

GABAergic microcircuits in the neostriatum

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The vast majority of neostriatal neurons and intrinsic intrastriatal synapses are GABAergic, the latter arising from axon collaterals of spiny projection neurons and from GABAergic interneurons. An important feature of the functional organization of the neostriatum has long been assumed to be the existence of a widespread lateral inhibitory network mediated by the axon collaterals of spiny projection neurons. However, these collateral connections have recently been demonstrated electrophysiologically to be relatively weak – in contrast to feedforward interneuronal inhibition, which exerts strong effects on spike timing in spiny neurons. These new data are incompatible with current ‘winner-take-all’ models of lateral inhibitory function in the neostriatum, and they force a modification of established concepts of the functional roles of feedback inhibition in this nucleus.

The neostriatum is the largest of the nuclei that make up the basal ganglia and is the main input structure for this system. The principal neuron is the GABAergic spiny projection neuron, which accounts for 77.0–97.7% of neurons in the neostriatum [1–4]. The remaining interneurons have been classified, based on morphology, neurochemistry and physiology, into one population of cholinergic cells and at least three distinct types of GABAergic interneurons. The GABAergic interneurons colocalize the Ca²⁺-binding proteins parvalbumin or calretinin, or neuropeptide Y, somatostatin and NADPH diaphorase [5].

The principal excitatory afferents to neostriatal spiny neurons arise from the cerebral cortex and thalamus [6]. The anatomy and physiology of these glutamatergic afferents, particularly those from cerebral cortex, are well understood. However, until relatively recently, the intrinsic microcircuitry of the neostriatum – the functional synaptic connections between spiny neurons and interneurons and between various interneurons and spiny neurons, which are mediated by GABA and ACh – has been much more difficult to decipher. This is because the various neostriatal interneurons exist in very small numbers relative to the spiny neurons and because neostriatum lacks a laminar organization akin to that seen in hippocampus, cerebral cortex and elsewhere (and

therefore exhibits no stereotyped organization or segregation of synaptic inputs). However, in recent years the advent of whole-cell recording in brain slices under visual control [7,8] has made it possible to identify and target the less abundant cell types in neostriatal slices for recording [9], and thus has both greatly facilitated our ability to record from interneurons and increased the frequency of success at recording from pairs of synaptically connected neurons.

GABA-mediated inhibition in neostriatum

Neostriatal spiny neurons are characterized by a dense and extensive local axon collateral field that usually extends over a volume similar to or slightly larger than the dendritic arborization of the parent neuron [10] (Figure 1a). Early intracellular labeling studies revealed that the principal targets of these axon collaterals were other spiny neurons [11,12] (Figure 1b). It was logical to assume that this local axon collateral plexus was the substrate for a powerful lateral inhibitory network [13], and many computational models of the neostriatum were based on this premise [14–16].

Some early physiological studies hinted at the possibility of collateral inhibition in neostriatal neurons based on antidromic stimulation or shunting of substantia nigra-evoked excitatory postsynaptic potentials (EPSPs) [17–18]. Furthermore, disruption of intrastriatal GABAergic circuitry by intrastriatal injection of bicuculline *in vivo* caused a fourfold increase in the spontaneous activity of spiny neurons [19]. However, these results can also be accounted for by mechanisms other than collateral inhibition. In a subsequent attempt to address specifically this issue, Jaeger and colleagues [20], using sharp electrode intracellular recordings, were unable to detect collateral inhibitory postsynaptic potentials (IPSPs) resulting from antidromic activation of neostriatal spiny neurons *in vivo* or *in vitro*, or to detect synaptic interactions between simultaneously recorded pairs of nearby spiny neurons in striatal slices, even when their axonal and dendritic fields were seen to overlap. Similarly, cross-correlations of spiny neurons recorded intracellularly *in vivo* in rats [21], or extracellularly from pairs of neurons in small clusters in awake behaving monkey caudate or putamen [22], failed to show any evidence of inhibitory (or other) interaction. Jaeger *et al.* [20] concluded that collateral inhibition among spiny neurons was weak or non-existent, and

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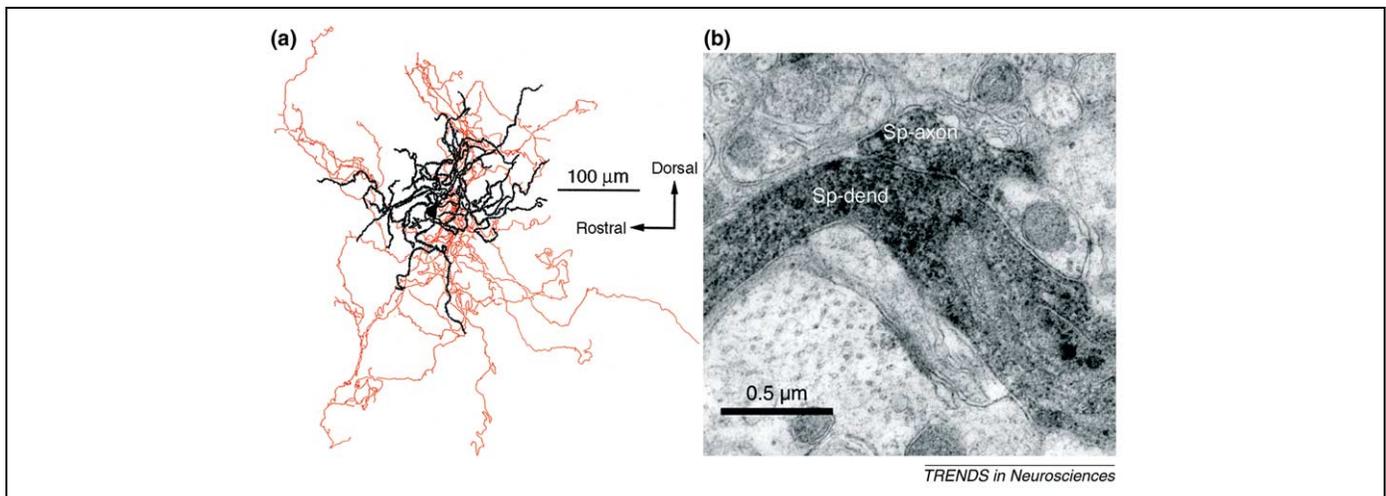


Figure 1. Neostriatal spiny projection neurons. **(a)** Drawing-tube reconstruction of a neostriatal spiny neuron from an adult rat stained intracellularly with biocytin *in vivo*. Dendrites are in black; axon collaterals are in red. **(b)** Electron micrograph of a symmetric axodendritic synapse between two striatal spiny neurons stained intracellularly with horseradish peroxidase. Abbreviations: Sp-axon, axon terminal of one intracellularly stained striatal spiny neuron; Sp-dend, dendrite of a second intracellularly stained striatal spiny neuron.

speculated that if it did exist, it was likely to play a relatively subtle modulatory role, with most of the strong inhibition in neostriatum probably mediated by GABAergic interneurons [23]. As we shall see, both predictions are probably correct.

Feedforward inhibition through GABAergic interneurons

The best-characterized striatal GABAergic interneuron is the parvalbumin-containing interneuron. It belongs to a class of cells that exist in the neocortex, hippocampus and elsewhere that are classified as fast-spiking (FS) interneurons [24–26]. These neurons exhibit brief action potentials, large and rapidly peaking spike afterhyperpolarizations, and relatively linear current–voltage curves. Although capable of sustained activity at >200 Hz with little or no spike-frequency adaptation, more modest depolarization induces a characteristic phasic firing pattern consisting of short bursts of action potentials at constant interspike interval separated by periods of no spiking [9,27–29].

In mature brain slices [from rats of postnatal day (P)24–P32] [30], approximately one-quarter of spiny neurons recorded within 250 μm of an FS interneuron were found to be synaptically connected. The synaptic response was an IPSP mediated predominantly or exclusively by GABA_A receptors [28]. The connection was never reciprocal; in all cases the direction of connection was from the interneuron to the spiny neuron. Two notable characteristics of the IPSP were its large amplitude and low failure rate. At their most depolarized subthreshold membrane potential (i.e. in their ‘up-state’) [31], unitary IPSPs generated by a single action potential in one presynaptic FS interneuron were ~1 mV in amplitude. Summation was very effective and under these conditions compound IPSPs resulting from a short burst of presynaptic action potentials could reach several mV. Under voltage clamp, the inhibitory postsynaptic current (IPSC) at a holding potential of –70 mV exhibited a mean of -213 ± 73 pA [29]. Assuming a driving force of 70 mV for

the synapse under these conditions, this suggests a mean inhibitory postsynaptic conductance (IPSG) of 3 nS. The strength of this synapse is even more impressive when one considers that it exhibits a failure rate of <1% (Figure 2), consistent with multiple synaptic contacts between each interneuron and a postsynaptic spiny cell [28,29]. In functional terms, the feedforward inhibition is extremely potent, as action potentials in single interneurons can delay or effectively block the occurrence of spikes in spiny neurons [28] (Figure 3).

Calculations of the divergence and convergence of the innervation of spiny neurons by FS interneurons yield upper and lower limits of the number of spiny neurons contacted by a single FS interneuron as 568 and 142, respectively, and those of FS interneurons synapsing on each spiny neuron as 4 and 1, respectively [28]. Because GABAergic interneurons, in addition to FS interneurons, also participate in feedforward inhibition of spiny neurons eliciting IPSPs that appear similar or identical to those elicited by the FS interneurons [28], the functional interneuronal divergence and convergence ratios are probably slightly lower and higher than these estimates, respectively.

Striatal FS interneurons exhibit gap junctions [32], so it was not surprising that they were also found to be electrotonically coupled [28]. Of seven pairs recorded, three were found to be electrotonically coupled with ratios of 3%, 7% and 20%. The coupling was not strong enough for a spike in one neuron to elicit an action potential in a coupled neuron. However, even weak (3%) coupling was sufficient to synchronize depolarization-induced action potentials in two electrotonically connected FS neurons. In the cases where action potential bursts occurred simultaneously in the neurons, the coincident spikes occurred with variability equivalent to only a small fraction of the mean interspike interval (ISI). This electrical coupling was similar in all respects to that subsequently described between FS interneurons of the neocortex [33]. These data suggest that, as has been proposed in cortex, striatal FS interneurons might

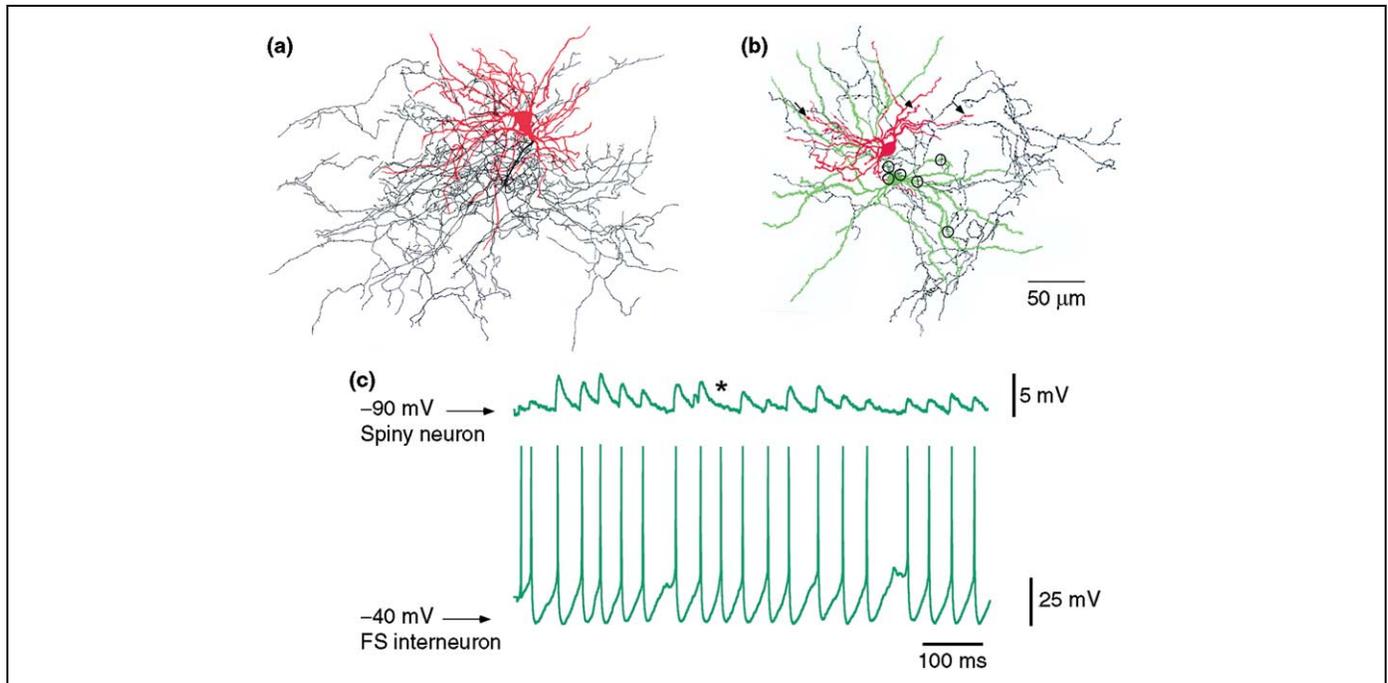


Figure 2. Neostriatal fast-spiking interneurons. **(a)** Drawing-tube reconstruction of the more common (larger) fast-spiking (FS) cell morphology labeled with biocytin after whole-cell recording *in vitro* in a slice from a 25-day-old rat. Dendrites are in red; axons are in black **(b)** Drawing-tube lucida reconstruction of a different FS interneuron (dendrites in red, axons in black) and a synaptically connected spiny projection neuron (green) stained with biocytin after whole-cell recording *in vitro* in a slice from a 25-day-old animal. The interneuron is morphologically different from the one shown in (a), exhibiting pronounced dendritic varicosities (arrowheads), larger axonal boutons and only a moderately dense axonal arbor. The light microscopically identified putative contact sites (circled) are mostly perisomatic. Dendrites of the spiny cell are densely covered with spines, indicating that the neuron is morphologically mature. Local collaterals of the postsynaptic spiny neuron are not shown, for clarity. **(c)** Series of action potentials in a presynaptic FS interneuron (bottom) evoked by depolarizing current injection result in very reliable inhibitory postsynaptic potentials (IPSPs) in a postsynaptic spiny neuron (top). The IPSPs are reversed in polarity because the spiny neuron is hyperpolarized. There is only one failure (asterisk) out of 20 consecutive presynaptic spikes. Panels (a) and (b) are modified, with permission, from Ref. [28].

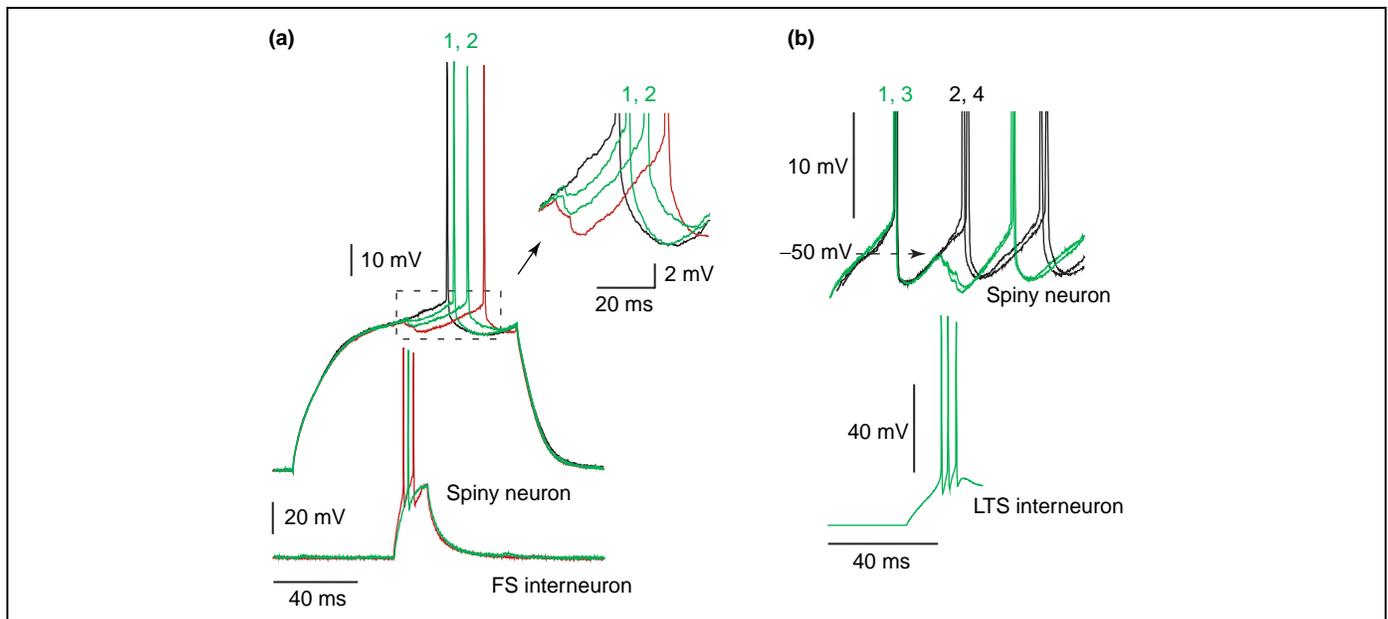


Figure 3. Interneuronal modulation of action potential generation in spiny neurons. **(a)** A single action potential elicited in a spiny neuron by current injection (upper black trace) is delayed by inhibitory postsynaptic potentials (IPSPs) evoked by single spikes (lower green trace) or a spike doublet (lower red trace) of a fast-spiking (FS) interneuron. The delay is variable (compare green spikes 1 and 2), and the spike doublet (red traces) is more effective than single spikes. The inset shows the IPSPs at higher gain. **(b)** The same experiment, conducted in a pair consisting of an low-threshold-spiking (LTS) interneuron (lower trace) and a spiny neuron (upper traces). The LTS of the interneuron elicits three fast spikes (lower trace) evoking compound IPSPs (upper green traces) that prevent the firing of the spiny neuron (compare green traces 1 and 3 with black traces 2 and 4) for ~20 ms. The trials were performed in the order of numbering (first and third trials with interneuron stimulation, second and fourth without), indicating the stability of the postsynaptic cell and the reliability of the inhibition. Reproduced, with permission, from Ref. [29].

Box 1. How strong is the inhibition among spiny neurons in the neostriatum?

Functional interpretation of the inhibition among projection neurons depends crucially on the extent to which a single neuron can influence the firing of its postsynaptic targets. The amplitude of the inhibitory postsynaptic potential (IPSP) near action potential threshold provides a useful measure of this. Published amplitudes for the spiny neuron collateral IPSP vary from 0.17 mV [34] to 2.15 mV [35], differing by a factor of 12 and supporting mechanistically different models of functioning. Much of this difference results from differences in the recording conditions. To obtain a more uniform picture, we estimated what the IPSP amplitude would be near threshold if these differences were compensated for (Table I). The corrected IPSPs are 0.17–0.34 mV, representing only a twofold difference between lowest and highest estimates. Because the increased electrotonic attenuation resulting

from lower input resistances was not taken into account, the higher amplitudes obtained after input resistance correction are overestimates of the *in vitro* or *in vivo* amplitudes.

The effect of collateral inhibition on postsynaptic firing was not directly examined in these studies but can be estimated by comparison with fast spiking (FS)–spiny connections [28]. As the delay of a postsynaptic action potentials is approximately linearly related to the amplitude of the IPSP, a single 0.34 mV IPSP will delay the firing of a postsynaptic spike by only ~2 ms (with the postsynaptic neuron firing at 20–50 Hz), compared with >25 ms delay imposed by the FS–spiny neurons synapse. Therefore, it is unlikely that single spiny neurons have a significant effect on the firing rate or action potential timing of postsynaptic spiny neurons.

Table I. Comparison of IPSP and IPSC amplitudes in studies examining collateral inhibition between spiny neurons^a

Preparation	IPSP or IPSC amplitude	V _n (mV)	E _{Cl} (mV)	R _{in} (MΩ)	Normalized IPSP amplitude (mV)	Probability of connectivity	Probability of innervation	Refs
25–45-day-old slice	-0.277 ± 0.046 mV (-0.157 to -0.319 mV)	-50	-62.4	71.1 ± 5.2	-0.171 ± 0.028 (0.093–0.197)	9/45, tested two ways	10.0% unidirectionally	[34]
Slice co-culture	2.15 ± 0.38 mV	-75	-60.2	531 ± 4	-0.28 ± 0.05	26/69, tested two ways (including eight reciprocals)	24.6% unidirectionally	[35]
23–30-day-old slice	31 ± 11 pA (G = 0.6 nS)	-80	-20.8	194 ± 22	-0.3 ± 0.1	13/38, tested two ways (including one reciprocal)	18.4% unidirectionally	[38]
> 5-week-old slice	51 ± 39 pA (15–250 pA)	-70	-2.0	128 ± 35 (CsCl)	-0.34 ± 0.25	39/325, tested one way	12.0% unidirectionally	[37]

^aNormalized amplitudes for the inhibitory postsynaptic potential (IPSP) were calculated as estimates of what the amplitude would be at the up-state membrane potential *in vivo* (i.e. the most depolarized subthreshold membrane potential, -49 mV) [52], with normal E_{Cl} [34] and an input resistance of 70 MΩ [28,34]. When only voltage-clamp data were available, IPSPs were estimated by simulating a single-compartment model, using the peak conductance and decay time constant of the inhibitory postsynaptic current (IPSC) and the input resistance and time constant of the spiny neurons. The average IPSP reported in Ref. [34] excludes failures, and was adjusted by multiplying the reported average amplitude by a factor of one minus the failure rate.

function together to create GABAergic interneuronal networks that precisely control spike timing in spiny neurons.

Feedback inhibition through spiny neuron axon collaterals

Tunstall *et al.* [34] were the first to demonstrate inhibitory interactions between spiny neurons with intracellular current-clamp recordings from pairs of spiny neurons in slices taken from mature rats. The collateral IPSPs were small (mean 277 ± 46 μV, excluding failures) and only reliably detected by averaging hundreds of sweeps. They exhibited a variable but fairly high failure rate (38 ± 14%). The fact that the synaptic interactions among spiny neurons are so weak and prone to failure explains how they eluded detection in the previous studies. Similar to the interneuron IPSPs, the collateral IPSPs were mediated by GABA_A receptors. Of the 45 pairs recorded, synaptic connection was found in nine. In all nine cases, the connection was unidirectional, thus corresponding to 10% chance of finding a collateral synaptic response.

These findings were soon confirmed in visualized whole-cell recordings from adjacent neurons in organotypic co-cultures of substantia nigra, striatum and cortex [35]. Under these experimental conditions, the mean IPSP amplitude was greater than that reported in slices [34]. However, much of this difference is likely to be due to differences in preparation and recording conditions, including a considerably greater input resistance for the spiny neurons in culture (Box 1; Table 1). The failure rates in culture were comparably variable and high (~50%). In these co-cultures, collateral IPSPs were observed in 38%

of the pairs recorded. Reciprocal connections were detected in 31% of the connected pairs, although in many cases the IPSP from one direction of transmission was much larger than that from the other. From such data [27,36], one can infer that there is likely to be greater connectivity in the co-cultures than that found *in vivo* or in acute slice preparations.

Whole-cell voltage-clamp recordings from pairs of spiny neurons in acute slices revealed IPSCs consistent with these reports [37,38]. The incidence of connectivity in these studies was 12–18% – the same range as previously reported in the acute slice current-clamp experiments – and in three studies, only one connected pair in 70 was found to be reciprocally connected [35,37,38].

Spiny neuron collateral IPSCs were also demonstrated by Guzman *et al.* [39] by recording GABA_A IPSCs in striatum evoked by electrically stimulating the globus pallidus to antidromically activate spiny neurons and activate axon collaterals, or evoked by stimulating the striatum (which would generate both collateral and interneuronal IPSPs). Consistent with the data from paired recordings, the presumed pure collateral IPSCs were smaller than those evoked by a combination of spiny cell collaterals and interneurons.

The measurements of the connectivity among spiny neurons allow an estimate of the degree of convergence among these cells. Within the range of the dendritic tree of a single spiny neuron there are ~2850 other spiny neurons [40]. If, as already suggested, the connectivity is ~12–18%, each cell should receive input from ~475 other spiny neurons. This is at least 100 times the convergence

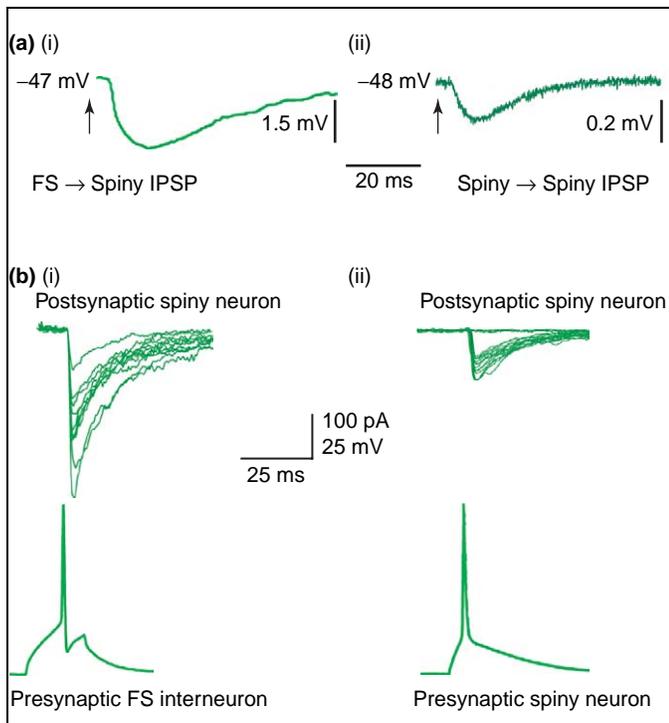


Figure 4. Inhibitory postsynaptic potentials (IPSPs) and currents (IPSCs) in spiny neurons elicited from fast spiking (FS) interneurons are larger than those elicited from other spiny neurons. (a) Comparison of IPSPs elicited from a FS interneuron (i) and a spiny cell axon collateral (ii), recorded in spiny neurons in neostriatal slices under similar conditions of membrane potential, driving force and input resistance. (Note that the amplitude scales are different.) (b) Comparison of IPSCs recorded in spiny neurons in neostriatal slices under identical conditions (140 mM internal CsCl). The IPSCs from elicited from the FS interneuron (i) are much larger than those from the spiny cell (ii). There are frequent failures in the collateral IPSP, in contrast to the high reliability of the FS synapse. Panel (a) modified, with permission from Refs [28,34]; (b) modified, with permission from Ref. [29].

seen for the FS interneurons. This enormous difference in the number of synapses suggests that spiny cell mutual inhibition should be much more influential than indicated by the physiological experiments. If all the spiny neurons in the vicinity were to fire at once, it should be possible to generate an IPSC with ~ 400 times the conductance seen in the paired recordings.

What accounts for the differences in synaptic strength between feedforward and feedback inhibition?

When measured in identical preparations under the same recording conditions, the spiny neuron collateral IPSC is only between one-quarter and one-sixth the amplitude of the interneuron–spiny neuron IPSC measured at the soma [29,37] (Figure 4). Although it is more difficult to compare the relative amplitudes of the two IPSPs or IPSCs quantitatively, estimates based on other reports consistently indicate that the amplitude of the collateral synaptic response is smaller than that of the interneuron–spiny neuron IPSP or IPSC recorded at the soma [28,29,34,38,39].

Several factors could account for the difference in amplitude. One is a different degree of electrotonic attenuation of the input depending on synaptic location. Although some of the synapses made by neostriatal spiny neurons onto other spiny neurons are onto the soma [11,12,41], intracellular labeling studies reveal that 88% of their local

collateral synapses end on dendrites or spines, with only 12% of the terminals forming symmetric synapses onto cell bodies [11]. By contrast, parvalbumin-positive terminals, most of which originate from FS interneurons, tend to form pericellular baskets around the somata of spiny neurons [32,42,43]. Despite their relatively small size and restricted dendritic arborization, their strong inward rectification and densely spinous dendrites confer considerable electrotonic length to spiny neurons, which would make the effects of synaptic inputs to the spiny region of the dendrite much smaller at the soma than at the site of synaptic contact [6]. Thus, axon collateral synaptic responses would be expected to be smaller than interneuron–spiny cell synaptic responses when recorded at the soma, strictly on the basis of anatomical considerations. In support of this, recording conditions that reduce the effect of electrotonic distance increase the size of the collateral IPSP about threefold [37].

Another factor is the average number of synapses (N) made by a presynaptic neuron onto each postsynaptic neuron to which it is connected synaptically. Data from reconstruction of intracellularly stained connected pairs are not yet available, but quantal analysis of synaptic potentials in response to short trains of presynaptic action potentials [44] has revealed that, although $N \leq 3$ for the collateral connection, $N \geq 7$ for the FS–spiny cell synapse [37].

Other properties of two GABAergic synapses appear very similar [37]; thus, the differences in the amplitudes of the spiny cell collateral synapse and the FS–spiny synapse arise from the location and the number of synapses formed by each, as illustrated schematically in Figure 5.

Functional roles of interneuronal and axon collateral inhibition in neostriatum

In contrast to original expectations based on anatomical observations [11], but consistent with subsequent predictions from electrophysiological studies [20,23], most GABA-mediated control of spiking in spiny neurons appears to involve striatal interneurons (even though there are many times more spiny neuron collateral synapses than interneuron–spiny cell synapses). The interneurons exert powerful inhibition; even a single spike in one interneuron can delay or prevent spiking in a spiny neuron. Because significant inhibition can be exerted by a single neuron, there is no need for synchronous activation of many neurons to achieve a strong but brief inhibitory influence on many spiny neurons. Interneurons also often fire at high rates, allowing temporal summation of the somatic inhibition exerted by these cells [28]. Because striatal interneurons are active during periods of cortical excitation that produce up-states [27], the pattern of activation of GABAergic interneurons during these episodes could play a key role in determining the moment-to-moment pattern of firing of spiny neurons during an up-state.

Recurrent inhibition by spiny neurons, conversely, is made up of many weak inputs from nearly as many different spiny cells. Although spiny neurons within inhibitory range of each other often enter the up-state together, they do not fire promptly at the start of up-states

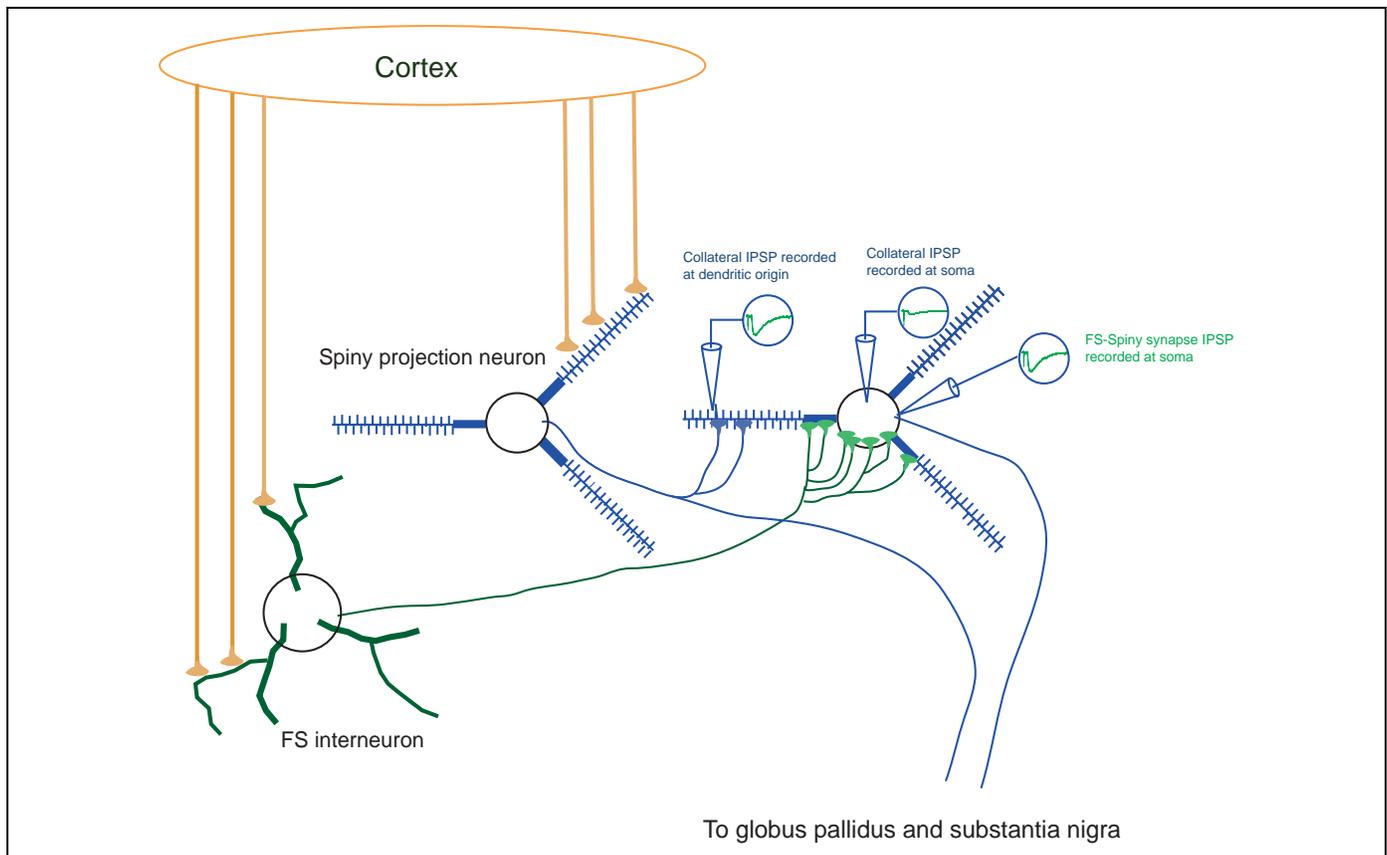


Figure 5. Schematic illustration of the neostriatal GABAergic microcircuitry. Although the spiny neuron collateral inhibitory postsynaptic potential (IPSP) is very similar to the interneuron IPSP at its origin in the spiny region of the dendrite, when recorded at the soma the collateral IPSP is much smaller. This is because each spiny neuron makes very few collateral synapses, each of which is located distally on neighboring spiny neurons, whereas fast-spiking (FS) interneurons make a larger number of synapses, which are located more proximally on each spiny neuron.

[21,45], and the firing of spiny neurons in the up-state is generally not correlated [21]. Thus, the background spontaneous firing of spiny neurons usually lacks the synchrony required to exert a powerful brief inhibition comparable with that exerted by inhibitory interneurons.

What, then, is the role of the spiny neuron axon collaterals? Could they subservise ‘winner-take-all’ inhibition of the type envisaged for networks performing input pattern categorization? Based on the relatively small size of the synaptic response at the soma, and the clear absence of reciprocal innervation, it is clear that the original notions of a lateral inhibitory network performing ‘winner-takes-all’ competitive inhibition [13–16] is no longer tenable, or is at best in need of major conceptual revision [45]. One class of revision of these models, in which lateral inhibition is strong during network training but can become weak after acquisition of the pattern classification task [16,46], can also be dismissed, unless the anatomical features of the network (e.g. the degree to which cells are reciprocally connected) are also adjustable during training. There is currently no indication that this occurs. For example, during development of the neostriatum, connectivity in the network would be predicted to be higher than in adults. Anatomically, the local collaterals of striatal neurons do not show a period of exuberant overgrowth during development [47], and preliminary measurements of connectivity between pairs of spiny neurons during development suggest that connectivity

gradually increases postnatally, towards adult levels [37]. Finally, studies of the axonal collateral arborizations of corticostriatal axons have shown that these extend over a much larger volume of the striatum than the local collaterals of spiny neurons [10,30,48]. Thus, the spiny cell collaterals do not exert inhibition of an appropriate spatial scale for subserving competition among spiny cells for the exclusive representation of specific patterns among a group of shared cortical input neurons [48].

Because of their predominantly dendritic location, it is likely that the recurrent inhibitory synapses formed by spiny neurons are well situated to control dendritic, rather than somatic, events. Although the conductance change generated by these synapses might be too small to produce a large somatic IPSP, because of the high input resistance seen by synapses in the distal dendrites the IPSP might be very potent locally. Thus, the spiny cell collateral IPSP could very effectively attenuate or block the transient effects of a nearby corticostriatal or thalamostriatal EPSP. Furthermore, by attenuating such EPSPs, the spiny cell axon collaterals might play an important role in blocking Ca^{2+} -dependent changes in the synaptic efficacy of specific corticostriatal or thalamostriatal synapses that depend on activation of NMDA receptors [49,50]. Other important possible local effects include attenuation of backpropagation of action potentials into the dendrites [51] or effects on the ability of local excitation to overcome dendritic inwardly rectifying K^+ conductances, which

tend to maintain the spiny neurons in their most hyperpolarized subthreshold membrane potential (i.e. their down-state) [31].

Concluding remarks

The original concept of the neostriatum as a large 'winner-takes-all' lateral inhibitory network is no longer viable because of the weakness of individual collateral synapses and the lack of reciprocal connectivity. Interneuronal inhibition, however, is strong and likely to play a major role in regulating spike timing. Both concepts need to be incorporated into the next generation of computational models of neostriatal function. The operational characteristics of the neostriatal axon collateral system remain to be determined, and are likely to be far more complex than our original simple view of lateral inhibition.

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