Functional diversity and specificity of neostriatal interneurons

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The firing of neostriatal spiny neurons in response to an excitatory input is modulated and sculpted by a variety of factors. Neostriatal interneurons are phenotypically diverse and have properties that enable them to specifically, but differentially, influence the activity of spiny neurons. Each of the three types of GABAergic interneurons produces a strong inhibitory postsynaptic potential in spiny neurons, the function of which is probably to influence the precise timing of action potential firing in either individual or ensembles of spiny neurons. By contrast, the role of cholinergic interneurons is to modulate the sub- and supra-threshold responses of spiny neurons to cortical and/or thalamic excitation, particularly in reward-related activities. Both classes of interneurons are important sites of action of neuromodulators in neostriatum, and act in different but complementary ways to modify the activity of the spiny projection neurons.

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Abbreviations

ACh	acetylcholine
FS	fast-spiking
GABA	γ-aminobutyric acid
GPe	external segment of the globus pallidus
IPSC	inhibitory postsynaptic current
IPSP	inhibitory postsynaptic potential
LTS	low threshold spike
MSN	medium-sized densely spiny neuron
NPY	neuropeptide Y
PLTS	persistent and low-threshold spike
TAN	tonically active neuron

Introduction

The neostriatum (caudate-putamen) is the major division of the basal ganglia; it receives the majority of afferent input and is arguably the principal site within the basal ganglia where information processing occurs. The neostriatum receives input from the whole of the cortical mantle. The corticostriatal axons mainly innervate the GABAergic (γ-aminobutyric acid) medium-sized densely spiny neurons (MSNs), which account for the large majority of neostriatal neurons. These MSNs, in turn, project preferentially to the output nuclei of the basal ganglia or to the external segment of the globus pallidus (GPe) and thence to the output nuclei. Under resting conditions MSNs are hyperpolarized and silent. Increased activity of many convergent corticostriatal neurons (and possibly thalamostriatal neurons as well) depolarizes MSNs to the 'up state', from which additional excitatory inputs, an alteration in the strength of the synapses or an alteration in the balance of excitatory and inhibitory inputs leads to the firing of action potentials [1]. This phasic activity of the MSNs leads to altered rates and patterns of firing in the output nuclei through the 'direct' route and the 'indirect' route, which includes the GPe and subthalamic nucleus, and hence the targets of the basal ganglia. Although there are other routes by which extrinsic information reaches the basal ganglia (most notably through the corticosubthalamic pathway) it is clear that the response of MSNs to cortical and other inputs is the very essence of what the basal ganglia do.

The activity of individual and ensembles of MSNs is not solely dependent upon excitatory input but also on other factors, including dopaminergic and cholinergic neuromodulation and GABAergic inhibition from the local axon collaterals of MSNs and neostriatal interneurons (for recent review see Bolam *et al.* [2]). Neostriatal interneurons, which account for only a small proportion of all neostriatal neurons (2–3% in rodent [3•] and possibly up to 23% in primates [4]), are phenotypically diverse and highly specific in their properties enabling them to modulate and sculpt the response of MSNs to cortical input.

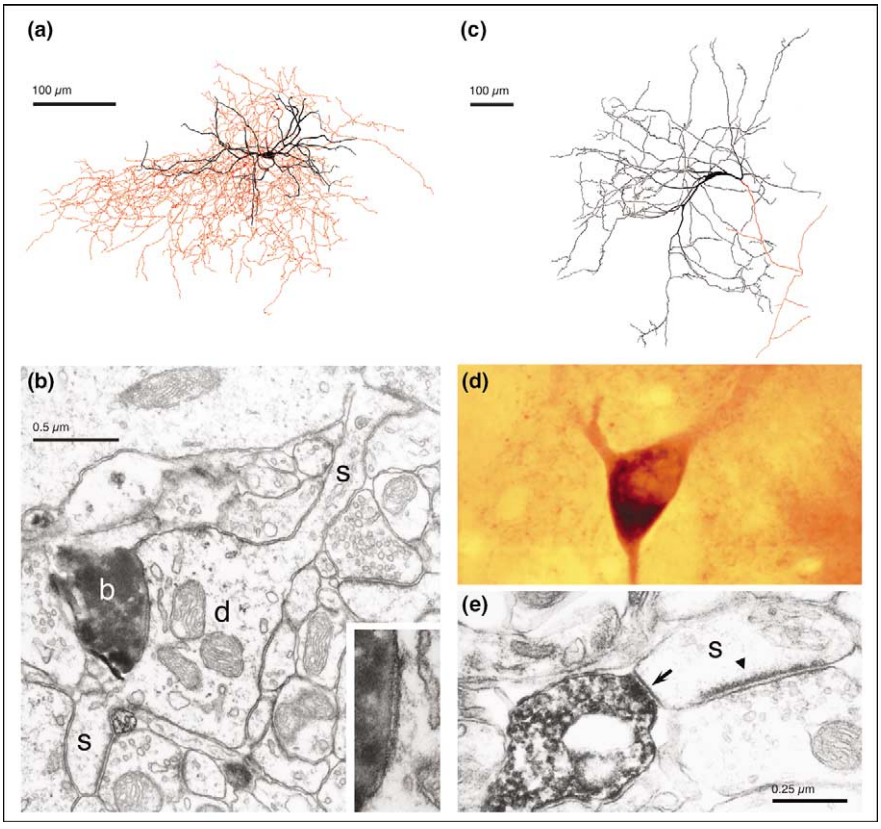
GABAergic interneurons

There are three subtypes of GABAergic interneurons in the neostriatum that can be distinguished neurochemically. One expresses the peptides somatostatin and neuropeptide Y (NPY) as well as the enzymes NADPH diaphorase and nitric oxide synthase. The other two express the calcium binding proteins parvalbumin or calretinin [5]. Together, the GABAergic interneurons comprise about 2% of the total neostriatal cell population [3•].

Parvalbumin interneurons

The best characterized GABAergic interneurons are those that express parvalbumin. On the basis of their

Figure 1



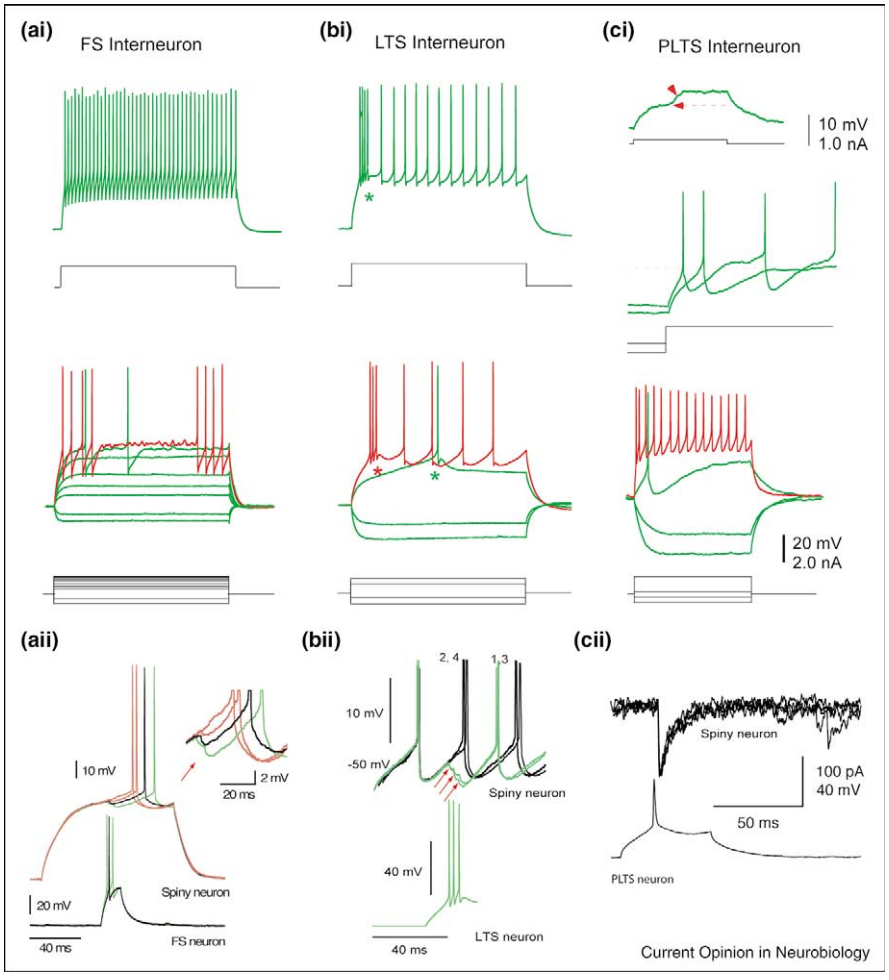
Morphological characteristics of FS GABAergic interneurons and cholinergic interneurons. **(a)** Reconstruction of FS GABAergic interneuron from an adult brain slice stained with biocytin after whole cell recording *in vitro*. The soma and dendritic tree are in black and the axon is in red. Note that the dense axonal plexus has close to 5000 varicosities. **(b)** Electron micrograph of one of the varicosities of the same neuron. The bouton (b) is in symmetrical synaptic contact with the dendritic shaft (d) of an MSN (see inset). The spines (s) emerge from the dendrite. **(c)** Reconstruction of soma and dendrites (black) and first few branches of the axon of a cholinergic interneuron recorded *in vivo*. Note the large size of the soma and extensive dendritic tree compared with the cell in (a), which is at a higher magnification (modified with permission from [34]). **(d)** Immunolabeling for choline acetyltransferase in the neostriatum. A large cholinergic neuron (~25 μm in diameter) is in the centre of the field. The neuropil contains a high density of immunoreactive boutons, which are all derived from the cholinergic interneurons. **(e)** Electron micrograph of a choline acetyltransferase-positive bouton forming symmetrical synaptic contact (arrow) with a spine (s) that also receives asymmetrical synaptic input (arrowhead).

electrophysiological properties they are referred to as fast-spiking (FS) interneurons [6]. Their somata average 16–18 μm in diameter and issue aspiny dendrites that branch modestly. There is some morphological heterogeneity, with one subtype exhibiting a relatively restricted and varicose dendritic arborization in the region of 200–300 μm in diameter, and the other displaying a more extended non-varicose dendritic field 500–600 μm in diameter with a larger soma [6,7]. The neuron is characterized by an extremely dense local axonal plexus that is heavily invested with presynaptic boutons (Figure 1).

Unbiased stereological estimates of parvalbumin interneurons put their numbers at about 0.7% of the total in rat neostriatum [3•,8]. There is a strong medio-lateral gradient in the distribution of parvalbumin-positive axons and terminals, which suggests that these cells might be more integral to functioning in the lateral striatum than those in the medial striatum [9]. The neurons are similar in many ways to parvalbumin-expressing GABAergic interneurons in cortex [10] and hippocampus [11]; they exert powerful monosynaptic inhibition of the principal neurons through multiple perisomatic synapses and are themselves electrotonically coupled [7,12••] by way of gap junctions [13].

Little is known about how these neurons fire *in vivo* [14]. *In vitro* they are strongly hyperpolarized and silent. Although capable of sustained firing at 200–300 Hz, with little or no spike frequency adaptation when strongly depolarized by current injection, more moderate depolarizing current or exposure to nicotinic agonists [15••] causes the neurons to begin to fire short bursts of narrow action potentials. These have fast, deep hyperpolariza-

Figure 2



Electrophysiological characteristics of neostriatal GABAergic interneurons. **(ai)** Responses to hyper- and de-polarizing current pulses in a FS interneuron from a mature slice. Note the sustained high frequency firing to a large depolarizing pulse with little or no spike frequency adaptation (upper) and the large amplitude, rapidly developing spike afterhyperpolarization and characteristic intermittent firing to smaller depolarizing pulses (lower). **(aii)** A single action potential elicited in a spiny neuron by current injection (2 upper red traces) is delayed by IPSPs evoked by single spikes (lower black trace) or a spike doublet (lower green trace) of an FS interneuron. The inset shows the IPSPs at higher gain. **(bi)** Responses to hyper- and de-polarizing current pulses in a LTS interneuron from a mature slice. Present are single spikes or short bursts riding on LTSs (asterisks) and biphasic spike afterhyperpolarizations. **(bii)** Burst of three spikes evoked in a presynaptic LTS neuron delays the firing of depolarization-induced spiking of a MSN. The LTS evokes compound IPSPs (upper green traces 1 and 3) that prevent the firing of the spiny projection cell (black traces 2 and 4) for approximately 20 ms. The momentary firing rate is decreased by 35%. The trials were performed in the order of numbering, indicating the stability of the response of the postsynaptic cell and the reliability of the inhibition. **(ci)** Responses to hyper- and de-polarizing current pulses in a PLTS interneuron from a mature slice. Upper trace shows the plateau potential characteristic of the PLTS cell. Middle trace shows rebound LTS on recovery from hyperpolarization. Lower shows responses to hyper- and de-polarization current injection. Note the difference between these traces and those in (bi) and (bii). **(cii)** Single spike in a PLTS neuron elicits a large IPSC in a postsynaptic MSN.

tions. Epochs of firing are interspersed with periods of silence that are characterized by subthreshold membrane oscillations (Figure 2) [6,7,16,17]. The oscillations are voltage and sodium dependent and are responsible for triggering the intermittent spike bursts [17], which are likely to be the most common pattern of firing *in vivo* [14].

Parvalbumin-containing interneurons receive a powerful excitatory input from cortex that is different in character from the input received by MSNs [18•], GABAergic input from MSNs and other parvalbumin-containing neurons including neurons of the GPe [19,20]. They also receive a cholinergic input [21].

The predominant synaptic target of the FS interneuron identified by parvalbumin immunostaining, single cell filling or electrophysiological analysis, is the MSN [14,22,23]. Single spikes in FS interneurons produce large

unitary inhibitory postsynaptic potentials (IPSPs) in perithreshold MSNs of ~1 mV, and short bursts of action potentials in FS interneurons lead to IPSPs that can summate up to 7 mV in MSNs. The IPSP is strong enough to delay or completely suppress firing in MSNs [7], and is much larger and more powerful at the soma than the IPSP produced by the axon collaterals of the MSN [12••,24].

Neuropeptide Y, nitric oxide synthase and somatostatin interneurons

A second neostriatal GABAergic interneuron was distinguished by the absence of parvalbumin but the presence of NPY, somatostatin, nitric oxide synthase and NADPH diaphorase [25,26]. These medium sized neurons comprise 0.8% of neostriatal cells in rats [3•] and have the least dense axonal arborization of any of the neostriatal interneurons [6]. The neurons receive both cholinergic and dopaminergic input [9] and are characterized electrophysiologically by low threshold calcium spikes (LTS) and a prolonged calcium dependent plateau potential (Figure 2c). They have therefore been termed persistent and low-threshold spike (PLTS) neurons [5,6]. Single action potentials in the cells produce large inhibitory postsynaptic currents (IPSCs) in MSNs (Figure 2c). Release of nitric oxide from these neurons might also play a part in regulating corticostriatal synaptic plasticity [27].

Calretinin interneurons

The third GABAergic interneuron colocalizes the calcium binding protein calretinin. These neurons make up 0.8% of neostriatal neurons in rats [3•]. They are of medium size, possess few, aspiny, infrequently branching dendrites and are relatively sparse in the caudal aspects of the neostriatum [28]. There are no electrophysiological data from intracellularly labeled cells identified as calretinin-positive, thus their electrophysiological profile remains unknown. However, in whole cell recordings, Koós and Tepper [7] encountered several examples of a neostriatal cell type not previously described. This neuron was similar in some respects to the PLTS neuron described by Kawaguchi [6], as it fired prominent LTSs; however, it lacked the prolonged depolarizations of the PLTS neuron and expressed a different spike morphology (Figure 2b). Similar to the FS interneuron, these neurons exert powerful monosynaptic inhibition on MSNs that can delay or block spiking (Figure 2b). Given the differences between this neuron and the more frequently reported PLTS interneuron, it is not unreasonable to wonder if these physiological characteristics could be those of the calretinin-positive interneuron.

Functional roles of neostriatal GABAergic interneurons

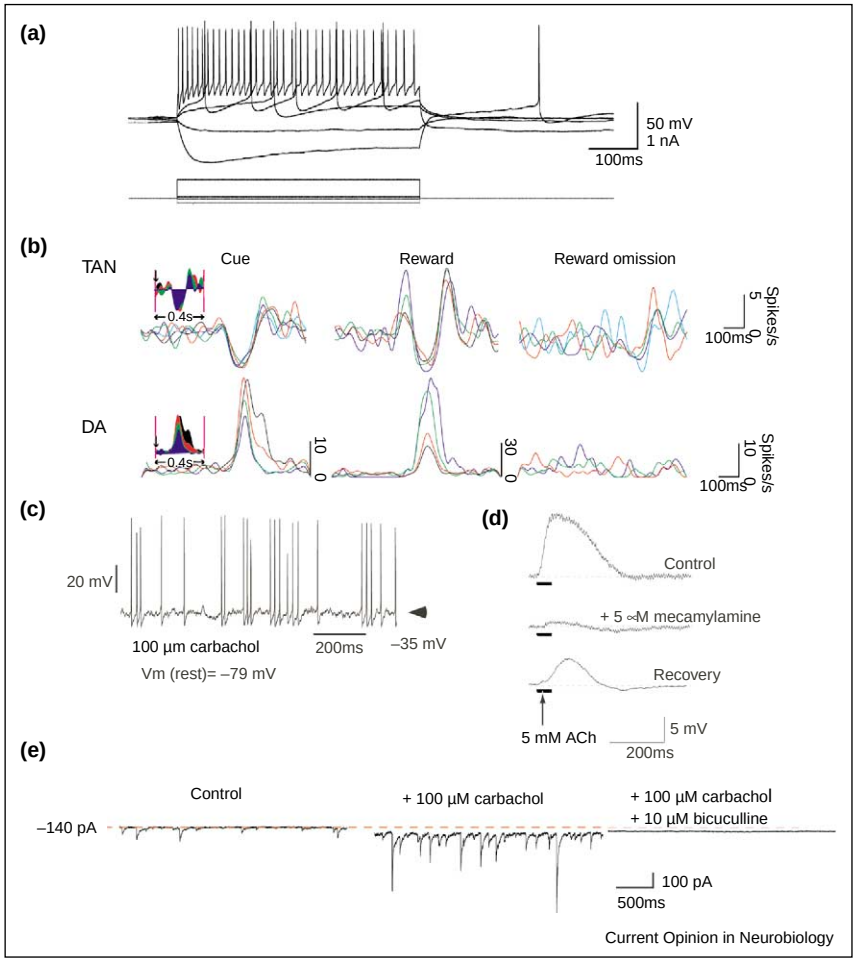
Each of the neostriatal GABAergic interneurons potently and monosynaptically inhibits MSNs, producing large IPSPs and/or IPSCs recordable at the soma (Figure 2). Given the differences in the physiology of the interneurons, it is likely that each subserves a slightly different role. By contrast, although the intrinsic mechanisms differ, each of the defined physiological subtypes can fire short bursts of action potentials that lead to fast and powerful suppression of spiking in MSNs. Thus, it now appears that the most powerful GABAergic modulation of spike timing in the output neurons is effected by the GABAergic interneurons. The spiny cell axon collaterals, although more numerous than interneuronal axons, do not produce strong effects at the soma [12••,29•] and probably function more to modulate local dendritic events [30,31]. Some of the key issues that remain to be elucidated are the circumstances under which the different populations of GABA interneurons fire and the precise timing of this firing in relation to activity in MSNs and corticostriatal afferents.

Cholinergic interneurons

The largest neurons in the neostriatum, with a somatic diameter that can be in excess of 40 μm, are the giant aspiny neurons. They were first identified as interneurons by Kölliker (see [32] for discussion of Kölliker's work), and are now known to be cholinergic interneurons on the basis of choline acetyltransferase immunolabeling [33]. They comprise only ~0.3% of the neurons in the rat neostriatum [3•], although, similar to the GABAergic interneurons they are likely to be present in greater abundance in humans and other primates [4]. The cholinergic interneurons emit 3–6 thick, smooth or sparsely spiny primary dendrites that branch modestly to form a dendritic arborization up to a millimeter in diameter [34]. Excitatory afferents arise from cortex and thalamus [35,36•]. The neurons also receive inhibitory GABAergic inputs from spiny neurons as well as dopaminergic inputs from the substantia nigra [9]. The dense and widespread local axon collateral plexus of the cholinergic interneuron is largely restricted to the neostriatal matrix where it primarily targets the MSNs [9,37], although GABAergic interneurons also receive cholinergic synaptic inputs [15••,21].

In vivo intracellular recordings show that the cholinergic interneurons typically fire slowly and regularly, with action potentials of long duration and lengthy and slow spike afterhyperpolarizations (Figure 3) [34]. These characteristics are distinct enough from the other neostriatal neurons to enable one to distinguish these neurons from the MSNs and other interneurons *in vivo* during extracellular recordings. This characteristic pattern of activity became a synonymous descriptor for these neurons, termed TANs as an abbreviation of tonically active neurons (for review see Bennett and Wilson [38]). Although they fire most often in this tonic mode, both *in vivo* and *in vitro* the cholinergic interneuron is capable of expressing a variety of firing patterns, some of which overlap with those of the MSNs [39]. Thus, given the apparent

Figure 3



Properties of cholinergic interneurons. **(a)** Representative whole cell current clamp recording of a large aspiny neostriatal neuron in a rat neostriatal slice. Note the regular, tonic firing, large, slow spike afterhyperpolarizations, and the prominent sag in response to hyperpolarizing-current injection owing to activation of hyperpolarization-activated cation current (I_h). **(b)** Responses of a TAN and a nigral dopaminergic neuron to a visual cue predicting a reward (left), the presentation of the reward (middle) and the omission of a predicted reward showing the coincidence of the pause response in the TAN and the increased firing in the dopaminergic neuron. **(c)** FS interneuron is strongly depolarized and induced to fire by bath application of carbachol in a neostriatal slice. **(d)** Local pressure application of acetylcholine (ACh) strongly depolarizes another FS interneuron and the response is blocked by the nicotinic antagonist, mecamylamine. **(e)** Voltage clamp recordings from a MSN showing small, infrequent spontaneous IPSCs (left). Bath application of carbachol greatly increases the frequency and amplitude of the IPSCs (middle) that are blocked by bicuculline, showing that they are $GABA_A$ mediated. Thus, in addition to acting directly on MSNs through postsynaptic muscarinic receptors, ACh can mediate fast inhibition of MSNs through its excitation of FS interneurons. (b) Is modified from Morris *et al*. [46•] with permission. (c) Modified from Koós and Tepper [15••] with permission.

ease with which TANs can be recorded in both primates and rodents (despite their small number), it is possible that not all TANs are cholinergic interneurons. Conversely, all rat neostriatal cholinergic interneurons might not always fire tonically [38].

Functional role of the cholinergic interneurons

In primates, TANs were initially shown to respond to reward [40]. Subsequently, they were shown to acquire a stereotypical, synchronous pause of ~200 ms in their activity in response to visual or auditory cues that predict saliency or reward in operant tasks [41]. These responses are crucially dependent upon input from both the nigrostriatal dopaminergic projections and the thalamostriatal projections, as the pause response disappears if either pathway is interrupted [36•,42]. These responses differ between TANs in the putamen and those in the caudate. For example, the putamen TANs respond more frequently to the GO signal for lever release, whereas the caudate TANs seem more responsive to associative instructions [43,44]. This is consistent with a motor-related function for putamen interneurons and a associative-cognitive function for caudate interneurons. Thus, the TANs, along with the dopaminergic nigrostriatal

neurons that respond to similar stimuli with a co-incident short increase in activity (Figure 3b) [45], have been proposed to participate in the modulation of the activity of MSNs and hence, the functioning of the neostriatal circuits that underlie reward-based learning and/or motivated behavior [44,46•].

Interneurons as sites of action of neuromodulators

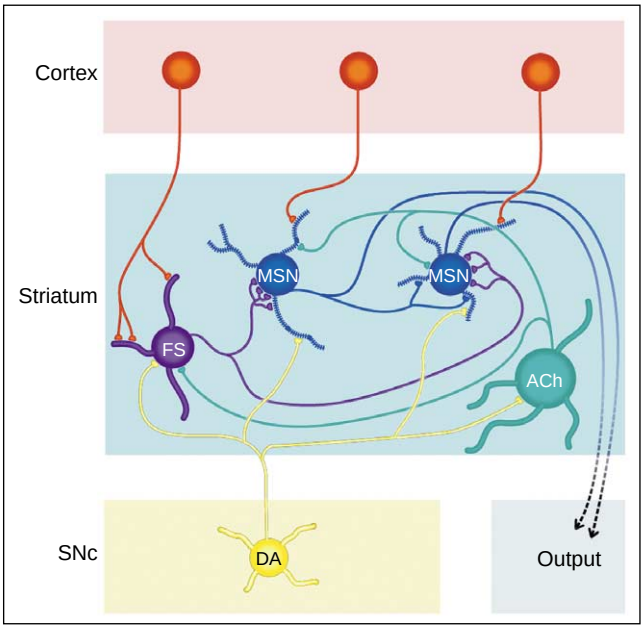
GABAergic and cholinergic interneurons comprise an important locus of action for the neurotransmitters and/or neuromodulators, dopamine and acetylcholine in the neostriatum [47•,48,49•]. Dopamine and acetylcholine do not produce frank excitation or inhibition by direct depolarization or hyperpolarization of the membrane of MSNs, and their effects are largely restricted to neuromodulatory actions on voltage-gated sodium, potassium and calcium channels [49•,50,51]. By contrast, dopamine directly depolarizes and excites both FS and LTS interneurons through activation of a postsynaptic D1-like receptor [52,53], probably a D_5 receptor [47•]. Dopamine also affects GABAergic transmission presynaptically, however, these effects are somewhat more controversial and contradictory than their postsynaptic effects on neostriatal interneurons [20]. Overall, the most cohesive picture suggests a D2-like dopamine receptor-mediated presynaptic inhibition of GABA transmission in the neostriatum [47•,54].

Similar to dopamine, acetylcholine can act as a fast neurotransmitter on GABAergic interneurons. Acetylcholine or carbachol potently depolarizes and excites FS interneurons through activation of a non-desensitizing nicotinic receptor [15••]. This effect is particularly interesting as it might represent one way for the stimulus-dependent pause of cholinergic neurons to be rapidly transduced to the MSNs. At the same time, the FS-spiny cell synapse is strongly inhibited by acetylcholine that acts upon on a presynaptic pirenzapine-sensitive muscarinic receptor (Figure 3c,d) [15••].

Conclusions

The neostriatum, similar to the hippocampus and neocortex, possesses a variety of GABAergic interneurons defined on the basis of their chemical and physiological phenotypes (Figure 4). Each of these is in a position to influence both the timing and the pattern of firing of the principal neuron in the neostriatum. Their precise roles remain to be elucidated but will depend upon their afferent input, the localization of their terminals on MSNs and when they fire in relation to MSN activity. Unlike the hippocampus and neocortex, the neostriatum also contains a prominent population of cholinergic interneurons the role of which is modulatory and underlies, in part, the plasticity of excitatory synapses and neostriatal networks that is exhibited during context-dependent behaviour.

Figure 4



The microcircuit of the neostriatum. The canonical microcircuit of the neostriatum consists of two MSNs, a FS GABAergic interneuron, a cholinergic interneuron and inputs from the cortex and the dopamine neurons of the substantia nigra pars compacta (SNc). FS interneurons are involved in the control of spike timing in MSNs, whereas by contrast the cholinergic interneurons have a more subtle modulatory influence on the activity of MSN. The interneurons themselves are targets of the dopaminergic input to the neostriatum and the activity of FS interneurons is also influenced by the cholinergic interneuron. Figure from [2] with permission.

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