Cholinergic modulation of striatal microcircuits

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Abstract
The purpose of this review is to bridge the gap between earlier literature on striatal cholinergic interneurons and mechanisms of microcircuit interaction demonstrated with the use of newly available tools. It is well known that the main source of the high level of acetylcholine in the striatum, compared to other brain regions, is the cholinergic interneurons. These interneurons provide an extensive local innervation that suggests they may be a key modulator of striatal microcircuits. Supporting this idea requires the consideration of functional properties of these interneurons, their influence on medium spiny neurons, other interneurons, and interactions with other synaptic regulators. Here, we underline the effects of intrastralial and extrastriatal afferents onto cholinergic interneurons and discuss the activation of pre- and postsynaptic muscarinic and nicotinic receptors that participate in the modulation of intrastriatal neuronal interactions. We further address recent findings about corelease of other transmitters in cholinergic interneurons and actions of these interneurons in striosome and matrix compartments. In addition, we summarize recent evidence on acetylcholine-mediated striatal synaptic plasticity and propose roles for cholinergic interneurons in normal striatal physiology. A short examination of their role in neurological disorders such as Parkinson’s, Huntington’s, and Tourette’s pathologies and dystonia is also included.

Introduction
Cholinergic interneurons (ChIs) contribute to give striatum its place among structures with the highest levels of acetylcholine (ACh) in the brain (Zhou et al., 2002). Without a doubt, these interneurons exert a strong and complex modulation of striatal microcircuits. These large interneurons form synapses with medium size spiny neurons (MSNs) and other numerous smaller GABAergic interneurons of which there are 10 subtypes and counting (Tepper & Koos et al., 2017). ChIs can be identified by their electrophysiological characteristics (Goldberg & Wilson et al., 2017) and by immunoreactivity of their enzymatic profile (Mesulam et al., 1984). The morphology of ChIs, the richness of their synaptic contacts as well as the expression of a variety of receptors has attracted the attention of neuroscientists. More than 1000 research articles on ChIs, published during the last two decades, have enriched the understanding of their function.

Striatal acetylcholine receptors
An early study indicated that destroying possible afferent pathways to striatum ‘cortex, thalamus, globus pallidus or ventrotegmental area’ did not affect the activity of choline acetylase nor acetylcholinesterase (AChE) or the histochemical staining within the nucleus (McGeer et al., 1971; Lynch et al., 1972). This led to the proposal that interneurons were the main intrinsic source of striatal ACh. We now know of external sources of ACh that arrives from the pedunculopontine and laterodorsal tegmental nuclei (Dautan et al., 2014), but the main source of striatal ACh still is the spontaneously active ChIs (Kitaï & Surmeier, 1993; Pisani et al., 2007; English et al., 2012; Goldberg et al., 2012). At the cellular level, ACh exerts its actions through the activation of two families of receptors, muscarinic (mAChR) and nicotinic (nAChR). The mAChRs belong to the G-protein-coupled receptor (GPCR) family (Caulfield, 1993). These receptors are divided into group I (M1, M3, and M5) and group II (M2 and M4). Group I receptors are coupled to Gq11 proteins via α subunits that activate protein kinase C (PKC) and phospholipase C (PLC) leading to the production of inositol triphosphate and diacylglycerol that results in an increase in intracellular calcium. Group I receptors are found in striatal MSNs of both the direct (dMSN) and indirect (iMSN) pathways. In MSNs, these receptors are postsynaptically in dendritic spine necks and extrasynaptically located (Hersch & Levey, 1995; Yan et al., 2001). Group II receptors are coupled to Gαo proteins, inhibit adenylyl cyclase (AC) activity and close voltage-activated calcium (CaV) CaV2.2 channels while opening inwardly rectifying potassium channels (Kir3) following GPCR activation (Caulfield, 1993; Nathanson, 2000; Eglen, 2006; Haga, 2013). Muscarinic M2 receptors act as autoreceptors on ChIs and are located mostly extrasynaptically suggesting a role in volume neurotransmission (Bernard et al., 1998).
M₂ receptors act as inhibitory heteroreceptors on striatal neuropeptide Y-somatostatin expressing (NPY-SOM) GABAergic interneurons and on corticostriatal glutamatergic terminals (Hersch et al., 1994; Bernard et al., 1998).

The high degree of similarity of the orthosteric ligand-binding site in all five types of muscarinic receptors is the main reason it has been difficult to identify subtype-selective ligands (Eglen, 2006; Dencker et al., 2012) and a reason why the dissection of specific cholinergic effects on neuronal activity and release has been difficult to achieve. Nevertheless, new pharmacological tools such as the highly specific antagonist peptide isolated from the green mamba snake venom are now being used (Jerusalinsky et al., 2000; Karlsson et al., 2000; Rowan & Harvey, 2011; Servent et al., 2011). Similarly, positive allosteric modulators and allosteric agonists are becoming promising tools, even providing some therapeutic potential for several central nervous system diseases (Digby et al., 2010; Bock et al., 2017).

Acetylcholine release is regulated by presynaptically located hetero- and autoreceptors. Muscarinic autoreceptors M₂/M₄ (Hersch et al., 1994; Ding et al., 2006), via direct G_{lo}ₐₐₐₐ-mediated inhibition of presynaptic CaV₂.2 and CaV₂.1 channels linked to exocytosis. Another presynaptic control of release is regulated by the M₄ auto- and heteroreceptor activation of the barium-sensitive potassium currents carried through Kᵥ3 potassium channels in Chls (Yan & Surmeier, 1996; Ding et al., 2006) and corticostriatal terminals (Calabresi et al., 1998a).

Nicotinic (nAChR) receptors are pentameric ligand-gated ion channels that consist of either heteromeric subunit combinations of α subunits (α2-10) and β subunits (β2-4; Exley & Cragg, 2008; Gotti et al., 2009). The most common types of nAChR in striatum are the homomeric α subunits (α7) and αβ*2*. The αβ*2* subcomposition acts as an autoreceptor in Chls, as a postsynaptic heteroreceptor in GABAergic interneurons and as a presynaptic heteroreceptor in GABA, serotonin, and dopamine axon terminals (Eskow Jaunarajs et al., 2015). The reported subunit composition on GABAergic interneurons is proposed to have the α4β2* and α4α5β2* subtypes (Eskow Jaunarajs et al., 2015).

Characteristics of cholinergic interneurons

Anatomical

In general, anatomical studies have revealed that Chls immunoreactive for choline acetyltransferase (ChAT), with a large multipolar cell body of 23–50 μm in diameter and widespread aspiny dendrites that arborize up to 1 mm (Kimura et al., 1981; Bolam et al., 1984b; Wilson et al., 1990) with 3–6 primary dendrites that extend in a radial pattern (Doig et al., 2014). Electron microscopy of rat striatal tissue performed by Doig et al., 2010, 2014 indicates that Chls receive a prominent inhibitory input and that most of excitatory input is from thalamic afferents; a single Chl receives 8450 ± 694 connections of which the majority are symmetric. Moreover, there are approximately three times more vesicular glutamate transporter type 2 (vGLUT2)-positive thalamic terminals than vesicular glutamate transporter type 1 (vGLUT1)-positive cortical terminals in an individual Chl (Doig et al., 2014). It is important to mention that boutons expressing vGLUT1 and vGLUT2 are the highest in the dorsal one-third in the rat striatum (Wouterlood et al., 2012). However, since vGLUT2 is also expressed in some dopamine terminals in ventral striatum (Stuber et al., 2010), it is harder to isolate thalamic inputs.

In spite of the comparative small number of Chls (Lehmann et al., 1979; Bolam et al., 1984a; Bennett & Wilson, 1999; Bennett et al., 2000; Kreitzer, 2009; Girasole & Nelson, 2015), their long and many branched axons allow a widespread release of ACh (Bolam et al., 1984a; Contant et al., 1996; Calabresi et al., 2000). Initially, Chls were described as homogeneously dispersed; however, in mice, a greater concentration of Chls in the dorsomedial compared to ventrolateral areas was observed following a stereological reconstruction (Matamales et al., 2016). A correlation between this distribution and the presence of vGLUT1 and vGLUT2 contribute to a possible segregation of function.

Similar to dopaminergic axon varicosities, cholinergic ones, form few structurally defined synaptic connections, therefore favoring a slow cholinergic volume transmission (Descaries et al., 1997; Zhou et al., 2001; Aznavour et al., 2003; Coppola et al., 2016; Ovespian et al., 2016; Dunant & Gisiger, 2017). The integration of a striatal cholinergic tone established by volume and synaptic transmission is considered to act within neuronal networks to change their balance of activity to possibly initiate neuronal ensembles with specific functions (Fuxe et al., 2012).

Electrophysiological

The spontaneously active firing characteristic of Chls ensures the basal cholinergic tone (Kawaguchi et al., 1995; Lee et al., 1998; Wilson, 2005). These neurons have high input resistance, a broad action potential duration (Wilson et al., 1990; Tubert et al., 2016), a depolarized, and often changing, resting membrane potential that is usually fixed at −60 mV with a low holding current (Threlfell et al., 2012). These interneurons also called ‘tonically active neurons or TANs’ and ‘autonomous pacemakers’ are able to produce action potentials at 2–10 Hz in the absence of synaptic input (Bolam et al., 1984a; Wilson et al., 1990). Behind this tonic or pacemaking mechanism, it is an interplay of several ionic conductances (Wilson et al., 1990; Pisani et al., 2007). Their pacemaker cycle begins with an initial tetrodotoxin-sensitive sodium current-induced depolarization that leads to calcium influx from CaV₂.2 channels. This first calcium influx in turn activates the calcium and voltage-activated big potassium currents (BK). This potassium influx contributes to membrane repolarization and the activation of the CaV₂.2 current that, in turn, activates the small-conductance calcium-activated potassium current (SK). This second potassium current induces a medium duration after-hyperpolarization (mAHP) of 100–200 ms that defines the spike pattern and spike width (Kawaguchi, 1992; Bennett et al., 2000; Goldberg & Wilson, 2005). A decrease in intracellular calcium levels reduces the SK current and consequently the mAHP. The Iₖᵣ inward cyclic nucleotide-gated cation current (HCN) redepolarizes the membrane to about −60 mV, with a resulting inactivation of the outward potassium A-type Kᵥ₄ current. At the end of the cycle, depolarization is slowed down, the persistent sodium current is activated, and the threshold for an action potential is reached, beginning a new sequence (Bennett et al., 2000; Goldberg & Wilson, 2005; Deng et al., 2007; Pisani et al., 2007).

Another feature of Chls is a long pause in the tonic firing that follows bursts of action potentials. Their intrinsic properties allow Chls to fire in regular, irregular, and in burst fashion interspersed with long pauses (Bennett et al., 2000; Goldberg & Wilson, 2005, 2017; Wilson, 2005; Sanchez et al., 2011). During a burst, a subthreshold accumulation of calcium through CaV₁,2 channels recruits an additional potassium current that, in turn, produces a long-lasting (several seconds) hyperpolarization (sAHP) (Wilson & Goldberg, 2006; Tubert et al., 2016).

It is considered that the delta frequency activity of these interneurons results from the combination of synaptic inputs and intrinsic mechanisms (Beatty et al., 2015). A muscarinic-dependent coherence between motor cortex and Chls can be established following optogenetic stimulation at both beta and low gamma frequencies.
A key intrastriatal microcircuit is formed by connections between MSNs, interneurons, and ChIs. In general, 60% of the total intrastriatal synaptic contacts are GABAergic and somatodendritic (Gonzales et al., 2013; Gonzales & Smith, 2015). Medium size spiny neurons that release substance P and dynorphin (Bolam et al., 1986; Pickel et al., 2000; Perez et al., 2007) or enkephalin (Le Moine et al., 1994; Jobourian et al., 2005) contact and modulate ChIs. Importantly, opposite actions are described for their effects: excitatory for substance P (Aosaki & Kawaguchi, 1996; Bell et al., 1998; Perez et al., 2007; Govindaiah et al., 2010) and a powerfully inhibitory for opioid agonists (Mulder et al., 1984; Jobourian et al., 2005; Ponterio et al., 2013). Axon collaterals of MSNs contact Chls (Bolam et al., 1986; Lapper & Bolam, 1992; Bennett & Wilson, 1998; Gonzales et al., 2013; Guo et al., 2015). In rhesus monkeys, striatal output neurons of both types contact Chls (Gonzales et al., 2013); however, in rodents, substance P containing terminals of dMSNs contact Chls (Bolam et al., 1986; Martone et al., 1992). Microcircuits where Chls are connected among themselves through GABAergic interneurons can be seen when a single action potential produced in a Chl evokes nAChR-mediated polysynaptic GABA<sub>A</sub> inhibitory postsynaptic currents (Sullivan et al., 2008). Connectivity with an incidence of 9 Chls to 12 MSN has been observed following MSN optogenetic stimulation (Chuhma et al., 2011). Some interactions of Chls occur between reciprocally connected Chls (Pakhotin & Bracci, 2007) and with the GABAergic NPY-low threshold spiking subtype (Vuillet et al., 1992). It would be important to determine if striatal GABA<sub>A</sub> receptors contain the δ subunit that has been shown to be persistently active and to control presynaptic excitability in the spinal cord (Liu et al., 2017).

**Extrastriatal**

**GABAergic**

Extrastriatal GABAergic afferents arrive to striatum from three different GABAergic afferents, two from GP and one from substantia nigra par compacta (SNC) (Fig. 2; Table 2). In GP, the arky pallidal-type A (GP-TA) and the prototypic-type I (GP-TI) have been classified by electrophysiological (Mallet et al., 2008), anatomical (Bevan et al., 1998), and molecular (Mallet et al., 2012; Mastro et al., 2014; Abdi et al., 2015) techniques. The GP-TA express preproenkephalin gene and FoxP2 or Meis2 transcription factors (Abdi et al., 2015) and contact cholinergic, nitric oxide synthase (NOS) interneurons, and MSNs (Mallet et al., 2012). SNC terminals that corelease dopamine and GABA synchronically modify the activity of Chls (Chuhma et al., 2014; Straub et al., 2014), both types of MSNs, and other interneurons (Tritsch & Sabatini, 2012).

**Glutamatergic**

Presynaptic regulation of ACh release has an important function in control of the excitability in striatal microcircuits (Fig. 2). The regulation of dopamine release mediated by a glutamate-ACh link has become important, and metabotropic glutamate (mGlu) receptors are being explored as potential targets for the treatment of neurodegenerative diseases (Ribeiro, 2005). As indicated before, glutamatergic fibers from both cortex and intralaminar thalamus form asymmetric synaptic contacts on striatal Chls but with a higher proportion of synaptic contacts from thalamic inputs (Doig et al., 2014). Cortical axons contact distal striatal dendrites, and thalamic axons contact striatal somas and dendritic shafts (Lapper & Bolam, 1992). In primates, approximately 20% of synaptic connections to Chls are presumed glutamatergic and localized on the distal dendrites (Gonzales et al., 2013; Gonzales & Smith, 2015), and in rodents, the soma and proximal dendrites of Chls are the targets of glutamatergic input (Doig et al., 2014). However, both cortical and thalamic stimulation induces short latency responses in Chls and effects of the different afferent synaptic locations have been explored. Compared to responses induced by thalamic stimulation, cortical responses are less robust and attenuate if the stimulation is repeated (Doig et al., 2014). These differences could mediate the length of the pause and strength of the rebound; sustained thalamic input seems to keep cholinergic firing followed by long pauses with no rebound. Moreover, the variable intrinsic activity of Chls seems more important than the location of the afferents in the moment-to-moment variability in the size of neuronal recruitment (Kosillo et al., 2016). The section 'Influence of cholinergic interneurons within the striatal microcircuits: dopaminergic terminals' describes other experiments...
that have contributed to clarify the role of glutamate receptors selectively activated by cortical or thalamic afferents.

ChIs express postsynaptic and presynaptic ionotropic and metabotropic glutamate heteroreceptors (Testa et al., 1994; Landwehrmeyer et al., 1995; Bell et al., 2002; Deng et al., 2010). A membrane depolarization (Vorobjev et al., 2000; Cepeda et al., 2001) and modulatory actions mediated by PKC are observed in ChIs (Di Chiara et al., 1994; Calabresi et al., 1998a) following the activation of postsynaptic glutamate ionotropic receptors, that is, n-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), or kainic acid.

The presynaptic activation of these receptors on ChIs increases ACh release (Consolo et al., 1996). In striatal microcircuits, mGluRs modulate excitability and neurotransmitter release (Conn et al., 2005). The group-III member, mGlu7, is not expressed in ChIs (Pisani et al., 2002) but expressed presynaptically as autoreceptors where it decreases the probability of release and in turn postsynaptic cholinergic excitibility (Bell et al., 2002). Group-II mGlu2/3 receptors are expressed pre- and postsynaptically in ChIs (Testa et al., 1994; Bell et al., 2002). As presynaptic heteroreceptors, they decrease glutamate release with a consequent depression of excitatory postsynaptic potentials (Martella et al., 2009). The mGlu2/3 autoreceptors (and GABA_B receptors) dampen glutamate release, decrease postsynaptic excitatory responses, and can produce a transient depression (Martella et al., 2009) and long-term depression (LTD) (Kupferschmidt & Lovinger, 2015). Moreover, mGlu2/3 receptors are predominantly coupled to Gi/o proteins that mediate inhibition of AC activity and also to other cell signaling pathways involved in neuroprotection. For example, extracellular signal-regulated kinase activation attenuates rotenone toxicity on dopaminergic neurons (Ribeiro, 2005). ChIs also express group-I mGlu1/5 (Bell et al., 2002), especially in dendrites (Mitriano & Smith, 2007). The activation of mGlu1/5 receptors induces membrane depolarization (Calabresi et al., 1999b; Bell et al., 2002; Martella et al., 2009).

Dopaminergic

Dopaminergic SNC afferents exert a robust striatal influence due to their tonic spontaneous activity (1-8 Hz) and broad terminal field arborization (Prens & Parent, 2001; Schultz, 2007; Matsuda et al., 2009); a single dopamine neuron has a dense terminal field that occupies 3% of striatal volume with axonal varicosities forming synapses every 2 μm (Arbuthnott & Wickens, 2007). D2 receptors located postsynaptically on ChIs reduce autonomous firing through voltage-sensitive sodium...
To refer these selected references by no means reflect all the evidence gathered through more than 40 years of research, apologies for unintended omissions.

### Table 1. References supporting connectivity illustrated in Fig. 1

| # | From | To  | References |
|---|------|-----|-------------|
| 1 | Cortex | TH | Ibanez-Sandoval et al. (2010) |
| 2 | Cortex | FS | Bennett & Bolam (1994); Mallet et al. (2005); Fino et al. (2008) |
| 3 | Cortex | PLTS | Fino et al. (2009); Ibanez-Sandoval et al. (2011) |
| 4 | Cortex | ChIs | Lapper & Bolam (1992); Ding et al. (2010); Doig et al. (2014); Guo et al. (2015) |
| 5 | Cortex | NPY/NGF | Ibanez-Sandoval et al. (2011); Assous et al. (2017) |
| 6 | Cortex | MSN | Someggi et al. (1981); Barral et al. (1999); Ding et al. (2010); Doig et al. (2010); Huerta-Ocampo et al. (2014) |
| 7 | SNc | ChIs | Chuhma et al. (2014), Straub et al. (2014) |
| 8 | Thalamus | MSN | Ding et al. (2010); Doig et al. (2010); Dube et al. (1988); Sadikot et al. (1992); Huerta-Ocampo et al. (2014) |
| 9 | Thalamus | TH | Assous et al. (2017) |
| 10 | Thalamus | FS | Kita (1993) |
| 11 | Thalamus | ChIs | Lapper & Bolam (1992); Ding et al. (2010); Doig et al. (2010) |
| 12 | Thalamus | NPY/NGF | Assous et al. (2017) |
| 13 | ChIs | MSN | Bolam et al. (1986); Bernard et al. (1992); Lapper & Bolam (1992); Hersch & Levey (1995); Bennett & Wilson (1998); Alcantara et al. (2001); Yan et al. (2001); Chuhma et al. (2011); Goldberg & Reynolds (2011); Goldberg et al. (2012); Gonzales et al. (2013); Guo et al. (2015); Phelps et al. (1985); Izzo & Bolam (1988) |
| 14 | TH | MSN | Ibanez-Sandoval et al. (2010); Freund et al. (1984) |
| 15 | TH | PLTS | Assous et al. (2017) |
| 16 | FS | MSN | Kita (1993); Koos & Tepper (1999); Gittis et al. (2010); Bennett & Bolam (1994) |
| 17 | FS | FS | Koos & Tepper (1999); Gittis et al. (2010) |
| 18 | FS | PLTS | Gittis et al. (2010); Szydlowski et al. (2013) |
| 19 | PLTS | MSN | Kawaguchi (1993); Gittis et al. (2010) |
| 20 | PLTS | ChIs | Elghaba et al. (2016); Straub et al. (2016) |
| 21 | NPY/NGF | ChIs | Assous et al. (2017) |
| 22 | NPY/NGF | MSN | English et al. (2012) |
| 23 | MSN | ChIs | Mulder et al. (1984); Bolam et al. (1986); Le Moine et al. (1994); Aosaki & Kawaguchi (1996); Bell et al. (1998); Pickel et al. (2000); Jabourian et al. (2005); Perez et al. (2007); Govindiaaah et al. (2010); Gonzales et al. (2013); Porteiro et al. (2013); Gonzales & Smith (2015) |
| 24 | MSN | MSN | Wilson & Groves (1980); Taverna et al. (2008); Burke et al. (2017) |
| 25 | ChIs | PLTS | Vuillet et al. (1992); Elghaba et al. (2016) |
| 26 | ChIs | FS | Chang & Kita (1992); Koos & Tepper (2002); English et al. (2012) |
| 27 | ChIs | NPY/NGF | Assous et al. (2017) |
| 28 | ChIs | FA | Faust et al. (2015); Faust et al. (2016) |
| 29 | ChIs | Dopamine terminals | Jones et al. (2001); Zoli et al. (2002); Salminen et al. (2004); Exley & Cragg (2008); Gotti et al. (2009); Threlfell et al. (2012); Gonzales & Smith (2015) |
| 30 | ChIs | Autoreceptors | Ding et al. (2006); Pakhotin & Bracci (2007) |
| 31 | FA | MSN | Faust et al. (2015); Faust et al. (2016) |

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channels (Maurice et al., 2004; Ding et al., 2010) or hyperpolarization-activated HCN currents (Deng et al., 2007).

The dopamine–ACh interaction is mediated by D₂ and D₁/5 receptors. D₁/D₅ subtypes are expressed in dendrites (Bergson et al., 1995; Yan & Surmeier, 1997; Yan et al., 1997) and D₂ receptors are located in soma, dendrites, and axons (Alcantara et al., 2003). The activation of D½/D₅ receptors in slice preparations enhances ChIs excitability (Centonze et al., 2003b; Ding et al., 2011). Apparently, a cAMP-dependent mechanism allows the closure of potassium channels and promotes the opening of nonselective cation channels (Aosaki et al., 1998). Cholinergic receptors expressed in the dopaminergic axon terminal fields modulate dopamine release; nAChRs increase dopamine release (Imperato et al., 1986; Calabresi et al., 1989) whereas presynaptic M₄ mAChRs reduce it (Foster et al., 2014). At the somatodendritic level, both nAChRs and M₄ mAChR increase spontaneous activity (Foster et al., 2014). Other effects on dopamine release mediated by other mAChR subtypes appear related to the stimulation of receptors located in non-dopaminergic neurons (Zhang et al., 2002a).

Using optogenetic stimulation of dopaminergic terminals in vitro, a biphasic modulatory action on ChIs was similar to the pause-rebound response of putative Chls recorded in vivo. This consisted in a decrease in spike rate and a delayed excitatory response that peaked 0.4–0.6 s after stimulation (Straub et al., 2014).

Although presynaptic D₂ receptors on Chls limit ACh release through voltage-gated Cav2 channels, an important control of downstream processes is also provided by the regulators of G-protein signals (RGS) (Anderson et al., 2009). Ding et al. (2006) observed that following dopamine depletion, M₄ rather than D₂ receptors alter signaling in Chls. In the absence of dopamine, M₄ autoreceptors suffer the attenuation of Ca₂⁺ channel opening and pacemaking by upregulation of the expression of RGS9. Consistently, significant decreases of RGS9 protein concentration and mRNA were observed in dopamine depleted animals following L-DOPA treatment (Yin et al., 2011).

**Other afferents**

Axon terminals releasing serotonin, histamine, or adenosine are known to modulate the activity of Chls. Serotonin afferents from the dorsal raphe nucleus (Miguelez et al., 2014) induce a direct excitatory effect on Chls through 5-HT₂ (Blomeley & Bracci, 2005) and 5-HT₄ receptors (Bonci et al., 2007). Similarly, histamine-containing afferents from the hypothalamic tuberomammillary nucleus (Bolam & Ellender, 2016) depolarize Chls by the activation of GPCR histamine receptor type 1 (H₁) (Bell et al., 2000). In nucleus accumbens, the activation of Chl H₃ receptors decreases their spontaneous activity, but this effect can only be observed in accumbens since striatum does not seem to express this histamine receptor subtype (Varaschin et al., 2018). The purine nucleoside, adenosine, is released by neurons and glia. Of the four subtypes of GPCR adenosine receptors in brain, the A₂A subtype is mostly expressed in striatum (Dunwiddie & Masino,
Striatal A1 and A2A receptors in ChI are potent regulators of striatal ACh release with opposite effects (Preston et al., 2000; Song et al., 2000). Concomitant dopamine D2 and A2A receptor stimulation inhibits ACh release (Song & Haber, 2000; Tozzi et al., 2011). Moreover, adenosine reverses N-type calcium currents in ChIs and both MSNs through membrane G-protein pathways (Song et al., 2000; Hernandez-Gonzalez et al., 2014). In spite of their relative small number, ChIs within the striatal microcircuits form enmeshed axonal projections with an extensive neuromodulatory presynaptic and postsynaptic effect (Descaries et al., 1997; Descaries & Mechawar, 2000) and most likely, interact with all neuronal elements through synaptic and volume transmission (Threlfell & Cragg, 2011). The modulation of striatal microcircuits by ChIs is exemplified in studies involving neuronal excitability and neurotransmitter release (Figs 2 and 3).

Influence of cholinergic interneurons within striatal microcircuits

In spite of their relative small number, ChIs within the striatal microcircuits form enmeshed axonal projections with an extensive

Medium spiny neurons

ChIs synapse onto dendritic spines (Hersch & Levey, 1995; Alcantara et al., 2001) of iMSN and dMSNs (Izzo & Bolam, 1988; Bernard et al., 1992; Yan et al., 2001; Goldberg et al., 2012). In electrophysiologically identified MSNs, ACh evokes complex
excitatory actions by direct modulation of several ionic currents, mainly potassium, sodium, and calcium (Pineda et al., 1995; Perez-Rosello et al., 2005; Shen et al., 2007; Carrillo-Reid et al., 2009). Both dMSNs and iMSNs express M1 receptors, and their activation increases neuronal excitability by the enhancement of the persistent sodium conductance and by directly or indirectly depressing potassium currents (Akins et al., 1990; Galarraga et al., 1999; Figueroa et al., 2002; Perez-Rosello et al., 2005; Shen et al., 2005, 2007; Carrillo-Reid et al., 2009; Goldberg et al., 2012; Perez-Ramirez et al., 2015). Both M1, M4 receptors are expressed in dMSNs (Santigo & Potter, 2001; Yan et al., 2001; Goldberg et al., 2012), and the activation of M4 with muscarinic increases MSN excitability by enhancing Cao1 channels (Hernandez-Flores et al., 2015).

A strong depolarization induced by glutamatergic striatal afferents triggers a postsynaptic release of endocannabinoids (eCB). CB1 receptors are one of the most abundantGPCRs in the central nervous system and are located at excitatory and inhibitory presynaptic and axonal compartments. CB2 receptors are primarily localized in microglia (Kendall & Yudowski, 2016). CB1 receptors are coupled to pertussis toxin-sensitive G110 type G-proteins, and their striatal activation results in a presynaptic long-term depression in corticostriatal synapses (Adermark & Lovinger, 2007).

Chls are also important regulators of striatal eCB. ACh produces an indirect modulatory effect in the regulation of striatal plasticity through the eCB system (Oldenburg & Ding, 2011). At inhibitory synapses, M1 agonist reduces postsynaptic Cao1,3 currents that, in turn, decrease eCB production and activation of presynaptic CB1R, which may be an important source of the increased activity in striatum in the absence of dopamine when such inhibition would be removed. The symbol code depicts the receptor types and their location.

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### Table 2. References supporting connectivity illustrated in Fig. 2

| Letter | References |
|--------|------------|
| a      | Hersch et al. (1994); Testa et al. (1994); Calabresi et al. (1998c); Hernandez-Echeagaray et al. (1998); Barral et al. (1999); Bell et al. (2002); Pisani et al. (2002); Conn et al. (2005); Ribeiro (2005); Pakhotin & Bracci (2007); Martella et al. (2009); Campos et al. (2010); Ding et al. (2010); Atwood et al. (2014); Pancani et al. (2014); Kupferschmidt & Lovinger (2015); Shen et al. (2015); Banerjee et al. (2016); Howe et al. (2016) |
| b      | Testa et al. (1994); Bell et al. (2002); Martella et al. (2009); Johnson et al. (2017); Pisani et al. (2002); Conn et al. (2005); Ding et al. (2010); Atwood et al. (2014); Ribeiro et al. (2017) |
| c      | Di Chiara et al. (1994); Consolo et al. (1996); Calabresi et al. (1998b); Vorobjev et al. (2000); Cepeda et al. (2001); Deng et al. (2010); Kosiol et al. (2016) |
| d      | Calabresi et al. (1998a); Calabresi et al. (1999a) Bell et al. (2002); Conn et al. (2005); Mitran & Smith (2007); Ribeiro et al. (2017) |
| e      | Hersch et al. (1994); Yan & Surmeier (1996); Bernard et al. (1998); Azam et al. (2003); Ding et al. (2006); Eskow Januarajs et al. (2015) |
| f      | Yan et al. (1997); Bennett & Wilson (1998) |
| g      | Bernard et al. (1998); Sullivan et al. (2008); English et al. (2012); Eskow Januarajs et al. (2015); Elghaba et al. (2016); Straub et al. (2016); Assous et al. (2017) |
| h      | Weiner et al. (1990); Jones et al. (2001); Zhou et al. (2001); Zoli et al. (2002); Salminen et al. (2004); Gotti et al. (2009); Livingstone & Wonnacott (2014); Chuham et al. (2014); Foster et al. (2014); Straub et al. (2014); Wang et al. (2014); Gonzales & Smith (2015); Howe et al. (2016); Garcao et al. (2014) |
| i      | Richfield et al. (1989); Bergson et al. (1995); Yan et al. (1997); Yan & Surmeier (1997); Aosaki et al. (1998); Alcantara et al. (2003); Centonze et al. (2003a); Cabrera-Vera et al. (2004); Maurice et al. (2004); Ding et al. (2006); Dang et al. (2007); Ding et al. (2010); Ding et al. (2011) |
| j      | Bernard et al. (1992); Hersch et al. (1994); Santiago & Potter (2001); Yan et al. (2001); Perez-Rosello et al. (2005); Hernandez-Flores et al. (2015) |

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The interrelation between MSNs, glutamatergic cortical afferents, ChIs, and presynaptic action on dopamine terminals opens deliberation as to whether other receptors located in these microcircuits have a direct or indirect effect on MSNs (see Fig. 3).

GABAergic interneurons

Symmetrical synapses between labeled MSNs and interneurons are observed in striatum (Bennett & Bolam, 1994). GABAergic interneurons may not only be influenced by cortical or thalamic inputs but also by local ChIs. For example, excitatory activation of GABAergic interneurons by nAChR are frequently reported (Sullivan et al., 2008; English et al., 2012; Luo et al., 2013; Ibanez-Sandoval et al., 2015; Munoz-Manchado et al., 2016).

Within striatal microcircuits, there is a neuronal chain that follows glutamatergic input to Chls, then inputs to NPY-NGF interneurons, and finally GABAergic input to MSNs evidenced in vitro following multicellular recordings and calcium imaging. The activation of nAChRs on GABAergic interneurons induces a global decrease in neuronal activity indicating a general activation of inhibitory GABAergic interneurons (Plata et al., 2013). Similarly following synchronized activation of Chls, the GABAergic NPY-NGF subtype produces the inhibition of MSNs mediated by Chl to GABAergic interneuronal synapses and then to MSN (Faust et al., 2015, 2016). The recurrent inhibition of Chls is sensitive to nicotinic antagonists therefore not mediated by the GABAergic interneuron (Sullivan et al., 2008; English et al., 2012). Optogenetic activation of glutamatergic thalamic afferents to Chls provides a nicotinic excitatory input to NPY-NGF interneurons that in turn modulate MSN activity (Assous et al., 2017). Within this neuronal chain, it is still unknown if other interneurons such as the FA subtype also participate.

Additionally, persistent low-threshold spiking (PLTS) interneurons are highly excited by cortical afferents (Assous et al., 2017) and are directly and indirectly modulated by both nACh and mACh receptors. The amplitude of striatal intracellular responses mediated by GABA decreases in the presence of muscarine and ACh (Sugita et al., 1991).

A mutual excitatory interaction exits between Chls and PLTS: Chls acting on nAChR directly excite PLTS interneurons and indirectly through mAChR on unidentified GABAergic terminals. The net effect of a tonic cholinergic action on the GABAergic interneurons is inhibitory as both nicotinic and muscarinic antagonists reverse the inhibition (Elghaba et al., 2016). This evidence suggests that interconnected Chls and GABAergic interneurons form a subcircuit that could allow flow of information independent of classical inputs such as MSNs to FSI (Luo et al., 2013; Faust et al., 2015, 2016).

Dopaminergic terminals

It is clear that synaptic release modulated at the terminal level, independent of the cell body, is a major component of the striatal microcircuits (Rice & Cragg, 2008). It has been calculated that within a sphere of striatal tissue of 20 μm in diameter, point-to-point synaptic communication for dopamine and ACh terminals takes place. Axons of dopamine and cholinergic neurons contribute each ≈ 400 terminals that are intermingled with other 2000–4000 unidentified terminals (Descaries et al., 1997). Such observations led Agnati et al. (1986), as quoted by Fuxe et al. (2013), to propose the concept of volume transmission as a non-junctional mode of intercellular communication. By modeling striatal dopamine spillover after quantal release, Rice & Cragg (2008) concluded that uptake does not limit the initial overflow from an extrasynaptic or synaptic release site, resulting in the formation of a cloud of dopamine that can reach extrasynaptic dopamine receptors which are more abundant than the synaptic receptors.

Studies of cholinergic modulation of dopaminergic terminals suggest that ACh diminishes dopamine release via nAChRs located on dopamine terminals (Rice et al., 2011); however, when dopamine release and the activity of Chls could be simultaneously monitored with fast scan voltammetry, a synchronous activation of Chls increased striatal dopamine release; for references, see Cachope & Cheer (2014). Therefore, endogenous release of ACh directly triggers striatal dopamine release (Cachope et al., 2012) and Chls synchronized by their thalamic input promote dopamine release (Threlfell et al., 2012). The prolonged debate about the interrelation between dopamine and ACh release has been slowly resolving, as more data are gathered. We now know that presynaptic nAChRs are highly expressed on striatal dopaminergic terminals (Jones et al., 2001; Zhou et al., 2001; Zoli et al., 2002; Salminen et al., 2004; Gotti et al., 2009; Livingstone & Wonnacott, 2009; Garcao et al., 2014; Wang et al., 2014; Gonzales & Smith, 2015; Howe et al., 2016), and that their activation facilitates dopamine release (Exley & Cragg, 2008).

Combined light activation of dopamine terminals and chemogenetic stimulation of Chl potentiates dopamine release (Aldrin-Kirk et al., 2018). Moreover, a neurotoxic dopamine depletion plus chemogenetic activation of Chls in vivo increases the use of previously akinetic forelimbs induced by a low dose of L-DOPA; however, the activation of Chl combined with a D2 agonist (quinpirole), but not a D1 agonist, increases the L-DOPA-induced abnormal involuntary movements (Aldrin-Kirk et al., 2018). This is congruent with other observations of exacerbation of dyskinesias by D2 agonists in mice (Alcacer et al., 2017) and increases in dyskinesias seen by the activation of M1 receptors on dMSN in combination with presynaptic M2 blockade (Bernard et al., 1992; Yan et al., 2001).

When considering microcircuits, different affinities or the complete absence of ACh (in knockout mice) can produce different modulatory effects. For example, a low affinity α7-containing nAChR will quickly become desensitized with a resulting decrease in cholinergic modulation; on the contrary, a high affinity α4β2-containing nAChR will desensitize more slowly, with a resulting increase in modulatory effect of ACh. Moreover, a ChAT knockout results in mice with no Chls and produces increased phasic-to-tonic dopamine signal with altered dopaminergic and glutamatergic tone (Patel et al., 2012).

The participation of corticostriatal and thalamostriatal afferents on dopamine release has been clarified using selective optogenetic activation; increases in dopamine release by the corticostriatal terminal field are mediated by nAChR but modulated by mAChR. Moreover, the increase in dopamine release results from the action of AMPA receptors on Chls that promote short-latency action potentials. Dopamine release driven by thalamostriatal afferents involves additional activation of NMDA receptors and action potential generation over longer timescales (Kosillo et al., 2016).

If the presence of NMDA receptors in thalamic afferents is observed, it would be interesting to know if they act as ‘sniffers’ of spillover glutamate release, have neurotrophic/neuroprotective function, or are involved in the modulation of postsynaptic responses.

Glutamatergic terminals

As mentioned before, striatal glutamatergic afferents arrive from cortex and thalamus (Ding et al., 2010; Doig et al., 2014), and presynaptic mAChRs (subtypes M1, M2, M3, M4) are located on axon terminals (Hersch et al., 1994). Electrophysiological in vitro
Co-release from cholinergic interneurons

Although it goes against the Dale’s principle of one neurotransmitter per neuron, the concept of corelease is now more accepted (Hnasko & Edwards, 2012). The presence of the glutamate type 3 vesicular transporter (vGLUT3) in neurons typically indicates the possibility of corelease (Kljakic et al., 2017). In striatum, a high expression of the glutamate transporter vGLUT3 is seen in a population of vesicles that express both vGLUT3 and vesicular acetylcholine transporter (vAChT) (Gras et al., 2002; Amilhon et al., 2010; Kljakic et al., 2017). Striatal corelease of ACh and glutamate has been determined following two main strategies: electrophysiological and genetic manipulation. Following the electrophysiological approach, there are two studies: one reports that optical stimulation of ChIs induces in MSNs two glutamate-dependent responses (Higley et al., 2010) and another reports that ACh release following synchronous ChIs triggers an action potential-independent presynaptic release of GABA colocalized in dopaminergic terminals (Nelson et al., 2014).

With the genetic approach, it was observed that following the deletion of the vAChT gene and subsequent elimination of ACh release, alterations in gross motor skills and in performance attributed to ACh, are still present most likely as a consequence of coreleased glutamate (Guzman et al., 2011).

Several questions must be answered regarding this topic: Does corelease for both neurotransmitters occur at the same time? Is release differentially regulated? Is release spatially coupled? How does the presence of two neurotransmitters contribute to microcircuit function? Does the ratio neurotransmitters change?

Striosome and matrix compartments

Almost 40 years ago, Graybiel & Ragsdale (1978) reported two distinct densities or compartments in the distribution of AChE in the striatum of primates and cats. These two compartments are called striosomes or patches, and matrix. Striosomes receive dopamine afferents from SNc and glutamatergic afferents from medial prefrontal, anterior cingulate, orbitofrontal, and anterior insular cortices (Benarroch, 2016). Stereological analysis in humans finds a differential distribution of ChIs with most of them located in the periphery of the striosomes (Bernace et al., 2007). Similarly in rodents, ChIs are found in the border of striosomes (Kubota & Kawaguchi, 1993) with extended processes into both compartments (Kubota & Kawaguchi, 1993). In recent reviews, ChIs are described as preferentially located in the matrix (Crittenden & Graybiel, 2011; Crittenden et al., 2017).

Using new tools, attempts to exclusively stimulate one compartment in vitro are clarifying the location of ChIs. Whole-cell patch recordings of ChIs with a posteriori identification of their compartment location revealed that GABAergic currents mediated by nAChRs are more frequently observed in the matrix than the striosome (Inoue et al., 2016), and the photoactivation of the matrix compartment with independent local stimulation and patch-clamp recordings revealed lack of synaptic connectivity between matrix and striosomes (Lopez-Huerta et al., 2016). The presence of ChIs in the areas high in calbindin-D28K and ChAT (Prensa et al., 1999) referred to as the ‘peristriosomal boundary’ reaffirm the location of ChIs between as well as within matrix and striosome compartments (Brimblecombe & Cragg, 2017).

A separation between matrix and striosomes has been established in rats by their different thalamic afferents. Unzai et al. (2017) reported that striatum and nucleus accumbens receive afferents to the striosome compartment mostly from thalamic midline nuclei, whereas the intralaminar nuclei innervate the matrix compartment. Moreover, whereas most terminal fields form en passant boutons, clusters or plexus containing many boutons are observed on terminal fields of the parafascicular nucleus. From the functional point of view, information from these two thalamic areas support the function previously inferred (Vertes et al., 2015): limbic (emotional) control for the striosomes and sensorimotor associative for the matrix (White & Hiroi, 1998; Crittenden & Graybiel, 2011; Buot & Yelnik, 2012).

Participation of cholinergic interneurons in striatal plasticity

It is broadly believed that long-lasting changes in synaptic efficiency at corticostriatal synapses are the cellular basis of motor learning (Pisani et al., 2007; Fino & Venance, 2011; Deffains & Bergman, 2015). These plastic changes have been shown as LTD or as long-
term potentiation (LTP). Early reports of striatal long-term changes indicated that either LTP or LTD could be produced by high frequency stimulation of cortical or thalamic glutamatergic inputs along with postsynaptic depolarization (Calabresi et al., 1992; Lovinger et al., 1993; Wickens et al., 1996; Centonze et al., 2001).

Further studies revealed that the precise timing and order between presynaptic and postsynaptic action potentials dictate the occurrence of either LTP or LTD in the paradigm of spike-timing-dependent plasticity (STDP) (Markram et al., 2011). As in the case of long-term changes induced by high-frequency stimulation, STDP-induced LTD and LTP was also induced in corticostriatal synapses (Fino et al., 2008; Pawlik & Kerr, 2008; Shen et al., 2008; Fino & Venance, 2011; Shindou et al., 2011; Jedrzejewska-Szmeek et al., 2017). Two variables are important for corticostriatal STDP: the frequent in vivo bombardment of pre- and postsynaptic inputs onto striatal neurons, and the presence of modulators like ACh, dopamine, or serotonin. Extracellular ACh and the level of M1 receptor stimulation control the direction of LTP or LTD (Calabresi et al., 1999a; Centonze et al., 1999). Additionally, cholinergic modulation of eCB synthesis has been linked to these long-lasting processes (Wang et al., 2006; Narushima et al., 2007).

The interaction between dopamine and ACh is important in the regulation of MSN excitability and plasticity. It appears that in vitro cortical inputs first activate striatal GABAergic FS interneurons, then ChIs, and finally MSNs (Fino et al., 2008). This order of events provides a facilitating effect on the MSNs while they receive cortical information and so define the direction of the plasticity (Deffains & Bergman, 2015).

High-frequency stimulation of cortical or thalamic afferents that synapse onto ChIs leads to an early monosynaptic glutamate-dependent depolarization (EPSP) followed by an intrastratal disynaptic GABAergic hyperpolarization (IPSP). In the presence of a GABAergic antagonist, induction of LTD depends on a rise in intracellular calcium and the activation of dopamine D1/D5 but not D2 receptors (Suzuki et al., 2001; Bonsi et al., 2004; Oswald et al., 2015). Moreover, in the absence of a GABAergic antagonist, the LTP of IPSPs recorded in ChIs is presynaptically mediated. The amplitude of each unitary induced IPSP is the same whereas their frequency increases (Suzuki et al., 2001; Miura et al., 2002). Other experiments suggest that the direction of STDP is determined by the rheobase of the ChIs. If the minimal current amplitude to evoke an action potential is low, LTD is observed in the recorded ChI, whereas LTP is induced if the ChI has a high rheobase (Fino et al., 2008; Fino & Venance, 2011).

The study of plasticity of cortical input to striatal GABAergic interneurons is limited due to their low population prevalence and cellular variability. So far, there are a few studies describing STDP on FS or PLTS-NOS expressing interneurons (Fino et al., 2008, 2009). However, with the help of transgenic mice targeting specific interneurons, in the near future, the knowledge in this field will grow.

**ACh and striatal microcircuits**

Tonically active ChIs are central in any analysis of the striatal microcircuits and perhaps should be considered within a functional relevant microcircuit. In order to be able to clearly isolate neuronal microcircuits in behaving animals, technical advances are needed. The study of neuronal ensembles was originated by the analysis of the spatiotemporal organization of groups of neurons. To perform the mathematical analyses to reveal interacting neuronal ensembles as multidimensional microcircuits, many neurons should be recorded at once (Yuste, 2015; Carrillo-Reid et al., 2017). Although single cell studies have been valuable revealing direct postsynaptic actions, sometimes conflicting interpretations can occur using the recordings of many interacting cells (Carrillo-Reid et al., 2011). In recent years, these calcium-imaging techniques have provided the most powerful tool to study spontaneous or drug-induced neuronal modulation of ≈60–80 striatal neurons for at least 20 min without losing the single cell resolution (Carrillo-Reid et al., 2008).

In the section ‘Influence of cholinergic interneurons...’ we described that the stimulation of striatal ChIs through mAChRs activation excites GABAergic interneurons that in turn induce recurrent inhibition in themselves and nearby ChIs (Sullivan et al., 2008). This effect could conceivably impact the activity in the whole population of striatal neurons. To study this possibility, Plata et al. (2013) artificially increased activity in the whole population of striatal neurons by bath application of NMDA or a previous chronic dopamine depletion. Under these conditions, it is clear that bath application of 1 μM nicotine clearly inhibits the hyperactive microcircuits.

Excitatory striatal activation of MSNs mediated by mAChRs has also been reported (Lv et al., 2017). The activation of M1 receptors enhances a persistent sodium current that can synchronize a large population of MSNs (Carrillo-Reid et al., 2009). Moreover, M1 receptor activation inhibits the persistent K+ current or the M-current in the dendritic/spine compartment of MSNs (Perez-Ramirez et al., 2015) and as expected, a specific antagonist of M1 receptors also decreases striatal neuronal activity (Hernandez-Flores et al., 2015). The influence of ChI on Kv7 channels is relevant, since these channels are widely expressed and are known to control neuronal excitability, the resting membrane potential, the spiking threshold, and to set the firing frequency within the burst and the subsequent hyperpolarization that follows a burst (Greene & Hoshi, 2017).

**Movement disorders related to cholinergic interneurons**

Impairment of striatal ChIs is central in the production of movement disorders (Pisani et al., 2007); altered cholinergic signaling is seen in a diverse class of syndromes that include Parkinson’s disease (PD; Brichta et al., 2013; Kalia et al., 2013; Ztsou et al., 2016), dystonia (Peterson et al., 2010; Eskow Jaunarajs et al., 2015; Scarduzio et al., 2017), Tourette’s syndrome (Xu et al., 2015; Albin et al., 2017), and Huntington’s disease (Di Filippo et al., 2007).

Parkinson’s disease is a common neurological disorder characterized by a decreased dopamine level. Early clinical and experimental studies revealed that PD was also characterized by increased extracellular levels of ACh (Barbeau, 1962; Cachope & Cheer, 2014). Indeed, the earliest pharmacological treatment of PD consisted of administration of anti-cholinergic agents (e.g., weak antimuscarinic diphenyldramine, benzotropine, orphenadrine; Fahn, 2014). However, the cumulative effect of anti-cholinergic medication ‘anti-cholinergic burden’, and the ‘anti-cholinergic risk’ associated with a decrease in the use of anti-cholinergic in old hospitalized patients. In a study of databases reporting side effects of anti-cholinergics, Salahudeen et al. (2015) compiled a list of those anti-cholinergics frequently prescribed and indicated that medicated patients suffer more frequent falls and hip fractures, increased dyskinesias, and suffer from hallucinations, blurry vision, and memory impairment than non-medicated patients.

The elevation of cholinergic signaling in PD is directly related to the alterations in ChI spiking (Tanirumia et al., 2018). As described before, M4 autoreceptors in ChIs slow firing rate and ACh release (Zhang et al., 2002b). In the rodent model of PD, dopamine
depletion induces an upregulation of RGS4-dependent processes that result in decreased M3 signaling in ChI (Ding et al., 2006). Alternative RGS modulation of ACh release might aid future treatment of patients. Experiments using the same animal model of PD report that halorhodopsin photoinhibition of ChIs in mice reduces akinesia, bradykinesia, and sensory motor neglect; however, in wild-type mice, the specific striatal blockade of M1 and M4 receptors has a similar effect. This suggests that the main participants in the absence of ACh are likely the M1 and M4 receptors since specific striatal blockade of M1 and M4 receptors has a similar effect (Ztaou et al., 2016). These results agree with the electrophysiological studies of muscarinic and dopaminergic interactions described in (Hernandez-Flores et al., 2015).

Recently Burbulla et al. (2017), using long-term cultures of human-induced pluripotent stem cells-derived dopamine neurons, has demonstrated a toxic cascade triggered by dysfunctional mitochondria that can induce neuronal pathological changes and cellular dysfunctions observed in PD. Now, research is centered on whether the same toxic mitochondrial intracellular cascade is present in the genetic and idiopathic forms of the disease. More work may eventually demonstrate the primary cause of SNc dopamine neuron death.

Dystonia involves intermittent or sustained abnormal involuntary muscle contractions that produce twisting postures in the absence of other neurological signs. Repetitive movement and uncontrolled muscle contractions can start early in childhood (Valente et al., 1998; Klein & Fahn, 2013). Early onset of dystonia is a genetically determined mutation in the gene TOR1A (Sciamanna et al., 2012). As in PD, the reciprocal modulation between dopamine and ACh is at the center of dystonia. For instance, high doses of anti-cholinergics (trihexyphenidyl) are used in the treatment of this disease (Burke et al., 1986). Electrophysiological experiments in ChIs of mice overexpressing mutant torsin A show that the sensitivity of a D2 agonist-mediated inhibition of Ca2,2 N-type current is increased. Following D2 agonists, a reduction in mAHP and threshold for action potentials is expected (Sciamanna et al., 2011). In mice with a conditional knockout of the dystonia 1 protein, the activation of thalamostriatal inputs induces a short pause and increased rebound activity in ChIs that could result from a postsynaptic increase and a presynaptic decrease in M1 and M2-dependent currents (Sciamanna et al., 2012).

Gilles de la Tourette’s syndrome is a neurodevelopmental disorder characterized by motor and phonic tics, usually measured by the Yale Global Tic Severity Scale (Leckman et al., 1989). In the last few years, several advances have been achieved toward the understanding of the neuropathology of this syndrome.

The participation of ChIs in this syndrome is supported by postmortem findings of a significant 49% loss of cholinergic and 42% loss of parvalbumin-positive FS interneurons with a no significant change in ≈ 20% in DARPP-32 expression in MSNs (Kataoka et al., 2010); however, targeted toxin lesion of ChIs in the dorsolateral striatum of adult mice fails to show any abnormal stereotypes (Xu et al., 2015). Moreover, the radiotracer [18F] fluorothoxy-benzovesamicol that is successfully used to image overexpressed vAChT in mice (Janickova et al., 2017) failed to detect changes in the number of ChIs in Tourette’s syndrome patients (Albin et al., 2017), perhaps obscured by the pedunculopontine cholinergic afferents.

Since stereotypy is regarded as a predominant aspect of this syndrome, using cocaine-induced stereotyped behaviors to test the function of ChIs, it is observed that a lesion of ChI or blockade of mAChR (scopolamine) prolongs the time course of the stereotypy, whereas blockade of dopamine D2 receptors (raclopride) stops the stereotypy presumably by increasing the extracellular cholinergic concentration (Aliane et al., 2011). These results suggest that a restoration of cholinergic transmission may have important consequences in the arrest of stereotypy. This is supported by a decrease in stereotyped behaviors in children following the administration of a cholinesterase inhibitor (donepezil) (Cubo et al., 2008).

Pharmacological animal models of the syndrome have been produced following blockade of striatal GABA A receptors. In mice, rats, and monkeys, intrastriatal administration of specific GABA A antagonists (picrotoxin or bicuculine) induces increased activity in striatum and its outputs (i.e., subthalamic nucleus and thalamus) and motor abnormalities similar to tics (McCaìn et al., 2009; Bronfeld et al., 2013), for review, see Yael et al. (2015).

Huntington’s is a progressive late-onset neurodegenerative disease characterized by psychiatric symptoms and cognitive deficit. It is caused by a CAG trinucleotide repeat in the gene encoding huntingtin. The resulting huntingtin accumulates forming inclusion bodies with other proteins, initially in neurons of striatal and cortical motor and prefrontal areas (Shepherd, 2013). In postmortem human tissue and rodent models of the disease, there is a striatal pre- and postsynaptic loss of GABA, glutamate, dopamine, and muscarinic acetylcholine receptors (Penney & Young, 1982; Dure et al., 1991) and a preferential degeneration of MSNs (Reiner et al., 1988) with a faster loss in iMSNs (Cha et al., 1998; Deng et al., 2004; Starr et al., 2008). Although the number of ChIs is relatively normal (Ferrante et al., 1987), these interneurons have decreased the levels of vAChT and ChAT (Smith et al., 2006). In an animal model of the disease (Q14-huntington-like mice), Deng & Reiner (2016) studied the specific vGLUT2 thalamic inputs to ChIs. They observed a reduction in the extension of the dendritic trees, with a subsequent loss of synapses, as also reported before (Deng et al., 2013). The authors propose that a reduced thalamic excitatory drive onto MSNs could be responsible for an initial observed hyperkinesia in mice. Then, a subsequent loss of dMSNs could lead to the permanent hypokinesia in this animal model.

In recent years, interest has shifted in somewhat different directions. Two examples: (i) attention to the posttranslational modifications of huntingtin by the covalent attachment of a small ubiquitin modifier (SUMO) protein (PIAS1). PIAS1 participates in the huntingtin accumulation of inclusion bodies and as expected, a reduction in PIAS1 prevents the formation of inclusion bodies and reduces inflammation (Ochaba et al., 2016). (ii) Attention to the participation of NMDA receptors in neuronal degeneration pointing to the molecular link between mutant huntingtin and the synaptic retrieval of the GluN3A subunit of the NMDA receptors. Mutant huntingtin redirects an intracellular store of juvenile NMDA+GluN3A to the surface of the neurons favoring neuronal loss. Overexpression of GluN3A in normal mice induced synapse loss. Moreover, as expected, the genetic ablation of GluN3A subunits improves motor performance and decreases cell loss in mutant mice (Marco et al., 2013).

Conclusions and future directions

There is an emerging idea that like dopamine, ACh is necessary at a minimum concentration to maintain striatal function. The complex distribution of the receptors for ACh and the tonic activity in the cells themselves suggests a ‘maintenance’ role. The input to these interneurons from cortex and thalamus allows them access to goal-directed behavioral contexts (from cortex?) and to attentional and arousal internal signals (from thalamus?). The pause in firing that
accompanies newly learned cues is similar in timing with the burst of dopamine activity that itself may generate the later burst of activity in the ChIs.

It is easy to imagine that these temporary changes in extracellular transmitter concentrations are a mechanism to remodel striatal functional microcircuits to adjust to the change in circumstances that initiated the pause. The intimate involvement of ACh in the long-term changes in excitability in striatal cells in vitro is also an indication that such a scheme might be involved in the response to novel cues that are recognized as significant by the animal. In this scenario, the distribution of receptors on both cells and terminals suggests that the organization of synaptic microcircuits in the striatum might underlie the changes in functional assemblies that result in changes in behavior.

Methods to identify these functional assemblies and demonstrate their sensitivity to local transmitter concentrations are being developed. They will provide information about the detailed physiology of such changes in function and perhaps begin to make sense of the detailed receptor localizations in the striatal microcircuitry. Work on optogenetic manipulation of the ‘maintenance transmitters’ is already leading to direct tests of their role. Moreover, methods to image activity, at single cell resolution, in groups of related neurons in freely moving animals are developing. We are reaching a time when such ideas cease to be speculation and become testable hypotheses about the role of acetylcholine in animal behavior.

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Conflict of interest
The authors declare no conflict of interest, financial, or otherwise.

Author contributions
N.A. and T.H.F. wrote the manuscript; M.G.M. wrote some sections and edited the manuscript; T.H.F. made the figures. G.W.A. reviewed the manuscript and provided formulation of comprehensive research goals, mentorship, and leadership.

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