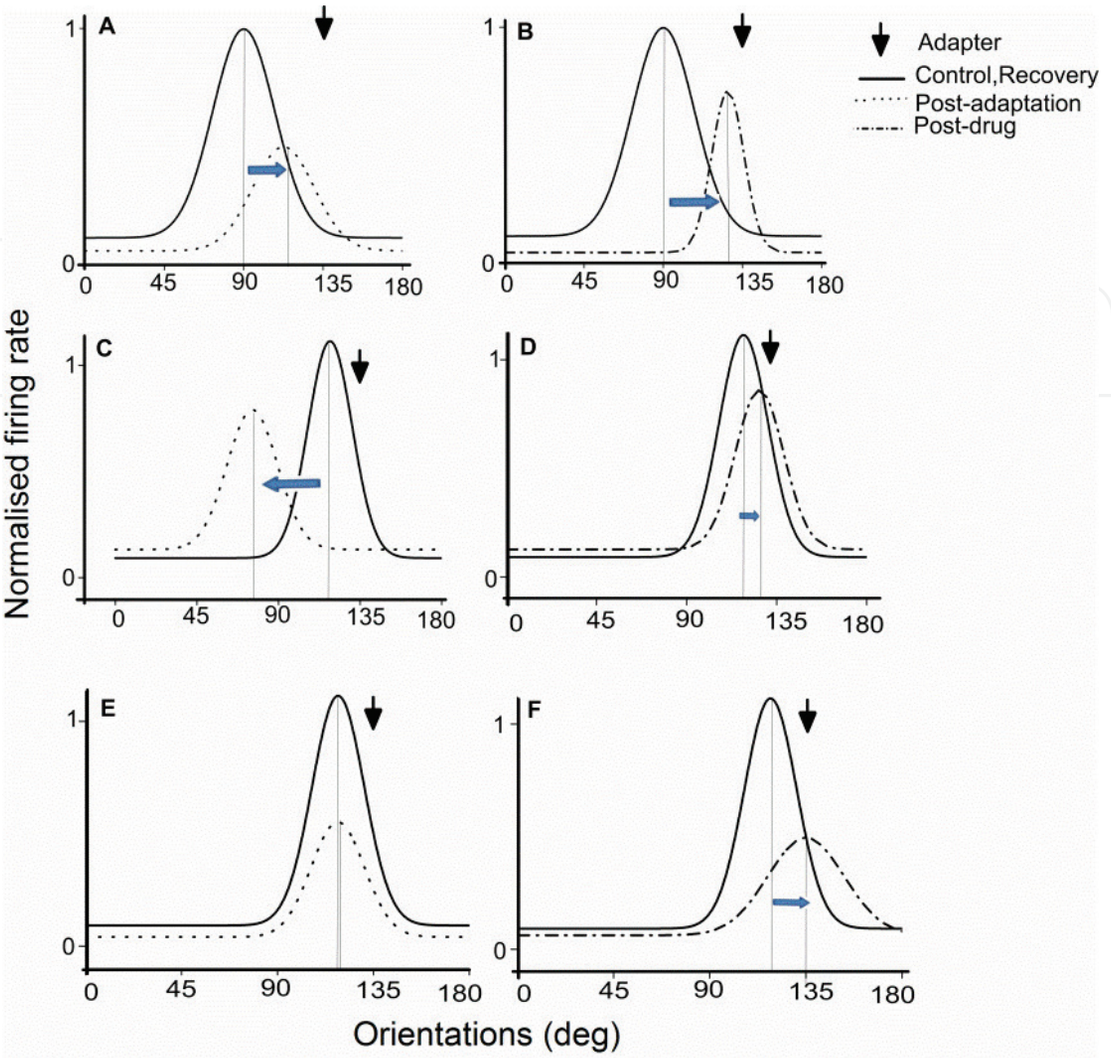

Figure 5. Effect of serotonin on the response of cells. A and B: amplified attractive effect of the drug—(A) model of Gaussian fit of normalized responses of one neuron for control (bold) and post-adaptation (dot). Black arrow represents adapting orientation. Gaussian fits show a shift of the tuning curve (attractive shift). (B) The Gaussian fit of normalized responses of the same neuron after recovery (bold) and after the second adaptation during serotonin application (dashed); the new attractive shift is bigger. C and D: inversion of the repulsive shift by the drug—(C) the Gaussian fit of normalized responses of one neuron for control (bold) and after the first adaptation process (dot). Black arrow represents adapting orientation. Gaussian fits show a shift of the tuning curve (repulsive shift). (D) The Gaussian fit of normalized responses of the same neuron after recovery (bold) and after the second adaptation during serotonin application (dashed). Note the inversion of repulsive shift after drug administration. (E) The Gaussian fit of normalized responses of one neuron for control and post-adaptation conditions (bold and dot curves, respectively). Black arrow represents the adapter. Gaussian fits that are superimposed show a non-significant shift after the first adaptation. (F) The Gaussian fit of normalized responses of the same cell for recovery and second adaptation in the presence of serotonin (bold and dashed curves, respectively). The tuning curve is shifted toward the adapter in the presence of the drug.

4.3.1. Molecular mechanisms of feed-forward plasticity

4.3.1.1. Glutamatergic receptors

Excitatory transmission is mediated by ionotropic glutamatergic channels' receptors AMPA and NMDA, which contribute to regulating membrane depolarization and calcium

permeability, through mGluR (metabotropic glutamate) receptors, which trigger downstream signaling cascades. Evidence exists that each of these receptor types may promote plasticity in visual cortex [95].

Frenkel et al. [15] have shown that a process similar to long-term potentiation (LTP) depending on NMDA receptor activation by repetitive activation leads to increased insertion of synaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor allowing strengthening of responses to repeated stimuli. This model of molecular plasticity is present both in juvenile and adult animals. The structure of NMDA receptors varies NR1, and either of NR2A or NR2B subunits, and they regulate the membrane depolarization and intracellular calcium level. Therefore, the excitatory transmission mediated by glutamate-gated NMDA receptor is affected. It is very well known that during post-natal development, the ratio NR2A/NR2B transits from low to high. Decreasing this ratio promotes plasticity by affecting the threshold for LTP. Since it was shown that ketamine blocks the NMDA receptors [96], there is a decrease in plasticity. Indeed, ketamine is an NMDA non-competitive antagonist. When the NMDA receptor is active, ketamine binds to it by sealing the lumen of the channel. Therefore, it creates a physical obstacle to ion currents through the channel pore. When the channel closes, ketamine becomes trapped [97]. Because plasticity requires NMDA receptor activation [98], the deprivation decrease of this activity leads to a reduction in inhibition effect on plasticity. Contrary to the effect of ketamine, it was demonstrated in adult rats that serotonin restores the NMDA-dependent long-term potentiation. Metabotropic glutamate receptors are also involved in cortex plasticity independently of its subtype [95]. It is worth noting that fluoxetine potentiates plasticity by increasing glutamatergic synaptic transmission [99].

In the brain, AMPA receptors are primarily composed of GluR2 and either GluR1 or GluR3 subunits. Synaptic strength, resulting in LTP and, by some effect, plasticity, are significantly determined by AMPA receptor [100]. Other finding shows that ketamine is a non-selective blocker of NMDA channel, and it also acts on AMPA/kainate receptors. Therefore, it seems that ketamine is a blocker of two ionotropic glutamate receptor channel-types in a concentration-dependent manner. This effect was determined by using whole-cell patch clamp technique and mediated by pharmacologically isolated AMPA/kainate receptor channels on membrane proprieties of pyramidal neurons of gerbil neocortex including the auditory cortex. Results show that ketamine lowers the amplitude of fast EPSPs mediated by AMPA/kainate receptor channels. In addition, ketamine increased the resting input resistance (RI). By Ohm's law, a small increase in cellular resistance outweighs the impact on synaptic efficacy, resulting in a corresponding increase in membrane potential that was due in part to a partial blockade of AMPA/kainate receptor channels. The outcome of this is that the reduction of fast synaptic currents attenuates depolarizing changes that contribute to voltage-dependent release of magnesium to achieve the threshold for NMDA receptor channels open states.

4.3.1.2. Calcium: a second messenger

Glutamate-gated AMPA and NMDA receptors regulate intracellular calcium level. As a second messenger, calcium activates many intracellular signaling cascades mainly including three critical kinases (ERK: called ERK, extracellular signal-regulated kinases; PKA: protein kinase

A; and CaMKII alpha: calcium/calmodulin-dependent protein kinase II alpha) [101–104]. These kinases may modulate synaptic strength and induce plasticity by phosphorylating plasticity-regulating molecules or mediating changes in target gene transcription synaptic signaling molecules by activating C-AMP response element-binding protein (CREB) [105]. CREB levels mediated by visual stimulation decrease with age, showing the involvement of other pathways promoting plasticity in the adult cortex [106].

4.3.1.3. GABAergic inhibition and BDNF downstream events

An indirect consequence of adjustments of GABAergic (gamma-aminobutyric acid-mediated) circuitry could be implied in changes in visually evoked responses. It was found that the infusion of brain-derived neurotrophic factor (BDNF) during monocular deprivation probably reduced the GABAergic transmission and reinstalled plasticity [88, 107–109]. The same pathway is induced by chronic treatment of fluoxetine exhibits in rats. Indeed, fluoxetine decreases GABAergic inhibition and thereby increases BDNF expression. Serotonin transmission has a similar effect as it potentiates the BDNF-trkB signaling path. Hence, fluoxetine and serotonin promote plasticity in adult rodents.

4.3.1.4. Structural plasticity

Several investigations demonstrate that sensory experience influences both structure and dynamics of dendritic spines which underlines structural plasticity [110, 111]. In visual cortex, reducing the density of spines leads to a decrease in the deprived-eye drive [112]. Moreover, the spine stabilization is induced by NMDA and AMPA synaptic activation [113]. It appears that ketamine increases spine dynamics by blocking NMDA receptors.

Several studies show that agonists of adrenergic and cholinergic systems facilitate the onset of ocular dominance plasticity [114, 115]. The effect of fluoxetine resulting in a restoration of ocular dominance plasticity to adults, probably due to a correlative reduction in inhibition, underlines an analogous function for the serotoninergic system [99].

Neuromodulators affect plasticity possibly to their ability to modulate thresholds for LTP/LTD induction by modifying the intracellular calcium concentration via second messenger pathways [116, 117]. Moreover, it seems that these neuromodulators systems selectively interact with growth factors to affect plastic changes. For instance, acetylcholine fibers host the majority of the receptors for the neurotrophin nerve growth factor. Therefore, this system may mediate the effects of the growth factor [118, 119] on ocular dominance plasticity.

4.3.1.5. Contribution of neuromodulators to cortical plasticity in relation to feed-forward mechanisms

Adrenergic, cholinergic, and serotoninergic systems are essential for the primary function of visual cortex. Indeed, they control the morphological reorganization of the circuitry. For instance, the application of noradrenaline and serotonin modulates, in an age-dependent manner, the number of synapses. Interestingly, these systems facilitate the ocular dominance

plasticity possibly by modulating thresholds for LTP/LTD induction resulting in modification of intracellular calcium concentration. Maya Vetencourt and co-authors [88] showed that the administration of fluoxetine restores ocular dominance plasticity in adults, possibly due to a correlative reduction in inhibition.

Knowing that preferential orientation of neurons may change following adaptation or could be modified using specific compounds, underlines plasticity within the adult cortex, and adds a ray of hope in various clinical situations. However, the mechanisms responsible for the constant changes in the adult brain are not fully elucidated; that is why, the plasticity is a key property, which we should more investigate.

5. Conclusions

Senses make us alive by detecting a diverse set of external signals with incredible sensitivity and specificity. We are thus capable of detecting changes in our environments and adjusting our behavior appropriately. Sensory cortices are thus referred to as "plastic," wherein changes across brain systems and related behaviors modulate as a function of the time and the nature of experience. There are missing links of knowledge concerning unimodal sensory deprivation on the direct functioning of neighboring primary sensory areas and missing sensory modalities. Moreover, a few cross-modal studies have opened gates toward the understanding of the interaction between multimodal sensory areas. There is a need to determine the multimodal nature of primary sensory areas and the extent to which the structural changes that can be observed ultimately leading to behavioral changes. Future studies implying high-resolution approach would be able to clarify the roles of these areas in compensatory sensory changes and brain reorganization. Still, summarizing from the discussion of the role of sensory areas and sensory regions exhibiting multisensory conduct is it not fair to ask; Is cortex essentially multisensory? Is cortex plastic or elastic? After describing different studies and results from our own and few other protocols, we may suggest that the answer is indeed YES. Cortex is essentially multisensory! Moreover, the argument that brain is plastic or elastic is still yet to be further scrutinized. It may be concluded that external factors govern the dynamics of the brain and the extent and nature of experience at different stages of life could be the most deciding factor or brain plasticity.

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