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Inhibitory interneurons of macaque primary visual cortex

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Chapter I

General introduction

The main functional cellular unit of the brain is the neuron (Figure 1.1). Due to its electrically polarized membrane and specialized ionic channels, such a cell is capable of receiving signals from other cells (either depolarizing or hyperpolarizing), generating an action potential, propagating it along the length of its axon, and then relaying this information to another cell. The relay process between two neurons is based, in the classical description, on the conversion of the neuronal electrical signal to a chemical one, at the location of the synaptic cleft. The synapse (Figure 1.2) is a specialized relay space between two communicating neurons, where a presynaptic neuron releases a chemical neurotransmitter that, by binding to specific receptors, will lead to a depolarization (or hyperpolarization) of the postsynaptic neuron, and the generation (or extinction) of an electrical signal in this cell (Kandel et al. 2012).

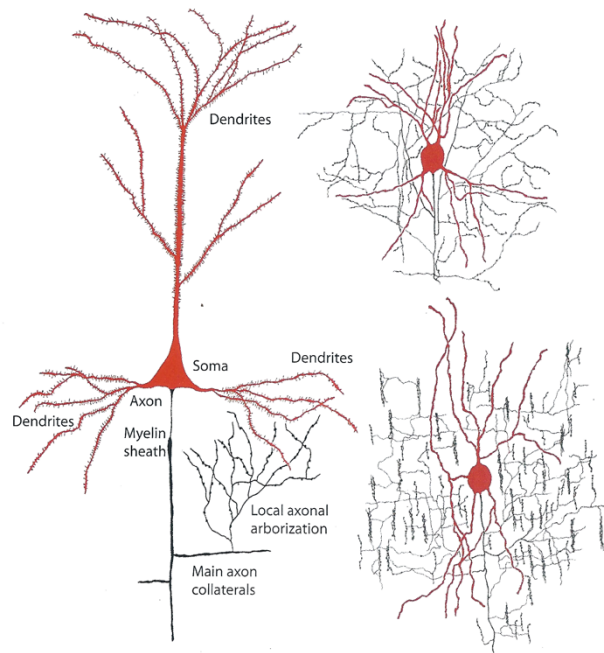


Figure 1.1: Schematic representation of neuronal cells. (A) Typical pyramidal cell. (B) “Common type” interneuron (Ramón y Cajal 1899b). (C) Chandelier cell. The dendrites and somata are shown in red, the axonal arborisations in black. Modified from DeFelipe (2010 p.12).

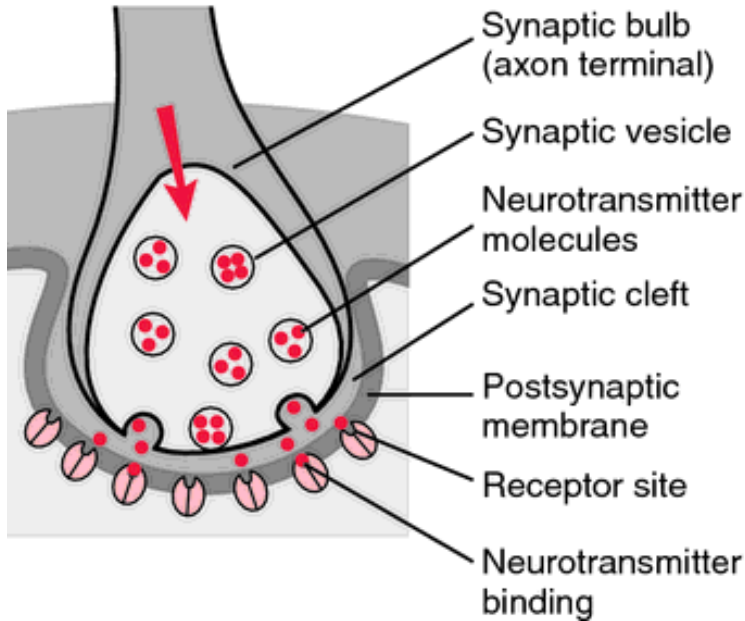


Figure 1.2: Schematic representation of the synaptic relay between two neurons. Modified from Applegate (2000 p.176).

A presynaptic cell that elicits depolarization in a postsynaptic cell is an excitatory neuron, because it leads to the generation of activity in the cell it targets. Excitatory neurons are dominant in the nervous system, and were the first, and most extensively characterized, and modelled (Curtis and Cole 1938; Cole and Curtis 1939, 1941; Hodgkin and Katz 1949; Shanes 1949; Bullock and Hagiwara 1957).

A presynaptic cell that leads to the hyperpolarization of the postsynaptic membrane is an inhibitory neuron. Inhibitory neurons play a crucial role in controlling the activity of the cortical network (Horridge 1968; Isaacson and Scanziani 2011; Fino et al. 2013). In the primary visual cortex, by suppressing activity of other neurons, inhibitory interneurons determine the tuning of excitatory neurons, they contribute to orientation selectivity and surround suppression (Burkhalter 2008; Isaacson and Scanziani 2011; Adesnik et al. 2012; Li et al. 2012).

There are many types of inhibitory neurons and various schemes for classifying them (Markram et al. 2004; Ascoli et al. 2008; Burkhalter 2008). The current work is aimed at systematizing and clarifying inhibitory neuronal architecture of macaque primary visual cortex (V1).

We explored several anatomical features of inhibitory interneurons together with their functional implications. We believe that the new insights we provide will allow for better modelling and prediction of cortical processing, as well as better translation of rodent models to primate applications.

Mouse v. macaque

The development of therapies for human (primate) in rodent models assumes some degree of equivalence of cortical organization between rodent and primate architecture. To assess this in the context of inhibitory interneurons, we compared the expression of calcium binding proteins (CBPs) in primary visual cortex (V1) of mouse and macaque (Kooijmans et al. in preparation; **Chapter II**).

Labelling based on CBPs – parvalbumin (PV), calbindin (CB) and calretinin (CR) is routinely used for primate interneuronal population identification. In macaque, CBPs label interneurons exhaustively, separating them into largely distinct populations (Kooijmans, Sierhuis et al. in preparation; Van Brederode et al. 1990; Härtig et al. 1996; Pinheiro Botelho et al. 2006; Sherwood et al. 2007; Disney and Aoki 2008; Ma et al. 2013; Kooijmans et al. 2014). CBPs make up an intrinsic classification system, besides a labelling scheme, as they are the same class of molecule and have scalable calcium binding behaviour properties due to the “EF-hand” motif expression, directly relevant for their cellular function (Chard et al. 1993; Lewit-Bentley and Réty 2000; D’Orlando et al. 2002; Schwaller et al. 2002; Grabarek 2006; Barinka and Druga 2010). Unlike the low co-expression of CBPs present macaque (Van Brederode et al. 1990; Härtig et al. 1996; Sherwood et al. 2007), there is significant documented co-expression of CBPs in mouse (Park et al. 2002; Gonchar et al. 2007). As a result, the more efficient labelling system for rodent uses a CBP – PV, a hormone – somatostatin (SST), and the serotonin receptor 5HT3a (Lee et al. 2010; Rudy et al. 2011) for separating largely independent inhibitory interneuronal populations.

There is no direct correspondence between the two labelling schemes,

which makes it difficult to translate mouse data to primate. We checked the cross-species distribution correspondence of the PV-CB-CR labelling scheme, as SST and 5HT3a are suboptimal cell markers in macaque (Hendry, et al. 1984; Campbell et al. 1987; Jakab and Goldman-Rakic 2000; Watakabe, et al. 2009). We compared the two species directly, using antibodies that recognized aminoacid sequences preserved between the two mouse and macaque, and used automated counting methods and objective thresholding of the acquired images. We analysed the expression of CBPs along the depth of the cortex in a continuous manner, to also assess sub-layer patterns of expression (Kooijmans et al. in preparation; Chapter II).

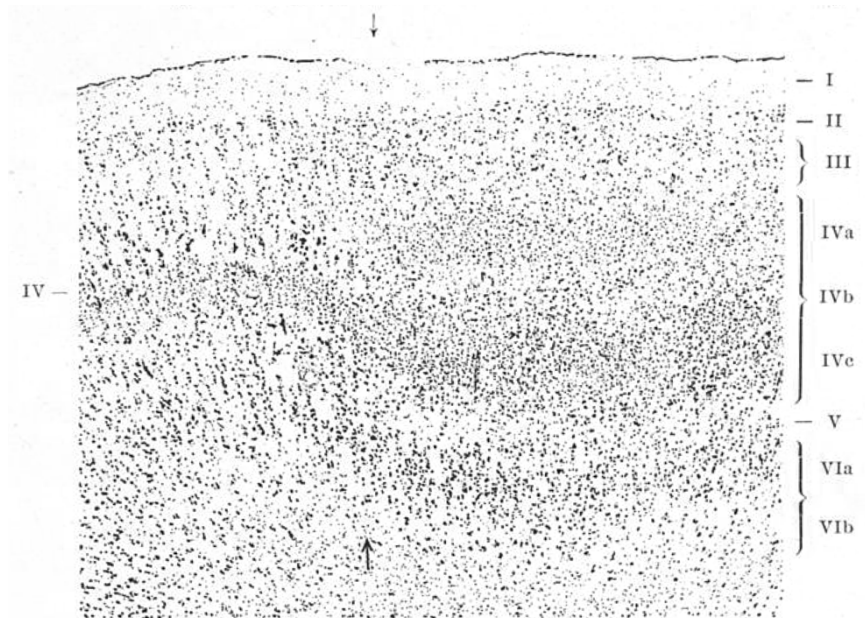


Fig. 12. Erwachsener Mensch. 25:1, 10 μ .
Übergangsstelle des Calcarinatypus (↓) wie in Fig. 11. Die Schichten sind die gleichen: rechts die achtschichtige Rinde der Area striata (Feld 17 unserer Hirnkarten), links der sechsschichtige Occipitaltypus der Area occipitalis (Feld 18).

Figure 1.3: Typical layer organization of primary visual area V1 (right of arrow). Modified from Brodmann (1909 p.33).

Primary visual cortex

We focused on primary visual cortex (V1) (Figure 1.3), as it is the morphologically most complex (Brodmann 1909), as well as one of the

most extensively described cortical areas (Ramón y Cajal 1899a; Mai and Paxinos 2011). V1 is the first cortical processing station in the visual processing stream (Figures 1.4 & 1.5). Its layer organization is very distinctive (Figure 1.3), and strongly preserved in primates (Brodmann 1909).

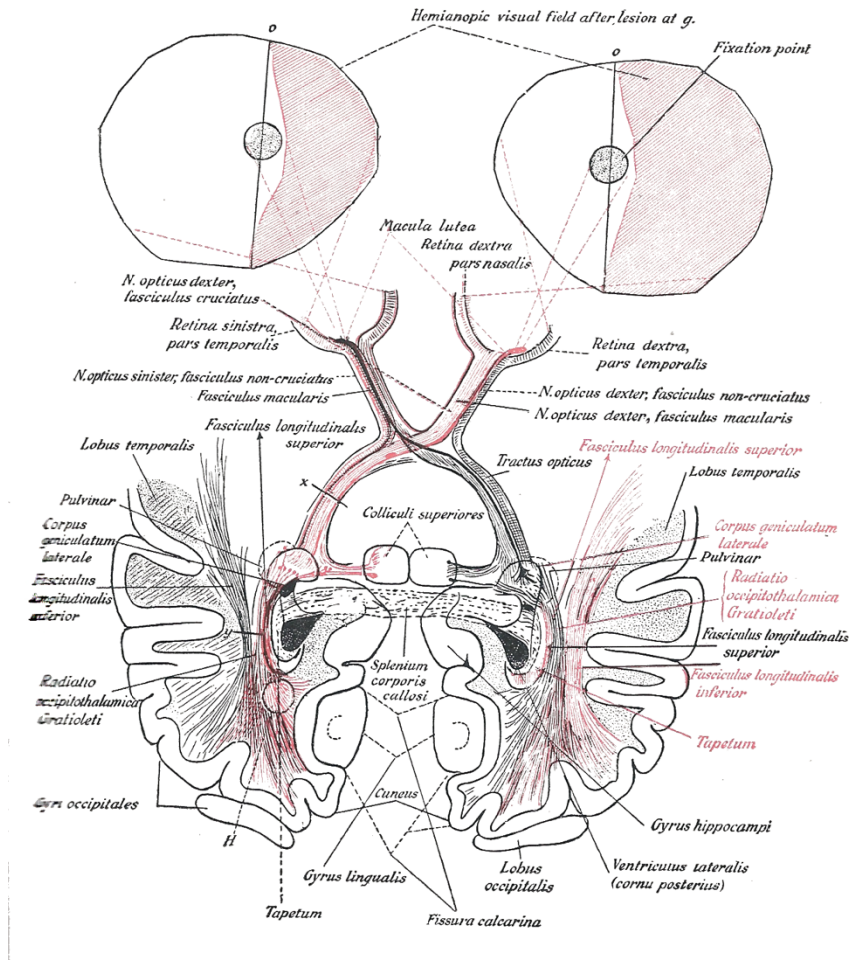


Figure 1.4: The primary visual cortex (along fissura calcarine / the calcarine fissure), as the first cortical procession station in the visual stream. Modified form Barker (1899 p.829).

In primates, the visual system occupies a large portion of the cortical surface, and it is the dominant sensory modality (Witten and Knudsen 2005). The visual system, and V1 in particular, are a benchmark for both anatomical and physiological studies. The shared organizational traits of primary sensory areas, resulting from their similar processing demands,

make V1 data highly relevant for other modalities as well (Mai and Paxinos 2011).

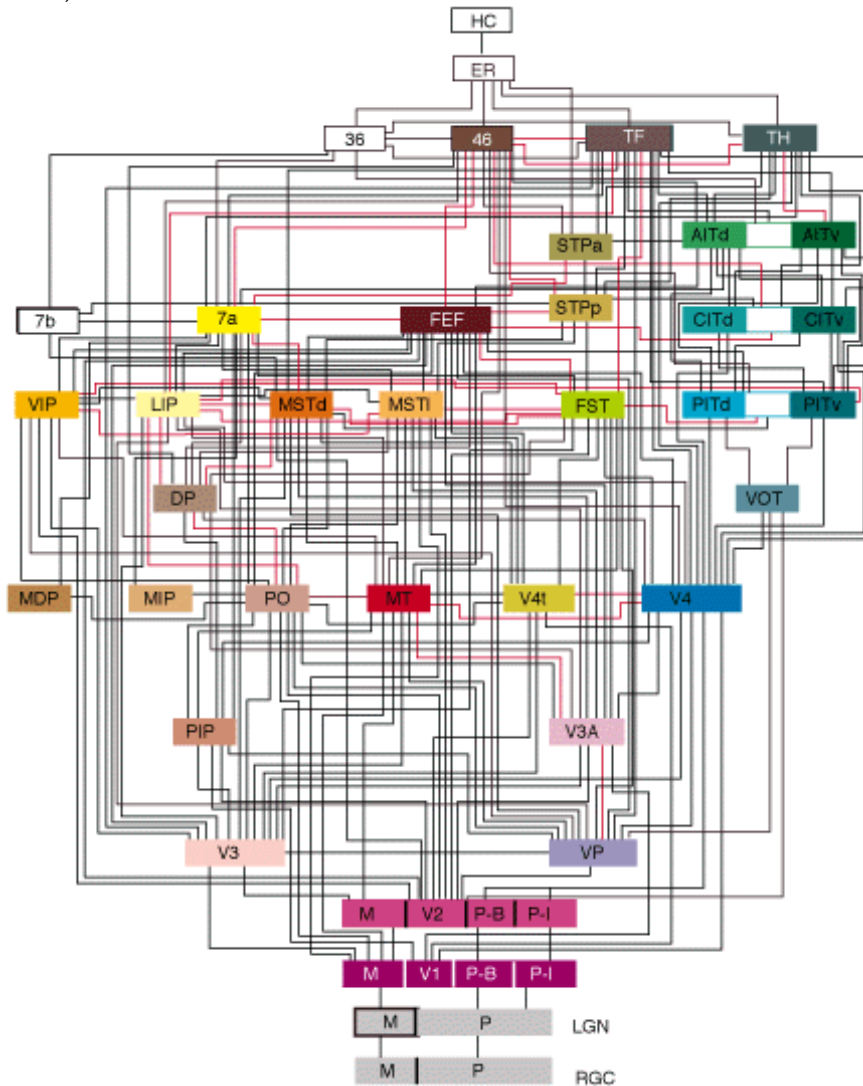


Figure 1.5: Hierarchy of cortical areas in macaque visual processing. Initial information enters hierarchy at the bottom level. Modified from Felleman and Van Essen (1991 p.30).

Feedforward and feedback processing

V1 receives input from the retina via the lateral geniculate nucleus (LGN) (Figures 1.4 & 1.5), and relays it to higher cortical areas involved in visual

processing (Felleman and Van Essen 1991) (Figure 1.5). This type of information processing is labelled feed-forward, as the neural signal flow goes from the receptor in the retina to the LGN, V1, V2, and so forth, to areas that perform increasingly complex computations (Felleman and Van Essen 1991). V1 also receives information from other “higher” cortical areas involved in visual processing. This type of relay is feedback processing, as the transmission of information occurs backwards, from more remote cortical areas to V1. The layers targeted by feedforward and feedback projections to macaque V1 are distinct (Rockland and Pandya 1979; Lund 1988; Rockland 1994).

Feedforward and feedback neural signatures can be differentiated using a figure-ground segregation task (Lamme 1995). This task requires a monkey to identify a figure defined by texture on a differently textured background (Figure 1.6). The figure size for the original task is larger than the receptive fields of recorded V1 neurons, with no predicted difference between a textured figure and a textured background at the level of the V1 receptive field. The time course of the neural signal associated with this task in V1 shows two components, which suggests differential involvement of feedforward and feedback processing (Figure 1.6). The first component is similar for receptive fields located either on a figure or on the ground. This phase of the signal is most likely exclusively driven by feedforward (retina to LGN to V1) detection of texture, in a recorded visual field. The second component of the signal is different for the figure and ground conditions, showing enhanced neuronal activity for the figure, and reduced activity for the ground condition. Due to the smaller-than-figure size of the receptive field recorded, this effect cannot result from feedforward information flow from the retina. This neuronal signature has been attributed to some form of recurrent processing, either lateral (within V1) or feedback (higher areas to V1) (Lamme 1995; Li et al. 2001; Rossi et al. 2001; Li 2003; Self et al. 2012, 2013). Interestingly, the two phases of the figure-ground segregation signal originate in layers of V1 that correspond to feedforward and feedback long-range projections (Rockland and Pandya 1979; Lund 1988; Rockland 1994; Self et al. 2013). They also appear to be associated with distinct oscillatory frequencies that originate in these layers (Van Kerkoerle et al. 2014).

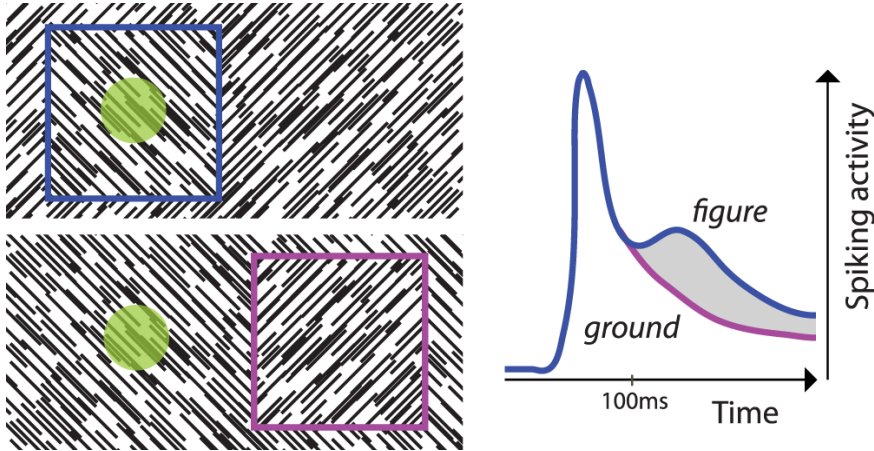


Figure 1.6: The neural correlates of figure-ground assignment in V1. Neurophysiological studies have found that the late (>100ms) spiking activity of neurons in V1 is increased when their receptive field (red circle) is placed on a figure (upper panel, figure outlined for clarity) compared to when they are responding to the background (lower panel), even for identical texture inside the receptive field. This figure-ground modulation (grey region in the right graph), is likely the result of feedback from higher visual areas. Modified from Self et al. (2015 p.2).

Classification of inhibitory interneurons

Neurons can be classified using a variety of criteria, including function, projection target, morphology, and firing behaviour. Functionally, the majority of neurons are excitatory, causing depolarization and potentially leading to an increase in the activity of neurons they target synaptically. The main excitatory neurotransmitter is glutamate (Nieuwenhuys et al. 2007; Kandel et al. 2012). A smaller number of neurons (20-30%) are inhibitory, reducing the activity of interneurons they target, via the neurotransmitter gamma-aminobutyric acid (GABA) (Markram et al. 2004; Isaacson and Scanziani 2011; Luft 2014). A third group consists of modulatory neurons that regulate the function of a group of targeted neurons via diffuse neurotransmitter release, rather than relay signals via synaptic transmission. The cell bodies of neurons belonging to modulatory systems are, however, located in subcortical nuclei (Nieuwenhuys et al. 1998, 2007). As a result, excitatory and inhibitory cell types dominate the neocortical population.

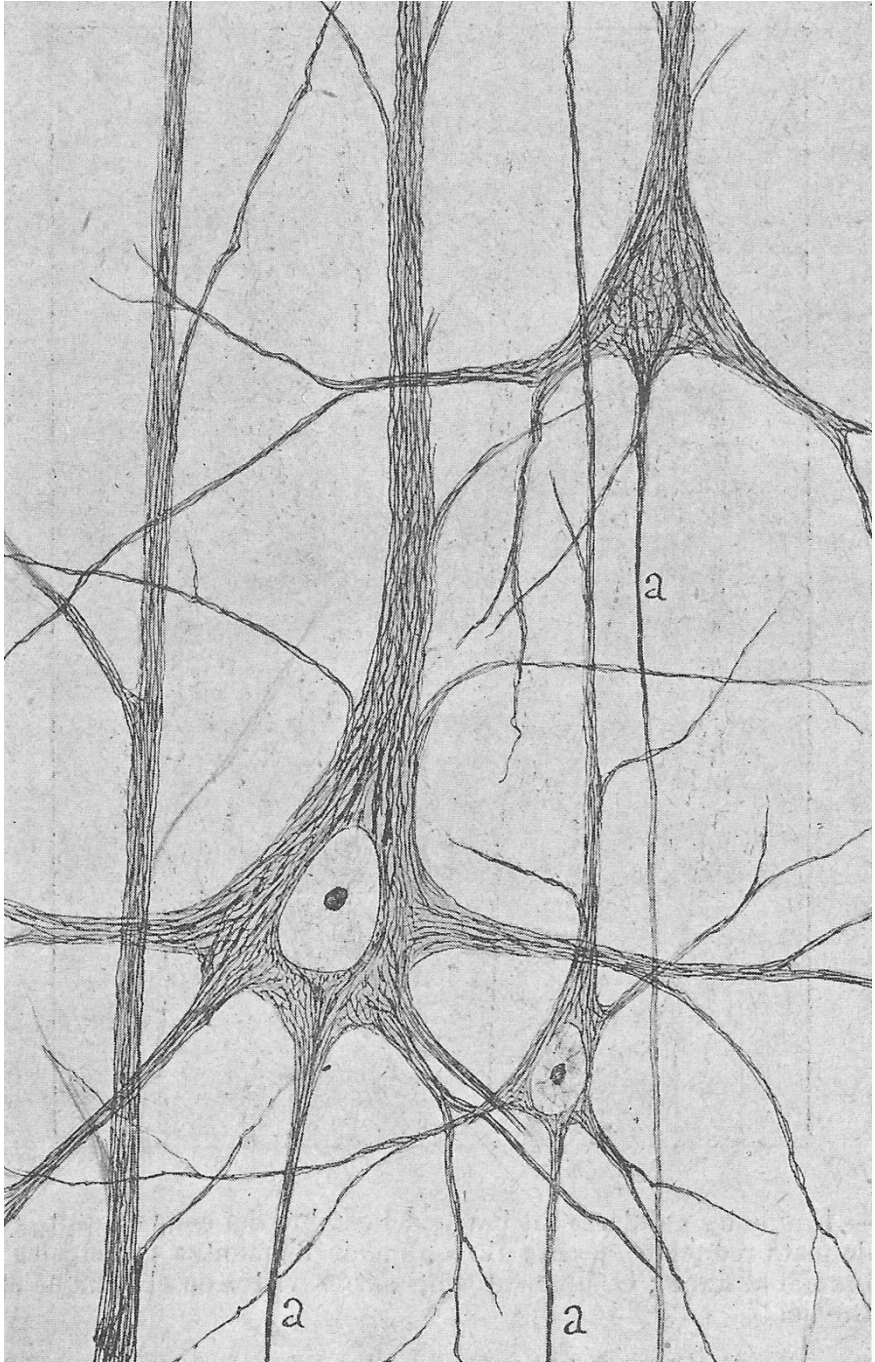


Figure 1.7: Typical morphology of pyramidal cells. Modified from Ramón y Cajal (1904 p.820).

Another way to classify neurons is by the location of their projection target. Neurons that project to other structures, cortical or subcortical, are (long-range) projection neurons. Ramón y Cajal named these “long-axon” neurons (1899b). Neurons that project within the structure where their cell body is located, without their axon leaving the cortex, can be referred to as either local-circuit neurons or interneurons (Ramón y Cajal 1899b; Nieuwenhuys et al. 2007). Ramón y Cajal identified these as “short-axon” cells (1899b).

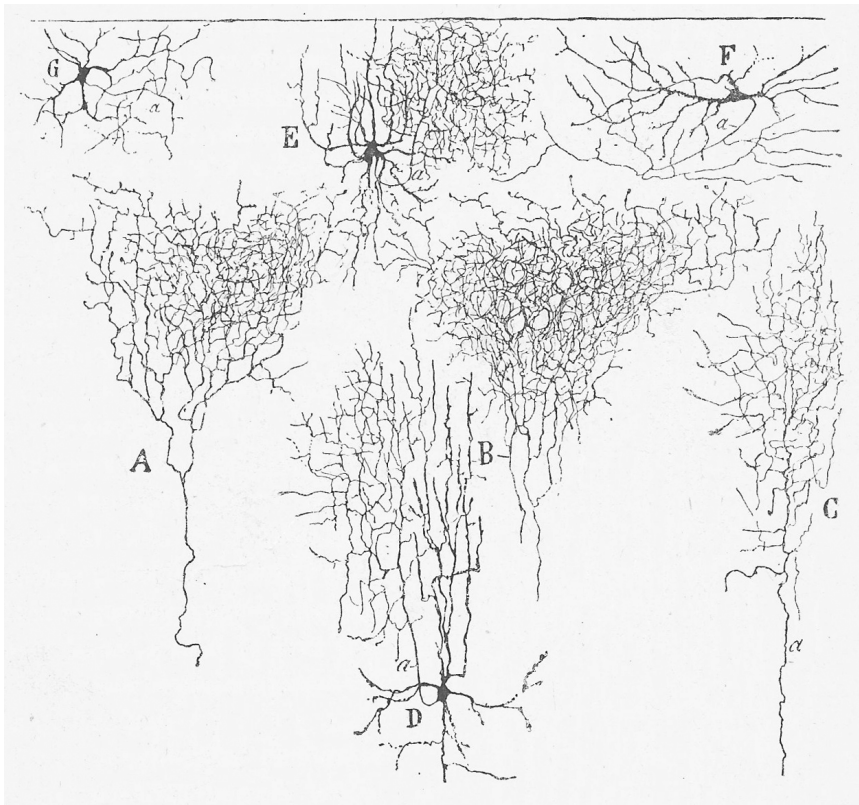


Figure 1.8: Overview of interneuronal morphologies as first documented by S. Ramon y Cajal (1904 p.811).

Morphologically, the vast majority of neurons is pyramidal (Ramón y Cajal 1899b; DeFelipe and Jones 1998; Nieuwenhuys et al. 2007) (Figure 1.7). This applies to most of projection-, as well as local-circuit neurons. The remaining local-circuit morphologies are spiny stellate, neurogliaform, chandelier, basket, nest basket, vertically oriented (bipolar, bitufted, double bouquet), Martinotti, and horizontal (Ramón y Cajal 1899b; Jones 1984;

Kisvárdy et al. 1986; Kisvárdy et al. 1990; DeFelipe and Jones 1998; Nieuwenhuys et al. 2007; DeFelipe et al. 2013) (Figure 1.8). Of these, only spiny stellate morphologies are excitatory as a rule. Therefore, cortical inhibitory interneuron types, although they constitute a numerical minority, account for the majority of morphological variation.

According to firing behaviour, cortical neurons are either regular spiking, fast spiking, or intermediate spiking. Excitatory neurons are generally regular spiking, while inhibitory interneurons can be either fast spiking or intermediate spiking (Zaitsev et al. 2005; Burkhalter 2008).

Since inhibitory interneurons are a morphologically heterogeneous group (Ramón y Cajal 1904; Lund 1987; Lund et al. 1988; Lund and Yoshioka 1991; Lund and Wu 1997; DeFelipe and Jones 1998; Nieuwenhuys et al. 2007; Burkhalter 2008; Isaacson and Scanziani 2011), much work has been dedicated to further differentiating between different types (Markram et al. 2004; Ascoli et al. 2008; Burkhalter 2008). There are, however, shared traits of inhibitory interneuronal groups in macaque, which divide them into two groups, and correlate with calcium-binding proteins they express. These traits include subcortical progenitor group origin (Ma et al. 2013) and firing patterns (Zaitsev et al. 2005). Such findings suggest that there are underlying commonalities, and possibly more functional cohesion than there is morphological.

Glutamate receptors

Glutamate is the principal excitatory neurotransmitter in the central nervous system (Nieuwenhuys et al. 2007; Kandel et al. 2012), and glutamate receptors mediate the majority of excitatory input to inhibitory interneurons.

A large variety of glutamate receptors (GluRs) introduces additional complexity to synaptic transmission, while binding the same substrate (glutamate). According to impact of substrate, GluRs can be divided into either metabotropic or ionotropic (Dingledine et al. 1999; Kandel et al. 2012; Sherman 2013; Rondard and Pin 2015). Metabotropic receptors

(mGluRs) activate biochemical cascades that lead to the modification of other proteins. There are eight different subunits identified so far, which have been divided into three groups, according to sequence similarity, pharmacology, and transduction mechanism (Pin and Duvoisin 1995; Pin et al. 2003; Kandel et al. 2012; Rondard and Pin 2015). Ionotropic glutamate receptors (iGluRs) are trans-membrane ionic channels that undergo a conformational change following substrate binding, resulting in the flow of ions through the cellular membrane, effectively leading to its depolarization (Dingledine et al. 1999; Kandel et al. 2012). These can be divided into AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazole-propionate), kainate, and NMDA (N-Methyl-D-aspartate) receptors, according to the alternate agonist substrate they bind (Dingledine et al. 1999; Kandel et al. 2012). In the current work, we concentrated on the expression of AMPARs and NMDARs, as the predominant glutamate receptor classes (Kooijmans, Self, et al. in preparation; Kooijmans et al. 2012, 2014; **Chapters III & IV**).

AMPA receptors (AMPARs) are the fast-acting class of glutamate receptors. Four AMPAR-subunits have been characterized, GluA1 through GluA4, which are expressed by excitatory and inhibitory neurons in macaque V1 (Carder and Hendry 1994; Carder 1997). The subunit composition of individual AMPA receptors determines their permeability for sodium (Na^+), potassium (K^+), and calcium (Ca^{2+}) ions, with AMPARs containing the GluA2 subunit impermeable for Ca^{2+} (Lerma et al. 1994). Furthermore, different AMPAR subunits play distinct roles in synaptic plasticity (Kessels and Malinow 2009).

NMDA receptors (NMDARs) on the other hand, mediate slow synaptic transmission, and are involved in long-term potentiation and depression (Bliss and Collingridge 1993; Dingledine et al. 1999; Shipton and Paulsen 2014), as well as synaptic integration for discrete dendritic inputs (Larkum et al. 2009). There are three described subunit groups for of the NMDA receptor: GluN1, GluN2 and GluN3. The GluN1 subunit is glycine binding and has eight splice variants (Conti et al. 1997; Köhr 2006). There are no documented spatial or functional particularities of GluN1 splice variants. GluN2 is the only glutamate-binding NMDA subunit and has four documented isoforms A, B, C and D (Standaert et al. 1996;

Dingledine et al. 1999; Küppenbender et al. 2000; Cull-Candy and Leszkiewicz 2004; Clarke and Johnson 2006; Erreger et al. 2007). GluN3 is again a glycine binding subunit, with two isoforms, A and B (Chatterton et al. 2002). Typical NMDA receptors consist of four subunits, most frequently two GluN1 and two GluN2 subunits. The replacement of one GluN2 by a GluN3 is also possible, resulting in reduced the Ca^{2+} permeability of the receptor (Henson et al. 2010). Such subunit configurations require glutamate as an agonist, glycine as a co-agonist. More recent results demonstrate that GluN1 and GluN3 subunits can also form tetrameric receptors which are glycine binding and de facto not glutamate receptors (Chatterton et al. 2002).

Receptor expression and pharmacology

Many basic receptor-mediated synaptic mechanisms such as long-term potentiation (LTP) and long-term depression (LTD) were first demonstrated in excitatory neurons (Siegelbaum and Kandel 1991; Bear and Malenka 1994). The rules governing LTP correlate with glutamate receptor expression, including AMPA to NMDA receptor ratio (Kullmann et al. 2000; Kopec et al. 2006; Rasch et al. 2011), as well as AMPAR and NMDAR subunit composition (Jia et al. 1996; Kopec et al. 2007; Kessels and Malinow 2009; Kessels et al. 2009; Foster et al. 2010). Excitatory neurons preponderantly express the AMPAR GluN1/2 and GluN2/3 dimers (Wentholt 1996; Leuschner and Hoch 1999; Ayalon and Stern-Bach 2001; Kessels and Malinow 2009) and several heteromeric NMDAR (Luo et al. 1997; Hatton and Paoletti 2005; Paoletti and Neyton 2007; Paoletti 2011).

Inhibitory interneuronal functional properties, ranging from firing patterns to LTP rules, are different from those of excitatory cells (Zaitsev et al. 2005; Burkhalter 2008), and likely correlated with the receptor expression on interneurons (Moreau and Kullmann 2013).

We therefore set out to explore whether there are glutamate receptor patterns specific to inhibitory interneurons (Kooijmans, Self, et al. in preparation; Kooijmans et al. 2012, 2014; **Chapters III & IV**). We

analysed the probability of expression of AMPAR subunits GluA1 through 4, as well as NMDAR GluN2A through D, independently for each subunit on each CBP-IR population. We found that there are two distinct expression profiles for glutamate receptors, which correlate with interneuronal firing patterns, as well as CBP expression. High GluA2 and GluA3 expression, low GluA1 and GluA4, as well as low overall GluN2 expression define the first expression profile, characteristic of PV-IR cells. In contrast, high GluA1, GluA4, as well as GluN2A through D, with low GluA2 and GluA3 characterize CB-IR and CR-IR cells (Kooijmans, Self, et al. in preparation; Kooijmans et al. 2012, 2014; **Chapters III & IV**). This receptor expression division points towards different synaptic calcium influx for the two inhibitory interneuronal groups, which, combined with the different calcium buffering properties of the CBPs may give rise to their functional differences.

In the context of receptor expression, we tested the impact of AMPAR versus NMDAR blockers on early visual processing (Self et al. 2012; **Chapter V**). We assessed this for a figure-ground segregation task in macaque (Lamme 1995), in which the neuronal response pertaining to feed-forward and recurrent processing have been extensively characterised (Lamme 1995; Roelfsema et al. 2002; Super and Roelfsema 2005; Self et al. 2013; Van Kerkoerle et al. 2014). For this task, we found that the AMPAR blocker CNQX mostly affected feed-forward processing, while the generic NMDAR blocker APV reduced the difference between the figure and ground signals for recurrent processing. The majority of this impact is most likely due to blockage of excitatory activity. However, when investigating the GluN2B specific blocker Ifenprodil, we also observed reduced difference in recurrent processing, but with an overall increase of neuronal activity, suggesting GluN2B expression is related to inhibitory feedback (Self et al. 2012; **Chapter V**).

Thesis organization

This thesis is concerned with systematizing and clarifying layer organization of inhibitory interneurons, and characterising their expression of glutamate receptors, in macaque primary visual cortex.

Since the development of therapies for primates in rodent models assumes some degree of equivalence of cortical organization between the two, we first compared the expression of calcium binding proteins in primary visual cortex of mouse and macaque (**Chapter II**). Next, we explored the distribution of AMPA and NMDA glutamate receptor subunits on different classes of inhibitory cells, to understand the impact of excitatory inputs, and their integration, in interneurons (**Chapters III & IV**). Furthermore, we studied the impact of AMPA and NMDA receptor blockers in a complex visual task (**Chapter V**).

To address the points listed above, we conducted a series of anatomical and physiological experiments, using a variety of techniques. Importantly, we employed objective automated analysis for anatomical data, and provided numerous new insights into systematic mapping of interneurons.

The results are organised in scientific journal articles, some already published, and others currently in preparation, as indicated for each chapter.

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