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Examen des effets comparatifs de l'adaptation sur les réponses des neurones des couches supra et infragranulaires à l'aide de stimulations visuelles et acoustiques dans le cortex visuel du chat

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Examen des effets comparatifs de l'adaptation sur les réponses des neurones des couches supra et infragranulaires à l'aide de stimulations visuelles et acoustiques dans le cortex visuel du chat

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RÉSUMÉ

Dans le cortex visuel primaire (V1 ou l'aire 17) du chat, les neurones répondent aux orientations spécifiques des objets du monde extérieur et forment les colonnes d'orientation dans la zone V1. Un neurone répondant à une orientation horizontale sera excité par le contour horizontal d'un objet. Cette caractéristique de V1 appelée sélectivité d'orientation a été explorée pour étudier les effets de l'adaptation. Suivant un schéma d'entraînement (adaptation), le même neurone ayant initialement répondu à l'orientation horizontale répondra désormais à une orientation oblique. Dans cette thèse, nous étudions les propriétés d'ajustement d'orientation de neurones individuels dans des couches superficielles et plus profondes de V1 dans deux environnements d'adaptation. En raison de la grande interconnectivité entre les neurones de V1, nous émettons l'hypothèse que non seulement les neurones individuels sont affectés par l'adaptation, mais que tout le cortex est reprogrammé par l'adaptation.

Des enregistrements extracellulaires ont été effectués sur des chats anesthésiés. Les activités neuronales ont été enregistrées simultanément aux couches 2/3 et à la 5/6 à l'aide d'une électrode de tungstène. Les neurones ont été adaptés à la fois par stimulation visuelle et son répétitif selon deux protocoles différents. Dans les deux cas, une plage stimulante constituée de sinusoïdes à défilement a été présentée pour évoquer les réponses dans V1 et générer des courbes de réglage d'activité multi-unités. La connectivité fonctionnelle entre les neurones enregistrés a été démontrée par un corrélogramme croisé entre les décharges cellulaires captées simultanément.

En réponse à l'adaptation visuelle, les neurones des couches 2/3 et 5/6 ont montré des glissements attractifs et répulsifs classiques. En revanche en comparant le comportement des neurones de l'une et l'autre couche, on a observé une tendance équivalente. Les corrélogrammes croisés entre les trains de neurones des couches 2/3 et 5/6 ont révélé des décharges synchronisées entre les neurones. Durant l'adaptation au son, en l'absence totale de stimuli visuel, le glissement des courbes d'accord a été observés chez l'une et l'autre couche indiquant ainsi un changement de la sélectivité de l'orientation. Toutefois, il faut prendre note du

fait que les cellules des deux couches ont un glissement aux directions opposées ce qui dénote un comportement indépendant.

Nos résultats indiquent que les réponses des neurones du cortex V1 peuvent être évoqués par stimulation directe ou indirecte. La différence de réponses à différents environnements d'adaptation chez les neurones des couches 2/3 et 5/6 indiquent que les neurones de l'aire V1 peuvent choisir de se comporter de la même façon ou différemment lorsque confrontés à divers' stimuli sensoriels. Ceci suggère que les réponses dans V1 sont dépendantes du stimulus environnemental. Aussi, les décharges synchronisées des neurones de la couche 2/3 et de la couche 5/6 démontre une connectivité fonctionnelle entre les paires de neurones. En définitive on pourrait affirmer que les neurones visuels subissent une altération de leur sélectivité en construisant de nouvelles cartes de sélectivité. À la lumière de nos résultats on pourrait concevoir que le cortex en entier serait multi sensoriel compte tenu de la plasticité entre les zones sensorielles.

Mots clés: cortex visuel, plasticité, adaptation, sélectivité d'orientation, multi sensorialité, connectivité fonctionnelle, corrélation, audio-visuel.

ABSTRACT

In the cat primary visual cortex (V1 or area17), neurons fundamentally respond to orientations of the objects in the outside world. Neurons responding to specific orientations form the orientation columns in V1. A neuron responding to a horizontal orientation will get optimally excited towards the outline of a horizontal object. This feature of the visual cortex known as orientation selectivity has been continuously explored to study the effects of adaptation. Following a training paradigm called adaptation, the same neuron that was inherently responding to the horizontal orientation will respond to an oblique orientation. In this thesis, we seek to examine the orientation tuning properties of individual neurons in superficial and deeper layers of V1 in different adaptation environments. Due to the extensive interconnectivity between V1 neurons, we hypothesize that not only do individual neurons get affected by adaptation paradigm, but the whole cortex is reprogramed.

To this aim, extracellular recordings were performed in conventionally prepared anesthetized cats. Neural activities were recorded simultaneously from layer 2/3 and layer 5/6 using a tungsten multichannel electrode. Neurons were adapted with a visual adapter (visual adaptation) and a repetitive sound (sound adaptation) in two different settings. Both types of adaptations were performed uninterrupted for 12 minutes. In both settings, sine-wave drifting gratings were presented to evoke responses in V1 and generate tuning curves from the recorded multiunit activity. The functional connectivity between the recorded neurons was revealed by computing cross-correlation between individual neuron pairs.

In response to visual adaptation, layer 2/3 and 5/6 neurons displayed classical attractive and repulsive shifts. On comparing the behaviour of the neurons in either layer, an equivalent tendency was observed. Cross-correlograms between the spike trains of neurons in layers 2/3 and 5/6 revealed synchronized firing between the neurons suggesting coordinated dynamics of the co-active neurons and their functional connections. During sound adaptation, where the visual adapter was completely absent, shifts in the tuning curves were observed in either layer indicating a novel orientation selectivity. However,

it is noteworthy that cells in both layers shifted in opposite directions indicating independent behaviour. V1 neurons might have an additional role besides processing visual stimuli. The visual neurons may have demonstrated multisensory properties when stimulated indirectly through neighbouring sensory regions.

Our results indicate that primary visual neurons can be evoked by direct or indirect stimulation. The difference in the responses of layer 2/3 and layer 5/6 neurons towards the different adaptation environments indicate that neurons in V1 may behave similar or different towards the different sensory stimulus. This suggests that V1 responses are stimulus dependent. Additionally, the synchronized firing of layer 2/3 and layer 5/6 neurons towards visual adapter signify an existence of functional connectivity between the neuron pairs. Together, it can be summarised that visual neurons undergo an alteration of selectivity by building new orientation maps that ultimately potentiates plasticity within sensory regions that are highly suggestive of entire cortex being multisensory.

Keywords: Visual cortex, plasticity, adaptation, orientation selectivity, multisensory, functional connectivity, correlation, audio-visual

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ABBREVIATIONS

V1: A17, area 17, Primary Visual Cortex

V2: A18, area 18, Secondary Visual Cortex

V3: Visual area 3/ Brodmann area 19

V4: Visual area 4

MT: Middle temporal visual area/ V5

LGN: Lateral Geniculate Nucleus

PV: Parvalbumin

NMDA: N-methyl-D-aspartate/ NMDAR

Nogo: Nogo receptor (NgR)

OMgp: Oligodendrocyte myelin glycoprotein

MAG: Myelin-associated glycoprotein

SC: Superior colliculus

AES: Anterior ectosylvian sulcus

Min: minute

ACG: Auto correlogram

CCG: Cross correlogram

PCA: Principal component analysis

OSI: Orientation Selectivity Index

Ca2+: Calcium ion

Ms: millisecond

FS: Fast spiking/ interneurons

RS: regular spiking/ excitatory neuron

I dedicate this thesis to

my mother Tashi Angmo (Amuu)

&

my husband Ashish Mehta (Ashi)

who at different times have been an immense source of inspiration

and encouragement

in my life.

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I would not deny that I was also on a kind of personal journey during my PhD since I was away from my husband and family for initial six months that too for the first time in my life. It was emotionally

challenging for me, but now, when I look back from where I began, I see myself as an independent and a more confident person!

I thank every single person that had been associated in the success of this journey. I wish everyone happiness and success for life!

Thanks to all of you for making me what I am today!

Nayan Chanauria

CHAPTER 1: INTRODUCTION

1.1. Visual System Organization

1.1.1. Overview

Visual areas in humans are made up of about 5 billion neurons which is approximately 25% of the cortex. The continuous exploration on the visual cortex revealed that there are many areas of the vision including areas V1, V2, V3, V4 and MT which were best defined regarding structure, topography and physiological properties (Felleman & Van Essen, 1991; Kujovic *et al.,* 2013). These regions are involved in processing a multitude of visual information such as shape, color, orientation, size, and movement, etc. resulting from the various visual information processing pathways. The cortex of mammals such as monkeys, cats, and humans are usually divided into different areas that process a specific function.

1.2. Primary Visual Cortex

Among all the visual areas, the primary visual cortex (V1) is historically the most studied part of the brain. It is the part of the cerebral cortex that is responsible for processing visual stimuli. Because of its stripy appearance this area is also known as striate cortex. It is the simplest and earliest recognized cortical visual area, highly specialized for processing information about static and moving objects and is implicated in pattern recognition. The primary cortical area of cats embody a columnar organization, meaning that neurons within a column perpendicular to the surface of the cortex have similar response properties i.e. similar position, and similar orientation selectivity (Hubel *et al.,* 1977; Blasdel & Salama, 1986). These domains of orientation selectivity are known as orientation columns (Hubel & Wiesel, 1959; 1962a). In an orientation column, neurons optimally respond to the same orientation and can be evoked by oriented bars of light. A neuron responding to a horizontal orientation will get optimally excited towards the outline of a horizontal object. This feature of the visual cortex is known as orientation selectivity. Each hemisphere of

the cat brain has a visual cortex. The right visual cortex receives information from the left visual field, and the left visual cortex from the right visual field. There is another system of alternating columns, which corresponds to the separation of afferents from both eyes. These are the ocular dominance columns. The ocular dominance columns represent bands of cortical tissue alternately occupied by afferents from the left eye or right eye (Shatz & Stryker, 1978; Horton & Hocking, 1996; Adams *et al.,* 2007). These bands are particularly pronounced at the cortical layer IV, which receives the afferent endings of the lateral geniculate nucleus. Thus, the visual cortex is organized into functional maps of orientation, spatial frequency, ocular dominance, temporal frequency which are integrative to each other. This parallel organization of visual system is involved in the establishment of two major visual pathways: ventral and dorsal pathways which are vital for the object recognition. The ventral pathway is involved in the processing the characteristics of the objects (shapes, colours, materials), that is, object recognition including faces. The dorsal pathway in the cortex, which ends in the parietal lobe, is associated with spatial vision (action/location) of objects (Mishkin *et al.,* 1983; DiCarlo *et al.,* 2012).

The primary visual cortex, or area 17, is divided into six layers from layer 1 to layer 6 which comprise different types of neurons (Hubel & Wiesel, 1959). Each layer has its own peculiarities (Figure 1.1). The interconnectivity between primary visual cortical area is very specific. Functionally, layers 1-3 are often grouped together and called the superficial layers of the cortex. Layer 1 has very few neurons but many axons, dendrites and synapses. Layers 2 and 3 consists of a dense array of cell bodies and many local dendritic interconnections. These layers appear to receive a direct input from the LGN (Fitzpatrick *et al.,* 1983; Hendry & Yoshioka, 1994). The outputs from layers 2 and 3 are projected to other cortical areas. Layers 2 and 3 are hard to distinguish based on simple histological stains of the cortex therefore referred to as one when discussing their features. Layer 4 receives the primary input from the LGN body and sends the output to layer 5 and layer 6. Layer 5 contains relatively few cell bodies compared to the surrounding layers. It sends a major output to the superior colliculus, a structure in the midbrain. Layer 6 is dense with cells and sends a large output back to the LGN (Thomson & Bannister, 2003). Classically, superficial layers

project onto layer 4 and forward outputs to new cortical areas. The feedback projections tend to come from the deep layers and terminate in layers 1 and 6 (Felleman & Van Essen, 1991). But Constantinople and Bruno (Constantinople & Bruno, 2013) challenged the dogma of flow of information by reporting that deeper cortical layers along with layer 4 can be directly and simultaneously activated by the thalamic input in rats. This reflects that layer 5/6 is not necessarily the only port of information flow to other cortical layers.

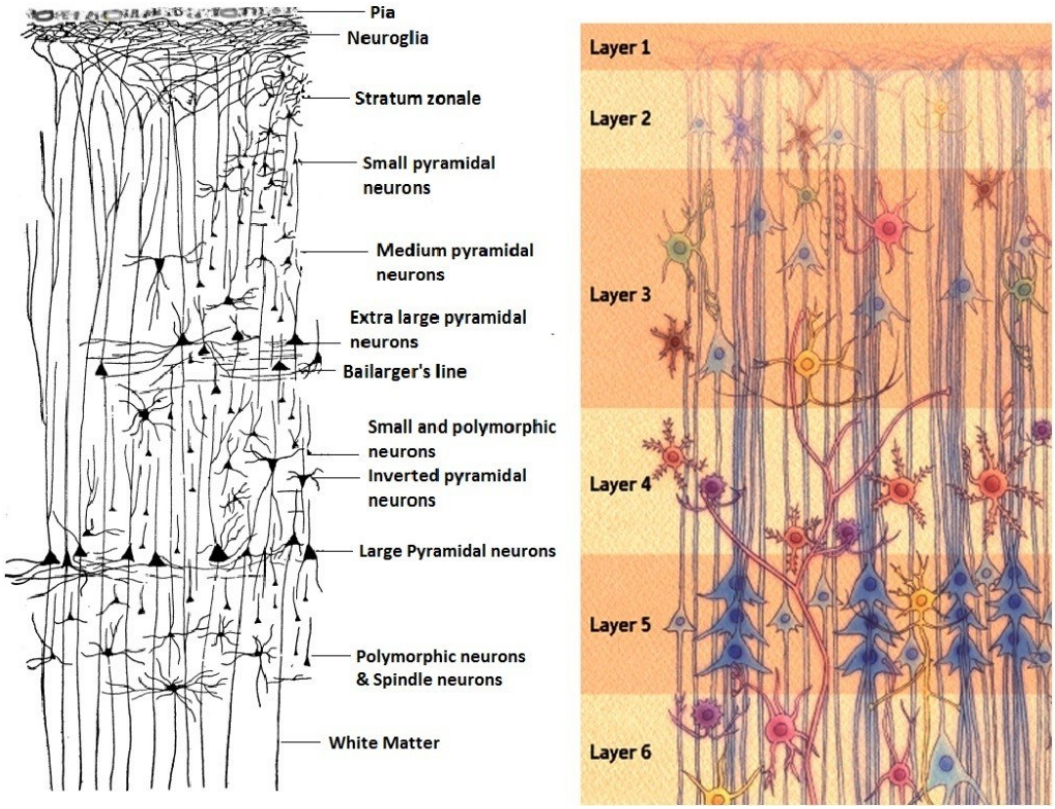

Figure 1.1

A cross-section of the cerebral cortex showing layers of the cortex (https://imgur.com/gallery/xCAoW)

Hubel and Wiesel (Hubel & Wiesel, 1959) also observed that neurons responding to orientations were specifically organized. By introducing an electrode through the cortex perpendicular to the surface (Figure 1.2, left), they encountered neurons with similar properties regardless of whether they have simple or complex receptive fields, i.e. responding to similar orientations and stimuli from the same eye. Thus, the

concept of orientation selectivity in the columns was introduced. If the penetration angle was tangential (Figure 1.2, right), the neurons changed in a predictable way: the orientation selectivity of the neurons varied from 180° up until 1 mm of the cortex in a continuous way. It was deduced that, in this way, the electrode had passed through several orientation columns. However, it should be noted that the continuous variation of orientations on the same plane of the cortex can be broken punctually or on a so-called "fracture" line. When the electrode crosses these two types of discontinuity, the orientation can vary abruptly by an angle of more than 45° (Blasdel & Salama, 1986; Blasdel, 1992).

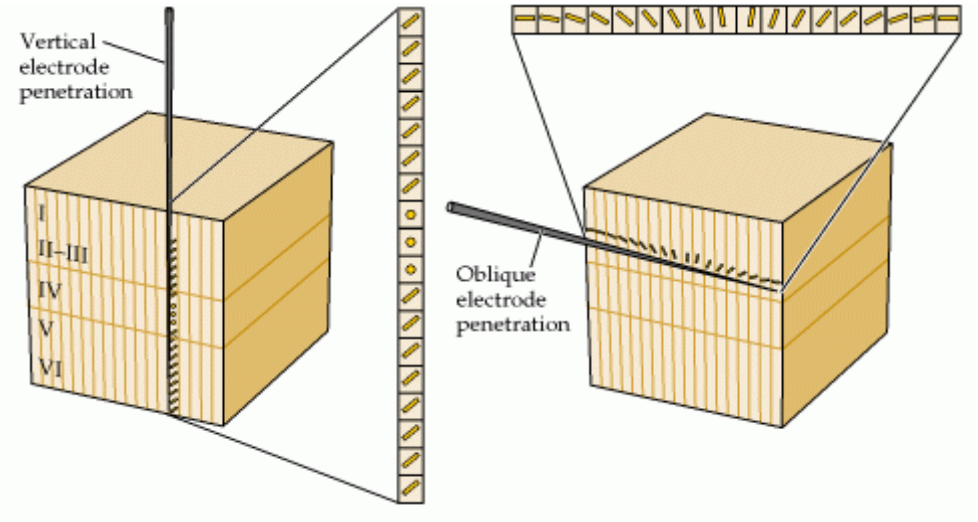

Figure 1.2

Penetrations of electrodes perpendicular (left) or parallel (right) to the cortical surface. The orientations giving the most response to each electrode progression are indicated in the vertical and horizontal bars

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1.2.1. Associated visual areas

In addition to the primary visual cortex (V1), there are many neighbouring visual areas whose functions are crucial in visual processing. Secondary visual area V2 or area 18 of the cat shows strong reciprocal connections with primary visual area V1 or area17 (Symonds & Rosenquist, 1984; Salin *et al.,* 1995). V1

project its X geniculate cells inputs onto V2 (Freund *et al.,* 1985; Dreher *et al.,* 1992). Along with the structural association, these areas also undergo functional interactions towards orientation tuning, as it has been shown that inactivation of V1 changes the orientation sensitivity of V2 cells (Chabli *et al.,* 1998). It has also been shown that V2 modulates V1 responses, either by augmenting or by decreasing neuronal firing rates, without radically affecting their orientation or speed (Martinez-Conde *et al.,* 1999). The neurons in V2 share many properties with V1 area neurons (Bonhoeffer & Grinvald, 1993) though they also have many differences (Sengpiel *et al.,* 1999). The major difference between V1 and V2 is that V1 receives its input from LGN, and V2 additionally receives its input from V1. Thus, V1 and V2 have mutual relationship as they are dependent on feed-forward and feed-back inputs.

In a classical study (Symonds & Rosenquist, 1984), authors confirmed that corticocortical pathways in the cat visual system may originate not only from the traditionally found layer 2/3 but from any layer of the cortex. Layer 6 of area 19 and PMLS may project to area17 and PMLS alone to area 18 (Gilbert and Kelly, 1975; Kawamura and Naito, 1980). They additionally confirmed the revelations of previous studies (Shtaz, 1977; Innocenti, 1981; Segraves and Rosenquist, 1982) that projections from area 17 to outside originate from deeper layers of area 17.

The authors concluded through retrograde tracing and retinotopy technique that specific visual areas provide vital information to a set of visual areas locally anatomically located to that specific area whereas poses modulatory influences onto those visual areas that are located anatomically apart. Due to this reason, any single visual area cannot be placed in a hierarchical order with other visual areas because cells in a specific area might project forwards to backwards at the same time.

The mentioned study also revealed that projections to visual areas are evoked depending upon the target areas. Tracing of axons in different layers of area17 disclosed that projections that come out of area 17 are layer specific towards specific visual areas. In addition, another important revelation was made. A visual area receives its afferents from among different layer of the different cortical areas that supports the

discussion of this thesis. Therefore, all these areas are interconnected by neural projections that can be observed in a specific cortical area or between different areas.

1.3. Receptive field properties of neurons

The term receptive field was originally coined by Sherrington (Sherrington, 1906). Classically, receptive field defined by a region in space in which the presence of a feature excites the neuron and augments its firing (Hartline *et al.,* 1978). Receptive fields have been identified for neurons of the auditory system, the somatosensory system, and the visual system in response to spatial localisation, specific frequencies and amplitudes. Receptive fields can be empirically characterized by fixing the animal in space and presenting the feature, thus selectivity of a neuron can be determined. For example, random presentation of a series of sine-wave drifting gratings tilting gradually by small angles to a group of neurons in a primary visual cortex evokes neuronal responses to the specific angles. Layer 2/3 neurons preferentially respond to stimuli such as bars having characteristics as orientation, spatial frequency, direction, length. Neurons in different layers are classified into single cells, complex and hyper complex cells depending on the properties of their receptive fields. Simple cells are mainly found in layers 4 and 6 and have ON-OFF sub fields. Complex neurons do not have defined ON or OFF receptive fields, and a stimulus presented anywhere in the receptive field evokes a response, that is why complex cells have larger receptive fields than the simple cells. Therefore, a complex cell does not exhibit adjacent excitatory and inhibitory zones within its receptive field (Hubel & Wiesel, 1962). Layer 2/3 neurons are almost exclusively occupied by complex cells (Gilbert & Wiesel, 1979). Hyper complex cells are known to have very large receptive fields. They emerge when complex neurons' axons (interspersed with different orientations) converge. When a line is presented within the receptive field of a hyper complex cell, its response starts to decline beyond a specific length of the line because of the antagonistic excitatory and inhibitory regions (Hubel & Wiesel, 1965; Gilbert & Wiesel, 1979).

1.4 Neuronal Selectivity

The hallmark of the neurons in the somatosensory system, the auditory system, and the visual system is that they have organized receptive fields (Hubel & Wiesel, 1965; Kozlov & Gentner, 2016). Here neurons are selective to a specific range of stimuli (Hubel & Wiesel, 1959). The adjacent neurons in the primary visual cortex actively respond to edges or bars of contrast, when presented an orientation in their receptive field. Each neuron is programmed to respond to an "optimal orientation" for which its discharge activity or empirically defined firing rate is maximum. All orientations of an edge or a bar are represented in approximately equal proportions at the pinwheels (Figure 1.3), a region at the centre where all orientations intersect (converge). The English term pinwheel here describes the fact that the colored areas seem to turn around an axis like the wings of a reel (Maldonado *et al.,* 1997). The orientation selectivity of neurons recorded from different regions of the cortical map varies from 0 to 1, where closer the OSI is to one, the stronger the orientation selectivity (Bachatene *et al.,* 2012a; Cattan *et al.,* 2014; Bachatene *et al.,* 2015a; Bachatene *et al.,* 2015b; Chanauria *et al.,* 2016). For any neuron, these values are calculated by generating tuning curves of the neurons from the firing rates of the same neurons for different orientations (Butts & Goldman, 2006). A tuning curve is an empirical description and estimation of parameters that shows the best fitting model function for a single neuron (Swindale, 1998b). A cartoon is shown in Figure 1.4 depicting how a tuning curve is generated.

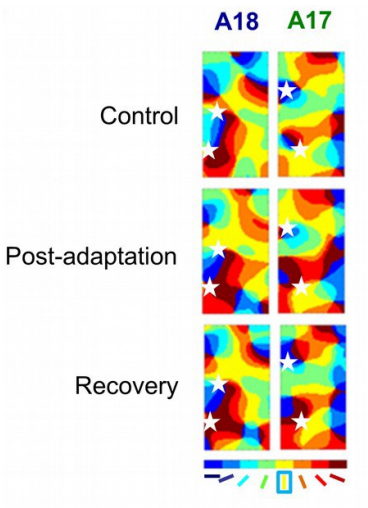

Figure 1.3

Changes in pinwheel organization at the same location in A17 and A18 (columns) in control (upper row), following adaptation (middle row) and recovery (lower row) conditions. The orientation inside the blue square under the colored bar indicates the adapting orientation (Cattan et al., 2014)

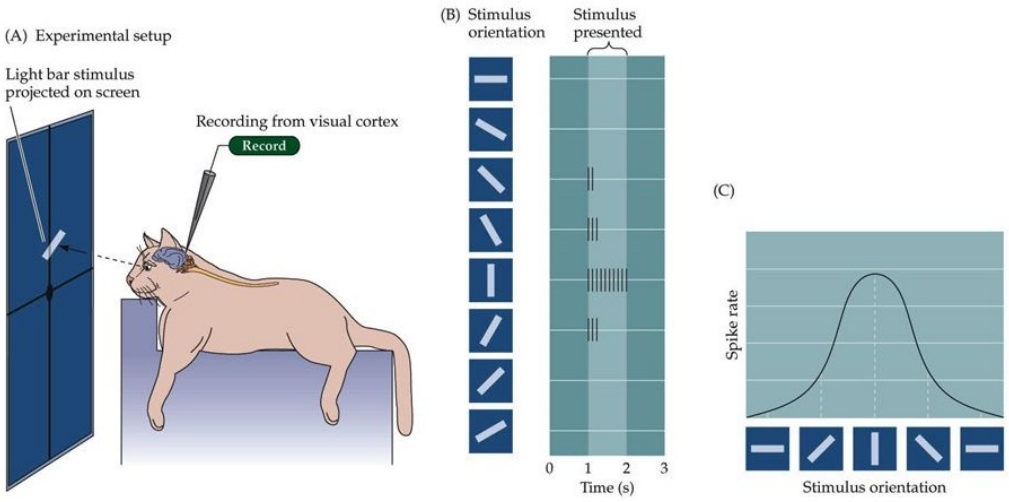

Figure 1.4

(A) Experimental setup where range of orientations are presented to the neurons (B) Variation of response (right) towards different orientations (left) (C) Following the recording of the neuronal response towards different orientations a tuning curve can be calculated and generated and a figure.

1.5. Physiological Classification of cells

Primary visual cortex is divided into different layers and different cells across layers perform specific function. Two types of cells are mainly observed in the visual cortex: pyramidal cells and inhibitory interneurons. Pyramidal cells are excitatory neurons projecting onto other brain regions whereas interneurons are inhibitory in nature and are mainly convoluted in feedback/ feedforward mechanisms (Tremblay *et al.,* 2016). Each layer corresponds to specific cell type and connectivity in primary visual cortex. Pyramidal cells are found in layers 2/3, 5 and 6 and are the only neurons that send axons outside the cortex whereas layer 4 is dominated by stellate cells. The supragranular layers consist of layers 1 to 3 and layers 5 and 6 constitute the infragranular layers. Neurons recorded electro physiologically can be segregated into excitatory pyramidal cells and inhibitory interneurons based on ascending slope of the spike-waveform and based on their firing patterns (Niell & Stryker, 2008; Bachatene *et al.,* 2012a; Bachatene *et al.,* 2012b; Vinck *et al.,* 2013; Bachatene *et al.,* 2015a). The RS or regular spiking neurons, can be putatively linked to the pyramidal neurons, whereas the FS or fast spiking neurons may be associated to the inhibitory interneurons (Niell & Stryker, 2008; Bachatene *et al.,* 2012a; Bachatene *et al.,* 2012b; Vinck *et al.,* 2013; Bachatene *et al.,* 2015a). The major difference between an FS and an RS is that the FS has a steeper ascending slope than the RS (Niell & Stryker, 2008). In other words, the FS spike-width is smaller than the RS spike-width. In cats the dissociation of the interneurons and pyramidal cells based upon this technique is not entirely possible as pyramidal neurons may show the fast spiking outline (Nowak *et al.,* 2003). Thus, it is to be considered while classifying or inferring the data based on ascending-slope discrimination of spike-waveforms in cats.

1.6 Similarity with other vertebrates

Over a period of years, monkeys, cats, and mice are being commonly used in neurophysiological experiments for understanding cortical mechanisms in general and visual pathways. The cats' visual system

is congruent to many species (Tyler *et al.,* 1998; Kaschube *et al.,* 2010) even to humans', thus making them a suitable model for understanding the brain better and even give insights into human brain function. Lower vertebrates like rats and mice have a salt-and-pepper cortical organisation and lack the orientation columns like cats, monkeys and humans. Yet, they exhibit neuronal selectivity as many orientations are intermingled in a small tissue volume (Ohki *et al.,* 2005; Van Hooser, 2007). Neurons in cat share similarity with neurons in primate in many ways e.g. the receptive fields in the retina and the LGN are concentrically arranged in cats and monkeys (Swindale, 1997; Jeffries *et al.,* 2014). Furthermore, the X and Y ganglion cells classification is similar in function in monkeys and cats (Dreher *et al.,* 1976). Also, both simple and complex cells are found in primates and cats (Hubel & Wiesel, 1968). Additionally, experimentation in different models have established that the human visual system indeed shares the features with the cat visual system (Blake, 1979). Of course, it is undeniable that there are certain differences e. g. human visual system has much better color-discrimination power than the cat visual system (Loop & Bruce, 1978). For all the mentioned reasons, cats have been continuously chosen as a model for researchers in neuroscience to study and investigate different facets of the brain functioning.

1.7 Critical period and adult plasticity

During early development, the brain undergoes a period of enhanced plasticity known as the critical period. Critical period was introduced by the pioneering work of Wiesel and Hubel (Wiesel & Hubel, 1963) in their studies in the developing visual system of cats. The critical period can last from about 3 weeks to several months in cats. Critical periods are described as the times during which sensory experience is imperative for the development of the brain and to establish the circuitry of neurons constantly by varying experiences. This early experience drives inhibition between neurons and helps carve the critical period plasticity (Trachtenberg JT, 2015). The maturation of cortical inhibition just after eye-opening of the new born is also necessary for the establishment of experience-dependent ocular dominance plasticity in the visual cortex. Ocular dominance plasticity relies on counteraction between two eyes to drive cortical responses.

Monocular occlusion leads to a behavioral reduction in responses to the deprived eye, an effect that is mediated in primary visual cortex (Prusky *et al.,* 2000). Two decades ago, the first direct experimental control over the induction of ocular dominance plasticity was achieved by altering local circuit excitation/inhibition (E/I balance) (Hensch *et al.,* 1998a). Subsequent experiments showed that the potential for plasticity is retained throughout life until an inhibitory threshold is attained (Fagiolini & Hensch, 2000). More specifically, it is the late maturation of inhibitory Parvalbumin-positive large basket (PV) cells that mediates this form of plasticity (Fagiolini *et al.,* 2004). Do PV cells control the opening of critical periods for other receptive field properties across multiple sensory domains is unclear and is an active area of research. The maturation of excitatory circuits has also been implicated in critical period induction. For many years, synaptic plasticity at excitatory synapses alone was thought to control ocular dominance plasticity, but experimental manipulations failed to produce changes in vivo (Hensch & Stryker, 1996; Hensch *et al.,* 1998b; Renger *et al.,* 2002). However, mice with immature excitatory circuits arising from targeted gene-disruption of NR2A, a subunit of the N-methyl-D-aspartate (NMDA) glutamate receptor, fail to develop orientation selectivity despite normal visual experience (Fagiolini *et al.,* 2003). Thus, the maturation of inhibitory and excitatory circuits controls distinct features of visual cortical plasticity. Rapid functional plasticity is converted to long lasting structural changes by a variety of pre- and postsynaptic mechanisms. Axonal outgrowth is inhibited when presynaptic Nogo receptors and PirB receptors bind to oligodendrocyte released Nogo, OMgp, and MAG (Atwal *et al.,* 2008; Schwab, 2010). This, in turn, consolidates functional circuits and reduces plasticity (McGee *et al.,* 2005; Syken *et al.,* 2006). Postsynaptically, monocular deprivation increases proteolytic (tPA-plasmin) activity (Mataga *et al.,* 2002), leading to increased dendritic spine motility (Oray *et al.,* 2004). This is followed by transient elimination and regrowth of spines in favor of the non-deprived eye (Mataga *et al.,* 2004). Along these lines, accelerating the maturation of dendritic spines by deletion of intracellular adhesion molecule 5 (Icam5) accelerates the window of plasticity for auditory thalamocortical connectivity (Barkat *et al.,* 2011). Finally, molecular brakes on modulatory systems play an active role in suppressing plasticity in adulthood.

Depletion of catecholamines by the administration of 6-OH-dopamine, which selectively destroys dopaminergic and noradrenergic neurons, prevents ocular dominance plasticity in kittens (Kasamatsu & Pettigrew, 1976; Bear *et al.,* 1983). Chronic administration of fluoxetine, a selective serotonin reuptake inhibitor, can restore plasticity in adult visual cortex by increasing the expression of brain-derived neurotrophic factor, which had previously been implicated in developmental plasticity (Hanover *et al.,* 1999), and decreasing intracortical inhibition (Maya Vetencourt *et al.,* 2008). Finally, negative regulation of cholinergic modulation by Lynx1 facilitates E/I balance and prevents ocular dominance plasticity in adulthood (Morishita *et al.,* 2010). While many studies over the last forty years have uncovered mechanisms underlying plasticity within a sensory domain, how sensory experience affects the processing and organization across sensory modalities is much less clear.

Therefore, 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 reorganisation of neuronal network that become resilient with maturity.

1.8 Visual Adaptation and plasticity

Neurons have an amazing tendency to change their properties in response to the environment that confers the brain plasticity. It was considered that the orientation selectivity of the neurons in the cortical columns remains stable in the primary visual cortex established early in life during the "critical period" (Tanaka *et al.,* 2009). However, different studies in various laboratories have shown that even in mature brain, the neural network restructures beyond the critical period following birth (Dragoi *et al.,* 2000; Godde *et al.,* 2002). Adult V1 neurons modify their original selectivity acquired just after birth to a new preferred orientation following adaptation (Dragoi *et al.,* 2000; Ghisovan *et al.,* 2009; Bachatene *et al.,* 2012b; Cattan *et al.,* 2014). Nowadays, it is widely known that presentation of a prolonged non-optimal stimulus, called adapter, induces a change in neuronal selectivity. In other words, neurons learn to respond to a non-

preferred stimulus. This phenomenon is known as adaptation (Dragoi *et al.,* 2000; Ghisovan *et al.,* 2009; Bachatene *et al.,* 2012b; Cattan *et al.,* 2014). As a consequence of this adaptation, the neurons shift their tuning either towards or away from the adapter exhibiting attractive or repulsive shifts (Dragoi *et al.,* 2000; Ghisovan *et al.,* 2009; Bachatene *et al.,* 2012b) and the cortex is remapped (Dragoi *et al.,* 2000; Godde *et al.,* 2002). This shift of orientation preference is defined as the plasticity of visual cortex. Similar results have been obtained for other features of the stimulus such as spatial frequency (Marshansky *et al.,* 2011), direction of motion (Kohn & Movshon, 2004) and speed (Movshon, 1975). The cortices of higher mammals such as cats, monkeys and humans are organised into domains of selectivity called orientation columns. These columns extend down from layer 1 to layer 6. Reports demonstrate that layer 2/3 primary visual neurons show these classical attractive and repulsive shifts (Dragoi *et al.,* 2000; Ghisovan *et al.,* 2009; Bachatene *et al.,* 2012b; Cattan *et al.,* 2014). Layer 2/3 and layer 5/6 neurons are one of the most important computational processing units in the cortical column to decipher the information flow within the cortical circuit (Gilbert & Wiesel, 1989; Kisvarday & Eysel, 1992; Binzegger *et al.,* 2004; da Costa *et al.,* 2010; Cain *et al.,* 2016). Numerous studies suggest the importance of layer 2/3 and how adaptation affects these neurons (Dragoi *et al.,* 2000; Ghisovan *et al.,* 2009; Bachatene *et al.,* 2012b; Cattan *et al.,* 2014). Layer 5/6 neurons are continuously involved in feed forward and feedback loops in response to an input, but there is no evidence of how adaptation affects these neurons.

A study by Bachatene and co-authors (Bachatene *et al.,* 2015c) showed in superficial layers of the visual cortex that mean of amplitude of shift of adapted neurons was similar to the mean of the non-adapted neurons. The study exposed that along with the adapted neurons that acquire the new selectivity on adaptation, the neurons far away from the adapted site also acquired a new selectivity. The authors also showed that this process a systematic progression that starts by the acquisition of new selectivity by orientation column at the site of adaptation and is automatically acquired by the neurons in the neighbouring column respect to its previous column. The authors named the phenomenon as ‘domino effect’. Therefore,

we assume that not only the neurons specific to a layer 2/3 change but all neurons down an orientation column change thereby exhibiting domino effect, consequently leading to whole cortex reprogramming.

1.9 Neuronal Connectivity within the primary visual cortex

The organization of synapses between neurons is fundamental to different brain functions. The dense and self-projecting local synaptic connectivity of neurons in the sensory cortex is not arbitrary. The connectivity patterns between cells have a role in the processing of specific brain regions. Neurons are anatomically connected through synapses. It was first exposed by (Sholl, 1956; Gilbert & Wiesel, 1979). In the visual cortex, a neuron carries tiny microscopic structures on the dendrites called spines. The spines keep on budding and shrinking in response to experiences (Alvarez & Sabatini, 2007). The study of modifying synapses have revealed that spines can emerge and disappear depending upon the input or may remain stable over a period (Kasai *et al.,* 2010; Dur-e-Ahmad *et al.,* 2011; Ebrahimi & Okabe, 2014; Jung & Herms, 2014; Hasegawa *et al.,* 2015; Kellner *et al.,* 2016). Thus, the cortex restores short- and long-term plastic changes.

Between neighboring neurons, e.g. within 100 micrometers in the supragranular layers of the cortex, neurons make up to 3-6 contacts with each other (Hellwig, 2000; Frick *et al.,* 2008; Stepanyants *et al.,* 2008; Brown & Hestrin, 2009) whereas this probability may decrease substantially with distance (only one contact beyond 500 micrometers) (Hellwig, 2000). Neurons may also make lateral synaptic connections in the cortex. e.g., in the monkey prefrontal cortex, monosynaptic connections may exist between excitatory neurons across cortices (Melchitzky *et al.,* 2001). The translation of sensory information from the outside world needs a coherent representation in the brain, and it is a due to the emergence of coordinated and harmonized firing activity of groups of neurons (Alivisatos *et al.,* 2012). These groups of neurons that synchronize together to perform a computational task are called cell assemblies (Hebb, 1949). Several studies have reported the co-activation of small groups of neurons in response to applied stimuli (Fujisawa

et al., 2008; Buzsaki, 2010; Denman & Contreras, 2014; Schwindel *et al.,* 2014; Bharmauria *et al.,* 2015; Bharmauria *et al.,* 2016). Some have highlighted the significance of functional networks within these assemblies (Fujisawa *et al.,* 2008; Buzsaki, 2010; Harris & Mrsic-Flogel, 2013; Singer, 2013; Denman & Contreras, 2014; Miller *et al.,* 2014; Bharmauria *et al.,* 2015; Carrillo-Reid *et al.,* 2015; Bharmauria *et al.,* 2016). While these studies have primarily demonstrated the existence of the cell assemblies in superficial layers, coordinated activities between individual neurons in superficial and deeper layers is not very well explored yet.

Although it has been known that the neocortex is anatomically and functionally columnar, the size of the neocortex, its cell composition, synaptic organization, expression of signaling molecules, and function of various types of ‘‘columns’’ are dramatically different to each other (Mountcastle, 1997). The basic repeating unit of the mature neocortex is the minicolumn. A minicolumn contains a narrow chain of neurons extending vertically across the cellular layers 2-6 and perpendicular to the pial surface (Mountcastle, 1978). Minicolumns contain essential different neural cell types, interconnected vertically. Many minicolumns form cortical columns. Columns only vary from 300 to 600 μm in diameter, across species even if brains differ in volume by a factor of 10 (Mountcastle, 1997). The laminar location of cortical neurons, their cell bodies, is determined during the development (Popovitchenko & Rasin, 2017). Neurons have complicated morphologies and properties that typically span multiple layers. Therefore, it is essential to refer to neurons from a specific layer. e.g. a neuron whose cell body lies in layer 5 will be known as layer 5 cell. However, this cell having its body in layer 5 is distributed across multiple cortical layers through its dendrites and axon. Thus, it is the merging of different components of neurons and connectivity patterns in the layered cortex that needs to be taken into account (Major *et al.,* 2013). In cats, L1 consists mainly of axon terminals from subcortical sources synapsing onto apical dendrites of pyramidal cells whose somata and feedforward inputs to basal dendrites that are in deeper layers (Herkenham, 1980; Felleman & Van Essen, 1991; Binzegger *et al.,* 2004; Rubio-Garrido *et al.,* 2009; Cruikshank *et al.,* 2012). Layer 2/3 and layer 5/6 work in parallel but independently in processing the stimuli. They are highly

interconnected eg. it was found in an in-vitro study (Thomson *et al.,* 2002), that layer 3 pyramidal cell synapsed onto a large layer 5 pyramidal cell in cat V1. The structural study of the connections by the same group (Kisvarday *et al.,* 1986) reported two layer 3 pyramidal cells axons in cat V1 synapsed with both superficial and deep layers with spiny cells and GABAergic smooth dendrites. In another study (Koestinger *et al.,* 2018) using serial section electron, microscopic reconstructions revealed a heterogenous postsynaptic dendrite originating from both smooth and spiny neurons, indicating that the descending projection does not merely drive the layer 5 output cells, but participates in a complex circuitry in the deep layers. Distinct L5 populations are differentially connected with superficial layers and with each other that suggest the existence of distinct subnetworks within neocortical circuits (Lefort *et al.,* 2009; Feldmeyer, 2012). It appears that although there is extensive interconnectivity between neurons in visual processing networks, there is certainly a bias observed towards connectivity with cells that share functional properties. Therefore, it was of interest to explore how neuronal connectivity exists between superficial and deeper layer neurons in response to adaptation protocols. For this purpose, to calculate the functional connectivity, cross-correlation computation was implemented.

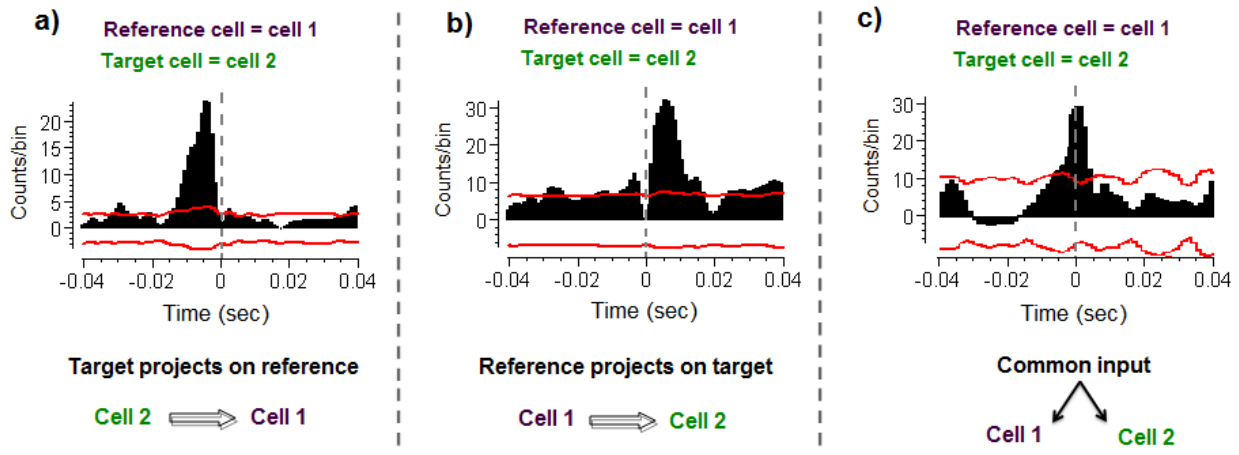

Figure 1.5

Possible cross correlograms between two neurons (a reference and a target). A typical cross correlogram between two neurons, to interpret the relation between them, is obtained by keeping one of the neurons as reference and calculating the spikes of the other neuron with reference to it (Bachatene et al., 2012).

Figure 1.5 displays possible patterns of cross correlograms between two neurons. The three examples illustrate the time relations between two neurons as revealed by shifted and corrected cross correlograms when one neuron is reference and the other is the target. To eliminate the possibility of stimulus-induced-relationship between two neurons, a shifted cross correlogram is obtained. A shift corrected cross correlogram is a histogram obtained by shifting the spikes of the reference cell by one or two cycles of stimulation. After this, the shifted cross correlogram is subtracted (corrected) to remove the stimulus-locked -component. Figure 1.5a corresponds to an example of a target cell projecting onto the reference cell. In this case, the target neuron fires few milliseconds before the reference cell since the peak of the cross correlogram appears few milliseconds before zero. This means that the target cell caused the reference cell to spike. Figure 1.5b corresponds to the reference cell projecting onto the target cell. In this example, the target neuron fires a few milliseconds after the reference cell as the peak of the cross correlogram can be seen a few milliseconds after zero. Here the target cell was excited by the reference cell. Figure 1.5c attributes to the synchrony between two neurons, as the peak straddles zero, or the peak can be seen on both sides of the zero. This indicates a common excitatory input to both neurons which probably is mostly from other neuron/ neurons. In all the three examples the peak is traced only within the 5 ms offset of zero as 5 ms has been the popular standard time window used to reveal the functional connections between the neurons (Alloway and Roy, 2002; Bharmauria *et al.,* 2015; Bharmauria *et al.,* 2016).

2.0 Plasticity at multisensory convergence regions

The processing of the real-world stimulus involves multiple senses and processing. This complex task takes place in the brainstem. Information from multiple sensory modalities meets at the superior colliculus to

direct eye movements and behavior (Sprague, 1972; Stein *et al.,* 1980; Meredith & Stein, 1983). This is a dominant feature observed across species such as mammals (Stein *et al.,* 1980), birds (Knudsen, 1983), reptiles (Hartline *et al.,* 1978), and fish (Roeser & Baier, 2003). Multisensory integration depends upon sensory experience and develops by more experience e.g., after monocular deprivation vision may guide the spatial location of an auditory stimulus (Knudsen & Knudsen, 1985). The NMDA receptors play a significant role in mediating the expression of new neuronal responses induced by experience (Feldman *et al.,* 1996) while inhibitory circuits functionally suppress the original responses (Zheng & Knudsen, 1999). This kind of early experience leaves a long-lasting effect even after normal sensory experience has been restored (Linkenhoker *et al.,* 2005) which might explain the enhanced plasticity in adult owls (Knudsen, 1998). In mammals, interactions between superior colliculus (SC) and other associated multisensory areas has been very well studied and SC has been identified as the convergence zone of processing multisensory stimuli. The processing of visual and auditory representations in the SC also depends on the age and the experience (King *et al.,* 1988; Wallace & Stein, 1997). In cats, integration in the SC is dependent on input from the anterior ectosylvian sulcus (AES) (Wallace *et al.,* 1993; Wallace & Stein, 1994). This territory in the cortex contains cells that respond to unisensory and multisensory stimuli such as auditory, visual, and somatosensory stimuli (Wallace *et al.,* 1992; Jiang *et al.,* 1994). It has been demonstrated that reversible deactivation of AES reduces specific multisensory response enhancement without affecting a neuron's modality-specific response (Jiang *et al.,* 2001). Classically, this sort of multisensory integration was thought to occur in higher-order association cortices after primary unisensory processing (Felleman & Van Essen, 1991). More recently, it has been shown that multisensory integration can occur in areas previously suspected as unisensory. Visual and somatosensory processing has been reported in early auditory areas (Foxe *et al.,* 2000; Schroeder & Foxe, 2002; Brosch *et al.,* 2005), and individual neurons in cat visual cortex can be driven by auditory stimuli (Morrell, 1972). These results have challenged the traditional views of cortical processing (Wallace *et al.,* 2004) and promote the fact that neocortex could be multisensory when interacting with the outside environment (Ghazanfar & Schroeder, 2006).

CHAPTER 2: HYPOTHESIS AND OBJECTIVE

2.1 Hypothesis

Neuroplasticity exists due to changing in response properties of the cortical neurons in response to a long-term occurrence of a visual input. Primary visual cortex (V1) has been the most studied area in the brain and the neurons here are inherently sensitive towards a feature. Neurons are grouped into small columns according to their response preferences towards that feature. These columns are systematically organised at regularly spaced intervals and cover the entire cortical representation of the visual field. V1 neurons responding to an orientation in different layers of the V1 give rise to the orientation columns that run down from layer 1 to layer 6. This property can be modified by enforcing different stimuli on the V1 neurons for different time intervals. Therefore, V1 neurons are magnificently plastic. Using plasticity of V1 neurons as a tool, visual neurons can be used to study the adaptation effects on the neurons by imposing a non-preferred stimulus. Layer 2/3 neurons or superficial layer neurons exhibit traditional shifts in the orientation selectivity measured by tuning curves. Since layer 5/6 neurons comprise of extensive dendritic trees, these neurons are believed to be the most important information processing units that constantly are found implicated in the neurons' regulatory mechanisms. Despite several adaptation studies, it remains unexplored how these neurons respond to visual adaptation when stimulated simultaneously with layer 2/3 neurons at the same time down the column. Typically, visual information is received by layer 4 neurons from LGN and processed within the supra-granular layers (layer 2/3) of the visual cortex and then projected to deeper layer neurons (layer 5/6). Therefore, layer 2/3 and layer 5/6 neurons are the principal units in the cortical computational processing to make sense of the information flow within the cortical circuit. However, how the neurons in the two layers communicate with each other in response to the visual adaptation remains unexplored.

Sensory cortex has been assumed to be fundamentally multisensory due to varied observations as an outcome of comparative studies of responses when visual neurons were stimulated both by light and sound. It does not appear suspicious because visual neurons are inherently dominant to a visual stimulus, but by coupling the two different stimuli – audio and visual, enhanced response were observed by the same neurons that were exposed to only light (Atilgan *et al.,* 2018). Recently, researchers have confirmed a modulation of the response in mice V1 neurons when excited indirectly by presenting a different sensory input (Ibrahim *et al.,* 2016). Primarily, these results had been observed in mice. Therefore, we wanted to explore how V1 neurons in cats, where the V1 organisation is columnar, respond to a prolonged adaptation with an auditory stimulus.

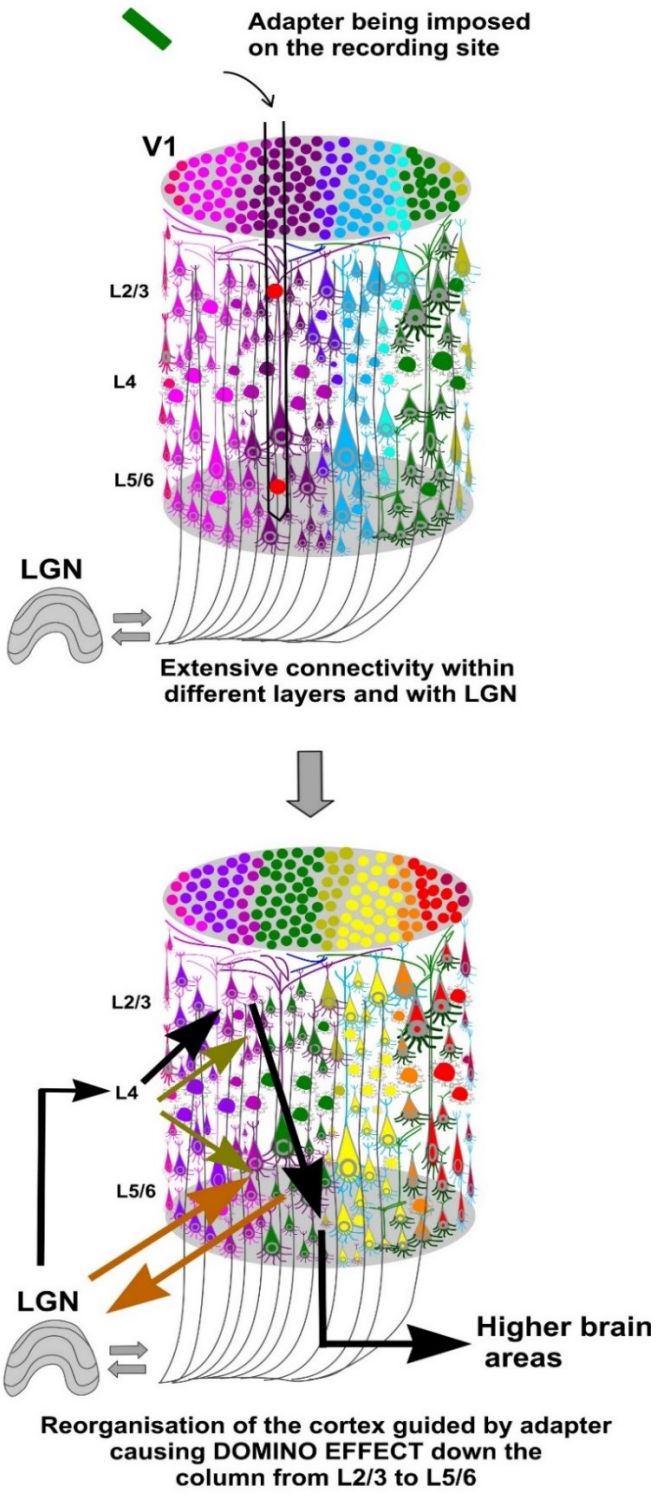

Figure 2.1

A model illustrating domino effect originating within the supragranular layers of the orientation columns and extending downwards to infragranular layers down the column.

Therefore, the two hypotheses are:

1) During adaptation, the entire orientation column is modified thereby exhibiting domino effect, that consequently leads to the whole cortex reprogramming.

2) Visual neurons when adapted with a repetitive sound stimulus, change their selectivity and attain new orientation preferences as a result of their multisensory properties.

2.2 Objectives

The above hypotheses lead to three objectives:

1) To investigate how the infra-granular cells (layer 5/6) respond to visual adaptation.
2) To cross correlate the spike trains of neuron pairs of layers 2/3 and layer 5/6 to reveal the functional connection and observe how adaptation affects this functional connectivity.
3) To investigate how acoustic stimulation impinges upon supra and infragranular neurons.

In the current study, we record supragranular and infragranular layer neurons simultaneously using a multichannel depth electrode contacting V1 at 300-500 μm and ~1100 μm and adapt the neurons under observation continuously uninterrupted for 12 min. The novelty of the current study lies in the fact that, neuronal activity from the adapted upper and deeper layer neurons of the cortical column has never been recorded simultaneously which underlines the importance of how neurons in a cortical column behave with respect to each other towards adaptation. This work is promising as it allows us to amplify our knowledge on the plasticity of adult brain which may have implications in the field of physiological and clinical studies such as neuromodulation by non-invasive brain stimulation (NBS), electro-convulsive therapy (ECT) and even be extended to neurological disorders by blocking further brain damage e.g. Stroke, Parkinson's disease, Dystonia, (Thickbroom & Mastaglia, 2009).

Previous recordings in the primary visual cortex, using a similar approach, have led to a solid understanding of the behaviour of neurons towards adapter gratings for different durations of time. It has

been found that groups of neurons recorded from a recording site share similar orientation selectivity. In layer 2/3, it has been confirmed that group of neurons recorded from one site is affected by an identical mechanism in response to the external stimulus called 'adapter' (Nemri *et al.,* 2009). Dragoi and authors (Dragoi *et al.,* 2000) showed that neurons recorded (single-unit recordings) between cortical depths 500-1500 µm show a shift in orientation tuning in response to gratings (separated by 22.5°) when adapted for 2 min. This study also revealed that neuronal shifts are independent of cortical depth. Therefore, based on prior investigations, we suppose layer 5/6 neurons to attain new selectivity towards adaptation mechanism. More importantly, comparative results of simultaneously recorded neurons will be revealed as these will be one of the original results of this thesis. The depth criteria for the two layers will be estimated mainly by LFPs patterns and multiunit neuronal activity. Together these physiological methods will give an insight into the understanding of interlayer interactions in response towards adaptation.

It is apparent from present-day investigations that apart from the layer-specific differences in morphological features, many functional properties of neurons are also dependent on cortical layer or cell type. Besides, the cortical columnar microcircuitry is viewed as a block of interconnected yet distinct neuronal networks in which each layer possesses somewhat unique patterns with different inputs, projection targets, and feedback connections (Mountcastle, 1997, Callaway, 1998, Douglas and Martin, 2004, Harris and Shepherd, 2015). Therefore, we might observe some differences from the expected results.

Further insights would be gathered by testing responses of visual neurons towards sound stimulation. Whether the visual neurons respond towards sound? How will visual adaption differ from an auditory adaptation of visual neurons? Will sound increase or decrease the potential plasticity in our model? The results would be highly significant as the adaptation protocols can be compared with respect to the tuning properties of the visual neurons, and new insights can be gathered for future explorations.

Neurons sharing orientation preference are mostly connected with each other and are represented by the iso-orientation domains in an orientation map. Neurons situated close to pinwheels are connected to neurons

having a wide range of orientation preference (Maldonado *et al.,* 1997; Schummers *et al.,* 2004). This investigation is based on electrophysiological recordings; therefore, we might observe some differences due to the fact that the locations of neurons in the orientation map can affect their shift amplitude, the direction of shift, etc. This study focuses more toward a comparison between the global response pattern of supra- and infragranular neurons and not on response behaviour of an individual neuron. However, on a more in-depth examination, individual cells might display different responses.

Presently, using similar strategies, new results have been exposed in rodents. Using electrophysiology Ibrahim and co-authors (Ibrahim *et al.,* 2016) have demonstrated sharpening of orientation tuning curves towards an auditory stimulus. Iurilli and colleagues (Iurilli *et al.,* 2012) have also revealed that the presentation of a high-amplitude sound stimulus resulted in the hyperpolarization of the membrane potential of V1 neurons resulting in inhibition.

CHAPTER 3: COMPARATIVE EFFECTS OF ADAPTATION ON LAYERS II- III AND V-VI NEURONS IN CAT V1

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3.1 Abstract

V1 is fundamentally grouped into columns that descend from layers II–III to V–VI. Neurons inherent to visual cortex are capable of adapting to changes in the incoming stimuli that drive the cortical plasticity. A principle feature called orientation selectivity can be altered by the presentation of non-optimal stimulus called 'adapter'. When triggered, LGN cells impinge upon layer IV and further relay the information to deeper layers via layers II–III. Using different adaptation protocols, neuronal plasticity can be investigated. Superficial neurons in area V1 are well acknowledged to exhibit attraction and repulsion by shifting their tuning peaks when challenged by a non-optimal stimulus. Layers V–VI neurons in spite of partnering layers II–III neurons in cortical computation have not been explored simultaneously toward adaptation. We believe that adaptation not only affects cells specific to a layer but modifies the entire column. In this study, through simultaneous multiunit recordings in anesthetized cats using a multichannel depth electrode, we show for the first time how layers V–VI neurons (1000–1200 μm) along with layers II–III neurons (300–500 μm) exhibit plasticity in response to adaptation. Our results demonstrate that superficial and deeper layer neurons react synonymously toward adapter by exhibiting similar behavioral properties. The neurons displayed similar amplitude of shift and maintained equivalent sharpness of Gaussian tuning peaks before and the following adaptation. It appears that a similar mechanism, belonging to all layers, is responsible for the analog outcome of the neurons' experience with adapter.

3.2 Introduction

Neuroplasticity refers to the brain's ability to reorganize itself as a result of experience. It was previously thought that neuroplasticity declines with aging, but it is now well established that neurons in the mature brain can alter their properties, too (Holtmaat & Svoboda, 2009). Several experiments using specific protocols (such as visual deprivation, environmental enriching, and adaptation) have demonstrated that neurons can modify their properties well into adulthood. Visual adaptation has been the approach to understanding the phenomenon of plasticity and we continue to uncover new findings in different regions of the brain.

Visual cortex (V1) is the classical model to study neuronal plasticity. V1 cortices of higher mammals are organized into domains of preferred selectivity known as orientation columns. Neuronal orientation selectivity can be altered by imposing a non-optimal stimulus (adapter) within receptive fields of neurons for a certain period (Dragoi *et al.,* 2000; Kohn, 2007; Ghisovan *et al.,* 2009; Nemri *et al.,* 2009; Bachatene *et al.,* 2012; Cattan *et al.,* 2014). Contingent upon the stimulus duration, neurons change their orientation selectivity either toward or away from the adapter, exhibiting attractive or repulsive shifts, respectively (Dragoi *et al.,* 2000; Kohn, 2007; Jeyabalaratnam *et al.,* 2013). Shorter adaptation durations (< 3 min) largely produce repulsive shifts (Dragoi *et al.,* 2000), whereas longer duration adaptation (up to 12 min) imparts attractive shifts (Dragoi *et al.,* 2000; Ghisovan *et al.,* 2009; Bachatene *et al.,* 2012; Jeyabalaratnam *et al.,* 2013; Cattan *et al.,* 2014).

An orientation column is divided into supragranular or upper layers (layers I and II–III), the central granular layer (layer IV), and infragranular or lower layers (layers V and VI). Neurons in a column are highly similar with respect to stimulus properties such as orientation, direction, speed, contrast, spatial frequency, etc. (Hubel *et al.,* 1977; Blasdel & Salama, 1986). Conventionally, information is received by layer IV neurons from the lateral geniculate nucleus (LGN), processed in the supragranular layers of the visual cortex, and then projected on to infragranular neurons. Interestingly, recently investigators (Agmon

& Connors, 1992; Meyer *et al.,* 2010; Wimmer *et al.,* 2010; Oberlaender *et al.,* 2012; Constantinople & Bruno, 2013; Rah *et al.,* 2013; Pluta *et al.,* 2015) have shown that deeper cortical layers receive direct thalamic input that activates infragranular neurons. This suggests that layer IV is not necessarily the only port of information flow to other cortical layers.

Historically, numerous studies have investigated the effects of adaptation on layers II–III neurons (Dragoi *et al.,* 2000; Bachatene *et al.,* 2013, 2015; Jeyabalaratnam *et al.,* 2013; Cattan *et al.,* 2014). One of these reports (Dragoi *et al.,* 2000) has shown that neurons recorded between 500 and 1500 μm of cortical depth also display a shift in orientation tuning in response to the adapter. However, no report has simultaneously explored the effects of adaptation on layers II–III and V–VI neurons. As the cortical column extends from layers II–III to V–VI, and because of extensive connectivity (Helmstaedter *et al.,* 2009; Jiang *et al.,* 2013; DeNardo *et al.,* 2015; Lee *et al.,* 2015) between supra- and infragranular neurons, we hypothesize that effect of adaptation is not confined to specific layer of the cortex but it prevails throughout the column, subsequently gained by neurons of adjacent columns, leading to whole cortex reprogramming. Therefore, it is of interest to simultaneously examine the effects of adaptation on both layers II–III and V–VI.

We used anesthetized cats to investigate the effects of adaptation on simultaneously recorded supra- and infragranular layer neurons using a multichannel depth electrode in V1 at 300–500 μm and 1000–1200 μm from the surface. We found that layers II–III and V–VI neurons exhibited comparable attractive and repulsive shifts with no significant differences in the average shift amplitudes and orientation selectivity. In line with our recent findings (Bachatene *et al.,* 2015) and the results of this investigation, we suggest that supra- and infragranular layer neurons change their selectivity in parallel in response to adaptation which possibly explains that supra- and infragranular neurons interact with each other in a column. This study also points toward specific feedforward and feedback loops between supra- and

infragranular neurons that may be responsible for robust functional reprogramming of orientation columns in V1 (Bachatene *et al.,* 2015).

3.3 Materials and Methods

3.3.1 Ethical approval

Electrophysiological recordings were performed in the area 17 of six adult domestic cats (*Felis catus*) of either sex. The animal surgery procedure and electrophysiological recordings were performed according to the guidelines of the Canadian Council on Animal Care and were approved by the Institutional Animal Care and Use Committee of the University of Montreal. Animals were supplied by the Division of Animal Resources of the University of Montreal. Experiments were carried out in accordance with the guidelines approved by the NIH in the USA, the Canadian Council on Animal Care, and the Institutional Animal Care and Use Committee of University of Montreal (CDEA) regarding the care and use of animals for experimental procedures.

3.3.2 Anesthesia

Cats were first sedated with acepromazine maleate [1 mg/kg, intra-muscular (i.m.), Atravet; Wyeth-Ayerst, Guelph, ON, Canada] and atropine sulfate (0.04 mg/kg, i.m., Atrosa; Rafter, Calgary, AB, Canada), and anesthetized with ketamine hydrochloride (25 mg/kg, i.m., Rogarsetic; Pfizer, Kirkland, QC, Canada). Anesthesia was maintained during the surgery with isoflurane ventilation (2%, AErrane; Baxter, Toronto, ON, Canada). After the surgery, cats were paralyzed by perfusion of gallamine triethiodide (40 mg/kg, intravenous, Flaxedil; Sigma Chemical, St Louis, MO, USA), fixed in a stereotaxic apparatus, and artificially ventilated with O_2/N_2O (30: 70) mixture containing isoflurane (0.5%). Paralysis was maintained by perfusion of gallamine triethiodide (10 mg/kg/h) in 5% dextrose lactated Ringer's nutritive solution throughout the experiment.

3.3.3 Surgery

Lidocaine hydrochloride (2%; Xylocaine, AstraZeneca, Mississauga, ON, Canada) was injected subcutaneously as a local anesthetic during the surgery. A tracheotomy was performed for artificial ventilation, and one forelimb vein was cannulated. Before fixing the animals on the stereotaxic apparatus, xylocaine gel (5%; Astra Pharma, Mississauga, ON, Canada) was applied on the pressure points to reduce pain and sensation. Proper depth of anesthesia was ensured throughout the experiment by monitoring the EEG, the electrocardiogram, and the expired CO_2. The end-tidal CO_2 partial pressure was kept constant between 25 and 30 mmHg. A heated pad was placed beneath the cat to maintain a body temperature of 37.5 °C. Tribrissen (30 mg/kg/day, subcutaneous; Schering-Plough, PointeClaire, QC, Canada) and Duplocillin (0.1 mL/kg, intra-muscular; Intervet, Withby, ON, Canada) were administered to the animals to prevent bacterial infection. A craniotomy (1 × 1 cm) was performed over the primary visual cortex (area 17/18, Horsley-Clarke co-ordinates P0–P6; L0–L6). The underlying dura was removed, and the depth electrode was positioned in area 17. The pupils were dilated with atropine sulfate (1%; Isopto-Atropine, Alcon, Mississauga, ON, Canada) and the nictitating membranes were retracted with phenylephrine hydrochloride (2.5%; Mydfrin, Alcon). Plano contact lenses with artificial pupils (5 mm diameter) were placed on the cat's eyes to prevent the cornea from drying (University of Montreal, PQ, Canada). At the end of each experiment, the cats were killed with a lethal dose of pentobarbital sodium (100 mg/kg; Somnotol, MTC Pharmaceuticals, Cambridge, ON, Canada) by an intravenous injection.

3.3.4 Visual stimulation

Stimulation was performed monocularly. After clearly detectable activity was obtained, the multiunit receptive fields (RF) were mapped by using a hand-held ophthalmoscope (Barlow *et al.,* 1967). Receptive field edges were determined by moving a light bar from the periphery toward the center until a response was evoked. Visual stimuli were generated with a VSG 2/5 graphic board (Cambridge Research Systems,

Rochester, England) and displayed on a 21-inch Monitor (Sony GDM-F520 Trinitron, Tokyo, Japan) placed 57 cm from the cat's eyes, with 1024 × 768 pixels, running at 100 Hz frame refresh. This is schematized in Fig. 3.1A. Stimuli were drifting sine-wave gratings covering the excitatory RF (Maffei *et al.,* 1973). The receptive fields were located centrally within a 15° radius from the fovea. Contrast and mean luminance were set at 80% and 40 cd/m^2, respectively. Optimal spatial and temporal frequencies were set at 0.24 cycles/deg and in the range 1.0–2.0 Hz (at these values V1 neurons are driven maximally) by sine-wave drifting gratings (Bardy *et al.,* 2006).

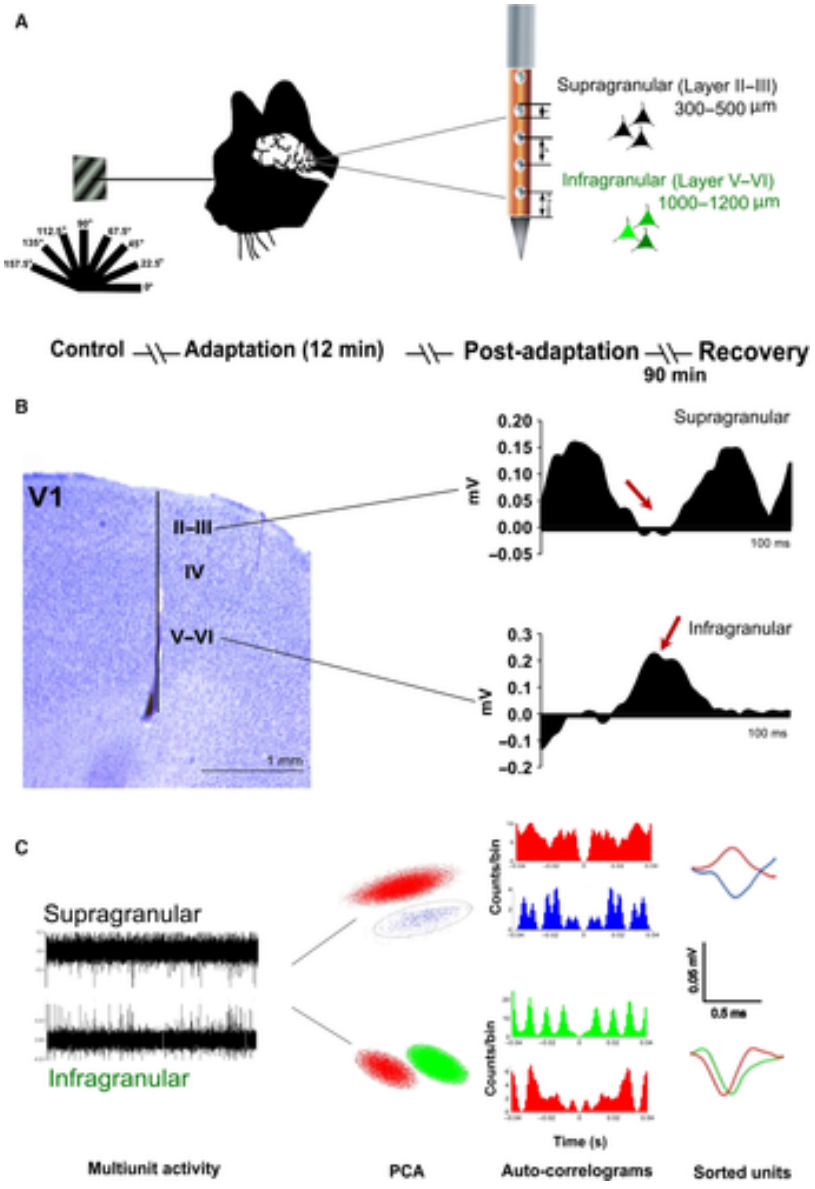

Figure 3.1

(A) Cartoon showing the two depths at which electrode tips contact V1. A summary of the protocol is also shown below figure (B). To the left, a histological section of cat V1 showing the correct positioning of electrode and recording depth. On the right, local field potentials for layers II–III and V–VI, recorded for a single electrode penetration is shown. (C) An example of neuronal spike sorting employing spike waveforms, principal component analysis, and auto correlograms.

3.3.5 Electrophysiological recording

Multiunit activity in the primary visual cortex was recorded using a tungsten multichannel depth electrode (0.1–0.8 MΩ at 1 KHz; Alpha Omega Co. USA Inc.; Fig. 3.1A, right). The recordings were performed in both hemispheres of the cat's brain. The electrode consisted of four microelectrodes in a linear array (inter-electrode spacing 500 μm) enclosed in stainless steel tubing. The signal from the microelectrodes was amplified, band-pass filtered (300 Hz–3 KHz), digitized, and recorded with a 0.05 ms temporal resolution (Spike2, CED, Cambridge, UK). We recorded at average cortical depths of 300–500 and 1000–1200 μm simultaneously from both sites. To further confirm the location of contacting electrodes, histological staining and local field potentials (LFP's) were recorded for every site where the electrode tip was lowered. Figure 3.1B (left) shows a histological section of area 17 and confirms the location of the electrode at the appropriate depth. Furthermore, LFPs were recorded (low-pass filtered between 10 and 100 Hz) to observe the sink-source dipoles. To evoke LFP's, a series of drifting gratings oriented at 0°–157.5° separated by 22.5° was presented (each oriented flash lasted 100 ms) covering the whole screen of the monitor. Figure 3.1B (right) displays the LFP traces of layers II–III and V–VI neurons. The inversion of polarity (positive–negative LFP, red arrows) at both electrodes further validates the correct positioning of electrodes.

The multiunit activity of neurons was recorded simultaneously from layers II–III and V–VI. Figure 3.1C (right) shows an example of neuronal isolation (spike sorting) from the multiunit activity. Spike

sorting was done offline using Spike2 package, CED, Cambridge, England. The single units were discriminated based upon the spike waveforms, principal component analysis (PCA), and auto correlograms (ACG). The respective PCA, ACGs, and spike waveforms are shown to the right (Fig. 3.1C).

3.3.6 Adaptation protocol

After manually mapping the receptive fields, eight different orientations were presented randomly one-by-one within the receptive fields of the neurons. Eight oriented sine-wave drifting gratings were presented in a random order ranging from 0° to 157.5° at regular intervals of 22.5°. Each orientation was presented in a block of 25 trials (each trial lasted 4.1 s) with varying inter-stimulus (1–3 s) intervals during which no stimulus was presented. Thus, the presentation of one oriented drifting grating lasted ~180 s (including all trials and inter-stimulus intervals; Fig. 3.1A). Once the control orientation tuning curves were characterized, an adapting oriented stimulus (non-optimal orientation) was presented continuously for 12 min (Fig. 3.1A) within the receptive fields of neurons. The adapting stimulus was a drifting grating whose orientation was chosen based on the multiunit activity values obtained at control conditions and was generally set within 22.5°–67.5° of the neurons' preferred orientations. No recordings were performed during this adaptation period. Immediately after the adaptation procedure, recordings were performed starting with the adaptor orientation and initially preferred orientation followed by recording of remaining orientations in a random fashion. Finally, the tuning curves were computed as below.

3.3.7 Data

The Gaussian tuning fits were computed for neurons pre- and post-adaptation using the function below:

where *y*0 is the offset, *xc* is the center, *w* is the width, and *A* represents the area under the Gaussian fit. The firing rates were normalized in Prism and Gaussian tuning curves were generated in the scientific software

Origin. The direction and magnitude of shifts were calculated as the distance between peak positions of the fitted Gaussian tuning curves before and after adaptation (the difference between the initially preferred and newly acquired). An attractive shift was attributed to the displacement peak of the orientation tuning curve in the direction of the adapter while a repulsive shift was indicated by a displacement of the tuning peak in opposite direction (away from the adapter). As indicated in the methods these displacements should be > 5° to be considered as a significant shift.

Moreover, we also measured the orientation selectivity index (OSI) of a neuron by dividing the firing rate at the orthogonal orientation by the firing rate at the preferred orientation and subtracting the result from 1 (Ramoa *et al.,* 2001; Liao *et al.,* 2004; Bachatene *et al.,* 2013). The closer the OSI is to 1, the stronger the orientation selectivity. Finally, the sorted neurons were classified into regular and fast spikes on the basis of the spike width (Bartho *et al.,* 2004; Schwindel *et al.,* 2014; Bharmauria *et al.,* 2015). Spikes with a width ≤ 0.3 ms were identified as fast spiking neurons (FS) and > 0.3 ms as regular spiking (RS) neurons.

3.3.8 Statistical tests

Three datasets were tested for statistics: (i) amplitudes of shift (attractive and repulsive) values; (ii) OSI values of neurons pre- and post-adaptation; and (iii) spike-width values. These data were tested for normal distribution using the D'Agostino & Pearson omnibus normality test. Based on the results obtained, parametric student *t*-test (unpaired) was applied to the values of shift amplitudes. Furthermore, all four groups (attractive shift values in layers II–III and V and repulsive shift values in layers II–III and V) were compared with ANOVA. On the other hand, non-parametric Mann–Whitney test was employed to the values of OSI and spike width of neurons as these distributions were not normal. The Pearson coefficient was calculated to find any correlation between the data groups. To infer the difference in proportions *z*-test was used. Consequently, comparisons were drawn between attractive and repulsive populations and spike-width

values obtained for either layer. Finally, a regression analysis was done to find correlation between spike-width values and amplitude of attractive and repulsive shifts.

3.4 Results

The goal of this investigation was to explore the effect of adaptation on simultaneously recorded neurons from supra- and infragranular layers. In total, 97 neurons were recorded and analyzed for the effects of 12 min adaptation on each layer. A comparative post-adaptation behavioral distribution of cells in either layer is shown in Fig. 3.2. The gray shades and green shades represent the supra- and infragranular layers, respectively. The color scheme is respected throughout the manuscript. In fact, neurons in both layers exhibited similar shift tendencies. The graph on the upper right shows the proportion of cells showing attractive and repulsive shifts. On comparing the proportion of attractive shifts between the two layers, infragranular neurons exhibited a higher proportion ($P = 0.05$, *t*-test) of attractive shifts as compared to supragranular neurons. However, this is not the case for repulsive shifts ($P = 0.70394$, *t*-test).

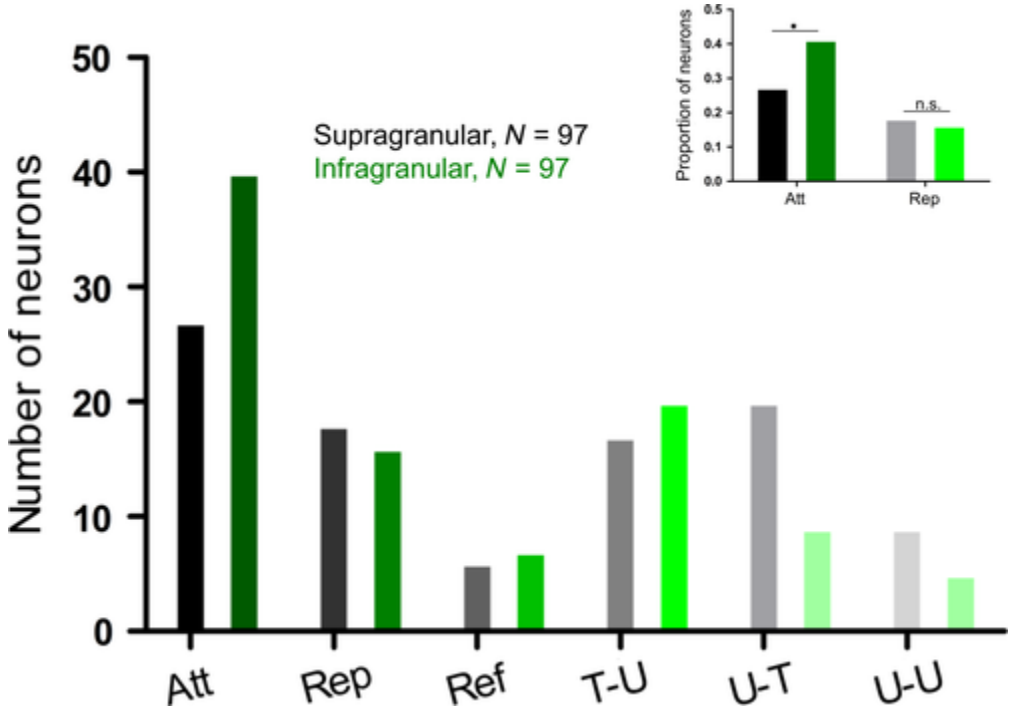

Figure 3.2

Comparative distribution of neurons according to the behavior shown after 12 min of adaptation. The graph on the upper right side compares proportion of neurons exhibiting attractive and repulsive shifts.

A part of the remaining population refracted the adapter and did not show any significant shift (< 5°) in orientation tuning (Bachatene *et al.,* 2013, 2015; Jeyabalaratnam *et al.,* 2013). The corresponding proportion of repulsive shifts for both layers was found to be comparable (06 neurons in supra- and 07 in infragranular layers). A fraction of tuned (T) neurons lost their selectivity post-adaptation and was categorized as T-U (17 in supra- and 20 in infragranular layers). Moreover, some untuned (U) neurons acquired novel selectivity after adaptation and were categorized as U-T (20 neurons in supra- and 09 in infragranular layers). A proportion analysis was not performed on these latter datasets as we were primarily interested in comparing only attractive and repulsive behaviors across layers. Such novel selectivity has been reported previously in mice (Jeyabalaratnam *et al.,* 2013). It is to be underlined that neurons with an orientation selectivity index (OSI) < 0.5 were classified as untuned (Bharmauria *et al.,* 2015, 2016). Finally, a minority of neurons (09 in supra- and 05 in infragranular layers) remained untuned before and after adaptation (U to U).

3.4.1 Layers II–III and V–VI primary visual neurons co-ordinate to acquire a novel preference

The effects of adaptation have been extensively studied in layers II–III neurons (Dragoi *et al.,* 2000; Bachatene *et al.,* 2013, 2015; Jeyabalaratnam *et al.,* 2013; Cattan *et al.,* 2014). Because a column extends from layers II–III to V–VI, it was of interest to investigate the effects of adaptation on simultaneously recorded neurons from both layers. Thus, we examined the post-adaptation orientation tuning curves of simultaneously recorded layers II–III and V–VI neurons. Figure 3.3 shows typical examples of adaptation effects (shifts in orientation selectivity) on both layers after 12 min of adaptation. In Fig. 3.3A, an example of each type of effect (attractive, repulsive, and no shift) is shown for layers II–III. The top and middle rows show the raw tuning curves of neurons pre- and post-adaptation. The superimposed Gaussian fits are shown

at the bottom demonstrating the shifts. To the left, an attractive shift is illustrated. In the control condition, the neuron was optimally tuned to 158.47° (OSI = 0.9; R^2 = 0.6). After adapting the neuron for 12 min with a 45° grating (red arrow), the selectivity of the neuron (OSI = 0.9; R^2 = 0.5) shifted toward the adapter (57.34°), that is, the neuron exhibited an attractive shift. The middle column shows an example of a repulsive shift. The neuron in this case changed its preference away from 91.24° (OSI = 0.9; R^2 = 0.8) to 30.77° (OSI = 0.9; R^2 = 0.6) after being challenged with 112° adapter. Similarly, the third column (extreme right) illustrates an example of a refractory neuron. This neuron did not change its preference after adaptation with 45° grating and maintained its selectivity at approximately 67°. The selectivity minutely changed from 67.1° (OSI = 0.8; R^2 = 0.5) to 68.22° orientation (OSI = 0.8; R^2 = 0.8) and it was deemed non-significant.

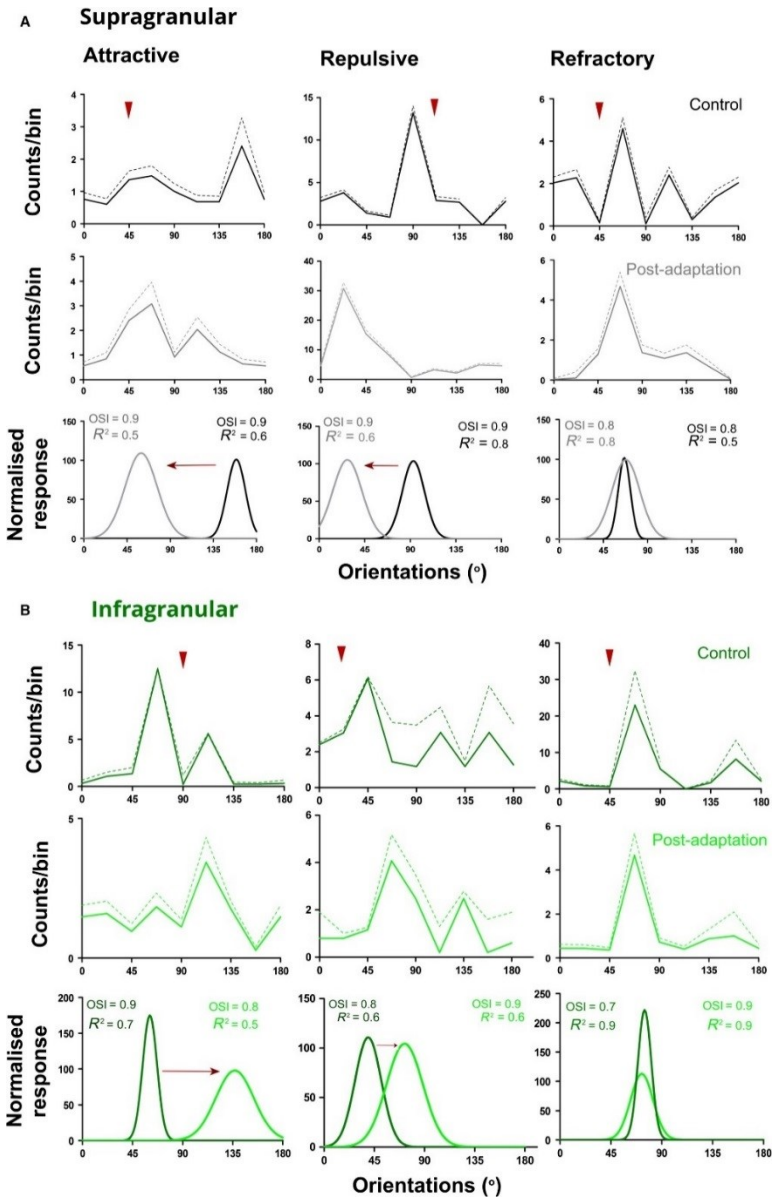

Figure 3.3

(A) Typical examples in layers II–III showing attractive shift, repulsive shift, and no shift post-adaptation. (B) Typical examples in layers V–VI showing attractive shift, repulsive shift, and no shift after adaptation.

In a similar fashion, the results are demonstrated in Fig. 3.3B for layers V–VI neurons. To the left, a typical example of an attractive shift is illustrated. The neuron was originally selective to 52.61° orientation (OSI = 0.9; R^2 = 0.7) but acquired a novel optimal selectivity of 136.54° (OSI = 0.8; R^2 = 0.5) after 12 min of adaptation with 90°. The middle column represents an example of a repulsive shift. Here, the layers V–

VI neuron was optimally tuned to 39.57° orientation (OSI = 0.8; R^2 = 0.6). After imposing the 22.5° adapter, the neuron changed its preference away from the adapter to 72.30° orientation (OSI = 0.9; R^2 = 0.6) showing a repulsive shift. Finally, on the right, a refractory neuron is displayed. This neuron, in spite of being adapted with 45° adapter, did not change its preference. It maintained its preference around 74° and changed its selectivity non-significantly from 74.2° (OSI = 0.7; R^2 = 0.9) to 73.4° (OSI = 0.9; R^2 = 0.9).

Furthermore, the amplitudes of attractive and repulsive shifts were plotted to compare the magnitude of orientation shift in layers II–III and V–VI neurons (Fig. 3.4A). The difference in mean (±SEM) amplitude of attractive shifts for layers II–III (mean = 49.68 ± 4.37) and V–VI neurons (42.23 ± 3.77) was found not significant (*t*-test, P = 0.1030). A similar result was found for the amplitude of repulsive shifts (mean ± SEM) 33.06 ± 3.96 and 32.88 ± 5.18 for layers II–III and V–VI, respectively (*t*-test, P = 0.9778). However, attractive shifts (Att = 49.67 ± 4.36; Rep = 33.06 ± 3.958) in layers II–III were found dominant over repulsive shifts (P = 0.0056). Moreover, on comparing all four groups (one-way ANOVA, P = 0.0361), the mean difference was found to be significant. This could be indicative of individual cells in both layers behaving independently yet following a similar trend globally.

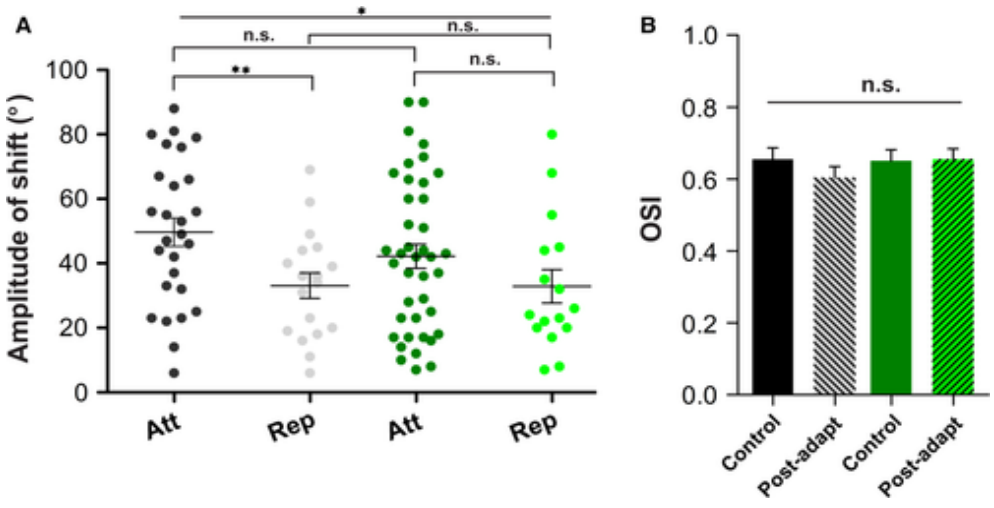

Figure 3.4

(A) Graph showing comparison between magnitude of attractive and repulsive shifts and mean shift.

(B) Mean OSI of layers II–III and V–VI neurons before and after adaptation.

In addition, Orientation Selectivity Index (OSI) was also computed for all the neurons in layers II–III and V–VI to investigate the tuning sharpness of neurons before and after adaptation. Figure 3.4B shows the mean of OSI for 97 neurons each for layers II–III and V–VI at control and post-adaptation conditions. The mean (mean ± SEM) OSI for neurons at control and post-adaptation conditions was found to be 0.65 ± 0.03 and 0.60 ± 0.03 (Mann–Whitney test, $P = 0.7863$) for layers II–III neurons and 0.65 ± 0.03 and 0.65 ± 0.02 (Mann–Whitney test, $P = 0.2446$) for layers V–VI neurons, respectively. The difference in mean OSI was not significant in both layers which further indicate that neurons in layers II–III and V–VI acquire the new selectivity in an analog mode, thus maintaining the homeostasis post-adaptation. These results also support the fact that, following adaptation, the orientation columns (extending from layers II–III to V–VI) tilt in such a fashion that the functional dogma of columns is maintained as shown previously (Bachatene *et al.,* 2015). To summarize, following adaptation the cellular dynamics in a column remain unchanged which reflects that the 'entire block' of cells is displaced after being challenged by the adapter.

3.4.2 Relation between the spike width and amplitude of shift

Neurons were dissociated into broad/regular spiking (RS) and narrow/fast spiking neurons (FS) on the basis of their spike width (Bharmauria *et al.,* 2015, 2016). The RS and FS neurons have been putatively linked to excitatory and inhibitory neurons (Nowak *et al.,* 2003; Niell & Stryker, 2008; Vinck *et al.,* 2013). It was reported that a large population of excitatory neurons in cats' visual cortex exhibit narrow spike shape, consequently not permitting a clear distinction between pyramidal and inhibitory cells (Nowak *et al.,* 2003). Nevertheless, in this study, a spike-width threshold of 0.3 ms was chosen to separate the neurons (Bharmauria *et al.,* 2015, 2016; Fig 3.5). Figure 3.5A illustrates separated neurons. Neurons having spike width > 0.3 ms were categorized into RS neurons, whereas neurons exhibiting a spike width ≤ 0.3 ms were classified into FS neurons. The division was performed separately for both layers. The inserts of spike waveforms on the right side of Fig 3.5A (gray and green) illustrate how the classification was done. Layer V neurons showed a wide range of spike width in comparison to layers II–III. However, on averaging the

values of spike widths for different groups, the values were found comparable in both layers. The proportion of RS and FS cells was found no different from each other as evident from Fig 3.5C (shows the proportion of RS and FS cells). The *z*-test for proportion was performed for both layers (*P*-value = 0.50926). To see the global pattern of RS and FS groups in either layer, mean ± SEM of RS and FS neurons was calculated (Fig 3.5B). The mean values were found to be 0.47 ± 0.01 and 0.24 ± 0.01 for layers II–III and 0.48 ± 0.01 and 0.24 ± 0.006 for layers V–VI, respectively. For this data, a non-parametric Mann–Whitney test was employed. The *P*-values for RS and FS data were found to be 0.5084 and 0.5155, respectively.

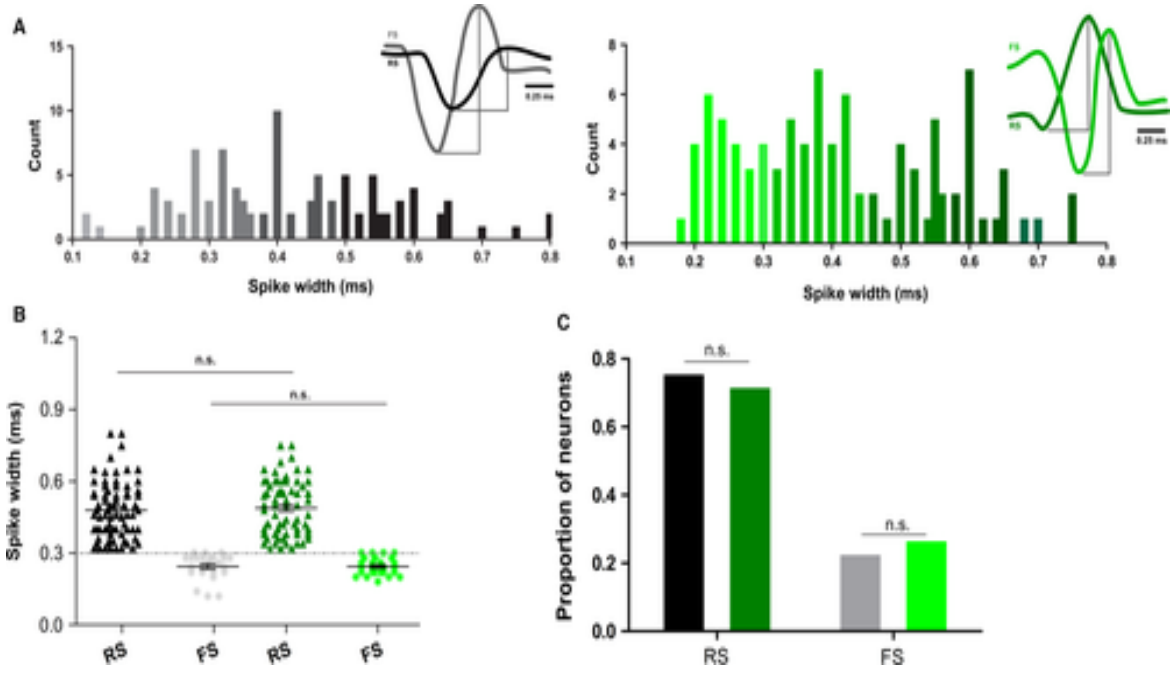

Figure 3.5

(A) Distribution of layers II–III (black) and V (green) neurons into putative excitatory and inhibitory neurons on the basis of spike-width analyses. The inserts illustrate how neurons were categorized. (B) Graph showing comparison of spike-width values for both layers. (C) Proportion of RS and FS neurons in both layers.

In addition, a subcategorization was performed to compare the direction of shift with the type of cell. This was done to compare shift trends in RS and FS neurons (Fig. 3.6). We found layers II–III

(mean ± SEM = 52.60 ± 4.65) and V–VI (mean ± SEM = 45.96 ± 4.80) RS neurons shifting towards the attractive direction with the largest amplitude (*t*-test, $P = 0.3271$). This tendency of RS neurons was also observed in the repulsive direction, but with a lesser magnitude. The means (mean ± SEM) of the amplitude of repulsive shifts in layers II–III and V–VI RS neurons were found comparable (*t*-test, $P = 0.6181$) and their values were found to be 32.88 ± 7.64 and 33.70 ± 4.78, respectively. Moreover, layers II–III FS (attractive = 40 ± 7.32; repulsive = 33.20 ± 4.11) and V–VI FS (attractive = 34.46 ± 5.54; repulsive = 31.50 ± 12.05) neurons also exhibited shifts in attractive ($P = 0.6181$) and repulsive ($P = 0.8747$) directions showing comparable values of means. The proportion of neurons showing attractive and repulsive shifts (Fig. 3.6, insert on the upper right) was computed which showed that FS neurons in layer V shift more toward the adapter, i.e., in the attractive direction in comparison to layers II–III neurons. Lastly, neurons exhibiting no shifts were also included in the graph, but no significance was observed between groups. This indicated that overall, in supra- and infragranular layers both RS and FS neurons showcase attractive and repulsive shifts and with a similar tendency of shifts post-adaptation.

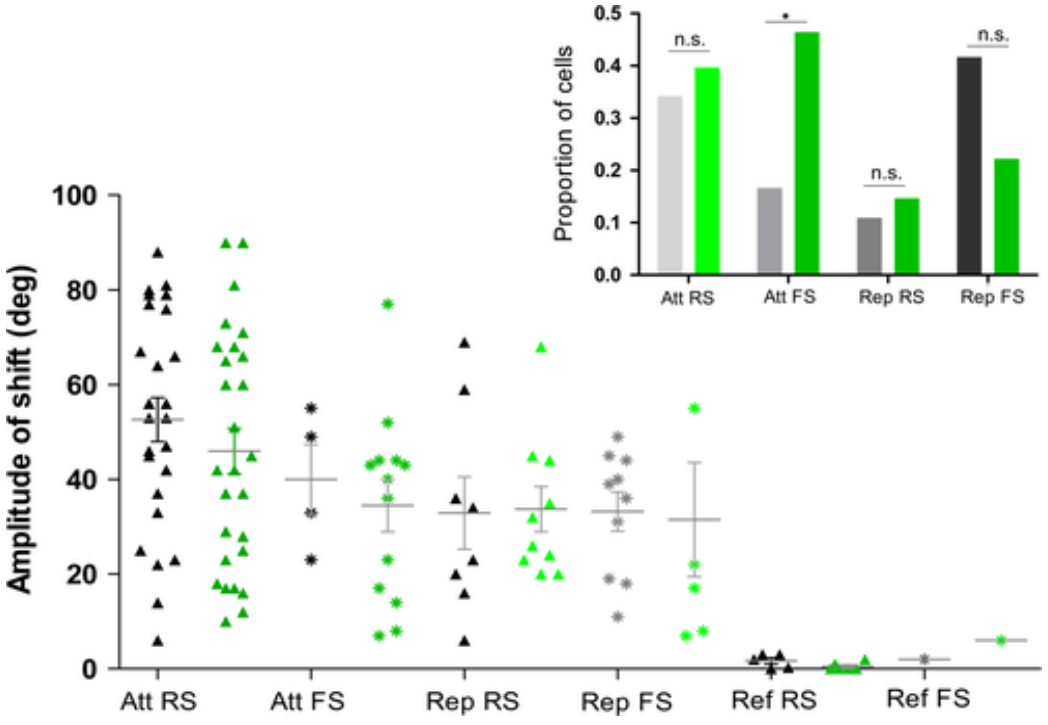

Figure 3.6

Graph showing magnitude of shift subdivided on the basis of directions of shift and the type of neuron in both layers. An insert comparing populations of subgroups across layers is shown on upper right side.

To further see a correlation between spike-width values and amplitude of shifts, a regression analysis for either layer was done (Fig. 3.7). None of the four groups showed a relation between compared values. Thus, all above analyses seem to indicate that cells within a column operate in a uniform fashion implying that cells of the entire cortical column from superficial to deep layers change their properties toward imposed non-preferred orientation following adaptation. However, it is important to note that individual cells could play different and specific roles in achieving an equilibrium state.

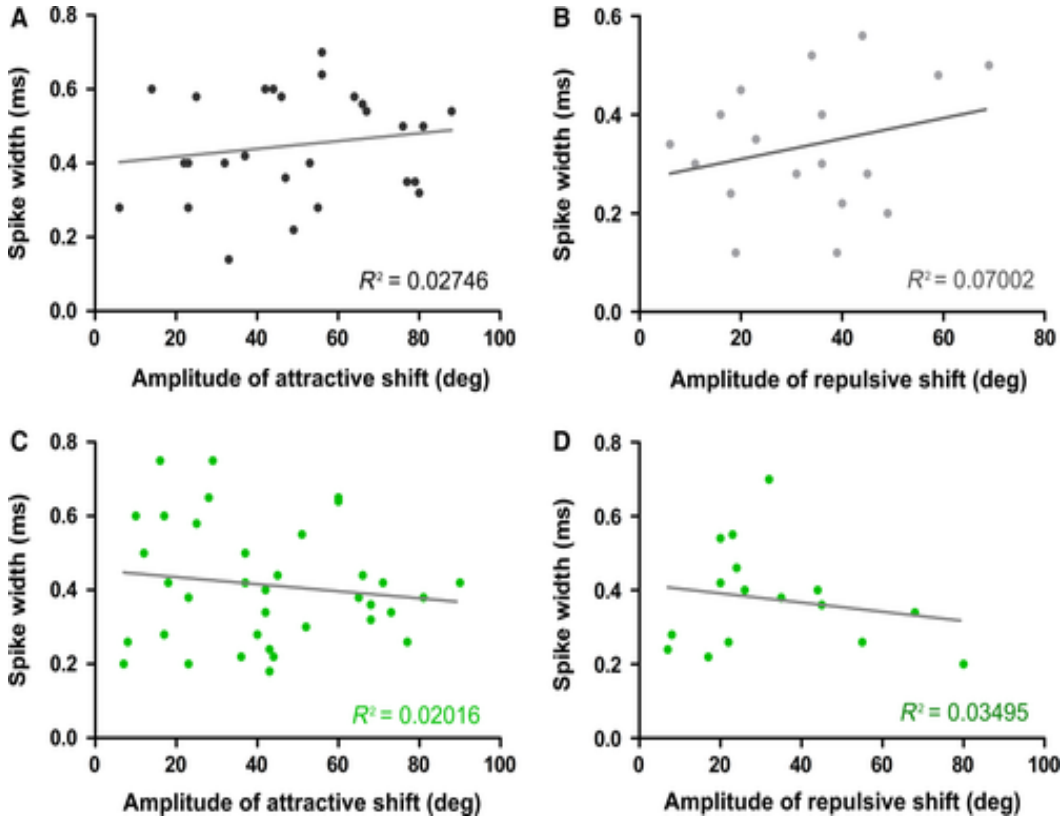

Figure 3.7

Regression analysis for comparing relation between spike width and amplitude of attractive and repulsive shifts. (A, B, C, and D) are graphs for attractive and repulsive shifts in layers II–III and V, respectively.

To the best of our knowledge, this is the first comparative study of the simultaneously recorded layers II–III and V–VI neurons in adult cat V1 in response to adaptation that shows an overall picture of events occurring in an orientation column following adaptation.

3.5 Discussion

In summary, we demonstrated that layers II–III and V–VI neurons acquired comparable orientation selectivity shifts after 12 min of adaptation. The main results of this investigation are as follows: (i) In addition to the layers II–III, layers V–VI neurons also exhibit orientation selectivity shifts; (ii) the mean amplitudes of attractive and repulsive shifts in both layers are comparable; (iii) the average OSI pre- and post-adaptation in either layer is similar, and (iv) the mean amplitude of shifts of RS and FS neurons in both layers is about equal. These results are in line with the previous findings by Bachatene *et al*. (2015) who showed that neurons in supragranular layers reprogram their orientation selectivity when adapted visually and this reprogramming is so systematic that neurons even in the non-adapted columns acquire the new selectivity with respect to the previous column which seems to be guided by the adapting column.

Layers II–III neurons exhibit attractive and repulsive shifts (Ghisovan & Nemri, 2008; Ghisovan *et al.,* 2009; Nemri *et al.,* 2009; Bachatene *et al.,* 2012). In this investigation, we show for the first time that infragranular layers V–VI neurons also show these classical shifts in orientation selectivity in conjunction with layers II–III neurons in response to adaptation.

Generally, neurons recorded from an electrode tip shift their orientation selectivity in a similar direction. In other words, this small pool of neurons recorded from the same tip is affected by an identical mechanism in response to the external stimulus called ‘adapter’ (Nemri *et al.,* 2009). A previous study based on adaptation (Dragoi *et al.,* 2000) showed that neuronal shifts are independent of cortical depth. Anatomical evidence suggests that neurons sharing orientation preference are mostly connected with each other and are present in the orientation domains, whereas neurons situated close to pinwheels are connected

with neurons having a wide range of orientation preference (Maldonado *et al.,* 1997; Schummers *et al.,* 2004). This investigation is based on electrophysiological recordings, however, the fact that locations of neurons in the orientation map can affect several of their inherent features, for example, shift amplitude, the direction of shift, etc., cannot be ignored. It would be inequitable to compare individual populations recorded from different regions of the orientation map. Hence, this study focuses more toward the global response pattern of supra- and infragranular neurons and not on response behavior of an individual neuron. Nevertheless, when the subpopulations are examined deeply, different properties are displayed by individual cells, for example, some clusters (recording from a single site down the column) are homogeneous showing attractive shifts, whereas others are heterogeneous displaying attraction and repulsion. This is one of the possible reasons for a large variance of the shift amplitudes and it explains why neurons in either layer display a large range of orientation shift amplitude.

The orientation selectivity index (OSI) which is calculated by the sharpness of the tuning curve of a neuron was also calculated for both layers at control and post-adaptation conditions. The OSI was comparable for layers V–VI and II–III neurons confirming the neurons maintained an optimal tuning prior to and post-adaptation.

Next, the neurons were classified into RS and FS cells putatively referred to as excitatory and inhibitory neurons, respectively, throughout the literature (Povysheva *et al.,* 2006; Fries *et al.,* 2007; Gouwens *et al.,* 2010; Hofer *et al.,* 2011). Firstly, we observed both groups of cells showing attractive and repulsive shifts. It indicated that shift in orientation selectivity is independent of V1 neuron type. Secondly, we also found fast-spiking neurons exhibiting a repulsive shift of smaller magnitude as compared to regular-spiking neurons exhibiting attractive shifts. Similar results were confirmed previously (Bachatene *et al.,* 2012) for supragranular layers II–III neurons. Lastly, we found equal proportions of putative excitatory and inhibitory neurons in our data which suggested that the regular- and fast-spiking neurons exist in balance across cortical layers.

To further infer a relation between the type of neuron and the direction of shift, we subcategorized RS and FS neurons into three groups: cells showing attractive shifts, repulsive shifts, and no shift (Bachatene *et al.,* 2012). The observation revealed that RS neurons shift with a higher magnitude than fast-spiking neurons in both layers. This is indeed indicative of RS neurons being more plastic than FS neurons. Another important observation was made about fast-spiking neurons. Layers II–III FS neurons were found more likely to shift in a repulsive direction rather than attractive direction and this pattern was reversed in the layer V. It could also be indicative of a possible specific role of inhibitory neurons in the adaptation process. A recent review (Naka & Adesnik, 2016) discussed several types of inhibitory neurons in layer V that play specific roles in different types of inhibition mechanisms particularly in layer V. Layers II–III neurons form the densest projection on layer V neurons and synaptically recruit them to fire. This generates a robust feedforward inhibition. Connectivity studies in different regions of the brain suggest that this feedforward inhibition between layers II–III and V neurons is unique as different layer V neurons receive different strengths of excitatory inputs from layers II–III neurons (Otsuka & Kawaguchi, 2009; Pouille *et al.,* 2009; Adesnik & Scanziani, 2010; Jin *et al.,* 2014; Jiang *et al.,* 2015; Pluta *et al.,* 2015). Layer V is not only an output layer but also an important input layer as it receives inputs from all other cortical layers (Markram *et al.,* 2015). Therefore, it is worth noting the role of inhibitory neurons specifically in layer V. This could potentially form another possible explanation of how neurons across layers behave differently yet they maintain equilibrium inside the orientation column.

3.5.1 Adaptation mechanism

The underlying mechanism of adaptation may involve transient changes at the synapse level occurring at different timescales dependent on the duration of adaptation (Kohn, 2007). Adaptation mainly involves a decrease in the response to the initially preferred orientation and increasing the response toward the dominant orientation. This decrease in the firing rate generally occurs at the individual level and could be a consequence of a change in membrane properties of V1 cells, for example, hyperpolarization (Carandini

& Ferster, 1997) or synaptic depression or slow hyperpolarizing of Na^+ channels (Sanchez-Vives *et al.,* 2000). Inhibition and excitation play a major role in creating and maintaining the equilibrium by recurrently modulating the response gain in local cortical circuits (Ben-Yishai *et al.,* 1995; Douglas *et al.,* 1995; Somers *et al.,* 1995). Other disinhibitory mechanisms may also be critical to maintaining homeostasis during the adaptation process.

3.5.2 Possible functional implications

It has been amply demonstrated and suggested that a neuron's single dendritic branch receives synaptic inputs from differently tuned neurons. This enables the neuron to be able to elicit a response to a wide range of inputs by making synaptic associations. The dominant input then drives the corresponding synapses giving rise to an optimal selectivity for the neuron (Jia *et al.,* 2010; Bachatene *et al.,* 2013; Wertz *et al.,* 2015). Within this framework, the imposition of an adapter grating strengthens the synapses related to it, thus potentiating a novel selectivity for the neuron. Thus, a new adjustment between the excitation and inhibition after the adaptation period facilitates the neurons to acquire a new selectivity.

A possible explanation is that repulsion is a consequence of a default reaction. Following adaptation, the 'new' preferred orientation acquired by the same neuron is an outcome of a differential decrease in response to the initially preferred orientation, while flank orientations far from the adapter in the tuning curve remain relatively unchanged. However, the latter orientations evoke a stronger response and became dominant. Therefore, attractive shifts are the outcome of dual modulation of responses, a push–pull mechanism that simultaneously diminishes responses to the original preferred orientation and increases firing to orientations close to the adapter. Consequently, the final data obtained are the product of modifications in ratios between excitatory and inhibitory inputs. As similar results are observed in supra- and infragranular layers, it is reasonable to conclude that in both layers excitatory and inhibitory populations share similar mechanisms (Kohn & Movshon, 2004; Ghisovan *et al.,* 2009). Moreover, the excitatory and inhibitory loops may also be implicated in this robust recalibration of neuronal selectivity (Froemke, 2015).

In the passage of neuronal information in the visual cortex, layer IV neurons are the receiving units of the information coming from the thalamus (LGN), and these neurons project the information to layers II–III neurons. Furthermore, the information is conveyed to infragranular layers V–VI neurons (Kapfer *et al.,* 2007; Otsuka & Kawaguchi, 2009; Apicella *et al.,* 2012; Jiang *et al.,* 2015). In addition, several studies demonstrate that there are abundant anatomical connections between layers II–III and V–VI neurons (Lowenstein & Somogyi, 1991; Thomson & Bannister, 2003). However, it has also been shown that infragranular layers receive a direct input from the thalamic cells (Constantinople & Bruno, 2013; Pluta *et al.,* 2015). These inter-neuronal relationships may be the basis for shifts in these layers occurring through a common mechanism(s).

The co-active groups of neurons are termed as microcircuits or cell assemblies (Buzsaki, 2010; Harris & Mrsic-Flogel, 2013; Singer, 2013; Bharmauria *et al.,* 2014, 2015; Miller *et al.,* 2014). The behavior of individual neurons in these assemblies is dependent on inputs from neighboring or distally located neurons horizontally or as a function of depth. The dynamics of the synapses induce a change in the orientation tuning of neurons during the process of training layers II–III and V–VI neurons together. Therefore, goal-directed functional synaptic communications configure the underlying mechanisms for the neurons to change their tuning across different layers (Felsen *et al.,* 2002). Moreover, shifts in orientation selectivity are credited to the short-term plasticity of intra-cortical connections. Therefore, these interactions between synapses of neighboring neurons (horizontally or as a function of depth) support the plasticity in the brain (Harvey & Svoboda, 2007).

Collectively, we observed that cortical layers V–VI and II–III neurons show similar responses to adaptation which suggests that neurons in supragranular and infragranular layers strive in alliance with each other, suggesting that neurons not specific to a layer respond to adaptation distinctively, but the whole V1 column changes leading to a whole cortex re-orientation. Considering the cortical column as a functional unit of the visual cortex, it appears that neurons in a column choose to perform in unison to propagate a

comprehensive harmony in the cortical column which is preserved from column to column and, as a consequence of training one of the columns, the whole cortex is re-calibrated toward maintaining that balance to achieve its stable state.

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CHAPTER 4: SOUND INDUCES CHANGE IN ORIENTATION PREFERENCE OF V1 NEURONS: AUDIO-VISUAL CROSS-INFLUENCE

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4.1 Abstract

In the cortex, unimodal sensory regions often respond to stimuli of other sensory modalities and exhibit plasticity. The goal of the current investigation was to test evoked responses of primary visual cortex (V1) neurons when an adapting auditory stimulus is applied in isolation. Using extracellular recordings in anesthetized cats, we demonstrate that, unlike the prevailing observation of only slight modulations in the firing rates of the neurons, sound imposition in isolation entirely shifted the peaks of orientation tuning curves of neurons in both supra- and infragranular layers of V1. Our results suggest that neurons specific to either layer dynamically integrate features of sound and modify the organization of the orientation map of V1. Intriguingly, these experiments present novel findings that the mere presentation of a prolonged auditory stimulus may drastically recalibrate the tuning properties of the visual neurons and highlight the phenomenal neuroplasticity of V1 neurons.

KEYWORDS

Plasticity, primary visual cortex, orientation selectivity, cross-modal, audio-visual, non-visual input

4.2 Highlights

- Prolonged application of sound shifts preferred orientation of neurons in area 17 of cats.
- Orientation tuning shifts in the individual neurons in supra- and infragranular layers of V1.
- Supra- and infragranular layers of V1 operate together but also as distinct compartments following sound adaptation.
- Visual cortex is specifically and dynamically impacted by non-visual stimuli.
- Sound adaptation certainly modifies the organization of orientation maps in V1.

4.3 Introduction

For the longest time, inputs to a primary sensory area have been believed to be mainly modality specific. However, it was until recently (Ghazanfar & Schroeder, 2006; Kayser & Logothetis, 2007) that a direct and more specific interaction between the early sensory cortices of different modalities was discovered. Since then, more studies have suggested that the meeting and interaction of information from different senses begin within the low-level sensory areas (van Atteveldt *et al.,* 2014; Ten Oever *et al.,* 2015). Direct anatomical connections from V1 to A1 are still not precisely known, but across species there are different indirect pathways that have been discovered and suggest connectivity between different primary sensory regions. It has been shown in gerbils that secondary visual area V2 is directly connected with A1 (Budinger *et al.,* 2006). In cats, (Hall & Lomber, 2008) few direct projections from auditory cortex to V1 targeting only the peripheral visual field have been identified. An alternative yet slightly longer pathway between A1 and V1 through the heteromodal association cortical area (superior temporal polysensory area and superior temporal sulcus (STP / STS) was also revealed and presumed to send feedback to both A1 and V1 (Schroeder & Foxe, 2002). A critical imaging study (Liang *et al.,* 2013) revealed in humans that there might be salient locations within V1 that respond to specific cross-modal inputs related to the spatial pattern of activation of a primary sensory cortical area (e.g., V1).

Recently, more elaborate studies in rodents have exposed new findings. Physiological investigations of Ibrahim and co-authors (Ibrahim *et al.,* 2016) have demonstrated sharpening of orientation tuning in conjunction with an enhancement of the response to the preferred orientation of the cell in mice towards a low-contrast visual stimulus accompanied by an auditory stimulus. Lurilli and colleagues (Iurilli *et al.,* 2012) revealed that the presentation of a high-amplitude sound stimulus resulted in the hyperpolarization of the membrane potential of V1 neurons resulting in inhibition.

Despite extensive experimentation to explore wide-ranging interactions in the cortex, the understanding of cross-modal processing during the absence of direct stimulation of a corresponding sensory region remains implicit. To date, most studies have limited the presentation of stimuli for a very short duration. Additionally, rodents have been the first choice for electrophysiological experimentation in this direction and humans are limited to functional imaging techniques.

In the present investigation, a sound stimulus was applied to V1 neurons in cats in the complete absence of visual input for 12 minutes. Through extracellular recordings in area 17 of anesthetized cats, we found that in the presence of only a sound stimulus, the orientation tunings of simultaneously recorded layer 2/3 and layer 5/6 visual neurons were altered while exhibiting shifts in their tuning, that is a change of the preferred orientation. Also, the orientation selectivity shift magnitude was found to be larger in layer 5/6 neurons. We argue and suggest that the modification in the tuning properties was solely potentiated by the continuous repetition of the sound stimulus for 12 min and the spatial-temporal structure of the sound.

Interestingly, layer 2/3 neurons displayed an intriguing shift pattern towards horizontal orientations unlike cells of layer 5/6. Our data illustrate a novel extension to audio-visual cross-influence demonstrating that even an isolated application of a sound can robustly induce a reorganization of area V1.

4.4 Experimental Procedures

4.4.1 Ethical approval

Eight adult domestic cats (*Felis catus*), of either sex, were used for experiments adhering to the guidelines approved by the NIH in the USA and the Canadian Council on Animal Care. Cats were supplied by the Division of Animal Resources of the University of Montreal. The animal surgery and electrophysiological recording procedures were performed according to the guidelines of the Canadian Council on Animal Care

and were approved by the Institutional Animal Care and Use Committee of the University of Montreal (CDEA).

4.4.2 Anesthesia

Cats were initially sedated with a mixture of Acepromazine (Atravet, 0.1 mg/kg, s.c., Wyeth-Ayerst, Guelph, ON, Canada) and atropine sulphate (Isopto Atropine, 0.04 mg/kg, s.c., Atrosa; Rafter, Calgary, AB, Canada) followed by a dose of anesthetic ketamine (Narketan, 40 mg/kg, i.m.; Vetoquinol, QC, Canada). Anesthesia was maintained during the surgery with isoflurane ventilation (2%, AErrane; Baxter, Toronto, ON, Canada). After the surgery, cats were fixed on the stereotaxic and were paralyzed by perfusion of gallamine triethiodide (Flaxedil, 40 mg/kg, i.v.; Sigma Chemical, St Louis, MO, USA). Artificial ventilation was maintained by a mixture of O_2/N_2O (30:70) and isoflurane (0.5%). The paralysis was continued by perfusion of gallamine triethiodide (10 mg/kg/h) in 5% dextrose lactated Ringer's nutritive solution (i.v., Baxter, Mississauga, ON, Canada) throughout the experiment.

4.4.3 Surgery

Local anesthetic xylocaine (2%; AstraZeneca, Mississauga, ON, Canada) was injected subcutaneously during the surgery before any opening of the skin. A heated pad was placed beneath the cat to maintain a body temperature of 37.5 °C. Antibiotics Trimethoprim and Sulfadiazine (Tribrissen; 30 mg/kg/day, subcutaneous; Schering Plough, Pointe-Claire, QC, Canada) and Benzylpenicillin procaine and Benzylpenicillin benzathine suspension (Duplocillin; 0.1 mL/kg, intra-muscular; Intervet, Withby, ON, Canada) were administered to the animals to prevent bacterial infection. First, a vein of the animal's forelimb was cannulated. Then tracheotomy was performed to artificially ventilate the animal. A proper depth of anesthesia was ensured throughout the experiment by monitoring the EEG, the electrocardiogram, and the expired CO_2: O_2 saturation was kept in check using an Oximeter. The end-tidal CO_2 partial pressure was kept constant between 25 and 30 mmHg. Third, craniotomy (1*1 cm square) was performed over the

primary visual cortex (area 17/18, Horsley-Clarke coordinates P0-P6; L0-L6). The underlying dura was removed, and the multichannel electrode was positioned in area 17. The pupils were dilated with atropine sulfate (1%; Isopto-Atropine, Alcon, Mississauga, ON, Canada) and the nictitating membranes were retracted with phenylephrine hydrochloride (2.5%; Mydfrin, Alcon). Plano contact lenses with artificial pupils (5 mm diameter) were placed on the cat's eyes to prevent the cornea from drying. Finally, at the end of the experiment, the cats were sacrificed with a lethal dose of pentobarbital sodium (100 mg/kg; Somnotol, MTC Pharmaceuticals, Cambridge, ON, Canada) by an intravenous injection.

4.4.4 Stimuli and experimental design

Two types of stimuli were used - visual and audio. The receptive fields were located centrally within a 15° radius from the fovea. Monocular stimulation was performed. Receptive field edges (RF) were explored once clear detectable activity was obtained using a handheld ophthalmoscope (Barlow *et al.,* 1967). This was done by moving a light bar from the periphery toward the center until a response was evoked. Contrast and mean luminance were set at 80% and 40 cd/m^2, respectively. Optimal spatial and temporal frequencies were set at 0.24 cycles/deg and in the range 1.0–2.0 Hz (at these values V1 neurons are driven maximally) for drifting sine-wave gratings (Bardy *et al.,* 2006). Then, gratings were presented randomly as visual stimuli covering the excitatory RF to compute the orientation tuning curves of neurons (Maffei *et al.,* 1973). Visual stimuli were generated with a VSG 2/5 graphics board (Cambridge Research Systems, Rochester, England) and displayed on a 21-inch Monitor (Sony GDM-F520 Trinitron, Tokyo, Japan) placed 57 cm from the cat's eyes, with 1024×9×768 pixels, running at 100 Hz frame refresh (Figure 4.1A). The gratings moved unidirectionally in eight possible orientations presented randomly one by one. Each randomly presented oriented grating was given 25 times for 4s each with an inter-stimulus interval of 1-3s. Subsequently, the animal was exposed to broadband noise-like auditory stimuli comprising a range of frequencies. The auditory stimulus (3s 78 dB SPL) consisted of temporally orthogonal rippled combinations (TORC's) with varying frequency components from 250 Hz to 8000 Hz (Fritz *et al.,* 2003). The 3s stimulus

was played continuously for 12 minutes, delivered by a pair of external loudspeakers, positioned perpendicularly relative to the animal's axis at 57cm to the center of the fixation axis of the animal. The frequency response range of the speakers (range of audible frequencies the speaker can reproduce) was 120 Hz-18 KHz. For some recordings, the speakers were also displaced laterally at the same plane, at 30 cm on either side from the center of the fixation axis of the cat (Figure 4.1 A). This was done to test the change in responses if any when the position of the speakers was changed. The sound frequency and intensity were cyclical and optimized and set according to the experiment design using Bruel and Kjaer Spectris Group Sonometer. The stimulus was optimized on a standard C-scale of the sonometer for both ears. The spectrogram of the sound stimulus displaying varying frequencies is shown in Figure 4.1B. Immediately after the 12-min presentation of the acoustic stimulus, a series of drifting gratings was presented again in a random order (each oriented grating was presented 25 times where each of the 25 presentations was 4s and inter-stimulus time interval lasted 1- 3s). It must be emphasized that sound was applied in isolation, that is, no visual stimulus was presented during the sound application. Finally, a recovery period of 90 minutes was given for neurons to return to their optimal state (Figure 4.1 C).

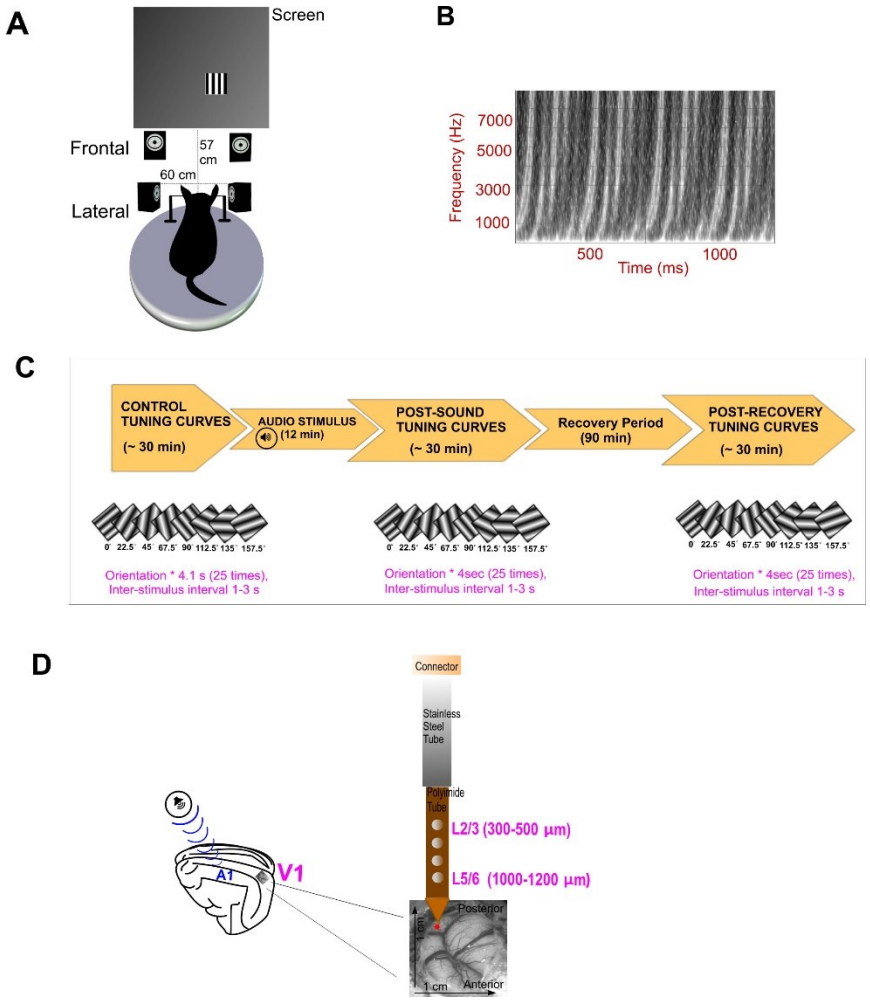

Figure 4.1

Experimental set up of stimulation, neuronal recordings and sound stimulus (A) Cartoon of the anesthetized cat fixed on the stereotaxic apparatus. Visual stimulus (shown as black and white gratings) was presented inside the receptive fields of test neurons. The sound stimulus was delivered by a pair of speakers occasionally placed frontal or lateral to the axis of the animal (B) The spectrogram of the sound stimulus is displayed. The spectrogram shows that sound stimulus was played in a constant frequency modulation (FM) pattern. (C) A pictorial representation of the steps followed during the protocol. Two types of stimuli were applied: Visual and auditory. Visual stimuli (sine-wave drifting oriented-gratings) were presented in a random order. Each orientation was presented 25 times and each trial lasted 4 s with

a 1–3 ms inter-stimulus interval followed by the presentation of the sound stimulus for 12 min. Then, the same set of visual stimuli was presented again in a random order. A recovery period of 90 min was offered after which the gratings were presented again randomly (D) Illustration of the electrode used to record neuronal activity. Neurons were recorded using multichannel electrode from depths 300-500 µm, and 1000-1200 µm from the primary visual cortex (V1)/area 17 before and after auditory stimulation.

4.4.5 Electrophysiology

Multiunit activity in the primary visual cortex of anesthetized cats was recorded using a tungsten multichannel electrode (0.1–0.8 MΩ at 1 KHz; Alpha Omega Co. USA Inc). Neural activity was recorded from both hemispheres of the cat's brain opening one side at a time. The electrode consisted of four microelectrodes enclosed in stainless-steel tubing in a linear array with an inter-electrode spacing of 500 µm. The recorded signal from the microelectrodes was acquired using Spike2, CED, Cambridge, UK. The signal was further amplified, band-pass filtered (300 Hz–3 KHz), digitized, displayed on an oscilloscope and recorded with a 0.05 ms temporal resolution. Recordings were performed at average cortical depths of 300–500 µm and 1000–1200 µm (Chanauria *et al.,* 2016) simultaneously from both sites as depicted in Figure 4.1 D. Spike sorting was done offline using same Spike2 package, CED, Cambridge, UK. Figure 4.2 shows an example of neuronal isolation (spike sorting) from the multiunit activity. As a precautionary measure, it was essential to affirm that we did not isolate the same unit twice, as the same unit may exhibit different waveforms depending upon several factors. Thus, the single units were distinguished based upon the spike waveforms, principal component analysis (PCA), and autocorrelograms (ACG) (Bharmauria *et al.,* 2015; Bharmauria *et al.,* 2016). The respective PCA, ACGs, and spike waveforms are also shown along in Figure 4.2.

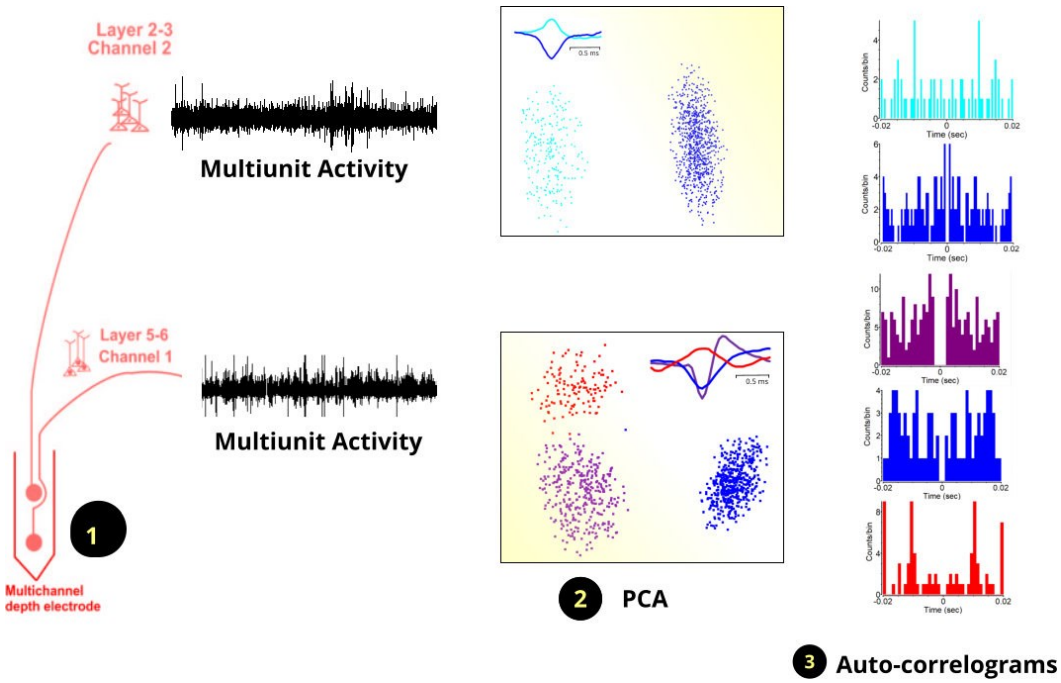

Figure 4.2

An example of the spike sorting process for isolation of single units is exhibited. Part 1 displays the neurons that have been recorded simultaneously from layer 2/3 and layer 5/6 of V1. Multiunit activity from both layers is also displayed alongside. Part 2 shows the principal component analysis of the dissociated waveforms. The superimposed average waveforms of dissociated spikes from multi-unit recordings are also shown. Part 3 displays the auto-correlograms for the separated single units. No events at zero represent the refractory period of neuron that confirms the individuality of each neuron.

4.5 Data Analysis

4.5.1 Tuning curves

After sorting neurons offline, the numerical value of orientation selectivity was calculated for each neuron at control and post-sound presentation conditions. Since applied gratings were separated by intervals of 22°, orientation peaks of tuning curves values were obtained by fitting a Gaussian non-linear curve on the raw orientation tuning values obtained at each orientation for each neuron. The Gaussian fits were calculated

on trial-averaged data collected from 25 trials of the same stimulus at each orientation. Each point in Gaussian fits is the range of responses and thus represents the total response function. The Gaussian tuning fits were computed using the function below:

$$y = y0 + \left(A \div \left(w \times \sqrt{\left(\frac{\pi}{2}\right)}\right)\right) \times e^{\left(-2 \times \left(\frac{x-xc}{w}\right)^2\right)} \quad \text{(Equation 1)}$$

where *y0* is the offset, *XC* is the center, *w* is the width, and *A* represents the area under the Gaussian fit. The firing rates were normalized and gaussian tuning curves were generated in the scientific software Origin. The above procedure indicates the preferred orientation with better accuracy. The same method was carried in controls and following sound adaptation. The magnitude of shifts was computed as the distance (subtractions) between peak positions of the fitted Gaussian tuning curves before and after the presentation of sound (the difference between the initially preferred and newly acquired). The following formula was applied to calculate the shift magnitudes:

$$\text{Shift magnitude} = (XC_{Post} - XC_{Pre}) \quad \text{(Equation 2)}$$

where XC is the central value derived from the Gaussian fit.

According to past studies, a difference of >5º is considered as a significant shift (Ghisovan *et al.,* 2009; Bachatene *et al.,* 2012a; Bachatene *et al.,* 2013; Bachatene *et al.,* 2015c; Chanauria *et al.,* 2016). A magnitude of <5º indicated a neuron that retained its initially preferred orientation even after the presentation of sound. These calculations are critical as the interval of 22° between the stimulus orientations

is relatively large, which makes it difficult to deduce an exact value of orientation tuning from only raw curves.

4.5.2 Orientation Selectivity Index (OSI)

Further, the Orientation Selectivity Index (OSI) of each neuron was computed by dividing the firing rate of the neuron at the orthogonal orientation by the firing rate of the same neuron at the preferred orientation, and subtracting the result from 1 (Ramoa *et al.,* 2001; Liao *et al.,* 2004). The closer the OSI is to 1, the stronger the orientation selectivity.

$$\text{Orientation Selectivity Index} = 1 - (FR_{\text{Orthogonal}} / FR_{\text{Preferred}}) \qquad \text{(Equation 3)}$$

where FR is the firing rate of the same neuron.

4.5.3 Bandwidths (BW)

Tuning bandwidths were calculated based on the full width at half magnitude (FWHM) of the Gaussian tuning curves for each neuron (Ringach *et al.,* 2002; Moore *et al.,* 2005). Bandwidths are measured to deduce the sharpness of orientation tuning curves of the neurons.

$$\text{FWHM (Bandwidth)} = 2\sqrt{2 \ln 2} \qquad c = 2.35482c \qquad \text{(Equation 4)}$$

where ln is the logarithm and c is the gaussian root mean square width.

4.5.4 Response Change Index (RCI)

To quantify the response disparity between stimulus conditions for each neuron, the traditional method of measuring response change index was used (Stevenson *et al.,* 2014; Meijer *et al.,* 2017) where the values of the RCI are normalized and can be used as a parameter to describe both enhancement and suppression. The values may range from -1 to 1 in which negative values indicate response suppression and positive values indicate response enhancement.

$$RCI = (FR_{Post\text{-}sound} - FR_{Control}) / (FR_{Post\text{-}sound} + FR_{Control}) \quad \text{(Equation 5)}$$

where FR is firing rate of the same neuron

4.6 Statistical Tests

Four datasets from layers 2/3 and 5/6 at control and post-sound conditions were tested for statistics (i) orientation tuning values (ii) Bandwidth values (iii) Orientation Selectivity Index (OSI) values and (iv) Response Change Index (RCI) values. These data were first tested for normal distribution using the Shapiro Wilk normality test. Based on the results obtained, parametric and non-parametric tests were applied on data sets. Consequently, comparisons were drawn between values of different parameters for either layer. Detailed information of tests can be found in legends of the figures as well as the results.

The current investigation focused on how visual cells reacted towards oriented gratings when a sound stimulus was presented solely in the absence of any other visual stimulation. The extracellular activity of V1 neurons was simultaneously recorded from the layer 2/3 and 5/6 down the column. The Gaussian tuning curves of neurons in layer 2/3 and layer 5/6 were compared between the control and post-sound situations. In total, 239 cells were recorded during different experiments out of which 124 neurons belonged to the layer 2/3 and the remaining 115 to the layer 5/6. These pools were used for further analysis and statistics.

4.7 Results

4.7.1 Impact of repetitive auditory input on orientation tuning of visual neurons: A typical example.

Figure 4.3 shows the typical result of a recorded neuron pair from layer 2/3 and layer 5/6. Two typical orientation tuning curves in raw forms are shown as (A) and (C) for layer 2/3 and layer 5/6 respectively. To infer the exact value of orientation preference, non-linear Gaussian fits were generated and are shown for the supra-granular (Figure 4.3B) and infra-granular cell (Figure 4.3D) for either condition. It must be emphasized that both cells were recorded simultaneously from the same electrode and the recording sites were separated by ~500 microns. The supra-granular cell exhibited an optimal orientation at 94.29° while the optimal orientation of the infra-granular layer was 96.70°, suggesting that the electrode was lowered in the same orientation column since optimal orientations are about equal. Following sound application, both cells displayed a novel optimal orientation. The peak of the optimal orientation of the supra-granular cell shifted to 110.92° indicating a displacement of 16° whereas the peak of the infra-granular cell moved in the opposite direction to 74.94° demonstrating shift amplitude of 21°. The opposite displacement of the peaks of optimal orientation tuning suggests that these shifts cannot be attributed to a global and spontaneous fluctuation of the firing rates. Each cell behaved independently. Furthermore, numerous studies have shown that, while the magnitude of the optimal responses may vary, the optimal orientation preference exhibits stability. Indeed, the optimal orientation remains the same for hours and even days and these controls were shown by Bachatene and colleagues (Henry *et al.,* 1973; Frenkel *et al.,* 2006; Lutcke *et al.,* 2013; Bachatene *et al.,* 2015c). Therefore, the significant change in orientation selectivity is due to the experience of visual neurons with the sound. Unlike previous studies where a modulation of response was remarked after the presentation of auditory stimulus for a few milliseconds (Iurilli *et al.,* 2012; Ibrahim *et al.,* 2016),

intriguingly, in this investigation, a complete shift in the curves of the orientation tuning of neurons was observed following the sound application.

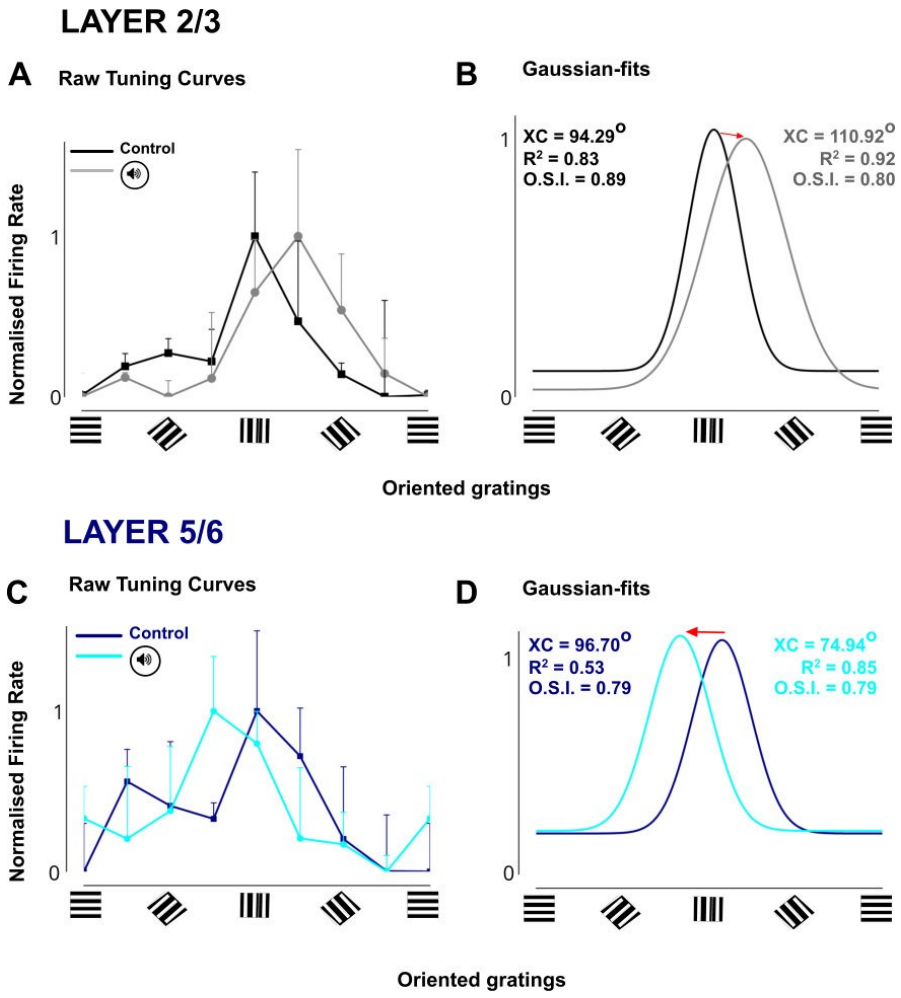

Figure 4.3

Typical examples of shift of orientation tuning peaks. The figure represents a pair of layers 2/3 and layer 5/6 neuron recorded simultaneously during the protocol. The bars signify standard error of the mean (mean ± SEM) over 25 trials at each presented oriented grating. The direction of shift is highlighted by an arrow (A) Raw orientation tuning values were compared for layer 2/3 neuron at control and post-sound conditions. A clear change in selectivity can be observed (B). To deduce the exact values of

orientation tuning, raw values were fitted using the Gauss function. An overlap of the initially preferred and the new selectivity has been depicted along with the XC, R^2 and OSI values. (C) Raw tuning curves of layer 5/6 neuron at control and post-sound conditions are displayed (D) Gaussian fitted tuning curves for layer 5/6 neuron over raw data is shown. The values of XC, R^2 and OSI are also displayed alongside the curves.

4.7.2 Neurons in supra- and infragranular layers regain their original optimal orientation tuning

Figure 4.4 shows examples of layer 2/3 and layer 5/6 neurons displaying a change in orientation selectivity during the presentation of oriented gratings at different steps of the recording protocol. Figure 4.4 A shows typical example of layer 2/3 neuron that was initially tuned to 82.06°. This indicated the optimal tuning of the neuron. Following the experience with 12 min of sound stimulus the same neuron changed its initially preferred orientation selectivity to a new preference of 32.80°. This neuron returned towards its original orientation selectivity, i.e., 78.01° after the rest period of 90 min. Likewise, the layer 5/6 neuron shown in Figure 4.4B recovered back from its new tuning peak of 115.73° to 91.09° after about 90 min of recovery time, which was quite close to its original optimal orientation tuning to 98.57°.

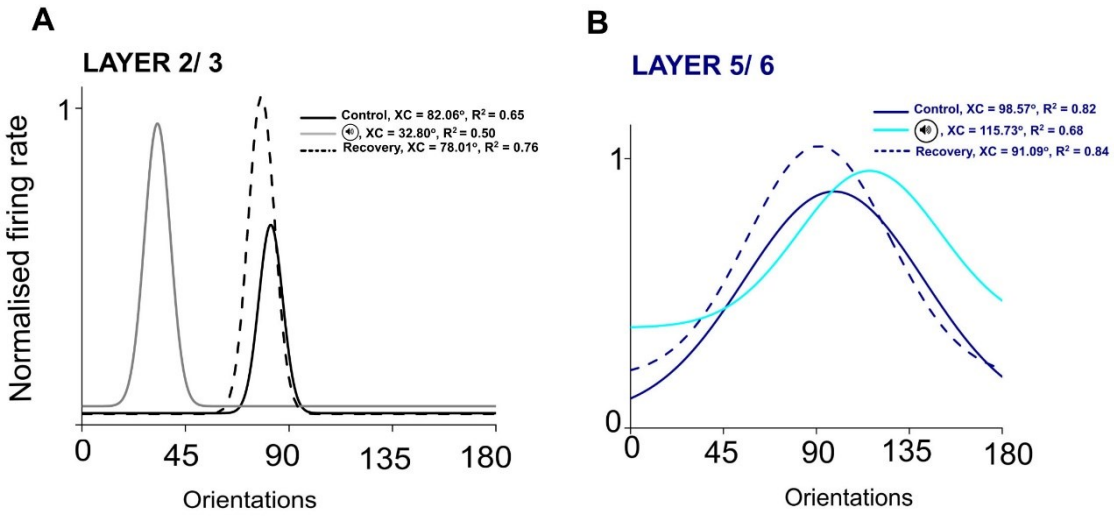

Figure 4.4

Typical examples of layer 2/3 and layer 5/6 neurons' gaussian fits showing a change in orientation tuning curves at control, post-sound and recovery stages. Both neurons clearly recovered back toward their original optimal after going through a resting period of 90 minutes. Figure 4.4A presents a layer 2/3 neuron that was optimally tuned to 82.06$^{o.}$ After 12 min of sound presentation the same neuron changed its orientation selectivity to 32.80^{o}. Undergoing a rest period of 90 min, the same neuron returned towards its original orientation selectivity, i.e., 78.01^{o}. Similarly, the layer 5/6 neuron shown in Figure 4.4B displays behavior of a neuron at different stages of sound adaptation protocol. The neuron was tuned to 98.57^{o} initially, which was modified by the 12 min sound presentation to 115.73^{o}. Finally, after the duration of 90 min, the same neuron gained its original orientation selectivity to 91.09^{o}.

4.7.3 Shift amplitude and sound source localization

The orientation tuning values of individual neurons at control and post-sound conditions are illustrated in Figure 4.5. On these datasets, a non-parametric statistical method was applied. The significant differences are indicated by solid black lines above each plot. The graphs A-C display values of orientation tuning peaks when speakers were placed laterally on either side of the animal with respect to the fixation axis of the animal. Figure 4.5A and 4.5B show the change in orientation tuning values pre- and post-sound for layer 2/3 and layer 5/6 neurons, respectively. In Figure 4.5A (left side), on comparing the two conditions, the values were found to be significantly different. In Figure 4.5B (left side), the orientation preference values covered the full spread of presented gratings (range 0^{o} to 157.5^{0}). Remarkably, the post-sound preferred orientations of layer 2/3 neurons appeared to have a significant bias towards horizontal orientations (range 0^{o} to 50^{o}), whereas this trend was not observed for cells in layer 5/6. The significant bias observed could be attributed to the variation of orientation selectivity by the properties of the auditory stimulus itself, or to the distinct mechanisms that drive the interaction between auditory and visual cortex. Further, different behaviors of neurons in different layers toward the same stimulus indicate different stages of cortical processing of the stimulus in the orientation column (Martinez *et al.,* 2005). The overall mean

of the individual values (individual values and mean both shown) for the three experimental steps (control, post-sound application, recovery ~90 min following sound application) are shown as inserts on the right side of Figure 4.5A and Figure 4.5B. Further, mean orientation tuning values of layer 2/3 and 5/6 neurons at control and post-sound conditions were compared using Repeated measures ANOVA, P value = 0.0177 (refer to Figure 4.5C). The means (mean ± SEM) for the four mentioned data sets were 81.41 ± 4.952, 18.15 ± 1.882, 83.33 ± 4.566 and 71.38 ± 4.332, respectively. These four data sets were compared with one another using Tukey's multiple post-comparison tests. Three out of six groups (layer 2/3 control versus layer 2/3 post-sound, layer 2/3 post-sound versus layer 5/6 control and layer 2/3 post-sound versus layer 5/6 post-sound), were found to be significantly different, whereas the remaining three groups (layer 2/3 control vs layer 5/6 control, layer 2/3 control vs layer 5/6 post-sound, and layer 5/6 control versus layer 5/6 post-sound) were found statistically non-significant.

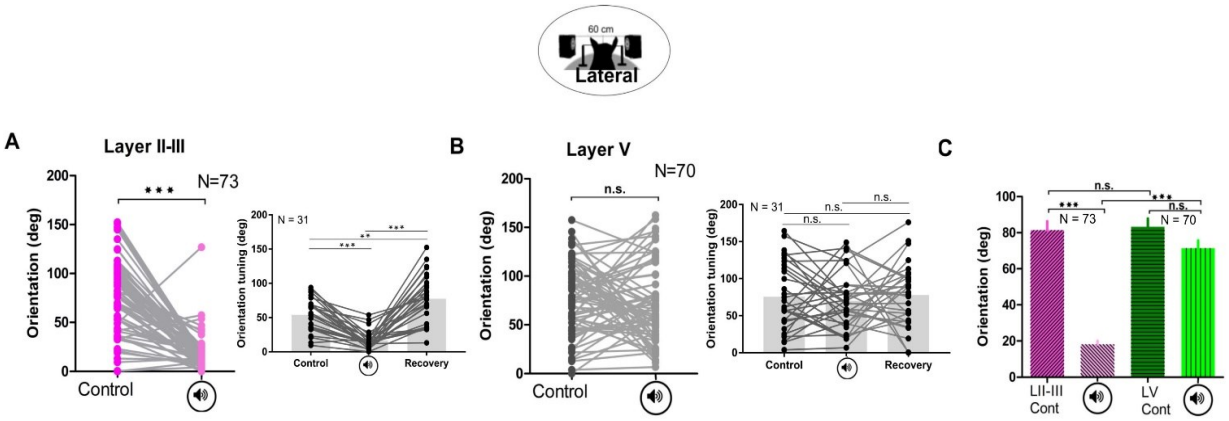

Figure 4.5

Acoustic stimulation results in modification of orientation preference in layer 2/3 and layer 5/6 neurons. (A) A plot of orientation tuning values for layer 2/3 neurons (N = 73), at control and post-sound presentation conditions is displayed (Wilcoxon matched-pairs signed rank test, P value <0.0001). On the right side, the histogram in grey and black shows the comparison of means of orientation selectivity values of (N = 31 out of 73) neurons at control, post-sound and recovery conditions (Wilcoxon matched-pairs signed rank test: Cont-Post-sound , P value <0.0001; Control-Recovery, P value <0.0047; Post-

sound -Recovery, P value <0.0001) (B) The graph shows the orientation tuning values for layer 5/6 neurons (N = 70) for control and post-sound conditions (Wilcoxon matched-pairs signed rank test, P value = 0.2280). The histogram in grey and black on the right side shows the comparison between means of orientation selectivity values (N = 31 out ot 70) at control, post-sound and recovery conditions (Wilcoxon matched-pairs signed rank test: Cont-Post-sound , P value = 0.6152; Control-Recovery, P value = 0.4487; Post-sound -Recovery, P value = 0.8325) (C) This graph shows a comparison of means of orientation tuning values of layer 2/3 (N = 73) and layer 5/6 (N = 70) at control and post-sound condition.

To explore the effects of displacement of the sound source, the speakers were positioned in the front of the animal. Figure 4.6A and 5.6B showed the variation in displacements of orientation tuning for layer 2/3 (N = 08) and layer 5/6 neurons (N = 11), respectively, at control and post-sound conditions. Layer 2/3 neurons showed a similar bias for horizontal orientations (tested significant statistically) in comparison to layer 5/6 cells. Figure 4.6C revealed the comparison of mean of orientation tunings of the above mentioned four groups. As an outcome of Repeated measures ANOVA, the comparison turned out to be non-significant. The means (mean ± SEM) for the mentioned four datasets were found to be 69.34 ± 13.21, 14.79 ± 4.90, 90.22 ± 11.91, and 91.24 ± 11.38, respectively (Figure 4.6 C). Using Tukey's multiple post comparison test, two out of six groups; layer 2/3 post-sound vs layer 5/6 control and layer 2/3 post-sound vs layer 5/6 post-sound were statistically different whereas the remaining four groups layer 2/3 control vs layer 2/3 post-sound, layer 2/3 control vs layer 5/6 control, layer 2/3 control vs layer 5/6 post-sound and layer 5/6 control vs layer 5/6 post-sound were found statistically non-significant at the same confidence level. These results were similar to results obtained when the speakers were placed laterally on either side of the animal, thus revealing a lack of difference in responses of neurons. Together, these results displayed the extended plastic nature of layer 2/3 neurons over layer 5/6 neurons and confirmed that displacing the speaker position did not bring any response change.

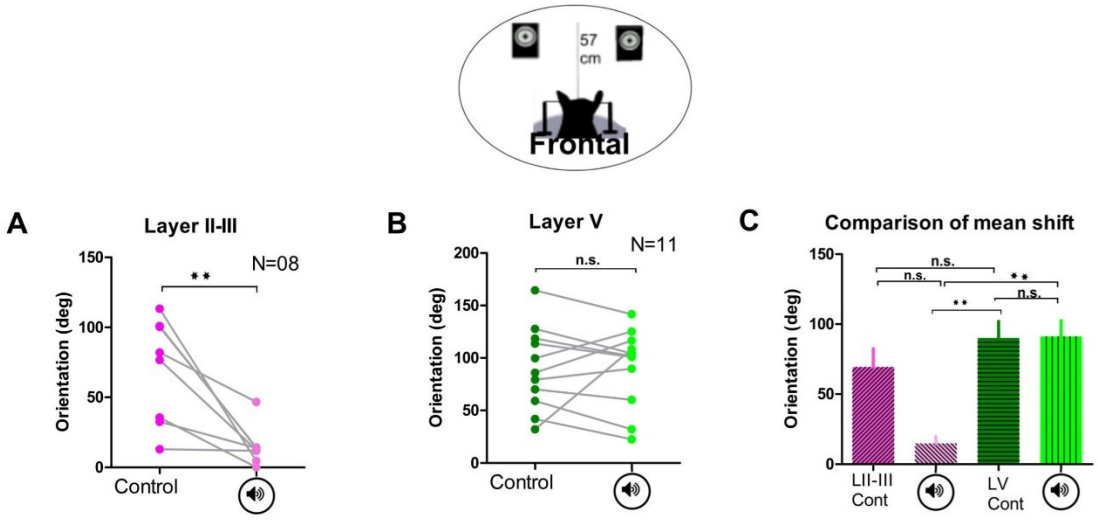

Figure 4.6

The graphs A-C show results when the speakers were positioned in front of the animal. A non-parametric statistical approach was followed since the data did not pass the Shapiro Wilk normality test. Connected points represent individual cells (A) Orientation tuning values for layer 2/3 neurons (N = 08) were plotted at both conditions and the difference was found to be significant (Wilcoxon matched-pairs signed rank test, P value = 0.0078) (B) Change in orientation tuning values of layer 5/6 neurons (N = 11) are displayed in the graph and the difference was found to be non-significant (Wilcoxon matched-pairs signed rank test, P-value = 0.8984) (C) Histogram of mean of amplitudes at control and post-sound conditions. The four groups (layer 2/3 control and post sound, and layer 5/6 control and post-sound) were compared using Repeated measures ANOVA. The means (mean ± SEM) for the four mentioned data sets were 69.34 ± 13.21, 14.79 ± 4.908, 90.22 ± 11.91 and 91.24 ± 11.38 respectively. Further, using Tukey's multiple post comparison test, the differences between all groups were calculated. Two out of six groups, layer 2/3 post-sound vs layer 5/6 control and layer 2/3 post-sound vs layer 5/6 post-sound were statistically different, whereas the remaining four groups, layer 2/3 control vs layer 2/3 post-sound, layer

2/3 control vs layer 5/6 control, layer 2/3 control vs layer 5/6 post-sound, and layer 5/6 control vs layer 5/6 post-sound, were found statistically non-significant at the same confidence level..

4.7.4 Sound impacts bandwidth of supra- and infra-granular neurons

The sharpness of orientation selectivity can be evaluated by measuring the bandwidth at half height of the orientation Gaussian tuning curve (Ringach *et al.,* 2002; Moore *et al.,* 2005). With this approach, we compared the tuning bandwidth of all neurons in either layer in control and post-sound conditions. The graphs shown in Figure 4.7 are a compilation of bandwidth analyses on layer 2/3 and layer 5/6 neurons. Figure 4.7A shows the difference in bandwidth for layer 2/3 neurons (N = 60). The large variance of the bandwidth of a neuron indicates broadening of selectivity for a range of orientations signifying a large contribution of flank orientations in the overall tuning of the neuron. Such an increase observed in our data strongly proposes that sound repetition induced the development of a different preferred orientation in the same neuron with a broader tuning curve. From this figure, overall, the tuning bandwidth at half magnitude (FWHM: full width at half magnitude) was found to be slightly enlarged at post-sound condition but not significantly different. This effect can be further understood by relating the results observed in Figure 4.4A where values of orientation preference for layer 2/3 cells held a bias towards the horizontal orientation's post-sound application. It gives the impression as if the neurons recorded from different sites in layer 2/3 were affected similarly on the application of sound and made all superficial layer neurons respond towards the sound in the same way. Similarly, in Figure 4.7B, layer 5/6 cells (N = 80) also showed a similar increment in the bandwidth responses. These were found to be statistically significant (Wilcoxon matched-pairs signed rank test, P-value = 0.0697). These results suggested that though both layers displayed similar behavior following the sound stimulus, nonetheless layer 5/6 cells exhibited broader shifts of tuning curves in comparison with layer 2/3 cells (refer to Figure 4.4B).

To test an overall trend, the mean values of neurons' bandwidths were compared with each other in both layers (Figure 4.7C). All groups were compared with each other using Repeated measures ANOVA.

The means (means ± SEM) for the mentioned four data sets were 17.53 ± 2.29, 28.14 ± 3.59, 22.74 ± 2.73 and 72.52 ± 4.38 respectively. Two out of six groups, (layer 2/3 post-sound vs layer 5/6 post-sound and layer 5/6 control vs layer 5/6 post-sound), were found to be significantly different (Tukey's multiple post comparison test), whereas others (layer 2/3 control vs layer 2/3 post-sound and layer 2/3 control vs layer 5/6 control) were found statistically non-significant at the same confidence level. In summary, these results showed a global deviation of layer 5/6 cells with higher means of bandwidths.

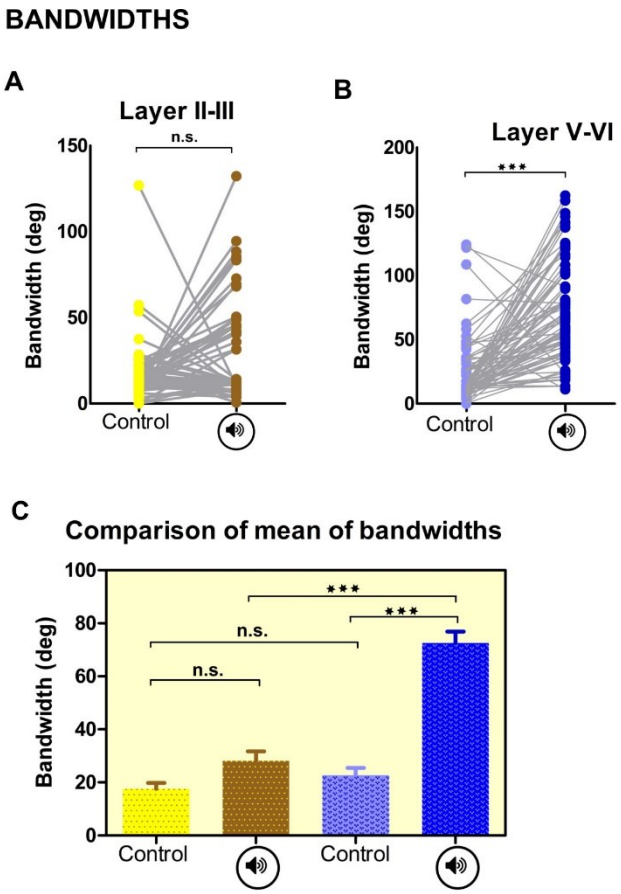

Figure 4.7

The sharpness of orientation selectivity. A non-parametric statistical approach was followed to measure significance between data sets. Connected points represent individual cells (A) The numerical values of bandwidths were plotted for layer 2/3 cells (N = 60) at control and post-sound conditions (Wilcoxon matched-pairs signed rank test, P-value = 0.0663) (B) A similar plot of bandwidth values for layer 5/6

neurons (N=80) is shown (Wilcoxon matched-pairs signed rank test, P-value = 0.0697) (C) Graph showing mean of bandwidths at control and post-sound condition. All four groups (layer 2/3 control, layer 2/3 post-sound, layer 5/6 control and layer 5/6 post-sound) were compared in this analysis using One-way ANOVA. The means (mean ± SEM) for the mentioned four data sets were 17.53 ± 2.293, 28.14 ± 3.595, 22.74 ± 2.736, and 72.52 ± 4.389 respectively. Further, with the help of Tukey's multiple post comparison tests the differences between all four datasets were calculated. Three groups (layer 2/3 control vs layer 5/6 post-sound, layer 2/3 post-sound vs layer 5/6 post-sound and layer 5/6 control vs layer 5/6 post-sound) were found significantly different whereas remaining groups (layer 2/3 control vs layer 2/3 post-sound, layer 2/3 control vs layer 5/6 control and layer 2/3 post-sound vs layer 5/6 control) tested statistically non-significant at the same confidence level.

4.7.5 Orientation Selectivity Index (OSI)

In line with the previous reports (Dragoi *et al.,* 2001; Ringach *et al.,* 2002; Atallah *et al.,* 2012; Denman & Contreras, 2014) neurons having an OSI superior or equal to 0.4 can be classified as sharply tuned cells. In this investigation OSI values for all cells have been pooled to generate the figure. Figures 8A and 8B show scatter plots for regression analyses for layer 2/3 neurons (N = 124) and layer 5/6 neurons (N = 115) at control and post-sound conditions, respectively. Layer 2/3 experienced more variation of response after sound application in comparison to layer 5/6. Overall, the OSI remained the same for either layer at both control and post-sound conditions yet layer 5/6 neurons experienced more dispersed evoked responses towards all presented orientations (Figure 8B). The comparison between all groups (using Tukey's multiple post comparison tests) showed that layer 2/3 neurons experienced a decline in selectivity of the preferred orientation (Figure 8C). Two out of six groups (control layer 5/6 vs post-sound layer 2/3, control layer 2/3 vs post-sound layer 2/3) were found to be significantly different, whereas the remaining four groups' differences were found to be non-significant. These results also correspond to our results from bandwidth data. The broadening of tuning curves after the imposition of sound lead to a decrease in mean OSI.

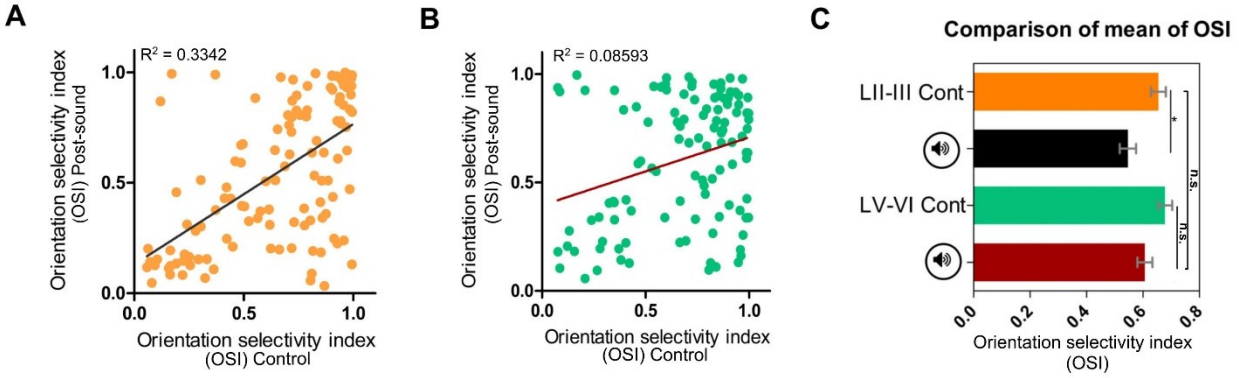

Figure 4.8

Orientation Selectivity Index (OSI) (A) OSI values calculated for layer 2/3 neurons (N = 124) at control and post-sound conditions are displayed as scatter plots and the regression line has been plotted (P-value<0.001; R2 = 0.3342) (B) Similar plot with regression analysis is also shown for layer 5/6 neurons (N = 115) at both circumstances (P-value = 0.0015; R2 = 0.08593) (C) The values of OSI from either layer for both conditions was compared using Repeated measures ANOVA. Only two groups tested statistically different for means (control layer 5/6 vs post-sound layer 2/3, and post-sound layer 2/3 and control layer 2/3) whereas remaining groups were not found different at any significance level.

4.7.6 Response change index (RCI): Response modulation comparison between orientations

As described in the methods section the modulation of response magnitude was calculated for all cells and for all applied oriented gratings. The values for layer 2/3 (N = 124) and layer 5/6 (N = 115) cells have been pooled to generate the analyses. Results are compiled in Figure 4.8. The means RCI (mean ± SEM) of all layer 2/3 and layer 5/6 neurons (Figure 9A) were -0.03435 ± 0.02 and 0.03098 ± 0.02 and were found statistically non-significant (Mann Whitney Test, P-value = 0.0682). In layer 2/3, responses fluctuated roughly with the same magnitude for all tested orientations. The differences between all possible pairs among all orientations were measured by Repeated measures ANOVA and Tukey's multiple comparison tests was applied to compare variances among means. The differences between all orientations in layer 2/3 were found to be non-significant (Figure 4.8B). Interestingly, in layer 5/6 (Figure 4.8C) the largest RCI was

determined for orientations close to the vertical axis (recall cells in both layers were recorded simultaneously). A closer analysis indicates that RCI regularly declined to become negligible in both directions as evoked responses moved away from vertical to horizontal orientations. Only five (0° vs 90°, 22° vs 90°, 45° vs 90°, 90 vs 135° and 90° vs 157°) out of twenty-eight groups tested were significantly different. This analysis, however, unveils another important observation. When RCI was analyzed at individual orientations, we found that, in supragranular layers, the firing rate decreased for most orientations whereas in infragranular an opposite effect was observed. Nevertheless, the overall response variation is balanced (refer to Figure 4.9A). Altogether, layer 2/3 neurons experienced response suppression and layer 5/6 neurons experienced response enhancement.

Finally, the striking inverse response modification of layer 2/3 and layer 5/6 neurons further suggests that neurons in supra- and infra-granular layers behave differently towards the identical stimuli conditions and it appears cells of both layers behave independently to process information. This kind of behavior where layers conduct themselves differently towards the same stimulus is indicative of different stages of cortical processing in a particular column (Martinez *et al.,* 2005)**.**

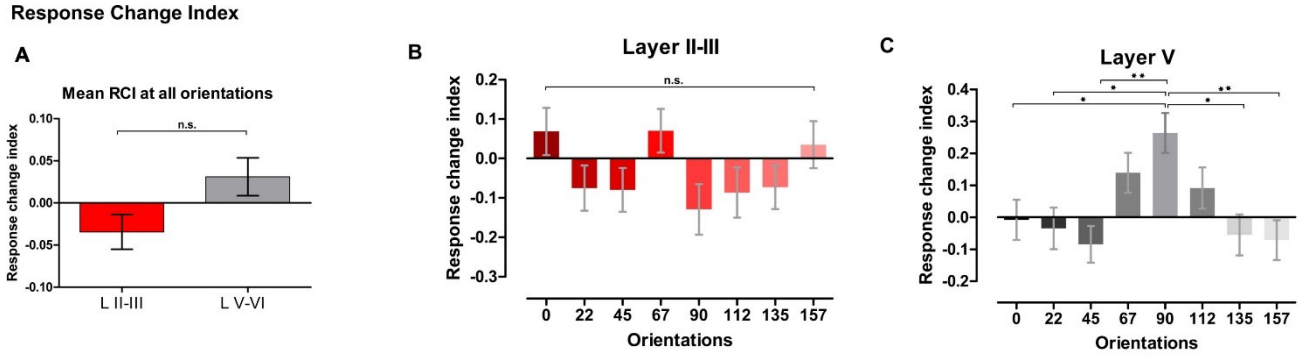

Figure 4.9

Response Change Index (RCI). A non-parametric method was opted for statistical validations (A) Histogram showing mean of RCI of all test neurons in either layer at all presented orientations (0° - 157.5°, separated by 22. 5°). The mean RCI (mean ± SEM) of all layer 2/3 and layer 5/6 neurons were -

0.03435 ± 0.02054 and 0.03098 ± 0.02241 and statistically non-significant (Mann Whitney Test, P-value = 0.0682) (B) A graph showing histograms of RCI at different orientations for layer 2/3 cells. The differences between all possible pairs among all orientations were measured by Repeated measures ANOVA and Tukey's multiple comparison test. (C) A similar analysis was done on layer 5/6 neurons, and the histogram was generated. Five groups out of all possible paired comparisons (0° vs 90°, 22° vs 90°, 45° vs 90°, 90° vs 135°and 90° vs 157.5°) tested significantly different, whereas, for rest of the groups, the mean of RCI was not significantly different.

4.8 Discussion

The present study aimed to investigate the responses of visual neurons of V1 when stimulated by a repetitive auditory stimulus whose frequency and power varied cyclically, presumably driving many putative synaptic inputs as auditory cells respond to many different sounds. The investigation revealed three main findings following adaptation protocol to sound. First, and the most important result, we observed shifts in the orientation tuning curves in cat's supra -and infra-granular layer neurons implying new orientation selectivity. Second, superficial and deeper layer neurons, recorded from the same columns at the same time, seemed to behave differently.

Moreover, occasionally cells in both layers shifted in opposite directions indicating independent behavior. Third, neurons in infra-granular layer 5/6 exhibited larger shifts of their orientation selectivity than the layer 2/3 neurons. Collectively, these findings suggest that neurons in the primary visual cortex (V1) might have a supplementary role in addition to processing a visual stimulus. Surely, these observations unveil that neurons in the primary visual cortex may alter their orientation preference since the peak of the tuning curves points to a novel preferred orientation.

4.8.1 Methodological considerations

We recognize that anesthesia affects the frequency of neuronal firing, especially when comparing anesthetized with behaving animals. Under anesthesia, neurons fire more sparsely and with lower firing rates (Barth & Poulet, 2012). Land (Land *et al.,* 2012) revealed the effect of isoflurane on the cortical processing in a cross-modal study of the visual and auditory cortices of mice. However, the effects observed in Land's study were an outcome of a deliberate decrease and increase in the levels of isoflurane during the recording sessions. In the present case, anesthesia was kept constant. Also, several findings argue against a significant influence of anesthesia. In general, anesthesia decreases the neuronal responsiveness globally. Shifts in the orientation tuning curves are ascribed to a decrease of responses to preferred orientation and simultaneously an increase to non-preferred orientation, that is, a push-pull mechanism. Similar shifts in orientation selectivity were reported when the adapting stimuli were visual in many species (Dragoi *et al.,* 2000; Ghisovan *et al.,* 2008; 2009; Bachatene *et al.,* 2012; Jeyabalaratnam *et al.,* 2013; Chanauria *et al.,* 2016).

Furthermore, the shifts in supra- and infra-granular layers were in the opposite direction. Additionally, supra-granular cells exhibited a tendency to shift their axis of orientation toward horizontal while infra-granular cells shifted the preferred orientation over the entire spectrum (note that cells were recorded simultaneously with the same electrode, and orientations were applied in random order). In cats, it has been shown that orientation selectivity does not occur at the LGN (lateral geniculate nucleus) level but is initiated at the cortical level (Dragoi *et al.,* 2001; Bouchard *et al.,* 2008). Infra-granular cells exhibited response change indexes increase predominantly for orientations close to vertical. Thus, such differential effects are difficult to reconcile with the global effects of anesthesia.

It could be of concern as to why a stimulus of 12 min was chosen. The reason behind the choice was first, to stimulate the auditory cortex with varying frequencies for a prolonged duration that could further impact the visual cortex. The current literature showing effects of the auditory stimulus on visual

neurons used short sounds that induced modulation of the firing rate. Thus, it became of interest to observe responses of visual neurons in response to a longer duration sound. Since it was already established that 12 min duration is enough to entirely change the tuning properties of neurons we used a sound stimulus for 12 min. The sound stimulus lasted 3s and was presented uninterruptedly for 12 min. Therefore, the duration of the sound stimulus was selected to compare the effects with visual adaptation (Chanauria *et al.,* 2016) and auditory adaptation on supra- and infra-granular visual neurons. It was of utmost interest to see if neurons behaved similarly or not by triggering the visual cortex by another modality. Of course, it remains crucial to examine the effect of sounds with different properties and different durations on the visual cortex; that will help better understand the interactions between auditory and visual cortex.

4.8.2 Layers behave as separate compartments

Our results also show that the application of sound differentially affected layers 2/3 and 5/6, thereby also reconfiguring the layout of orientation maps in the V1. Ibrahim and co-authors (Ibrahim *et al.,* 2016) demonstrated that layer 2/3 neurons' responses are suppressed by the A1 signals. Layer 2/3 neurons keep receiving the information for 12 min and presumably the intensity of the inhibitory drive increases with the duration of adaptation. Interestingly, it has been suggested that a supplementary excitatory feedback drive initiated in A1 may interact with layer 5/6 neurons (Fritz *et al.,* 2003; Muckli & Petro, 2013; Vetter *et al.,* 2014; Muckli *et al.,* 2015; Ibrahim *et al.,* 2016). This dual projection of neurons in supra- and infra-granular layers may elucidate shifts of tuning curves in the opposite direction (see example tuning curve). It is also known that each visual cortical layer has unique connections and these specific connections probably serve discrete functions. Thus, connections in each layer are dedicated for different purpose. Therefore, towards the same stimuli, neurons in different layers evoke different response properties indicating sequential stages of cortical processing (Martinez *et al.,* 2005). In summary, the application of sound differentially affected the layers 2/3 and 5/6.

4.8.3 Layer 2/3 and layer 5/6 neurons change orientation preferences

In line with the previous studies in visual adaptation, many authors have described changes in orientation selectivity after a short (less than a minute) (Dragoi *et al.,* 2000) or long light adaptation (Ghisovan *et al.,* 2008; 2009; Bachatene *et al.,* 2012; Bachatene *et al.,* 2013; Bachatene *et al.,* 2015; Chanauria *et al.,* 2016) (several minutes). Usually, the protocol requires the frequent or continued application of a non-preferred property of the adapter such as orientation. In the above experiments, the peak of the orientation tuning curve is displaced either toward (attractive) or away (repulsive) from the adapting orientation. In all cases, such protocol results in the emergence of novel orientation selectivity. Neurons undergo a push-pull mechanism (Bachatene *et al.,* 2012; Bachatene *et al.,* 2013; Bachatene *et al.,* 2015; Chanauria *et al.,* 2016) that is characterized by the decrease and increase of the firing rates at the initially preferred and the adapting orientation (newly acquired) respectively.

In the current investigation, the non-preferred stimulus traditionally referred to as visual adapter is absent and is replaced by exposure to a sound stimulus imposed in seclusion for several minutes uninterruptedly. Results revealed that such presentation of sound shifts the orientation tuning curves of individual visual neurons in supra- and infra-granular layers of area 17 of cats. Consequently, the sound seemed to exert distinctive effects in addition to the global modulatory influence. As orientation selectivity is formed at the cortical level, thanks to aligned thalamic inputs upon the cortical recipient neurons, the changes of orientation selectivity are unlikely to happen at thalamic levels, where cells have mostly concentric receptive fields (although some units may exhibit a slight orientation bias). Further, we found populations of neurons (layer 2/3 and layer 5/6) exhibiting enhanced or diminished responses while the overall response of the population remained balanced (Figure 7A). Notably, at 90° orientation, a clear enhancement of response is seen whereas suppression occurs in layer 2/3 neurons. Layer 5/6 cells experienced an increase in excitation.

It has been noted that short duration sounds produce weak visual responses (Brady, 2011; Deneux *et al.,* 2018). Repeated presentation of the sound stimulus for a prolonged duration may be accountable for eliciting stronger responses in V1. Undoubtedly, the repeated stimulation aids in crossing a threshold capable of generating the required strength of interaction given that substantial auditory input reaches V1. This sort of mechanism can logically happen in layer 2/3 where pyramidal neurons receive direct inputs from the auditory cortex, as 12 min time is enough to encode the raw embedded visual information within the audio stimulus. The bias we observed may perhaps be a consequence of such a process, and that is why we notice an orientation bias towards horizontal axis for layer 2/3 neurons but not in layer 5/6. Also, this predisposition could be inherently induced because of the property of the sound itself. It has been known for many years now that visual cortex is a stimulus-driven structure (Doron *et al.,* 2002; Izraeli *et al.,* 2002; Piche *et al.,* 2007; Chabot *et al.,* 2008). The non-visual information in the stimulus can transmit from non-visual sensory structures to the visual cortex by direct cortico-occipital (temporo-occipital?) pathways and circumvent the higher order cortex. Xu and co-authors (Xu *et al.,* 2012) suggested that functional mixing of inputs from two different sources could allow for facilitative non-linear interactions within individual dendrites that may lead to the bias towards horizontal orientations. This non-linearity may yield a preference towards the horizontal orientations. Another important revelation from a previous study (Deneux *et al.,* 2018) suggests that the increasing intensity of sound strengthens the neuronal response. The intensity of the stimulus we used was kept the same for the 3s, and the same 3s time was repeated for 12 min.

4.8.4 Inhibitory mechanisms

Recent studies have suggested that sound modulates light responses by impacting inhibitory neurons in the V1 cortex (Iurilli *et al.,* 2012; Kayser & Remedios, 2012; Pluta *et al.,* 2015; Ibrahim *et al.,* 2016). A very recent report (Deneux *et al.,* 2018) revealed that auditory cortex neurons project to V1 inhibitory neurons in superficial layers, especially layer 1. Indeed, area A1 sends axons to V1 where they connect to inhibitory interneurons (Iurilli *et al.,* 2012). As summarized by Meijer and authors in their paper (Meijer *et al.,* 2017),

auditory stimuli suppress VIP interneurons which inhibit SOM cells which in turn suppresses PV (Parvalbumin; GABAergic interneurons) cells and distal dendrites (involved in non-local synapses) of supragranular pyramidal cells (Gentet, 2012; Meijer *et al.,* 2017). This specific pathway is activated precisely in response only to non-visual inputs (Deneux *et al.,* 2018). Indeed, pyramidal cells are entrenched by inhibitory cells (Tremblay *et al.,* 2016). Authors (Deneux *et al.,* 2018) reported that the observed inhibitory mechanisms originated in a dark setup, and these results could be applied to the current investigation since sound was applied in darkness. However, it must be underlined that inhibition was not directly tested in the present investigation consequently the above suggestions necessitate experimental evidence.

Furthermore, there is classical cross-orientation inhibition that may be added to above inhibitory processes initiated in A1 (Morrone *et al.,* 1982; Alitto & Dan, 2010; Priebe, 2016). Such steps may further contribute to changing of preferred orientation that result in shifts of selectivity. On similar lines, it has been hypothesized that sound exerts a divisive or additive influence, resulting in a decline or enhancement of light responses (Pluta *et al.,* 2015). These results were observed in mice yet similar explanations could apply to cats.

4.8.5 Supramodal nature and cross-modal influences in the cortex

Our results demonstrate a new case of audio-visual communication, and further substantiate the observations made by previous investigations in cross-modal plasticity. Unlike the relatively slight modulation of firing rate of neurons detected in previous investigations in mice (Iurilli *et al.,* 2012; Ibrahim *et al.,* 2016), we observed a much more vigorous response-change in our data, wherein V1 neurons experienced a complete shift in their orientation preference. This kind of modification was reported earlier in literature related to adaptation studies where neurons were only exposed to an adapting orientation (visual stimulus) and acquired newly preferred selectivity. These visual adaptation protocols pertain to the classical flow of information involving LGN to the input layer 4 of the V1 and then to layer 2/3 and finally to layer

5/6. In the current case, the visual adapter was absent, yet similar results were obtained. Indeed, in this case, it is the application of sound for several minutes that induced neurons to acquire a new preferred orientation. Though the principle underlying such interactions has not been fully discovered yet, the most suitable explanation that fits in with our results is the combination of cross-modal interactions and the supramodal nature of the visual cortex. The visual cortex is a stimulus-driven structure. Therefore, it exhibits a unique response pattern towards specific protocols and stimuli. It is hypothesized that, upon sensory activation, the visual cortex relies on the abstract representation of the sensory stimuli regardless of the sensory modality. Stimulus-specific reorganization of the cortex can be responsible for the recalibration of the sensory system. In the present study, healthy animals were monocularly stimulated. A supportive study (Muckli *et al.,* 2015) highlights that a significant source of information lies in the context of the stimuli. Muckli and colleagues state that any sensory stimulus involving a feature can potentially embody the global features of the stimuli that are enough to trigger a complex scene representation of the same sound stimulus in the visual cortex (Bar, 2004; Oliva & Torralba, 2007), especially when presented for a prolonged duration. Although these effects have been discussed mainly from imaging studies on humans, the underlying principle supports the suggestion of our data (Vogels, 1999; Muckli *et al.,* 2005; Vetter *et al.,* 2014; Muckli *et al.,* 2015).

Besides, from the spectrogram it can be noticed that the sound stimulus has a structure and a direction in its frequency modulation. The stimulus quite creates the illusion of the oriented gratings for the auditory neurons and due to the repetitive nature of the stimulus it also has specific time-frequency organization that is yet again equivalent of oriented gratings for the auditory neurons. Therefore, these embedded features of the sound seem potential to modulate the activity of V1 neurons.

4.9 Conclusion

The recent finding of the early involvement of the visual cortex in the integration of multimodal information has led to the testing of different stimuli towards non-corresponding primary sensory regions. During

experimentation in this direction, different research groups have discovered a slight modulation of response with respect to short sound exposure. Our data demonstrate that prolonged sound presentation (sound adaptation) entirely modifies the tuning properties of individual cells and consequently reorganizes the cortical orientation maps in V1. Our results further substantiate and support that primary visual cortex is indeed inherently multisensory in nature. Nevertheless, a crucial and detailed inspection is required to fully fathom the mechanisms of communication between the primary sensory areas.

4.10 Acknowledgments

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CHAPTER 5: ARE SENSORY NEURONS IN THE CORTEX COMMITTED TO ORIGINAL TRIGGER FEATURES?

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5.1 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. Yet, it's 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 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 orientating 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 re-calibration of corresponding or neighboring sensory area(s) to re-direct the sensory function and exhibit remarkable expansion of neuroplasticity within the brain.

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

5.2 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 towards appropriate regions of the cortex. The regularity of these processes devises an organized circuitry of neuronal

connections elicited by a variety of stimuli. Thus, it is the early sensory experience that guides the evolution of neural circuitry in the cortex.

5.3 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 permanent process; 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.

5.3.1 Reorganisation 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 can 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 (Sur & Rubenstein, 2005). Another study by Sharma *et al.,* 2000 (Sharma *et al.,* 2000) examined and compared intrinsic connections in rewired A1 to normal A1 and normal V1. They found that diverting visual inputs to auditory cortex led to sharp orientation selectivity in rewired A1 and A1 maps are similar to V1 yet maps in A1 were not as clean as in normal V1. Further, it is also familiar now that during development, there is wide and unspecific sprouting of connections that are particularly strong for cortical-cortical connections (Innocenti & Price, 2005). In spite of 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 might provide auditory input to the MT during development. Considering, in normal adult monkeys, STS has a columnar alignment that interleaves pure auditory, pure visual and multisensory neurons (Beauchamp *et al.,* 2004) it seems plausible that the auditory input within STS may spread to nearby MRT during development and these aberrant contacts may stabilize during the visual deprivation period.

5.3.1.1 Disappearing of cortical borders in the barrel cortex by tactile learning

In monkeys, other type of tactile learning was used to show whether or not it was possible to change tactile receptive fields in the somatosensory cortex (Clark *et al.,* 1988). 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 5.1). To increase their chances to achieve synchronized stimulation of two adjacent fingers, they surgically fused them by connecting the skin, creating a syndactyly for digits 3 and 4 of owl adult monkeys. In (Clark *et al.,* 1988), the strict separation between fingers receptive fields disappeared, allowing them to merge where digits 3 and 4 representations in the cortex merged, to form a

new single receptive similar than that of a single unaltered finger. Stimulation of one of the two connected digits resulted 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.

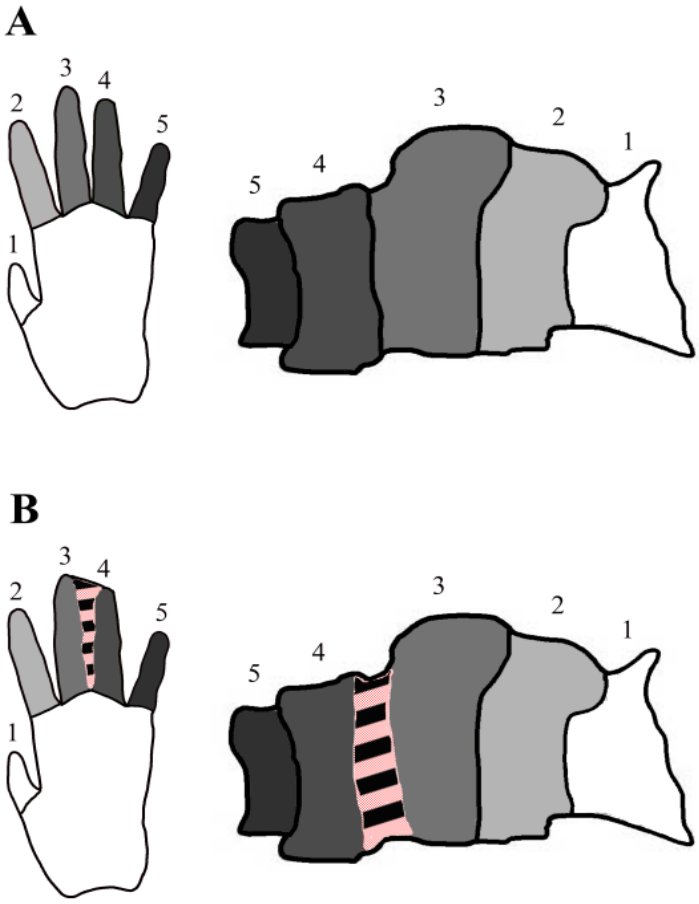

Figure 5.1

Model of cortical reorganization of area 3b following synchronous-stimulation of two fingers. (A) Normal monkey hand (left) with 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 to a reorganization of area 3b (right). Dotted area represents overlapping between fingers 3 and 4. (Model based on Clark et al., 1988)

5.3.1.2 Typical example: Reorganization of the somatosensory 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 (Merzenich *et al.,* 1984), 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 5.2). 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 the rule for the brain, plasticity reduces with age, yet these results suggested that somatosensory cortex is capable of reorganizing its cortical territories in order 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.

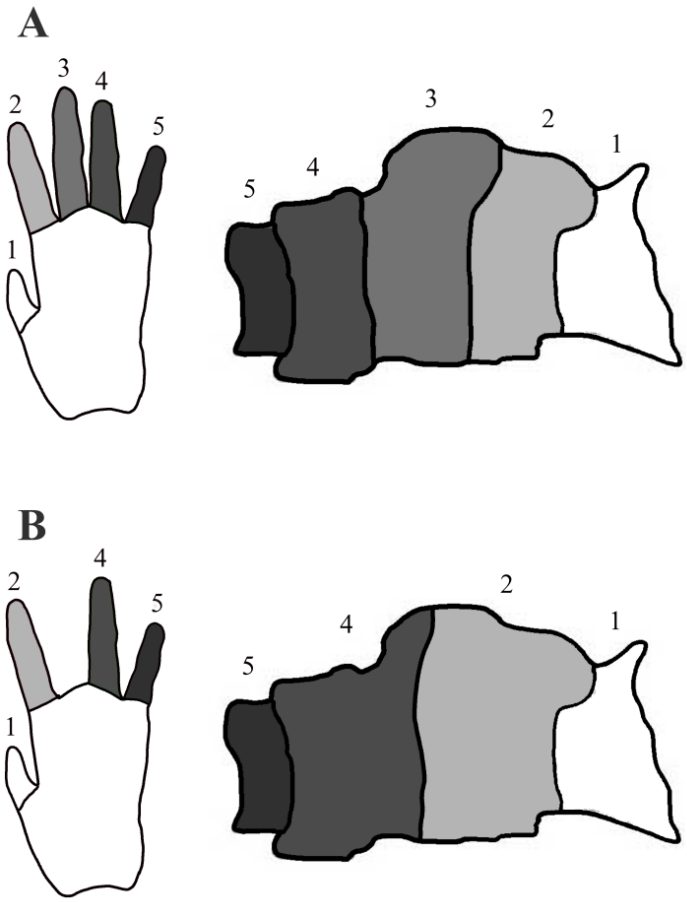

Figure 5.2

(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., 1984)

5.3.2 Congenital blindness

Reorganizing the somatosensory cortex was proved to be possible (Merzenich *et al.,* 1984; Clark *et al.,* 1988), but only within itself and with sensory loss occurring during adult life. In the study of Kupers *et al.,* 2006 (Kupers *et al.,* 2006), 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) (Bach-y-Rita & W. Kercel, 2003; Ptito *et al.,* 2005), showing that activation of occipital cortex could be achieved and increased using sensory substitution. However, it wasn't proved that activation of either cortex could be achieved without using sensory substitution. Subjects were then prepared for trans cranial magnetic stimulation of the occipital cortex (Ptito *et al.,* 2005), 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 of them resulting in an evoked response on different areas of the tongue. Hence, these results proved that early sensory deprived cortices can be involved in cross-modal plasticity, following training with sensory substitution techniques.

5.3.3 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 (Kandel, 2009) and vertebrates (Watroba *et al.,* 2001; Sur *et al.,* 2002; Basole *et al.,* 2003; Frenkel *et al.,* 2006; Kohn, 2007; Kokovay & Temple, 2007; McCoy *et al.,* 2009) 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 (Gourevitch & Eggermont, 2008). 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 (Armstrong-James *et al.,* 1994).The somatosensory cortex homunculus may be altered with both increased and decreased stimulation (Merzenich *et al.,* 1984). Therefore, neurons in the adult cortex, following manipulation of inputs, display novel response properties that were not present after normal brain's maturation. A majority of 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; induce 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 (Dragoi *et al.,* 2000; Kohn, 2007; Ghisovan *et al.,* 2009; Nemri *et al.,* 2009; Bachatene *et al.,* 2012b; Cattan *et al.,* 2014).

5.3.3.1 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 (Bouchard *et al.,* 2008). 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 (Clifford, 2002). Prolonged adaptation changes fMRI responses in V1 in an orientation-specific manner (Tootell *et al.,* 1998).

However, in various mammal's 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.,* 2006 (Frenkel *et al.,* 2006) 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.,* 2005 (Jin *et al.,* 2005), described response suppression resulting in shifts of the peaks of tuning curves away from the adapter, referred often 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 (Tolias *et al.,* 2005). 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 (Kohn & Movshon, 2003; 2004). On the other hand, Yang and Lisberger in 2009 (Yang & Lisberger, 2009), 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 an acquisition of a novel visual property induced by the learning procedure (Schlack & Albright, 2007). In parallel, more studies in V1 showed that evoked discharges in response to the originally preferred stimuli are selectively reduced (Krekelberg *et al.,* 2006; Hietanen *et al.,* 2007; Priebe *et al.,* 2010) but Krekelberg *et al.,* 2006 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 (Blakemore *et al.,* 1970; Levinson & Sekuler, 1976; Movshon & Lennie, 1979; Saul & Cynader, 1989).

A study (Jia *et al.,* 2010) 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 close 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 large spectrum of properties, one group of inputs would 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 (Jia *et al.,* 2010). 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 (Kohn & Movshon, 2003; Kohn, 2007; Ghisovan *et al.,* 2009; Marshansky *et al.,* 2011). A second adaptation performed (many minutes sometimes up to two hours) after the recovery from the first

episode of adaptation, yields similar results (Bachatene *et al.,* 2013). 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 (Fregnac *et al.,* 2010). 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 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. But overall, they found the critical period process 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 towards or away from adapting orientation or retaining or refracting their orientation tuning in some cases (Bachatene *et al.,* 2012b; Bachatene *et al.,* 2013). It was further confirmed by another study using optical imaging that following adaptation for 12 minutes the orientation maps are modified in response to the adapter (Cattan *et al.,* 2014) (Figure 5.3). A similar result was obtained in mice by Jeyadarshan *et al.,* 2013 (Jeyabalaratnam *et al.,* 2013). Further, an important study confirmed that a continuous adaptation on the recording site for 12min yields attractive and repulsive shifts wherein the shifts carry equivalent averages of 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 re-orientation 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 (Bachatene *et al.,* 2015c). Based on this observation and hypothesis Chanauria *et al.,* 2016 (Chanauria *et al.,* 2016) demonstrated that the typical behavioural response of visual neurons persists and can be observed in the layer 5/6 neurons too when recorded simultaneously with layer 2/3 neurons and further stressed that domino effect does not only exists in layer

2/3 neurons but inherently prevails within the neurons throughout the cortical column (Chanauria *et al.,* 2016).

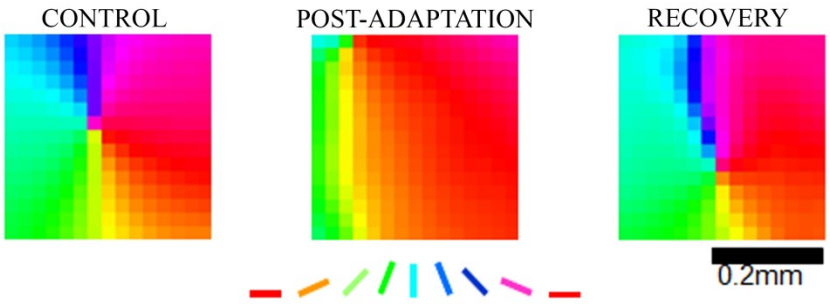

Figure 5.3

Reorganization of orientation columns in cat primary visual cortex shown by optical imaging. 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, previous preferred orientation regains their control territory.

(S. Cattan unpublished material)

5.3.4 Organization of somatosensory cortex and trigger features

All sensory receptors input to the somatosensory cortex and are then used by 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 (Penfield & Boldrey, 1937; Kell *et al.,* 2005; Cazala *et al.,* 2015). It has been shown that using somatotopic maps, a "Sensory Homonculus" 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 (Kell *et al.,* 2005). This was first demonstrated by Penfield and Boldrey (Penfield & Boldrey, 1937) 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 in 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 non-invasively. Techniques like functional magnetic resonance imaging (fMRI) to display brain activity based on blood oxygenation difference became at disposal (Kell *et al.,* 2005; Sanchez-Panchuelo *et al.,* 2010; Cazala *et al.,* 2015). 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 (Hubel & Wiesel, 1962b; Tusa *et al.,* 1978; Tusa *et al.,* 1979). 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 (Maier *et al.,* 1999) were found congruent in higher and lower vertebrates, An entire territory dedicated to whiskers inputs was also discovered (Lee & Erzurumlu, 2005). 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 primary somatosensory cortex (S1) in mice (Lee & Erzurumlu, 2005). Thus, it is no wonder that mice use their whiskers, prior to their vision, to locate and identify objects by their shape (Krupa *et al.,* 2001; Polley *et al.,* 2005; Anjum *et al.,* 2006; Mehta *et al.,* 2007; Connor *et al.,* 2010), but also by their texture (Lottem & Azouz, 2008; Boubenec *et al.,* 2014). The somatosensory cortex is generally shaped to collect and analyze surround information from the environment, with specific structures depending of the species.

5.3.4.1 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 (Woolsey & Van der Loos, 1970; Welker & Woolsey, 1974). In (de Kock & Sakmann,

2009b), 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 *et al.,* 2009 (de Kock & Sakmann, 2009a) 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 1,000-1,500 μm – corresponding to L5- displayed significant changes in spiking frequencies for quiet (non-whisking) and whisking states.

5.3.4.2 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 better get acquainted with their living space (Wu *et al.,* 2013). Wu *et al.,* based their study on this natural instinct (Wu *et al.,* 2013), and 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, showed in their arena-based experimental set-up. 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 didn't express memory in tactile less trial. Moreover, as whisker-less mice didn't show the same exploring pattern, their results also demonstrated that this tactile memory was vibrissae-based. With this study, by Wu *et al.,* 2013, (Wu *et al.,* 2013) 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 (Pacchiarini *et al.,* 2017). With the same kind of experimental set-up, trials were separated by 24 hours instead of 5 minutes. After analysis, it was shown that mice spent an average of 65.20% with the novel gratings (Pacchiarini *et al.,* 2017), thus indicating that the perceptual-learning-acquired memory could be maintained for a 24hours period.

5.3.5 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 (Ghazanfar & Schroeder, 2006; Driver & Noesselt, 2008) have provided evidence that multisensory interactions can be observed at early primary unimodal stages of sensory processing (Adeli *et al.,* 2014). 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 *et al.,* 2013 (Muckli & Petro, 2013) highlights the existence and importance of non-geniculate input to V1 by associated areas such as auditory cortex. Moreover, a fMRI report by Vetter *et al.,* 2014 (Vetter *et al.,* 2014) 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, (Ibrahim *et al.,* 2016) 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 anaesthetized cats. The stimulus 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 experience modulation of excitation and inhibition and attain 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 result obtained. The figure (Figure 5.4) 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 curves. Control curves are shown in bold and dotted curves shown for post-adaptation with sound.

The possible explanation to these results could be simply attributed to direct anatomical connections between primary sensory areas within the cortex (Ghazanfar & Schroeder, 2006) or an indirect pathway involving arousal of a multisensory area as a mediator to facilitate the modulation of responses (Driver & Noesselt, 2008). These mediator areas could be pulvinar, superior colliculus or other thalamic nuclei that act as ports of entry of information to primary areas.

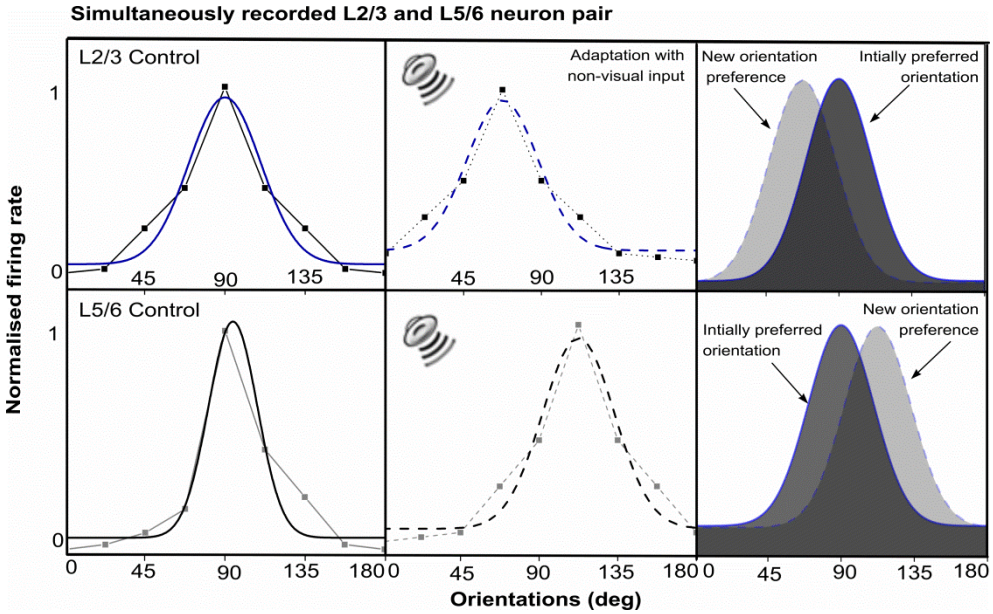

Figure 5.4

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 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 minutes. Modulation of firing rate can be observed accompanied to the alteration in selectivity. A similar response shift, yet in opposite direction can be observed in L5/6 neuron. This indicates that neurons in a column may choose to show a similar response yet behave independently towards the same stimulus.

5.3.6 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.,* in 2010 (Jia *et al.,* 2010) 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 that the most intensely stimulated dendritic segment 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 *et al.,* 2009 (Yang & Lisberger, 2009) 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 (Antonini & Stryker, 1993; Keck *et al.,* 2011). 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 memory retention throughout the entire life of an animal (Yang & Lisberger, 2009). A recent (Keck *et al.,* 2011) 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 very slow return to

preadaptation maps is attributed to structural modifications occurring in dendritic branches (Godde *et al.,* 2002).

5.4 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 (Frostig *et al.,* 1990; Bonhoeffer & Grinvald, 1991; Blasdel, 1992). 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) (Swindale, 1998a). In addition, investigations have demonstrated that the layout of orientation preference maps is roughly scattered around pinwheel centers, rather than aligned in slabs (Maldonado *et al.,* 1997; Godde *et al.,* 2002). Within pinwheels, adjacent neurons at the center of pinwheels display large differences in orientation preference. For example, neurons with orthogonal orientations are in proximity (Maldonado *et al.,* 1997; Basole *et al.,* 2003). 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.

5.5 Modulation of Plasticity by Drugs Application

In parallel with physiological processes inducing plasticity, drugs and other substances which operate as a neurotransmitter or selective neurotransmitter reuptake inhibitor modulate visual plasticity (Mataga *et al.,*

1992). Indeed, some of them such as the protein Lynx 1decrease the level plasticity and provoke stability by locking the cortical network (Morishita *et al.,* 2010).

5.5.1 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 (Maya Vetencourt *et al.,* 2008; Maya Vetencourt *et al.,* 2011). In line with the previously published data, it has been shown that after a treatment of ischemic stroke patient with Fluoxetine, there is a facilitation of the motor recovery compared to placebo subjects (Chollet *et al.,* 2011). Similar to the antidepressant Fluoxetine, it has been shown that the neurotransmitter Serotonin increase the attractive- a shift of a peak of the orientation tuning curve following adaptation in primary visual cortex V1 in anesthetized adult cats. Most neurons will serve as a reference for the other cells then recovery loses their stability and substitutes their original preferred orientation by a new one in the direction of the adapter. Repulsive neurons expressed as another previous kind of behavior cells plasticity mostly in direction of the 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 potentiating after long-term chronic administration in rats (Maya Vetencourt *et al.,* 2008; Wang *et al.,* 2008). In the same framework, Komlosi *et al.,* 2012 (Komlosi *et al.,* 2012) showed that the influence of fluoxetine on the polysynaptic transmission is relatively smaller than the serotonin action. In addition, it's shown that both drugs affect amply the shift magnitude but not the firing magnitude of neurons post-drug administration 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 fairly 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 acted at synapse level causing a drift (displacement) towards 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 of them significantly affect the response amplitude evoked by the adapter and the original preferred orientation but not those evoked by flank orientations that are not significantly changed.

Molecular processes are further developed below:

Overall, fluoxetine (SSRI) and serotonin (neurotransmitter) by acting in synaptic components promote sensitization of refractory cells (which maintain their preference after adaptation) and lead them to learn an unfamiliar stimulus, enhance the attractive effect of attractive cells, and contribute to increasing the plasticity for the repulsive cells. Training the neuron's ability shown in the adult primary visual cortex by experience drive synaptic reorganization can serve as a scaffold and contribute to cerebral pharmacological treatments or cognitive mechanisms such as learning or memory.

5.5.2 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 short-acting dissociative anesthetic. The preliminary results show that post-adaptation firing rate is lower than that of control. However, when ketamine was applied, post-adaptation firing rate decreased less compared to control. As adaptation is a mechanism to

understand plasticity, we conclude that ketamine, by reducing the neuronal potential to modify the response rate following adaptation, reacts as a short-term blocker of the orientation plasticity post-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 are measured before and after the application of ketamine. Our data shows that the following ketamine, the majority of cells shifted their optimal orientation. The comparison of the mean of OSI between control and post drug application revealed a significant decrease in the OSI post ketamine which implies that an application of ketamine weakened the initial orientation selectivity of neurons in V1. However, the bandwidth of orientation tuning curves didn't 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 function like show two populations of cells: ones had initially (in control condition) weak amplitudes but increase after ketamine application and the others had initially strong amplitudes but decrease after ketamine application (Figure 5.5). Thus, ketamine modulates downward or upward the initially highest amplitude Gaussian function like. However, we didn't know what factor this modulation is correlated. To assess and describe the variability of neurons response, a Fano Factor (FF) was calculated for each neuron by dividing the variance by the mean of firing rate of this neuron. The larger the Fano Factor is, the bigger 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 post ketamine FF decreases significantly, which is mean that ketamine declines the cells potential to reply variably at a big range of orientations. So, ketamine no only narrows the window of the variability of cells responses to stimuli but also weakened their orientation selectivity. Moreover, it was demonstrated that following ketamine application the FF value of spontaneous and evoked response remains similar while they were significantly different in absence of ketamine, which suggests that ketamine decreases the orientation selectivity of cells and brings their evoked activities in presence of stimuli closer to their spontaneous activities (Figure 5.5). The FF values of spontaneous responses calculate before and after ketamine application remain similar what reveals that ketamine doesn't

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 Gaussian function like, 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 underlines a kind of inhibitory effect on v1 potential plasticity. Molecular bases behind the cortex plasticity in general and how fluoxetine, serotonin, and Ketamine can modulate it, in particular, are discussed in the following section.

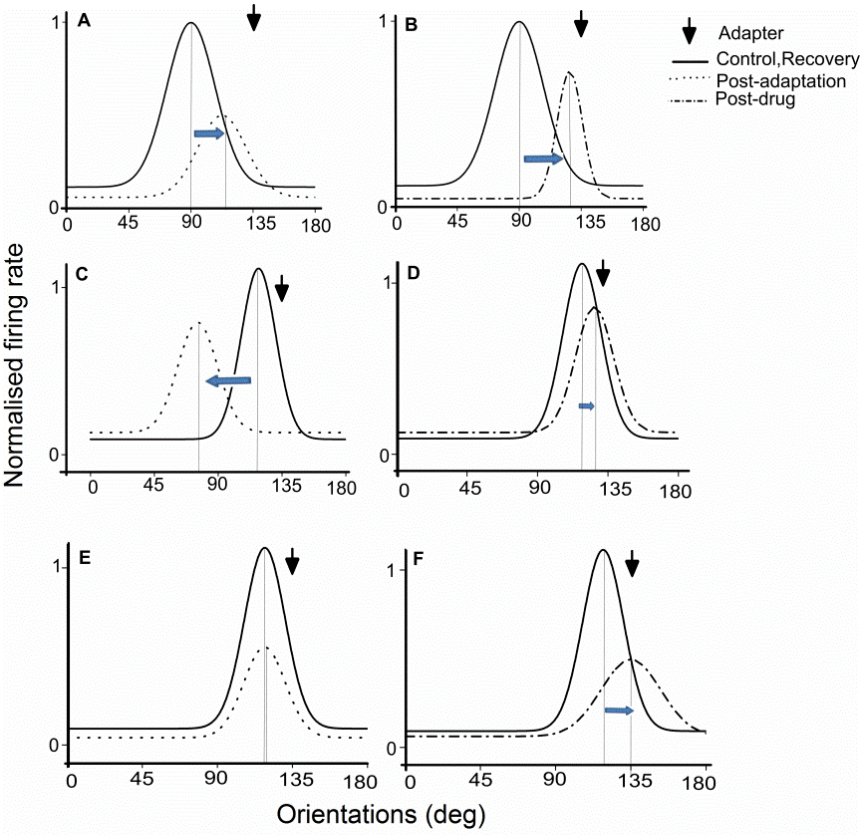

Figure 5.5

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 shift of the tuning curve (attractive shift). (B) 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) 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 shift of the tuning curve (repulsive shift). (D) 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) 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 below show a non-significant shift after the first adaptation. (F) 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 shifted toward the adapter in the presence of the drug.

5.5.3 Molecular mechanism of cortical plasticity and drugs pathways action

The studies on mammalian visual cortex have long been a field of discovery of mechanisms leading 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 derives from ancestral mechanisms occurs during development.

5.5.3.1 Molecular mechanisms of feed-forward plasticity

5.5.3.1.1 Glutamatergic receptors

Excitatory transmission is mediated by ionotropic glutamatergic channels receptor AMPA and NMDA, which contribute to regulating membrane depolarization and calcium permeability, through mGluR (metabotropic glutamate) receptors, which triggers downstream signaling cascades. Evidence exists that each of these receptor types may promote plasticity in visual cortex.

Frenkel *et al.,* 2006 (Frenkel *et al.,* 2006) have shown that a process similar to LTP (long-term potentiation) depending on NMDA receptor activation by repetitive activation leads to increased insertion of synaptic AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid)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 calcium intracellular level. Therefore, the excitatory transmission mediated by glutamate-gated NMDA receptor is affected. Evidence exists that during post-natal development the ratio NR2A / NR2B transit from low to height value. Decreasing this ratio promotes plasticity by affecting the threshold for LTP. Since, it was shown that ketamine blocks the NMDA receptors

(Chen *et al.,* 2009), yielding to a decrease of 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 become trapped (Beverly *et al.,* 1997). Because plasticity requires NMDA receptor activation, the deprivation decrease of this activity leads to a reduction in inhibition effect on plasticity. Contrary to the effect of ketamine, it was demonstrated that in adult rats, serotonin restores the NMDA- depending long-term potentiation. Metabotropic glutamate receptors are also involved in cortex plasticity independently of its subtype. It's worth noting that fluoxetine potentiates plasticity, by increasing glutamatergic synaptic transmission.

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, is significantly determined by AMPA receptor. Other finding shows that ketamine is a non- selective blocker of NMDA channel, it acts also on AMPA / Kainate receptors. Therefore, it seems that ketamine is a blocker of a 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 depressed the amplitude of fast EPSPs mediated by AMPA / Kainate receptor channels. In addition, ketamine increased the resting input resistance RI. In accordance with Ohm's law, small increases in cellular resistance outweighed 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 functional consequence is that the reduction of fast synaptic current attenuates depolarizing shifts that contribute to voltage dependent release of magnesium to achieve the threshold for NMDA receptor channels open states.

5.5.3.1.2 Calcium: a second messenger

Glutamate-gated AMPA and NMDA receptors regulate intracellular calcium level. As a second messenger, calcium activates many intracellular signaling cascades particularly three critical kinases (ERK: called ERK, extracellular signal-regulated kinases, PKA: protein kinase A, and ca MKII alpha: calcium/calmodulin-dependent protein kinase II alpha).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 CREB (C-AMP Response Element-binding protein).CREB levels mediate by visual stimulation decrease with age, showing the involvement of other pathways promote plasticity in the adult cortex.

5.5.3.1.3 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 BDNF (Brain-Derived Neurotrophic Factor) during monocular deprivation probably reduced the GABAergic transmission and reinstalled plasticity. 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 the same effect, it potentiates the BDNF-trkB signaling path. Hence, fluoxetine and serotonin promote plasticity in adult rodents.

5.5.3.1.4 Structural plasticity

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

Several studies show that agonists of adrenergic and cholinergic systems facilitate the onset of ocular dominance plasticity. 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.

Neuromodulators have an effect on plasticity possibly to their ability to modulate thresholds for LTP/LTD induction by modifying the intracellular calcium concentration via second messenger pathways. 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 on ocular dominance plasticity.

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

Adrenergic, cholinergic and serotoninergic systems are important for the basic 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 (Maya Vetencourt *et al.,* 2008) showed that the administration of fluoxetine restores ocular dominance plasticity to adults, possibly due to a correlative reduction in inhibition.

Learning that preferential orientation of neurons may change following adaptation or could be modified by the use of certain compounds underlines plasticity within the adult cortex and reveals a glimmer of hope in the face of various unfortunate 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, that we should more investigate.

5.6 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. Yet, there are missing links of knowledge with respect to unimodal sensory deprivation on the direct functioning of neighboring primary sensory areas and missing sensory modalities. Moreover, few cross-modal studies have opened gates towards the understanding of the interaction between multimodal sensory areas. Yet, 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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CHAPTER 6: CROSS-CORRELATION REVEALS SYNCHRONY WITHIN ADAPTED SUPRA AND INFRAGRANULAR LAYERS IN CAT V1

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6.1 Abstract

A characteristic feature of the visual cortex is its laminar organization. Each of these columns is divided into supra (upper) and infragranular (lower) layers wherein neurons have similar orientation selectivity. V1 neurons are highly plastic and change their orientation tuning peaks either towards or away from the adapter exhibiting attractive or repulsive shifts. Previous studies have shown in supragranular layers that following adaptation entire orientation map is re-organized, however no reports have shown in what way neurons in deeper layers form functional links with superficial layer neurons in response to adaptation. The cortical columns consist of layers and the extensive connectivity between these layers makes the cortical columns dynamic. We hypothesize that not only the neurons specific to a layer change their tuning properties, but neurons in the entire column connects functionally to process the adapter, leading to whole cortex reprogramming. To this aim, we simultaneously recorded layer 2/3 and 5/6 neurons in conventionally prepared anesthetized cats by lowering a multielectrode in V1 at depths of 300-500µm and 1000-1200µm. Cross-correlations were computed within and between the spike trains of neuron pairs of layers 2/3 and 5/6 to disclose functional connections between these layers and observe how adaptation affects this functional connectivity. Our data shows that the proportion of supra and infragranular layer neuron pairs exhibiting positive cross-correlations is relatively small. Conversely, neurons within the same layers show frequent positive cross-correlation. Furthermore, the mean strength of overall connections in all the three cases: within supragranular neurons, within infragranular neurons and between supra and infragranular neurons, remains the same. This suggests that connections between the supra and infragranular layer neurons are more specific and time correlated.

6.2 Introduction

Ever since the pivotal investigations of Hubel and Wiesel in 1962, it has been extensively established that the visual cortex is organized into columnar domains of orientation selectivity. A majority of neurons in a vertical column are selective to the same axis of orientation when presented within their respective receptive fields (RFs). When an electrode is lowered in the cortex in an oblique direction, the preferred neuronal orientation rotates systematically by about 16.5° for every 0.09 mm of the recording tip as it traverses orientation column to the next. Such a systematic sequence of columns predicts the subsequent orientation pattern (Blasdel & Salama, 1986; Blasdel, 1992). This organization depends on the notion that a columnar organization is an outcome of the segregated architecture of inter-neuronal connections leading to a relatively inflexible layout of the striate organization. For instance, neurons in the lateral geniculate nucleus (LGN) aligned along an axis connected to a single cortical cell give rise to the orientation selectivity. The structural organization of cerebral cortex rests on the six cortical layers that can be differentiated based on cell-types, circuits and functional selectivity of activity (Armstrong *et al.,* 1992; Thomson *et al.,* 2003; Douglas & Martin, 2004).

Coordinated activity across cortical layers critically underlies both local processing within cortical areas and directed interactions with other cortical and sub-cortical areas. The interlaminar circuitry of connections between neurons is highly complex. According to the most simplified version of the excitatory axonal projections and activations (Douglas & Martin, 1994; Douglas and Martin, 2004) layer 4 is the main recipient of thalamic sensory inputs that communicates the stimulus-evoked activity to supragranular layer 2/3, which in turn relay information to infragranular layers layer 5/6.

Lately, another model of evoked activity has been proposed that challenges the classical model. According to the latter, the thalamus directly projects sensory information to both layer 4 and infragranular layers (Constantinople and Bruno, 2013). It has also been shown that layer 5/6 cells respond to sensory stimulation

even before layer 2/3 neurons do (Thomson, 2010). Therefore, there is definitely an important role for infragranular layers in stimulus-evoked activity.

On adapting, neurons change their orientation tuning peaks either towards or away from the adapter exhibiting attractive or repulsive shifts (Dragoi *et al.,* 2000; Ghisovan *et al.,* 2009; Bachatene *et al.,* 2012). These are classic behavioral response towards the non-preferred orientation known as adapter.

In the sensory cortex, time correlated co-ordinated firing between neurons occurring at millisecond-scales leads to the formation of functionally emergent circuits (Singer, 1999; Barthó *et al.,* 2004; Fujisawa *et al.,* 2008; Buzsáki, 2010; Molotchnikoff & Rouat, 2012; Bharmauria *et al.,* 2014; Bachatene *et al.,* 2015). Depending on the organization of the selectivity of neurons for a specific feature, e.g. oriented stimuli in the primary visual cortex (V1), higher mammals exhibit a well-established columnar organization, wherein local neurons have differential selectivity for orientations (Harris and Mrsic-Flogel, 2013).

Cross-correlogram is an effective way to study synchrony between the neural spike trains (Perkel *et al.,* 1967, König *et al.,* 1995; Barthó *et al.,* 2004; Fujisawa *et al.,* 2008). Thus, we implemented cross correlograms within a ±5-ms quasi-synchrony window to explore functional connectivity within the neurons down the column. Using cross-correlograms, our lab has already shown that co-active neurons in layer 2/3 form cell-assemblies in response to differently oriented stimulus by framing a specific functional connectome in relation to a specific stimulus (Bretzner *et al.,* 2001; Duret *et al.,* 2006; Bharmauria *et al.,* 2012; Bharmauria *et al.,* 2015). We found that similarly tuned cells form functional connections and show positive cross-correlation. Layer 2/3 and layer 5/6 neurons synchronize their action potentials in response to the adapter and show sharp peaks straddling zero in cross-correlograms.

6.3 Materials and methods

6.3.1 Ethical approval

Electrophysiological recordings were performed in the area 17 of five adult domestic cats (Felis catus) of either sex. The animal surgery and electrophysiological recordings were performed in accord with the guidelines of the Canadian Council on Animal Care. The same were approved by the Institutional Animal Care and Use Committee of the University of Montreal. Animals were supplied by the Division of Animal Resources of the University of Montreal. Experiments were carried out by the guidelines approved by the NIH in the USA, the Canadian Council on Animal Care, and the Institutional Animal Care and Use Committee of University of Montreal (CDEA) regarding the care and use of animals for experimental procedures.

6.3.2 Anesthesia and surgery

Firstly, the cats were sedated with acepromazine maleate [1 mg/kg, intra-muscular (i.m.), Atravet; Wyeth-Ayerst, Guelph, ON, Canada] and atropine sulfate (0.04 mg/kg, i.m., Atrosa; Rafter, Calgary, AB, Canada). Then, the animals were anesthetized with ketamine hydrochloride (25 mg/kg, i.m., Rogarsetic; Pfizer, Kirkland, QC, Canada). When ready, a surgery was performed on the animals to prepare them for the stereotaxic apparatus. Anesthesia was maintained during the surgery with isoflurane ventilation (2%, AErrane; Baxter, Toronto, ON, Canada). Following surgery, cats were paralyzed by perfusion of gallamine triethiodide (40 mg/kg, intravenous, Flaxedil; Sigma Chemical, St Louis, MO, USA) and fixed in a stereotaxic apparatus. The cats were artificially ventilated with O_2/N_2O (30: 70) mixture containing isoflurane (0.5%). Paralysis was maintained by perfusion of gallamine triethiodide (10 mg/kg/h) in 5% dextrose lactated Ringer's nutritive solution throughout the experiment.

Lidocaine hydrochloride (2%; Xylocaine, AstraZeneca, Mississauga, ON, Canada) was injected subcutaneously as a local anesthetic during the surgery. A tracheotomy was performed for artificial ventilation. The cephalic vein in the forelimb was cannulated to insert the catheter for initiating an i.v. line. Xylocaine gel (5%; Astra Pharma, Mississauga, ON, Canada) was applied on the pressure points to reduce pain and sensation. Anesthesia levels were ensured throughout the experiment by monitoring the EEG, the electrocardiogram, and the expired CO_2. The end-tidal CO_2 partial pressure was kept constant between 25 and 30 mmHg. A heating pad was placed beneath the cat to maintain a body temperature of 37.5 °C. To prevent any bacterial infection, Tribrissen (30 mg/kg/day, subcutaneous; Schering-Plough, Pointe-Claire, QC, Canada) and Duplocillin (0.1 mL/kg, intra-muscular; Intervet, Withby, ON, Canada) were administered to the animals. A craniotomy (1 × 1 cm) was performed over the primary visual cortex (area 17/18, Horsley-Clarke co-ordinates P0–P6; L0–L6). The underlying dura was removed, and the electrode was lowered in area 17. The pupils were dilated with atropine sulfate (1%; Isopto-Atropine, Alcon, Mississauga, ON, Canada) and the nictitating membranes were retracted with phenylephrine hydrochloride (2.5%; Mydfrin, Alcon). Plano contact lenses with artificial pupils (5 mm diameter) were placed on the cat's eyes to prevent the cornea from drying (University of Montreal, PQ, Canada). The cats were sacrificed using a lethal dose of pentobarbital sodium (100 mg/kg; Somnotol, MTC Pharmaceuticals, Cambridge, ON, Canada) by an intravenous injection when the experiment was over.

6.3.3 Electrophysiological recording and Single unit isolation

Multiunit activity in the primary visual cortex was recorded using a tungsten multichannel depth electrode (0.1–0.8 MΩ at 1 KHz; Alpha Omega Co. USA Inc.). The recordings were performed in either hemisphere of the cat's brain. The electrode consisted of four microelectrodes in a linear array (inter-electrode spacing 500 μm) enclosed in stainless steel tubing. The signal from the microelectrodes was amplified, band-pass filtered (300 Hz–3 KHz), digitized, and recorded with a 0.05 ms temporal resolution (Spike2, CED,

Cambridge, UK). Recordings were done at an average cortical depths of 300–500 and 1000–1200 μm simultaneously from both sites.

The multiunit activity of neurons was recorded simultaneously from layers 2/3 and 5/6. Spike sorting was done offline using Spike2 package, CED (Cambridge, England) to isolate single units. The single units were discriminated based upon the spike waveforms, principal component analysis (PCA), and auto correlograms (ACG).

6.3.4 Visual stimulation and adaptation protocol

Stimulation was performed monocularly. After clearly detectable activity was obtained, the multiunit receptive fields (RF) were mapped by using a hand-held ophthalmoscope (Barlow *et al.,* 1967). Receptive field edges were determined by moving a light bar from the periphery toward the center until a response was evoked. Visual stimuli were generated with a VSG 2/5 graphic board (Cambridge Research Systems, Rochester, England) and displayed on a 21-inch Monitor (Sony GDM-F520 Trinitron, Tokyo, Japan) placed 57 cm from the cat's eyes, with 1024 × 768 pixels, running at 100 Hz frame refresh. Stimuli were drifting sine-wave gratings covering the excitatory RF (Maffei *et al.,* 1973). The receptive fields were located centrally within a 15° radius from the fovea. Contrast and mean luminance were set at 80% and 40 cd/m2, respectively. Optimal spatial and temporal frequencies were set at 0.24 cycles/deg and in the range 1.0–2.0 Hz (at these values V1 neurons are driven maximally) by sine-wave drifting gratings (Bardy *et al.,* 2006).

After manually mapping the receptive fields, eight different orientations were presented randomly one-by-one within the receptive fields of the neurons. Eight oriented sine-wave drifting gratings were presented in a random order ranging from 0° to 157.5° at regular intervals of 22.5°. Each orientation was presented in a block of 25 trials (each trial lasted 4.1 s) with varying inter-stimulus (1–3 s) intervals during which no stimulus was presented. Thus, the presentation of one oriented drifting grating lasted ~180 s (including all trials and inter-stimulus intervals). Once the control orientation tuning curves were

characterized, an adapting oriented stimulus (non-optimal orientation) was presented continuously for 12 min within the receptive fields of neurons. The adapting stimulus was a drifting grating whose orientation was chosen based on the multiunit activity values obtained at control conditions and was generally set within 22.5°–67.5° of the neurons' preferred orientations. No recordings were performed during this adaptation period. Immediately after the adaptation procedure, recordings were performed starting with the adaptor orientation and initially preferred orientation followed by recording of remaining orientations in a random fashion. Finally, the tuning curves were computed as below.

6.3.5 Data Analysis: Gaussian tuning fits and cross-correlation analysis

Once single cells were sorted out off-line from multi-unit activity accumulated during data acquisition, Gaussian tuning curves were constructed from raw data. We fitted our raw data with the Gaussian function to determine the precise preferred orientation of neurons. Then shifts in orientation preference were measured. We used the following Gaussian function:

where y_0 is the offset, X_c is the center, w is the width, and A represents the area under the Gaussian fit.

The shifts of peaks of tuning curves between pre- and post-adaptation conditions were calculated from the Gaussian fits using the following formula:

$$Shift = |Xc\ post - Xc\ pre|$$

where Xc is the central value derived from the Gaussian fit.

Cross-correlograms were computed between the spike trains of all the possible neuron-pairs at all the presented orientations to reveal the firing of one neuron (target) at a specific time-frame in relation to the firing of another neuron (reference). Then, bin counts were divided by the number of reference events to

normalize the counts per bin into probabilities. The bin-width was set at 1 ms. A statistical threshold of 95% for the significance of the bins was chosen and the probability of the neuron firing in a bin was computed as follows (Abeles, 1892).

Considering, the spike train is a Poisson train, the probability (P) of the neuron to fire in the small bin of the size b is:

$$P = F*b \text{ and } F = N/T$$

where 'F' is the neuron frequency,'T' is the total time interval, and 'N' is the number of spikes in that interval.

Raw CCGs were shift-corrected to eliminate the putative significant peaks due to the simultaneous stimulation of both cells (Perkel *et al.,* 1967). It is also to be noted that when two cells recorded from the same tip displayed synchronized their firing, their respective waveforms possibly will sum up. Therefore, the shape of the resultant waveform is rejected as it falls outside the range of the template. In the present case, 'synchrony' of spikes from the same tip is excluded from the analysis.

6.4 Results

The objective of the current investigation is to examine the functional connectivity between simultaneously recorded neurons from superficial and deeper layers when adapted. In the current study, 296 pairs of layers 2/3 neurons, 248 pairs of layers 5/6 neurons and 296 pairs of layer 2/3 and layer 5/6 were investigated from 20 recording sites. Neuron were classified into connected and unconnected pairs. Further, connected pairs were segregated into unidirectional, bidirectional and synchronized pairs. Neuron pairs that were untuned and unconnected have not been included to generate the figures.

6.4.1 Similar mean amplitude of shift observed in layer V and layer II-III neurons

Figure 6.1 shows a comparison of the mean amplitude of shift. Through this comparison, we wanted to see the orientation tuning change pattern within the superficial layers and deeper layers. The shifts have been further classified into attractive and repulsive. The results show a significant difference between layer 2/3 attractive and repulsive shifts as compared to layer 5/6. However, it is to be highlighted that mean amplitude for attractive and repulsive shifts across layers remains comparable.

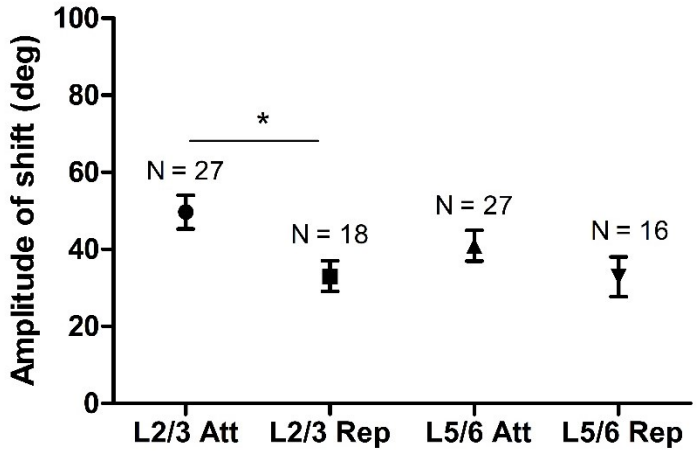

Figure 6.1

A comparison of the mean amplitude of shift of layer 2/3 and layer 5/6.

The mean of amplitude of shift L2/3 for attractive shifts was

found the highest (t-test, p-value = 0.0870, L2/3 Att vs L2/3 Rep)

6.4.2 Deducing the orientation selectivity among neurons of layer 2/3 and layer 5/6 by exploring the clusters

In this study, we define a cluster as a group of layer II/III and V/VI neurons recorded from the same site at the same time. The neurons in a cluster were analysed by plotting their orientation selectivity values at

control and post-adaptation conditions and calculating the means of the both followed by a comparison of the same. Clusters containing neurons which were untuned in control or post-adaptation conditions were not included in the figure generation. The colored sphere depicts neurons' orientation selectivity values. Red color displays values of orientation tuning for layer II/III neurons whereas green color displays layer V/VI neurons (Figure 6.2). The mean tuning of each cluster is shown at control and post-adaptation conditions. This analysis may suggest the global shift in tuning of simultaneously recorded layer II/III and layer V/VI neurons as a result of adaptation (Figure 6.2 A). The figure suggests that layer II/III and V/VI clusters were presumably closely tuned to an orientation before adaptation. Following adaptation clusters acquires a new orientation column tuning (Figure 6.2 B). In the clusters, neurons which are similarly tuned in both layers at control conditions approach the same orientation spread (range) post-adaptation. In few clusters, even if the neurons are not similarly tuned at the beginning they still achieve similar selectivity range post-adaptation. This reflects upon the tendency of layer II-III and layer V/VI neurons together to attaining new selectivity after 12 minutes of adaptation. This gives the suggestion of the whole orientation column acquiring the new selectivity.

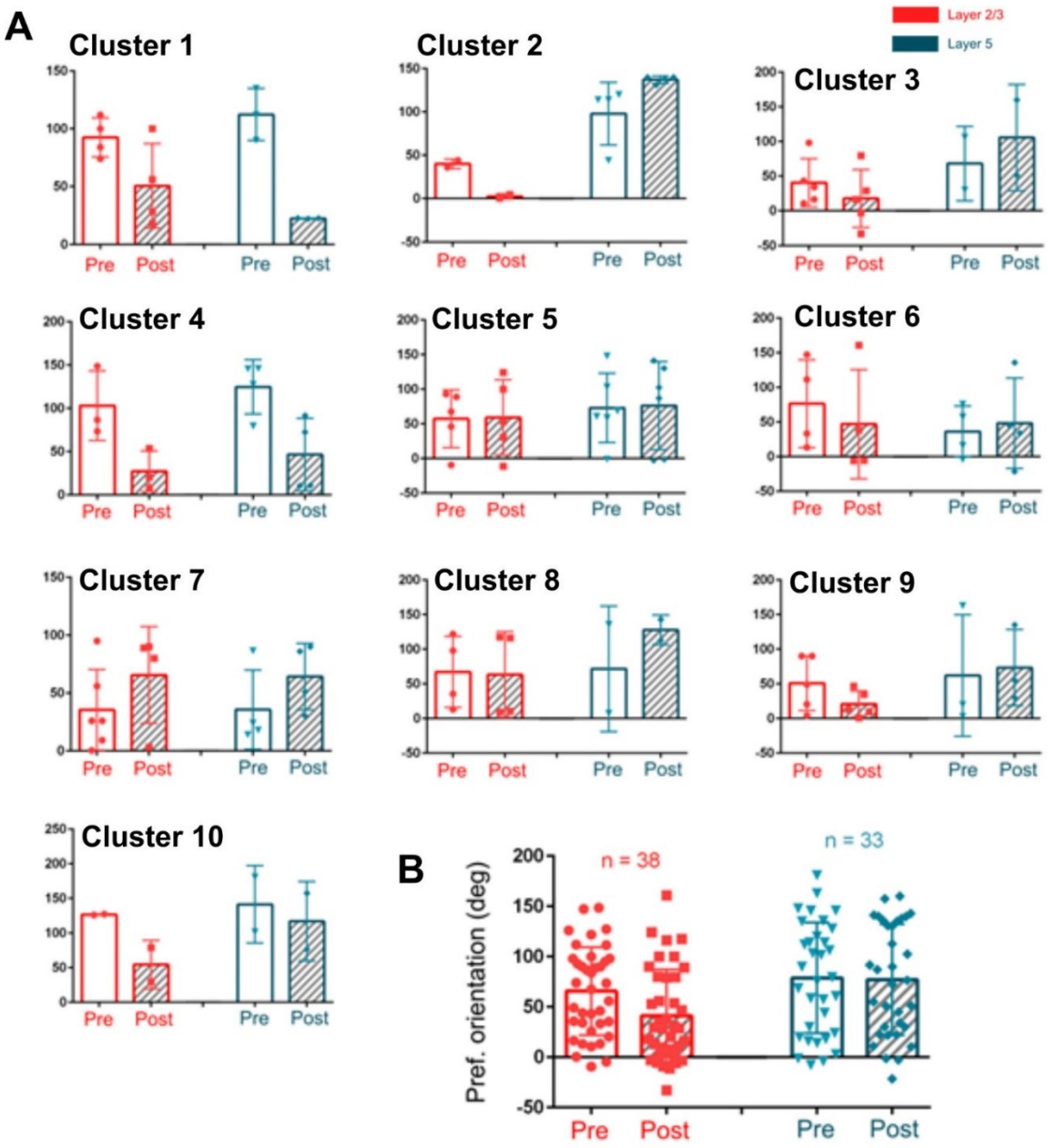

Figure 6.2

A graphical representation of the cluster analysis performed to examine the neurons in layer 2/3 and layer 5/6 (A) Each cluster refers to neurons simultaneously recorded from one electrode penetration down the column. Each cluster is broken down into individual neurons and their orientation tuning values

are plotted at control and post-adaptation conditions (B) Comparison of mean of preferred orientations at control and post-adaptation conditions for all clusters

6.4.3 Proportion of connections decrease following adaptation

Figure 6.3 shows functional connections revealed at ±5 ms in the cross correlogram. For layer II/III and layer V/VI the connections have been further differentiated into unidirectional and bidirectional. However, synchrony was ignored for the neurons recorded at same depth. A reduction in the proportion of bidirectional connections was found in layer II/III. Additionally, average number of intralayer and interlayer connections decrease signifying fewer connections. Furthermore, novel functional connections were found in layer V/VI.

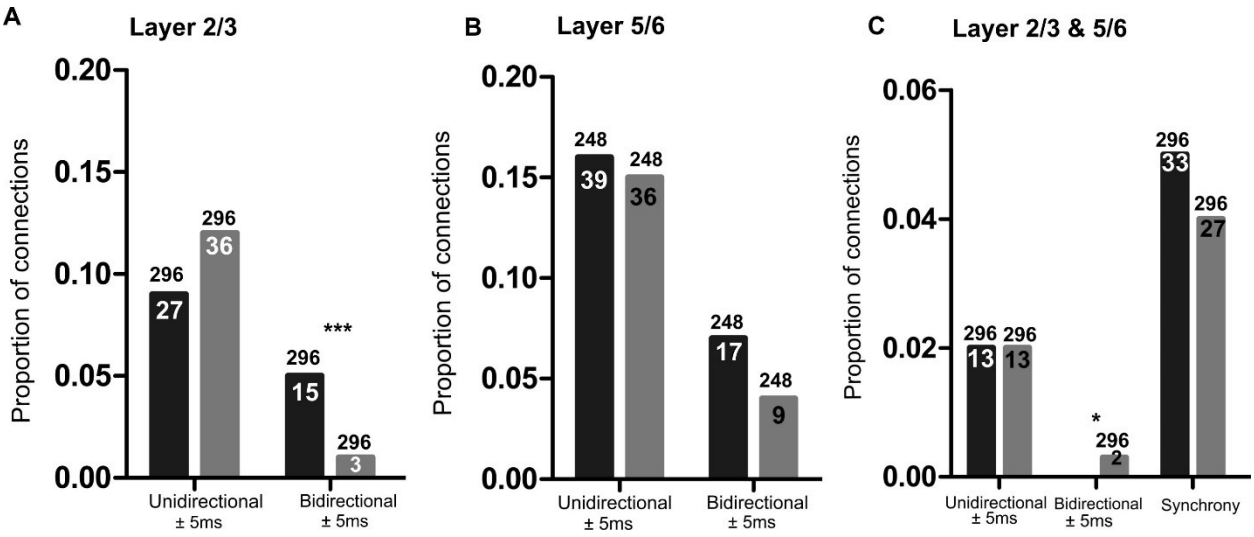

Figure 6.3

Proportion of connections at a time window of ± 5 ms classified into unidirectional, bidirectional and synchrony. (A) The ratio of unidirectional connections in layer 2/3 was found insignificant (z-test, P = 0.48) and bidirectional connections was found significant (z-test, P = 0.002) (B) The ratio of unidirectional (z-test, P = 0.53) and bidirectional (z-test, P > 0.05) connections in layer 5/6 was found insignificant (C) The ratio of unidirectional connections in layer 2/3 was found insignificant (z-test, P =

0.60) and bidirectional connections was found significant (z-test, P >0.05). The synchronized connections between layers was also found non-significant (z-test, P > 0.05)

6.4.4 Strength of connections in layer 2/3, layer 5/6 and between layer 2/3 and layer 5/6

Figure 6.4 shows comparison of the average probability of connection strength calculated by cross-correlograms. This value can be anything between 0 and 1. From the figure it can be observed that even though fewer connections exist between the neuron pairs of layers 2/3 and layer 5/6 (interlayer), the mean of strength of connections remains similar as no statistical difference is noted. This highlights the existence of a homeostatic interplay responsible for maintaining the overall balance in a V1 column.

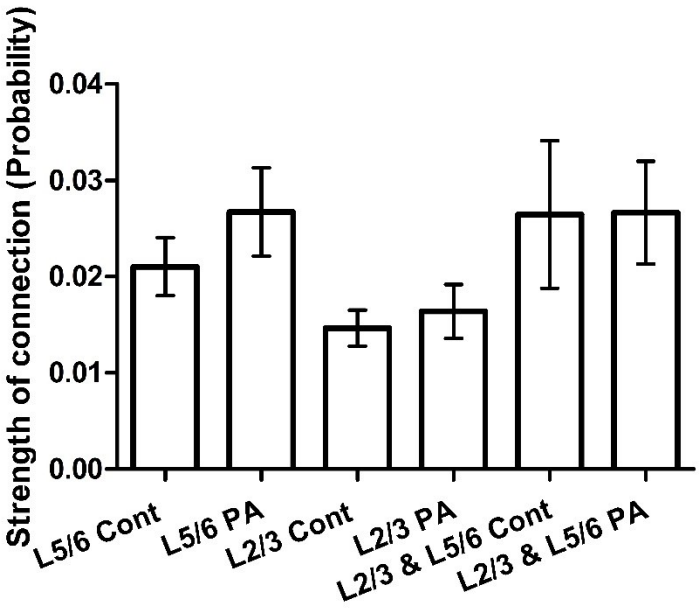

Figure 6.4

Strength of connections in layer 2/3, layer 5/6 and between layer 2/3 and layer 5/6

The strengths between all the six groups was found insignificant using repeated-measures ANOVA.

6.4.5 Typical example of a cross-correlogram between a layer 2/3 and layer 5/6 neurons pair

Figure 6.4 shows an example of cross-correlogram analysis of a layer 2/3 and layer 5/6 neurons pair before adaptation and after adaptation. The sharp peak at zero in the cross-correlogram indicates synchrony. This means that neurons firing is synchronised towards the stimuli. In part a it can be clearly seen that both cells of layer 2/3 make a positive cross-correlation with layer 5/6 neurons. This is depicted by the sharp peak above the confidence line (in red). These cell pairs have been recorded simultaneously and adapted with a 22° grating for 12 min. Following the adaptation process, the same pairs were observed at the adapting orientation i.e. 22°. The neuron pair still retained the peaks above the confidence line indicating positive cross-correlation.

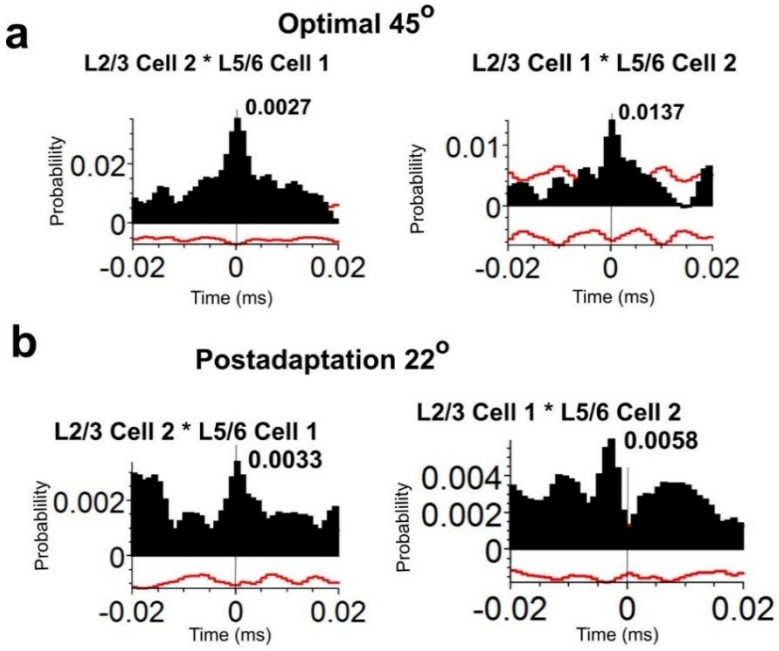

Figure 6.5

A typical example of a cross-correlogram between a layer 2/3 and layer 5/6 neurons pair. (a) Cross-correlogram between layer 2/3 and layer 5/6 neuron at their optimal orientation (b) Cross correlogram of the same neuron pair after adaptation at adapting orientation.

6.5 Discussion

In cats, V1 neurons are organised into homogeneous populations with similar response properties; yet, they exhibit abundant anatomical and functional connections with neurons in adjacent columns (DeAngelis *et al.,* 1999; Kisvárday *et al.,* 2000; Binzegger *et al.,* 2004; Stepanyants *et al.,* 2008; Martin & Schröder, 2013).

Synchronous spike trains within sensory systems have been known to play a key role in stimulus discrimination in the primary visual cortex (Samonds *et al.,* 2003), and are critical for inter-neuronal synaptic drives in vivo (Reid and Alonso, 1995; Alonso *et al.,* 1996; Reid, 2012; Denman and Contreras, 2014) as they provide highly efficient cues in establishing functional connections (Reid & Alonso, 1995; Reid, 2001). In cross-correlograms, the peak-position and the peak-strength quantify the time-correlated spiking of two neurons and reveal the level of functional connectivity between the two. Direct functional connections may be related to the increase in the firing probability of the target neuron in relation to the reference cell (Perkel *et al.,* 1967; Konig *et al.,* 1995; Bartho *et al.,* 2004; Fujisawa *et al.,* 2008; Reid, 2012; Bharmauria *et al.,* 2014; Denman and Contreras, 2014).

Stimulus features influence the correlation in firing between neurons (Gray *et al.,* 1990; Kohn & Smith, 2005; Ko *et al.,* 2013; Denman and Contreras, 2014). In columnar-organized cortices, neurons are clustered within cortical domains and connected. This connectivity is observed to be stronger between neurons sharing similar optimal tuning-properties (Alonso *et al.,* 1996; Csicsvari *et al.,* 1998; Alloway and Roy, 2002; Bartho *et al.,* 2004; Yoshimura *et al.,* 2005) and depends on optimal orientation and stimulus contrast (Kohn & Smith, 2005), stimulus direction (Bair *et al.,* 2001).

After adaptation, the impact of an applied orientation takes over the cell's excitability causing the emergence of a novel optimal orientation. This happens due to a specific excitatory drive, wherein one input

dominates over other inputs, thus, driving the synaptic strength above threshold that provides the cell its orientation selectivity.

In conclusion, neurons in a V1 column have numerous ways to harmonize the process of remembering the imprint of past stimulus and learning to respond to new imposed stimuli. These assorted changes in neuronal responses post-adaptation raise possibilities of existence of diverse courses which neurons choose to combat plasticity.

CHAPTER 7: GENERAL DISCUSSION

7.1 Methodological considerations

7.1.1 State of the animal

Anesthetized animals have been widely used as models to study the brain. Anesthesia affects the frequency of neuronal firing (Barth & Poulet, 2012). A study particularly relevant to sound adaptation experiments (Land *et al.,* 2012) revealed that isoflurane affects cross-modal processing in the visual and auditory cortices of mice. It was demonstrated that isoflurane hinders the inhibitory control of neuronal firing in the auditory cortex. This observation might complicate the conventional processing of auditory-visual projections. It is questionable that shifts in tuning curves reported in the present study are attributed to this phenomenon. We argue that the effects observed in the mentioned study (Land *et al.,* 2012) are due to an intentional modulation in the levels of isoflurane during the recordings. In the sound adaptation experiments, all the animals were prepared identically and, isoflurane levels were kept steady throughout the entire experiment.

7.1.2 Adaptation protocol duration

In our experiments, a continuous adaptation was performed for several minutes. Some authors argue that this kind of adaptation does not emulate natural conditions but employs stimuli of very short durations frequently presented to approach the conditions of natural visual fixations (Muller *et al.,* 1999; Patterson *et al.,* 2013). However, long adaptation is more potent in inducing plasticity and, consequently, stronger variations in neuronal responses. Others consider that response modulations of preferred orientations post-adaptation reveal after-effects (Benucci *et al.,* 2013). However, adaptation effects are constrained roughly around the original preferred orientation and the newly acquired orientation — responses at the original preferred orientation decline, while cells start responding to the novel optimal orientation with increased discharges (Dragoi *et al.,* 2000; Ghisovan *et al.,* 2009; Jeyabalaratnam *et al.,* 2013). Such dual effect is

difficult to reconcile with global aftereffects. Since after-effects are generally rapid (almost immediate), it unlikely produces the described changes in orientation selectivity following adaptation. As neuronal connections are dynamic, adaptation may lead to a transition of a neuronal network to a different equilibrium, reflecting new background conditions as a consequence of adaptation. For this reason, we believe that adaptive processes can be recorded either during or after adaptation.

Also, for the sound adaptation experiments, the choice of stimulus duration (12 min) could be of concern. It was essential that the stimulus we chose was able to stimulate the auditory cortex with varying frequencies for a prolonged duration that could further impact the visual cortex. Recent literature showing the effect of the auditory stimulus on visual neurons used a shorter length of sounds that only induced modulation of the firing rate. Hence, it became of utmost interest to detect responses of visual neurons in response to a longer duration sound. From the previous studies from our lab demonstrated that 12 min duration is enough to entirely change the tuning properties of neurons we used a sound stimulus for 12 min.

7.1.3 Spike sorting

The sorting of spikes from the multiunit activity is most crucial and initial part of separating neurons. Indeed, up-to-date technology allows researchers to isolate more than one neuron from a microelectrode. However, it is quite essential to determine the validity of a neuron because of the overlapping spikes and the bursting of neurons (Rey *et al.,* 2015). To further confirm that every sorted spike was unique, auto correlograms (ACG) and principal component analysis (PCA) were computed (Csicsvari *et al.,* 1998; Bartho *et al.,* 2004; Fujisawa *et al.,* 2008). No events at zero-time lag indicated by an empty period in the ACG authenticated the refractory period of a neuron, whereas the PCA analysis ascertained a separate cluster corresponding to a spike within a Mahalanobis distance of 2.5.

7.2 Visual adaptation in simultaneously recorded layer 2/3 and layer 5/6 neurons

In the first part of the investigation, it was revealed that simultaneously recorded layers 2/3 and layer 5/6 neurons exhibited comparable attractive and repulsive shifts amplitudes and values of orientation selectivity. Collectively, from the results by (Bachatene *et al.,* 2015c) and the results of the first part of this investigation (Chapter 3), we suggest that supra- and infragranular layer neurons change their selectivity in response to adaptation. Chapter 3 revolves around the interaction of supra-and infragranular neurons in a column. Further, this study also puts forth the implication of specific feedforward and feedback pathways between supra- and infragranular neurons that may be responsible for the reprogramming of orientation columns in V1 (Bachatene *et al.,* 2015c) as a result of functional associations.

Neurons in the primary visual cortex are fundamentally selective to stimulus properties such as orientation (Hubel & Wiesel, 1959; 1968). When presented with a preferred stimulus inside the receptive field of neurons, cells respond optimally. When presented with a range of orientations, it is characteristic to obtain an ideal Gaussian fit of the tuning curve for a neuron that reveals the preferred orientation. Such tuning properties are established during the critical period that follows birth (Chiu & Weliki, 2003; Tanaka *et al.,* 2009). Several studies have demonstrated that depending upon the duration of stimuli (frequent or prolonged presentation of a non-preferred orientation) induces modifications of the tuning curves of neurons (Dragoi *et al.,* 2000; Ghisovan *et al.,* 2009; Bachatene *et al.,* 2012b; Bachatene *et al.,* 2013; Jeyabalaratnam *et al.,* 2013; Cattan *et al.,* 2014; Bachatene *et al.,* 2015c). The non-preferred stimulus to which a neuron generally responds poorly is called a visual adapter, and the process of presenting this non-preferred stimulus to the neurons and training them to learn to respond to the adapter is referred to as adaptation. In other words, adaptation is a phenomenon of the ‘forced’ application of a non-preferred orientation (Krekelberg *et al.,* 2006). Following adaptation, the peak of a neuron’s tuning curve shifts either

towards the adapting orientation (attractive shifts) or away from it (repulsive shifts). Neurons could also stay unaffected to the adapter and resist a significant change. Similar results have been obtained for other features such as spatial frequency (Marshansky *et al.,* 2011) the direction of motion (Kohn & Movshon, 2004) and speed (Movshon, 1975).

Interestingly, nowadays it is acknowledged that the adaptation-induced plasticity occurs in adults too. Indeed, a fully mature brain can also undergo intense modification of tuning properties beyond the critical period just after birth. V1 neurons are selective for stimuli features such as orientation, spatial frequency, direction, and speed (Hubel & Wiesel, 1959; 1968; Movshon, 1975; Dragoi *et al.,* 2000; Kohn & Movshon, 2004; Marshansky *et al.,* 2011), but can modify their selectivity to functionally reorganize the visual cortex to an "adapted cortex" after stimulation. The primary visual neurons being organized into cortical domains exhibiting specific connectivity (Hubel & Wiesel, 1959; Stratford *et al.,* 1996; Yoshimura *et al.,* 2000). Visual training acts on the spiking activity of neuronal populations (Dragoi *et al.,* 2000; Kohn & Movshon, 2004; Ghisovan *et al.,* 2009; Bachatene *et al.,* 2012b; Bachatene *et al.,* 2013; Patterson *et al.,* 2013) and dynamically modulates the functional interactions between neurons. The primary visual cortex can recalibrate its input towards the adaptation process and reconfigure information processing. This reorganization of neuronal connections results in modified neuronal connectivity after an experience that facilitated the plasticity (Fahle, 2004). Many studies demonstrating neuronal connectivity have shown that neuronal coupling is related to the stimuli preference of neurons. Neurons sharing similar preferred features exhibit heightened connectivity (Stepanyants *et al.,* 2008; Ko *et al.,* 2011). In the primary visual cortex, cells sharing similar orientation selectivity are grouped into orientation columns, and neurons in the column can be evoked by a feature (Hubel & Wiesel, 1959; 1968; Csicsvari *et al.,* 1998; Alloway & Roy, 2002; Bartho *et al.,* 2004; Yoshimura *et al.,* 2005). Therefore, following a plastic modification, the neurons change their selectivity (Dragoi *et al.,* 2000; Ghisovan *et al.,* 2009; Bachatene *et al.,* 2012b) and the cortex is reorganized (Dragoi *et al.,* 2000; Godde *et al.,* 2002). However, the mechanisms underlying the specific

circuitry between simultaneously recorded layer 2/3 and layer 5/6 neurons following visual adaptation are yet unknown.

7.2.1 How layer 2/3 and layer 5/6 neurons work in parallel with each other?

In the past, numerous studies have mostly focused on investigating the effects of visual adaptation on layers 2/3 neurons (Dragoi *et al.,* 2000; Bachatene *et al.,* 2013; Jeyabalaratnam *et al.,* 2013; Cattan *et al.,* 2014; Bachatene *et al.,* 2015c). To the best of our knowledge, there is only one report (Dragoi *et al.,* 2000) demonstrating recordings between depths 500 and 1500 µm of cortical column. The recorded neurons also displayed a shift in orientation tuning in response to the adapter. However, no report has simultaneously explored the effects of adaptation on layers 2/3 and 5/6 neurons. Considering the extensive connectivity (Jiang *et al.,* 2013; DeNardo *et al.,* 2015; Lee *et al.,* 2015) between supra- and infragranular neurons and column descending from layer 2/3 to layer 5/6 we hypothesized that adaptation leads to complete cortex reorganization. Therefore, it is of interest to simultaneously examine the effects of adaptation on both layers 2/3 and 5/6.

In this part of the thesis, we revealed that infragranular layers 5/6 neurons also show these classical shifts in orientation selectivity in comparison with layers 2/3 neurons towards adaptation. It is generally observed that neurons recorded from a microelectrode modify their orientation selectivity in a similar direction because they share stimulus-response properties. Dragoi and co-authors (Dragoi *et al.,* 2000) have shown that neuronal shifts are independent of cortical depth. Through anatomical pieces of evidence, it can be suggested that neurons sharing orientation preference are mostly connected and are present in close vicinity in the orientation domains. Whereas neurons situated closer to pinwheels are connected with neurons having a wide range of orientation preference (Maldonado *et al.,* 1997; Schummers *et al.,* 2004). Supragranular and infragranular neurons were recorded simultaneously using an electrode that penetrated the orientation columns parallelly. It was observed that a group of neurons recorded from an electrode penetration (cluster) displayed specific properties. For example, some clusters (~40 %) exhibited

homogeneous behaviour showing only attractive shifts, whereas others behaved heterogeneous (~60 %) by displaying both attraction and repulsion. This observation explains the significant variance of the shift amplitudes. The OSI was comparable for both layers 2/3 and 5/6. The dynamic changes of individual cells during adaptation mechanism may explain the need of only a few neurons that can encode the occurrence of events in the environment, and this plasticity may be a fundamental property of the cortical function.

In conclusion, neurons in an orientation column share stimulus properties and mostly respond in a similar pattern towards visual adapter. The cortical column is considered as the functional unit of the visual cortex. Because of the imposition of the adapter for a prolonged duration, neurons in a column collaborate and act together in harmony in the cortical column. During the adaptation process, a tilt effect is observed from one orientation column to others. Due to this tilt effect down the column, the whole cortex is systematically reprogrammed during the adaptation process.

7.2.2 Adaptation mechanisms

The possible underlying mechanism of adaptation is based on the transient changes happening at the synapse level. These changes are dependent on the duration of adaptation (Kohn, 2007; Ghisovan *et al.,* 2009). In general, adaptation involves a decrease in response to the initially preferred orientation and an increase in the response toward the dominant orientation. The decrease in the firing rate following adaptation is attributed to the change in membrane properties of V1 cells such as hyperpolarization (Carandini & Ferster, 1997) or synaptic depression or slow hyperpolarizing of Na^+ channels (Sanchez-Vives & McCormick, 2000; Sanchez-Vives *et al.,* 2000a; b). The ratio of inhibition and excitation creates and maintains the equilibrium by recurrently modulating the response gain in local cortical circuits (Ben-Yishai *et al.,* 1995; Douglas *et al.,* 1995; Somers *et al.,* 1995). Other disinhibitory mechanisms may also be implicated in maintaining homeostasis during the adaptation process. A neuron's single dendritic branch receives synaptic inputs from differently tuned neurons. This triggers a response in the neuron to a wide range of inputs by making synaptic associations. The recurrent dominant input drives the corresponding

synapses that eventually initiates a new optimal selectivity for the neuron (Jia *et al.,* 2010; Bachatene *et al.,* 2013; Wertz *et al.,* 2015). Thus, an adjustment between the excitation and inhibition following the adaptation duration facilitates the neurons to acquire a new selectivity. Regarding the direction of shifts, a proper explanation is revealed in the literature. The repulsive shift is a consequence of a default reaction towards adaptation whereas an attractive shift is the outcome of a differential decrease in response to the initially preferred orientation, while orientations far from the adapter in the tuning curve remaining relatively unchanged. Therefore, attractive shifts are the outcome of dual modulation of responses, a push-pull mechanism that simultaneously diminishes reactions to the original preferred orientation and increases neuronal discharge to the orientations close to the adapter. Consequently, the final response obtained is an amplification of ratios of excitatory and inhibitory inputs. As similar results are observed in supra- and infragranular layers, it is reasonable to conclude that in both layers excitatory and inhibitory populations share same mechanisms (Kohn & Movshon, 2004; Ghisovan *et al.,* 2009). Moreover, the excitatory and inhibitory loops are also implicated in the recalibration of neuronal selectivity (Froemke, 2015; Froemke & Schreiner, 2015).

The classical pathway of neuronal information in the visual cortex initiates at layer four neurons which are the receiving ends of the information coming from the thalamus (LGN). Then layer 4 neurons pass the information to layers 2/3 neurons. Furthermore, the information is conveyed to infragranular layers 5/6 neurons (Kapfer *et al.,* 2007; Otsuka & Kawaguchi, 2009; Apicella *et al.,* 2012; Jiang *et al.,* 2015). Additionally, several studies demonstrate that there is extensive anatomical connectivity between layers 2/3 and 5/6 neurons (Lowenstein & Somogyi, 1991; Thomson & Bannister, 2003). Therefore, the existing inter-neuronal relationships between the layers of the cortex lay the foundation for modification of orientation tuning.

7.3 How prolonged auditory stimulation can affect the primary visual cortex neurons?

In this part of the investigation, it was revealed that a non-visual input induced an entire shift of orientation tuning that can be firmly attributed to the repetition of sound stimulus for 12min. As a result, a pattern of response enhancement and suppression was observed that brought about the change in the orientation tuning properties of individual neurons in supra and infragranular layers of V1. The results indicate that supra and infragranular layers of V1 function together but as distinct compartments towards the sound stimulus and dynamically integrate embedded representations of a non-visual stimulus. Besides being a reminiscent of the remarkable plasticity of visual neurons this part of the thesis is suggestive of the multisensory properties of the visual neurons.

The cortex remains intriguing. Despite years of investigation, both the purpose and underlying principles of the cerebral cortex are unclear. It is still mystifying how neurons in different neighbouring regions, can engage together and change the properties of the neurons. It is the robust yet fragile combination of both the cellular properties and architecture of the cortex that suggest a powerful functioning of the cortex. Sensory cortices respond fundamentally to the domain-specific information through their primary routes. However, sensory cortices may often process information from the other sensory area via cortical feedback and top-down pathways (Ghazanfar & Schroeder, 2006). These interactions between different sensory cortices seen explicitly in the primary visual cortex, challenge the classical theory of restricted multisensory processing to only higher cortex (Iurilli *et al.,* 2012). Auditory and visual cortices are often used as models to understand the multisensory function of the cortex. Instead of extensive experimentation in this area, it is not revealed completely how sensory areas display multisensory effects. There could be many reasons behind the multisensory association between the auditory and visual cortices. The function of multisensory representation in the visual cortex could be assumed to facilitate efficient

perceptual processing for optimized response. The processing of embedded representation in the auditory signals suggests that besides the spatial localization of auditory signals in the visual cortex, auditory representations also help to anticipate the type of visual input (Vetter *et al.,* 2014). Recently, a relevant mechanistic theory of how the active dendritic properties of pyramidal neurons provided an insight into audio and visual signals interaction in V1 (Larkum, 2013). Also, it is assumed that some early visual cortex activity might be of assistance to perception other than just function. It has been observed that when human subjects sleep or daydreams, we still observe activation patterns in the early visual cortex, but this activation alone cannot be understood to facilitate perception. Thus, it could be suggested that the early visual cortex is a privileged area serving internal visual representations and that other senses such as audition can modulate this.

Indeed, from the mentioned literature we got an insight into the processing of sensory information across different species but cats. The question remains unanswered in cats whether visual neurons can respond to a repetitive auditory stimulus. These results introduce another dimension to understanding the audio-visual communication in the cortex. The observations made by recent investigators to understand cross-modal plasticity involved a slight modulation of the firing rate of neurons (Iurilli *et al.,* 2012; Ibrahim *et al.,* 2016). These observations were done in mice where the cortical organization is 'salt and pepper.' Whereas in our investigation in cats, we observed a much more intense response-change in our data, wherein V1 neurons experienced a complete shift in their orientation preference. Here, the non-preferred stimulus traditionally referred to as visual adapter is completely absent and is replaced by exposure to a sound stimulus imposed in isolation for several minutes uninterruptedly. Since orientation selectivity is an inherent property of visual cortical neurons and is established at the cortical level, the thalamic inputs are aligned upon the cortical recipient neurons, the changes of orientation selectivity are unlikely to happen at thalamic levels. Therefore, the repeated stimulation in the present study facilitated visual neurons in surpassing a threshold that may be was required to trigger substantial visual input to reach V1.

Mechanistically, it is quite logical since layer 2/3 of V1 constitute of pyramidal neurons that receive direct inputs from the auditory cortex. In addition, from the visual adaptation studies from our lab, 12 min time has been proved enough to modify the tuning properties of a neuron.

Similarly, in the present study, 12 min time was enough to encode the raw embedded visual representations within the audio stimulus. It has been known for many years now that visual cortex is a stimulus-driven structure (Doron *et al.,* 2002; Izraeli *et al.,* 2002; Piche *et al.,* 2007; Chabot *et al.,* 2008). The non-visual information in the stimulus can transmit from non-visual sensory structures to the visual cortex by direct corticoccipital pathways and circumvent the higher order cortex.

Further, in this situation, the nonvisual signals do not undergo a modulation but only translate the stimulus-driven information. Xu and co-authors (Xu *et al.,* 2012) suggested that functional mixing of inputs from two different sources could allow for facilitative non-linear interactions within individual dendrites that may lead to the bias towards horizontal orientations. This non-linearity may clarify a preference towards the horizontal orientations. Therefore, an evident response bias towards horizontal orientation for layer 2/3 neurons was observed unlike in layer 5/6.

7.3.1 Possible mechanism of auditory modulation in primary visual cortex

The critical question of how sound mechanistically changes remain unanswered in cats. However, studies from other animal models will be discussed here to help build the possible underlying mechanism in cats. Also, the communication between functional auditory responses and their representations in the early visual cortex is unknown. Therefore, this thesis is a significant contribution in developing ideas to explore in this direction and strategizing the ideas to design protocols. Few studies in rodents offered insights into the auditory driven embedded information carried by the visual responses. Larkum and authors in 2013 (Larkum, 2013) demonstrated the dendritic gating of inputs to pyramidal neurons by feedback pathways. Collectively, the rodent data extensively lead to the fact that layer 5 neurons are involved in this sort of computation. The feedforward and feedback inputs arrive at discrete compartments of layer 5 pyramidal

neurons. The apical dendrites of layer 5 neurons receive the feedback and are critical for context-dependent gating of feedforward inputs. In somatosensory cortices, long-range feedback input to layer 1 has been found. The inputs are found near a second spike initiation zone, supporting calcium spikes, in the apical tuft of layer 5 pyramidal neurons of sensory cortices (Schiller *et al.,* 1997; Larkum & Zhu, 2002; Kuhn *et al.,* 2008) and suggest triggering top-down control on sensory processes. Contingent upon the fact that the second spike initiation zone receives coincident depolarization and a back-propagated spike from the cell soma, Ca^{2+} spikes triggering at the top of the apical dendrite, can transform a single somatic output spike into a 10 ms burst containing two to four spikes (Larkum *et al.,* 2001). This concludes that both dendritic tuft and somatic inputs are critical for the strength of feedback that can generate cell bursts. This interplay of feedforward and feedback signals integrated within individual pyramidal neurons (Larkum *et al.,* 1999) projects an idea of how the sensory cortices strategize to process the internal representations of real-world stimuli. Further, it is difficult to gain next level understanding into mechanisms about auditory modulation in the visual cortex since there are no investigations that record visual cortical neurons with visual inputs arriving at the soma and auditory-driven feedback to the tuft dendrites).

As mentioned before, presumably auditory modulation of visual cortex occurs via feedback inputs. Feedbacks could be initiating at auditory cortex to the early visual cortex onto the apical tuft dendrites in layer 1 of the early visual cortex. In mouse, such feedback-modulated circuits for perception have been observed between mouse motor and somatosensory cortices (Manita *et al.,* 2015). These projections between the two cortices also suggest that longer range connections between the auditory and visual cortices could conceivably support a similar process. This seems accurate since we also observed a stronger response in superficial layers of the cortex (layer 2/3) rather than layer 5/6 neurons. It was observed in our data that layer 2/3 neurons exhibited a response bias towards horizontal orientations after sound was presented. Of course, the reason for preference is not these feedbacks but if the response change index in compared, it is evident from the results that layer 5/6 experienced less response change than layer 2/3

neurons. Other questions concern the presence of such a mechanism in primates (especially humans). There is a definite need for advanced technologies and suitable paradigms, yet this thesis initiates new questions and unveils a new understanding in the audio-visual recognition. Most importantly, in the present study, the constant feedforward input was missing because of the absence of the visual adapter therefore how top-down signals in visual cortex function in the lack of feedforward input?

7.3.2 Circuits and mechanisms underlying cross-modal plasticity

The auditory adaptation of visual neurons; this part of the thesis was performed in the complete absence of visual input. Considering that cross-modal processing has generally been observed in the deprivation of a sensory system, our experiment set up to an extent emulate this aspect of processing. Therefore, it is essential to discuss. In our experiments, for a prolonged duration visual stimulus was cut off during the 12 min while only the sound was being presented to the visual neurons. Consequently, it is important to consider how cross-modal plasticity may be brought about shifts in the tuning curves of the neurons. Recent studies show that a primary sensory cortex can be under inhibitory (Kawashima *et al.,* 1995; Woodruff *et al.,* 1997; O'Leary *et al.,* 2002; Petkov *et al.,* 2004; Johnson & Zatorre, 2006) or excitatory cross-modal influence.

While the phenomenon of cross-modal plasticity has been known for some time, the circuit and signalling mechanisms underlying the concept remain largely unknown. The early blinds have thicker visual cortices as compared to the late blinds, suggesting reduced trimming during the critical developmental period (Jiang *et al.,* 2009). Whether this reflects intra- or intermodal connections is unclear, as they could not be differentiated. Dynamic modelling of fMRI, an indirect method of linking activity across brain regions, has supported direct auditory-visual intracortical connections (Klinge *et al.,* 2010). However, another study suggested indirect intracortical connections as the primary pathway for somatosensory-visual interactions (Fujii *et al.,* 2009). Animal studies provide support for peculiar structural connectivity after sensory deprivation. Early bilateral retinal ablation in monkeys (Rakic *et al.,* 1991) and

opossums (Kahn & Krubitzer, 2002) leads to a novel cytoarchitectonic area between primary and secondary visual cortices with a unique laminar structure and neurons that respond to auditory and somatosensory stimuli. Animals that are anophthalmic (Doron & Wollberg, 1994; Laemle *et al.,* 2006) have aberrant projections from subcortical auditory structures to the visual cortex, although this claim is sometimes disputed (Chabot *et al.,* 2008). Retinal projections rerouted to thalamic somatosensory (Frost & Metin, 1985) early in life form functional visual maps in primary somatosensory or auditory cortex.

Similarly, congenitally deaf mice have retinal projections to auditory thalamus and brainstem (Hunt *et al.,* 2005). In these studies, it is unclear if cross-modal projections are initially present and later pruned with normal visual experience or whether ectopic outgrowth occurs due to a lack of coherent visual activity. Very few anatomical studies support the prior idea. Cross-modal connections have been found between auditory and visual cortices in kittens reared in a normal light environment (Dehay *et al.,* 1988; Innocenti *et al.,* 1988). This input is pruned to low but still existent levels in adulthood (Hall & Lomber, 2008). In rats, a transient connection between auditory thalamus and primary somatosensory cortex has been reported, and which could be stabilized by whisker deprivation (Nicolelis *et al.,* 1991). Using enucleated mice as animal models, several studies have pointed out that there are direct as well as indirect pathways between visual and auditory cortices (Chabot *et al.,* 2007; Chabot *et al.,* 2008; Laramee *et al.,* 2011; Charbonneau *et al.,* 2012).

In conclusion, contrary to the traditional functional descriptions of V1 that are based only on visual processes, a part of this thesis demonstrated how auditory signals could modulate processing in V1 in healthy animals too. This part of the thesis also revealed that besides performing modality specific tasks primary visual cortex also exhibits multisensory properties when evoked indirectly. Our results are highly suggestive of cross-influence between primary visual cortex and primary auditory cortex. Our results may serve as a key contribution to strategize future experimentation in this direction.

7.4 What can we learn from the comparisons between 12 min of visual and 12 min of auditory adaptation of primary visual neurons?

Adaptation phenomena are widespread in the sensory systems and each sensory system reacts specifically to the adapting stimulus. Fundamentally, the visual cortex has been considered as a stimulus-driven structure, i.e., depending upon the input, sensory modality displays varied responses. Interestingly, recently animal and human studies have unveiled that the visual cortex responds to non-visual stimuli too. Primarily, it was commonly observed in individuals with congenitally visual deprivation indicating the supramodal nature of the functional representation in the visual cortex. However, recently this has come up as a common phenomenon during experimentation to explore multisensory properties of the cortex and cross-modal processing of the stimuli in the cortex.

It has been reported from visual adaptation studies that on imposing a non-visual stimulus or visual adapter, the tuning properties of the visual neurons could be modified for a duration of time. Considering the columnar architecture of the primary visual cortex (V1) we tested the responses of neurons in layer 5/6 in comparison to layer 2/3 neurons in response to 12 min visual adaptation. Many times, it has been suggested that columnar organization is a processing unit rather than an anatomically based structure. A recent study by (Bachatene *et al.,* 2015c) brought up a fundamental observation regarding the process of visual adaptation in the hyper column. During the adaptation process for a duration, neurons in V1 or area 17 shift the peak of their orientation tuning curve either in the direction of the adapter (attractive shift) or away from the adapter (repulsive shift). Based on the direction of the shift, the newly acquired optimal orientation presents a two-fold problem. The new selectivity acquired by the adapted neurons following the adaptation process may be represented twice inside the hypercolumn. Therefore, the emergence of a novel preferred orientation creates an orientation hole since the original axis is now deleted.

Consequently, an array of questions arise that without-a-doubt insist on revaluating the processing inside the hypercolumns at the adapted and non-adapted sites. They strongly suggested that orientation selectivity is a rapidly variable feature that is adjusted by the behaviour of specific neurons surrounding the tested neurons. Most importantly they concluded their remarks by saying that orientation columns are beyond their anatomy and are functionally dynamic units. In the first part of this thesis where visual adaptation experiments were done, and neurons were recorded from adapted layer 2/3 and layer 5/6 neurons simultaneously it was observed that neurons in a column behave similarly and produce tuning curve attractive or repulsive shifts depending upon the direction from the adapter. In the third part of the thesis where auditory stimulation experiments were performed, the shifts could not be categorized as attractive or repulsive due to the absence of visual adapter. However, a shift in the tuning curve was observed in a large proportion of neurons. This indicates that visual neurons can respond to a variety of sensory stimuli. To conclude this result showed that visual neurons process both visual and non-visual information and display multisensory properties.

In the visual adaptation study, ~14% of the total neurons deflected away from the adapter and showed repulsive behaviour. Further, ~ 5% of neurons refracted the visual adapter meaning neurons that did not display a significant shift in the orientation tuning following adaption. Bachatene and co-authors (Bachatene *et al.,* 2015c) demonstrated that within the dynamic interplay of neurons experiencing adaptation, neighbouring neurons might wire together to shift their responses in conjunction with each other toward the adapter whereas a minority may deflect away (repulsion) to participate in the conservation of the columnar dogma. In another opinion article (Bharmauria and Bachatene, 2016), the authors explained that neurons showing refractory behaviour set the reference for the adapted cells to undergo the adaptation and return to their original optimal orientation once the adaptation effect diminishes. It is due to this reference set by refractory neurons; other columns would systematically tilt to following the adjacent column eventually without leaving an orientation hole. Thus, repulsive neurons hold equal importance as

attractive neurons in response to visual adaptation. In the sound adaptation experiment, visual neurons are continuously stimulated by an auditory adapter that does not provide any visual stimulation.

Not even 1% of the neurons were found showing refractory behaviour. Since the visual adapter was completely absent, there was no need to have a set reference to process the tilt effect and to return to original optimal selectivity once the adaptation paradigm is over. However, the surprising observation was that even though visual neurons in the sound adaptation experiment did not have any set reference, most neurons recovered back to their original optimal state. Thus, the whole concept of the domino effect as an underlying principle of visual adaptation is left unexplained. This comparison raises the question of whether visual cortex follows any fundamental guiding principles related to specific processes. Also, another important observation was made. The visual cortex neurons are perhaps extremely plastic, more than they have been yet explored. The visual cortex responds accurately to the type of inputs provided. In other words, it seems that visual cortex evokes a customized response for every input stimulus. A study in monkeys (Shtoyerman *et al.,* 2000) revealed that orientation columns are perhaps a functional structure rather than anatomical. It seems to be initially constructed by parallel segregation of input fibres originating from the retina, and then from the lateral geniculate nucleus (LGN). These results may appear intriguing since orientation columns in the visual system are thought to be relatively stable after the critical period. Overall, it may be concluded that the visual cortex functions in a myriad of ways to process external signals.

Further, the most striking observation was the bias towards horizontal orientations in the visual neurons when adapted with sound. Layer 2/3 neurons showed a clear bias towards horizontal orientation after experience with the sound. This was not observed in layer 2/3 neurons when adapted with the visual adapter. This suggests that visual cortex is implicating novel pathways to process the auditory stimuli which are different from the mechanisms employed to process visual adaptation. This suggests that layer 2/3 and layer 5/6 neurons show a unique response pattern due to functional wiring of neurons towards the processing of adapter and behave as separate units in response to an adapted stimulus.

Collectively, all the observations reflect upon the mystic nature of the cortex and highlights that individual cortical neurons hold the capacity to undergo modification and process the imposed stimulus. Undoubtedly, this discussion raises many relevant points related to cortical sensory processing that can further be explored.

CHAPTER 8: FUTURE DIRECTIONS

Although numerous studies have highlighted the multisensory nature of the cortex, there remains a need to determine the exact mechanisms underlying the multisensory aspect of the cortex and how primary areas interact in different stimulus conditions to generate a structural change that ultimately leads to behavioural change.

Through this thesis, we have tried to understand the response of individual neurons in primary visual cortex towards different sensory stimuli. Our results suggest that visual cortex can process a visual stimulus as well as an auditory stimulus that highlights the potential multisensory nature of primary visual cortex.

To gain in-depth knowledge, a similar protocol, presenting the same sound but for different time durations would be ideal for exposing the underlying mechanistic details of the sound impacting V1 neurons. Similar experiments could be repeated on rodents (salt and pepper primary visual cortex) to compare the results across species. Moreover, a non-repetitive sound could also be introduced to the protocol to observe if there is a difference in response. Certainly, external factors govern the dynamics of the cerebral cortex. The type of incoming stimuli accompanied by the strength of its stimulation is crucial for developing plasticity.

This thesis indeed evokes many potential experiments that may unveil new characteristics of visual cortex by merely changing the outside environment.

In future, application of high-resolution approaches such as intrinsic optical imaging and fMRI in conjunction with electrophysiological techniques would be necessary to elucidate various roles (unimodal and multimodal) of sensory areas in the cerebral cortex. Using laminar fMRI, the fundamental mechanisms and the neuronal pathways underlying multisensory interaction and interareal communication can be

investigated in the human brain. This is highly relevant as predictions from different animal models can not be directly applied on human brain as there may be differences across species that exist. It will be important to combine laminar fMRI with standards that combine the information of behavior e.g if supragranular layers of V1 do mediate the integration of information from other senses (e.g. A1), the modulation of fMRI activity in supragranular V1 should be exploited to develop protocols that will help to understand interareal communication.

In summary, it is now possible to move beyond a simple description of cortex in terms of individual neurons and the connections between them for richer understanding of features of the cortex specially the compartments spanning several layers. There is a considerable knowledge of properties of neurons in each layer to be understand their dendritic properties and interactions with the location of synaptic inputs. In future, using different techniques, it is essential to investigate the synaptic features of neurons in each layer in order to understand the layering of the cortex and how sensory cortex interacts with each other.

CHAPTER 9: CONCLUSIONS

Humans' being is because of the sensory involvement. Our senses gather external information with unbelievable sensitivity and specificity and regulate our behaviour accordingly. This type of processing needs tremendous precision and coordination of all sensory systems especially visual system as it dominates over other senses and much more capable of collecting outside information.

The main result of the current thesis is that V1 neurons exhibit unique behaviour to different sensory stimuli. The visual cortex might have an additional role besides the general processing of visual stimuli. Individual neurons undergo an alteration of their orientation tuning properties, by building new orientation maps when exposed to a repetitive visual or repetitive sound stimulus. The visual neurons may have demonstrated multisensory properties when stimulated indirectly through neighbouring sensory region. The results obtained in this thesis propose and highlight the potential plasticity of the sensory systems and the consequent response towards stimuli.

The results from this thesis suggest that whole sensory cortex is multisensory and positively initiates new lines of thought in the area in addition to the present literature on multisensory integration and cross-modal plasticity.

As researchers there is an opportunity for us to embrace the technological development, take the research to next level to help us anticipate that many advancements in our understanding of human brain function will be gained from studying different animal models in its fully healthy state.

CHAPTER 10: REFERENCES

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Zheng, W. & Knudsen, E.I. (1999) Functional selection of adaptive auditory space map by GABAA-mediated inhibition. *Science*, **284**, 962-965.

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  Project Title: Comparative effects of adaptation on supra and infragranular layers with visual and acoustic stimulation in cat's visual cortex.
- M.Sc. Bioinformatics, Panjab University, Chandigarh, India (2008-2010)

  Project Title: Docking analysis of PI3K inhibitors to check their target specificity.
- B.Sc. (Honors) Biotechnology, Himachal Pradesh University, Shimla, India (2005-2008)

PROFESSIONAL WORK EXPERIENCE:

- Jan – Apr (2014 – 2018): Demonstrator, Dept of Biological Sciences
  - Principes de Physiologie animale
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- Sept – Dec (2014 – 2018): Demonstrator, Dept of Biological Sciences
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- Sept 2016 – Dec 2016: Chief Demonstrator, Department of Biological Sciences
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- Jan 2012 – Feb 2014: Lecturer, Department of Bioinformatics, Goswami Ganesh Dutta Dharam College
- Oct 2010 – Sep 2011: Research Assistant, Discovery Informatics Division, Indian Institute of Integrative Medicine

STUDENT SUPERVISION IN THE LAB:

- **(Supervisor: Dr. Stéphane Molotchnikoff)**
- Jan 2015 – Aug 2018: Afef Ouelhazi (Effect of Ketamine on visual cortical plasticity)
- May 2017 – Aug 2018: Rudy Lussiez (Effect of visual adaptation on orientation selectivity in cat secondary visual cortex (V2)
- May – Aug 2018: Assia Tsyvian-Dzyabko (Stability of tuning curves in mouse primary visual cortex (V1)

- (Supervisor: Dr. Amit Nargotra)
- Oct 2010 - Sep 2011: Omika Thakur, Charul Upadhyay (Docking analysis of cancer targets)

VOLUNTEER WORK:

- Jul 2004 – Apr 2008: Contributed as a member of an NGO - Helping Hands, Shoolini Institute of Life Sciences and Business Management, India. Conducted seminars to highlight the goals of the NGO
- May 2006: Received certificate of appreciation from Special Olympics Bharat for contributing to Special Olympics at Provincial Level, India.

SCHOLARSHIPS & PRIZES:

- Bourses de fin d'études doctorales, FESP, Université de Montréal. Jan 2018 – Oct 2018. COMPETITIVE (9000$)
- Bourses de la réussite étudiante, FESP, Université de Montréal. 2017-2018. COMPETITIVE (3800$)
- Best Poster Presentation Prize, CERNEC Meeting, 2016. COMPETITIVE. Certificate and reward prize (250$)
- CERNEC Scholarship, 2015-2016. COMPETITIVE. (10,000 $)
- Bourse d'exemption des droits de scolarité supplémentaires, Université de Montréal. 2014. FEE-WAIVER SCHOLARSHIP (30,000$)
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ARTICLES PUBLISHED:

1. Molotchnikoff S, Bharmauria V, Bachatene L, **Chanauria N**, JF Maya-Vetencourt (2019). The function of connectomes in encoding sensory stimuli. *Prog Neurobiol,* doi.org/10.1016/j.pneurobio.2019.101659.

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5. **Chanauria N**, Bharmauria V, Bachatene L, Cattan S, Rouat J, Molotchnikoff S (2016). Comparative effects of adaptation on layer II-III and layer V-VI neurons in cat V1. *Eur J Neurosci*, doi: 10.1111/ejn.13439.

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7. Bharmauria V, Bachatene L, Cattan S, Brodeur, **Chanauria N**, Rouat J, Molotchnikoff S (2016). High noise correlation between functionally connected neurons in V1. *Exp. Brain Research* 234(2):523-32. doi: 10.1007/s00221-015-4482-7.

   Individual contributions: VB did the experiments, analyzed the data and wrote the manuscript. LB, SC and NC participated in the experiments and analyses of data. JR contributed to the analyses of data. VB and SM conceived the idea of study. SM contributed to data analyses and manuscript writing.

8. Bharmauria V, Bachatene L, Cattan S, Brodeur, **Chanauria N**, Rouat J, Molotchnikoff S (2016). Network selectivity and stimulus-discrimination in the primary visual cortex: cell assembly dynamics. *Eur J Neuroscience* 43(2):204-19. doi: 10.1111/ejn.13101.

   Individual contributions: VB and SM conceived the idea of the study and contributed to data analyses and manuscript writing. VB did the experiments, analysed the data and wrote the manuscript. LB, SC and NC participated in experiments and analyses of the data. SB and JR contributed to analyses of the data.

9. Bachatene L, Bharmauria V, Cattan S, **Chanauria N**, Rouat J, Molotchnikoff S (2015). Summation of connectivity strengths in the visual cortex reveals stability of neuronal microcircuits after plasticity. *BMC Neurosci* 9; 16:64. doi: 10.1186/s12868-015-0203-1.

   Individual contributions: LB performed the experiments and analyzed the data including the statistical analyses. VB, SC and NC contributed to data analyses and writing of the paper. SM conceived the study and contributed to data analyses. LB and SM wrote the manuscript. JR contributed to data analyses.

10. Bachatene L, Bharmauria V, Cattan S, **Chanauria N**, Rouat J, Molotchnikoff S (2015). Electrophysiological and firing properties of neurons: categorizing soloists and choristers in primary visual cortex. *Neurosci. Letters* doi: 10.1016/j.neulet.2015.07.049.

    Individual contributions: LB performed the experiments and analyzed the data. VB, SC and NC contributed to data analyses and writing of the paper. SM conceived the study and contributed to data analyses. LB and SM wrote the manuscript. JR contributed to data analyses.

11. Bharmauria V, Bachatene L, Cattan S, **Chanauria N**, Rouat J, Molotchnikoff S (2015). Stimulus-dependent augmented gamma oscillatory activity between the functionally connected cortical neurons in the primary visual cortex. *Eur J Neurosci* 41: 1587-1596 doi: 10.1111/ejn.12912.

    Individual contributions: VB did the experiments, analysed the data and wrote the manuscript. LB, SC and NC participated in experiments and analyses of the data. S.B. and J.R. contributed to analyses of the data. VB and SM conceived the idea of the study and contributed to data analyses and manuscript writing.

12. Sharma D, Rah AB, Lambu RM, Hussain A, Yousuf SK, Tripathi AK, Singh B, Jamwal G, Ahmed G, **Chanauria N**, Nargotra A, Goswami A, Mukherjee D (2012). Design and synthesis of novel N, N′-glycoside derivatives of 3, 3′-diindolylmethanes as potential antiproliferative agents. *Med Chem Comm*. 3:1082-91 doi: 10.1039/C2MD20098H. (Carried out the testing of compounds using bioinformatics software)

CHAPTER PUBLISHED:

1. **Chanauria N**, Lussiez R, Ouelhazi A, Molotchnikoff S. Are sensory neurons in cortex committed to original trigger features? *InTechOpen,* Sensory Nervous System, 978-953-51-5595-9.

   Individual contributions: NC wrote the chapter and generated the figures. RL, OA and SM contributed to developing the chapter and generation of figures.

PEER-REVIEWED ARTICLES:

1. eN-NWR-0304-16. Reviewed for eNeuro

2. CerCor-2017-00123. Reviewed for Cerebral Cortex

ORAL PRESENTATIONS:

1. **Chanauria N**, Etindele-Sosso FA, Bharmauria V, Bachatene L, Cattan S, Rouat J, Molotchnikoff S. Auditory signal modulation in V1: Emergence of novel orientation selectivity. La 25^{ième} Journée Scientifique, Centre de recherche en neuropsychologie et cognition, March 2017).
2. **Chanauria N**, Bharmauria V, Bachatene L, Cattan S, Etindele-Sosso FA, Rouat J, Molotchnikoff S. Functional synchrony between the supra and infragranular neurons in the cat V1 pre- and post-adaptation: a homeostatic interplay. (2016). School of Optometry, UdeM.
3. **Chanauria N**, Bharmauria V, Bachatene L, Cattan S, Etindele-Sosso FA, Rouat J, Molotchnikoff S. After effects of sound exposure: Cortical neurons change their tune (2016). (RÉUNION BIANNUELLE CONJOINT UdeM-UdeS, NECOTIS at Université de Montréal.
4. **Chanauria N**, Bharmauria V, Bachatene L, Cattan S, Molotchnikoff S. Comparative effects of adaptation on supra (layer II/III) and infragranular (layer V/VI) layers in the adult cat visual cortex. (Journée scientifique, département des sciences biologiques, UdeM, 11 March 2015).
5. **Chanauria N**, Bharmauria V, Bachatene L, Cattan S, Molotchnikoff S. Comparative effects of adaptation on supra (layer II/III) and infragranular (layer V/VI) layers in the adult cat visual cortex. (Journée scientifique, centre de recherche en neuropsychologie et cognition, 13-14 March 2015).

6. **Chanauria N**, Bharmauria V, Bachatene L, Cattan S, Jeyabalaratnam J, Molotchnikoff S. Effect of sound on adaptation in primary visual cortex (V1) (2014). (RÉUNION BIANNUELLE CONJOINT UdeM-UdeS, NECOTIS at Université de Montréal.
7. **Chanauria N**, Nargotra A. *In silico* studies for drug discovery. (SLC meeting, Scientist Presentation, IIIM Jammu, India, 30 July 2010).

CONFERENCE ABSTRACTS:

2018

1. Modulation of cerebral plasticity by drug application: Modulation of cerebral plasticity by drug application: Effect of Ketamine on orientation selectivity and variability of neuronal responses. Ouelhazi Afef, **Chanauria Nayan**, Bachatene Lyes, Lussiez Rudy, Molotchnikoff Stèphane. (Society for Neuroscience, 2018-S-2818-SfN).
2. Effect of Visual Adaptation on Orientation Selectivity in Cat Secondary Visual Cortex (V2). Rudy Lussiez, **Chanauria Nayan**, Ouelhazi Afef, Molotchnikoff Stèphane. (Society for Neuroscience, 2018-S-2815-SfN).
3. Tsyvian-Dzyabko Assia, **Chanauria Nayan**, Lussiez Rudy, Ouelhazi Afef, Molotchnikoff Stéphane. La plasticité et multi-modalité des aires sensorielles primaires. XXVIIe Department Symposium, University of Montreal, 29 Mars 2018.
4. Ouelhazi Afef, **Chanauria Nayan**, Bachatene Lyes, Lussiez Rudy, Molotchnikoff Stèphane. Plasticité cérébrale: modulation de la sélectivité à l'orientation par l'application de la kétamine chez la souris. XXVIIe Department Symposium, University of Montreal, 29 Mars 2018.
5. Ouelhazi Afef, **Chanauria Nayan**, Bachatene Lyes, Lussiez Rudy, Molotchnikoff Stèphane. Plasticité cérébrale: modulation de la sélectivité à l'orientation par l'application de la kétamine chez la souris. Journée scientifique, Optometry, 23 Mars 2018.

6. Lussiez Rudy, **Chanauria Nayan**, Ouelhazi Afef, Molotchnikoff Stephane. Effet de l'adaptation sur les courbes d'accord à l'orientation dans l'aire visuelle 18 du chat. XXVIIIe Department Symposium, University of Montreal, 29 Mars 2018.

2017

1. **Chanauria N**, Bharmauria V, Bachatene L, Cattan S, Armel Sosso FA, Rouat J, Molotchnikoff S. Co-ordinated adaptive changes of layer 2/3 and layer 5/6 multiunit activity (MUA) orientation tuning in the cat visual cortex. (Society for Neuroscience: 2017-S-6415-SfN).
2. **Chanauria N**, Armel Sosso FA, Bharmauria V, Bachatene L, Cattan S, Armel Sosso FA, Rouat J, Molotchnikoff S. Auditory stimulation modulates orientation selectivity in V1. Canadian Association of Neuroscience 2017, Montreal.
3. **Chanauria N**, Armel Sosso FA, Bharmauria V, Bachatene L, Cattan S, Armel Sosso FA, Rouat J, Molotchnikoff S. Auditory signal modulation in V1: emergence of novel orientation selectivity. La 25^{ième} Journée Scientifique, Centre de recherche en neuropsychologie et cognition, March 2017.
4. Armel Sosso FA, **Chanauria N**, Molotchnikoff S. Première expérience visuelle : Impact sur la sélectivité cortico-neuronale. La 25^{ième} Journée Scientifique, Centre de recherche en neuropsychologie et cognition, March 2017).
5. Armel Sosso FA, **Chanauria N**, Molotchnikoff S. Orientation tuning curves and selectivity in V1: influence of the past stimulus. XXVIIe Department Symposium, University of Montreal.
6. Armel Sosso FA, **Chanauria N**, Molotchnikoff S. Preceding oriented visual target impacts responses to succeeding stimuli: An approach to memory. Journée scientifique, Optometry.

2016

1. **Chanauria N**, Bharmauria V, Bachatene L, Cattan S, Armel Sosso FA Rouat J, Molotchnikoff S. "Intriguing! Auditory stimulus shifts orientation selectivity of visual neurons in cat V1". (Society for Neuroscience: 2016-S-1454-SfN).

2. Armel Sosso FA, Bharmauria V, Bachatene L, Cattan, Ouelhazi Afef, **Chanauria N**, Stéphane Molotchnikoff. Orientation tuning curves and selectivity in V1: influence of the past stimulus. (Society for Neuroscience: 2016-S-2218-SfN).
3. **Chanauria N**, Bharmauria V, Bachatene L, Cattan S, Armel Sosso FA Rouat J, Molotchnikoff S. Functional synchrony between the supra and infragranular neurons in the cat V1 pre- and post-adaptation: a homeostatic interplay. Journée scientifique, Optometry.
4. **Chanauria N**, Bharmauria V, Bachatene L, Cattan S, Rouat J, Molotchnikoff S. Cross correlation investigation of neurons in supra and infragranular layers in cat V1 before and following adaptation. (Journée scientifique, centre de recherche en neuropsychologie et cognition, March 2016).
5. Armel Sosso FA, **Chanauria N**, Molotchnikoff S. Étude de la sélectivité neuronale post-stimulation visuelle chez la souris. (Journée scientifique, centre de recherche en neuropsychologie et cognition, March 2016).
6. Bachatene L, Bharmauria V, Cattan S, **Chanauria N**, Armel Sosso FA, Molotchnikoff S. Simulating spike-trains using Matlab. (2016). NECOTIS meeting.
7. Cattan S, Bharmauria V, Bachatene L, **Chanauria N**, Etindele-Sosso FA, Molotchnikoff S. La plasticité synaptique dans le néocortex. (2016, NECOTIS meeting).
8. Armel Sosso FA, Raouafi S, Cattan S, Bharmauria V, Bachatene L, **Chanauria N**, Molotchnikoff S. Relationship between cognitive impairment and the combined effects of environmental factors (9th Global Neuroscience Conference 2016).
9. Armel Sosso FA, **Chanauria N**, Cattan S, Bharmauria V, Bachatene L, Mansouri H, Ouelhazi A, Molotchnikoff S. Étude de la mémoire neuronale post-stimulation visuelle chez la souris (Symposium du département des sciences biologiques 2016).

2015

1. **Chanauria N**, Bharmauria V, Bachatene L, Cattan S, Rouat J, Molotchnikoff S. Cross correlation investigation of neurons in supra and infragranular layers in cat V1 before and following adaptation. (SfN-5547, 2015).
2. Bharmauria V, Bachatene L, Cattan S, **Chanauria N**, Molotchnikoff S. The 50-ms window of opportunity in V1 microcircuits. (SfN-15546, 2015).
3. Bachatene L, Bharmauria V, Cattan S, **Chanauria N**, Rouat J, Molotchnikoff S. Characterizing soloists and choristers in primary visual cortex. (SfN-8622, 2015).
4. Bachatene L, Cattan S, Bharmauria V, **Chanauria N**, Rouat J, Molotchnikoff S. Correlation and summation in the visual cortex reveal stable neuronal assemblies. (Journée scientifique, centre de recherche en neuropsychologie et cognition, 13-14 March 2015).
5. Bachatene L, Bharmauria V, Cattan S, **Chanauria N**, Rouat J, Molotchnikoff S. Sommation et correlation dans le cortex visuel (Journée scientifique, département des sciences biologiques, UdeM, 11 March 2015).
6. Cattan S, Bachatene L, Bharmauria V, **Chanauria N**, Molotchnikoff S. Modéliser les phénomènesd'adaptation dans le cortex visuel à l'aide de réseaux de neurones. (Journée scientifique, département des sciences biologiques, UdeM, 11 March 2015).
7. **Chanauria N**, Bharmauria V, Bachatene L, Cattan S, Molotchnikoff S. Comparative effects of adaptation on supra (layer II/III) and infragranular (layer V/VI) layers in the adult cat visual cortex. (Journée scientifique, département des sciences biologiques, UdeM, 11 March 2015).
8. **Chanauria N**, Bharmauria V, Bachatene L, Cattan S, Molotchnikoff S. Comparative effects of adaptation on supra (layer II/III) and infragranular (layer V/VI) layers in the adult cat visual cortex. (Journée scientifique, centre de recherche en neuropsychologie et cognition, 13-14 March 2015).
9. Balti M, Masri S, Bharmauria V, Bachatene L, Cattan S, **Chanauria N**, Molotchnikoff S. Souris vs Chat: lequel a la plus grande plasticité cérébrale? (Journée scientifique, département des sciences biologiques, UdeM, 11 March 2015).

10. Diab V, Massol S, Bharmauria V, Bachatene L, Cattan S, **Chanauria N**, Molotchnikoff S. Connectivité entre les neurones du cortex visuel et l'orientation de stimulus chez la souris. (Journée scientifique, département des sciences biologiques, UdeM, 11 March 2015).

2014

1. Bachatene L, Cattan S, Bharmauria V, **Chanauria N**, Rouat J, Molotchnikoff S. Plasticity in the visual cortex: Emergence of new orientation maps (Society for Neuroscience, Nov 2014, published #819.10/FF28) Selected as a Hot Topic by the Society for Neuroscience.
2. Rouat J, Bachatene L, Cattan S, Adeli M, Bharmauria V, **Chanauria N**, Molotchnikoff S. Noise and brain plasticity? (HUMAIN BRAIN PROJECT Workshop: Stochastic Neural Computation, November 27, 2014).
3. **Chanauria N**, Bharmauria V, Bachatene L, Cattan S, Rouat J, Molotchnikoff S. Comparative effects of adaptation on supra- and infra-granular layers in cat's visual cortex (Society for Neuroscience, Nov 2014, Published #819.19/GG5).C
4. **C**attan S, Bharmauria V, Bachatene L, Jeyabalaratnam J, Ribot J, Milleret C, **Chanauria N**, Molotchnikoff S. Les zones de fort gradient d'orientation sont plus plastiques dans le cortex visuel primaire du chat. (Journée scientifique du groupe de recherche en sciences de la vision, 4 April 2014).
5. **Chanauria N**, Bharmauria V, Bachatene L, Cattan S, Jeyadarshan J. Effect of sound on adaptation in primary visual cortex (V1) (RÉUNION BIANNUELLE CONJOINT UdeM-UdeS, NECOTIS at Université de Montréal on April 17, 2014).

2011

1. **Chanauria N**, Mahajan P, Nargotra A, Koul S, Vishwakarma R. Quantifying the relationship between PI3K inhibitory activity and energy value scoring function of a docking algorithm (Chemical Research Society of India, North Zone Meeting, Jammu University, 2011, p-72).

TRAININGS:

2010:

1. Nine months training at Discovery Informatics Division of Indian Institute of Integrative Medicine, Jammu, Jammu & Kashmir (Council of Scientific and Industrial Research), India on the project entitled "Docking analysis of PI3Kα inhibitors".

2008:

1. Three months training at Zydus Cadila, Baddi, Solan, Himachal Pradesh, India on the project entitled "Exposure to Industrial Training".

OTHER WORKSHOPS, SEMINARS, SUMMER SCHOOL ATTENDED:

2017:

1. Ecole d'été connectivité cérébrale, May 15-16, 2017. Québec City (Summer school).

2013:

1. Seven-day Faculty Development Programme on "Research Methodology in Bioinformatics'', October 15-22, G.G.D.S.D. College, Chandigarh, India.
2. International Conference on "Bio-products and the OMICS Revolution, March16-17, JIIT Campus, Noida, India.
3. Two-day workshop on "Role of E-Resources in Scientific Research", February 20-21, G.G.D.S.D. College, Chandigarh, India.
4. National level seminar on "Education Reforms: Challenges & Strategies", February 9, G.G.D.S.D. College, Chandigarh, India.
5. One-day seminar on "On being a scientist: legal &ethical aspects", January 30, G.G.D.S.D. College, Chandigarh, India.

2010:

1. Symposium on "Recent Advances and Challenges in Biotechnology", G.G.D.S.D College, Chandigarh, India.

2009:

1. UGC sponsored 2-day National Symposium on "Recent Advances in Biological Sciences", D.A.V. College, Chandigarh, India.

MEMBERSHIPS:

- Active member of SFN (Society for Neuroscience), USA
- Active member of CERNEC (Centre de Recherche en Neuropsychologie et Cognition), Montréal
- Active member of NECOTIS (Neurosciences Computationnelles et Traitement Intelligent des Signaux), Sherbrooke
- Active member of CAN (Canadian Association of Neuroscience)
- CINQ (Le Consortium d'imagerie en neurosciences et santé mentale de Québec)