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Striatal cholinergic interneurons and cortico-striatal synaptic plasticity in health and disease

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Abstract

Basal ganglia disorders such as Parkinson's disease, dystonia and Huntington's disease are characterized by a dysregulation of the basal ganglia neuromodulators (dopamine, acetylcholine and others) which impacts cortico-striatal transmission. Basal ganglia disorders are often associated with an imbalance between the midbrain dopaminergic and striatal cholinergic systems. In contrast to the extensive research and literature on the consequences of a malfunction of midbrain dopaminergic signaling on the plasticity of the cortico-striatal synapse, very little is known about the role of striatal cholinergic interneurons in normal and pathological control of cortico-striatal transmission. In this review, we address the functional role of striatal cholinergic interneurons, also known as tonically active neurons and attempt to understand how the alteration of their functional properties in basal ganglia disorders leads to abnormal cortico-striatal synaptic plasticity. Specifically, we suggest that striatal cholinergic interneurons provide a permissive signal which enables long-term changes in the efficacy of the cortico-striatal synapse. We further discuss how modifications in the striatal cholinergic activity pattern alter or prohibit plastic changes of the cortico-striatal synapse. Long-term cortico-striatal synaptic plasticity is the cellular substrate of procedural learning and adaptive control behavior. Hence, abnormal changes in this plasticity may underlie the inability of patients with basal ganglia disorders to adjust their behavior to situational demands. Normalization of the cholinergic modulation of cortico-striatal synaptic plasticity may be considered as a critical feature in future treatments of basal ganglia disorders.

Introduction

Dysfunction of the striatal cholinergic interneurons is highlighted in common human movement disorders such as Parkinson's disease (PD), dystonia and Huntington's disease (HD) ¹⁻⁴. In the striatum, cholinergic interneurons closely interact with the midbrain dopaminergic neurons. These two neuronal populations exhibit coincident physiological changes in their activity during behavior ^{5;6} and exert reciprocal control on the release of their neurotransmitters ^{3;7-11}. Therefore, basal ganglia (BG) disorders are often associated with an alteration of the normal balance between the midbrain dopaminergic and the striatal cholinergic system ^{1;4;12;13}.

Currently, the BG network is viewed as two functionally related subsystems ¹⁴⁻¹⁸. The first subsystem is the main axis which corresponds to the different BG structures that connect cortical fields to the motor centers of the brain. The second subsystem is composed of neuromodulators that include the midbrain dopaminergic neurons and striatal cholinergic interneurons which adjusts activity along the main axis. BG disorders are caused by a dysregulation of the neuromodulators that impact activity along the main axis. Figure 1.A schematically summarizes the current view of the complex connectivity of the BG network.

There is converging evidence suggesting that midbrain dopaminergic neurons adjust activity along BG main axis by encoding a reward prediction error signal ^{5;6;19-24} capable of modulating the (long-term) efficacy of cortico-striatal transmission ²⁵⁻²⁹. The midbrain dopaminergic system also has a pivotal role in the attribution of incentive values to cues that signal reward ^{20;30;31}. Therefore, midbrain dopaminergic neurons are involved in both the predictive/learning and motivational features of reward-related processes.

Physiologically, this long-term modulation (plasticity) in the efficacy of the cortico-striatal synapse is expressed as long-term potentiation and depression (LTP/LTD, respectively). LTP/LTD at cortico-striatal synapses are commonly viewed as the cellular substrate of

procedural learning and adaptive control behavior ^{4;13;32;33}. Accordingly, dysfunction of dopaminergic system leads to alteration of the plasticity of cortico-striatal transmission and to deficits in action selection, decision making and shifting behavioral aptitudes ³⁴⁻³⁹. Electrophysiological recordings showed that the responses of the striatal cholinergic interneurons encode a wide range of processes, from the incentive value of events to a prediction error signal ⁴⁰⁻⁴³. In vitro studies reported that striatal acetylcholine (ACh) level dictates the polarity of the plasticity (LTP vs. LTD) of the cortico-striatal synapse ²⁵. Nevertheless, little is known about the functional role of these cholinergic interneurons in the plasticity of cortico-striatal transmission. Moreover, the consequences of their malfunction in BG disorders are still elusive and deserve to be synthesized. In this review, we go over the main chemical, anatomical and electrophysiological features of the striatal cholinergic interneurons. Then, we discuss the functional role of their responses and their impact on the plasticity of cortico-striatal transmission in health. Finally, we discuss the consequences of dysregulation of the striatal cholinergic system and the plasticity of cortico-striatal transmission in pathological conditions such as PD, dystonia and HD.

Main chemical, anatomical and electrophysiological features of the striatal cholinergic interneurons

Interneurons comprise only ~5% of all striatal neurons ⁴⁴⁻⁴⁶ (but, see ^{47;48}). The remainder corresponds to GABAergic projection neurons, also known as medium spiny neurons (MSNs). Four striatal interneuron types have been described. Three of them are GABAergic neurons and coexpress different neuropeptides: one coexpress parvalbumin, one somatostatin, neuropeptide Y, NADPH-diaphorase and nitric oxide synthase and one calretinin. The fourth type is the cholinergic interneurons representing 1-2% of the total number of neurons in the striatum. They constitute the main ACh source for the

striatum. A recent study indicated that the striatum also receives extrinsic ACh innervation from the brainstem⁴⁹, however the relative importance of this external ACh innervation is still under investigation.

Morphologically, striatal cholinergic interneurons have a large soma (\varnothing 20-50 μ m), vast dendritic and axonal fields and are devoid of dendritic spines^{46;50;51}. Therefore, the morphological features of these giant aspiny neurons suggest that they are able to integrate synaptic inputs over large striatal regions and project to a wide area of the striatum⁴⁵. Striatal cholinergic interneurons are innervated by midbrain dopaminergic neurons⁵²⁻⁵⁴, MSNs^{51;55;56}, GABAergic interneurons^{57;58} and others cholinergic interneurons⁵⁸. However, like the MSNs, their main input is glutamatergic and arises from the cortex and the thalamus^{53;59-62}. Anatomical^{60;62} and physiological^{63;64} evidence suggests that striatal cholinergic interneurons are prominently targeted by thalamic afferents (from intralaminar nuclei). In return, they predominately project to the MSNs⁶⁵. The main afferent and efferent connections of the cholinergic interneurons and MSNs within the striatum are illustrated in figure 1.B. Based on neurochemical marker staining in the striatum, it has been shown that cholinergic interneurons are located in specific compartments, called matrixosomes (with rich cholinergic marker staining) and preferentially lie near the borders of compartments with low cholinergic marker staining (striosomes or patches)⁶⁶⁻⁶⁸. Therefore, it has been hypothesized that striatal cholinergic interneurons might convey information from MSNs in striosomes to MSNs in matrixosomes⁶⁹. However, even though there is clear evidence of this bipartite organization in rodents, non-human primates and humans, its functional role is still debated.

Physiologically, *in vitro* intracellular recordings revealed that striatal cholinergic interneurons hold a relatively depolarized resting membrane potential (\sim 60mV) and exhibit long lasting after-hyperpolarization following action potentials^{44;45;70;71}. Moreover, these interneurons tonically fire even in the absence of synaptic inputs indicating that

their tonic activity is supported by endogenous mechanisms⁷². A detailed description of the cellular mechanisms of their spontaneous discharge is provided by Goldberg and Wilson⁷³. This autonomous "pacemaking" activity has been confirmed in electrophysiological studies on behaving animals, where their spontaneous tonic discharge ranges between 2 and 12Hz^{6;40;41;43;74-78}. This spontaneous tonic discharge, in contrast to the very low spontaneous discharge of the MSNs, led to the common reference to striatal cholinergic interneurons as "Tonically Active Neurons"^{40-42;46;59}.

Behavioral neurophysiology and functional role of the striatal tonically active (cholinergic) interneurons

Electrophysiological recordings in the striatum of behaving monkeys showed that tonically active neurons respond to rewarding (but also aversive) events. The most common response of tonically active neurons consists of a short latency pause in the tonic firing rate, lasting few hundred milliseconds (~200ms), which is often flanked by initial and rebound excitatory periods^{5;42;43;79-84}. Figure 2.A depicts the classic population responses of tonically active neurons to behavioral events in the different striatal functional territories. This study did not report significant differences in responses of tonically active neurons to cues predicting food, air-puff or neutral outcome. However, other studies have demonstrated that their response features are significantly modulated by the motivational significance (appetitive vs. aversive) of an event^{5;85;86}. Therefore, tonically active neurons are probably involved in both the detection of motivational events and the signaling of the motivational value of these events^{40;41;43;75;86}.

Tonically active neurons acquire responses to the stimulus predicting the reward by repeatedly experiencing the stimulus-reward association (Fig.2.B)^{42;75;80;84}. Therefore, they are probably not only involved in the detection of incentive events, they would also play a role in reward-related learning processes^{42;75;80}. Delivery of unpredicted rewards

or temporal alteration of the predictability of rewards boost pauses of tonically active neurons (i.e., the principal component of their responses) to the reward itself (Fig.2.C)^{80;81;87;88}. These results were confirmed by findings showing stronger pauses for the outcome delivery in probabilistic⁵ vs. deterministic^{79;89} conditioning tasks. We therefore can conclude that tonically active neurons encode a positive reward prediction error (i.e., when reality is better than expected).

As regards the role of the tonically active neurons in the encoding of negative reward prediction error (i.e., when reality is worse than expected), it has been shown in Pavlovian⁵ and instrumental⁶ conditioning tasks that tonically active neurons also respond to the omission of expected rewards. These responses to reward omission, although their magnitudes are smaller, have the same polarity (i.e., pauses) as those observed for reward delivery. Therefore, responses of tonically active neurons probably signal the precise timing of expected incentive events which do not occur, via the encoding of an absolute prediction error signal. Recent studies identified a subset of tonically active neurons that respond with opposite changes in activity (albeit of smaller amplitude and longer duration) to reward delivery and reward omission (Fig.2.D)^{90;91}. This subset of tonically active neurons would be therefore able to provide a positive and negative or signed prediction error signal to the cortico-striatal system, in line with the computational temporal difference model of reinforcement learning^{92;93}. The question of whether the tonically active neurons represent a homogenous or heterogenous group of neurons is still debated (see cross-correlation studies below).

Cross-correlation analyses of simultaneously recorded tonically active neurons (Fig.3.A) revealed that the spontaneous spiking activity of the tonically active neurons is highly synchronized^{78;94}. In the same vein, signal/response correlation analyses demonstrated that tonically active neurons, widely distributed in the striatum, exhibit positive correlation coefficient values (Fig.3.B)⁹⁵, in agreement with single-unit studies showing a

homogeneity of their responses (Fig.2.A) ^{42;79}. Thus, as for the dopaminergic system ^{6;95-97}, tonically active neurons form a homogenous functional population over diverse territories and are capable of uniform modulation of the cholinergic tone in the striatum in response to incentive events.

Role of striatal acetylcholine in cortico-striatal synaptic plasticity

In the striatum, ACh affects multiple targets, with multiple time scales ⁹⁸. Here, we limit ourselves to the impact of ACh on long-term changes of the efficacy of cortico-MSN synapse. In this review, the term cortico-striatal synapse refers to the cortico-striatal synapse onto MSNs.

Over the last two decades, it has been shown the existence of LTP and LTD in the striatal MSNs ⁹⁹⁻¹⁰², but the mechanisms that rule the polarity of these changes are still unclear and debated ^{28;103;104}. Current opinion indicates that the precise timing/order between pre- and postsynaptic spiking activity dictates the polarity of long-term plasticity changes. This process, named spike-timing-dependent-plasticity (STDP) has been described in several brain structures ^{105;106}. Based on the conventional Hebbian rule, LTP is induced when postsynaptic activation follows presynaptic activation whereas reversing this order causes LTD. This bidirectional Hebbian STDP has also been observed at the cortico-striatal synapse ^{28;107}. However, Fino and colleagues ^{108;109} found that cortico-striatal bidirectional STDP might be controlled by a reverse Hebbian rule. Therefore, mechanisms that rule cortico-striatal bidirectional STDP are still under investigation, but there is evidence that the type of DA receptor (D1/D2) present on the MSNs and their level of activation play a critical role ²⁸.

In vivo, due to the large diversity and amount of presynaptic inputs received by postsynaptic elements, synapses are constantly adapting their synaptic efficacy as pre- and postsynaptic spikes collide. As a result, an emerging view suggests that STDP in

the striatum is further controlled by an additional factor involving neuromodulators ^{33;110}. Indeed, neuromodulator signals, such as the striatal ACh signal provided by responses of tonically active neurons might serve to spatially and temporally associate specific pre- and postsynaptic activities. In other words, ACh and other striatal neuromodulators (e.g., DA, serotonin) might enable the selection of certain input-output coincidences of pre- and postsynaptic neurons and make them eligible for changes in the synaptic plasticity. In line with this view, in vitro studies in the striatum showed that striatal ACh level dictates the polarity of the plasticity of the cortico-striatal synapse via activation of the MSN muscarinic postsynaptic receptors. Activation of M1-like postsynaptic receptors increases MSN excitability ^{111;112}. Accordingly, activation of M1 receptors favors MSN depolarization and thus plays a permissive role in LTP ^{25;113}. In contrast, decrease of the striatal cholinergic tone has been proposed to facilitate LTD ^{114;115}. In vitro studies reported that in response to cortical stimulation, striatal cholinergic interneurons are activated before MSNs ¹¹⁶. Therefore, striatal cholinergic interneurons appear to be ideally located (feed-forward) to modulate the excitability and the membrane potential of the MSNs before the latter receive cortical inputs. Striatal cholinergic interneurons might orchestrate the timing/order of the pre- and postsynaptic activity at the cortico-striatal synapse level and help govern the polarity of the plasticity.

However, this role of striatal cholinergic interneurons as a bidirectional regulator of plasticity in the cortico-striatal synapse needs to be moderated since overly fast and strong plasticity may lead to instability. Indeed, behavioral events such as conditional stimuli or rewards affect a large diversity of neuromodulators in the striatum such as DA, ACh, serotonin, histamine and others with direct and indirect impact on the cortico-striatal synaptic plasticity. For instance, the low striatal cholinergic tone accompanying pauses of tonically active neurons directly favors LTD, but also disinhibits the midbrain dopaminergic neurons via their nicotinic receptors and thus causes a bursty release of

DA in the striatum ^{7;10;117-119}. Such DA burst has been shown to be involved in the induction of cortico-striatal LTP ¹²⁰.

Therefore, determining the resulting effect of the modulation of striatal ACh in vivo conditions (several modulators and combinations of actions) on cortico-striatal synaptic plasticity is overwhelmingly challenging. It is likely that stereotypically synchronized pauses of tonically active neurons cause a transient significant reduction of the striatal cholinergic tone. This striatal ACh signal might serve as a driver or a permissive temporal window to favor specific input-output coincidences of pre- and postsynaptic neurons and thus allow long-term modulations of efficacy at specific cortico-striatal synapses.

Dysregulation of the striatal cholinergic system and cortico-striatal transmission in pathological conditions

- Parkinson's disease

In PD, degeneration of midbrain dopaminergic neurons resulting in striatal DA depletion causes a cascade of physiological changes, notably an increase in the striatal ACh level ^{4;12;13}. This DA-ACh imbalance in PD led to the initial use of anticholinergic drugs as treatment of the disease ^{121;122}. For a long time, a high striatal ACh level in PD was associated with a reduction in the activation of D2 receptors, located on cholinergic interneurons due to DA depletion ¹²³. Ding and colleagues ¹²⁴ showed that striatal DA depletion also provokes a reduction in the efficacy of M4 autoreceptors on cholinergic interneurons, resulting in a self-disinhibition of ACh release. In vitro recordings revealed that after acute striatal DA depletion cholinergic interneurons exhibit striking changes in their electrophysiological features such as an increase in the excitability, a reduction in the amplitude and duration of the after-hyperpolarization, as well as modifications in the shape, amplitude and duration of their spikes. These physiological changes might lead

to hyperactivity of the cholinergic interneurons ¹²⁵ (but, see ¹²⁶). In vivo, recordings of tonically active neurons in monkeys after MPTP injection ^{78;127} or DA antagonists administration ¹²⁸ showed a loss of their response for relevant behavioral events during associative conditioning tasks (Fig.4.A). Additionally, Raz and colleagues ⁷⁸ reported that after striatal DA depletion due to MPTP injection tonically active neurons displayed high synchronized oscillatory activity (Fig.4.B) which is probably shared by the whole BG network ¹²⁹.

Consequently, it is interesting to correlate the emergence of this abnormal pattern of activity in the tonically active neurons with the loss of cortico-striatal synaptic plasticity (both LTP and LTD) reported in vitro in the 6-hydroxydopamine (6-OHDA) lesioned rat ^{100;130-133}. As mentioned earlier, transient reduction in the striatal ACh level as observed during pauses of tonically active neurons might form a permissive temporal window for cortico-striatal synaptic plasticity ^{5;6}. Therefore, in PD, the pathological activity of the striatal cholinergic interneurons might cause a persistent unmodulated high level of ACh in the striatum. If this abnormal persistent activity is further modulated by oscillations, it may lead to periods of high/low ACh levels which are irrelevant from a behavioral point of view. This may be a major factor prohibiting any changes in cortico-striatal synaptic plasticity.

In parallel, structurally, it has been shown that DA depletion induced a shift towards greater ACh innervation of striatopallidal MSNs than striatonigral MSNs ¹³⁴. This redistribution of ACh synaptic connections between the striatopallidal and striatonigral MSNs might contribute to the selective pruning of spines and glutamatergic synapses in the striatopallidal MSNs, observed after striatal DA depletion ¹³⁵. Therefore, the elevation of ACh signaling in PD, by lowering the number of spines and glutamatergic contacts into the striatopallidal MSNs, might reduce opportunities to spatially and temporally associate pre- and postsynaptic activities. This would lead to a reduction in possibilities

for cortico-striatal synaptic plasticity at least for the striatopallidal MSNs. Remarkably, a recent study conducted on 6-OHDA lesioned rats repeatedly treated with L-DOPA found a reduction of the dendritic spines in MSNs (especially those expressing DA D1 receptors), concomitantly with the development of L-DOPA induced dyskinesia (LID) ¹³⁶. Additional studies in the rat model of LID revealed that maladaptive cortico-striatal synapse plasticity might play an important role in the development of LID ^{132;137}. In parallel, pharmacological reduction of the striatal cholinergic tone or specific ablation of cholinergic interneurons in parkinsonian mice attenuates LID ^{138;139}. Therefore, it has been proposed that exacerbated DA sensitivity of striatal cholinergic interneurons during parkinsonian state might contribute to the expression of LID, which suggests that striatal cholinergic interneurons represent a promising therapeutic target for the prevention and treatment of LID.

- Dystonia

Dystonia is a motor disorder characterized by involuntary twisting movements and abnormal postures ¹⁴⁰. DYT1 dystonia is the most frequent form of inherited (primary) dystonia and is linked to a single nucleic-acid mutation of the gene DYT1, resulting in an abnormal expression of the protein torsinA ¹⁴¹. Here, we limit our discussion to DYT1 dystonia.

One of the most effective treatments for DYT1 dystonia is the use of antagonists of the cholinergic muscarinic receptor ¹⁴². Unlike PD, in DYT1 and other genetic forms of dystonia there is no degeneration of the midbrain dopaminergic neurons. However, studies conducted on transgenic mouse model of DYT1 over-expressing the human mutated protein torsinA demonstrated abnormal coupling between dopaminergic and cholinergic signaling in the striatum and a pathological elevation of the striatal cholinergic tone ¹⁴³. In these transgenic mice, in vitro recordings revealed that D2

receptor activation via quinpirole (D2 DA receptor agonist) provokes membrane depolarization and increases the firing rate of the striatal cholinergic interneurons that should lead to an elevation of the striatal ACh level ¹⁴³. This result is unexpected since, in control animals, D2 receptor activation inhibits striatal ACh release ^{144;145} by reducing N-type calcium currents ¹⁴⁶. This paradoxical effect of D2 activation of ACh levels appears to be a consequence of a malfunctioning of the N-type calcium channels which reduces the amplitude of the medium after-hyperpolarization and thus increases the firing rate of the striatal cholinergic interneurons ⁷³.

As regards cortico-striatal synaptic plasticity in DYT1 dystonia, in vitro recordings in slice preparations from DYT1 mice revealed that cortico-striatal LTD cannot be induced whereas LTP is enhanced compared to the control group ¹⁴⁷. In addition, it has been demonstrated that normalizing the striatal ACh signaling in these DYT1 mice by administering either hemicholinium-3, a depletor of endogenous ACh, or muscarinic M1-like receptor antagonists (i.e., pirenzepine or trihexyphenidyl) restores normal cortico-striatal synaptic plasticity ¹⁴⁷. Therefore, these results are in line with the presumed role of striatal ACh level in determining the polarity of cortico-striatal synaptic plasticity ²⁵ and provide direct evidence that an excessive striatal ACh level underlies the cortico-striatal synaptic plasticity deficits observed in DYT1 dystonia.

Recently, in vitro recordings in mice with the DYT1 dystonia mutation showed that thalamo-striatal stimulation mimicking responses of tonically active neurons to incentive events evoked shortened pauses and abnormal spiking activity of the striatal cholinergic interneurons compared to the control groups ¹⁴⁸. It is tempting to speculate that this abnormal activity pattern of the striatal cholinergic interneurons by disrupting the cortico-striatal transmission/integration might affect the long-term cortico-striatal synaptic plasticity of animal models and patients suffering from DYT1 dystonia.

- *Huntington's disease*

HD is an inherited neurodegenerative disease characterized by a selective loss of MSNs in the striatum ^{149;150}. HD is caused by a mutation in the Huntingtin gene encoding the Huntingtin protein and is characterized by movement disorders (e.g., involuntary choreiform movements), behavioral and cognitive deficits ^{37;151}. Even though no specific degeneration of the striatal cholinergic interneurons has been described in HD ¹⁵²⁻¹⁵⁴, studies in HD transgenic mice have reported an abnormally low release of ACh in the striatum ^{2;155}, pointing out a role of these interneurons in the pathophysiology of the disease. Consistent with a malfunctioning of the striatal ACh signaling in HD, the density of the muscarinic receptors in post-mortem striatal tissue from HD patients is reduced ^{156;157}. In addition, further studies demonstrated that the level of both the vesicular acetylcholine transporter and choline acetyl-transferase are significantly reduced in the striatum of HD R6/2 transgenic mice, as well as in post-mortem striatal tissue from HD patients ^{154;155;158;159}. In parallel, Vetter and colleagues ¹⁵⁵ showed in HD R6/2 transgenic mice, an impairment of the presynaptic inhibition of the ACh via both M2 auto- and D2 heteroreceptors suggesting the emergence of presynaptic compensatory mechanisms to overcome the low striatal cholinergic tone observed in HD.

To date, little information is available regarding the impact of striatal cholinergic interneurons on the cortico-striatal synaptic plasticity in HD patients or animal models. However, in both the phenotypic rat model of HD (after chronic systemic 3-nitropropionic acid administration) and HD R6/2 transgenic mice, MSNs exhibit normal LTP but are not able to express LTD ². This lack of LTD expression occurs despite a low striatal ACh level which is known to favor LTD in normal condition ²⁵. Remarkably, certain studies indicate that both striatal ACh and DA level are reduced in HD ^{160;161} and an emerging view suggests that reduction of the ACh signaling might be accountable for the malfunction of D1 receptor-mediated excitation of striatal cholinergic interneurons ¹⁶¹.

Therefore, a better understanding of the abnormal ACh-DA coupling in HD appears to be essential to elucidate the mechanisms behind the abnormal cortico-striatal synaptic plasticity in HD.

Concluding remarks

One of the main cognitive deficits in BG disorders such as PD, dystonia and HD is the inability to adjust/switch behavior depending on situational demands ³⁴⁻³⁹. Seen from this angle, the ability to induce and reverse LTP and LTD at specific synapses appears to be critical. Indeed, LTP by reinforcing the synaptic strength of specific synapses would contribute to the information storage in neuronal networks. However, it is crucial that these same synapses are able to reverse this form of plasticity (i.e., induction of LTD) to allow extinction or "forgetting" processes ¹³² in response to new behavioral situations. Earlier genetic and pharmacological studies showed involvement of various striatal signaling molecules and circuits in behavioral flexibility ^{162;163}.

In this review we pointed out that the emergence of abnormal activity pattern in striatal cholinergic interneurons that accompanied the dysfunction of striatal ACh signaling in BG disorders might contribute to pathological cortico-striatal synaptic plasticity. This abnormal cortico-striatal synaptic plasticity probably underlies some of the clinical disturbances in learning and switching behaviors seen in patients with BG disorders. Table 1 summarizes the abnormal cortico-striatal synaptic plasticity observed in the major BG movement disorders concomitantly with striatal DA-ACh levels. We therefore suggest that future treatments of BG disorders should also be directed towards the normalization of the cholinergic (and other BG neuromodulators) modulation of cortico-striatal synapses.

Finally, dysregulation of BG neuromodulators is also often found in drug addiction ^{164;165} and in psychiatric diseases such as Tourette syndrome, obsessive compulsive disorders

(OCDs), and major depressive disorders ¹⁶⁶⁻¹⁷⁰. In Tourette syndrome, there is converging evidence that dramatic reduction of number of cholinergic interneurons in dorsal striatum contributes to behavioral manifestation of the disease ^{169;170}. In OCD patients, an attenuation of the cortico-striatal LTD after anterior capsulotomy has been concomitantly shown with an improvement in OCD symptoms. Thus, exacerbated cortico-striatal LTD might be one of the mechanisms underlying OCD symptoms ¹⁷¹. However, too little is known about aberrant cortico-striatal synaptic plasticity in psychiatric disorders and the involvement of the striatal cholinergic interneurons has not been addressed yet. It is time to fill this gap to better understand the pathophysiology of neurological and addiction/psychiatric BG-related diseases and use this knowledge to develop new therapeutic approaches ¹⁷².

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H.B.: 1A, 1B, 3B

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Tables and Figures

Table.1 Changes in striatal dopamine-acetylcholine levels and plasticity of the cortico-striatal synapse in movement disorders

	dopamine	acetylcholine	CS LTP	CS LTD
Parkinson's disease	-	+	↓	↓
DYT1 dystonia	?	+	↑	↓
Huntington's disease	?	-	N	↓

CS: cortico-striatal (MSN); LTP: long term potentiation; LTD: long term depression; N: normal;
?: unresolved, inconsistent results; - and +: low and high striatal level, respectively;
↓ and ↑: enhancement and impairment/loss, respectively

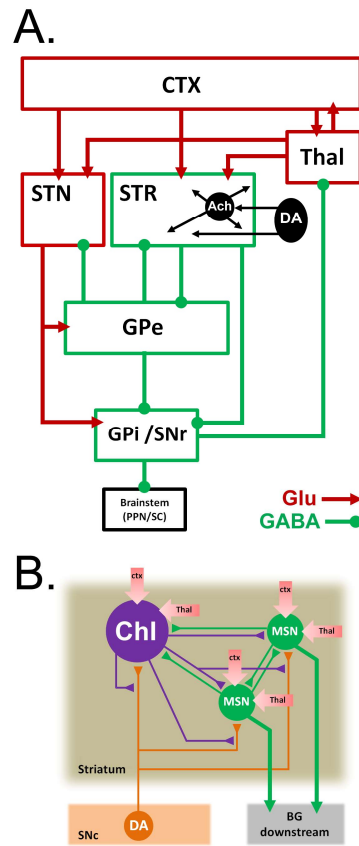


Figure 1: Cholinergic interneurons within basal ganglia network. (A) Schematic model of the basal ganglia network. Input structures of the BG (striatum and subthalamic nucleus) receive inputs from the cortex and the thalamus. The output structures of the BG (internal segment of the globus pallidus and the substantia nigra reticulata) project to the cortical (through the thalamus) and brainstem motor centers. Activity in BG main axis is controlled by different neuromodulators such as dopamine and acetylcholine which modulate the cortico-striatal transmission. Red and green arrows indicate the glutamatergic or GABAergic nature of the connection. CTX: cortex; Thal: thalamus; STR: striatum; STN: subthalamic nucleus; GPe-i: external and internal segment of the globus pallidus; SNr: substantia nigra reticulata; PPN: pedunclopontine nucleus; SC: superior colliculus; ACh: acetylcholine, DA: dopamine. **(B)** Main afferent and efferent connections of the cholinergic interneurons and medium spiny neurons within the striatum.

Cholinergic interneurons (ChIs) and medium spiny neurons (MSNs) are reciprocally connected and impacted by dopaminergic neurons (DA) from substantia nigra compacta (SNc). In return, cholinergic interneurons influence dopaminergic transmission. Vertical and horizontal red arrows represent the glutamatergic innervation from cortex (Ctx) and thalamus (Thal), respectively.

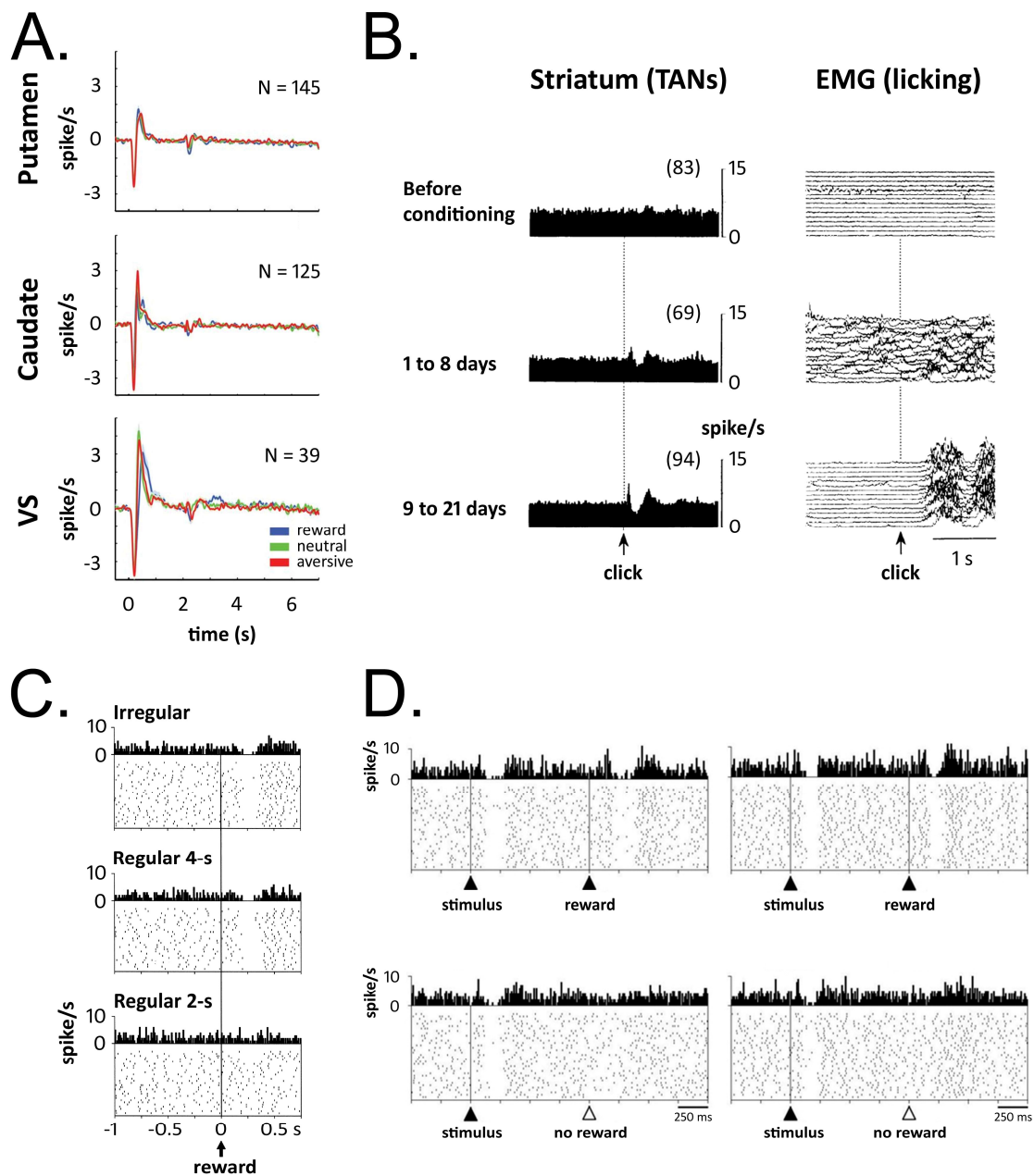


Figure 2: Response properties of tonically active neurons. (A) Average population responses of tonically active neurons to behavioral events in the putamen, caudate nucleus and ventral striatum (VS). Time 0 indicates the cue presentation followed by outcome delivery at time 2s. Color codes indicate cue value (reward, neutral, aversive). N indicates the number of neurons. *Adapted from Adler et al. (2013)*⁷⁹. **(B)** Emergence of population response of tonically active neurons to a click predicting a juice reward

(left), concomitantly with the acquisition of the conditional behavioral response, characterized by the alignment of the licking after the click when the juice is delivered (right). Numbers in parentheses indicate the number of neurons. EMG: electromyogram. *Adapted from Graybiel et al. (1994)* ⁴². **(C)** Example of a tonically active neuron responding to the reward when its delivery is hardly predictable (irregular or regular 4-s intervals), but not when reward prediction is facilitated (regular 2-s interval). *Adapted from Ravel et al. (2001)* ⁸⁷. **(D)** Example of two tonically active neurons responding with opposite changes in activity when predicted rewards were omitted (bottom, left and right). Both neurons respond with a pause to reward delivery (top, left and right). *Adapted from Apicella et al. (2009)* ⁹⁰.

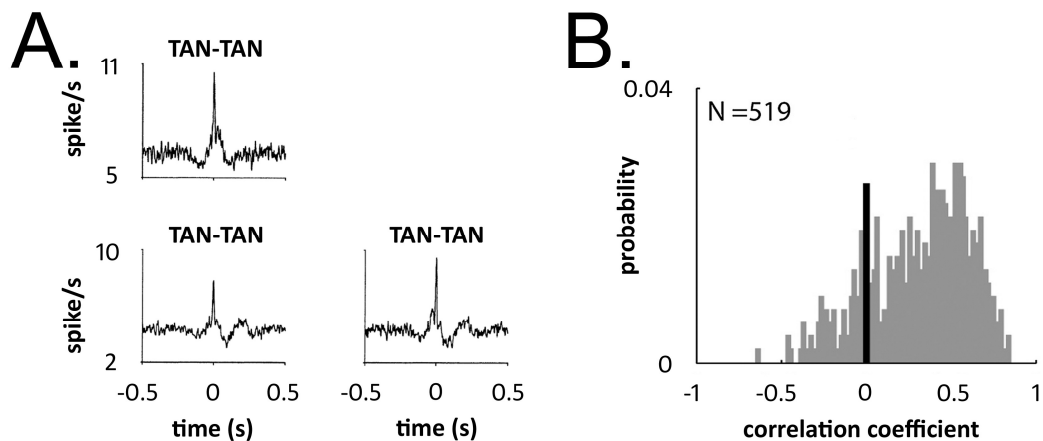


Figure 3: Homogenous activity of tonically active neurons (A) Crosscorrelograms of tonically active neurons recorded simultaneously in healthy non-human primates. The zero-centered peak in the crosscorrelograms indicates that the activity of tonically active neuron pair is highly synchronized. *Adapted from Raz et al. (1996)*⁷⁸. **(B)** Distribution of the response correlation of tonically active neurons to conditional cues. Response correlation quantifies (on a scale of -1 to +1) the similarity of the responses of a pair of neurons (recorded simultaneously or not) to the same event. The distribution of the correlation coefficients of tonically active neuron pairs is skewed toward positive values, suggesting a homogeneity of the responses of tonically active neurons to conditional cues. N indicates number of response pairs. *Adapted from Joshua et al. (2009)*⁹⁵.

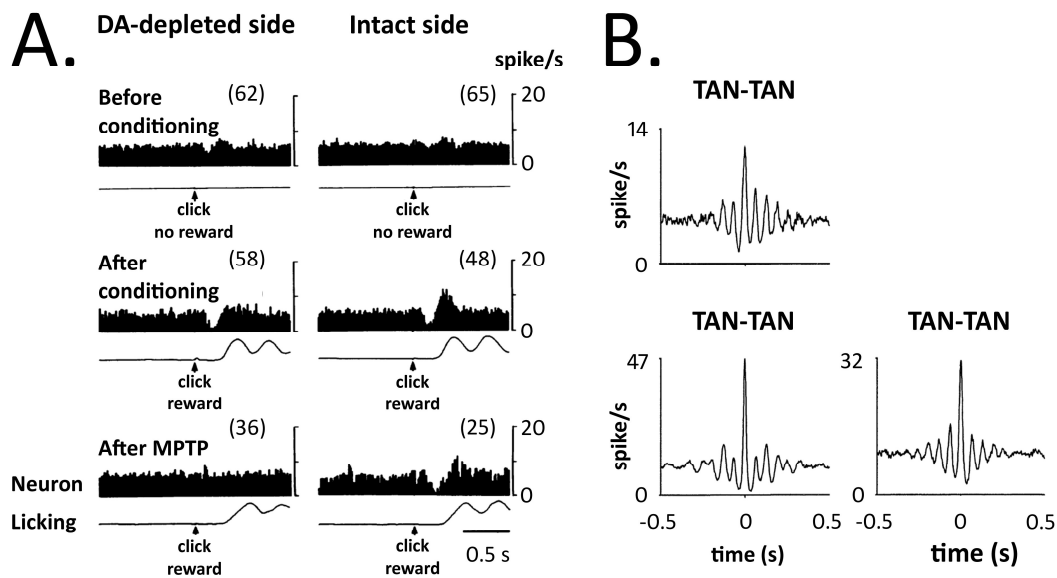


Figure 4: Alteration of the pattern of tonically active neurons after striatal dopamine depletion. (A) Average population responses of tonically active neurons to a conditional cue (click predicting a reward) before and after striatal dopamine depletion (MPTP treatment). Tonically active neurons acquire a response to the click after conditioning (middle). After MPTP (bottom), conditional responses of tonically active neurons disappear in the dopamine depleted side (left), but are maintained in the intact side (right). Numbers in parentheses indicate the number of neurons. Average licking movements are shown below each population histogram. *Adapted from Aosaki et al. (1994)*¹²⁷. **(B)** Crosscorrelograms of tonically active neurons recorded simultaneously in non-human primates after MPTP treatment. As in the healthy state, each activity of tonically active neuron pair is characterized by a central peak, but in addition the pattern of the crosscorrelograms changes and becomes oscillatory. *Adapted from Raz et al. (1996)*⁷⁸.