UNIFYING MODELS OF DEVELOPMENT, CIRCUITS AND SURROUND MODULATION IN THE PRIMATE PRIMARY VISUAL CORTEX

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LAY SUMMARY

ABSTRACT

Something to do with (**?**)

ACKNOWLEDGEMENTS

Thank you all

DECLARATION

I declare that this thesis was composed by myself, that the work contained herein is my own except where explicitly stated otherwise in the text, and that this work has not been submitted for any other degree or professional qualification except as specified.

Edinburgh, 2015

Philipp John Frederic
Rudiger, August 27, 2015

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ABBREVIATIONS

e.g. for example

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INTRODUCTION

1.1 ORGANISATION OF THE THESIS

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LITERATURE REVIEW

2.1 EARLY VISUAL SYSTEM

The early stages of mammalian visual system (pictured in figure 2.1) consist of the retina, where rod and cone photoreceptors convert incident photons into electrical and chemical signals. These signals are then further converted from analogue voltages into spike trains by retinal bipolar and ganglion cells and sent down the optic nerve to the lateral geniculate nucleus (LGN). Connections from the two eyes cross over at the optic chiasm to form projections of the right and left visual field contra-laterally. The connections from the retina map retinotopically onto the LGN, which ensures that nearby areas of LGN respond to nearby portions of the visual field. After the initial processing in the retina and LGN the visual stream is projected onto the primary visual cortex (V1).

Retinal processing begins, as previously mentioned, with the photoreceptors, which release glutamate into the synaptic terminal connecting them to bipolar or horizontal cells. The bipolar cells respond either as ON or OFF cells as the glutamate either de- or hyperpolarizes them basically turning on or off in response to light stimulation. The bipolar cells can make connections to a small or large number of photoreceptors or even be indirectly connected to them via horizontal cells, which leads to a large variance in receptive field size and structure.

In the retina, summation of various photoreceptor types gives rise to so called center-surround receptive fields. These ON- and OFF-center receptive fields can arise in bipolar cells but are more commonly associated with retinal ganglion cells (RGCs). This receptive field type responds most strongly to spots of light/dark moving through the visual field (as shown in figure 2.1) but can be characterized as simple edge detectors.

Much like the retina and many other areas of the brain, the LGN forms a laminar architecture, receiving input from RGCs and projecting axons to the primary visual cortex via the optic radiation. The separation of LGN cells into layers also corresponds to functional separations, as layers 1, 4 and 6 usually receive contra-lateral input, while layers 2, 3 and 5 receive ipsi-lateral inputs from the retina. Furthermore, different layers consist of different cell types, with ventral layers 1 and 2 containing larger so called magno-cellular (M) neurons and dorsal layers 3, 4, 5 and 6 containing

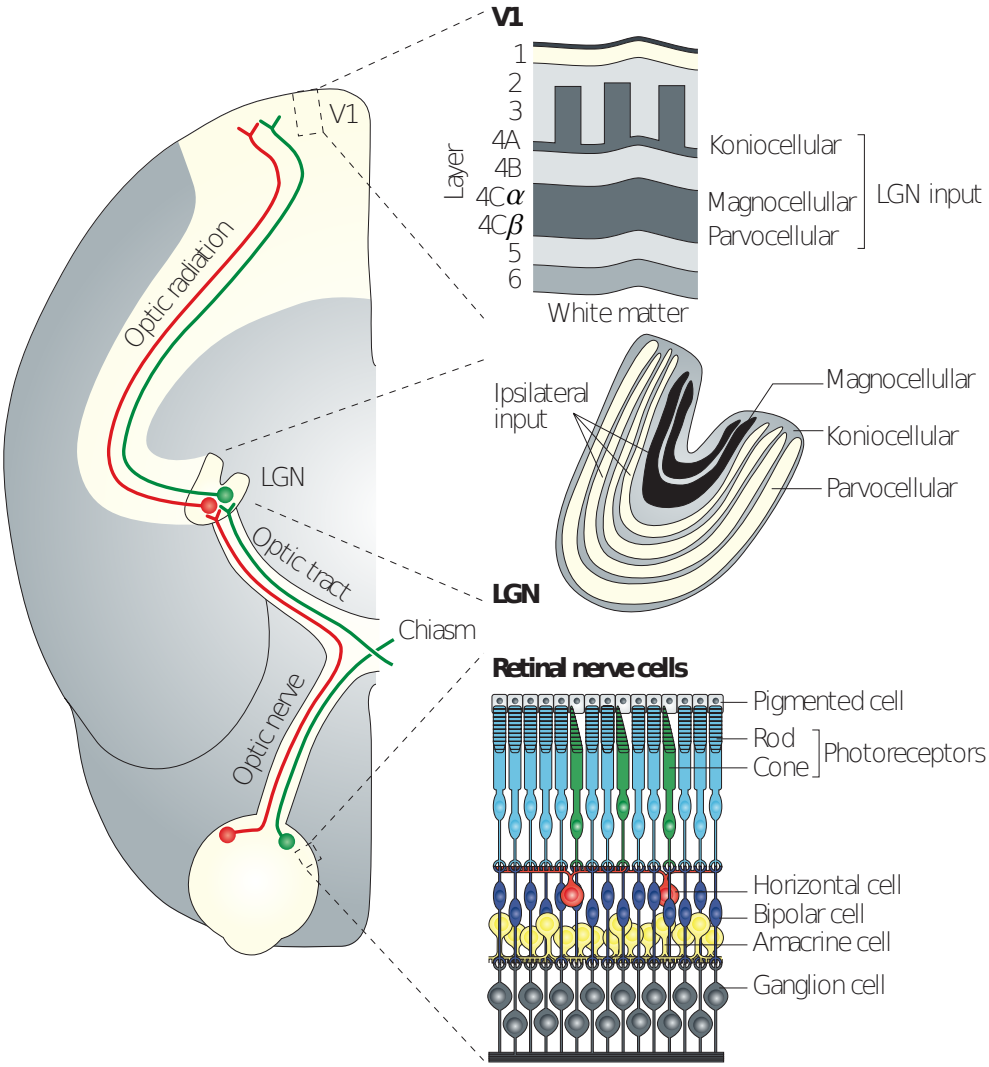

Figure 2.1: p
rimates(at least superficially the same for most other mammals) from the retina to the primary visual cortex (V1) via the lateral geniculate nucleus (LGN) of the thalamus. The left panel shows the pathway, while the right panels highlight noteworthy sections including the structure of the retina, the LGN and V1 broken down into their different layers and showing different cell types. Reprinted from Solomon et al. 2007 Solomon and Lennie (2007).

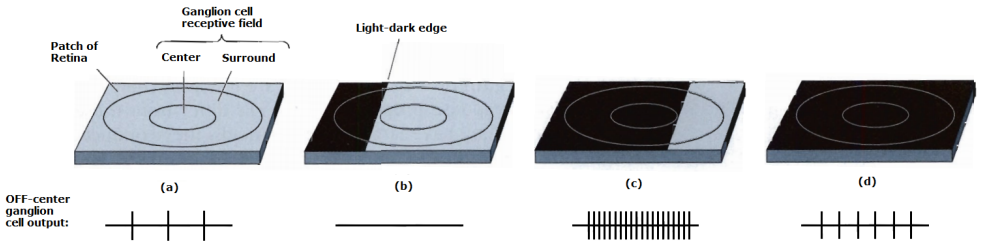

Figure 2.2: s
tructure of some retinal ganglion cells and LGN neurons, illustrating how a contrast edge activates different portions of the field and thereby results in different activation patterns. From left to right one can see that as the light-dark edge moves into the ON surround field spontaneous activity is suppressed and as it moves further over the OFF center field is deactivated causing activity to sharply spike. Adapted from Bear et al. (2006).

smaller parvo-cellular (P) neurons with intra-laminar neurons being referred to as konio-cellular (K). Since these three cell types are also present in the retina and make connections mainly with their own cell type it is theorized that each carries its own parallel information stream. Functionally, P-cells have displayed greater sensitivity to chromatic contrast and higher spatial frequencies, linking them to the processing of detail and color, while M-cells have been shown to have greater sensitivity for high temporal frequencies associating them with motion processing. In addition to the feedforward retinal input, the LGN also receives feedback connections from V1, the influence of which has not yet been fully clarified but will be explored later on.

2.1.1 *Primary Visual Cortex: Topographic Maps, Simple and Complex Cells*

The primary visual cortex (V1) or striate cortex provides the first cortical stage of processing of visual information. The cortex was classically divided into six layers but since many subdivisions have been added after functional sub-groups were discovered. Feedforward input from the LGN is received in layer 4Cα and 4Cβ , which receive input most of their input from M- and P-cells respectively. The neurons in layer 4 then send projections up to layers 2/3, which has a diverse intralaminar network of connections but also sends intracortical projections to a number of higher visual areas, while layers 5 and 6 provide feedback to the LGN.

Neurons in the primary visual cortex (V1) are tuned to respond to a variety of different features or complex combinations of such features, including orientation, spatial and temporal frequency, motion direction, colour or ocular origin. In many mammal species especially primates and carnivores, these feature preferences map smoothly and topographically onto the cortical surface. This mapping extends vertically through the layers of the cortex, giving rise to the notion of distinct cortical

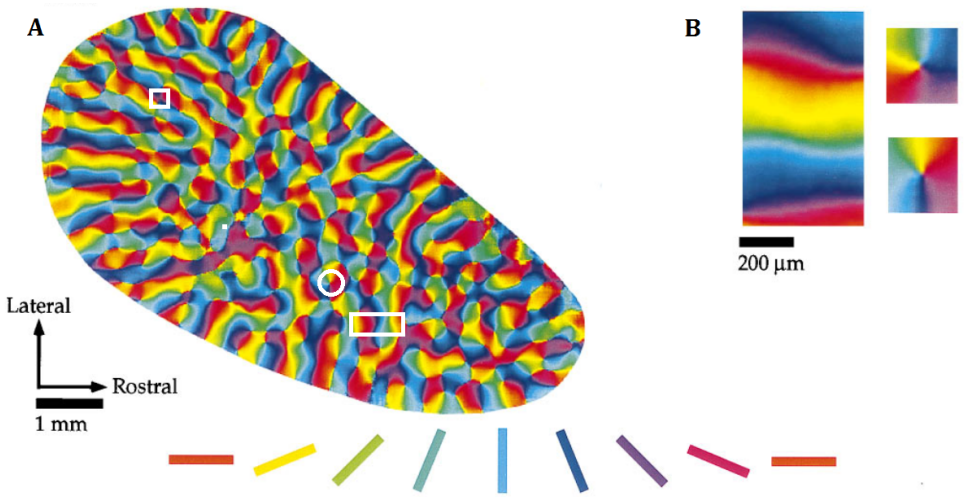

Figure 2.3: p
reference map in a ferret generated by overlaying the activity maps for different orientations and artificially colouring each area according to the orientation preference laid out in the legend below. The image also highlights three recurrent features of orientation maps in white. The square highlights a saddle point, where a patch of cortex selective for a particular direction is almost bisected by a patch selective to another direction. The circle highlights a pinwheel arrangement, where different orientations preference patches are arranged in a circular shape. Finally the rectangular shape highlights a linear zone in which orientation preference change continuously. B) Magnifications of a linear zone and two pinwheel arrangements. Adapted from Bosking et al. (1997).

columns. Retinotopy arises due to the mapping of visual information straight from the retina to the LGN and then to the cortex. Other response preferences such as orientation and direction selectivity rarely arise in the LGN and are usually thought of as an emergent phenomenon in the cortex.

The receptive fields of V1 neurons are different in that often are no longer simple ON- or OFF-centre surround fields, forming more complex spatiotemporal patterns. They are commonly modeled using Gabor filters as shown in Figure 2.1.1, which have elongated ON and OFF regions or lobes, generated by localizing a full-field sine grating with a Gaussian envelope. Orientation selectivity and spatial frequency preference are determined by the orientation and spacing of ON- and OFF-regions respectively. It is also possible for V1 cells to filter temporal patterns by employing spatio-temporal shifts in their ON and OFF lobes, giving rise to direction selectivity.

Orientation selective neurons can generally be classed as simple or complex cells, depending on whether they display some form of spatial/phase invariance. In reality this classification is less clear with cells being somewhere on a gradient from pure simple cells to a complex cell with the degree of phase invariance being the determining factor. Apart from phase invariance the neurons may also exhibit contrast

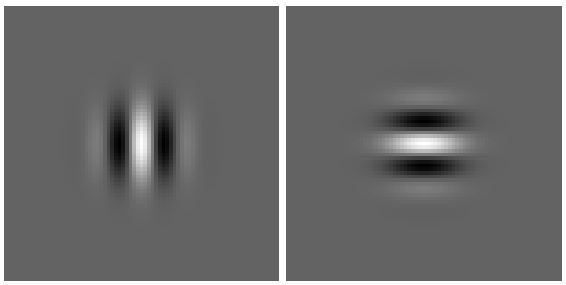

Figure 2.4: P
atches at 0 degree and 90/180 degree orientations with clearly visible ON (white) and OFF (black) regions.

invariance, such that even at very low contrast they will respond more strongly to their preferred orientation than to the orthogonal orientation.

In context of this project topographic feature maps and RF interactions play an important role as attention seems to be capable of selecting and enhancing the representation of stimuli in different feature dimensions. The functional organization of V1 arises during the development of the animal and are thought to be mediated largely by activity dependent processes as the next section will show.

2.1.2 *Development of Topographic Maps in V1*

The development and maturation of cortical topographic feature representations in the form of maps is closely linked to function and can reveal a lot about how the cortex is capable of capturing and encoding statistics of the natural world. Developmental studies involve imaging the same area of the cortex over a number of days and investigating what drives development of orientation maps and other topographic arrangements. Early developmental studies found, using relatively limited optical imaging techniques on ferrets shortly after eye opening, that the iso-orientation domains in the V1 develop very early in development and subsequently show very little change (Chapman et al., 1996) (pictured in figure 2.1.2). These and other experiments (**?**) showed that orientation preference develops even in absence of visual input although the maps do not fully mature. This seems to suggest that orientation maps and other topographic organizations develop initially even in absence of external visual input through internally generated visual activity such as retinal waves but then require external stimulation to fully mature.

In the initial stages of development various preprogrammed guidance cues set up the basic connectivity between the LGN and the cortical processing areas. Some successful models of development have focused on the afferent connections between the LGN ON and OFF cells and their targets in the visual cortex as the driving force

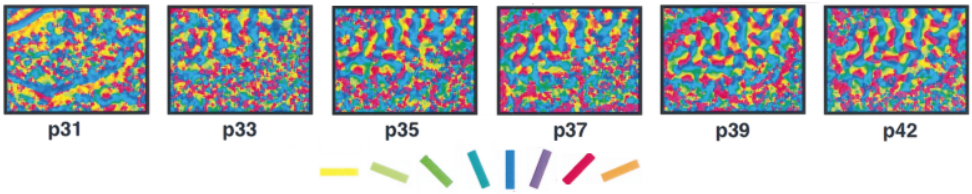

Figure 2.5: o
rientation map in ferret visual cortex from postnatal day 31 to 42 revealed using chronic optical imaging of intrinsic signals. Adapted from (Chapman et al., 1996).

behind the development of orientation columns (Jin et al., 2011). This is likely to tell only part of the story as even during prenatal development, retinal waves, consisting of periodic activity in retinal ganglion cells (RGCs), spread across the retina driving neighboring RGCs to fire in a correlated fashion, which allows the primary visual cortex to develop topographic feature maps (Firth et al., 2005). The most prominent proposals in theory and in models have been focused the termination pattern of both the geniculocortical afferents in layer 4 (Katz et al., 2000; Ringach, 2007) and adjustments in feedforward and lateral connectivity through activity dependent, competitive processes (Bednar and Miikkulainen, 2003).

It is now generally accepted that the development of topographic maps is driven activity dependent weight modification in form of Hebbian learning or some variant thereof. The LISSOM and GCAL models, which provide the basis of the modeling work proposed in this project have shown that robust map development can be achieved with a small number of relatively simple mechanisms including homeostatic plasticity, lateral gain control in LGN and lateral connectivity in V1 (Law, 2009) and will be considered in more detail at a later stage. These models can account for the development of orientation preference maps through both intrinsic activity including retinal, spindle and PGO waves of REM sleep (Bednar and Miikkulainen, 2003) and visually induced retinal activity. Experiments show that at the very least these processes are required to achieve the nely tuned precision, which can now be observed at single cell resolution (Ohki et al., 2005; **?**).

Lateral intra-areal connections in particular have been implicated in map development as their functional connectivity seems to be closely related to map structure (Gilbert and Wiesel, 1983). Experiments in layer 2/3 of the tree shrew involving orientation preference mapping and subsequent axonal staining have shown that although short range connections show no preference in their terminations, long range connections longer than 500, preferentially link neurons with co-oriented and co-axially aligned receptive fields (Bosking et al., 1997). In iso-orientation regions cells therefore make short-range connections largely with cells that prefer the same direction as them, while the connectivity at pinwheels short-range connections are made with

cells with a wide range of orientation preferences (**?**), allowing them to strongly influence topographic organization.

The development of the early visual pathway is probably driven by a number of mechanisms complementing each other at various stages starting with guidance cues setting up coarse predetermined connectivity patterns, which are then refined through Hebbian processes driven by in- and extrinsically stimulated activity. Although the structure of a neurons receptive field is constantly changing and varies widely from cell to cell, a lot of work has gone into measuring the exact structure and functional properties of neural receptive fields and their underlying anatomical correlates, the neurite arbors.

2.1.3 *Functional and Anatomical Properties of Neural Receptive Fields*

The spatial properties of RFs in the LGN and V1 are of particular interest in the context of this PhD project as they provide the basis of a realistic model of the parafoveal regions of the primary visual cortex in macaques. Before attempting to model the effects of higher- and extra-cortical influences on information processing in V1, the spatial properties of each set of afferent connections entering V1 need to be thoroughly understood and incorporated into the model.

The extents and structure of neural receptive fields are defined by the axonal and dendritic arborization of afferent, horizontal and feedback connections, whether that is in the LGN, the V1 or higher up in the cortical architecture. While these extents can theoretically be measured physically by tracing the neurites of a number of cells, this has only systematically been possible for corticogeniculocortical neurite complex as tracing studies have so far not been able to label RGC axons through the optic nerve to V1. Therefore spatial properties of LGN RFs have been estimated through stimulus driven protocols. The following sections will outline the methods employed in characterizing RFs and detail the relative contribution of afferent, lateral and feedback connections to para-foveal RFs in the LGN and V1 of macaques.

2.1.3.1 *Receptive Fields in the Lateral Geniculate Nucleus*

The spatiotemporeal structure of receptive field becomes increasingly more complex when moving up in the visual processing hierarchy. As described earlier, receptive fields in the LGN are primarily made up of antagonistic center-surround regions although Gabor-like lobes are also sometimes observed. Even at this early stage of processing, lateral and feedback connections can modulate neural responses and have been found to exert a suppressive effect (Hubel and Wiesel, 1961). More recent studies have concluded that this suppressive effect is mediated primarily by lateral connec-

tions and acts as a form of contrast-gain control allowing for the encoding of a high dynamic range of luminance values Bonin et al. (2005). As pointed out previously the LGN receives a large proportion of its inputs from feedback cells originating in layer 6 of V1, which itself receives inputs from the MT area (Sherman and Guillery, 2002). It is unclear how these feedback connections contribute to the RF properties of LGN neurons but most evidence suggests they are mainly involved in higher level modulatory processes especially in regard to the processing of motion and thus do not directly contribute to the RF structure (Sillito et al., 2006).

Estimating the relative contribution and effect of the various LGN afferents on its neural receptive fields has been attempted using a variety of protocols. Unfortunately little to no data is available from tracing studies, primarily because the LGN is embedded deep in the brain making it incredibly difficult to trace individual neurites from and to their origin. Therefore a number of protocols were developed by which the parameters of the center-surround fields could be estimated. After measuring the response of retinal ganglion cells (RGCs) to moving bar stimuli cats (Rodieck, 1965; Rodieck and Stone, 1965a), Rodieck and Stone (1965b) found that by fitting a Difference of Gaussian (DoG) model (see 2.1) to the data it was possible to estimate the relative strength and size of the central and surround portions of the receptive field. It wasn't until later that systematic recordings of this kind were carried out in the LGN of macaques at which point the moving bar stimuli were replaced with sine gratings of varying spatial frequency.

$$R = k_c e^{-\frac{f}{f_c}^2} - k_s e^{-\frac{f}{f_s}^2} \tag{2.1}$$

As not all papers can be considered, the data from three different studies making use of protocols with increasing complexity will be considered. Derrington and Lennie (1984) was the first of such studies, attempting to characterize the spatial and temporal properties of parvocellular LGN neurons in *Macaca mulatta* by fitting DoG models to the responses. The analysis and confidence intervals of this first study were rather limited so the first study that will be considered here is Spear et al. (1994), which also considered the effect of aging on receptive field properties. After mapping the receptive field position, they presented the macaques with sine wave gratings at a temporal frequency of 6 Hz, 10 spatial frequencies (0.1-10.8 cycles/deg in half-octave steps) and 7 contrasts (1.5-80% in 1 octave steps) and fit the first fundamental (F1) of the neural response with the DoG model (equation 2.1). All neurons were in the central 10 deg of the visual field and the results are broken down into magnocellular and parvocellular neurons (see 2.1.3.1). They found that the receptive field center ra-

	r_c (°)	r_s (°)	f_{opt} (cycles/°)
Magnocellular neurons			
Young Adult	0.103 ± 0.021 (3)	1.16 ± 0.48 (3)	0.87 ± 1.37 (3)
Old	0.126 ± 0.08 (3)	1.29 ± 0.84 (3)	0.63 ± 1.74 (3)
Parvocellular neurons			
Young Adult	0.087 ± 0.046 (10)	0.53 ± 0.039 (7)	0.94 ± 2.16 (11)
Old	0.097 ± 0.0057 (7)	0.64 ± 0.52 (6)	1.07 ± 2.26 (7)

Table 2.1: s
patial frequency (f_{opt}), RF center radius (r_c) and RF surround radius (r_s) of magno- and parvocellular neurons in central 10° of visual field. Values are means ± SD; number of animals is in parantheses (only animals in which the property was studied in ⩾6 cells included). Taken from Spear et al. (1994) Spear et al. (1994).

dius only increased very weakly with eccentricity, the smallest RF center radii were confined to parvocellular neurons and that the RF surround was significantly smaller in parvocellular layers. This provides a first estimate for the mean sizes of the central and surround portions of the classical RFs in macaque but the clear problem with this approach is that it completely ignores the influence of the non-classical surround and therefore may underestimate the extents of the central field, while overestimating the strength of the classical RF surround.

The next detailed study of LGN neural RFs was carried out by Levitt et al. Levitt et al. (2001), investigating the effects of visual deprivation on their visual response properties. The study additionally set out to determine the trans-species correspondence of so called X, Y and W pathways, which were identified in the cat. Furthermore it had the largest sample size of neurons to date and broke down their analysis by eccentricity. The stimulus protocol in this study involved sine gratings with a temporal frequency of 4 Hz, contrast of 50% and six spatial frequencies from 0.38 to 12 cycles/deg in octave steps. Although they fitted their data with the DoG model they failed to declare the RF surround radii, instead reporting the relative strength of the surround. As in the Spear et al. (1994) study they found little difference in RF center radii between parvo- and magnocellular neurons. They also found that magnocellular neurons had greater nonlinearity indices but could find no compelling evidence that magnocellular neurons can be classified into distinct linear (X) and nonlinear (Y) types. There was a tendency for parvocellular neurons to exhibit greater spatial resolution and the highest temporal resolution to be magnocellular. This seems to support the general conclusion reached by Derrington and Lennie (1984), which had additionally concluded that magno- and parvocellular neurons can be further identified by their chromatic properties. Finally, their analysis extended to earlier data from different species of macaque, which showed that there is some variation in the

	Eccentricity (°)	f_c (cycles/°)	r_c (°)	k_s
Magnocellular neurons				
(n)	(43)	(33)	(33)	(33)
Mean ± SD	2.71 ± 1.37	3.55 ± 1.94	0.089 ± 0.070	0.68 ± 0.37
Parvocellular neurons				
(n)	(110)	(82)	(82)	(82)
Mean ± SD	2.24 ± 1.13	4.57 ± 2.75	0.069 ± 0.076	0.52 ± 0.35

Table 2.2: s
patial frequency (f_c), RF center radius (r_c) and relative strength of surround mechanism (k_s) of magno- and parvocellular neurons in central 5° of visual space. Taken from Levitt et al. 2001 Levitt et al. (2001).

distribution of ON and OFF cells between *M. mulatta* and *M. fascularis*. Overall their results on spatial tuning match those found by previous studies quite closely, which is unsurprising as the measuring and fitting protocols were highly similar.

In an attempt to calculate the relative contributions of different neural connections, determine differences between the K-, M- and P-cellullar pathways and measure contrast dependent tuning, a number of more recent studies have introduced more complex measurement and fitting protocols. In particular, these experiments for the first time attempted to separate out the influence of the non-classical or extra-classical surround (ECRF or nCRF), which is thought to be mediated by lateral and feedback connections. Therefore, a new measurement and fitting protocol, introduced by Sceniak et al. (1999) in form of the integrated DoG (iDoG) model to describe spatial summation in the visual cortex, was used. Instead of measuring the response to varying spatial frequency, this protocol involves the presentation of drifting sine grating disks with varying apertures at the neurons optimum spatial frequency. The rationale behind this new protocol was that the optimal spatial frequency would maximally drive the CRF excitatory center, while minimizing the influence of the CRF surround. Therefore the resulting area summation tuning curve would represent only the response from the CRF excitatory center and the ECRF surround. Additionally the spatial frequency response measurement protocol was modified by confining the drifting sine gratings to a circular aperture, reducing influences from beyond the CRF. While these assumptions don't hold absolutely for reasons that will be discussed later, they provide a first systematic attempt at separating the contributions from the CRF and ECRF.

Sceniak et al. (2006) were the first to study spatial RF properties of LGN neurons of macaques by measuring both spatial frequency and area summation response functions and fitting the results with DoG and iDoG models respectively to estimate the

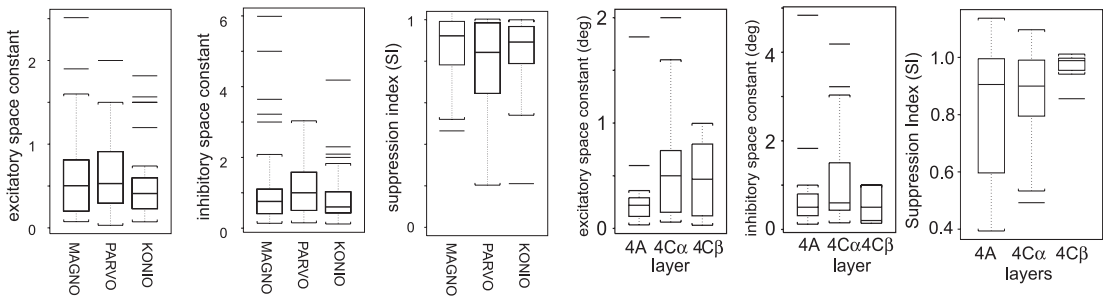

Figure 2.6: e
stimates for LGN excitatory CRF and ECRF suppressive surround and and Suppression Index (SI) as by their laminar and chromatic classification. Magnocellular ($n = 51$), Parvocellular ($n = 32$), Koniocellular ($n = 27$), Layers 4A, 4Cα, 4Cβ ($n = 70$). Taken from Sceniak et al. (2006).

spatial parameters of the probed neurons. The area summation curves were fitted using the following integrated Difference of Gaussians model:

$$R(s) = R_0 + K_e \int\int re^{-\frac{r^2}{a}}\, drd\theta - K_i \int\int re^{-\frac{r^2}{b}}\, drd\theta \tag{2.2}$$

where R_0 is the spontaneous response rate, K_e the excitatory gain, K_i the inhibitory gain, a the excitatory space constant and b the inhibitory space constant. The spatial frequency tuning curve on the other hand was fit with the following function, which represents a standard Difference of Gaussian model:

$$R = R_0 + R_e - R_i \tag{2.3}$$

where R_0 represents the spontaneous baseline activity and R_e and R_i represent the spatial weighting function of the excitatory and inhibitory Gaussians, which take the following form

$$R' = C.K\left[1 - e^{-\frac{f}{2\sigma^2}}\right] \tag{2.4}$$

where C is the stimulus contrast, K is the peak sensitivity, f is the spatial frequency and σ the space constant (radius of the Gaussian at $1/e$ of the peak). The results are shown in Figure 2.1.3.1 and summarized in Table 2.1.3.1.

The results from Sceniak et al. (2006) represent the best estimates of the spatial properties of LGN receptive fields. The first thing to note is the clear discrepancy between the estimates of CRF excitatory center radius estimates in this paper compared to previous estimates. This may be explained by the more homogenous distribution

	r_e^{crf} (°)	r_i^{crf} (°)	r_i^{ecrf} (°)	SI ($k_i r_i / k_e r_e$)
Magnocellular ($\tilde{x}$)	0.5	-	0.76	0.92 (0.87,0.97)
Parvocellular ($\tilde{x}$)	0.53	-	1.0	0.84 (0.74,0.94)
Koniocellular ($\tilde{x}$)	0.41	-	0.6	0.89 (0.82,0.95)
Layer 4A ($\tilde{x}$; n=17)	0.22 (0.15,0.28)	-	0.50 (0.30,0.73)	0.91 (0.73,1.10)
Layer 4Cα ($\tilde{x}$; n=35)	0.51 (0.34,0.65)	-	0.62 (0.30,0.90)	0.90 (0.84,0.96)
Layer 4Cβ ($\tilde{x}$; n=13)	0.46 (0.17,0.76)	-	0.51 (0.15,0.85)	0.99 (0.97,1.00)
Mean ($\bar{x}$; SI>0.1; n=76)	0.53 ± 0.06	1.4 ± 0.14	1.3 ± 0.26	0.85 ± 0.22
Mean ($\bar{x}$; n=136)	0.58 ± 0.04	-	1.3 ± 1.90	0.65

Table 2.3: o
n spatial RF properties of macaque LGN neurons between $2-5°$ of visual space as estimated using the DoG (see 2.3) and 2.4 and iDoG (see 2.2) models. The CRF exitatory radius (r_e^{crf}), ECRF inhibitory radius (r_i^{ecrf}) and SI were estimated from the data using the iDoG model, while the r_i^{crf} was estimated using the DoG model. The estimates are broken down by chromatic and laminar classification. The values are given as either medians or means, where $\tilde{x}$ is the median with with 95% confidence intervals (CI) given as (LCI,UCI) and $\bar{x}$ is the mean ± SD. Suppression Index (SI) is the ratio of the area under the inhibitory component over the area under the excitatory component. Compiled from Sceniak et al. (2006).

of cells as the sample population was taken exclusively from layer 4. Additionally the older protocol failed to confine the drifting sine grating to a disk, which may have resulted systematic underestimation of the excitatory component due to suppressive effects. While excitatory extents vary hugely across the various studies the suppressive surround estimates are fairly consistent. Furthermore, the spatial extent of the excitatory CRF centers were found to be contrast invariant, while both the ECRF and CRF suppressive surround extents were found to increase at lower contrast levels. In summary, looking back at all the studies considered here excitatory CRF extents are generally distributed between 0.05-0.5° in radius, while inhibitory CRF and suppressive ECRF radii are distributed distributed anywhere between 0.6-1.5° and the suppression index is quite high (SI>0.8) for 80% cells.

While these results provide the best estimates that are currently available the protocols used rely on a number of flawed assumptions. The DoG model fitted to the spatial frequency tuning curve relies on the assumption that no other components are contributing to the response. Although the limited size of the sine grating disk drive should reduce long range influences on the response and the ECRF surround is frequency invariant over a broader spectrum than the CRF, further contributing mechanisms cannot be excluded and may therefore affect the estimates. Similarly the iDoG model fitted to area summation tuning curves may be affected by a number of unaccounted mechanisms. Additionally the iDoG model (see 2.2) actually corresponds to an even luminance disk of variable size rather than the sine grating disks that were used by Sceniak et al. (2006). The decision to use technically incorrect stimuli was made to minimize the influence of the inhibitory CRF surround, which may itself still have some influence on the response. While all these limitations should be held in mind, it is still the best attempt at controlling unaccounted contributions and thus provides the best data on the spatial properties of macaque LGN RFs until detailed histological studies become feasible.

2.1.3.2 *Receptive Fields in the Primary Visual Cortex*

The receptive field properties of neurons in V1, in contrast to LGN neurons, have been characterized to a far greater extent with a number of studies publishing direct anatomical data on neurite arborization in addition to studies involving stimulus protocols such as those employed to characterize LGN RFs. A number of reviews have been published in the past decade to classify different portions of the receptive field and link them to their physiological substrate in the form of feedforward (FF), lateral and feedback (FB) connections. In order to attain a proper understanding of the spatial distribution of afferent neurites, populations of V1 neurons are targeted by, this section will summarize the results.

Recent analyses have established a more complex model for the classification of the spatial properties of neural RFs in V1 than the simpler classical and extra-classical RF structure utilized in earlier work. The structure of a V1 receptive field has been visualized by Angelucci and Sainsbury (2006) and can be seen in Figure 2.1.3.2. It is broken down into the minimum response field (mRF), the summation response field (sRF), which itself is broken down into the high contrast and low contrast summation RF (hsRF and lsRF) and the far surround. In particular, a distinction has been made between the near surround, which extends as far as the lsRF and a suppressive far surround that extends beyond the lsRF. The distinction between the hsRF and lsRF has been introduced to account for the contrast dependence of size tuning. Problematically not all studies nor even all the latest studies use this means of defining different portions of the RF, which may have led to discrepancies of how the sizes of different RF areas are reported. The following sections will attempt to integrate the results from studies employing different means of classifying RFs.

The studies reviewed in Angelucci and Sainsbury (2006) seem to indicate that geniculocortical FF projections integrate signals in the hsRF, while lateral connection underly the lsRF and may thus account for the contrast dependence of spatial summation as well as modulatory effects in the near surround. Classification through measurement of spatial dimensions and onset latencies indicate that inter-areal FB connections seem to be responsible for modulatory influences from the far surround. The influence and spatial properties of each of these projections will be detailed in the following sections.

Geniculocortical Afferents and the Minimum and High Contrast Summation RF The primary visual cortex receives most of its driving inputs through the three previously detailed M-, P- and K-cellular geniculocortical pathways. The M-pathway principally terminates in layers 4Cα and 6, the Parvocellular afferents terminate in layers 4A, 4β and 6, while K-cells primarily target layer 1 and some regions of layer 3. By combining anatomical-tract tracing with physiological recording the spatial extents of feedforward connections have been measured in detail and linked back to the different RF regions.

The minimum response field as defined above is commensurate to the classical RF and is usually mapped using drifting gratings masked to a small disk of optimal parameters for that particular neuron. It is surrounded by the high contrast summation RF, which is measured by increasing the size of a drifting grating disk at high contrast until the neuron reaches its peak response. Using a combination of tracing and electrophysiological recording (Angelucci and Sainsbury, 2006) found that the visuotopic extent of LGN afferents matches the hsRF size of the target V1 neuron.

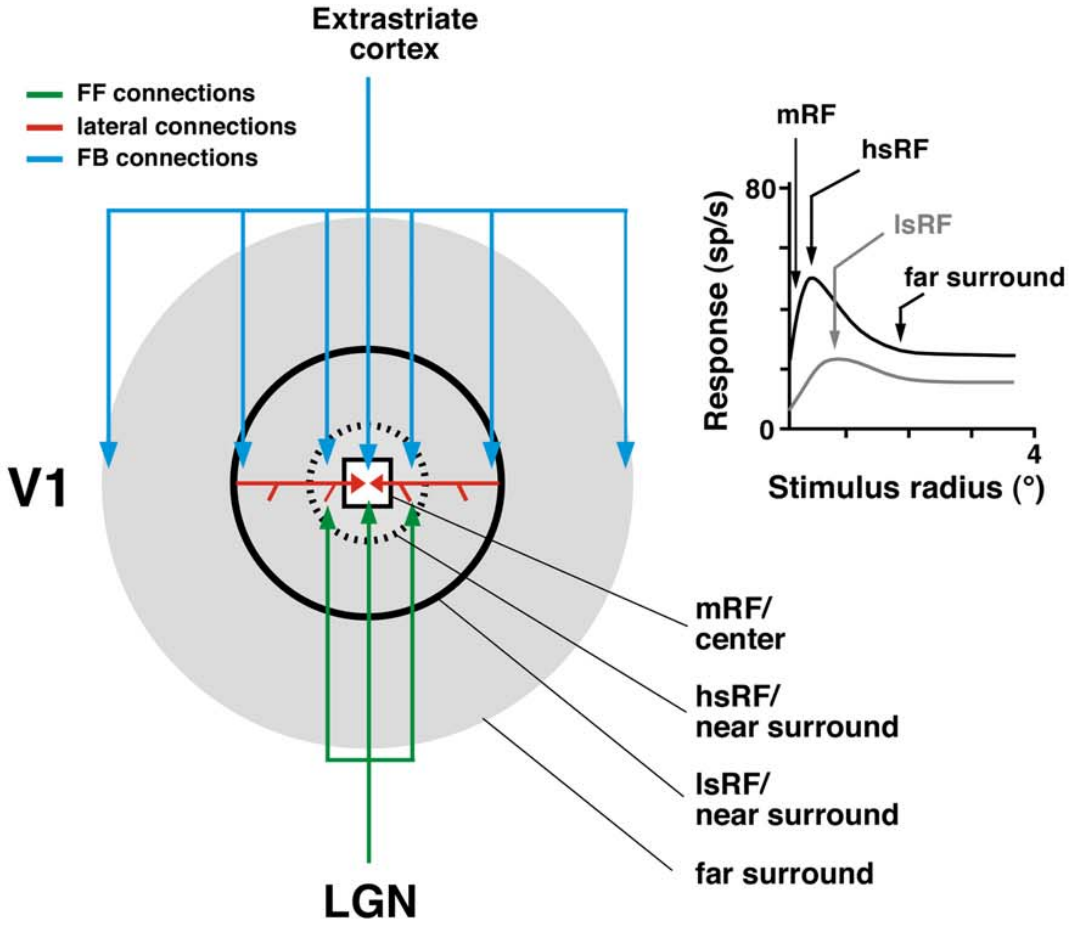

Figure 2.7: s
howing the minimum receptive field (mRF), high contrast summation RF (hsRF) and low contrast summation RF (lsRF). Taken from Angelucci and Bressloff (2006).

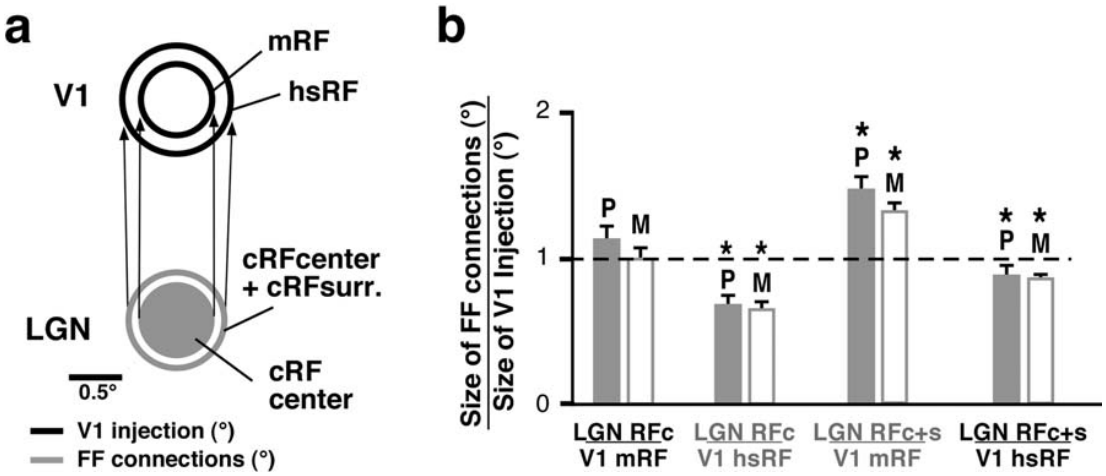

Figure 2.8: c
haracterisation of RF structure and the spatial structure of geniculocortical projections to V1 in (a) diagramatic and (b) chart form. Both demonstrate that the mRF and hsRF are coextensive with the spatial extents of geniculocortical afferents to V1. Taken from Angelucci and Bressloff (2006).

The diagram and bar chart in Figure 2.1.3.2 show how closely the estimates from tracing studies match the results from physiological classifications of RF areas for magno- and parvo-cellular pathways. The close match between these different experiments suggests geniculocortical afferents may underly the extent of a V1 neuron's mRF. Recent evidence has also shown that the an LGN neurons hsRF is roughly commensurate with a V1 cell's mRF. This seems to suggest that the mRF of V1 cells is a product the summation of LGN cells at their peak spatial summation, while the hsRF region of V1 neurons is defined by the integration of excitatory inputs from partially suppressed LGN cells. Beyond that it seems likely FF components partially contribute to surround suppression in V1, however the spatial scales of surround modulation as well as its orientation specificity seem to rule out LGN afferents as the major contributor to the modulatory surround (Angelucci et al., 2002; Angelucci and Sainsbury, 2006).

Having established the contribution of geniculate afferents to the RF of V1 neurons its time to look at their spatial distribution. In their extensive studies and culminating review paper, Angelucci et al. Angelucci and Bressloff (2006) first fitted the iDOG to the spatial summation response curve of a number of V1 neurons, injected the recording sites with tracers and then measured the labeled connections and cell bodies. The linear extents of the labeled connections were converted to visual field coordinates using magnification factor (MF) estimates by Van Essen et al. (1984). Additionally the anatomic extent of the label was measured in LGN and again converted to visual space coordinates using MFs measured by Connolly and Van Essen (1984) and LGN

RF size estimates by Derrington and Lennie (1984). These calculations were used to arrive at the aggregate receptive field (ARF) size, which takes the form:

$$ARF_{deg} = D^{\circ} + RF_{mean} \tag{2.5}$$

where RF_{mean} is the mean RF size of cells recorded at the edge of the injection site, which could reflect the mRF, hsRF or lsRF, and D° is defined as:

$$D^{\circ} = D_{mm}/MF_{mm/deg} + S_{deg} \tag{2.6}$$

where D_{mm} is the diameter, $MF_{mm/deg}$ is the magnification factor and S_{deg} is the RF scatter at the injection site. The results (shown in table 2.1.3.2) show a close match between mRF and hsRF sizes as estimated in V1 and sizes of the RF center and RF center + surround as measured in LGN, once again reaffirming the idea that the mRF and hsRF are primarily driven by geniculocortical afferents. The latest review (Angelucci and Bressloff, 2006) has measured the size of the hsRF in V1 neurons of macaques at 2-8° eccentricity as having mean of about $1^{\circ} \pm 0.1$, which is roughly 2.2x larger than the mRF of the same cell based on results from Angelucci et al. (2002) and Levitt and Lund (2002). Estimates from the latest anatomical study summarized in table 2.1.3.2 provides slightly higher estimates with means of 1.09° and 1.41° in layer 4Cα and 4A/Cβ respectively.

In addition to the spatial extents of V1 RFs, Angelucci and Sainsbury (2006) also estimated the number of LGN afferents that would contact an individual V1 neuron. According to their estimates a single neuron in layer 4Cα can be expected to receive roughly 11 projections from LGN M-cells. Although they were not able to put their own estimates to the Parvocellular pathway, based on anatomical data from cats they determined that on average 10 geniculate cells converge on a V1 layer 4 cell having observed only a maximum of 30. They conclude that the geniculocortical pathway in macaques exhibits an even lower level of convergence than in cats.

In summary, evidence from anatomical and electrophysiological data seems to suggest that the hsRF of V1 neurons and by proxy the geniculocortical afferents are on average between 1.0-1.5° in size, exhibiting highly limited convergence with only about 10 cells targeting a single layer 4 V1 cell.

Lateral Connections and the Low Contrast Summation RF Horizontal, lateral or intra-areal connections have been proposed as the mechanism for a number of observed phenomena, including the contrast dependence of size tuning, which is why it is

	V1 injection ARF size (°)						LGN label ARF size (°)			
	mRF			hsRF			RFc		RFc+s	
Ecc.	L4Cα	L4A/4Cβ	L6	L4Cα	L4A/4Cβ	L6	L1	L6	L1	L6
3	0.67	0.69	0.66	1.02	1.32	1.19	0.67	0.77	0.91	1.02
2.5	0.53	0.55	0.72	0.89	1.20	1.36	0.53	0.54	0.77	0.78
2.75	-	0.56	0.72	-	1.31	1.46	-	0.51	-	0.76
4.2	0.75	0.84	0.73	1.12	1.44	1.59	0.68	0.57	0.93	0.83
5	0.76	0.78	-	1.13	1.35	-	0.66	0.61	0.91	0.89
8	-	1.21	-	-	1.72	-	-	1.14	-	1.46
5.2	0.88	0.97	0.88	1.27	1.55	1.78	0.77	0.83	1.03	1.11
Mean	0.72	0.8	0.74	1.09	1.41	1.48	0.66	0.71	0.91	0.98
SD	0.058	0.089	0.037	0.063	0.066	0.1	0.038	0.085	0.041	0.094

Table 2.4: F
eedforward Connections from LGN to V1 in a number of macaque subjects as measured using retro- and antero-grade staining between 2.5-8° eccentricity. Taken from Angelucci and Sainsbury (2006).

thought they underly the extent of the lsRF. Classically it has been assumed that lateral connectivity manifests itself through short-range excitatory and long-range inhibitory connections (von der Malsburg, 1973; Obermayer et al., 1990). More recent studies have indicated that intra-laminar projections usually originate in excitatory pyramidal neurons in layers 2/3, 4B, upper 4Cα and 5/6 and at least in layers 2/3 have been shown to target 80% excitatory and 20% inhibitory neurons. The spatial scale of these connections has led several studies to conclude that they may mediate modulation of RF center properties in the near surround (Angelucci et al., 2002). Lateral connection could therefore provide a simultaneous mechanism for a number of observed effects including the expansion of the summation RF at low stimulus contrast (Sceniak et al., 1999), colinear facilitation (Mizobe et al., 2001) as well as suppression from the near surround outside the hsRF but within the lsRF (Sceniak and Hawken, 2001; Levitt and Lund, 2002). The previous section showed that such phenomena could not be adequately accounted for by geniculocortical afferents, measurement of spatial extents and response latencies of horizontal connections reaffirm this view and have shown that the lsRF and lateral connections are coextensive (Angelucci et al., 2002).

Apart from the exact spatial dimensions of horizontal connections, it is important several other functionally important properties. While layer 2/3 neurons display patchy connectivity, linking regions with similar functional properties such as orientation preference or ocular dominance, this has been shown not to be the case in macaque layer 4B, upper 4Cα (Angelucci et al., 2002). In addition, it was found

Cortical Layer	Mean ± SD	Range
2/3 (n = 10)	6 ± 0.7	3-9
4B/4Cα (n = 8)	6.7 ± 0.7	4.7-10
5/6	7.9 ± 1.6	6.3-9.5

Table 2.5: l
ateral connections between 2.5-7.5° eccentricity broken down by layer given as D_{mm} along V1's elevation axis. Taken from Angelucci et al. (2002).

that horizontal connections in macaque V1 are isotropic in visual space unlike the anisotropy along the axis of preferred orientation observed in tree shrews (Bosking et al., 1997) and several other species. This may also indicate that contour completion in macaques is mediated by feedback connections. Horizontal connections have been shown to illicit only subthreshold responses (Hirsch and Gilbert, 1991) and are thus limited to modulatory influence. However, as the surround modulation extends far beyond the monosynaptic spread of lateral connections it is unlikely they account for modulation from the far surround. Polysynaptic chains of lateral connections are also an unlikely substrate for the far surround due to the slow conduction velocity of their axons. In particular, Bair et al. (2003) showed that onset latencies of suppression from the far surround were almost equal to the delays from the near surround. This makes it likely that far surround modulation is mediated primarily by inter-areal feedback connections, which we will look at in detail at a later stage.

Having established that spatial profile of lateral connections is commensurate to that of the lsRF and vice versa the data from both sources will be laid out and analyzed. Anatomic data suggests that the spatial spread of lateral connections can be anywhere between 3-10 mm (on average 6-7 mm) in total length (Angelucci et al., 2002), which is broken down by layer in table 2.1.3.2. Along its principal axis the visuotopic monosynaptic spread of V1 horizontal connections has a mean of 2.47° ± 0.3°. This falls well within the range of estimates for the lsRF as published in a number of studies (Shushruth et al., 2009; Sceniak et al., 1999; Sceniak and Hawken, 2001), which were fit with the same integrated DoG model and stimulus protocol as used in the Sceniak et al. (2006) paper on the spatial properties of LGN neurons, reviewed previously.

In summary, there is strong evidence that lateral connections underly the extent of the lsRF and mediate a number of effects in the near surround, including contrast dependent size tuning, colinear facilitation and low contrast suppression. Unlike in other species horizontal connections are isotropic but do exhibit patchy connectivity in layer 2/3. The extents of horizontal connections range between 3-10 mm, which averages to around 2.5° in visual space.

Feedback from Higher Cortical Areas and the Far Surround As the previous to sections have shown, modulatory influences to V1 RFs extend well beyond the spatial spread of both geniculocortical afferents and horizontal connections. This extended modulatory field is known as the far surround and is thought to be mediated by feedback from higher cortical areas. The far surround has generally been characterized as suppressive, especially for iso-oriented gratings in the center and far surround. More detailed analysis has shown that the far surround can also exhibit response facilitation under some stimulus conditions. This section will characterize the function, termination patterns and spatial extents of feedback connections from higher cortical areas to V1.

The notion of a hierarchical organization of cortical visual areas has been around for quite some time and more recent analysis of feedforward and feedback connections has affirmed this view. At the bottom of this hierarchy is V1, sending partially segregated FF projection to areas V2, V3, V4 and visual area middle temporal (MT), which all send FB projections back to V1 (Felleman and Van Essen, 1991). Feedforward projection from V1 to V2 arise mainly from layer 4B and to a lesser degree from layer 2/3 and 6. Feedback connections on the other hand arise from layers 2/3A and 5/6 and terminate in the same layers from which FF connections are sent, which means the cells projecting up the hierarchy often overlap with the termination regions of FB projections being sent back down (Angelucci et al., 2002).

Just like lateral connections FB connections do not drive their target cells, exhibiting only modulatory influence on the RF center (Bullier et al., 2001). Inactivation of areas V2 and MT has been shown to reduce the firing rate of V1 neurons to stimuli in their RF center (Hupé et al., 1998), suggesting FB inputs are summed with FF inputs to increase activity. The exact balance between excitation and inhibition of FB connections is so far not very well explored in macaques but evidence from rats suggest that they almost exclusively target excitatory cells. However Angelucci and Bressloff (2006) and Schwabe et al. (2006) have proposed a regimen where FB connections in the far surround target pyramidal neurons, which in turn send monosynaptic horizontal connections to excitatory and inhibitory neurons in the RF center and can thus mediate both suppressive and facilitatory effects depending on stimulus properties.

Feedback connections have been thought to underly a number of top-down effects in V1, including attention (Treue, 2003), the reverse hierarchy theory of visual learning (Ahissar and Hochstein, 2004) but more recent studies have suggested they contribute directly to the response of V1 neurons to simple visual patterns (Angelucci et al., 2002; Angelucci and Bullier, 2003; Schwabe et al., 2006). Notably Schwabe et al. (2006) and Ichida et al. (2007) seem to have resolved the conflicting evidence about the far surrounds suppressive and facilitatory role. Using both experimental and theoret-

ical work they found that while the far surround is suppressive under high contrast conditions, the response of a neuron to a low contrast stimulus in the RF center is facilitated by a small annular stimulus in the far surround. This indicates that excitatory and inhibitory surround mechanisms have similar extents and that the sign of their contribution depends on changes in local excitation/inhibition balance brought about by surround stimulation.

The spatial and functional organization of the FB pathway is thought to differ significantly from FF connections. They seem to exhibit less precise retinotopic organization and terminate in a more diffuse fashion than FF connections. However, more recent evidence suggests that at least a subset of FB connections exhibit patchy and functionally specific termination patterns (Angelucci and Bressloff, 2006). Evidence from new world primates has also shown that V2 FB axons to V1 link regions of similar orientation preference and that their terminal fields are anisotropic along the axis of the preferred orientation of the originating cell in V2 (Shmuel et al., 2005). The discrepancy between different studies in finding diffuse and patchy FB termination patterns may be attributable to different labeling methods and given that CTB labeling is the more mature and tested procedure it seems likely that FB connections do exhibit patchy terminations in layers 1B, 2/3, 4B and 5/6 and diffuse terminals in layer 1A. The observation of patchy connectivity is also consistent with their proposed functional role in mediating feature-specific influences from the far surround.

The anatomical spatial extents of FB connections from higher cortical areas have been measured in a number of tracing studies. Angelucci et al. (2002) provides a measurements broken down by area, measuring the extents of FB connections from V2, V3 and MT to V1 (see table 2.1.3.2). Once converted into degrees of visual space the results are the following: Feedback from V2 has a mean size of 3.4° in layer 2/3 and 3.8° in layers 5/6, FB from V3 a mean size of 5.6° in layers 2/3 and 6.7° and FB from MT a mean size of 15.3° and 26.6° in the upper and lower layers respectively. The largest far surround field measured was 28° in diameter and the measurement was still limited by the maximal presented stimulus size (Ichida et al., 2007). These results clearly indicate that cortical feedback to V1 increases in its spatial extents and becomes less spatially and retinotopically specific when moving up in the cortical hierarchy to the point where it covers huge portions of the visual field.

Feedback projection from higher cortical areas to V1 mediate a number of important contextual effects and has been implicated in the early stages of visual attention but also seem to be closely involved in the processing of simple visual stimuli. This section has summarized current knowledge on the spatial termination patterns of FB connections to V1, indicating how they could give rise to functional properties of V1 information processing. While this information will aid the development of

Connections	Mean ± SD	Range	Anisotropy ratio
FB V2 → V1 (n = 3)	6.8 ± 0.4	6.4-7.6	2 ± 0.1
FB V3 → V1 (n = 3)	13.4 ± 0.5	12.9-13.9	2 ± 0.2

Table 2.6: m
acaque FB connections to V1 between 2.5-7.5° eccentricity broken down by layer given as D_{mm} along V1's elevation axis. Adapted from Angelucci et al. (2002).

a strongly constrained model, without an understanding of the information content being fed back to V1 from higher cortical areas understanding of their true function will be limited.

2.2 THE INTERNAL CIRCUITRY OF STRIATE CORTEX

The previous section outlined the overall structure of the early visual system, breaking down the contribution of inputs from various sources on the receptive field (RF) of neurons in primary visual cortex (V1). While this provides general anatomical constraints and sheds some light on the functional circuitry underlying many of the contextual effects that have been observed in the primary visual cortex, it does not address many of the fundamental questions about the functional significance of recurrent cortical processing. In particular, it does not address the delicate balance in both strength and spatial extent between excitation and inhibition that is required to halt runaway excitation, sparsify the inputs and thereby allow for the formation of concentrated activity bubbles around which self-organization can take place. This section will cover how the understanding of intra-cortical connectivity has evolved and how this has been reflected in various developmental and non-developmental models.

2.2.1 *The Mexican Hat*

Before complex tracing and circuit reconstruction techniques became available, considerations about the connectivity profiles in the cortex were largely theoretical or based on data from other anatomical structures, which were at the time more amenable to study. Anatomical data and electrophysiological studies in the retina had shown that there is a strong lateral inhibitory component involved in decorrelating photoreceptor activities, thereby enabling more efficient coding of the input (Atick and Redlich, 1992). Lateral inhibition was taken to be a general principle of sensory systems and, among others, Blakemore et al. (1970) suggested repulsive interactions between neighboring contours could account for psychophysical data. Further evi-

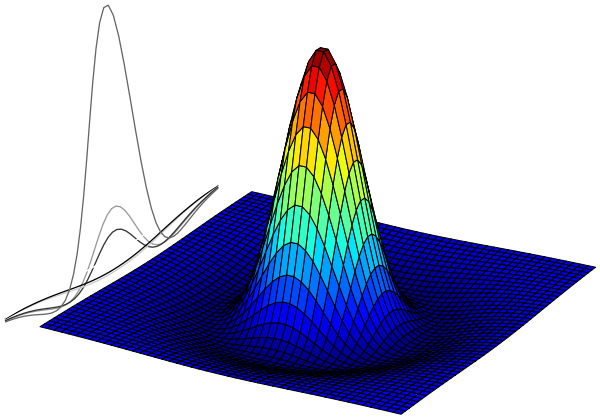

Figure 2.9: M
exican Hat connectivity.

dence of lateral inhibition as a general feature of sensory systems was provided by a variety of theoretical models of self-organization, highlighting the necessity of effective local excitatory and long range inhibitory interactions for the formation of local activity bubbles, which in turn provided the basis for orderly map organization (von der Malsburg, 1973; Miller et al., 1989).

The connectivity profile employed in the various self-organizing map models became known as the Mexican hat profile due to its strong resemblance to a sombrero. A simulated Mexican hat profile is shown in 2.2.1 generated through a simple difference of Gaussian (DoG), whereby a small positive Gaussian kernel is combined with a larger inhibitory kernel. A large variety of cortical models have successfully employed this connection profile to explain a variety of effects ranging from topographic map organization, orientation tuning and contextual effects. Problematically, it is unclear how biologically realistic the assumption of strong local excitation and broadly tuned or untuned inhibition is.

Since then a number of lines of evidence have come together to show that this spatial connectivity profile does indeed seem to exist, at least when considering the aggregate circuit under certain stimulus conditions. Electrophysiological and optical imaging have both confirmed that strongly driven cortical neurons receive strong local excitation and long-range lateral inhibition (Grinvald et al., 1994; Sceniak and Hawken, 2001). At high contrasts Grinvald et al. (1994) showed that a neuron responding to a small, central grating stimulus in isolation exhibits far greater levels of activity than when presented with a co-linear surround stimulus alongside the central stimulus. This highlights an interaction between the center and surround RF that

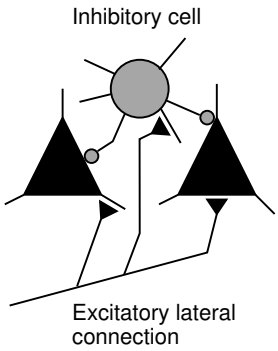

Figure 2.10: Local microcircuit for long-range suppression through di- or poly-synaptic circuit in V1. Reproduced from Miikkulainen et al. (2005) as adapted from Weliky et al. (1995).

is not only dependent on the orientation statistics but also on the contrast levels in the input. In particular Hirsch and Gilbert (1991) and Weliky et al. (1995) showed that lateral connections impinging onto a neuron would exert a small excitatory effect, when embedded in a low contrast surround, while high contrast would flip the sign of these contextual influences and suppress the central neurons activity. Additionally, Hirsch and Gilbert (1991) found that laterally evoked EPSPs, presumably underlying facilitatory effects, experienced strong voltage-dependent enhancement, speculating that this would allow stimuli in the surround to modulate cRF responses without driving the response on its own. This provides functional evidence that the aggregate circuit can produce a Mexican hat profile under the right stimulus conditions but also suggests that the underlying circuitry is more complex.

Precisely how these two input-dependent modes of contextual integration emerge is unclear. However, as anatomical tracing techniques have become more sophisticated and biomarkers for different cell types were discovered, attempts have been made at teasing apart the cortical circuit. These anatomical surveys showed that long-range connections extending beyond a single orientation column were almost exclusively excitatory and 80% of these excitatory synapses target other excitatory pyramidal neurons (Hirsch and Gilbert, 1991; Kisvárday et al., 1997). The remainder of these connections were shown to target inhibitory interneurons, which would in turn contact pyramidal neurons, suggesting a di- or poly-synaptic mechanism for long range suppression. On the basis of some of this work Douglas and Martin (1991) developed what has become known as the canonical microcircuit for the neocortex. This circuit includes separate inhibitory and excitatory neurons, which are driven by thalamic afferents and recurrent connections. Further work has fleshed out the spatial profiles of these connections, which ultimately gave rise to the simplified circuit described in Figure 2.10. This goes some way toward reconciling anatomy with the experimentally measured functional connectivity profile at high contrast levels.

More recent attempts at reconciling anatomy with function have been able to further resolve some of the problem. In particular, there is clear evidence showing that excitatory synapses onto excitatory and inhibitory neurons differentially target their recipient neurons. Excitatory connection onto inhibitory interneurons seem to preferentially synapse perisomatically, in contrast with recurrent long-range excitatory connections which have been shown to target their recipient neurons dendritically (Gilbert and Wiesel, 1990; McGuire et al., 1991). Additionally, at least a subset of inhibitory interneurons seem to preferentially target the soma of pyramidal and stellate cells they inhibit (Markram et al., 2004). On that basis it is reasonable to assume that inhibitory connections are, in general, stronger and may act divisively.

Although these divergent properties of excitatory and inhibitory neurons were only discovered recently it had long been proposed that inhibitory interneurons are inherently more effective at suppressing activity than recurrent excitatory connections are at exciting the network, but due to a high threshold or some other related mechanism the inhibitory neurons are not strongly recruited unless there is strong afferent input (Sillito, 1979), as would be the case under high contrast conditions. Although it is now clear that network effects allow for strong long-range inhibition through di- or poly-synaptic connections under the right stimulus conditions, the mechanisms by which contrast dependent behaviors emerge from the cortical circuit are still only vaguely characterized.

A number of models have been developed to explain contrast dependence of contextual effects on the basis of the general principle of asymmetry between the response properties of excitatory and inhibitory neurons. One of the first to publish such a model were Stemmler et al. (1995), who suggested inhibitory neurons require higher external input rates before activating because they receive significantly less spontaneous background input as compared to excitatory neurons, an effect known as stochastic resonance. Although this mechanism has at least been theoretically reaffirmed (Bezrukov and Vodyanoy, 1997), there is no experimental data establishing it as a functionally significant mechanism in V1. Other models, hoping to account for a wider array of RF effects implement such a mechanism directly by setting a higher threshold in the inhibitory population and introducing very strong lateral excitation of inhibitory neurons (Schwabe et al., 2006). Another suggestion was made by Somers et al. (1998), who in addition to a simple threshold asymmetry, also point to the claim by Thomson and Deuchars (1994) and others (Abbott et al., 1997; Tsodyks and Markram, 1997), that synaptic depression causes recurrent excitation to quickly decline in efficacy during high frequency stimulation, while facilitation of excitatory synapses onto inhibitory interneurons increases transmission efficacy as presynaptic firing rates increase (Thomson et al., 1995). The suggestion that inhibitory neurons

have a higher contrast threshold has become very popular in the theoretical literature of the past 20 years, however as of yet there is only limited evidence to support this core assumption and there are a number of alternative or concurrent mechanisms that may explain all or at least some of the contrast dependent effects.

As the last paragraphs have shown, inhibition and in particular surround inhibition are at the core of the major discussions on contrast dependent effects and surround modulation and a more thorough understanding of the spatial, temporal and functional dynamics of surround inhibition is required.

2.2.2 *Surround Suppression: Feedforward or Feedback?*

The last section highlighted how little we still know about the origin of surround suppression and inhibition. There is still significant controversy whether surround suppression originates in feedforward or feedback pathways or whether both contribute over different spatial scales. This includes suggestions that surround suppression in the classical RF are mediated through synaptic depression in the thalamo-cortical afferents (Carandini et al., 2002), broadly tuned inhibition by thalamo-cortical recipients, long-range excitation of local inhibitory interneurons or even through various feedback mechanisms. This section will detail the evidence for each of these proposals, the possibly anatomical origin of each of these mechanisms and tease apart the circuit by looking at interactions between surround suppression, stimulus size and contrast.

Since the circuitry of the cortex is so complex, the task of segregating feedforward and feedback contributions to surround suppression is highly difficult. Although only a starting point, one way of starting to tease these two possible contributions apart is to look at the time course of suppression. In the literature early and late components to surround suppression have been identified. The early component is characterized as being driven by lower CRF contrasts with spatio-temporally broad band tuning and little adaptation (Levitt and Lund, 1997; Cavanaugh et al., 2002). The late component on the other hand is driven more strongly by high contrast stimuli in the CRF, has sharp spatio-temporal tuning and can be strongly affected by adaption (Levitt and Lund, 1997). Evidence suggests that the early, broadly tuned component originates in the LGN and the thalamocortical recipient layer of visual cortex (Blasdel and Fitzpatrick, 1984; Hawken et al., 2009). In monkey cortex in particular, this broadly tuned suppressive effect is only weakly evident in the LGN and is thought to arise much more strongly in layer 4 of striate cortex (Webb et al., 2005), which may have some correspondence to the broadly tuned inhibitory population identified by Hirsch et al. (2003). Carandini et al. (2002) on the other hand suggest

that there is a synaptic explanation for surround suppression, primarily due to the speed with which the suppression arrives, its immunity to cortical adaptation and the fact that it is restricted to the CRF. However, they concede that synaptic depression doesn't account for gain control and the abolishment of cross-orientation suppression by $GABA^A$ blockade, so a mechanism that can account for all these phenomena may still be preferable. In that vein, Webb et al. (2005) propose two inhibitory mechanism one of which sums local activity in a neurons CRF and divides the response of the CRF and the later component that receives inputs from a much larger area but provides narrowly tuned suppression. The broadly tuned component in particular has a strong relationship with contrast gain control, which has been firmly established to act divisively. Independent work by Xing et al. (2005) supports the suggestion of two inhibitory components and further expand on the size dependence of these two components. Specifically, they conclude that the tuned component is recruited far more strongly for larger stimuli, which seems to confirm a contribution from beyond the CRF.

This recent work has identified two clear and distinct inhibitory components but have not yet fully described which mechanisms and circuits they are mediated by, the next section will attempt to address this shortcoming.

2.2.3 *Distinct Inhibitory Populations*

In order to begin teasing apart the origin of intracortical surround suppression mediated by local inhibitory circuits it is necessary to consider the different candidate cell classes. While there are a long list of different inhibitory cell types based on their morphology and spiking behavior, recent techniques have divided inhibitory into several broad, functionally distinct classes based on their immunoreactivity. The two cell types considered here are parvalbumin (Pv-ir) and somatostatin (Sst-ir) immunoreactive neurons, which are primarily differentiated by the cellular locus of their synaptic targets. While Pv-ir neurons seem to target pyramidal cells perisomatically, Sst-ir neurons target their recipients dendritically. The following subsections will detail the anatomical, physiological and functional differences between these cell classes.

2.2.3.1 *Parvalbumin Immunoreactive cells*

The two main cell types, which exhibit parvalbumin immunoreactivity are the chandelier and basket cells (Binzegger et al., 2004). While chandelier cells make up only a small fraction of GABAergic neurons in the cortex and are primarily found in layer 2/3, the fast-spiking (FS) basket cells are the predominant interneuron subtype in the mammalian cortex across all lamina, accounting for 42% in layer 2/3 and layer 5 and

78% in layer 4 of the cat (Hogan et al., 1992; Huxlin and Pasternak, 2001) and up to 74% across cortical layers in macaque (Van Brederode et al., 1990). The abundance in the thalamocortical recipient layers and the fact that they preferentially target the soma and proximal dendrites of spiny neurons with multiple strong synapses, exhibiting high probability of GABA release (Freund and Katona, 2007; Markram et al., 2004), ensures basket cells are of tremendous interest. On that basis it has been suggested that the perisomatic connectivity profile of basket cells gives them the ability to provide shunting inhibition to layer 4 spiny neurons, acting divisively to control their response gain (Wilson et al., 2012).

Basket cells can be further subdivided, primarily based on their size, into clutch and large basket cells. However all basket cells can make multiple connections onto a target pyramidal neuron (Somogyi et al., 1983) and have a considerable spatial extent (Kisvárday et al., 2002). In particular, studies in cat area 17 and macaque V1 have identified basket cells 1-2 mm in extent (Somogyi et al., 1983; Lund, 1987; Lund and Yoshioka, 1991; Martin et al., 1983) and single cell tracing studies have even identified large basket cells, which give off a roughly uniform number of boutons across a large diameter spanning up to two hypercolumns (Buzás et al., 2001). A schematic representation of the basket cell connectivity profile is summarized and compared against both the orientation column structure and the excitatory connection profile in Figure 2.2.3.1. Functionally such a connectivity profile may indicate that basket cells can suppress neurons with widely varying orientation, which may implicate basket cells as an important mechanism to sharpen orientation preference.

In terms of their spiking behavior Pv-ir cells are characterized as being fast fast-spiking (FS) neurons, often firing in bursts with a very short response latency. Further, evidence from somatosensory cortex in rodent and lagomorph species suggests they receive strong input from thalamocortical afferents arriving in layer 4 and very effectively suppress sustained firing from spiny neurons receiving inputs from the thalamus (Swadlow, 2003), implicating them in feedforward inhibition. This feedforward inhibition circuit is shown in Figure 2.2.3.1. Their effectiveness in suppressing feedforward activity can be explained by the large number of thalamocortical axons they receive, which exhibit faster kinetics than those targeting spiny neurons (Cruikshank et al., 2007; Gabernet et al., 2005), and the fact that they evoke large inhibitory responses in spiny cells (Cruikshank et al., 2007; Gabernet et al., 2005).

It is also important to note that the thalamocortical synapses onto the Pv-ir population have been shown to be depressed by repetitive activation, resulting in weaker feedforward inhibition at high stimulation frequencies (Gabernet et al., 2005), a property which may indicate lower activation of the PV population at high contrasts. The Pv-ir population may also play an important role in network homeostasis as activity

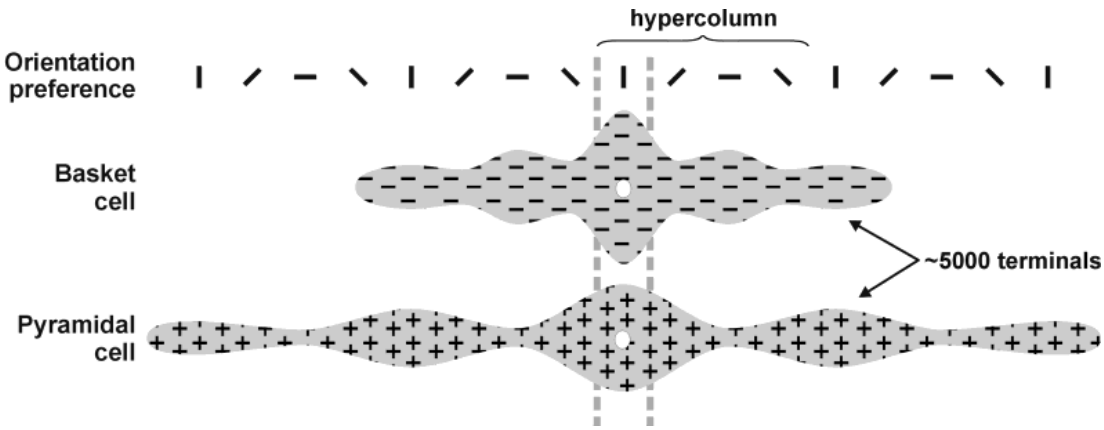

Figure 2.11: l
ong-range basket cell and excitatory connectivity with the underlying orientation preference structure. Upper legend represents different orientation domains in the cortical topographic map. Grey dotted lines indicate the orientation column within which soma of the simplified basket cell and excitatory neuron are found. The grey field with minus signs indicates the extent of inhibition provided by the basket cell connections considered in the current study. The grey region with plus signs indicates the excitatory field of a stereotypical pyramidal cell based on previous data by Bosking et al. (1997); Kisvárday et al. (1997) and others. The height of the grey plus/minus regions indicates the number of axon terminals provided in that column. While basket cell terminals show local maxima every half hypercolumn distance, pyramidal cell terminals are maximal at every full hypercolumn distance. Reproduced from Buzás et al. (2001).

blockade has been shown to decrease the efficacy of Pv-ir inhibition (Bartley et al., 2008), thereby indirectly up-regulating activity in excitatory cells. Further, selectively up-regulating Pv-ir cells using optogenetic stimulation was shown to have a similar effect as lowering the contrast, which is to increase preferred size and weakening surround suppression (Nienborg et al., 2013). This is compatible with the idea that Pv-ir neurons provide strong feedforward inhibition such that the input drive in the cortex is decreased, as would be observed under low contrast conditions. Overall then, Pv-ir neurons show strong interaction with stimulus contrast and may be involved in regulating the gain of the network with complex implications for the contrast response of the network.

There is still considerable debate on the extent to which this subpopulation is tuned to a particular orientation. Most visuo-cortical models employ broad, non-specific GABAergic inhibition (Somers et al., 1998; Troyer et al., 1998). This seems to be supported by anatomical evidence, which has long shown that inhibitory projections are generally diffuse and display low specificity for specific stimulus features (Albus and Wahle, 1994; Kisvárday et al., 1997). Further, electrophysiological data paints a similar picture, revealing suppression that is broadly tuned for stimulus attributes, providing orientation unspecific suppression from a visual region that is coextensive with the classical RF (DeAngelis and Robson, 1992). Recent attempts at studying the Pv-ir neurons at the single neuron level have revealed a mixed picture. While the cells as a whole were broadly tuned to various stimulus features, individual branches often displayed very high specificity, which may underlie subfield antagonism and contribute to a push-pull configuration (Kisvárday et al., 2002). Studies in mouse visual cortex seem to confirm such a dual purpose of Pv-ir neurons, although they also find higher heterogeneity in the Pv-ir population (Runyan et al., 2010). This may indicate a laminar differentiation in function as studies of Pv-ir neurons in the thalamocortical recipient layer 4 have characterized them to exhibit very broad tuning, due to their low spiking threshold and more convergent inputs (Ma et al., 2011). However, even in layer 2/3 most Pv-ir cells displayed broad orientation tuning (Hofer et al., 2011). Further studies in cat area 17 find very similar results identifying a class of inhibitory complex cells in layer 4 exhibiting weak orientation tuning (Hirsch et al., 2003), which can primarily be accounted for by the tuning of synaptic responses and a lower spike threshold (Nowak et al., 2008). Further study will be needed to confirm whether these results extend to the primate, however it is clear that basket cells generally display weaker tuning than spiny neurons in V1.

Based on our current knowledge of Pv-ir cell population and more specifically the basket cells, it is clear that they provide a good candidate mechanism to account for a number of phenomena. Their fast response profile, large spatial extent and

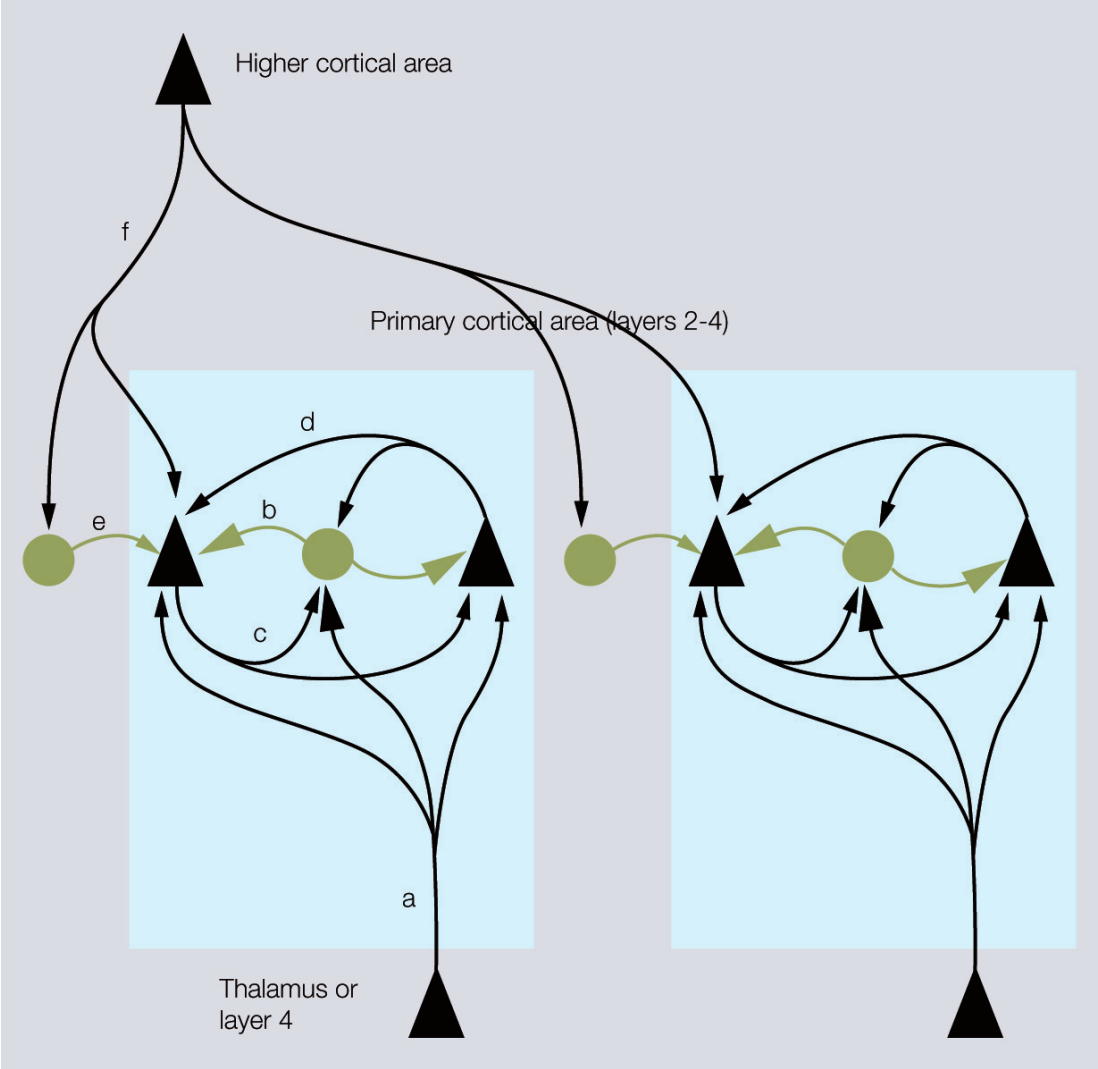

Figure 2.12: p
arvalbumin-immunoreactive neurons in thalamocortical, interlaminar and interareal cortical circuits. Feedforward excitatory thalamocortical inputs to pyramidal cells, spiny stellate neurons () and fast spiking interneurons () in layers 2-4 (a). Inputs to interneurons are stronger (large arrowheads) than inputs to spiny cells. PV neurons provide strong (large rectangular endings) feedforward inhibition (b) to spiny cells. Feedback inhibition (c) results from PV neurons that are excited by the same spiny neurons that they inhibit. These reciprocally connected spiny neuron/PV neuron pairs share common inputs (e.g., cells in layer 4 from thalamus or cells in layer 2/3 from layer 4) creating recurrent excitatory (d) and inhibitory subnetworks (contained within blue shaded boxes). 'Lateral' inhibition (e) of these subnetworks results from PV neurons that are driven by excitatory feedback connections (f) from outside the subnetworks (e.g., by layer 5 to layer 2/3 connections or feedback from higher cortical areas). Notice that 'lateral' inhibition is weaker (small rectangular endings) than feedforward and feedback inhibition and impinges on multiple subnetworks. Reproduced from Burkhalter (2008).

the relative weakness in their orientation tuning may allow them to carry out fast, adaptive gain control, broadly tuned suppression and thereby sharpen the orientation preference of the PNs in their vicinity. So while synaptic depression may still provide an alternative explanation for many of these phenomena, it is likely that the Pv-ir population carries out at least some of these functions.

2.2.3.2 *Somatostatin Immunoreactive cells*

The Sst-ir population has been characterized to a lesser extent, but a general consensus is beginning to emerge around their function and electrophysiological properties. The Sst-ir cells account for around half of the non-PV-expressing neurons (Gonchar et al., 2007; Xu et al., 2010) and preferentially synapse onto distal dendrites and dendritic tufts of pyramidal neurons (Di Cristo et al., 2004; Silberberg and Markram, 2007), on the basis of which it has been suggested that Sst-ir neurons act subtractively (Wilson et al., 2012).

In trying to characterize the excitatory inputs to Sst-ir cells in layer 2/3 of the mouse, Xu and Callaway (2009) determined that unlike Pv-irs, the main source of excitation of Sst-irs were horizontal axons within layer 2/3 not the ascending layer 4 axons. This property also contributed to the size dependent responses of the Sst-irs, which were shown to be recruited progressively more strongly when they were exposed to optogenetic photostimulation of increasing diameter. Importantly, the Sst-ir response grew larger even when photostimulation reached beyond its maximal dendritic extent, demonstrating that the recruitment of increasingly more distant pyramidal cells provided their main excitatory drive. This putative circuit is shown in Figure 2.2.3.2, exhibiting their pooling of tuned, excitatory input from pyramidal cells across a large area, providing only very local inhibition. Additionally it seems that Sst-ir interneurons are capable of disinhibiting the thalamocortical recipient layer 4 by targeting Pv-ir cells (Xu et al., 2013).

In terms of their response properties the Sst-ir neurons have been shown to exhibit much lower levels of spontaneous and evoked activity, stronger orientation and direction selectivity and longer response latencies than Pv-ir neurons in mouse visual cortex (Ma et al., 2011). These properties are consistent across both layer 2/3 and 4 and may point to a role in gating later arriving intracortical excitatory inputs. In terms of their tuning properties Sst-ir neurons display smaller On/Off subfields with less overlap than nearby spiny neurons and orientation tuning on par with pyramidal neurons. While most data on their tuning properties comes from rodent visual cortex, which does not exhibit a topographic organization of orientation tuning, it seems the stronger orientation selectivity of Sst-ir cells can be accounted for by their preferential connectivity to neurons with similar orientation preference as well as a

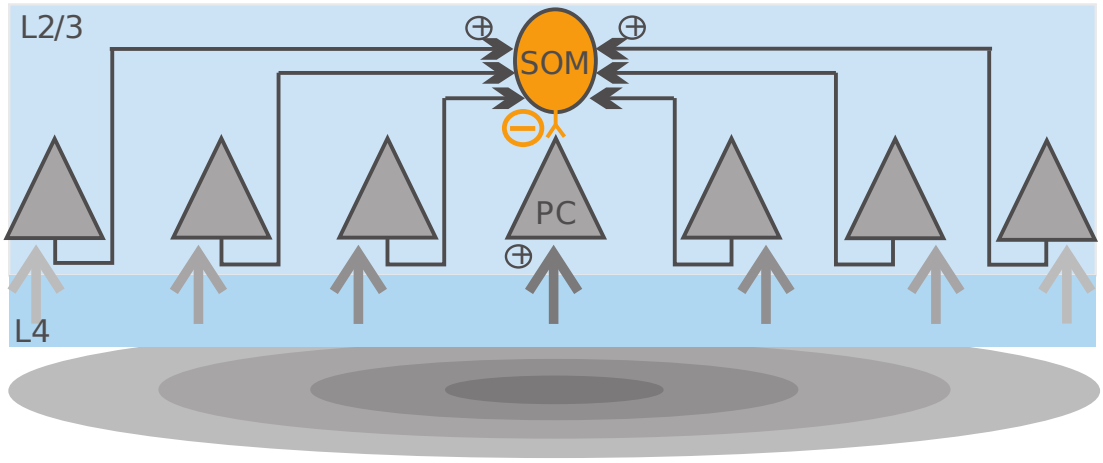

Figure 2.13: i
llustration of the cortical circuit in layer 2/3 contributing to surround suppression. As a visual stimulus expands (larger stimuli are shown in lighter grey), recruitment of adjacent PCs increases Sst-ir excitation through horizontal axons (horizontal arrows). Reproduced from Adesnik et al. (2012).

higher spiking threshold and weaker excitatory inputs (Bartley et al., 2008). Another interesting feature of Sst-ir response properties is the fact that although their excitatory inputs are weak, they are facilitating resulting in delayed but strong activation under high frequency stimulation (Beierlein et al., 2003; Bartley et al., 2008; Tan et al., 2008). Based on these properties, Sst-ir neurons would only be recruited to provide significant inhibition if the stimulus contrast or size reaches a certain level (Adesnik et al., 2012). Thus they could provide a direct mechanism for contrast dependent size tuning and surround modulation effects, being only weakly recruited when contrast or stimulus size is low but becoming strongly activated at higher contrast levels and for larger stimulus sizes.

Another suggested role for Sst-ir neurons is the gating of feedback signals on the distal dendrites of principal neurons. The Martinotti cells, which provide strong axonal projections to layer 1 of the cortex, make up a large proportion of Sst-ir neurons in layer 2/3 of the cortex and are therefore well placed to suppress feedback signals arriving in the superficial layers of the cortex (Fanselow et al., 2008; Gentet et al., 2012). In the rodent somatosensory cortex, Gentet et al. (2012) showed that Sst-irs in layer 2/3 become spontaneously active during passive wakefulness but are strongly suppressed during active whisking behavior, presumably by the vasoactive intestinal peptide (Vip)-ir population. The Sst-ir cells may therefore be involved in mediating top-down control of sensory processing, effectively gating context-dependent processing in a state dependent manner.

In summary, Sst-ir neurons seem to provide delayed and feature-selective feedback inhibition, which puts them in a good position to effectively gate late arriving intra-

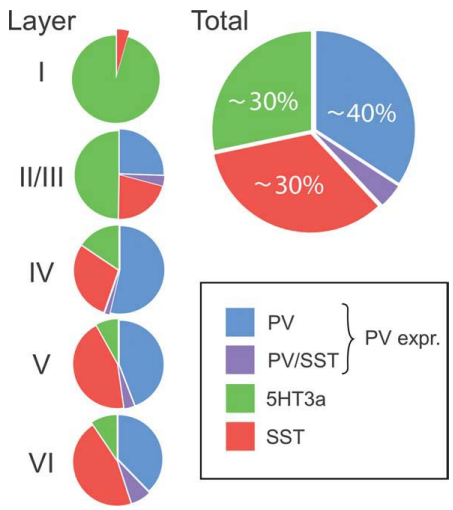

Figure 2.14: c
ortex by immunohistological marker. Reproduced from Rudy et al. (2011).

cortical excitatory inputs arriving from either lateral or feedback connections but may also be implicated in suppressing feedforward inhibition by inactivating layer 4 Pv-ir cells.

2.2.4 *Vasointestinal peptide expressing interneurons*

The previous review focused primarily on the two most common types of inhibitory interneurons, the Parvalbumin (PV) and Somatostatin-expressing (Sst) cells, since then a number of studies have focused on the role of 5HT3ar-expressing interneurons and particularly the vasointestinal peptide (Vip)-expressing subgroup (Fu et al., 2014; Higley, 2014; Kepecs and Fishell, 2014; Lee et al., 2013).

The Vip subgroup is particularly concentrated in upper, associative layers and feedback layers of the cortex, as shown in figure 2.2.4 by Rudy et al. (2011). The most striking finding was their central role in state dependent modulation during active whisking tasks. Lee et al. (2013) found that S1-projecting vM1 pyramidal neurons strongly recruited Vip-expressing interneurons in superficial layers of somatosensory barrel cortex, which in turn inhibited somatostatin-expressing interneurons causing effective disinhibition of cortical pyramidal cells. These results could were then affirmed through optogenetic stimulation of Vip neurons in mouse V1, artificially mimicking the effects locomotion (Fu et al., 2014). When considered in conjunction with previous studies that established strong cholinergic and nicotinic inputs to Vip neurons from the basal forebrain (Wickersham et al., 2007), this suggests a strong involvement of Vip neurons in a cortical circuit responsible for the enhancement of activity in sensory cortex by behavioural state.

2.2.5 *Somatostatin and Parvalbumin expressing interneurons*

The previous review provided a detailed review of the literature on Somatostatin-expressing (Sst) interneurons, summarizing them as a population of inhibitory cells with a delayed response and feature-selective inhibition, which may be involved in long-range surround suppression and disinhibition of the feedforward pathway. Recent studies, have further refined this story, indicating that while Sst neurons may be involved in orientation dependent surround suppression in the superficial layers (Adesnik et al., 2012), their inactivation has little effect on surround suppression in deeper layers (Self et al., 2014). Although, a recent study looking at the contribution of feedback on surround suppression has shown that by cooling extrastriate visual cortex, surround suppression could be significantly reduced, these results also seem to confirm that there is a strong source of tuned surround suppression within striate cortex (Nassi et al., 2013). The precise origin of delayed orientation-tuned suppression in primary visual cortex therefore remains unclear, however current evidence indicates that both somatostatin neurons and cortical feedback contribute to this effect.

Another study in auditory cortex once again confirmed the previously described properties of Sst and Parvalbumin (PV) expressing interneurons, hypothesizing that 'while PV neurons may provide broadly tuned feedforward inhibition for a rapid control of ascending inputs to excitatory neurons, the delayed and more selective inhibition from SOM neurons may provide a specific modulation of feedback inputs on their distal dendrites' (Li et al., 2014).

Overall these results seem to confirm the general conclusions drawn about PV and Sst-neurons in last years review, and at the very least suggesting that no major revisions to the multi-population model developed over the course of this PhD will be required.

2.2.5.1 *Connectivity between different cell types*

In order to gain an understanding of the circuits the different interneuron cell types are involved in, it is important to consider their interconnectivity. Several studies have sought to determine the connectivity between Pv-ir, Sst-ir and other interneuron types. The core findings of these studies determined that Pv-ir cells preferentially inhibit one another, Sst-expressing cells avoid one another and inhibit all other types of interneurons particularly the Pv-ir cells (Xu et al., 2013), while a third type, the Vip-ir cells preferentially inhibit Sst-ir cells (Pfeffer et al., 2013). This connectivity profile is schematically represented in Figure 2.2.5.1. In mouse cortex the Pv-ir, Sst-ir and Vip-ir cells accounted for about 40%, 18% and 8% of the GABAergic population,

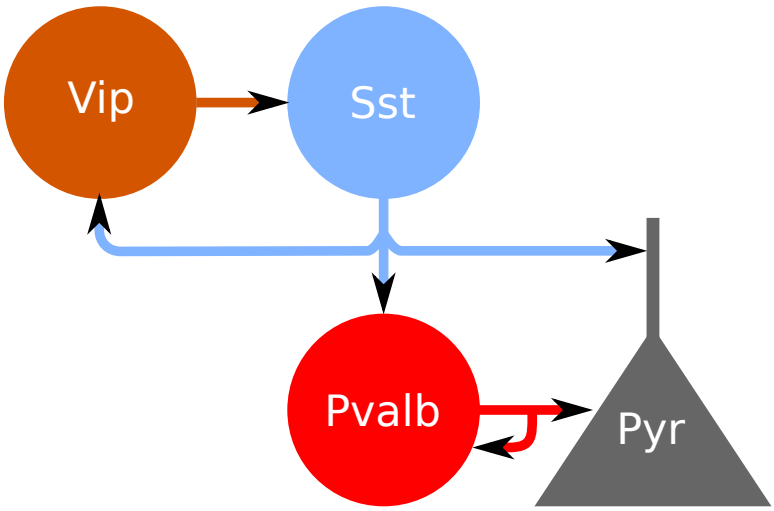

Figure 2.15: p
arvalbumin (Pv), vasoactive intestinal peptide (Vip) expressing and pyramidal (Pyr) cell types. Adapted from Pfeffer et al. (2013).

respectively (Xu et al., 2010), and although these percentages vary considerably across species Pv-ir and Sst-ir are always the two most commonly expressed GABAergic populations.

Recent tracing techniques have also been able to establish that excitatory cells provide orientation specific inputs to the inhibitory population. Using viral tracing techniques Liu et al. (2013) are able to trace inputs to inhibitory and excitatory neurons in the cat visual cortex. While their work

2.3 INTERACTIONS BETWEEN NEUROMODULATORS AND V1 CIRCUITRY

The neuromodulatory influences on the circuitry of primary visual cortex, described in the previous literature review are mediated by their influence on the circuitry that is internal to the primary visual cortex. As the prime interest of this report and the PhD project is to characterize the influence of cholinergic modulation on V1 circuitry, this section will detail how cholinergic basal forebrain inputs may be modulating the different cell types described above and how this may give rise to the effects that were described in the PhD proposal. It will also try to provide a general framework of cholinergic modulation.

As outlined in the previous report there are two main groups of acetylcholine receptors (AChRs), nicotinic and muscarinic, hereto referred to as nAChRs and mAChRs, respectively. While nAChRs are primarily expressed presynaptically on thalamocortical afferents, mAChRs are expressed throughout the cortex on a large variety of cell types with highly divergent effects. The recent review by Thiele (2013) provides

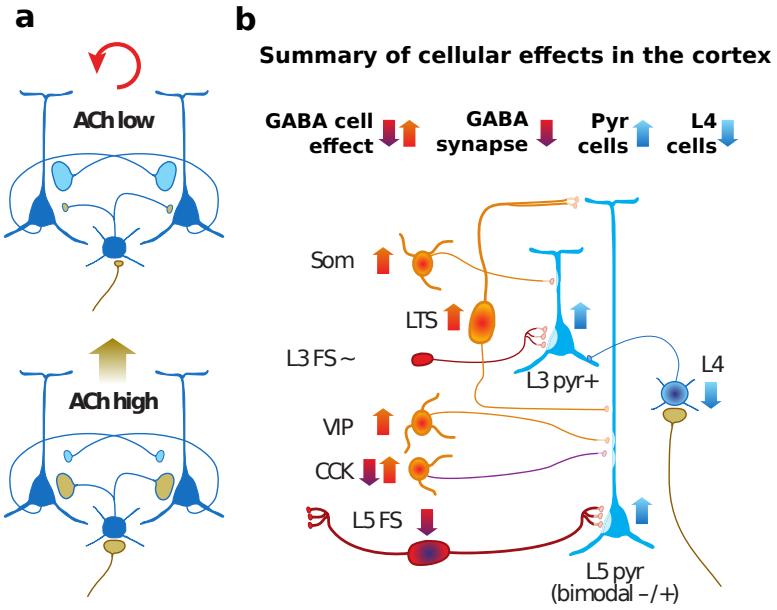

Figure 2.16: C
holinergic effects on the processing of feedforward versus internal information. When acetylcholine (ACh) is low, synaptic efficacy of intrinsic connections is high, while feedforward synaptic efficacy is average. Therefore, information flow is dominated by recurrent processing. When ACh is high, feedforward synaptic efficacy is high (through presynaptic nicotinic mechanisms), while synaptic efficacy of intrinsic connections is reduced (through M2-type receptor mediated mechanisms). In this mode, processing is dominated by feedforward information. (b) Overview of muscarinic effects on cortical circuitry, which may enable efficient filtering of information. Arrows indicate whether neuronal activity is increased or decreased by muscarinic signaling. Reduced intensity of colors at synaptic sites indicates that the synaptic efficacy is reduced by muscarinic signaling. The diagram does not provide immediate insight into the likely consequences of the effects, but rather intends to give a graphic overview of the main effects reported in the literature. Reprinted from Thiele (2013).

a thorough summary on the effects of muscarinic and cholinergic signaling within neocortical circuits, highlighting the fact that the data is still relatively sparse, often contradictory and do not yet point to a definite theory of cholinergic modulation. However, in addition to laying out the evidence, summarized in the schematics shown in Figure 2.3, two main theories of cholinergic modulation of neocortical circuits are discussed. The influential theory that cholinergic signaling simply reduces intracortical processing in favor of feedforward processing is assessed as simplistic, although it may provide a good first approximation of the effects. As an alternative, Thiele suggests that it may be involved in enabling efficient filtering of information to satisfy current task demands but points out this theory too needs further refinement. By identifying the core circuits affected by cholinergic signaling it may be possible to close in on a more refined framework and refine current theories.

In order to begin modeling the effects of cholinergic modulation and possibly shed some light on the different frameworks of their action, it is important to establish their effect on the different cell classes that have been identified and characterized hereto. In the mammalian neocortex both mAChRs, in their m1 and m2 subtypes (Tigges et al., 1997), and nAChRs (Han et al., 2000) are expressed at significant levels. Nicotinic AChRs are primarily expressed presynaptically in thalamic axons arriving in primary sensory areas and have been shown to boost the response gain of layer 4C principal neurons (Disney et al., 2007; Gil et al., 1997). In layers 2,3 and 5 on the other hand, the main effect of nicotinic application seems to be general suppression mediated by nAChR expression on different interneuron classes.

Muscarinic AChRs are strongly expressed in different GABAergic populations but particularly among Pv-ir neurons, which show strong expression of the m1 receptor subtype in their somata (87% of cells) and much weaker expression of the M2-subtype 31% of cells), which was generally restricted to the axons (Disney and Aoki, 2008). Surprisingly however several studies have indicated that the intrinsic excitability of FS cells is unaffected by cholinergic agonists (Gulledge et al., 2007; Kruglikov and Rudy, 2008). Conversely synapses by FS cells onto pyramidal cells in layers 3, 4 and 5 seem to be strongly downregulated through an M2-receptor mediated mechanism (Kruglikov and Rudy, 2008), which may powerfully reduce feedforward inhibition. At the same time it remains unclear what role the strong somatic expression of m1-AChRs may serve in modulating Pv-ir responses. Non-FS interneuron to pyramidal cell connections also seem to be downregulated by cholinergic modulation (Yamamoto et al., 2010), while there seems to be a strength dependent effect on inter-interneuronal connections, whereby weak connections are strengthened while strong connections are weakened, indicating that cholinergic modulation of GABAergic synaptic transmission is differentially regulated depending on the postsynaptic neuron subtype and connection strength. To underscore these diverse effects, muscarinic-induced activation of both Sst-ir and ViP-ir cells has been observed (Kawaguchi, 1997).

In the spiny neuron population there also seems to be significant heterogeneity among modulatory effects. In rat barrel cortex for example, m4-AChR receptor activation causes hyperpolarization among layer 4 spiny neurons, which effectively reduces onward communication (Eggerman and Feldmayer, 2009). On the other hand, through m1-receptor mediated effects layer 2/3 and layer 5 pyramidal cells are depolarized (Eggerman and Feldmayer, 2009), which would result in filtering out of weak signals impinging on thalamocortical recipient neurons, while onward communication is boosted. Recurrent excitation on the other hand seems to be reduced through both nicotinic and muscarinic pathways (Levy et al., 2006). Interestingly the nicotinic

pathway seems to reduce recurrent excitation in an activity dependent manner, due to its dependence on NMDA receptor activation.

As can be seen the effects of nAChR and mAChR activation on cortical circuits is highly complex and far from fully characterized. However several clear effects of acetylcholine on V1 circuitry can be identified:

- Thalamocortical synapses onto layer 4 spiny neurons are boosted in efficacy.
- Layer 4 spiny stellate cells are suppressed filtering out weak inputs.
- Layer 2/3 pyramidal cells are facilitated, amplifying signals arriving from layer 4.
- FS basket cell responses are mostly unaffected but their synaptic GABA release is suppressed through axonal m2-receptor activation.
- Sst-ir cells are depolarized through muscarinic receptor activation.
- Recurrent excitation is reduced through both muscarinic and nicotinic mechanisms.

2.4 GABAERGIC REGULATION OF PLASTICITY AND COLUMN STRUCTURE

Experience dependent plasticity has been shown to shape the organization of the sensory cortex during the critical period and beyond. Dark rearing (Fregnac and Imbert, 1978) and monocular deprivation (MD) experiments (Shatz et al., 1978) in particular have confirmed the fundamental importance of sensory experience in shaping the development of the cortex. The mechanisms controlling the onset of the critical period and regulation of plasticity thereafter have also been studied extensively and a large body of evidence points to the important role of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) in regulating synaptic plasticity. However as the above paragraphs have shown the population of GABAergic neurons is highly heterogeneous with hugely divergent anatomical and functional profiles. Using specific pharmacological and genetic populations it has been possible to narrow down the involvement of certain interneuron subtypes in shaping critical period plasticity and column structure in the cortex.

One of the first indications that GABAergic circuits are involved in shaping plasticity came when it was shown that a gene-targeted disruption of the GABA synthetic enzyme glutamic acid decarboxylase 65 (GAD65) could delay critical period onset indefinitely (Fagiolini and Hensch, 2000). In order to further narrow down

the specific GABA circuits underlying visual cortical plasticity, more specific pharmacological manipulations were required. On that basis Fagiolini et al. (2004) used benzodiazepine infusions, known to selectively enhance GABA type A ($GABA_A$) receptor-mediated currents through the $\alpha 1$ subunit (Rudolph et al., 1999), in conjunction with MD to prematurely trigger ocular dominance plasticity in mice. These $GABA_A$ receptor-$\alpha 1$ subunits are preferentially enriched at somatic synapses receiving input from Pv-ir large basket cell terminals (Klausberger et al., 2002), strongly implicating large basket cells in visual cortical plasticity.

Beyond controlling the timing of critical period plasticity further experiments using benzodiazepines have shown strong effects on the columnar organization of the cortex. The experiment by Hensch and Stryker (2004) locally infused regions of cat area 17 with the $GABA_A$ agonist diazepam and an inverse agonist (DMCM) and studied the effects on the ocular dominance columns. Chronic treatment with diazepam had little effect in the functional properties of mature cortical neurons in vivo apart from enhancing inhibitory postsynaptic currents. However, the treated hemisphere exhibited reduced binocularity of single unit responses and wider OD columns near the infusion site. Infusion with the benzodiazepine inverse agonist DMCM had the inverse effect, resulting in less discrete and narrower columns near the infusion site. These results suggest that the diazepam mediated enhancement in competition reduces binocularity of single-unit responses, as well as sharpening and widening the anatomical segregation of monocular regions near the infusion site. This once again suggests that $GABA_A$ inhibitory currents, primarily originating from Pv-ir neurons in the cortex, are fundamentally important to shaping the plasticity and organization of the cortex.

In order to establish how ocular dominance plasticity emerges during monocular deprivation, Kuhlman et al. (2013) developed even more precisely targeted pharmacological manipulations. By selectively expressing specific receptors on Pv-ir cells they were able to selectively up- and down-regulate their activity. Their results indicate that a rapid, but transient reduction in Pv-ir cell firing restores pyramidal cell firing to pre-deprivation levels allowing competitive plasticity to occur. Pv-ir neurons therefore seem to play a permissive role in visual cortical plasticity. Interestingly adult sensory plasticity such as reinforced associative learning occurs through a similar mechanism, where cholinergic activation of layer 1 interneurons suppresses Pv-ir neural activity allowing associative fear learning to occur (Letzkus et al., 2011). All this work suggests a crucial role for Pv-ir neurons in controlling cortical plasticity during the critical period and beyond.

2.5 FUNCTIONAL ROLES OF INTRACORTICAL CONNECTIVITY

A major feature of the neural code in the cortex is the elimination of redundancy in order to achieve a sparse representation of the input or if there is insufficient information to fill in the missing information based on remembered statistics of the visual world. Sparse coding in developmental models of the primary visual cortex can be achieved by allowing lateral inhibitory connections to develop non-isotropic connectivity, which allows the network to learn the redundant features of the input and suppress them. If such development is not allowed to take place and isotropic surround suppression is employed, cross-orientation stimuli, belonging to a separate object or contour may be suppressed, thus reducing the information content encoded by the network. Therefore long-range isotropic suppression has to be considered destructive (Miikkulainen et al., 2005). Similarly, strong lateral excitation will activate neural ensembles representing non-existing inputs based solely on previous input statistics. While this is desirable when very little information is available it can disrupt sparse code formation by expanding the activity bubble or causing the false detection of a stimulus. Therefore the sensory cortex has to maintain a fine balance not only between excitation and inhibition but also in combining past information with the feedforward information stream arriving in the cortex. Identifying and modeling the circuits involved in these processes is a fundamental challenge for neuroscience and will hugely contribute to extending our understanding of cortical information processing.

Over the last decade evidence for multiple separate inhibitory populations, subserving different functions, has been considerably strengthened. Although their precise properties in regard to morphological and electrophysiological heterogeneity are still unclear there are a number of identifiable circuit elements. Afferent input provides strong, low latency excitation to the Pv-ir neurons in the thalamocortical recipient layer 4, which in turn act as both a feedforward inhibition and dynamic gain control mechanism on the broadly activated excitatory cell population. This results in local decorrelation of the neural activity, which allows recurrent excitation to amplify the activity in the local neural ensemble. Meanwhile Sst-ir neurons begin to integrate the local activity through the local and long-range orientation-specific lateral connections. If their inputs are sufficiently strong they will activate allowing this polysynaptic circuit to reduce long range correlation in the input activity, further reducing redundancy. If they are only weakly activated on the other hand, long-range lateral excitatory connections aren't outcompeted and the circuit can fill in weak or missing information based on past statistics. Under such regimen the differential recruitment of the two separate inhibitory populations would be responsible for a

shift in cortical state from a mode of redundancy-reduction and feature discrimination to one of visual inference. Additionally, modulatory inputs to the cortex like cholinergic modulation arriving from the nucleus basalis may mediate a number of effects, whether that is a shift in the circuit from a down-state, where information is recurrently processed, to a feedforward heavy up-state, by reducing feedforward inhibition and boosting feedforward excitation, or a mode in which task-relevant information is selectively filtered, is still unclear. The following sections will outline how these possibilities have begun to be explored by constructing a model based on the available experimental evidence and will outline plans to begin testing some of these different hypothesis.

2.6 CONTEXTUAL MODULATION AND ATTENTION

The computational task in vision is to map visual experience to the cortical representation of that particular stimulus or if no such representation exists, to extract lower level features in order to encode them for future reference. Using this statistical model the brain is then able to decide, which visual features carry behavioral importance and which can be safely ignored. As such the neocortex has to combine prior information with the incoming information stream and quickly and reliably identify the most salient stimuli. It has often been argued that this process is mediated by bottom-up and top-down processes, although it seems likely that there is close coupling between the two. This section will outline high level models of attentional modulation, attempts to understand the neurobiological processes behind them and more basic contextual modulation phenomena may underly many of these higher level effects.

2.6.1 *Models of Attentional Modulation*

The advent of the predictive coding theory of cortical information processing formalized by Rao and Ballard (Rao and Ballard, 1999) suggests that incoming visual information is combined with encoded natural image statistics inherent in the feedforward and lateral connections of the cortex in a process similar to Bayesian inference. Since then a number of papers have linked attention to surprise and uncertainty (Feldman and Friston, 2010; Itti and Baldi, 2009; Rao, 2005; Yu and Dayan, 2005), suggesting that it acts as a mechanism to reduce uncertainty by combining stimulus related activity and internal priors in a probabilistic manner. A theory of attentional modulation that can account not only for specific attention related effects but also resolve some of the implementational details of predictive coding and the various routing problems

associated with the hierarchical organization of the cortex would be of tremendous interest.

The number of algorithmic models of attention range from relatively unspecific descriptive models, such as the attentional spotlight analogy (Posner et al., 1980), to functional models such as the relatively recent normalization based structural models by **?** and Lee and Maunsell (2009). The list of models of attention is seemingly endless so it is infeasible to provide even a grazing overview, but after a long history of descriptive models perhaps one of the most widely recognized models of attention has been the so called biased competition model by Desimone and Duncan (1995), in which they suggest that objects in the visual field compete for control of behavior through both top-down and bottom-up mechanisms. While top-down mechanisms select objects of behavioral relevance, bottom up mechanisms separate salient stimuli from their background.

Another widely recognized model of attention is feature similarity gain (**?**) later extended to feature based attention (Maunsell and Treue, 2006), which suggests that attention adjusts the gain of each neuron depending on the similarity between the observed stimulus and currently attended feature. The more recent normalization model of attention proposed by **?** combines the predicted effects of both into one relative simple mechanism, which is to multiply the stimulus related activity by an attentional field, the result of which is then normalized by the aggregate suppressive drive. In particular, it predicts a dissociable effect of contrast and attentional modulation, which has since been confirmed by various studies (Lee and Maunsell, 2009; Pooresmaeili et al., 2010). Further, the suggestion that normalization can be applied not only spatially but also in other stimulus feature dimensions raises the possibility that spatial attention is just a subset of feature attention.

These types of mechanisms also have some links to the predictive coding theory of cortical computation as they provide a mechanism of combining stimulus related activity with prior information encoded in the lateral and feedback connections. A paper by Spratling (2010) formalizes this mechanism as a true predictive coding model by modeling the primary visual cortex through an interaction between afferent inputs, which compete with predictive neurons acting through divisive feedback to represent the stimulus in error-coding neurons. Although these models are successively more predictive none truly begins to explains what neural mechanisms underly these processes. Although a complete description at this level will be beyond reach for some time it may be possible to start linking these processes back to their neurobiological implementation in the brain.

2.6.2 *Theory of Cholinergic Modulation and Attention*

Although there are very few models addressing attention at the implementational level, much more is known about the neurobiology of attention than just a few years ago. Information from the RF center and the surround is integrated in a process heavily mediated by neuromodulators and feedback connections including those involved in attention.

Contextual influences mediated through lateral connectivity have been closely associated bottom-up attention possibly representing learned priors of natural image statistics established through development and learning (Seriès et al., 2003). In addition, a number of studies have implicated cholinergic, noradrenergic and glutamatergic neurotransmitter pathways in modulating FF thalamo-cortical, lateral intra-areal and FB intracortical connections.

In a recent review paper, Harris and Thiele (2011) argue that the brain and the neocortex in particular constantly adapts how information is integrated and routed. Although they focus primarily on cortical states, synchrony and other temporal phenomena, the review identifies a number of structures involved in modulating processing in the cortex (visualized in Figure 2.6.2). This includes cholinergic projections from the cholinergic nuclei in the brain stem and the basal forebrain, noradrenergic projections from the locus coerulus and serotonergic projections from the Raphe nucleus targeting cortical and subcortical visual areas. In addition to these extracortical feedback connections, Harris and Thiele argue that glutamatergic feedback connections from the frontal eye fields (FEF) project down along the cortical visual hierarchy inducing shifts in attention at the behavioral and neuronal level. Overall this line of argument suggests that the interaction between all these feedback projections with their cortical targets provide the substrate for shifts in cortical state and attention.

In order to provide a coherent theory of what these neuromodulators are doing it is once again paramount to bind experimental observations together in a framework that is concerned with the computational purpose of the system. Before attempting to understand the precise physiology and action of individual neurotransmitter pathways, which are far from fully being fully understood, let's consider their action in the larger computational framework of predictive coding. Although still rather tentative, Yu and Dayan (2005) argue that acetylcholine and noradrenaline act as signaling mechanisms for the coding of uncertainty, forming a crucial part in the cortical inference algorithm hypothesized by the predictive coding theory. They hypothesize based on a number of observations that acetylcholine signals, what they describe as expected uncertainty, while noradrenaline signals unexpected uncertainty. While the distinction isn't always clear cut, broadly speaking expected uncertainty refers to sit-

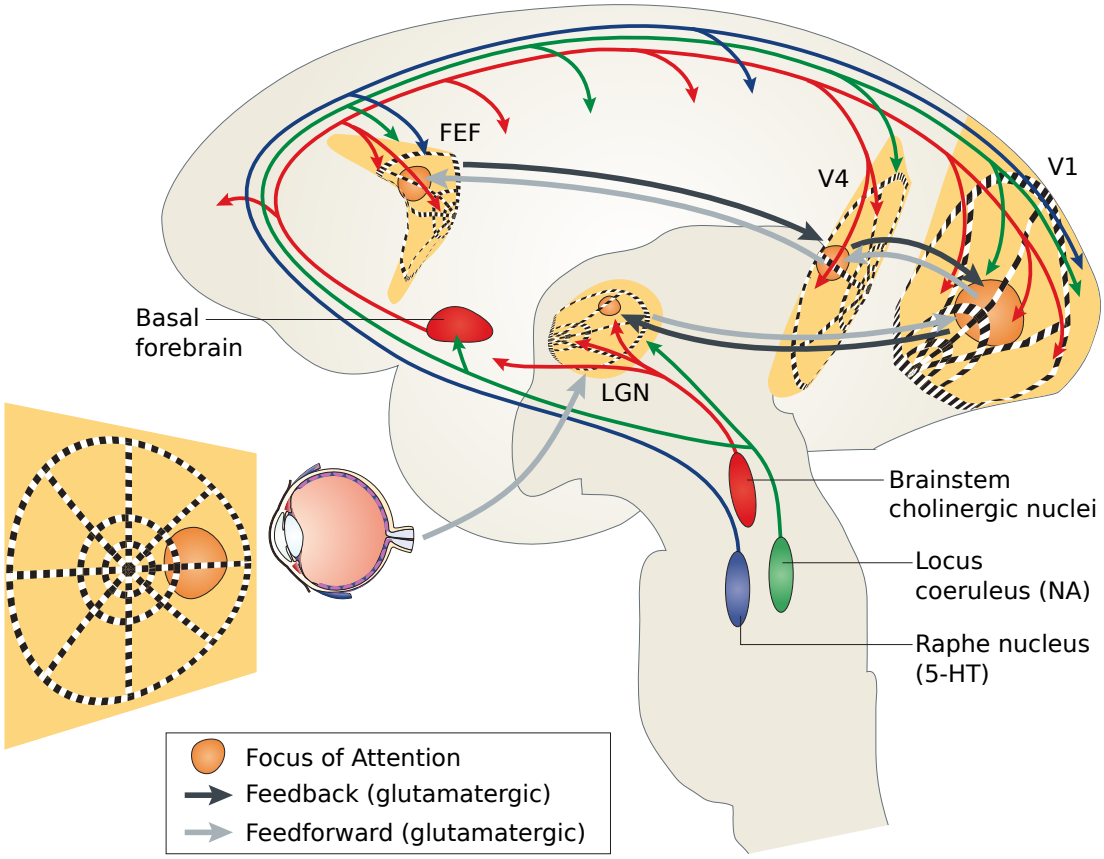

Figure 2.17: s
tate changes and attention. Taken from Harris and Thiele (2011).

uation where a certain cue isn't entirely reliable and therefore needs to be scrutized in high detail without necessarily relying on the inherent predictions of the cortex, while unexpected uncertainty would arise when the predictive capacity of a variable is suddenly severely compromised necessitating a shift or refocusing of attention.

2.6.3 *Mechanisms of Visual Attention*

Acetylcholine has been implicated in a number of cognitive functions including excitability, attention, learning, memory, wake and sleep cycles and cortical modulation of sensory information processing. It is unclear how the cholinergic system regulates or at the very minimum modulates this wide range of functions, so it is important to get a thorough understanding of its different mechanisms of action at the channel, synaptic, cellular and network level.

The cholinergic pathways (Ch1-Ch6) originate in the the basal forebrain, which itself has been implicated in global attention and arousal states (Jones, 2004). The nucleus basalis provides cholinergic input to a number of brain areas including the cortex and the thalamus, which has been through the Ch5-6 and Ch4 pathways respectively. The cortical pathway (Ch4) mainly originates from the nucleus basalis magnocellular (NBM) with a topographic organization (Woolf, 1991). In addition, labeling studies have identified small populations of cholinergic bipolar intracortical interneurons in layer 2/3 of the cortex (von Engelhardt et al., 2007). Among population of neurons in the NBM projecting to the cortex 30-25% are GABAergic neurons, whose axons primarily target cortical GABAergic interneurons acting to disinhibit them (Lucas-Meunier et al., 2003). The remainder release ACh in the cortex, a process which is regulated by modulation of cholinergic neurons in the NBM or by cholinergic terminals in the cortex.

Acetylcholine receptors in the cortex can be roughly classified into nicotinic and muscarinic AChRs. The nicotinic and muscarinic AChRs are differentially expressed in neuronal subtypes with mAChRs being more commonly found in inhibitory intracortical neurons (Disney et al., 2006), while nAChRs have been determined to be preferentially expressed pre-synaptically in the thalamo-cortical recipient layer 4C of V1 (Disney et al., 2007). Nicotinic receptors are permeable to Na^+, K^+ and Ca^{2+} ions, with particular permeability to Ca^{2+}, which can cause rapid increases in intracellular Ca^{2+} concentration and thus influence cellular Ca^{2+}-sensitive processes downstream. Through this mechanism and their presynaptic positioning, nAChRs can modulate neurotransmitter release (Lucas-Meunier et al., 2003), which has been found to effect a multiplicative response gain enhancement in layer 4C (Disney et al., 2007). The muscarinic receptor type itself has several genetically defined subtypes,

namely m1-m5. Of these the m1 and m2 AChRs are known to be strongly expressed in primates and correspond to the two pharmalogically classes of mAChRs, M1 and M2 (Disney et al., 2006). In the neocortex mAChRs exhibit a clear laminar distribution with strong expression primarily in layers 2/3 and 5. It was found that GABAergic neurons primarily expressed the m1 subtype, where they are usually found expressed somatically, while glutamatergic neurons primarily express mAChRs dendritically (Lucas-Meunier et al., 2003). Further it seems as if mAChR expression on glutamatergic neurons is relatively low in lower visual areas, increasing in V2 relative to V1, suggesting ACh primarily acts through inhibitory mechanisms in V1. This has been affirmed by a recent study showing that ACh suppresses response gain outside of layer 4C, by strengthening inhibition (Disney et al., 2012). In the past it was thought this suppressive effect is mediated by m2-type mAChRs, which act to reduce glutamate release (Hasselmo and McGaughy, 2004; Roberts et al., 2005; Yu and Dayan, 2005) but the expression data seems to contradict this. More recent studies indicate that the ACh mediated suppression is caused almost entirely by increased GABA release and $GABA_A$ receptor activation, itself driven by m1-type mAChR activation. This hypothesis would also account for the observation that attentional effects are weakest in area V1, where mAChR expression on glutamatergic neurons is weakest, increasing in strength as one moves up the cortical hierarchy (Disney et al., 2006). Nonetheless Soma et al. (2012) found substantial mAChR-mediated response gain enhancement even in area V1, suggesting ACh much like attention can mediate significant facilatory and suppressive effects in V1.

At the subcortical level, experiments by Goard and Dan (2009) showed that response reliability was improved through a pathway acting on the LGN projecting from the basal forebrain indirectly either through cortico-thalamic or a pathway involving the reticular thalamic nucleus (RTN), which has been called "gatekeeper" of the LGN. The feedback loop involving the nucleus basalis, RTN and LGN seems most likely to be involved in very coarse gating of the visual stream such that a modelling approach could assume a fully aware state in which thalamic gating is ignored. This reduces the initial scope of this project to the action of a particular neurotransmitter in a particular region of the brain, namely acetylcholine and the primary visual cortex, although it may well be extended at a later stage.

A number of studies have noted and investigated the similarity in the activation profiles of cholinergic innervation and attentional modulation in V1. This seems to be backed up by evidence that shows that much like attention, topical acetylcholine application reduces the effect of long-range lateral connectivity, thereby reducing spatial summation (Roberts et al., 2005), suppressing contextual influences and effectively decorrelating the cortical activity (Goard and Dan, 2009). Further investigation con-

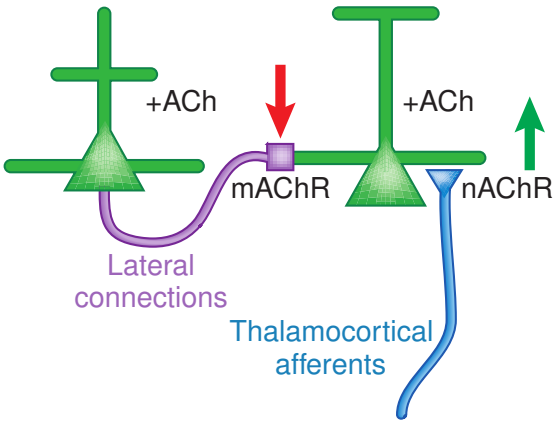

Figure 2.18: a
nd muscarinic ACh receptors in cortical circuits (Thiele, 2009).

cluded that these attention-mediated changes in spatial integration are eccentricity-dependent such that spatial summation is reduced in the parafoveal regions and expanded in more peripheral visual areas (Roberts et al., 2007). Additionally it was shown that ACh causes a broadening of orientation tuning in a majority of cells, while only sharpening them in a small number of other cells (Zinke et al., 2006). Research by Soma et al. (2012) has delineated the effects of muscarinic and nicotinic AChR activation on response gain, showing mAChR activation in particular mediates a significant increase in response gain, which could be almost completely blocked by applying an mAChR antagonist and any residual effects could be removed by blocking both m- and nAChRs. A limited effect of nAChR activation on increases in the mean firing rates was also demonstrated by further studies (Herrero, 2011), although mAChR blockade was shown to have the opposite effect. The same study found that mAChR activation was distributed equally among layers except layer 4C, in which nAChR activity dominates. Finally a substantial amount of evidence has accumulated showing that ACh also reduces the Fano factor, i.e. the firing rate variability (Herrero, 2011). This provides clear evidence of ACh on orientation tuning, spatial summation, response gain modulation and firing rate variability, effects closely associated with attention.

The precise influence of acetylcholine on surround modulation has at times been hard to discern as there are a number of effects to be delineated. Broadly speaking surround modulation can be broken down into facilatory and inhibitory effects acting over different spatial and time scales and differentially activated by different contrasts, eccentricities and stimulus features. As stated before both attention and iontophoretic ACh application were shown to reduce spatial integration (Roberts et al., 2005, 2007) and mAChRs were found to be expressed largely on intracortical neurons thought to be involved in spatial summation beyond the cRF. Additionally some ev-

idence seems to indicate ACh alters the membrane spatial and temporal integration constants (Lucas-Meunier et al., 2003) further complicating the dissociation of mechanisms. A number of studies have nonetheless attempted to classify the effects on both colinear facilitation and suppression. In particular, counter to initial theoretical considerations, it seems flanker induced surround suppression is actually facilitated by mAChR activation, as their blockade was shown to reduce the suppressive drive (Herrero, 2011). The effect on surround facilitation was similar although several studies noted that only very few neurons exhibited flanker induced facilitation in the first place (Pooresmaeili et al., 2010). So although in theory almost everyone agrees that both attention and acetylcholine boost feedforward information and reduce spatial integration and extra-classical surround effects, it is unclear under which conditions these effects can be observed and what mechanisms drive them.

A particular issue that has not yet been resolved is the discrepancy between the highly localized effect of attentional neuromodulation and the comparatively coarse effect of ACh innervation. Suggested resolutions to this problem include the recent discovery of cholinergic interneurons (von Engelhardt et al., 2007), found in layer 2/3 of V1 as well as interactions with spatially specific glutamatergic feedback connections (Herrero et al., 2008; Sarter et al., 2009). Overall however it seems evidence is strong that both nAChRs and mAChRs are involved in mediating activity in V1 by boosting feedforward activity from the thalamus and modulating the spatial integration of V1 neurons with efferent connections to higher layers with clear data as to the contribution of each.

Overall the entire mechanism of attentional feedback is poorly understood and it makes sense to focus particularly on the aspects that can easily be implemented in a powerful yet simple model. Cholinergic signalling in V1 provides exactly such a target system as it has been implicated in a number attention mediated effects and can be straightforwardly translated into their mechanisms of action, one reducing the effect of long range contextual influences on V1 receptive fields, thereby decorrelating the input and secondly a gain mechanism boosting behaviourally relevant signals in the thalamo-cortical connections. Additionally, it seems to interact with glutamatergic feedback connections from higher cortical areas, further expanding the range of interactions that can be investigated.

2.6.4 *Contextual and Attentional Phenomena in V1*

A number of phenomena associated with attention and contextual modulation, including iso-orientation suppression or facilitation, boundary detection, contour completion and noise exclusion have been observed in V1. Although these phenomena

are generally associated with bottom-up attention they lay the foundation for higher level phenomena such as pop-out and figure-ground segregation and may reveal more about general mechanisms applying also to higher visual areas.

Basic contextual effects such as iso-orientation suppression have already been discussed and models have begun to suggest the functional connectivity mediating implicating both lateral and feedback connections. While, Li (2002) has proposed that pre-attentive bottom-up processes allow V1 to generate a saliency map of the visual input. However, the fact that higher cortical areas have also been associated with saliency signaling and the lack of long range intra-areal connectivity in V1 suggest that while it can encode local saliency, feedback is required to globally integrate saliency across visual space.

Feedback modulation of V1 activity has been implicated in a number of effects, spatial attention being chief among them. Spatial attention is thought to be able to select multiple low and high level objects in the visual space across V1 and higher visual areas (McMains and Somers, 2004). It is thought to underly noise exclusion, observed by Dosher and Lu (2000) and may be explained by effects similar what has been experimentally observed during ionphoretic application of ACh. Other effects that have been commonly been associated with feedback in some form are the signaling of illusory contours, which have been shown to be negatively signaled or deemphasized in V1 (Ramsden et al., 2001) and boundary detection (Poort et al., 2012). In the planning section, concrete proposals will be made suggesting what mechanisms may account for these phenomena and how they can be implemented.

2.6.5 *Attention and Learning*

In addition to immediate effects of visual attention on V1 a number of studies have investigating the link between visual attention and perceptual learning. The exact role of attention in perceptual learning has long been under dispute although one prevailing theory advocated by Seitz and Dinse (2007) suggests that boosting stimulus related activity beyond a learning threshold will induce perceptual learning. This theory explains seemingly contradictory experiments, which had shown that perceptual learning occurs even without attention (Watanabe et al., 2001) by showing that sufficiently tuned experimental protocols can boost stimulus related activity to the point where it induces learning.

A further controversy that has not yet been fully resolved is concerning the actual physiological locus of perceptual learning. Competing views have suggested that the behavioral improvements associated with perceptual learning arise through task dependent pooling of signals in early visual areas (Ghose et al., 2002). A number of

experiments since then have shown that a number of perceptual learning effects can be explained through plasticity in the early visual system. One study for example showed that individual neurons in V1 can take on novel functional properties related to the trained shapes in a shape discrimination task (Li et al., 2004), another showed that long-term improvement in orientation identification tasks could be linked to sharpening of orientation tuning curves of V1 neurons (Schoups et al., 2001). This has led Gilbert et al. (2001) to conclude that: "perceptual learning arises from a combination of changes in local circuits at early cortical stages in sensory processing and feedback influences coming from higher order cortical areas". Offering some support for this theory is the finding by Zivari Adab et al. (2011) that in macaque V4 perceptual learning resulted in decreased response variability and an increase in the difference in mean activity for the trained orientations in a noisy orientation discrimination task, which Seitz (2011) argue shows that although low level plasticity may not account for all or even the majority of perceptual learning it can and does occur.

2.7 DEVELOPMENTAL MODELS OF THE PRIMARY VISUAL CORTEX

As it is thought that the cortex captures statistics about the sensory streams to construct internal models of the world, it is clear that function, structure and development are closely linked. Recognizing this close association, Dr. Bednar began developing models of the sensory cortex (Bednar and Miikkulainen, 2003) based on self-organizing maps (SOMs). Since then these models have been refined substantially but still implement the retina, LGN and V1 as a set of neuronal sheets with feedforward and lateral connectivity self-organizing into the complex topographic maps as seen in carnivore and primate species. It can explain the development of robust yet adaptive topographic maps using only a small set of mechanism including contrast-gain control, an adaptive single-neuron threshold, and lateral connectivity giving rise to GCAL (Law et al., 2011). Extensions of this model explaining the development of complex cells and of contrast dependent size tuning (Antolík and Bednar, 2011) as well as a continuous time model incorporating LGN/V1 onsets using hysteresis functions are in development (Stevens, 2011).

The GCAL model is based on several core observations about information-processing in V1 and the cortex in general. As previous sections have shown, the primary visual cortex of primates responds strongly to specific low-level features in its visual input including orientation, color and direction. Selectivity to these features are conserved across a wide range of contrasts and neurons form topographic feature maps across the surface of V1 by virtue of self-organization. While these experimentally confirmed findings are specific to vision, the concept of equipotentiality proposes that different

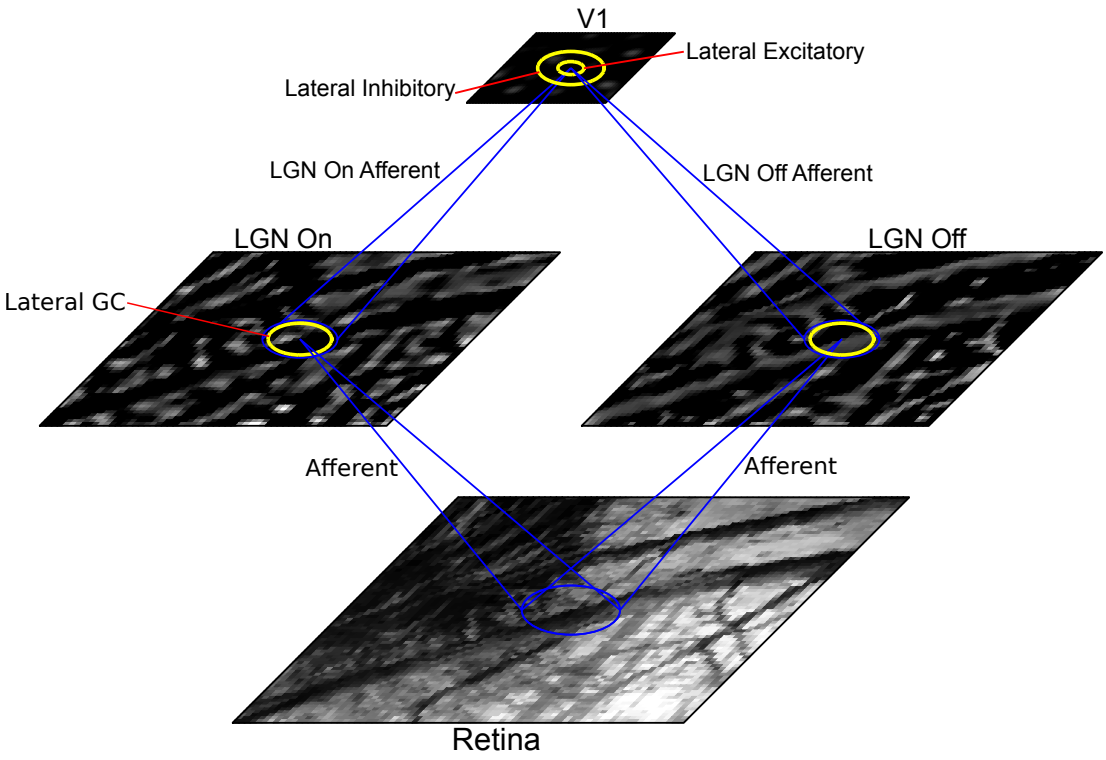

Figure 2.19: o
f simple cells with surround modulation, retinotopic organization and orientation preference maps. It consists of a retinal sheet, two RGC/LGN for ON and OFF cell responses and one V1 sheet, connected with intra- and inter-areal projections. The sheets are drawn to scale, with larger sheets for the RGC/LGN and retinal layers to avoid edge effects. Projections are illustrated with blue (feedforward connections) and yellow (lateral connections) ovals with cones converging on their target, all drawn to scale to show their spatial extents. RGC/LGN sheets consist of units with hardwired Difference of Gaussian RFs with ON and OFF center-surround regions. LGN Afferent projections to V1 are initially unspecific but develop Gabor-like RF structures through Hebbian learning as they are observed experimentally.

areas in the cerebral cortex are cytoarchitectonically highly similar, becoming differentiated based largely on the statistical patterns in their inputs during development and are thus capable of capturing any sensory modality. While details surrounding this hypothesis are still controversial, experiments such as those by Sur et al. (1990) have at least partly validated this view. In this particular study, experimentalists rewired optic nerve axons to interface with neurons in the medial geniculate nucleus (MGN), part of the pre-cortical auditory pathway, and subsequently showed that neurons in the primary auditory cortex (A1) would become receptive to features usually associated with V1. This is behind much of what has made V1 such a popular model area for neuroscience and suggests that many of the insights that can be gleaned from the study of V1 could be applied to the cortex as a whole.

The architecture of the GCAL model in its simplest form and as it will initially be used in this project relies on only four sheets, a retinal sheet for the presentation of stimuli, two RGC/LGN sheets and a V1 sheet. These sheets are connected with different intra- and inter-areal connection fields. This simple model can only be used to demonstrate retinotopy, orientation preference and the emergence of simple cell-like RFs but more complex models have been shown to additionally account for complex cells, ocular dominance, motion direction, spatial frequency, temporal frequency, disparity and color. All these models are trained by presenting it with a visual input on the retina, allowing the response to propagate through the different sheets and then adjusting the connections weights to V1 neurons based on a local learning rule. The response of a given neuron j at time $t + \delta t$ can be calculated as the thresholded dot product between the activations of every input neurons i at time t, or $\eta_i(t)$, and their associated weights stored in the connection field:

$$\eta_j(t+\delta t) = \sigma\left(\sum_p \gamma_p \sum_{i \in F_{jp}} \eta_i(t)\omega_{ij}\right) \tag{2.7}$$

where η_i is the activation of all units i in connection field F_{jp}, which contains all neurons unit j receives its inputs from. ω_{ij} is the connection weight from i to j. σ is a half-wave rectifying function with a variable threshold point (θ) dependent on the average activity of the unit, effectively acting as a homeostatic mechanism, pulling the activity of neuron back to a desired level. γ_p is an arbitrary multiplier for the overall strength of all connections i in projection p and thus a free parameter.

The connection weights ω_{ij} are adjusted after each iteration using a simple Hebbian learning rule, capturing correlations between pre- and post-synaptic activities. The Hebbian connection weight update for unit j is expressed as a function of the presynaptic activity η_i, the post-synaptic response η_j and the Hebbian learning rate α, taking the form:

$$\omega_{ij}(t+1) = \frac{\omega_{ij}(t) + \alpha\eta_j\eta_i}{\sum_{k \in F_{jp}} (\omega_{kj}(t) + \alpha\eta_j\eta_k)} \tag{2.8}$$

This function also constrains runaway changes in weights by employing divisive post-synaptic weight normalization and thus eliminates the instability associated with classical Hebbian learning.

This limited number of mechanisms already gives rise to an incredibly robust model of development of topographic map development and generates different experimentally observed RF profiles. To add further robustness to the model and to

allow it to respond across a wide range of contrasts, contrast-gain control was introduced in the LGN sheets (marked as Lateral GC). This mechanism was closely modeled on the divisive normalization model introduced and validated by Bonin et al. (2005). Finally, the lateral excitatory and inhibitory fields in the V1 sheet give rise not only to the topographic map structure but also to some surround modulation effects. In particular, it can explain the size tuning properties of V1 neurons as the excitatory field will boost the response to a growing centered disk up to a certain peak, after which point the lateral inhibitory field dominates and reduces the response to the stimulus as it grows further. It may also explain effects such as iso-orientation suppression but this has as of yet not been explored in detail.

Overall, due to the simplicity of its mechanisms and its explanatory strength, GCAL provides an ideal starting point to explore the contribution of feedforward, lateral and feedback components to V1, how bottom-up attention can arise and how top-down attention can modulate the processing architecture.

2.8 HOMEOSTASIS: BALANCING EXCITATION AND INHIBITION IN A NETWORK

While much of the work over the past two years involved disentangling the network dynamics between excitatory and inhibitory populations, little to no attention has been given to mechanisms that could stabilize activity between the different populations. Therefore this section will briefly look at the evidence for homeostatic mechanisms regulating the dynamics between excitatory and inhibitory cell classes.

The Turrigiano (2011) review provides a broad overview of the role of synaptic and intrinsic homeostatic mechanisms in neural tissues during experience dependent circuit refinement and their contribution to network stability. The schematic in figure 2.8, shows how these different mechanisms can regulate the balance of excitation and inhibition received by a neuron. In context of the ongoing modeling work as part of this PhD, it is particularly interesting that high network activity can increase the excitatory currents onto GABAergic interneurons. This homeostatic mechanism is driven by activity dependent regulation of the *Narp* gene, which is secreted presynaptically by pyramidal neurons and accumulates preferentially at excitatory synapses onto PV interneurons (Chang et al., 2010). Such a mechanism could be employed within the multi-population model to achieve greater robustness during self-organization.

2.9 NATURAL IMAGE STATISTICS, SPARSITY AND HORIZONTAL CONNECTIONS

It has long been hypothesized that connectivity in the cortex captures the statistics of the sensory input in order to perform predictions and maintain sparse represen-

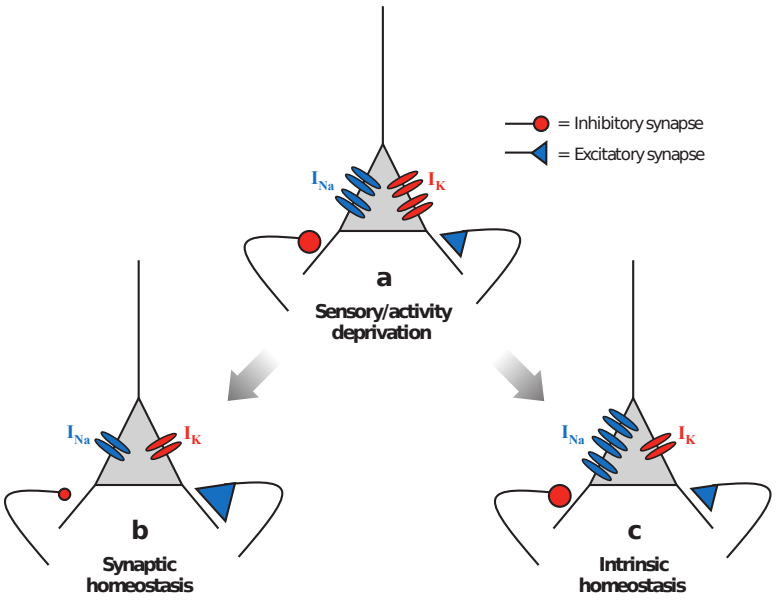

Figure 2.20: m
echanisms for the homeostatic regulation of neuronal firing. (a) Synaptic homeostasis changes the balance of inward and outward voltage-dependent conductances. (b) Intrinsic homeostasis regulates the intrinsic excitability by altering the balance of inhibitory and excitatory ion channels. Reproduced from Turrigiano (2011).

tations of novel inputs (Simoncelli and Olshausen, 2001). A wide range of work has explored the role of the distributions of light intensities, color statistics and spatial correlations in natural images. In particular, the power law distribution of spatial frequencies in natural images has been widely discussed in the literature but ultimately this largely seems to reflect the scale invariance within natural images (Ruderman, 1997).

Numerous studies and models have since been devised to address whether the visual system takes advantage of the correlational structure of natural images. These types of normative models were able to show that surround inhibition, whether subtractive or divisive, could cancel out correlations effectively whitening or decorrelating the activity in the visual system (Srinivasan et al., 1982; Atick and Redlich, 1992). In doing so they quickly found that simple decorrelation wasn't sufficient to optimally represent natural images because whitening does not eliminate all structure in a natural image, e.g. edges and lines remain. By introducing an explicit sparsity constraint, Olshausen and Field (1996) were able to develop V1-like simple cell receptive fields with varying orientations, spatial frequencies and sizes. These models indicated that sensory system was optimizing two contstraints, sparsity and statistical independence. However, even these approaches cannot achieve complete statistical in-

dependence since there are higher order correlations even between non-overlapping receptive fields.

By introducing divisive normalization, Schwartz and Simoncelli (2001) were able to show that these types of dependencies could be further eliminated. Furthermore, the weights used in the computation of the normalization signal could be specifically optimized to maximize the independence of the normalized responses. Additionally, they demonstrated that the optimal weights were at least partly due to the prevalence of extended contours in natural images. Attempting to quantify the co-occurence statistics of contours in natural images, Geisler et al. (2001) demonstrated that the performance in contour detection tasks could be predicted by a local grouping rule derived from the co-occurence statistics. The first explicit link to horizontal connectivity was made by Sigman et al. (2001), who noted that the pattern of long-range patchy connectivity in the primary visual cortex, linking iso-orientation columns has a close corespondence with the observation of co-circularity in natural image statistics. Noting the processes of iso-orientation suppression and contour integration, they argue that iso-orientation suppression may serve to further reduce redundancies in neural coding, thereby achieving greater statistical independence, which would explain why neural responses appear most sparse when presented with natural stimuli. Secondly, observing that visual cortex can also exhibit colinear faciliation under low contrast conditions (Sceniak et al., 1999; Kapadia et al., 1999), they suggest that under low signal-to-noise conditions the cortex may act to enhance repeated statistics to aid the identification of contours and form.

These theoretical studies have hugely advanced our thinking about the computations performed by the early visual cortex, however very little work has been done to look at the actual structure of horizontal connectivity in V1, largely due to the difficulty in obtaining data from more than just a few cells. Even on the question whether horizontal connections are anisotropic along the axis of preferred orientation of the neuron, as would be expected from theoretical studies, there is conflicting evidence. The result has been confirmed in monkey (Sincich and Blasdel, 2001), tree shrew (Bosking et al., 1997) and cat (Schmidt et al., 1997), but conflicting results exist in macaque Angelucci et al. (2002). By performing analyses on an old tree shrew dataset Hunt et al. (2011) investigated whether horizontal connections captured the co-circularity of natural image statistics. Although they found neurons, which exhibited co-circularity and anti-cocircularity and hypothesize a role for both, given the small number of lateral connections fields and the fact that second order properties are highly sensitive to even small errors in the data, it is unclear how strong this result is. Further research in this area is desperately needed.

3

SPATIALLY CALIBRATING MODELS OF PRIMARY VISUAL CORTEX

The Gain Control Adapation Lateral model (GCAL) has been able to demonstrate robust, yet adaptive development of orientation maps, largely due to the mechanisms it is named after. However, although it is a good model of map development, matching the time course of selectivity and stability measurements in ferret V1 (see Stevens et al. 2013), it was never developed to be spatially calibrated or closely match anatomy.

In this notebook we will explore the literature on the spatial scales of connectivity in the early visual system and then adjust the connectivity in the GCAL model to be consistent with our anatomical and electrophysiological knowledge about macaque V1. Where macaque data is not available some of the estimates will be taken from cat primary visual cortex.

We will begin by looking at the size of receptive fields in the lateral geniculate nucleus and then progress toward V1, looking at feedforward and intracortical connectivity. Additionally we will pay attention to the difference in observed connectivity between excitatory and inhibitory neurons, which will further highlight how difficult it is to find correspondence between the GCAL model, with only one cell class and the real anatomy.

3.1 SPATIALLY CALIBRATING LGN RECEPTIVE FIELDS

The results from Sceniak et al. (2006) represent the best estimates of the spatial properties of LGN receptive fields in macaque as they employ more a more refined measurement protocol than older studies (full discussion can be found in my First Year Review). The estimated excitatory extents in this study are significantly larger than previous estimates, while the suppressive surround estimates are fairly consistent. Furthermore, the spatial extent of the excitatory CRF centers were found to be contrast invariant, while both the ECRF and CRF suppressive surround extents were found to increase at lower contrast levels. In summary, looking back at all the studies considered here excitatory CRF extents are generally distributed between 0.05-0.5 deg in radius, while inhibitory CRF and suppressive ECRF radii are distributed distributed anywhere between 0.6-1.5 deg and the suppression index is quite high (SI>0.8) for 80% cells.

The spatial profile of LGN Receptive Fields is usually estimated by measuring the response of LGN neurons to moving bar stimuli with varying extents and spatial frequencies. The resulting size tuning curves are then fit using a Difference of Gaussian (DoG) model, expressed as a function of either the spatial frequency (DoGf) or the radius (DoGr).

DoGr: $R = k_c e^{-\frac{r}{r_c}^2} - k_s e^{-\frac{r}{r_s}^2}$

DoGf: $R = k_c e^{-\frac{f}{f_c}^2} - k_s e^{-\frac{f}{f_s}^2}$

More recent papers have also attempted to fit the size response curves with integrated Difference of Gaussian models

iDoG $R(s) = R_0 + K_e \int\int re^{-\frac{r^2}{a}}\, drd\theta - K_i \int\int re^{-\frac{r^2}{b}}\, drd\theta$

where $R_0 is the spontaneous response rate, K_e the excitatory gain, K_i the inhibitory gain, a the exci$

Using this methodology Sceniak et al. 2006 were able to fit excitatory and inhibitory space constants to a sample of 136 thalamocortical afferents in macaque V1.

4

EXPLORING THE ROLE OF INHIBITION IN CORTICAL DEVELOPMENT

5

MODELLING THE EFFECTS OF VISUAL STATISTICS ON LONG-RANGE LATERAL CONNECTIVITY IN VISUAL CORTEX

6

MODELING THE EFFECT OF VISUAL INPUT STATISTICS ON SURROUND MODULATION IN V1

7

NEUROMODULATION OF VISUO-CORTICAL INFORMATION PROCESSING

8

GENERAL DISCUSSION

The end

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