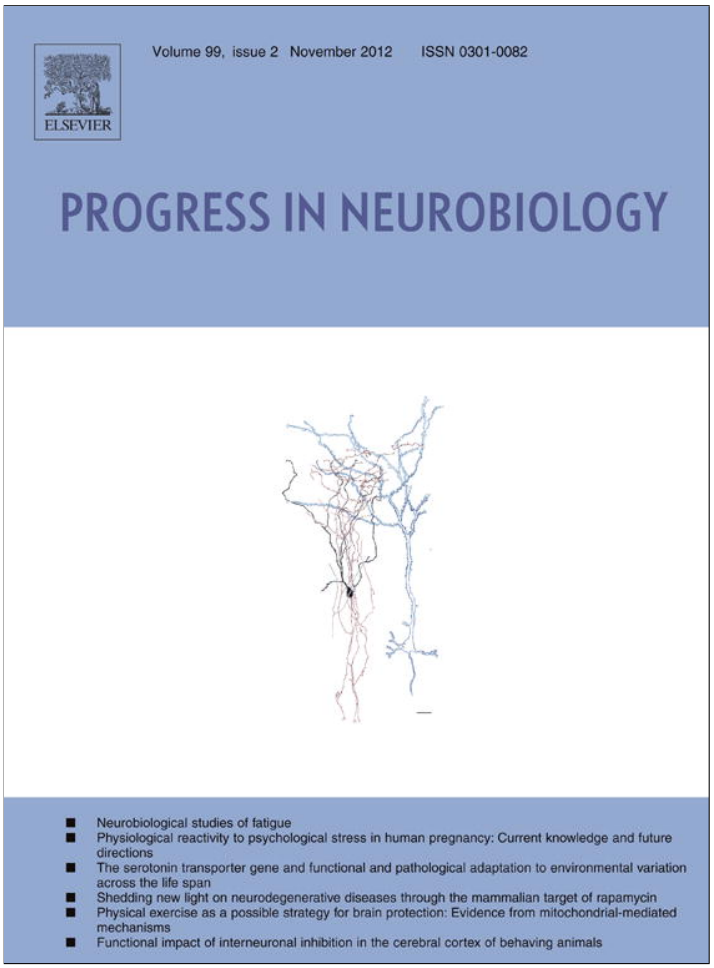

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Functional impact of interneuronal inhibition in the cerebral cortex of behaving animals

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ABSTRACT

This paper reviews recent progress in understanding the functional roles of inhibitory interneurons in behaving animals and how they affect information processing in cortical microcircuits. Multiple studies have shown that the morphological subtypes of inhibitory cells show distinct electrophysiological properties, as well as different molecular and neurochemical identities, providing a large mosaic of inhibitory mechanisms for the dynamic processing of information in the cortex. However, it is only recently that some specific functions of different interneuronal subtypes have been described in behaving animals. In this regard, influential results have been obtained using the known differences of interneurons and pyramidal cells recorded extracellularly to dissociate the functional roles that these two classes of neurons may play in the cortical microcircuits during various behaviors. Neurons can be segregated into fast-spiking (FS) cells that show short action potentials, high discharge rates, and correspond to putative interneurons; and regular-spiking (RS) cells that show larger action potentials and correspond to pyramidal neurons. Using this classification strategy, it has been found that cortical inhibition is involved in sculpting the tuning to different stimulus or behavioral features across a wide variety of sensory, association, and motor areas. Recent studies have suggested that the increase in high-frequency synchronization during information processing and spatial attention may be mediated by FS activation. Finally, FS are active during motor planning and movement execution in different motor areas, supporting the notion that inhibitory interneurons are involved in shaping the motor command but not in gating the cortical output.

Contents

1. Introduction . . . 164
2. Cortical microcircuits, the ups and downs of an old concept: the columnar organization . . . 164
   2.1. Columns and the numerous types of cortical interneurons . . . 164
3. Interneuronal subtypes and their diverse functions . . . 165
4. Inhibition, cell tuning, and mapping of variables . . . 167
5. Indirect measures of the role of inhibition in behaving animals . . . 169
   5.1. Functional interplay of putative pyramidal and interneuron subgroups in behaving primates . . . 170
   5.2. The case in the motor areas . . . 174
6. Technical challenges . . . 175
7. Conclusions . . . 175
   Acknowledgements . . . 176
   References . . . 176

Abbreviations: FS, fast-spiking; RS, regular-spiking; LS, late-spiking; LTS, low-threshold spiking; S1, somatosensory cortex; V1, primary visual cortex; M1, primary motor cortex; PFC, prefrontal cortex; GABA, γ-amino butyric acid; ITC, inferior temporal cortex; PP1, putative pyramidal1; PP2, putative pyramidal2; antiPD, anti-preferred direction; GAD, glutamic acid decarboxylase; PV, parvalbumin; CB, calbindin; SST, somatostatin; CCK, cholecystokinin; VIP, vasoactive intestinal peptide; CR, calretinin; NPY, neuropeptide Y; vGlut1, vesicular glutamate transporter 1.

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1. Introduction

Inhibition was established as an active process in neural computations in the early 20th century by Sherrington. In the brain, this process is mediated by the neurotransmitter γ-amino butyric acid (GABA), and its pharmacology has been instrumental for designing analgesics, anti-epileptics, and especially for mood-altering drugs. With the development of the Golgi neural staining method, Ramon y Cajal along with many important neuroanatomists that followed him, described a dozen morphologically distinct types of inhibitory interneurons in the cerebral cortex. These non-spiny inhibitory cells constitute about 20% of all cortical neurons and are characterized by their distinctive short axon and their local connections with the spiny pyramidal neurons, which in turn send projections to other cortical and subcortical structures. Despite the numerous qualitative morphological studies on interneurons, the roles of cortical inhibition in the representation of behavioral information at the microcircuit and the large neural network levels are still largely unknown. Important recent advances, however, have been made using intracellular recordings of multiple pairs of interconnected neurons in vitro and in vivo. These techniques allow for the quantitative analysis of network architecture from cells that are histologically and neurochemically identified, and they also permit the investigation of the physiological properties of local synaptic connections and the characterization of the intrinsic properties of interconnected pyramidal and interneuronal subtypes. On the other hand, electrophysiological studies have exploited the known differences in the action potential duration of interneurons and pyramidal cells recorded extracellularly to dissociate the functional roles that these two classes of neurons may play in different behaviors. However, the information that has been generated from the microcircuit and system network neurophysiology is still not well integrated due, in large part, to methodological problems. Hence, this review gives a general picture of the large gap of knowledge linking the functional impact of interneuronal inhibition from microcircuits to the systemic level of cortical organization in behaving animals.

2. Cortical microcircuits, the ups and downs of an old concept: the columnar organization

A neural microcircuit is defined as a minimal number of interacting neurons that can collectively produce a functional output, and different types of microcircuits have been identified throughout the central nervous system (Silberberg et al., 2005; Shepherd and Grillner, 2010). The vertical assembly of highly interconnected neurons spanning cellular layers II–VI has been proposed as the (or a) fundamental unit of the cortical microcircuit upon which information processing is derived. Based on anatomical observations, Lorente de Nó (1938) was the first to suggest a vertical arrangement of neurons as functional units. Then, working on the somatosensory cortex (S1) of anesthetized cats and monkeys, Vernon Mountcastle found experimental evidence for a functional column (Mountcastle, 1957; Powell and Mountcastle, 1959). He was followed by Hubel and Wiesel (1959, 1969, 1977) with their discovery of the orientation selective columns in the primary visual cortex (V1) of the same species. The main initial finding that support the hypothesis of vertical neurophysiological units or modules consisted of recording cells with similar functional properties (e.g. receptive field location) when the electrode showed trajectories that were perpendicular to the pial surface and crossed all cortical layers. In contrast, when the recording electrode traversed a trajectory parallel to the cortical surface, neurons showed a progressive change in their functional profile, such as the orderly variation in orientation preference of V1 cells at increments of 30–50 μm. These findings led to the view that minicolumns, a group of ~100 neurons forming a vertical cylinder of ~50 μm (Rockel et al., 1980), represent the smallest information processing units of the cortex (Mountcastle, 1978). In fact, minicolumns can be visualized as prominent bands of cells running radially through the cortical layers in Golgi or Nissl-stained sections (Rockel et al., 1980). In addition, it was suggested that minicolumns are further organized into functional modules of a higher order called cortical columns (or hypercolumns), each consisting of several minicolumns connected by short-range horizontal connections and representing all possible values of the variable encoded in the minicolumns. Consequently, one of the important functions of columnar organization is the mapping of two or more variables into the x–y dimensions of the cortical surface (Mountcastle, 1997; Buxhoeveden and Casanova, 2002).

The columnar organization of the cortex has been studied with numerous anatomical, molecular, and functional techniques including different staining methods, intra- and extracellular recordings, optical imaging, expression of early genes, anatomical characterization of axonal ending patch-like clusters, and staining of enzymatic activity (e.g. cytochrome oxidase patches). Columns have been described in many forms in V1 (ocular dominance, orientation, color blobs, etc. [Horton and Adams, 2005; Lu and Roe, 2008]), the extrastriate visual cortex (Extra-striate visual cortices 2, 3, and 5 [Zeki, 1993; Ts'o et al., 2009]), the primary auditory cortex (isofrequency [Merzenich and Brugge, 1973; Morel et al., 1993]), the rodent S1 (barrels, (Woolsey and Van der Loos, 1970; Helmstaedter et al., 2007; Schubert et al., 2007)), and the motor cortex (M1) (efferent zones [Asanuma and Rosén, 1972] and preferred direction [Amirikian and Georgopoulos, 2003; Georgopoulos et al., 2007]).

2.1. Columns and the numerous types of cortical interneurons

It is important to mention that the concept of a cortex consisting of repetitions of the same fundamental microcircuit has been persistently questioned due to the highly variable size, functional properties, and cell composition of the columnar types (Horton and Adams, 2005; Douglas and Martin, 2007; Swindale, 1990). In addition, the modular heterogeneity can be seen across cortical areas of the same species and between species (Douglas and Martin, 2007). Furthermore, multiple modules can overlap partially or even completely within the same cortical anatomical space (Swindale, 1990). In consequence, it has been impossible to find a canonical microcircuit that corresponds to a stereotypical cortical column (Nelson, 2002; Douglas and Martin, 2004). This is particularly true when considering the large assortment of cortical interneuronal subtypes, their complex intrinsic and extrinsic connectivity, as well as the obvious difficulties in classifying them. For example, in V1 there are at least nine major morphological subtypes of interneurons throughout layers II–VI, each showing between two and eight different electrophysiological response profiles, and each of these with two to five potential molecular/neurochemical subtypes (Toledo-Rodriguez et al., 2004; Silberberg et al., 2002). In addition, the relative proportions of the different cell types within a given layer, and of the same cell type across layers can also vary substantially. Hence, in order to include the large diversity of interneurons, a canonical cortical circuit should have an enormous size and contain hundreds of thousands of neurons (Silberberg et al., 2002), which contrasts with the small size of the minicolumns and columns proposed initially. Now, the lack of interneuronal stereotypy in the cortex is due in part to their diverse ontogeny (Wonders and Anderson, 2006; Fishell, 2007). Interneurons are produced in the medial ganglionic eminence and the ventral caudal ganglionic eminence of the basal telencephalon, as well as in an expanded subventricular zone (Wonders and Anderson, 2006; Corbin and Butt, 2011). An important feature is

that different types of interneurons have different origins and migrate to the cortex along specific tangential migratory pathways, which are independent of the radial glial guides for pyramidal cells, whose ontogeny is very stereotypic (DeCarlos et al., 1996; Anderson et al., 1997; Tamamaki et al., 1997; Letinic and Rakic, 2001; Miyoshi et al., 2007).

Overall, neuroscientists are still searching for a unifying principle of cortical modular organization, a common microcircuit template from which multiple variations could be formed. What it is evident is that there is a strong tendency for a periodic representation of parameters in the cortex, and that similar anatomofunctional properties are observed in the vertical domain, involving all layers. Besides the discrepancies in structural stereotypy, it is important to clarify that the original concept of columnar organization also contemplated the existence of dynamic physiological mechanisms to maintain the columns. Mountcastle not only suggested that the defining properties for columns depend on both the afferent inflow and the intracortical processing, but also emphasized that the degree to which these two variables define the columnar properties can vary between cortical areas (Mountcastle, 1978, 1997). Of course, the large variety of interneurons could contribute in many different ways to the flow of intracortical information, producing columns with different sizes and functional profiles. Indeed, what is just now starting to be understood is how the interneuronal activity shapes the information processing of the cortical microcircuits, depending on the cortical area under study (Berger et al., 2009).

3. Interneuronal subtypes and their diverse functions

In the last 15 years, many studies have described, in the slice preparation or in anesthetized rodents, a large diversity of cortical interneurons (Table 1). In view of the large variety of electrophysiological, neurochemical, and molecular subtypes of inhibitory cells in the cortex, the nomenclature and classification of the original dozen morphological types of interneurons has become a difficult task. Recently, an international group of researchers met in Ramon y Cajal's birth place, Petilla Spain, with the purpose to determine a "universal" classification system for cortical interneurons (Petilla Interneuron Nomenclature Group, 2008). Not surprisingly, this group of experts could not agree on a conclusive scheme, although they were clear on the need for a multifactorial experimental approach in order to identify different interneuronal subtypes. Thus, multimodal information obtained from single neurons that includes a variety of morphological features, molecular markers, as well as electrophysiological properties, has been used to classify interneuronal subtypes using clustering analysis. Such efforts have proposed a classification scheme for specific subtypes of interneurons (Gallopin et al., 2006; Table 1). However, it has been shown that some interneurons show a set of multimodal properties that cannot be classified into the "generic" subtypes (Gallopin et al., 2006; Table 1).

Nevertheless, with respect to their role in the microcircuit dynamics, inhibitory neurons can be classified in two ways: according to the orientation of their axonal arbors or by their axonal targets (Somogyi, 1989; Jones, 1993). The axonal fields can be local (neurogliaform, small and nest basket cell, chandelier cell), vertical (double bouquet cell, Martinotti cell, bipolar cell, and bitufted cell), or horizontal (large basket cell, Cajal-Retzius cell [Figs. 2–8]) (DeFelipe, 2002; see Figs. 1 and 2). Conversely, using the axonal targets as classification scheme, interneurons can be divided into four classes of cells specialized in targeting: distal dendrites (Martinotti cells [Figs. 2–7]); mid-range and proximal dendrites (double-bouquet [Figs. 1-b and 2–5], bipolar [Figs. 2–6], and neurogliaform [Figs. 2–4] cells); soma and perisomatic dendrites (large, nest, and small basket [Figs. 1a and c, and 2 and 3] cells); and the initial segment of the axon (chandelier cells [Figs. 1d and 2-2]) (Markram et al., 2004). The combination of these two features confers on interneurons enormous capabilities to control the inflow, the internal processing, and the outflow of information inside the microcircuits of the cortex. Inhibitory cells targeting preferentially the distal dendritic regions play an important role in the integration and control of input information. Neurons that innervate most of the dendritic domain can also influence the dendritic processing and integration of synaptic inputs (Miles et al., 1996). In addition, these cells can participate in synaptic plasticity and modulate the generation and propagation of dendritic calcium spikes (Larkum et al., 1999; Traub, 1995). Cells that preferentially innervate the somatic domain allow presynaptic neurons to control the gain of summed potentials and the discharge rate of the target cells (Tamás et al., 1997; Miles et al., 1996; Freund and Katona, 2007). These interneurons are also involved in synchronizing local circuits (Cobb et al., 1995; Tukker et al., 2007). Finally, inhibitory cells whose axons target the initial segment of the pyramidal axons can veto the action potential generation of the cells, thereby controlling the output of the target neuron (Inda et al., 2006; Woodruff and Yuste, 2008).

On the other hand, the position and orientation of the axonal arbor have a critical influence on the intra- and inter-columnar processing. Lateral inhibition, a mechanism that defines the columnar width, mainly depends on two types of interneurons: (1) basket cells that provide inter-columnar inhibition within the layer of their cell body (Kisvárday et al., 1993; Figs. 2 and 3), and (2) Martinotti cells that project to lamina I and then send horizontal collaterals across several columns, producing a large inhibitory field (Helmstaedter et al., 2009; Wang et al., 2004a,b; Fig. 2.7). Inside a column, interneurons maintain in balance the level of excitation over a large range of input magnitudes, generating a coordinated increase in excitatory and inhibitory conductances (Borg-Graham et al., 1998; Gibson et al., 1999). However, large excitation–inhibition imbalances can occur transiently during stimulation, imbalances that can shape the responses of pyramidal cells as we will show below (Haider and McCormick, 2009). The response equilibrium inside the microcircuits depends on the inhibitory modulation within and between layers. Thus, interneurons can form combinations of connections with one or more pyramidal cells not only to prevent over-excitation but also to sculpt the overall output of the column (Helmstaedter et al., 2007; Silberberg and Markram, 2007).

Another important aspect in the interaction between pyramidal cells and interneurons is the wide spectrum of depressing and facilitating synapses that are established among them (Beierlein et al., 2003; Markram et al., 2004). Thus, particular dynamic synapses can define different conditions for cell recruitment. For example, pyramidal neurons recruit Martinotti cells through facilitating synapses, making this type of interneuron unresponsive to transient activation of inputs. In contrast, many large basket cells receive depressing synapses, and they are instantly activated by sharp inputs. The opposite effect is observed when the microcircuit is subjected to prolonged periods of excitation (Wang et al., 2002).

The functional impact of the dynamic change of the excitation–inhibition equilibrium inside and outside the column is under study, particularly in the rat using patch-clamp techniques (Helmstaedter et al., 2007; Berger et al., 2009; Varga et al., 2011). At this point, one might speculate that the large diversity of interneurons is the product of evolutionary pressure to develop a cortical tissue with an enormous capacity for information processing. This capacity is critical in order to cope with the behavioral exigencies of a dynamic environment.

Table 1
The electrophysiological, molecular, and morphological properties of three different cell groups in the cortex are compared across the literature.

Reference	FS interneurons			NFS interneurons			Pyramidal		
	AP width (ms)/ firing pattern	Molecular markers	Morphology/area/species	AP width (ms)/firing pattern	Molecular markers	Morphology/area/ species	AP width (ms)/ firing pattern	Molecular markers	Morphology/ area/species
Cauli et al. (2000)	0.43/nonadapting	PV, CB	Nonpyramidal/parietal/rat	0.48/adapting 0.69/RS 0.54/irregular spiking	SST, CB VIP, CCK VIP,CB, CR, CCK	Nonpyramidal/ parietal/rat	1.27/adapting	CCK	Pyramidal/ parietal/rat
Karagiannis et al. (2009)	0.6/nonadapting	PV, CB	Basket/somatosensory/rat	0.9/adapting 0.9/adapting, bursting 1.0/adapting	SST, CB, NPY VIP NPY	Martinotti Bipolar Neurogliaform/ somatosensory/rat	1.4/adapting	vGlut1, CB	Pyramidal/ somatosensory/rat
Ali et al. (2007)	0.27/nonadapting	PV	Multipolar/visual/rat	0.48/adapting-stuttering-bursting	ND	Martinotti-bitufted-bipolar-double bouquet visual/rat			
	0.26/nonadapting	PV	Multipolar/visual/rat	0.48/adapting-stuttering-bursting	ND	Martinotti-bitufted-bipolar-double bouquet visual/rat			
Gallopin et al. (2006)	0.7/nonadapting	NPY, CCK	Non pyramidal/ somatosensory/rat	1.0/adapting 1.0/adapting	SST; CB, CR VIP, CR	Nonpyramidal/ somatosensory/rat	1.4/RS adapting	vGlut1, CCK	Pyramidal/ somatosensory/rat
Tseng and O'Donnell (2007)	0.53/nonadapting	ND	Non-pyramidal/PFC/rat	0.89/adapting	ND	Nonpyramidal/PFC/rat			
Klostermann and Wahle (1999)	0.9/nonadapting	ND	Basket/occipital/rat	2.6/LTS	ND	Martinotti/occipital/rat	2.3/RS adapting	ND	Pyramidal/ occipital/rat
Hu et al. (2011)	0.21/nonadapting	ND	Nonpyramidal/ "barrel"/rat	0.35/adapting	ND	Non pyramidal/ "barrel"/rat			
Cho et al. (2010)	0.61/nonadapting	PV, CCK	/visual/rat	0.97/LS 0.99/bursting 1.04/RS	CCK, NPY VIP, CCK CCK, SST	Neurogliaform Bipolar-bitufted Nonpyramidal /visual/rat	1.42/adapting	SST	Pyramidal/ visual/rat
Kawaguchi (1995), Kawaguchi and Kubota (1997)	0.43/nonadapting	PV	Basket, chandelier/ frontal/rat	0.77/LS 0.75/LTS 0.94/bursting	No PV SST VIP, CR	Neurogliaform Martinotti Bipolar, double bouquet, arcade/ frontal/rat			
Miyoshi et al. (2007)	0.7/nonadapting, delayed	PV	Basket/somatosensory/ mouse	1.2/RS 1.3/bursting	SST CR, VIP	Bitufted Bipolar-bitufted-double bouquet/ somatosensory/mouse			
Erisir et al. (1999)	0.60/nonadapting	PV	Nonpyramidal/ somatosensory/mouse	1.71/adapting RS, LTS	No PV	Nonpyramidal/ somatosensory/mouse			
McCormick et al. (1985)	0.32/nonadapting	GAD	Basket/somatosensory/ guinea pig				0.80/RS adapting 0.80/bursting		Pyramidal/ somatosensory/ guinea pig
Nowak et al. (2003)	0.28/nonadapting	ND	Basket/visual/cat				0.61/RS adapting 0.31/chattering 0.60/bursting	ND	Pyramidal/visual/cat
Krimer et al. (2005)	0.37/nonadapting	ND	Basket-chandelier/ PFC/macaque	0.67/adapting	ND	Bitufted, double bouquet, neurogliaform, basket/PFC/macaque	0.73/RS adapting	ND	Pyramidal, neurogliaform/ PFC/macaque
Zaitsev et al. (2009)	0.32 0.38/nonadapting	PV PV	Chandelier basket/PFC/macaque	0.68 0.74 0.53/continuous adapting	SS + CB CR CR	Martinotti Double bouquet Basket/PFC/macaque			
Total mean ± SD	0.46 ± 0.19 < NFS and Pyr			0.90 ± 0.45 = Pyr			1.06 ± 0.56 = NFS		

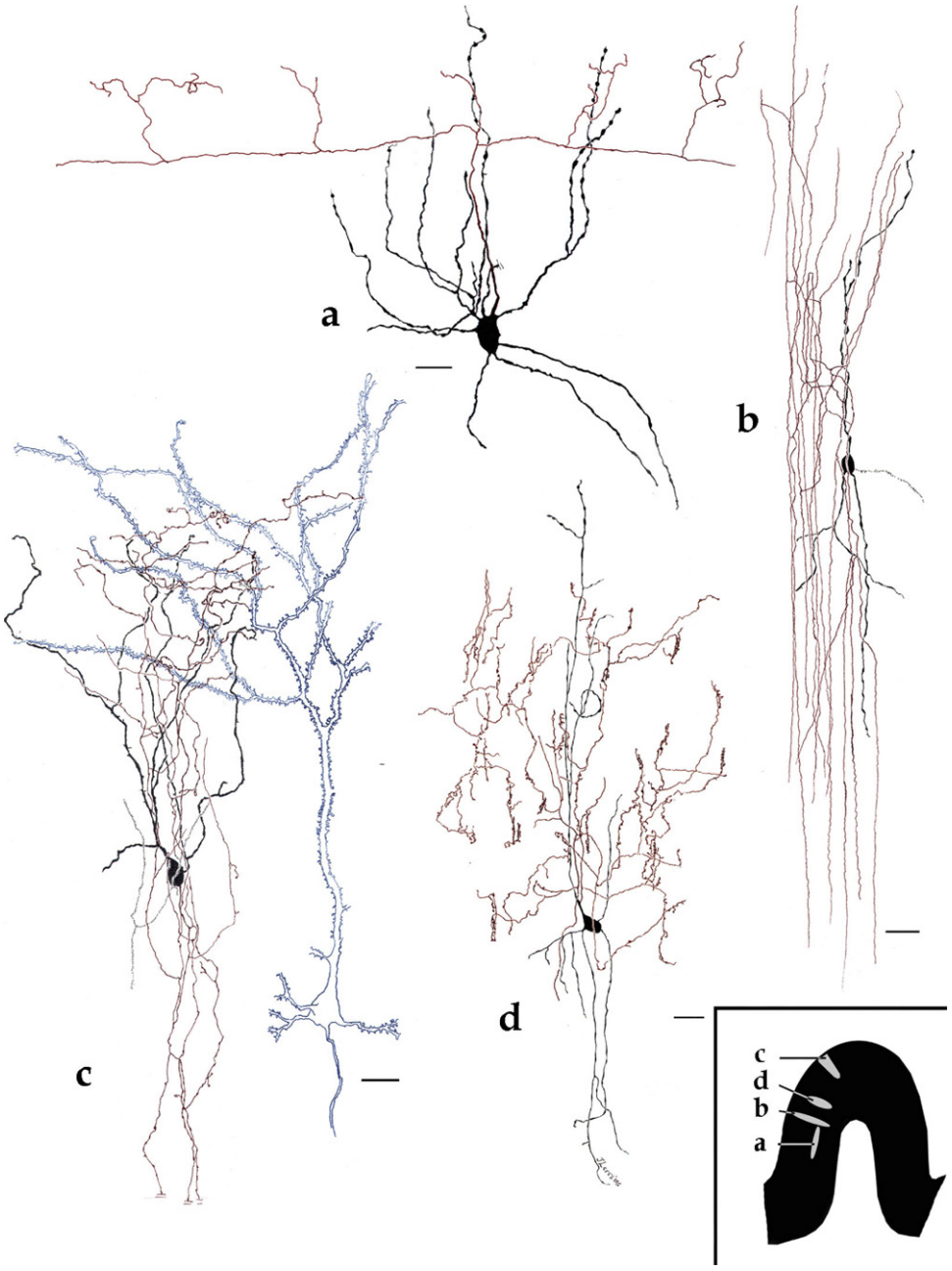

Fig. 1. Dendritic (black) and axonal (red) fields of interneurons in the supplementary motor cortex. (a) Large basket (nest-forming) neuron; (b) double bouquet cell; (c) small basket cell with arched, ascending, axon. Note the distribution of the axon in association with distal dendrites of a 3rd layer pyramid (blue); (d) chandelier cell. Rapid Golgi technique, adult green monkey. Inset: Sites of neuronal sampling in the supplementary motor cortex. Calibration scale = 20 μm.

4. Inhibition, cell tuning, and mapping of variables

Numerous studies in behaving rats, cats, and monkeys have reported that sensory, motor, and cognitive information can be represented in the central nervous system by neurons that are tuned to distinct behavioral parameters. Selectivity for stimulus properties, for example, is a cell-defining characteristic at different levels of the sensory systems. Again, cell tuning depends on both the anatomically precise convergence of inputs as well as the microcircuit dynamics, and these two factors not only vary between cortical areas but even between layers inside a column. Thus, cell tuning can show a columnar organization accompanied by a tangential mapping of the behavioral variable. There are reasons to suggest that these three features (tuning, columns, and maps) are closely interrelated and depend on the intrinsic dynamic processing of a cortical area, which in turn largely depends on inhibitory mechanisms. This interrelation is becoming evident for orientation tuning in V1, which is probably the most studied sensory phenomenon to date. Orientation selectivity originates in simple cells of layer IV by virtue of convergent inputs from thalamic neurons whose receptive fields are arranged in rows (Hubel and Wiesel, 1962; Reid and Alonso, 1995; Jin et al., 2008). This feedforward tuning mechanism relies on the spike threshold, contrast saturation, and spike-rate rectification of simple cells to shape their critical features of orientation tuning (Priebe and Ferster, 2008). However, it is important to consider that the number of thalamic inputs is considerably smaller than the number of excitatory synapses from local intracortical sources. Hence, interactions within the local network are essential for shaping and maintaining the orientation selectivity of cortical

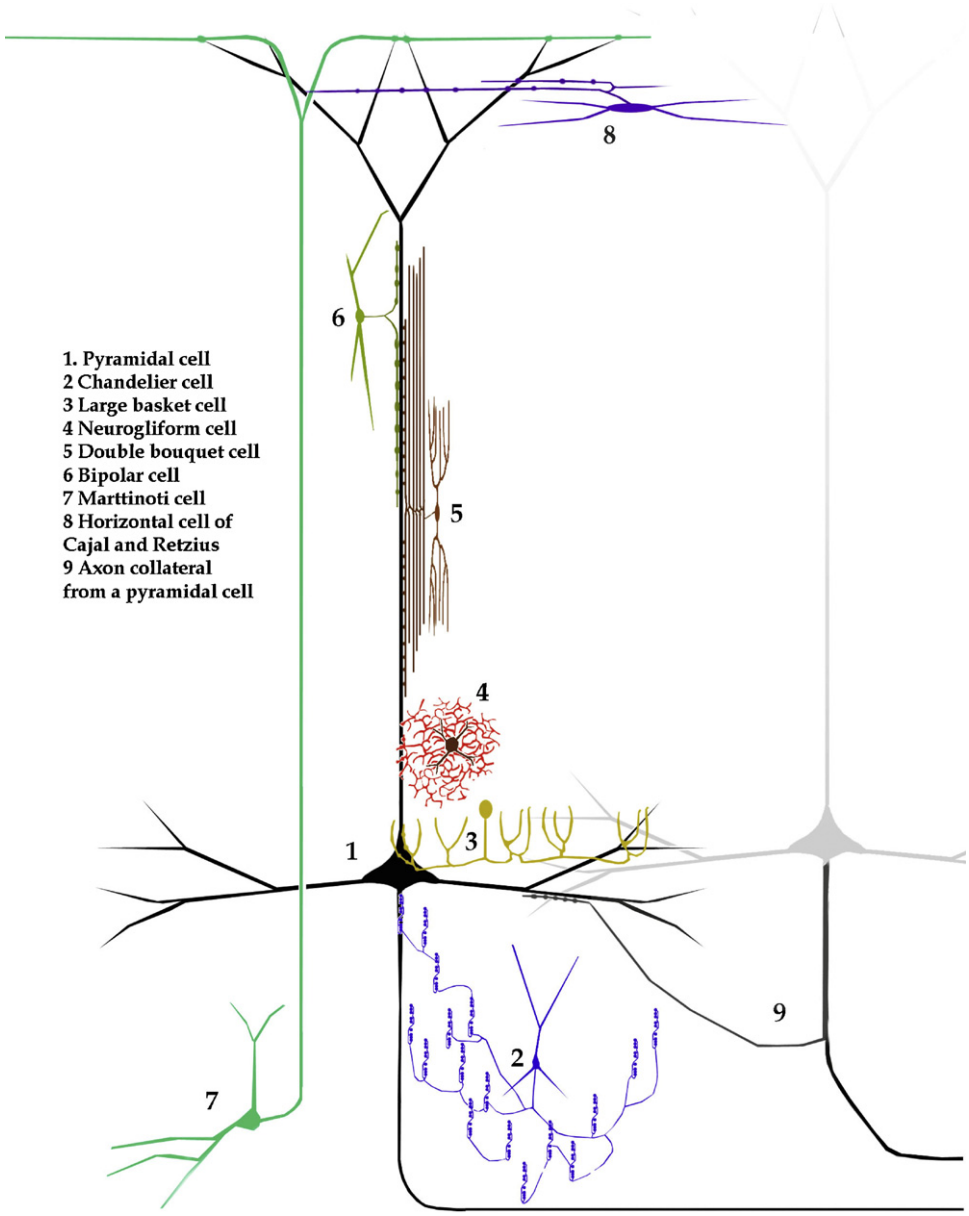

Fig. 2. Cartoon showing synaptic interactions between neocortical neurons and pyramidal cells (black and gray). Inhibitory neurons are depicted according to region of the pyramidal cell where their the axon establishes the main contacts.

neurons inside the minicolumn (Douglas et al., 1989, 1996). In fact, orientation tuning may be re-computed in different cortical layers, by the use of different synaptic integration mechanisms. The resulting selectivity, however, is not homogenous. Orientation selectivity varies systematically with laminar location and even within a layer, and the spectrum of selectivity ranges from extremely sharp tuning to completely unselective responses (Ringach et al., 2002). In this scenario, inhibition has a variable and complex effect on the shaping of the orientation tuning curve. Recent intracellular recordings in cats have demonstrated that V1 neurons receive inhibition that is not tuned, inhibition that can peak at their preferred orientation, or inhibitory inputs that are orthogonal or oblique to their preferred orientation (Monier et al., 2003). Cross-orientation and iso-orientation inhibition play different roles in the information processing of tuned cells. The former sharpens sensory tuning to its final state by vetoing any residual excitation evoked by non-preferred orientation (Shapley et al., 2003; Ringach et al., 2003), whereas the latter is usually broadly tuned and cancels out the wide angle responses but leaves the tuning curve around the peak orientation unchanged (Ferster, 1988; Nowak et al., 2008; Liu et al., 2011; Xing et al., 2011).

The functional diversity of inhibition and the variety of tuning profiles inside a microcircuit coincides with what we discussed before: cortical interneurons may change the local network dynamics in many ways, depending on their laminar and columnar location, as well as their anatomofunctional identity. For example, it has been shown also that V1 neurons in layer V have inhibitory tuning that is orthogonal to the preferred orientation of the cell, whereas neurons in other layers showed a tendency to be iso-oriented to excitation (Martinez et al., 2002). Furthermore, the broadening of orientation tuning that results from local iontophoresis of GABA antagonists is strongest outside of the input layers (Sillito, 1975; Sato et al., 1996). Unfortunately, the variety of roles that interneurons might play in the genesis of V1 orientation tuning and its columnar and tangential organization has not been matched by sufficient knowledge about the morphological, electrophysiological, and neurochemical nature of these inhibitory cells (Gilbert, 1993; Hirsch and Martinez, 2006).

Cross-feature inhibition has been documented in virtually every sensory modality. In vivo studies, particularly in the anesthetized rat, have shown that inhibition sharpens selectivity by limiting the ability of non-optimal inputs to evoke action potentials for whiskers in the somatosensory system (Moore and Nelson, 1998; Zhu and Connors, 1999), odors in the olfactory system (Wilson and Mainen, 2006), sounds of different frequency in the auditory system (Brosch and Schreiner, 1997; Calford and Semple, 1995), and different tastes in the gustatory system (Vandenbeuch et al., 2004). Interestingly, a recent study demonstrated that the time lag between the onset of input excitation relative to inhibition in neurons of the rodent whisker system produces a systematic change of discharge rate, depending on the direction of whisker deflection (Wilent and Contreras, 2005). In the preferred direction, excitation precedes inhibition, but as the direction diverges from the preferred, this time lag decreases. Hence, neural tuning can be achieved also throughout the transient temporal imbalance in the excitation–inhibition inputs.

Despite the recent progress on the functional characterization of inhibition in cortical processing, the kind of detailed in vivo analysis performed over the years on orientation tuning in V1 is urgently required for other sensory, cognitive, and motor cortical systems. This fundamental research will expand our knowledge concerning the anatomofunctional substrate for neural representations of other behavioral variables.

5. Indirect measures of the role of inhibition in behaving animals

The role of GABAergic inhibition in information processing has been studied intensively in the rodent barrel system by means of simultaneous intracellular recording of two or more neurons. Labeling the recorded cells has allowed researchers to examine their morphological and cytochemical properties (Sarid et al., 2007; Helmstaedter et al., 2007; Meyer et al., 2011). These direct methods are difficult to implement in behaving monkeys, so an alternative strategy followed recently in task-performing monkeys, is to use the electrophysiological fingerprints of putative inhibitory interneurons and pyramidal cells as captured by extracellular recordings (Figs. 3 and 5). Vernon Mountcastle (Mountcastle et al., 1969) was the first to suggest that cortical neurons could be segregated into regular-spiking (RS) and fast-spiking (FS) cells in the awake monkey. He suspected that FS cells could be interneurons. In fact, whole cell voltage recordings and intracellular labeling in slice preparations of the monkey prefrontal cortex (PFC) have shown that FS neurons correspond mainly to multipolar parvalbumin-positive basket and chandelier cells, whereas the RS correspond to the pyramidal neurons (Krimer et al., 2005; Zaitsev et al., 2009). FS interneurons generate short-duration action potentials and are capable of discharging at high frequencies with little spike frequency adaptation, which contrasts with the pyramidal cells' long-duration action potential and their common non-adapting (regular-spiking) discharge profile (see Fig. 3; Table 1) (Gonzalez-Burgos et al., 2005; Zaitsev et al., 2009). Overall, experiments in anesthetized animals and slice preparations from different species, such as the rat, cat, monkey, guinea pig, and human, and across multiple brain areas, including hippocampus, prefrontal cortex, visual cortex, and somatosensory cortex have confirmed the existence of FS cells with basket and chandelier cell morphology, that show molecular and electrophysiological properties that clearly distinguish them from RS cells (McCormick et al., 1985; Foehring et al., 1991; Tasker et al., 1996; Markram et al., 1997; Henze et al., 2000; Nowak et al., 2003; Gonzalez-Burgos et al., 2005; Povysheva et al., 2006; Zaitsev et al., 2009). In addition, these studies have shown that RS cells correspond to pyramidal neurons. The difference in action potential duration between FS and RS is due, in part, to the expression of different classes of K+ (the Kv3.1 and Kv3.2 channels) and Na+ channels that differ from one another in their kinetics (Martina and Jonas, 1997; Martina et al., 1998; Erisir et al., 1999).

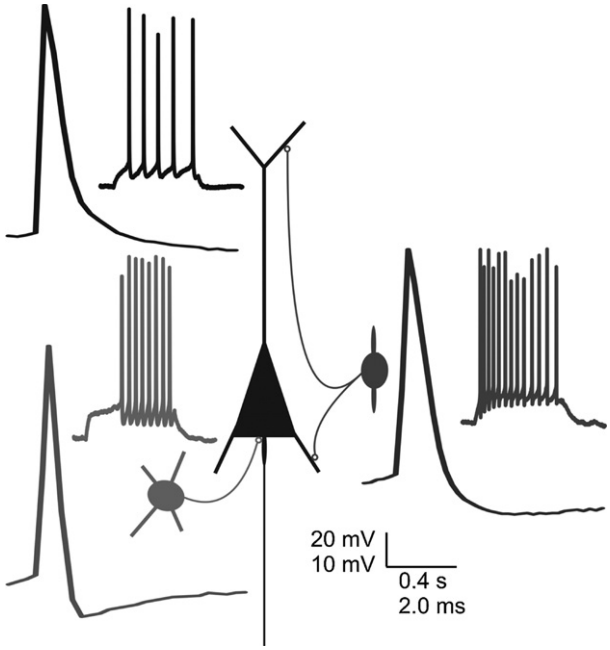

Fig. 3. Firing patterns and spike waveforms of different cortical neurons in patch clamp recordings. Representative voltage recordings of individual spikes and trains of action potentials produced in response to intracellular depolarizing steps. In response to a depolarizing current step, the pyramidal neuron (black) fire action potentials with low frequency. The action potentials are followed by a hyperpolarizing after-potential that increases in duration and produces spike frequency adaptation. Spike adaptation is reflected as a decrease in instantaneous discharge rate despite the sustained depolarization. Most of the cells exhibiting this firing pattern correspond to the typical pyramidal cell. An example of a peri-somatic targeting interneuron that fires at higher frequency than regular spiking neurons is depicted in light grey. These "fast spiking" neurons show strong hyperpolarizing after-potentials that do not increase in duration during the sustained depolarization, allowing their high frequency firing with minimal change in the instantaneous discharge rate (non-adapting firing). The cells exhibiting this firing pattern include neurons with diverse morphology but that generally correspond to either basket or chandelier interneurons. Dendritic targeting interneurons, shown here in dark gray, exhibit very diverse firing patterns including bursting, irregular, adapting, stuttering or low-threshold spiking. However, the firing pattern of these interneurons can be classified as adapting-non-fast-spiking. The example illustrates an adapting interneuron that fires trains of action potential of higher frequency than a regular spiking. In contrast with regular spiking neurons, the action potentials of these cells are followed by a strong hyperpolarizing after-potential that, in contrast with fast spiking interneurons, increases in duration and produces a remarkable spike frequency adaptation. Adapting-non-fast-spiking cells show very diverse morphology including Martinotti, bipolar, double bouquet or bitufted interneurons. If single action potentials are analyzed, peri-somatic targeting interneurons show the shortest action potentials followed by the more prominent hyperpolarizing after-potentials. Such characteristics clearly differentiate the action potentials of these cells from those produced by the other cell types. Despite their similar duration, action potentials of dendritic targeting interneurons can be distinguished from those of pyramidal neurons by their bigger hyperpolarizing after-potentials. All corresponding recordings (trains or individual potentials) are adjusted to the same scale. The smaller voltage and time values for the bar scales correspond to the individual action potentials.

Although the action potential width in the in vivo studies appeared to be the best criterion to discriminate between groups of neurons, the distribution of spike widths overlaps between the RS or FS neurons and other types of cortical neurons, called intermediate spiking cells (IS [Krimer et al., 2005]) or generally called non-fast spiking interneurons (Table 1). The IS in the PFC show intermediate values for many physiological properties, such as the time constant, spike duration, spike amplitude, and amplitude of fast and slow components after hyperpolarization.

Actually, intermediate spiking cells include those with the morphology of neurogliaform and double-bouquet interneurons (Krimer et al., 2005), and they seem to correspond to the regular-spiking nonpyramidal cells recorded in rat frontal cortex (Kawaguchi and Kubota, 1993, 1997). In addition, there are subclasses of excitatory pyramidal neurons, called intrinsically bursting and chattering cells (Nowak et al., 2003, 2008), that have characteristics that overlap with FS. This class of neurons show shorter-duration waveforms and higher mean activity than RS neurons, but can be discriminated from FS and RS due to their stereotypical pattern of bursting characterized by a bimodal interspike interval histogram (Gray and McCormick, 1996; Nowak et al., 2003). In summary, the in vitro characterization of cortical neurons, exemplified in Table 1, supports the classification of FS interneurons and RS pyramidal neurons as different cortical subpopulations. However, the literature also shows that the so-called non-fast spiking interneurons constitute a highly heterogeneous population of GABAergic interneurons, likely constituted by several subgroups, which share some characteristics with both FS interneurons and RS pyramidal neurons. The wide distribution of firing characteristics found among non-fast spiking interneurons may provide a source of confusion when a classification of cortical neurons is based on one or few firing characteristics, without morphological or molecular corroboration.

Current evidence suggests that the discrimination of putative interneuron and pyramidal cells based solely on extracellular spike properties should be considered tentative. Fig. 4 shows the distributions of spike durations obtained in different cortical areas and species in a large number of studies where the spike width was determined using the time between the trough and the peak of the action potential. As the distributions show, the overlap on the spike width of putative interneurons and pyramidal cells can be significant (Fig. 4). Furthermore, the results from behaving animals show a large variation in spike duration between areas, which accentuates the need for relative rather than absolute criteria for the separation of cell subgroups (see Table 2 and Fig. 4). An additional caveat, as Table 2 and Fig. 4 shows, is that these parameters acquire values that can vary depending on the extracellular recording methodologies. For example, high- and low-pass signal filtering can affect the spike waveform, decreasing its duration (Quian Quiroga, 2009). Consequently, an appropriate discrimination function between putative pyramidal and interneurons must take all these issues into consideration, as well as the physiological differences of these cell types as a function of the behavioral parameter(s) under study.The fact that there is some overlap in spike duration between the intrinsically bursting, chattering, intermediate spiking and the RS and FS cells underlines the importance of using additional electrophysiological parameters to increase the discrimination power between putative inhibitory interneurons and pyramidal subtypes in studies with extracellular recordings (Figs. 4 and 5). These parameters include: (1) the basal firing rate which is larger for FS, and is the most common extra parameter; (2) the interspike interval histogram, which is bimodal in intrinsically bursting and chattering neurons (Nowak et al., 2008), and show a larger coefficient of variation and a longer unimodal peak in FS than in RS cells (Cohen et al., 2009; Chen et al., 2008); (3) the features of the auto-correlogram, such as center of mass and time from zero to peak (Bartho et al., 2004); and (4) trough-peak ratio, which corresponds to the height of the waveform peak divided by the depths of its trough, is shallower in RS than FS, since in RS the repolarization of membrane potential is slower (Connors and Gutnick, 1990; McCormick et al., 1985; Mitchell et al., 2007). In addition, direct electrophysiological methods can be used to classify different cortical cell types, such as the antidromic identification of projection (pyramidal) cells, and the recording of monosynaptic interactions between pairs of simultaneously recorded neurons (Fig. 5). Using the latter approach with large numbers of recording electrodes, it has been confirmed that FS cells are inhibitory, as indicated by short-latency dips in the crosscorrelograms in the PFC and somatosensory cortex of the rat (Bartho et al., 2004), and in the inferior temporal cortex of the macaque (Tamura et al., 2004). In the former case, the antidromic identification of layer V pyramidal neurons in PFC that project to the superior colliculus, showed that all identified output neurons had long trough to peak durations, placing them within the RS class (Fig. 5; Johnston et al., 2009). Furthermore, efferent neurons identified antidromically in S1 and V1 of awake rabbits show the features of RS cells, namely, long spike durations and low spontaneous discharge rate; whereas putative interneurons, that receive thalamic inputs, show short spike durations and high spontaneous activity (Swadlow, 1988, 1989; see Table 2). While some researchers are not willing to make the assumption that fast-spiking neurons with brief action potentials are inhibitory, the use of direct methods has provided strong evidence indicating that acceptable classification of neurons can be achieved when spike-width and firing rate are used in conjunction (Isomura et al., 2009; Fig. 4). Nevertheless, a recent investigation using antidromic identification of pyramidal cells in the motor cortex suggests that pyramidal tract neurons have short action potentials that largely overlap in duration with those of FS neurons (Vigneswaran et al., 2011). These findings contrast with previous studies. Steriade in the 1970s described in M1 of monkeys that pyramidal output neurons, with antidromic invasion following peduncular and/or ventrolateral thalamus stimulation, showed low spontaneous firing rates and did not overlap with putative inhibitory interneurons (Steriade et al., 1974; Steriade, 1978). Similar observations were made in the rabbit motor cortex (Beloozerova et al., 2003). In these studies, motor cortical putative inhibitory interneurons were identified as cells that did not respond antidromically to stimulation in many tested sites but showed high spontaneous discharge rates (Steriade et al., 1974; Steriade, 1978; Beloozerova et al., 2003). However, these papers did not report the duration of the action potentials in these non-overlapping cell populations.

From two studies that used bi-dimensional clustering as well as direct methods to validate their classification (Bartho et al., 2004; Isomura et al., 2009), we could estimate that ~3% of neurons classified as excitatory are in fact inhibitory (3/87), and that the same percentage applies to neurons classified as inhibitory that are in fact excitatory (1/32). These constitute rough estimates of the misclassification errors arising from bi-dimensional clustering, and it should be noted that they necessarily increase if spike width is used as the only classification parameter.

5.1. Functional interplay of putative pyramidal and interneuron subgroups in behaving primates

Despite the caveats described in the previous section, interesting hypotheses on the role of interneurons in the brain representation of behavioral parameters have originated from the use of the FS and RS classification in animals performing specific tasks. Thus, the identification of putative interneurons and pyramidal cells using the width of the action potential and the basal firing rate has also been used to investigate the functional impact of inhibition in different cortical areas for sensory, motor, and cognitive behaviors as shown in Table 2. Considering the large literature in anesthetized animals describe above, it is not surprising that one of the key functional roles of FS cells in behaving animals is sharpening of cortical tuning. Putative inhibitory interneurons are more broadly tuned and tend to respond more strongly to inputs throughout many cortical areas. In the sensory system, these increased response properties facilitate

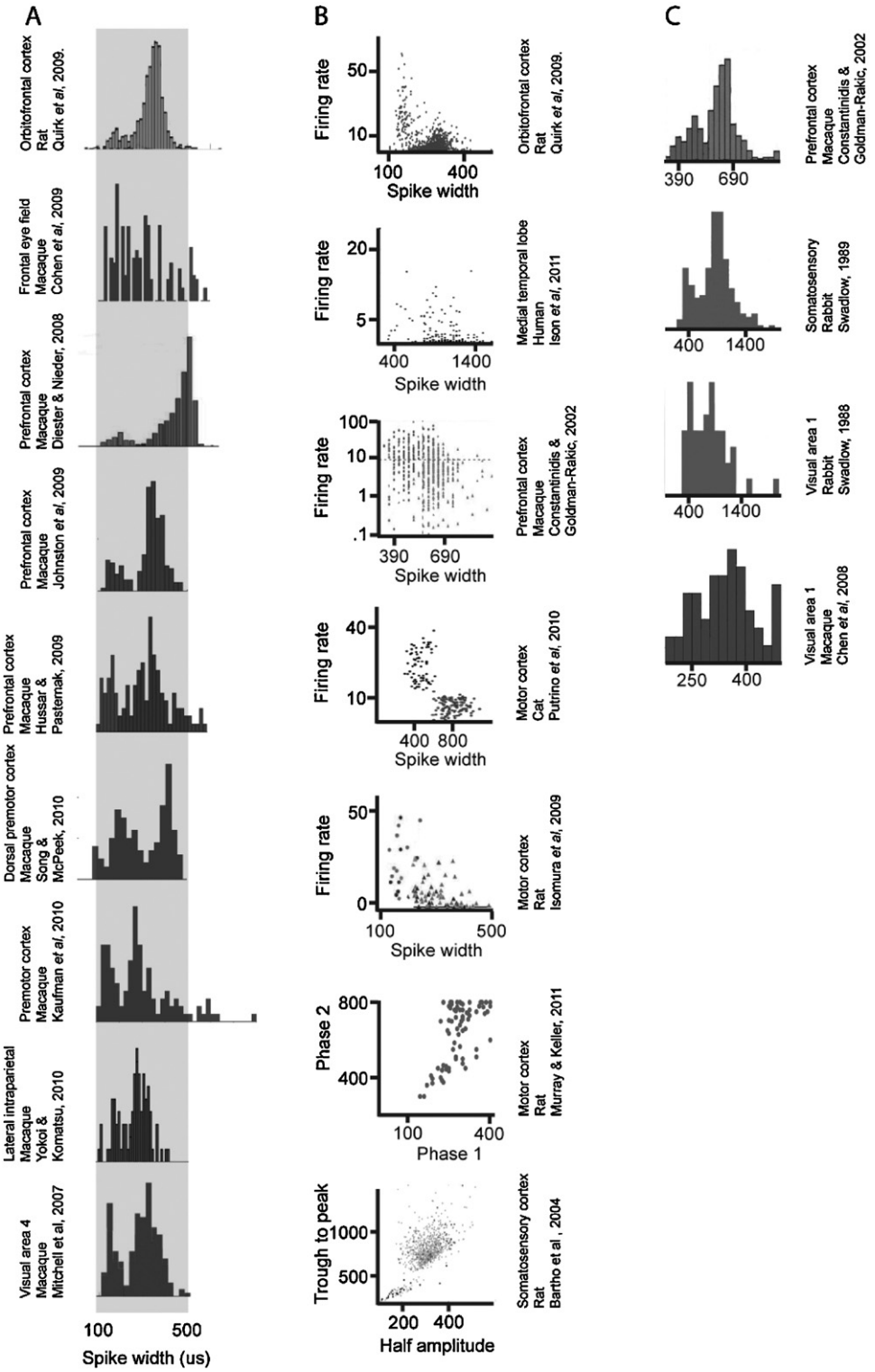

Fig. 4. Histograms and scatterplots of parameters that help distinguishing putative interneurons and pyramidal cells. (A) Frequency histograms (trough-to-peak) illustrate the range and overlap that exist in spike width within and across cortical areas and species. Absolute values of spike width depend strongly on recording filter settings so comparison across studies is less meaningful than comparisons within a single experiment. Although most studies show bimodal distributions, spike width alone rarely allows reliable classification of putative interneurons from pyramidal cells. (B) Firing rate is an additional parameter that is commonly used to improve the discrimination of putative interneurons and pyramidal cells (five top panels). Although two clusters of cells can be identified, there is significant overlap between them. In the two bottom panels other measurements of spike waveform were used to classify the neurons. (C) Although trough-to-peak is the most common parameter of spike width, other measurements are also used. However, they cannot be drawn on the same axis or at the same scale. As in (A), significant overlap of spike with between putative interneurons and pyramidal cells can be appreciated. Most of the studies we reviewed used direct methods to validate the classification of inhibitory and excitatory neurons (antidromic stimulation, crosscorrelation and juxtacellular labeling, among them). However, we show unclassified spike width and firing rate data to illustrate how these parameters are distributed among neurons and to stress the need to use direct methods to classify excitatory and inhibitory neurons.

Table 2
Review of the extracellular properties of putative interneurons and pyramidal cells in the literature.

Paper	Width criterion	Putative interneurons/ FS spike duration (ms)/SDR (Hz)	Putative pyramidal/ RS spike duration (ms)/SDR	Additional discrimination criteria	Brain area, species
Mountcastle et al. (1969)	NS	0.1–0.3/30–50	0.3–0.5/5–20	No extra parameter	S1 macaque
Swadlow (1988)	P2P	0.47/19	0.98/7	Antidromic identification	V1 rabbit
Swadlow (1989)	P2P	0.43/16.5	0.98/∼2	Antidromic identification	S1 rabbit
Wilson et al. (1994)	T2P	0.408/17	0.72/5	No extra parameter	PFC macaque
Gur et al. (1999)	T2P	0.26/13.5	0.39/3.7	Action potential amplitude and polarity.	V1 macaque
Rao et al. (1999)	P2P	0.67/NS	1.11/NS	No extra parameter	PFC macaque
Constantinidis et al. (2002)	P2P	0.47/4.6	0.64/15.4	Short-latency, monosynaptic interactions between neuron pairs	PFC macaque
Constantinidis and Goldman-Rakic (2002)	P2P	<0.54/>9.5	>0.54/<9.5	No extra parameter	PFC macaque
Beloozerova et al. (2003)	Not used	Not used/35.4	Not used/11.3	Antidromic identification	M1 rabbit
Bartho et al. (2004)	T2P	0.43/No difference in DR	0.86/no difference in DR	Short-latency, monosynaptic interactions between neuron pairs	S1 and PFC rat
Tamura et al. (2004)	T2P?	0.49/7.4	0.54/4.5	Short-latency, monosynaptic interactions between neuron pairs	IT macaque
Mitchell et al. (2007)	T2P	<0.2/9.4	>0.2/4.6	Trough-peak ratio	V4 macaque
Merchant et al. (2008)	P2P	0.42/12.6	0.8/5.4	Short-latency, monosynaptic interactions between neuron pairs	M1 macaque
Diester and Nieder (2008)	T2P	<0.28/13.7	>0.28/3	No extra parameter	PFC macaque
Atencio and Schreiner (2008)	T2P	<0.2/NS	>0.2/NS	Comparison between the initial and final phases of the spike waveform	A1 cat
Chen et al. (2008)	Beginning of first phase to peak of 2th phase	<0.275/no difference in DR	>0.275/no difference in DR	Interspike-interval distributions	V1 macaque
Cohen et al. (2009)	T2P	0.22/no difference in DR	>0.22	Response coefficient of variation, larger for thin	FEF macaque
Johnston et al. (2009)	T2P	<0.27/NS	>0.27/NS	Antidromic corticotectal identification	PFC macaque
Hussar and Pasternak (2009, 2012)	T2P	<0.2/17.2	>0.2/8.9	Interspike-interval distributions	PFC macaque
Isomura et al. (2009)	P2P	<0.5/∼20	>0.5/∼6	Yuxtacellular identification	M1 rat
Kaufman et al. (2010)	T2P	<0.19/NS	>0.22/NS	No extra parameter	PMd macaque
Song and McPeek (2010)	T2P	0.1–0.3/10.9	0.3–0.5/6.7	Trough-peak ratio	PMd macaque
Yokoi and Komatsu (2010)	T2P	<0.205/14.2	>0.225/8.2	No extra parameter	PP macaque
Putrino et al. (2010)	T2T	<0.6/26.1	>0.6/6.3	No extra parameter	M1 cat
Vigneswaran et al. (2011)	T2P	NS/NS	0.15–0.71/NS	Antidromic identification	M1 and F5 macaque
Murray and Keller (2011)	T2P	0.45/1.6	0.74/2.7	Short-latency, monosynaptic interactions between neuron pairs	M1 rat
Woloszyn and Sheinberg (2012)	T2P	<0.5/NS	>0.5/NS	No extra parameter	ITC macaque

feedforward inhibition in response to thalamocortical input. Across V1 (Swadlow and Weyand, 1987; Swadlow, 1988; Gur et al., 1999; Shapley et al., 2003; Mitchell et al., 2007), S1 (Simons, 1978; Swadlow, 1989, 2003; McCormick et al., 1985; Bartho et al., 2004), and the primary auditory cortex (Atencio and Schreiner, 2008), FS cells show broader tuning curves and higher response to stimuli and to thalamic stimulation than RS cells. Hence, the inhibition-mediated sculpting of excitatory cortical input is thought to be a key feature of perceptual processing. Furthermore, similar FS properties have been found in the inferior temporal cortex (Tamura et al., 2004), the frontal eye field (Cohen et al., 2009), the primary motor cortex (Merchant et al., 2008; Isomura et al., 2009; Murray and Keller, 2011), dorsal premotor cortex (Kaufman et al., 2010), and posterior parietal cortex (Yokoi and Komatsu, 2010). Therefore, broad and balanced inhibition might work effectively at the surround as well as the center of the tuning curve, presumably to sharpen the feature specificity of pyramidal cells through the so-called iceberg effect, across many areas and behavioral functions (Wehr and Zador, 2003; Isaacson and Scanziani, 2011). It is still unknown, however, whether the existence of modular organization in the behavioral variable has an impact on the properties of the inhibition that shapes the tuning.

It is important to mention that putative interneurons have been also implicated in shaping the tuning curves for different cognitive variables in the primate PFC. This includes sculpting the spatial memory fields during a memory saccade task (Wilson et al., 1994; Rao et al., 1999, 2000; Constantinidis et al., 2002; Wang et al., 2004a,b), as well as shaping the numerosity tuning curves where FS are again broadly tuned (Diester and Nieder, 2008), and show differential responses in the antisaccade task (Johnston et al., 2009). In recent studies, it has been shown in a visual motion direction discrimination task, that FS cells in PFC were more sensitive to behavioral context, reducing their direction selectivity when the direction of the stimuli was not relevant to the task (Hussar and Pasternak, 2009). However, during the delay period of

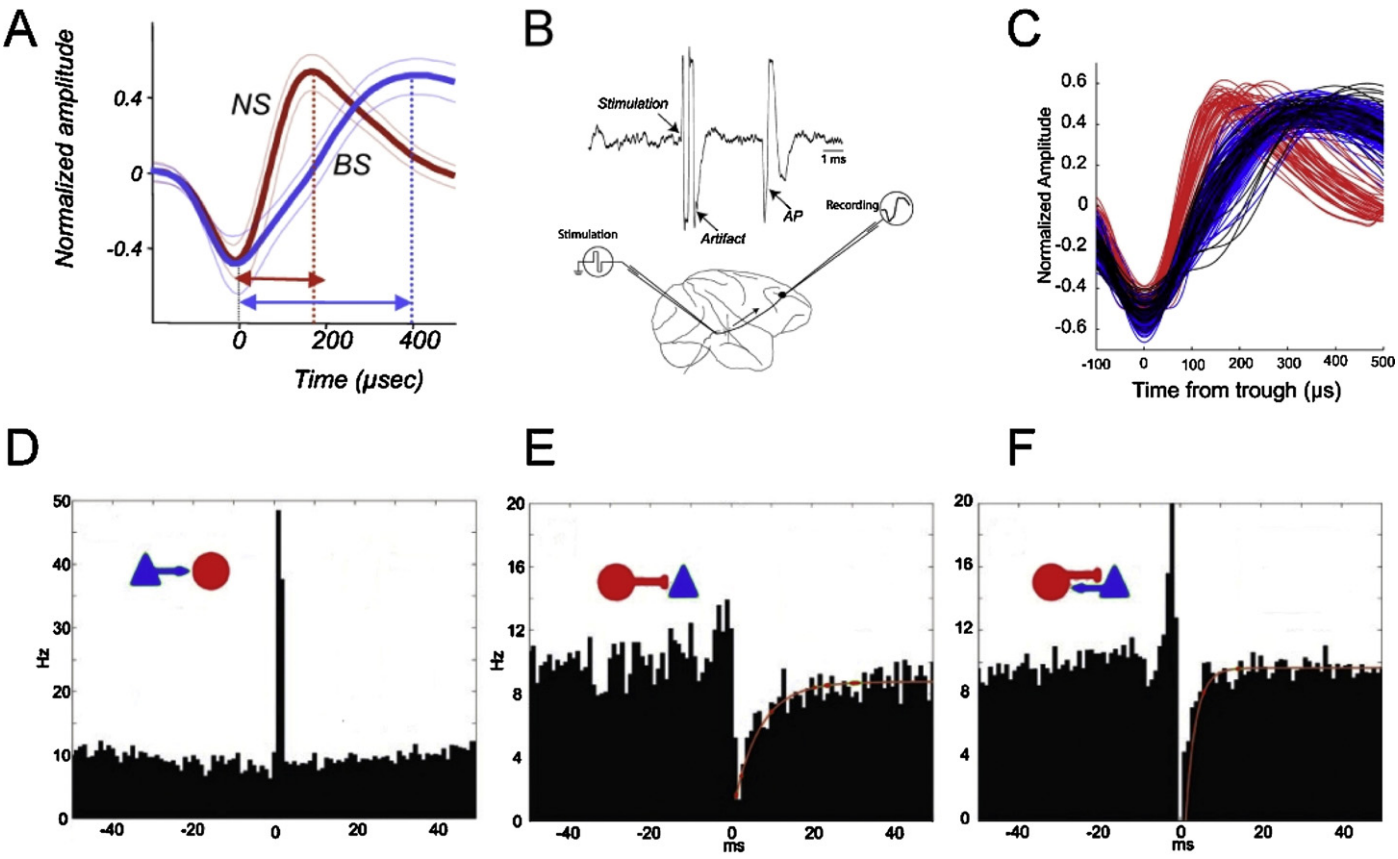

Fig. 5. Analytical and electrophysiological techniques commonly used to classify neurons into putative interneurons and pyramidal cells. (A) Spike width is usually defined as the time elapsed between the spike trough and peak. Two mean waveforms (±SD) illustrate the difference between narrow (NS) and broad (BS) spike neurons. (B) Antidromic stimulation can be used to unequivocally identify projection pyramidal neurons on a given cortical area. The figure illustrates the stimulation of axons originating in prefrontal cortex that project to the superior colliculus. By recording in the PFC while stimulating the colliculus, the experimenter can readily identify projection pyramidal neurons. (C) Mean spike waves of NS (red) and BS (blue) cells, classified according to spike width. In black are shown the spike waveforms of PFC pyramidal neurons that we antidromically identified. Note that, in this study, none of the excitatory pyramidal projection neurons was misclassified as NS. (D) Excitatory and inhibitory neurons can be identified by the influence on their synaptic targets. In the crosscorrelogram, the firing of an excitatory neuron increases the firing of its target neuron with a delay of ~2 ms. (E) The activity of an inhibitory neuron decreases the activity of its target neuron with a short latency. (F) On a reciprocal interaction, the inhibition of the excitatory neuron is preceded by an increase probability of firing, suggesting that the inhibitory neuron might be driven by the excitatory one. (A, from Hussar and Pasternak, 2009; B and C, from Johnston et al., 2009; D, E and F, modified from Bartho et al., 2004.)

the same task, RS cells were more likely than FS cells to carry memory-related signals (Hussar and Pasternak, 2012). Therefore, the interplay between putative interneurons and pyramidal cells in PFC seems to be fundamental for signal processing in a variety of cognitive functions.

In the case of mnemonic spatial tuning in the primate PFC, it has been proposed that iso-directional inhibition prevails within a functional column, whereas cross-directional inhibition is exerted primarily between functional columns (Wilson et al., 1994; Rao et al., 1999). The role of inhibition in spatial memory tuning was confirmed by the decrease in spatial selectivity after microinjections of GABA antagonists (Rao et al., 2000). In addition, a model study of a PFC recurrent cortical microcircuit during working memory found that different types of interneurons may play distinct roles in shaping and maintaining the spatial selectivity of neurons (Wang et al., 2004a,b). FS basket cells showed broader tuning compared with pyramidal cells, whereas the dendrite-targeting interneurons showed inverted tuning curves, with maximal inhibition in the preferred direction associated with a disinhibition mechanism that generates a persistently tuned activity in the network. Importantly, these model predictions were supported by empirical evidence in monkeys executing this task (Wang et al., 2004a,b).

On the other hand, recent studies have suggested that the increase in high-frequency synchronization during spatial attention may be mediated by FS activation. For example, in an interesting study of V4 activity during an attention-demanding task (Mitchell et al., 2007), it was found that FS putative interneurons show larger attention-dependent increases in absolute firing rate and significantly larger reductions in response variability (as measured by the Fano factor) than RS cells, when attention was directed towards the stimulus in the receptive field. The role of inhibition in this context may be to suppress neural responses evoked by distracter stimuli and to initiate the characteristic high-frequency synchronization during attentive periods (Fries et al., 2001; Mitchell et al., 2007). A subsequent study showed that FS in V1 enhanced their visual responses with increased attention task difficulty, whereas RS neurons suppressed their responses (Chen et al., 2008). These findings support the notion that putative interneurons make the stimulus detection more reliable at the focus of attention by switching the local networks to an oscillatory mode in the Gamma-band (30–80 Hz) frequency. Indeed, it is known that the majority of FS are basket, parvalbumin-positive interneurons (Connors and Gutnick, 1990; Kawaguchi and Kubota, 1997), which are coupled by electrical synapses to conform a distributed cortical inhibitory network (Galarreta and Hestrin, 1999; Gibson et al., 1999; Tamás et al., 2000; Hasenstaub et al., 2005). Electrical synapses alone (Galarreta and Hestrin, 1999; Gibson et al., 1999) can produce synchronous firing in pairs of FS cells interneurons in vitro. In addition, recent studies using optogenetics have shown that activation of parvalbumin-positive interneurons, but not pyramidal cells,

induces gamma band oscillation and enhances signal transmission in the cortical microcircuitry (Cardin et al., 2009; Cardin, 2012). Hence, FS cells may mediate spatial attention to the target stimulus and improve transmission of target information within the cortical microcircuitry and to other areas by promoting high-frequency oscillations. As a complementary point, multiple-site recording experiments have shown a large increase in synchrony between pairs of putative inhibitory, but not pyramidal, cells after tactile stimulation in M1 of the rat (Murray and Keller, 2011), and during a memory saccade task in the monkey PFC (Constantinidis and Goldman-Rakic, 2002). These results expand the spectrum of behaviors where FS synchronic activation can promote information processing in the cerebral cortex.

Finally, a recent study has investigated the role of FS on the processing of familiar and novel visual images in the inferior temporal cortex (ITC) of the macaque (Woloszyn and Sheinberg, 2012). The results showed that experience caused putative pyramidal neurons to respond more robustly to their best familiar compared to their best novel stimuli. In contrast, familiarity caused a dramatic decrease in the activity of FS cells. Therefore, these results suggest that visual experience can profoundly alter visual object representations in ITC. In this context, a possible role for the increased inhibitory output is the detection of novelty, which in turn can initiate the cascade of events that underlie the ensuing plasticity (Woloszyn and Sheinberg, 2012).

Overall, these studies highlight the importance of dissociating FS and RS populations in order to investigate the role of putative interneurons in dynamic information processing, learning, and network synchronization in complex behaviors. Needless to say, such high-order behavioral functions cannot be studied in anesthetized preparations, accentuating the importance of the electrophysiological dissection of putative interneurons and pyramidal cells in behaving animals, especially in monkeys.

5.2. The case in the motor areas

Neurons in M1 of behaving monkeys are tuned to movement direction: they show an orderly variation in activity as a function of the movement direction, with a peak in discharge rate in their preferred direction (PD; Georgopoulos et al., 1982). Recently, it has been shown that directional tuning in M1 has a columnar and small-scale organization (Amirikian and Georgopoulos, 2003; Georgopoulos et al., 2007; Georgopoulos and Stefanis, 2010). In addition, a large-scale organization was found in which the complete distribution of PDs is represented multiple times in M1 during the 3D center-out task, where the monkeys reached from a central location to the vertices of a cube (Narselaris et al., 2006a,b).

Merchant et al. (2008) used the action potential width and the spontaneous discharge rate cluster analyses to separate M1 neurons recorded during the center-out task into putative pyramidal and interneuronal groups. In addition, they used the short latency (<4 ms) negative or positive deflection in the spike-triggered average between pairs of cells as a functional correlate of monosynaptic inhibition or excitation in this clustering. Overall, the analyses showed that their data set was best characterized by 3 neural cell types: the previously reported FS (putative interneuron) and RS cells (putative pyramidal1 [PP1]), and another type of pyramidal neurons (putative pyramidal2 [PP2]) with high firing rates but long action potential widths. This second type of pyramidal cell is probably unique for motor and premotor areas (Kaufman et al., 2010; Taira and Georgopoulos, 1993), and it was observed more commonly in layer 5 (see also Supplementary Fig. 7a of Isomura et al., 2009). In this way, 25% of the neurons were classified as FS, 57% as PP1, and 17% as PP2. The distribution of tuning dispersion in the FS and PP1 cells was skewed towards low dispersion values. In contrast, the dispersion distribution of PP2 cells showed an unskewed profile with large values. Therefore, PP2 neurons were uniformly broadly tuned, with responses that were less directionally specific than the other two cell types. On the other hand, an analysis of onset response latencies showed that despite the large overlap in the onset response distributions, the FS activity occurred before PP1 directional responses. In contrast, the response onset of PP2 was short and very similar to the one observed for FS. Although, the onset response analysis is an indirect measure of functional relationships between cell types, these results suggest a potential functional link between FS and PP1 and that PP2 tuning is independent of FS inhibition.

Next, it was assumed that when the discharge rate of the neuron in the anti-preferred direction (antiPD) was larger than its spontaneous activity, a net excitation for all directions occurred. On the contrary, when the antiPD discharge rate was lower than the spontaneous activity of the cell, Merchant et al. (2008) assumed that inhibition was involved in sculpting the tuning curve. Interestingly, these authors found a strong relation between the degree of antiPD inhibition and the sharpening of directional tuning in a subpopulation of PP1 cells, such that for tuning dispersions below ~55 degrees, inhibition may play a major role by sculpting the directional specificity of motor cortical cells. In contrast, the antiPD of the broadly tuned PP2 neurons was not subjected to inhibition. A sliding-window analysis showed that an increase in antiPD inhibition accompanied by a decrease in tuning dispersion was evident from 150 ms before to 150 ms after movement onset. Hence, a subpopulation of PP1 cells was probably subjected to a dynamic process of activity suppression and an associated reduction in tuning dispersion during the time period most relevant for movement control. Interestingly, these changes were also associated with the increase in activity of the FS cells suggesting, indirectly, that the inhibitory input from local interneurons produced a decrease in tuning dispersion in the PPI subpopulation. The ideal scenario to prove such an interaction should be, first, the recording of pairs of FS-PP1 cells with short-latency dips in the spike-triggered average, confirming the inhibitory nature of the FS connection. Second, both cells should be directionally tuned. Then, the antiPD inhibition and the sharpening of directional tuning of the PP1cell should be observed, and finally, the comparison of the PDs between FS and PP1 could give information about whether an iso- or a cross-directional inhibition was involved in increasing the directional selectivity of the PP1 cell. Unfortunately such conditions are difficult to find and were not met in that study.

Overall, these results suggest that the selectivity for movement direction in a subgroup of putative pyramidal M1 cells may be sharpened by FS basket and/or chandelier cells. These PP1 neurons were distributed across all cortical layers, in contrast to PP2 cells, which were mainly localized in layers V–VI. An interesting and unresolved question is why the local circuits in M1 favor sharpening in a subgroup of tuned cells distributed across layers, while another group of cells in the output layers may owe their directional tuning exclusively to excitatory inputs.

On the other hand, the analysis of putative interneuronal firing has allowed in recent studies to test the role of inhibition as a gating mechanism in motor control in behaving animals (Kaufman et al., 2010; Isomura et al., 2009). According to the gating hypothesis, inhibitory activity would withhold motor information transfer until the appropriate time for action. In the motor and premotor cortices, inhibitory neurons would be active during the waiting periods until the time of movement execution, when they should cease firing. Interestingly, the evidence has conclusively shown that this not the case. Putative interneurons in M1 and the dorsal premotor cortex are not only active during movement planning but also during movement initiation and execution (Beloozerova et al., 2003; Merchant et al., 2008; Isomura et al.,

2009; Kaufman et al., 2010; Song and McPeek, 2010). In fact as shown in sensory areas, FS in motor areas are broadly tuned and more active than RS, especially during movement execution. The functional significance of the rise in inhibition during movement could be that once the incoming and local excitation rises, the relative rise in internal inhibition may serve to maintain a balance of excitation and inhibition (Shadlen and Newsome, 1998; van Vreeswijk and Sompolinsky, 1996). In addition, as mentioned earlier, the inhibition provided by FS can also play a crucial role in shaping the cell tuning to movement parameters, such as the direction of reaching in motor cortical cells (Merchant et al., 2008).

6. Technical challenges

The behaving animal preparation is ideal to study neural coding and the dynamics of network interactions in different cortical areas associated with high order behaviors, such as perception, memory, attention, abstraction, and voluntary motor control. In fact, optical imaging and multielectrode extracellular techniques in behaving animals are starting to give access to the flow of information processing and the neural representation of behavioral parameters in large cortical distributed systems. On the other hand, intracellular recordings of multiple pairs of interconnected neurons in vitro and in vivo allow the quantitative analysis of network architecture from cells that are histologically and neurochemically identified, and they also permit the investigation of the plastic physiological properties of local synaptic connections and the characterization of the intrinsic properties of interconnected pyramidal and interneuronal subtypes. However, it is evident that a substantial gap remains between the descriptions at the microcircuit level, usually performed in juvenile rodents, and the functional descriptions of the activity of groups of cells at the behavioral level, usually performed using extracellular recordings in adults rats and monkeys. Thus, since most studies of the in vivo response properties of cortical neurons are blind to the position in the cortical circuit, there is no structural or neurochemical description of the recorded cortical networks. Furthermore, the in vivo studies using intracellular recordings, normally performed in the anesthetized preparation, cannot record the neurons for long periods of time. New approaches are required that allow the simultaneous characterization of the functional response properties of individual neurons during task execution and the nature of elements of the cortical microcircuit in which they are located. Of course this is not a trivial methodological problem and no unique solutions can be envisioned in the near future. Nevertheless, important efforts have been made at both the microcircuit and behavioral levels. First, coating a subgroup of electrodes with fluorescent dyes has been a useful technique to build a model of the recording sites from multiple electrodes in a coordinate system with columnar- and cortical-layer information (Narselaris et al., 2005). The spatial resolution of such models, however, is still above 80 μm. In addition, juxtacellular labeling of neurons (Pinault, 1996) recorded extracellularly using the loose patch method has been used in V1 of anesthetized monkeys with excellent electrophysiological signals that last for hours and complete dendritic and axonal anatomical reconstructions that survive over a number of days (Joshi and Hawken, 2006). Indeed, a study using juxtacellular labeling and multiunit recordings showed that pyramidal cells that were identified histologically and neurochemically in the motor cortex of the rat, respond during the preparation, initiation or execution of a movement (Isomura et al., 2009). In contrast, fast-spiking interneurons, including parvalbumin-positive basket cells are only active during motor execution. Hence, this study had the ability to determine the motor-control processing impact of cell types that were identified not only by their electrophysiological fingerprints, but also using powerful anatomical methods (Isomura et al., 2009). Finally, the recent development of optogenetics, a technique that permits the specific excitation or inhibition of pyramidal or interneuronal subpopulations in vivo using light, is a promising methodological tool to study the physiological impact of interneurons in the processing dynamics of cortical microcircuits (Yizhar et al., 2011; Diester et al., 2011; Han et al., 2009). Thus, optogenetic targeting and stimulation of specific cell classes, including pyramidal cells as well as fast-spiking parvalbumin-expressing and low threshold-spiking somatostatin-expressing interneurons, has the enormous potential to reveal the distinct impact of local inhibitory populations on other neurons in the surrounding local network in the behaving animal (Han et al., 2011; Cardin, 2012).

Likewise, remarkable efforts have been made to obtain an integral model of cortical column in the rat by using: (1) in vitro and in vivo pair recordings, followed by anatomical reconstructions of the projecting and target cells across cortical areas; (2) the electrophysiological, neurochemical, and molecular information from such cells; (3) the quantitative estimation of the density of cells with different phenotypes and their local and extrinsic connectivity in different layers; (4) the data on the sensory evoked neuronal activity measured in vivo; and (5) the integration of information from all these sources to build realistic computational models of the average cortical column (Helmstaedter et al., 2007; Markram, 2006).

In this context, the identification of putative interneurons and putative pyramidal cells using the extracellular features of FS and RS cells has been a step in the right direction. This approach is beginning to characterize how a subgroup of interneurons, mainly basket and chandelier cells, participate in codifying behavioral information in the behaving monkey. The resulting findings could be used to generate predictions about the internal organization of the microcircuits underpinning this type of neural representation, and about the properties of their columnar and tangential organization.

7. Conclusions

The cortex is equipped with multiple GABAergic inhibitory systems which probably are critical elements for the neural underpinnings of high order behaviors. Cortical interneurons are quite diverse in terms of their morphology, molecular-neurochemical phenotype, and their intrinsic electrophysiological properties. They also show specificity in the pyramidal cell domains that they target. Altogether, these properties confer on interneurons enormous potential for sculpting information processing inside and across columns. For example, one important consequence of inhibition is that it can change dynamically the configuration of the microcircuit itself, by temporally disconnecting the inhibited subgroup of cells from the flow of information inside the cortical network. As more studies describe the details of how different interneurons shape the response selectivity of pyramidal cells and how they participate in coordinating the flow of information within and across cortical microcircuits, better computational models of the functional properties of columns can be constructed. Furthermore, these models can include the functional properties of FS and RS cells described in behaving animals using extracellular recordings. Consequently, such complex models can play an important role in bridging the gap between individual neurons and network interactions by generating an analytical framework within which particular predictions can be tested at both levels of cortical organization.

Conflicts of interest

The authors declare no conflicts of interest.

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