HAL
open science

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

Marc Deffains, Hagai Bergman

To cite this version:

Marc Deffains, Hagai Bergman. Striatal cholinergic interneurons and cortico-striatal synaptic plasticity in health and disease. Movement Disorders, 2015, 30 (8), pp.1014-1025. 10.1002/mds.26300 . hal-03838698

HAL Id: hal-03838698

https://hal.science/hal-03838698v1

Submitted on 9 Nov 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

Marc Deffains [1,2] & Hagai Bergman [1,2]

1 Department of Medical Neurobiology (Physiology), Institute for Medical Research Israel-Canada (IMRIC), The Hebrew University-Hadassah Medical School, Jerusalem, 91120, Israel

2 The Edmond and Lily Safra Center (ELSC) for Brain Sciences, The Hebrew University, Jerusalem, 91904, Israel

Corresponding author : Marc Deffains

Department of Medical Neurobiology (Physiology), The Hebrew University-Hadassah Medical School, POB 12272, Jerusalem, 91120, Israel. Email: marcd@ekmd.huji.ac.il

Word count : 3953 words

Running title : Cholinergic mechanisms of movement disorders

Key words : striatal cholinergic interneurons, tonically active neurons, cortico-striatal synaptic plasticity, Parkinson's disease, movement disorders

Financial disclosures / Conflict of interest : This work was supported by grants from the Edmond and Lily Safra Center (ELSC), the European Research Council (ERC), the Israel Science Foundation (ISF), the Israel-US Binational Science Foundation (BSF), the German Israel Science Foundation (GIF), the Adelis, Rostrees and Vorst foundations. There is no conflict of interest from any of the authors.

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 brainstem [49], however the relative importance of this external ACh innervation is still under investigation.

Morphologically, striatal cholinergic interneurons have a large soma (Ø 20-50µm), vast dentritic and axonal fields and are devoid of dentritic 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 striatum [45]. Striatal cholinergic interneurons are innervated by midbrain dopaminergic neurons [52-54], MSNs [51;55;56], GABAergic interneurons [57;58] and others cholinergic interneurons [58]. 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 MSNs [65]. 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 matrisomes (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 matrisomes [69]. 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 (~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 mechanisms [72]. A detailed description of the cellular mechanisms of their spontaneous discharge is provided by Goldberg and Wilson [73]. 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 probabilistic [5] 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 Pavlovian [5] and instrumental [6] 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 dentritic 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 administrating 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 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].

Authors' role: 1) Research project: A. Conception, B. Organization, C. Execution; 2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique;

M.D.: 1A, 1B, 1C, 3A, 3B

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

Full financial disclosures of all the authors for the past year

M.D received a postdoctoral fellowship from the Edmond and Lily Safra Center (ELSC). H.B. is a recipient of research grants from the European Research Council (ERC), the Israel Science Foundation (ISF), the Israel-US Binational Science Foundation (BSF), the German Israel Science Foundation (GIF), the Adelis, Rostrees and Vorst foundations.

Reference List

(1) Aosaki T, Miura M, Suzuki T, Nishimura K, Masuda M. Acetylcholine-dopamine balance hypothesis in the striatum: an update. *Geriatr Gerontol Int* 2010; 10 Suppl 1:S148-S157.

(2) Picconi B, Passino E, Sgobio C, Bonsi P, Barone I, Ghiglieri V et al. Plastic and behavioral abnormalities in experimental Huntington's disease: a crucial role for cholinergic interneurons. *Neurobiol Dis* 2006; 22(1):143-152.

(3) Pisani A, Bonsi P, Centonze D, Gubellini P, Bernardi G, Calabresi P. Targeting striatal cholinergic interneurons in Parkinson's disease: focus on metabotropic glutamate receptors. *Neuropharmacology* 2003; 45(1):45-56.

(4) Pisani A, Bernardi G, Ding J, Surmeier DJ. Re-emergence of striatal cholinergic interneurons in movement disorders. *Trends Neurosci* 2007; 30(10):545-553.

(5) Joshua M, Adler A, Mitelman R, Vaadia E, Bergman H. Midbrain dopaminergic neurons and striatal cholinergic interneurons encode the difference between reward and aversive events at different epochs of probabilistic classical conditioning trials. *J Neurosci* 2008; 28(45):11673-11684.

(6) Morris G, Arkadir D, Nevet A, Vaadia E, Bergman H. Coincident but distinct messages of midbrain dopamine and striatal tonically active neurons. *Neuron* 2004; 43(1):133-143.

(7) Cragg SJ. Meaningful silences: how dopamine listens to the ACh pause. *Trends Neurosci* 2006; 29(3):125-131.

(8) DeBoer P, Abercrombie ED. Physiological release of striatal acetylcholine in vivo: modulation by D1 and D2 dopamine receptor subtypes. *J Pharmacol Exp Ther* 1996; 277(2):775-783.

(9) Pisani A, Bonsi P, Centonze D, Calabresi P, Bernardi G. Activation of D2-like dopamine receptors reduces synaptic inputs to striatal cholinergic interneurons. *J Neurosci* 2000; 20(7):RC69.

(10) Rice ME, Cragg SJ. Nicotine amplifies reward-related dopamine signals in striatum. *Nat Neurosci* 2004; 7(6):583-584.

(11) Threlfell S, Lalic T, Platt NJ, Jennings KA, Deisseroth K, Cragg SJ. Striatal dopamine release is triggered by synchronized activity in cholinergic interneurons. *Neuron* 2012; 75(1):58-64.

(12) Benarroch EE. Effects of acetylcholine in the striatum. Recent insights and therapeutic implications. *Neurology* 2012; 79(3):274-281.

(13) Bonsi P, Cuomo D, Martella G, Madeo G, Schirinzi T, Puglisi F et al. Centrality of striatal cholinergic transmission in Basal Ganglia function. *Front Neuroanat* 2011; 5:6.

(14) Bar-Gad I, Bergman H. Stepping out of the box: information processing in the neural networks of the basal ganglia. *Curr Opin Neurobiol* 2001; 11(6):689-695.

(15) Bar-Gad I, Morris G, Bergman H. Information processing, dimensionality reduction and reinforcement learning in the basal ganglia. *Prog Neurobiol* 2003; 71(6):439-473.

(16) Goldberg JA, Bergman H. Computational physiology of the neural networks of the primate globus pallidus: function and dysfunction. *Neuroscience* 2011; 198:171-192.

(17) Gurney K, Prescott TJ, Wickens JR, Redgrave P. Computational models of the basal ganglia: from robots to membranes. *Trends Neurosci* 2004; 27(8):453-459.

(18) Parush N, Tishby N, Bergman H. Dopaminergic Balance between Reward Maximization and Policy Complexity. *Front Syst Neurosci* 2011; 5:22.

(19) Bayer HM, Glimcher PW. Midbrain dopamine neurons encode a quantitative reward prediction error signal. *Neuron* 2005; 47(1):129-141.

(20) Dayan P, Balleine BW. Reward, motivation, and reinforcement learning. *Neuron* 2002; 36(2):285-298.

(21) Fiorillo CD, Tobler PN, Schultz W. Discrete coding of reward probability and uncertainty by dopamine neurons. *Science* 2003; 299(5614):1898-1902.

(22) Nakahara H, Itoh H, Kawagoe R, Takikawa Y, Hikosaka O. Dopamine neurons can represent context-dependent prediction error. *Neuron* 2004; 41(2):269-280.

(23) Satoh T, Nakai S, Sato T, Kimura M. Correlated coding of motivation and outcome of decision by dopamine neurons. *J Neurosci* 2003; 23(30):9913-9923.

(24) Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. *Science* 1997; 275(5306):1593-1599.

(25) Calabresi P, Centonze D, Gubellini P, Pisani A, Bernardi G. Acetylcholine-mediated modulation of striatal function. *Trends Neurosci* 2000; 23(3):120-126.

(26) Kreitzer AC, Malenka RC. Striatal plasticity and basal ganglia circuit function. *Neuron* 2008; 60(4):543-554.

(27) Reynolds JN, Hyland BI, Wickens JR. A cellular mechanism of reward-related learning. *Nature* 2001; 413(6851):67-70.

(28) Shen W, Flajolet M, Greengard P, Surmeier DJ. Dichotomous dopaminergic control of striatal synaptic plasticity. *Science* 2008; 321(5890):848-851.

(29) Surmeier DJ, Ding J, Day M, Wang Z, Shen W. D1 and D2 dopamine-receptor modulation of striatal glutamatergic signaling in striatal medium spiny neurons. *Trends Neurosci* 2007; 30(5):228-235.

(30) Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Res Brain Res Rev* 1998; 28(3):309-369.

(31) Berridge KC, Robinson TE. Parsing reward. *Trends Neurosci* 2003; 26(9):507-513.

(32) Calabresi P, Picconi B, Tozzi A, Di FM. Dopamine-mediated regulation of corticostriatal synaptic plasticity. *Trends Neurosci* 2007; 30(5):211-219.

(33) Wickens JR. Synaptic plasticity in the basal ganglia. *Behav Brain Res* 2009; 199(1):119-128.

(34) Brown RG, Marsden CD. An investigation of the phenomenon of "set" in Parkinson's disease. *Mov Disord* 1988; 3(2):152-161.

(35) Cools AR, van den Bercken JH, Horstink MW, van Spaendonck KP, Berger HJ. Cognitive and motor shifting aptitude disorder in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1984; 47(5):443-453.

(36) Frank MJ, Scheres A, Sherman SJ. Understanding decision-making deficits in neurological conditions: insights from models of natural action selection. *Philos Trans R Soc Lond B Biol Sci* 2007; 362(1485):1641-1654.

(37) Lawrence AD, Sahakian BJ, Hodges JR, Rosser AE, Lange KW, Robbins TW. Executive and mnemonic functions in early Huntington's disease. *Brain* 1996; 119 (Pt 5):1633-1645.

(38) Lawrence AD, Hodges JR, Rosser AE, Kershaw A, ffrench-Constant C, Rubinsztein DC et al. Evidence for specific cognitive deficits in preclinical Huntington's disease. *Brain* 1998; 121 (Pt 7):1329-1341.

(39) Mink JW. The basal ganglia: focused selection and inhibition of competing motor programs. *Prog Neurobiol* 1996; 50(4):381-425.

(40) Apicella P. Tonically active neurons in the primate striatum and their role in the processing of information about motivationally relevant events. *Eur J Neurosci* 2002; 16(11):2017-2026.

(41) Apicella P. Leading tonically active neurons of the striatum from reward detection to context recognition. *Trends Neurosci* 2007; 30(6):299-306.

(42) Graybiel AM, Aosaki T, Flaherty AW, Kimura M. The basal ganglia and adaptive motor control. *Science* 1994; 265(5180):1826-1831.

(43) Kimura M, Rajkowski J, Evarts E. Tonically discharging putamen neurons exhibit set-dependent responses. *Proc Natl Acad Sci U S A* 1984; 81(15):4998-5001.

(44) Kawaguchi Y. Physiological, morphological, and histochemical characterization of three classes of interneurons in rat neostriatum. *J Neurosci* 1993; 13(11):4908-4923.

(45) Kawaguchi Y, Wilson CJ, Augood SJ, Emson PC. Striatal interneurones: chemical, physiological and morphological characterization. *Trends Neurosci* 1995; 18(12):527-535.

(46) Wilson CJ, Chang HT, Kitai ST. Firing patterns and synaptic potentials of identified giant aspiny interneurons in the rat neostriatum. *J Neurosci* 1990; 10(2):508-519.

(47) Graveland GA, DiFiglia M. The frequency and distribution of medium-sized neurons with indented nuclei in the primate and rodent neostriatum. *Brain Res* 1985; 327(1-2):307-311.

(48) Graveland GA, Williams RS, DiFiglia M. A Golgi study of the human neostriatum: neurons and afferent fibers. *J Comp Neurol* 1985; 234(3):317-333.

(49) Dautan D, Huerta-Ocampo I, Witten IB, Deisseroth K, Bolam JP, Gerdjikov T et al. A major external source of cholinergic innervation of the striatum and nucleus accumbens originates in the brainstem. *J Neurosci* 2014; 34(13):4509-4518.

(50) Bolam JP, Wainer BH, Smith AD. Characterization of cholinergic neurons in the rat neostriatum. A combination of choline acetyltransferase immunocytochemistry, Golgi-impregnation and electron microscopy. *Neuroscience* 1984; 12(3):711-718.

(51) Smith AD, Bolam JP. The neural network of the basal ganglia as revealed by the study of synaptic connections of identified neurones. *Trends Neurosci* 1990; 13(7):259-265.

(52) Chang HT. Dopamine-acetylcholine interaction in the rat striatum: a dual-labeling immunocytochemical study. *Brain Res Bull* 1988; 21(2):295-304.

(53) Dimova R, Vuillet J, Nieoullon A, Kerkerian-Le GL. Ultrastructural features of the choline acetyltransferase-containing neurons and relationships with nigral dopaminergic and cortical afferent pathways in the rat striatum. *Neuroscience* 1993; 53(4):1059-1071.

(54) Kubota Y, Inagaki S, Shimada S, Kito S, Eckenstein F, Tohyama M. Neostriatal cholinergic neurons receive direct synaptic inputs from dopaminergic axons. *Brain Res* 1987; 413(1):179-184.

(55) Bolam JP, Ingham CA, Izzo PN, Levey AI, Rye DB, Smith AD et al. Substance P-containing terminals in synaptic contact with cholinergic neurons in the

neostriatum and basal forebrain: a double immunocytochemical study in the rat. *Brain Res* 1986; 397(2):279-289.

(56) Martone ME, Armstrong DM, Young SJ, Groves PM. Ultrastructural examination of enkephalin and substance P input to cholinergic neurons within the rat neostriatum. *Brain Res* 1992; 594(2):253-262.

(57) Chang HT, Kita H. Interneurons in the rat striatum: relationships between parvalbumin neurons and cholinergic neurons. *Brain Res* 1992; 574(1-2):307-311.

(58) Vuillet J, Dimova R, Nieoullon A, Kerkerian-Le GL. Ultrastructural relationships between choline acetyltransferase- and neuropeptide y-containing neurons in the rat striatum. *Neuroscience* 1992; 46(2):351-360.

(59) Doig NM, Magill PJ, Apicella P, Bolam JP, Sharott A. Cortical and thalamic excitation mediate the multiphasic responses of striatal cholinergic interneurons to motivationally salient stimuli. *J Neurosci* 2014; 34(8):3101-3117.

(60) Lapper SR, Bolam JP. Input from the frontal cortex and the parafascicular nucleus to cholinergic interneurons in the dorsal striatum of the rat. *Neuroscience* 1992; 51(3):533-545.

(61) Reynolds JN, Wickens JR. The corticostriatal input to giant aspiny interneurons in the rat: a candidate pathway for synchronising the response to reward-related cues. *Brain Res* 2004; 1011(1):115-128.

(62) Sidibe M, Smith Y. Thalamic inputs to striatal interneurons in monkeys: synaptic organization and co-localization of calcium binding proteins. *Neuroscience* 1999; 89(4):1189-1208.

(63) Ding JB, Guzman JN, Peterson JD, Goldberg JA, Surmeier DJ. Thalamic gating of corticostriatal signaling by cholinergic interneurons. *Neuron* 2010; 67(2):294-307.

(64) Matsumoto N, Minamimoto T, Graybiel AM, Kimura M. Neurons in the thalamic CM-Pf complex supply striatal neurons with information about behaviorally significant sensory events. *J Neurophysiol* 2001; 85(2):960-976.

(65) Izzo PN, Bolam JP. Cholinergic synaptic input to different parts of spiny striatonigral neurons in the rat. *J Comp Neurol* 1988; 269(2):219-234.

(66) Graybiel AM, Ragsdale CW, Jr. Histochemically distinct compartments in the striatum of human, monkeys, and cat demonstrated by acetylthiocholinesterase staining. *Proc Natl Acad Sci U S A* 1978; 75(11):5723-5726.

(67) Graybiel AM, Baughman RW, Eckenstein F. Cholinergic neuropil of the striatum observes striosomal boundaries. *Nature* 1986; 323(6089):625-627.

(68) Kreitzer AC. Physiology and pharmacology of striatal neurons. *Annu Rev Neurosci* 2009; 32:127-147.

(69) Amemori K, Gibb LG, Graybiel AM. Shifting responsibly: the importance of striatal modularity to reinforcement learning in uncertain environments. *Front Hum Neurosci* 2011; 5:47.

(70) Wilson CJ. The mechanism of intrinsic amplification of hyperpolarizations and spontaneous bursting in striatal cholinergic interneurons. *Neuron* 2005; 45(4):575-585.

(71) Wilson CJ, Goldberg JA. Origin of the slow afterhyperpolarization and slow rhythmic bursting in striatal cholinergic interneurons. *J Neurophysiol* 2006; 95(1):196-204.

(72) Bennett BD, Wilson CJ. Spontaneous activity of neostriatal cholinergic interneurons in vitro. *J Neurosci* 1999; 19(13):5586-5596.

(73) Goldberg JA, Wilson CJ. Control of spontaneous firing patterns by the selective coupling of calcium currents to calcium-activated potassium currents in striatal cholinergic interneurons. *J Neurosci* 2005; 25(44):10230-10238.

(74) Alexander GE, DeLong MR. Microstimulation of the primate neostriatum. I. Physiological properties of striatal microexcitable zones. *J Neurophysiol* 1985; 53(6):1401-1416.

(75) Aosaki T, Tsubokawa H, Ishida A, Watanabe K, Graybiel AM, Kimura M. Responses of tonically active neurons in the primate's striatum undergo systematic changes during behavioral sensorimotor conditioning. *J Neurosci* 1994; 14(6):3969-3984.

(76) Benhamou L, Kehat O, Cohen D. Firing pattern characteristics of tonically active neurons in rat striatum: context dependent or species divergent? *J Neurosci* 2014; 34(6):2299-2304.

(77) Crutcher MD, DeLong MR. Single cell studies of the primate putamen. I. Functional organization. *Exp Brain Res* 1984; 53(2):233-243.

(78) Raz A, Feingold A, Zelanskaya V, Vaadia E, Bergman H. Neuronal synchronization of tonically active neurons in the striatum of normal and parkinsonian primates. *J Neurophysiol* 1996; 76(3):2083-2088.

(79) Adler A, Finkes I, Katabi S, Prut Y, Bergman H. Encoding by synchronization in the primate striatum. *J Neurosci* 2013; 33(11):4854-4866.

(80) Apicella P, Legallet E, Trouche E. Responses of tonically discharging neurons in the monkey striatum to primary rewards delivered during different behavioral states. *Exp Brain Res* 1997; 116(3):456-466.

(81) Apicella P, Ravel S, Sardo P, Legallet E. Influence of predictive information on responses of tonically active neurons in the monkey striatum. *J Neurophysiol* 1998; 80(6):3341-3344.

(82) Blazquez PM, Fujii N, Kojima J, Graybiel AM. A network representation of response probability in the striatum. *Neuron* 2002; 33(6):973-982.

(83) Deffains M, Legallet E, Apicella P. Modulation of neuronal activity in the monkey putamen associated with changes in the habitual order of sequential movements. *J Neurophysiol* 2010; 104(3):1355-1369.

(84) Shimo Y, Hikosaka O. Role of tonically active neurons in primate caudate in reward-oriented saccadic eye movement. *J Neurosci* 2001; 21(19):7804-7814.

(85) Ravel S, Legallet E, Apicella P. Tonically active neurons in the monkey striatum do not preferentially respond to appetitive stimuli. *Exp Brain Res* 1999; 128(4):531-534.

(86) Ravel S, Legallet E, Apicella P. Responses of tonically active neurons in the monkey striatum discriminate between motivationally opposing stimuli. *J Neurosci* 2003; 23(24):8489-8497.

(87) Ravel S, Sardo P, Legallet E, Apicella P. Reward unpredictability inside and outside of a task context as a determinant of the responses of tonically active neurons in the monkey striatum. *J Neurosci* 2001; 21(15):5730-5739.

(88) Sardo P, Ravel S, Legallet E, Apicella P. Influence of the predicted time of stimuli eliciting movements on responses of tonically active neurons in the monkey striatum. *Eur J Neurosci* 2000; 12(5):1801-1816.

(89) Adler A, Katabi S, Finkes I, Israel Z, Prut Y, Bergman H. Temporal convergence of dynamic cell assemblies in the striato-pallidal network. *J Neurosci* 2012; 32(7):2473-2484.

(90) Apicella P, Deffains M, Ravel S, Legallet E. Tonically active neurons in the striatum differentiate between delivery and omission of expected reward in a probabilistic task context. *Eur J Neurosci* 2009; 30(3):515-526.

(91) Apicella P, Ravel S, Deffains M, Legallet E. The role of striatal tonically active neurons in reward prediction error signaling during instrumental task performance. *J Neurosci* 2011; 31(4):1507-1515.

(92) Niv Y, Schoenbaum G. Dialogues on prediction errors. *Trends Cogn Sci* 2008; 12(7):265-272.

(93) Schultz W, Dickinson A. Neuronal coding of prediction errors. *Annu Rev Neurosci* 2000; 23:473-500.

(94) Kimura M, Matsumoto N, Okahashi K, Ueda Y, Satoh T, Minamimoto T et al. Goal-directed, serial and synchronous activation of neurons in the primate striatum. *Neuroreport* 2003; 14(6):799-802.

(95) Joshua M, Adler A, Prut Y, Vaadia E, Wickens JR, Bergman H. Synchronization of midbrain dopaminergic neurons is enhanced by rewarding events. *Neuron* 2009; 62(5):695-704.

(96) Arbuthnott GW, Wickens J. Space, time and dopamine. *Trends Neurosci* 2007; 30(2):62-69.

(97) Moss J, Bolam JP. A dopaminergic axon lattice in the striatum and its relationship with cortical and thalamic terminals. *J Neurosci* 2008; 28(44):11221-11230.

(98) Goldberg JA, Reynolds JN. Spontaneous firing and evoked pauses in the tonically active cholinergic interneurons of the striatum. *Neuroscience* 2011; 198:27-43.

(99) Calabresi P, Maj R, Mercuri NB, Bernardi G. Coactivation of D1 and D2 dopamine receptors is required for long-term synaptic depression in the striatum. *Neurosci Lett* 1992; 142(1):95-99.

(100) Centonze D, Picconi B, Gubellini P, Bernardi G, Calabresi P. Dopaminergic control of synaptic plasticity in the dorsal striatum. *Eur J Neurosci* 2001; 13(6):1071-1077.

(101) Lovinger DM, Tyler EC, Merritt A. Short- and long-term synaptic depression in rat neostriatum. *J Neurophysiol* 1993; 70(5):1937-1949.

(102) Surmeier DJ, Plotkin J, Shen W. Dopamine and synaptic plasticity in dorsal striatal circuits controlling action selection. *Curr Opin Neurobiol* 2009; 19(6):621-628.

(103) Calabresi P, Pisani A, Mercuri NB, Bernardi G. The corticostriatal projection: from synaptic plasticity to dysfunctions of the basal ganglia. *Trends Neurosci* 1996; 19(1):19-24.

(104) Mahon S, Deniau JM, Charpier S. Corticostriatal plasticity: life after the depression. *Trends Neurosci* 2004; 27(8):460-467.

(105) Abbott LF, Nelson SB. Synaptic plasticity: taming the beast. *Nat Neurosci* 2000; 3 Suppl:1178-1183.

(106) Sjostrom PJ, Nelson SB. Spike timing, calcium signals and synaptic plasticity. *Curr Opin Neurobiol* 2002; 12(3):305-314.

(107) Pawlak V, Kerr JN. Dopamine receptor activation is required for corticostriatal spike-timing-dependent plasticity. *J Neurosci* 2008; 28(10):2435-2446.

(108) Fino E, Glowinski J, Venance L. Bidirectional activity-dependent plasticity at corticostriatal synapses. *J Neurosci* 2005; 25(49):11279-11287.

(109) Fino E, Venance L. Spike-timing dependent plasticity in the striatum. *Front Synaptic Neurosci* 2010; 2:6.

(110) Pawlak V, Wickens JR, Kirkwood A, Kerr JN. Timing is not Everything: Neuromodulation Opens the STDP Gate. *Front Synaptic Neurosci* 2010; 2:146.

(111) Galarraga E, Hernandez-Lopez S, Reyes A, Miranda I, Bermudez-Rattoni F, Vilchis C et al. Cholinergic modulation of neostriatal output: a functional antagonism between different types of muscarinic receptors. *J Neurosci* 1999; 19(9):3629-3638.

(112) Shen W, Hamilton SE, Nathanson NM, Surmeier DJ. Cholinergic suppression of KCNQ channel currents enhances excitability of striatal medium spiny neurons. *J Neurosci* 2005; 25(32):7449-7458.

(113) Calabresi P, Centonze D, Gubellini P, Bernardi G. Activation of M1-like muscarinic receptors is required for the induction of corticostriatal LTP. *Neuropharmacology* 1999; 38(2):323-326.

(114) Centonze D, Gubellini P, Bernardi G, Calabresi P. Permissive role of interneurons in corticostriatal synaptic plasticity. *Brain Res Brain Res Rev* 1999; 31(1):1-5.

(115) Wang Z, Kai L, Day M, Ronesi J, Yin HH, Ding J et al. Dopaminergic control of corticostriatal long-term synaptic depression in medium spiny neurons is mediated by cholinergic interneurons. *Neuron* 2006; 50(3):443-452.

(116) Fino E, Deniau JM, Venance L. Cell-specific spike-timing-dependent plasticity in GABAergic and cholinergic interneurons in corticostriatal rat brain slices. *J Physiol* 2008; 586(1):265-282.

(117) Exley R, Cragg SJ. Presynaptic nicotinic receptors: a dynamic and diverse cholinergic filter of striatal dopamine neurotransmission. *Br J Pharmacol* 2008; 153 Suppl 1:S283-S297.

(118) Hyland BI, Reynolds JN, Hay J, Perk CG, Miller R. Firing modes of midbrain dopamine cells in the freely moving rat. *Neuroscience* 2002; 114(2):475-492.

(119) Zhang H, Sulzer D. Frequency-dependent modulation of dopamine release by nicotine. *Nat Neurosci* 2004; 7(6):581-582.

(120) Reynolds JN, Wickens JR. Dopamine-dependent plasticity of corticostriatal synapses. *Neural Netw* 2002; 15(4-6):507-521.

(121) Duvoisin RC. Cholinergic-anticholinergic antagonism in parkinsonism. *Arch Neurol* 1967; 17(2):124-136.

(122) Fahn S. The medical treatment of Parkinson disease from James Parkinson to George Cotzias. *Mov Disord* 2014.

(123) Maurice N, Mercer J, Chan CS, Hernandez-Lopez S, Held J, Tkatch T et al. D2 dopamine receptor-mediated modulation of voltage-dependent Na+ channels reduces autonomous activity in striatal cholinergic interneurons. *J Neurosci* 2004; 24(46):10289-10301.

(124) Ding J, Guzman JN, Tkatch T, Chen S, Goldberg JA, Ebert PJ et al. RGS4-dependent attenuation of M4 autoreceptor function in striatal cholinergic interneurons following dopamine depletion. *Nat Neurosci* 2006; 9(6):832-842.

(125) Fino E, Glowinski J, Venance L. Effects of acute dopamine depletion on the electrophysiological properties of striatal neurons. *Neurosci Res* 2007; 58(3):305-316.

(126) Hernandez LF, Kubota Y, Hu D, Howe MW, Lemaire N, Graybiel AM. Selective effects of dopamine depletion and L-DOPA therapy on learning-related firing dynamics of striatal neurons. *J Neurosci* 2013; 33(11):4782-4795.

(127) Aosaki T, Graybiel AM, Kimura M. Effect of the nigrostriatal dopamine system on acquired neural responses in the striatum of behaving monkeys. *Science* 1994; 265(5170):412-415.

(128) Watanabe K, Kimura M. Dopamine receptor-mediated mechanisms involved in the expression of learned activity of primate striatal neurons. *J Neurophysiol* 1998; 79(5):2568-2580.

(129) Raz A, Frechter-Mazar V, Feingold A, Abeles M, Vaadia E, Bergman H. Activity of pallidal and striatal tonically active neurons is correlated in mptp-treated monkeys but not in normal monkeys. *J Neurosci* 2001; 21(3):RC128.

(130) Calabresi P, Maj R, Pisani A, Mercuri NB, Bernardi G. Long-term synaptic depression in the striatum: physiological and pharmacological characterization. *J Neurosci* 1992; 12(11):4224-4233.

(131) Centonze D, Gubellini P, Picconi B, Calabresi P, Giacomini P, Bernardi G. Unilateral dopamine denervation blocks corticostriatal LTP. *J Neurophysiol* 1999; 82(6):3575-3579.

(132) Picconi B, Centonze D, Hakansson K, Bernardi G, Greengard P, Fisone G et al. Loss of bidirectional striatal synaptic plasticity in L-DOPA-induced dyskinesia. *Nat Neurosci* 2003; 6(5):501-506.

(133) Pisani A, Centonze D, Bernardi G, Calabresi P. Striatal synaptic plasticity: implications for motor learning and Parkinson's disease. *Mov Disord* 2005; 20(4):395-402.

(134) Salin P, Lopez IP, Kachidian P, Barroso-Chinea P, Rico AJ, Gomez-Bautista V et al. Changes to interneuron-driven striatal microcircuits in a rat model of Parkinson's disease. *Neurobiol Dis* 2009; 34(3):545-552.

(135) Shen W, Tian X, Day M, Ulrich S, Tkatch T, Nathanson NM et al. Cholinergic modulation of Kir2 channels selectively elevates dendritic excitability in striatopallidal neurons. *Nat Neurosci* 2007; 10(11):1458-1466.

(136) Nishijima H, Suzuki S, Kon T, Funamizu Y, Ueno T, Haga R et al. Morphologic changes of dendritic spines of striatal neurons in the levodopa-induced dyskinesia model. *Mov Disord* 2014; 29(3):336-343.

(137) Picconi B, Paille V, Ghiglieri V, Bagetta V, Barone I, Lindgren HS et al. l-DOPA dosage is critically involved in dyskinesia via loss of synaptic depotentiation. *Neurobiol Dis* 2008; 29(2):327-335.

(138) Ding Y, Won L, Britt JP, Lim SA, McGehee DS, Kang UJ. Enhanced striatal cholinergic neuronal activity mediates L-DOPA-induced dyskinesia in parkinsonian mice. *Proc Natl Acad Sci U S A* 2011; 108(2):840-845.

(139) Won L, Ding Y, Singh P, Kang UJ. Striatal cholinergic cell ablation attenuates L-DOPA induced dyskinesia in Parkinsonian mice. *J Neurosci* 2014; 34(8):3090-3094.

(140) Fahn S, Bressman SB, Marsden CD. Classification of dystonia. *Adv Neurol* 1998; 78:1-10.

(141) Albanese A, Lalli S. Update on dystonia. *Curr Opin Neurol* 2012; 25(4):483-490.

(142) Fahn S. High dosage anticholinergic therapy in dystonia. *Neurology* 1983; 33(10):1255-1261.

(143) Pisani A, Martella G, Tscherter A, Bonsi P, Sharma N, Bernardi G et al. Altered responses to dopaminergic D2 receptor activation and N-type calcium currents in striatal cholinergic interneurons in a mouse model of DYT1 dystonia. *Neurobiol Dis* 2006; 24(2):318-325.

(144) Clos MV, Garcia-Sanz A, Vivas NM, Badia A. D2 dopamine receptors and modulation of spontaneous acetylcholine (ACh) release from rat striatal synaptosomes. *Br J Pharmacol* 1997; 122(2):286-290.

(145) DeBoer P, Heeringa MJ, Abercrombie ED. Spontaneous release of acetylcholine in striatum is preferentially regulated by inhibitory dopamine D2 receptors. *Eur J Pharmacol* 1996; 317(2-3):257-262.

(146) Yan Z, Song WJ, Surmeier J. D2 dopamine receptors reduce N-type Ca2+ currents in rat neostriatal cholinergic interneurons through a membrane-delimited, protein-kinase-C-insensitive pathway. *J Neurophysiol* 1997; 77(2):1003-1015.

(147) Martella G, Tassone A, Sciamanna G, Platania P, Cuomo D, Viscomi MT et al. Impairment of bidirectional synaptic plasticity in the striatum of a mouse model of DYT1 dystonia: role of endogenous acetylcholine. *Brain* 2009; 132(Pt 9):2336-2349.

(148) Sciamanna G, Tassone A, Mandolesi G, Puglisi F, Ponterio G, Martella G et al. Cholinergic dysfunction alters synaptic integration between thalamostriatal and corticostriatal inputs in DYT1 dystonia. *J Neurosci* 2012; 32(35):11991-12004.

(149) Andre VM, Fisher YE, Levine MS. Altered Balance of Activity in the Striatal Direct and Indirect Pathways in Mouse Models of Huntington's Disease. *Front Syst Neurosci* 2011; 5:46.

(150) Galvan L, Andre VM, Wang EA, Cepeda C, Levine MS. Functional Differences Between Direct and Indirect Striatal Output Pathways in Huntington's Disease. *J Huntingtons Dis* 2012; 1(1):17-25.

(151) Li SH, Li XJ. Huntingtin-protein interactions and the pathogenesis of Huntington's disease. *Trends Genet* 2004; 20(3):146-154.

(152) Graveland GA, Williams RS, DiFiglia M. Evidence for degenerative and regenerative changes in neostriatal spiny neurons in Huntington's disease. *Science* 1985; 227(4688):770-773.

(153) Mangiarini L, Sathasivam K, Seller M, Cozens B, Harper A, Hetherington C et al. Exon 1 of the HD gene with an expanded CAG repeat is sufficient to cause a progressive neurological phenotype in transgenic mice. *Cell* 1996; 87(3):493-506.

(154) Smith R, Chung H, Rundquist S, Maat-Schieman ML, Colgan L, Englund E et al. Cholinergic neuronal defect without cell loss in Huntington's disease. *Hum Mol Genet* 2006; 15(21):3119-3131.

(155) Vetter JM, Jehle T, Heinemeyer J, Franz P, Behrens PF, Jackisch R et al. Mice transgenic for exon 1 of Huntington's disease: properties of cholinergic and dopaminergic pre-synaptic function in the striatum. *J Neurochem* 2003; 85(4):1054-1063.

(156) Hiley CR, Bird ED. Decreased muscarinic receptor concentration in post-mortem brain in Huntington's chorea. *Brain Res* 1974; 80(2):355-358.

(157) Wastek GJ, Stern LZ, Johnson PC, Yamamura HI. Huntington's disease: regional alteration in muscarinic cholinergic receptor binding in human brain. *Life Sci* 1976; 19(7):1033-1039.

(158) Ferrante RJ, Beal MF, Kowall NW, Richardson EP, Jr., Martin JB. Sparing of acetylcholinesterase-containing striatal neurons in Huntington's disease. *Brain Res* 1987; 411(1):162-166.

(159) Suzuki M, Desmond TJ, Albin RL, Frey KA. Vesicular neurotransmitter transporters in Huntington's disease: initial observations and comparison with traditional synaptic markers. *Synapse* 2001; 41(4):329-336.

(160) Callahan JW, Abercrombie ED. In vivo Dopamine Efflux is Decreased in Striatum of both Fragment (R6/2) and Full-Length (YAC128) Transgenic Mouse Models of Huntington's Disease. *Front Syst Neurosci* 2011; 5:61.

(161) Farrar AM, Callahan JW, Abercrombie ED. Reduced striatal acetylcholine efflux in the R6/2 mouse model of Huntington's disease: an examination of the role of altered inhibitory and excitatory mechanisms. *Exp Neurol* 2011; 232(2):119-125.

(162) Brooks SP, Dunnett SB. Mouse Models of Huntington's Disease. *Curr Top Behav Neurosci* 2013.

(163) Brown HD, Baker PM, Ragozzino ME. The parafascicular thalamic nucleus concomitantly influences behavioral flexibility and dorsomedial striatal acetylcholine output in rats. *J Neurosci* 2010; 30(43):14390-14398.

(164) Bamford NS, Zhang H, Joyce JA, Scarlis CA, Hanan W, Wu NP et al. Repeated exposure to methamphetamine causes long-lasting presynaptic corticostriatal depression that is renormalized with drug readministration. *Neuron* 2008; 58(1):89-103.

(165) Williams MJ, Adinoff B. The role of acetylcholine in cocaine addiction. *Neuropsychopharmacology* 2008; 33(8):1779-1797.

(166) Aliane V, Perez S, Bohren Y, Deniau JM, Kemel ML. Key role of striatal cholinergic interneurons in processes leading to arrest of motor stereotypies. *Brain* 2011; 134(Pt 1):110-118.

(167) Blier P, El MM. Serotonin and beyond: therapeutics for major depression. *Philos Trans R Soc Lond B Biol Sci* 2013; 368(1615):20120536.

(168) Denys D, de VF, Cath D, Figee M, Vulink N, Veltman DJ et al. Dopaminergic activity in Tourette syndrome and obsessive-compulsive disorder. *Eur Neuropsychopharmacol* 2013; 23(11):1423-1431.

(169) Kataoka Y, Kalanithi PS, Grantz H, Schwartz ML, Saper C, Leckman JF et al. Decreased number of parvalbumin and cholinergic interneurons in the striatum of individuals with Tourette syndrome. *J Comp Neurol* 2010; 518(3):277-291.

(170) Xu M, Kobets A, Du JC, Lennington J, Li L, Banasr M et al. Targeted ablation of cholinergic interneurons in the dorsolateral striatum produces behavioral manifestations of Tourette syndrome. *Proc Natl Acad Sci U S A* 2015; 112(3):893-898.

(171) Allendes FE, Lozano AM, Hutchison WD. Attenuation of long-term depression in human striatum after anterior capsulotomy. *Stereotact Funct Neurosurg* 2008; 86(4):224-230.

(172) Kalia LV, Brotchie JM, Fox SH. Novel nondopaminergic targets for motor features of Parkinson's disease: review of recent trials. *Mov Disord* 2013; 28(2):131-144.

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 impairement/loss, respectively

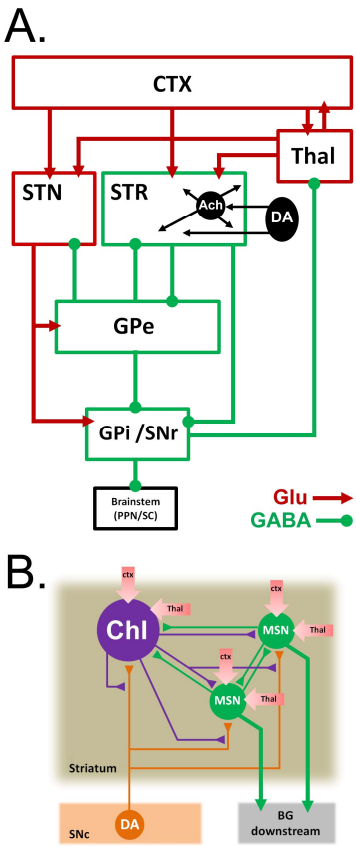

Figure 1: Cholinergic interneurons within basal ganglia network. (A) Schematic model of the basal ganglia network. Input structures of the BG (striatum and subthalamic nucleus) receive inputs from the cortex and the thalamus. The output structures of the BG (internal segment of the globus pallidus and 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: pedonculopontine nucleus; SC: superior colliculus; ACh: acetycholine, 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.

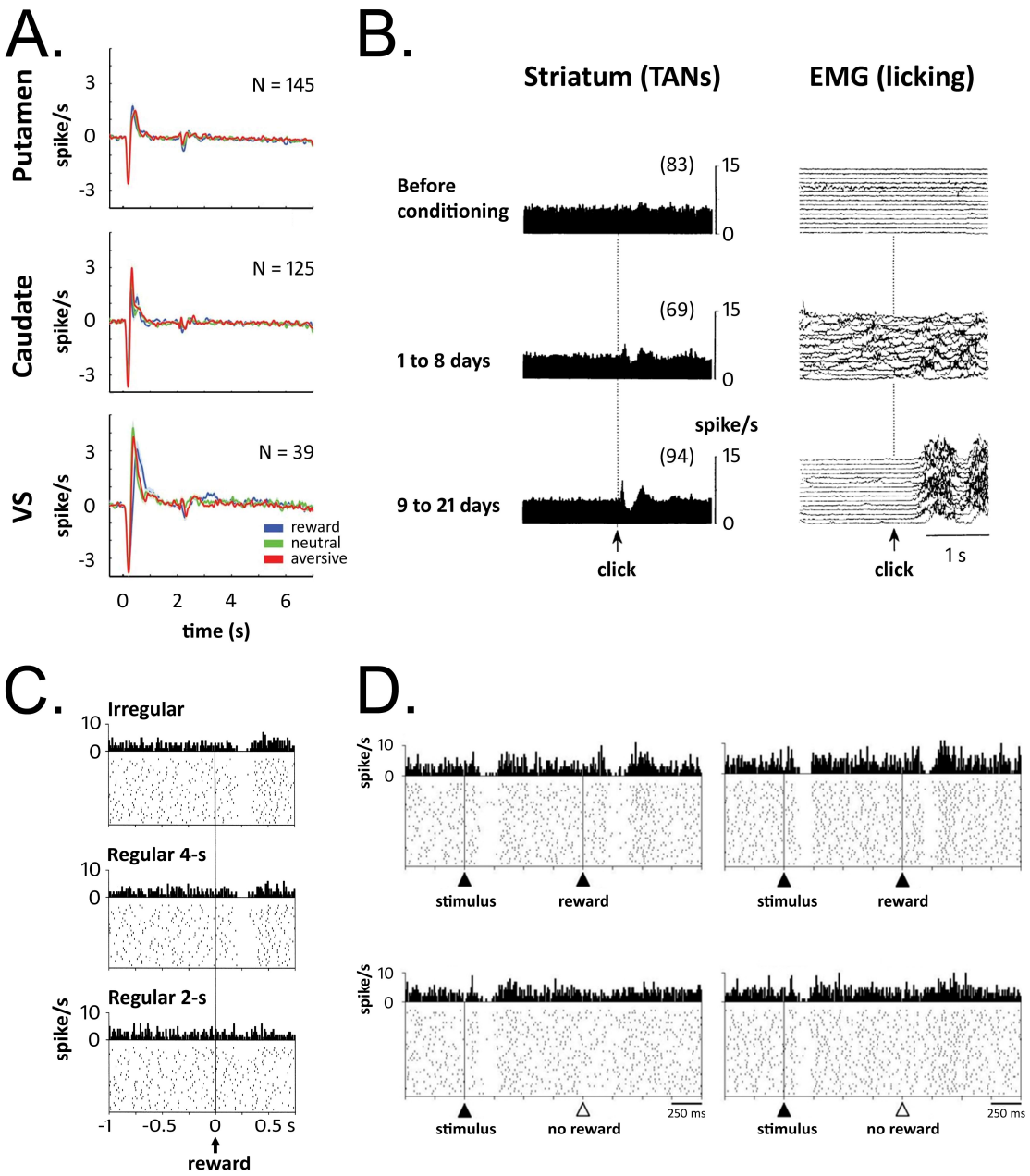

Figure 2: Response properties of tonically active neurons. (A) Average population responses of tonically active neurons to behavioral events in the putamen, caudate nucleus and ventral striatum (VS). Time 0 indicates the cue presentation followed by outcome delivery at time 2s. Color codes indicate cue 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].

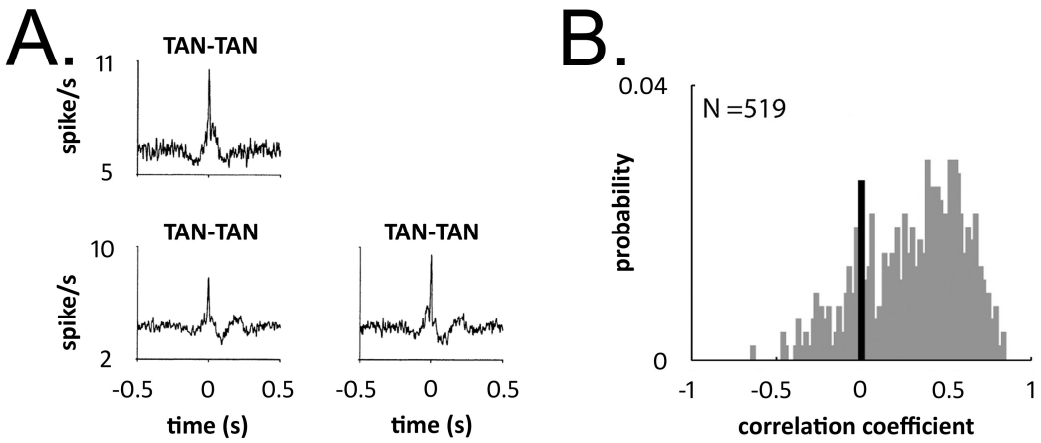

Figure 3: Homogenous activity of tonically active neurons (A) Crosscorrelograms of tonically active neurons recorded simultaneously in healthy non-human primates. The zero-centered peak in the crosscorrelograms indicates that the activity of tonically active neuron pair is highly synchronized. *Adapted 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].

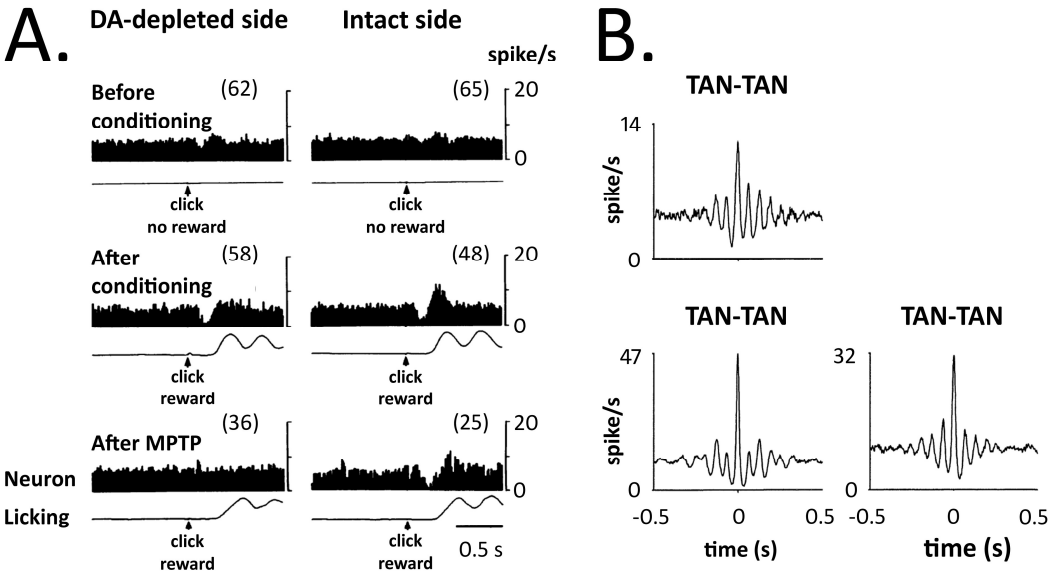

Figure 4: Alteration of the pattern of tonically active neurons after striatal dopamine depletion. (A) Average population responses of tonically active neurons to a conditional cue (click predicting a reward) before and after striatal dopamine depletion (MPTP treatment). Tonically active neurons acquire 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].