Handbook of Brain Microcircuits

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Prefrontal Cortex

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The frontal lobe, the most anterior part of the neocortex, is conventionally defined by its afferent pathways from the mediodorsal thalamus. It subdivides into agranular areas (which lack a granular layer 4) and granular areas (which have a layer 4) (Wise, 2009). The agranular frontal areas are shared by all mammals and include parts of the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC). The granular frontal areas, collectively called the prefrontal cortex (PFC), include the dorsolateral prefrontal cortex (DLPFC), ventral prefrontal cortex, frontal pole cortex, dorsal and medial prefrontal areas, and rostral orbitofrontal cortex. The granular frontal cortex is present in the primates but not rodents. Its volume is about 6700 mm^3 in the chimpanzee and 34,800 mm^3 in the human; the corresponding surface is 52.7% and 83.2% of the frontal lobe, or 11.3% and 28.5% of the entire neocortex, respectively (Elston, 2007).

The PFC plays a central role in a wide range of cognitive functions, such as working memory, decision making, planning, self-control, and problem solving (Miller and Cohen, 2001; Fuster, 2008). The functional versatility of the PFC is due in part to its extensive input–output connections with the rest of the brain. A recent study examined afferent connections into 25 cytoarchitectonically defined frontal areas in macaque monkey, using neuroinformatics analysis of anatomical connectivity data (Averbeck and Seo, 2008). It was found that inputs from 68 sensory, motor, and limbic areas reach each of 25 frontal areas either directly or through a single intermediate step (on average) within the frontal network. The frontal network is highly interconnected, with each area sending output to about nine other frontal areas with an intermediate or strong connection. At the same time, it is a heterogeneous structure: 25 frontal areas are hierarchically organized into five clusters, each

defined by a unique set of inputs. Inputs to each cluster from the frontal network are dominated by the other areas within the same cluster. The extrinsic inputs to each cluster are roughly characterized as follows: *(1)* The ventrolateral group receives inputs from ventral visual and auditory areas, *(2)* the dorsolateral group receives inputs from dorsal visual and auditory areas, *(3)* the caudoorbital group receives chemosensory (gustatory and olfactory) and interoceptive inputs, *(4)* the dorsomedial group is defined by its motor inputs, and *(5)* the ventromedial group is defined by its limbic inputs (hippocampus and amygdala). The PFC projects to many posterior cortical areas (but not the primary visual cortex, V1), as well as to the thalamus, basal ganglia, hippocampus, amygdala, and superior colliculus.

Despite the diversity in the degree of identifiable laminae across frontal areas, there is a simple organization rule for the projections between two frontal areas. Namely, when frontal areas are classified based on the number and definition of its cortical layers (level 1, lowest; level 5, highest), projection neurons from a lower level area originate mostly in the deep layers (5–6), and their axons terminate predominantly in the upper layers of a higher level area. Conversely, projection neurons from a higher level cortex are located mostly in the upper layers (2–3), and their axons terminate predominantly in the deep layers of a lower level cortex (Barbas et al., 2002).

Microcircuitry

Local circuitry within a PFC area shares the general layout with other neocortical areas but also displays marked differences. Notably, in macaque monkey and human, the basal dendrites of layer 3 pyramidal neurons have up to 10 times more spines, the site of excitatory synapses, in PFC than in the primary visual cortex (V1). This is not just because cells are larger but also spine density is higher in PFC: the basal dendritic arbors are more widespread in PFC pyramidal cells, and the spine density (the number of spines per unit of dendritic length) is four times greater, compared to V1. There is a progressive increase in pyramidal cells' synaptic integration along the processing hierarchy of the visual system, from V1, V2, V4, TEO, TE to PFC. Furthermore, pyramidal cells in DLPFC are larger and have more branched dendrites and more spines than those in the premotor cortex, which in turn are more spinous and display larger and more branched dendrites than in the primary motor cortex (Elston, 2007). Therefore, along the sensory-association-motor axis, prefrontal pyramidal neurons are empowered with the greatest capability of integrating synaptic inputs. If dendritic trees are composed of relatively independent compartments, large and highly branched dendrites of prefrontal pyramidal cells would enable them to differentially process and gate information flows from different sensory, motor, and limbic areas in a way and to an extent unlike any other cortical area.

Many computational purposes can be served by this capability, such as combining sensory cues, reward signals, and task rules in decision making. Equally importantly, this means that intrinsic PFC microcircuitry is endowed with strong excitatory recurrent connections. Indeed, a large fraction of excitatory synapses onto pyramidal cells originate from the local circuit. In the cat V1, ~20% of all excitatory synapses are horizontal synaptic connections between pyramidal cells in layer 2/3. Assuming that this holds true across species and cortical areas, combined with the fact that pyramidal cells have more than 10-fold more excitatory synapses in PFC than in V1, it is expected that pyramidal cells in PFC layer 2/3 are endowed with severalfold stronger interconnections than in V1. Furthermore, the patterns of these intrinsic connections are also unique in the PFC. In the superficial layers 2/3 of sensory cortical areas of macaque monkey, axonal collaterals from pyramidal cells form patches of terminals, with an average width of 230 μm and patch center-to-center distance of 430 μm. The patchy connections link neurons that are separated at long distances but display similar stimulus selectivity. Horizontal axonal projections also form patch-like patterns in motor cortex. By contrast, in the PFC, horizontal connections form strip-like patterns, rather than patches. The strip length is more than 1mm, the width of strips is about 270 μm, and the strip center-to-center distance averages 530 μm. The PFC in primates thus exhibits unique, strip-like, intrinsic connections (Lund et al., 1993).

REVERBERATORY EXCITATION

Strong lateral connections between pyramidal cells may be key to understanding the PFC circuitry and functions. The most studied process that depends on PFC is working memory, the brain's ability to actively hold and manipulate information in the absence of direct sensory stimulation. In monkey experiments, when a subject is required to actively hold information about a sensory cue (e.g., a visual object, a vibrotactile stimulus frequency, or a spatial location) across a short delay, neurons in the PFC display stimulus-selective persistent activity during the delay period (Fuster, 2008). This mnemonic activity must be internally maintained in order to subserve working memory, a candidate mechanism underlying persistent activity is recurrent synaptic excitation that is sufficiently strong to sustain cross-talk among pyramidal neurons (Goldman-Rakic, 1995; Wang, 2006). Computational models have shown that, in a canonical cortical circuit, self-sustained persistent activity emerges when the amount of recurrent connections exceeds a threshold level (Wang, 2006). Thus, the PFC may have a similar intrinsic organization as sensory areas, but quantitative differences (e.g., in the strength of interconnections) may be sufficient to give rise to qualitatively different behaviors (the emergence of persistent activity).

Interestingly, biophysically based circuit modeling predicted that recurrent excitation in a working memory circuit should not only be strong but

also slow relative synaptic inhibition in order to ensure network stability. More recent work showed that slow excitatory reverberation also provides a candidate circuit mechanism for gradually integrating information over time in decision making. A candidate substrate to implement slow excitation is the NMDA receptor–mediated synaptic transmission at local synapses. This possibility has been tested in *in vitro* physiological studies where the fast AMPA receptor (with a time constant of ~2 ms) and slow NMDA receptor (time constant ~50–100 ms) mediated components of synaptic currents were measured between pairs of connected pyramidal neurons. It was observed that, in adult rodents, pyramidal cells express more the NR2B NMDA subunits in the medial frontal area than in V1. As a result, the NMDA receptor–mediated currents at local synapses between pyramidal cells exhibit a two-fold longer decay time-constant and temporally summate a train of stimuli more effectively, in the frontal cortex compared to those in the primary visual cortex. Moreover, dopamine modulation greatly affects PFC functions, and dopamine D1/D5 receptors selectively enhance the NMDA receptor–mediated excitatory postsynaptic current. Finally, in behaving monkeys performing a working memory task, iontophoresis of drugs that blocked the NMDA receptors suppressed delay-period persistent activity of PFC, in support of an important role of the NMDA receptors in PFC processes.

Other slow positive feedback mechanisms have also been identified in the PFC. In particular, excitatory synapses between layer 5 pyramidal cells exhibit a stronger propensity for short-term facilitation (time constant of several hundred milliseconds) in the PFC than in V1 of young rodents, which could enhance recurrent excitation in an activity-dependent manner. There is also evidence that, in rodent layer 5 pyramidal cells of the medial frontal cortex, a calcium-dependent inward current induces a slow afterdeporalization (time constant of a few seconds). Prolonged depolarization of pyramidal neurons leads to further mutual excitation, providing another slow positive feedback through the interplay between synaptic dynamics and intrinsic ion channels in single cells (Wang, 2006). A commonality of these diverse types of cellular and synaptic positive feedback mechanisms is that they are slow, operating on the timescale of many tens of milliseconds to seconds. This is in support of the prediction from computational models that slow reverberatory dynamics represent a characteristic feature of PFC microcircuits, and it is well suited for underlying working memory and decision-making computations.

Synaptic Inhibition and Its Balance with Excitation

A general principle of cortical organization is a delicate balance between excitation and inhibition. Insofar as PFC local circuits are empowered by strong synaptic excitation, they should also be endowed with specialized inhibitory circuitry. Traditionally, fast-spiking, perisomatic targeting basket cells have

been the focus of studies of synaptic inhibition. However, in the cortex, there is a wide diversity of GABAergic interneurons, with regard to their morphology, electrophysiology, chemical markers, synaptic connections, and short-term plasticity molecular characteristics. Three largely nonoverlapping subclasses of inhibitory cells can be identified according to the expression of calcium-binding proteins parvalbumin (PV), calbintin (CB), or calretinin (CR). Interestingly, in macaque monkey, the distributions of PV, CB, and CR interneurons appear to be quite different in PFC compared to V1. In primary visual cortex, PV-containing interneurons (including fast-spiking basket cells) are prevalent (~75%), whereas the other two CB- and CR-containing interneuron types constitute of about 10% each of the total GABAergic neural population. By contrast, in the PFC, the proportions are about 24% (PV), 24% (CB), and 45% (CR), respectively. Thus, the non-PV-containing interneurons are predominant in the macaque monkey PFC. Curiously, this does not hold true in the rat frontal cortex, where PV-containing interneurons constitute 43%–61% of all GABAergic cells. GABAergic neurons represent a larger proportion of all neurons in monkey cortex (~25% in the medial PFC) than in rat frontal cortex (16%). This difference may reflect a differential increase of the absolute number of non-PV interneurons in monkeys. Therefore, primate PFC circuits are characterized by an increased proportion of GABAergic cells relative to rodents and a predominance of non-PV interneurons, unlike early sensory areas.

A circuit model suggests how these different interneuron types may work together in the PFC (Fig. 6.1). This model incorporates three subtypes of interneurons classified according to their synaptic targets and their prevalent interconnections. First, PV interneurons project widely and preferentially target the perisomatic region of pyramidal neurons, thereby controlling the spike output of principal cells and sculpt the tuning of the network activity pattern. Second, CB interneurons act locally, within a cortical column. They predominantly target dendritic sites of pyramidal neurons, hence controlling the inputs onto principal cells. Third, CR interneurons also act locally and project preferentially to CB interneurons. Note that the three interneuron types in the model should be more appropriately interpreted according to their synaptic targets, rather than calcium-binding protein expressions. For example, PV cells display a variety of axonal arbors, among which the large basket cells are likely candidates for the widely projecting perisoma-targeting cells. Similarly, CB interneurons show a high degree of heterogeneity, but some of them (such as double bouquet cells or Martinotti cells) are known to act locally and preferentially target dendritic spines and shafts of pyramidal cells. Finally, although many CR interneurons do project to pyramidal cells, anatomical studies show that a subset of CR cells avoids pyramidal cells, at least in the same cortical layer and preferentially targets CB interneurons. It is also possible that axonal innervations of a CR cell project onto pyramidal

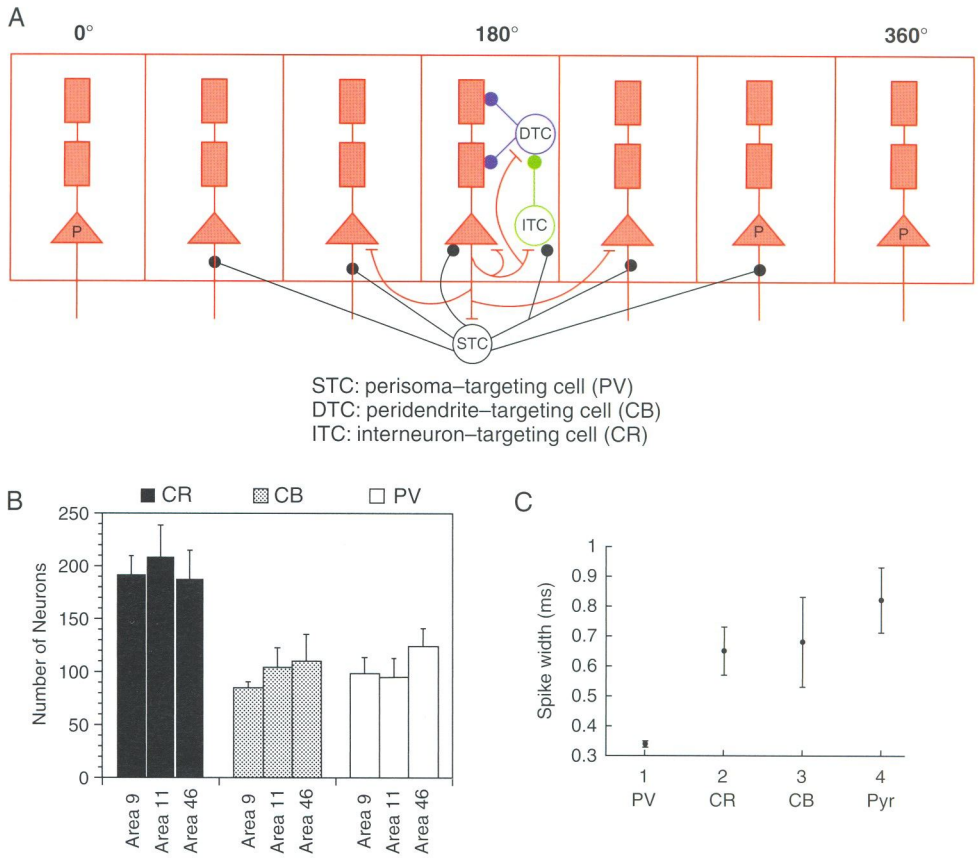

FIGURE 6–1. (*A*) A spatial working memory model with three subclasses of GABAergic interneurons. Pyramidal (P) neurons are arranged according to their preferred cues (a directional angle, from 0 to 360 degrees). There are localized recurrent excitatory connections and broad inhibitory projections from perisoma-targeting (parvalbumin-containing, PV) fast-spiking neurons to P cells. Within a column, calbindin-containing (CB) interneurons target the dendrites of P neurons, whereas calretinin-containing (CR) interneurons preferentially project to CB cells. Excitation of a group of pyramidal cells recruits locally CR neurons, which sends enhanced inhibition to CB neurons, leading to dendritic disinhibition of the same pyramidal cells. (Adapted from Wang et al., 2004 with permission) (*B*) Proportional distribution of PV-, CB-, and CR-expressing GABAergic cells in three subregions of the monkey prefrontal cortex. (Reproduced with permission from Condé et al., 1994) (*C*) Half-peak spike width for pyramidal neurons and three types of interneurons of macaque monkey prefrontal cortex. (Reproduced with permission from Zaitsev et al., 2005 and Povysheva et al., 2006)

cells in a different cortical layer while selectively targeting inhibitory neurons in the same layer.

Figure 6.2a–b shows a computer simulation of a biophysically detailed implementation of this circuit model for a spatial working memory task. When pyramidal cells in a column are excited by a transient extrinsic input,

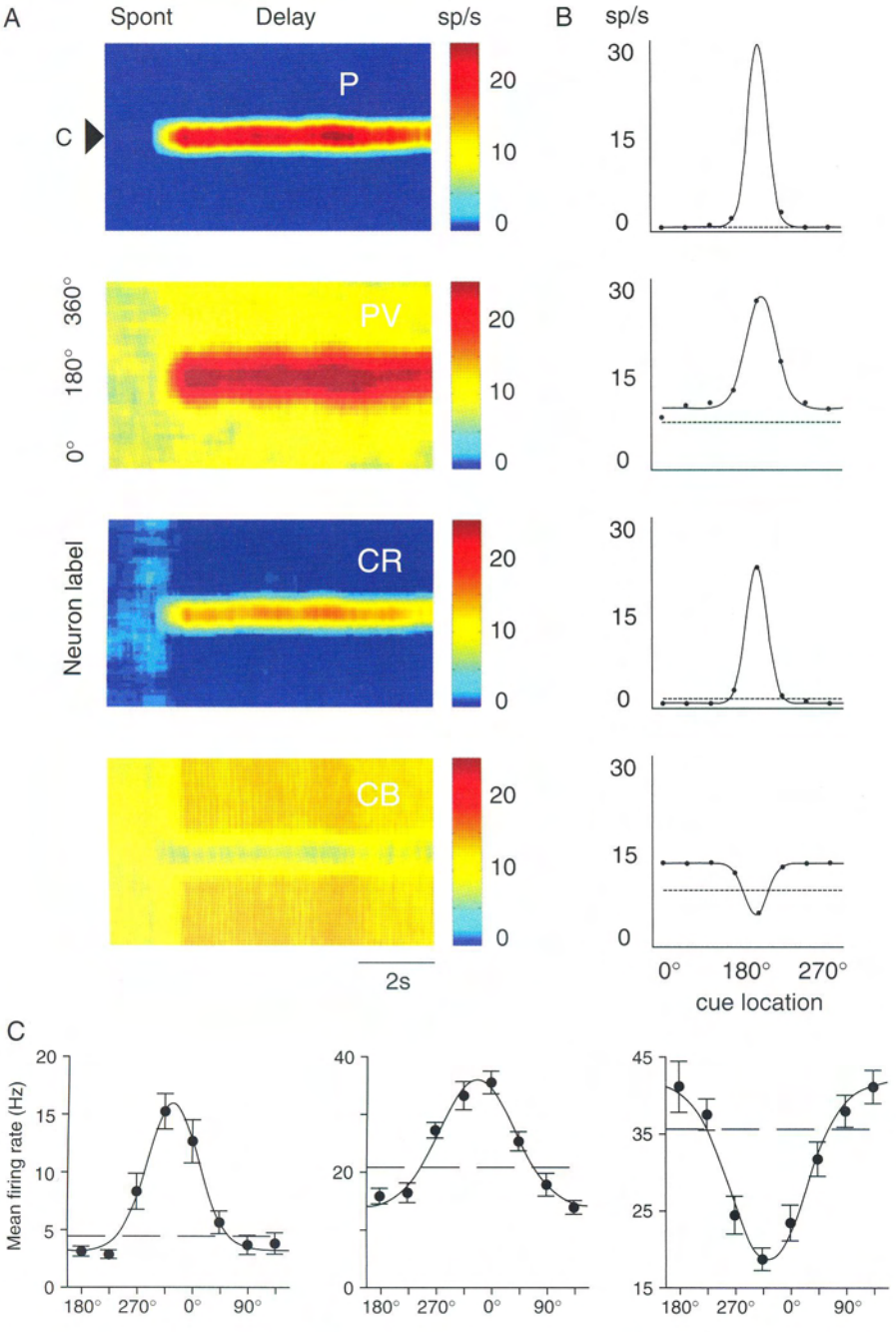

FIGURE 6–2. Computer simulation of a spatial working memory model schematically shown in Figure 6.1a, and comparison between the model and recorded PFC neuronal tuning curves. (*A*) Spatiotemporal activity patterns for the pyramidal cells and the three (PV, CB, and CR) inhibitory neuron populations during the cue and delay periods. Instantaneous firing rates are color coded. (*B*) Observed neuronal tuning curves (solid lines) during the delay period in the model simulations. Eight different cue positions are used. Dashed lines, spontaneous firing

FIGURE 6–2. continued
rate during the resting state. (*C*) Three kinds of recorded tuning curves in monkey dorsolateral prefrontal cortex during a spatial working task, with the same conventions as in (*B*). Solid line, the best Gaussian fit; dotted line, average firing rate during the last second of fixation. Note that the putative fast-spiking PV cell (*center*) has a higher spontaneous firing rate and wider tuning than the regular-spiking putative pyramidal cell (*left*), similar to what is found in the network simulations (*B*). An example of the inverted tuning curve is shown (*right*), with a high baseline activity (dashed horizontal line), strong reduced delay period activity for some cues, and slightly increased delay period activity for other cues. There are about 5% of recorded neurons showing these properties, which the model predicts to be putative CB interneurons that preferentially target pyramidal dendrites. Consistent with slice physiology (Fig. 6.1c), the spike width is the shortest for putative PV cells, the longest for putative pyramidal cells, and intermediate between the two for putative CB interneurons. (Reproduced from Wang et al., 2004)

they excite each other through interconnections. At the same time, activated CR interneurons suppress CB interneurons within the same column, leading to reduced inhibition (disinhibition) of the dendrites of the same pyramidal cells. The concerted action of recurrent excitation and CR interneuron-mediated disinhibition generates self-sustained persistent activity in these neurons, and the network activity pattern is shaped by synaptic inhibition from PV interneurons. Moreover, CB interneurons in other columns might be driven to enhance their firing activity; therefore, pyramidal cells in the rest of the network would become less sensitive to external inputs, ensuring that working memory storage is not vulnerable to behaviorally irrelevant distracters. A prediction of this model is that a small fraction of (putative CB) PFC neurons recorded from behaving monkey should show inverted tuning of mnemonic delay period activity, that is, a reduced firing relative to spontaneous activity selectively for some sensory cues. This prediction was confirmed in data analysis from a monkey spatial working memory task (Fig. 6.2c). Roughly 5% of recorded neurons in that experiment showed behavior that was predicted by the model for dendrite-targeting CB interneurons, consistent with the crude estimate of ~6% CB-containing interneurons (~24% of GABAergic cells, which in turn represent ~25% of all neurons).

Hence, different interneuron cell types show both division of labor and cooperation in subserving mnemonic PFC functions: stimulus selectivity, memory storage, and resistance against distracters. They also contribute differentially to the temporal dynamics, such as synchronous oscillations, during working memory (Wang, 2006). The inhibitory circuitry across different cortical layers may also show some specialized features in the PFC. For instance, a recent model suggests that connections from layer 5 to layer 2/3 excitatory and inhibitory neurons, and those from layer 6 to layer 4 interneurons, ought to be stronger in the frontal eye field than in V1 (Heinzle, 2007). Intriguingly, non-PV interneuron types may be differently involved in projections between

different prefrontal subregions. Indeed, there is anatomical evidence that, in the monkey PFC area 9, inputs from the neighboring area 46 and from anterior cingulated cortex area 32 similarly innervate excitatory neurons. However, GABAergic neuron targets are different: inputs from area 46 prevalently terminate onto CR-containing interneurons, while those from ACC predominantly terminate onto CB-containing interneurons (Medalla and Barbas, 2009). According to the model of Figure 6.1a, these findings imply that inputs from DLPFC area 46 serve to disinhibit pyramidal cells and boost their activity, while inputs from ACC effectively serve to inhibit dendrites of pyramidal cells, presumably contributing to gating inputs and resisting distraction, as the PFC actively maintains internal representations of sensory information, task rule, and so on. Note that in view of the high degree of heterogeneity among distinct areas in the PFC, it is likely that the inhibitory circuitry is also heterogeneous, adaptively tailored to each area's functional demands.

NEUROMODULATION

The PFC is a prominent target of afferents from the dopamine, norepinephrine, serotonin, and acetylcholine systems. Dopamine D1/D5 receptors are particularly concentrated in PFC and are prevalently located in the spines; thus, they are in a privileged position to modulate synaptic inputs. There is also evidence that both D1 and D2 dopamine receptors are expressed in GABAergic interneurons. Iontophoresis studies using behaving monkeys showed that mnemonic PFC neural activity in a delayed response task exhibits an inverted U-shaped dependence on the level of D1 receptor agonist concentration: working memory is impaired with either too little or too much dopamine D1 activity. Norepinephrine modulation of the PFC activity during working memory is also characterized by an inverted U-shaped influence curve. At the present, little is known about how neuromodulators differentially target distinct subclasses of interneurons. Notable is the anatomical evidence that serotonin 5-HT_{2A} receptors are preferentially expressed in pyramidal cells and perisomatic targeting interneurons, whereas 5-HT_3 receptors are mostly expressed in calbintin-containing dendrite-targeting interneurons and calretinin-containing interneurons. The functional implications of this specialization remain to be understood, in the context of recurrent network dynamics underlying cognitive functions.

SUMMARY

The PFC circuits are characterized by several features. First, their input–output connections with the rest of the brain are extraordinarily extensive.

Pyramidal neurons in PFC are greatly more spinous than in V1, and thus they have a very large capacity for synaptic integration. Second, PFC areas are endowed with strong intrinsic excitatory and inhibitory connections that are sufficient to generate persistent activity underlying working memory and competitive neurodynamics for decision making. A general principle is that excitatory feedback mechanisms underlying reverberation should be slow, in order to ensure network stability and to best serve such cognitive functions as gradual time integration of information in decision making. Third, excitation and inhibition are balanced dynamically. In the PFC, the synaptic inhibitory circuit is predominated by GABAergic cell subclasses that are not fast-spiking PV-containing interneurons. The increased abundance of other interneuron types (compared to sensory areas), which target pyramidal dendrites or regulate inhibitory circuit itself, may reflect the functional demand of selectively gating input pathways into the PFC in accordance with the behavioral context and goals.

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