Reciprocal interaction between striatal cholinergic and low-threshold spiking interneurons — A computational study

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Abstract
The striatum is the main input stage of the basal ganglia receiving extrinsic input from cortex and thalamus. The striatal projection neurons (SPN) constitute 95% of the neurons in the striatum in mice while the remaining 5% are cholinergic and GABAergic interneurons. The cholinergic (ChIN) and low-threshold spiking interneurons (LTS) are spontaneously active and form a striatal subnetwork involved in salience detection and goal-directed learning. Activation of ChINs has been shown to inhibit LTS via muscarinic receptor type 4 (M4R) and LTS in turn can modulate ChINs via nitric oxide (NO) causing a prolonged depolarization. Thalamic input prefentially excites ChINs, whereas input from motor cortex favours LTS, but can also excite ChINs. This varying extrinsic input with intrinsic reciprocal, yet opposing, effects raises the possibility of a slow input-dependent modulatory subnetwork. Here, we simulate this subnetwork using multicompartmental neuron models that incorporate data regarding known ion channels and detailed morphological reconstructions. The modelled connections replicate the experimental data on muscarinic (M4R) and nitric oxide modulation onto LTS and ChIN, respectively, and capture their physiological interaction. Finally, we show that the cortical and thalamic inputs triggering the opposing modulation within the network induce periods of increased and decreased spiking activity in ChINs and LTS. This could provide different temporal windows for selective modulation by acetylcholine and nitric oxide, and the possibility of interaction with the wider striatal microcircuit.

KEYWORDS
cortex, muscarinic, networks, nitric oxide, thalamus

Abbreviations: ACh, acetylcholine; AChE, acetylcholinesterase; ChIN, cholinergic interneuron; dSPN, direct striatal projection neuron; EPSP, excitatory postsynaptic potential; HFS, high-frequency stimulation; iSPN, indirect striatal projection neuron; KIR2/3, inward rectifier potassium ion channel subfamily 2 and 3; LTD, long-term depression; LTP, long-term potentiation; LTS, low-threshold spiking interneuron; M1R, muscarinic acetylcholine receptor 1; M4R, muscarinic acetylcholine receptor 4; NO, nitric oxide; NPY, neuropeptide Y; SABI, spontaneously active bursty interneuron; SOM, somatostatin; SPN, striatal projection neuron; THIN, tyrosine hydroxylase interneuron.

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1 | INTRODUCTION

The basal ganglia are involved in motor learning, action-selection and reinforcement learning. The main input stage, the striatum, consists of 95% striatal projection neurons of two types involved in the direct and indirect pathways (dSPNs and iSPNs), and in addition 5% interneurons (Burke, Rotstein, & Alvarez, 2017). The interneurons are either cholinergic or GABAergic. The cholinergic interneurons (ChIN) and the GABAergic low-threshold spiking interneurons (LTS) belong to a spontaneously active subgroup of interneurons—also including tyrosine hydroxylase interneurons (THIN) and the spontaneously active bursty interneurons (SABI) (Assous et al., 2018). Striatum is by far the largest structure of the basal ganglia and is one of the most modulated structures in the central nervous system where modulation by dopamine (DA), acetylcholine (ACh), adenosine and nitric oxide (NO), amongst others, is central to its operation. We will focus here on the interaction between ChINs and LTS in the striatal microcircuit.

The ChINs have a rich axonal arbour within the striatum (Suzuki, Miura, Nishimura, & Aosaki, 2001), are tonically active at rest and release acetylcholine. The level of ACh is regulated by the high expression of acetylcholinesterase (AChE) (Abudukeyoumu, Hernandez-Flores, Garcia-Munoz, & Arbuthnott, 2019). ChINs operate through muscarinic and nicotinic receptors and target LTS. In terms of function, the ChINs have been extensively characterized in their involvement in motivational encoding and responses to salient events and reward. They are also involved in synaptic plasticity, and it has been shown that the level of ACh influences whether long-term potentiation (LTP) or long-term depression (LTD) will occur at SPN synapses (Abudukeyoumu et al., 2019; Bruce et al., 2019; Deffains & Bergman, 2015; Lerner & Kreitzer, 2011; Nair et al., 2019; Nair, Gutierrez-Arenas, Eriksson, Vincent, & Hellgren Kotalveski, 2015).

On the other hand, LTS release not only GABA but also somatostatin (SOM), neuropeptide Y (NPY) and NO (Kawaguchi, Wilson, Augood, & Emson, 1995) and are modulated by acetylcholine and dopamine. Following direct activation of ChINs, LTS receive primarily a M4R-dependent inhibitory response (Melendez-Zaidi, Lakshminarasimhah, & Surmeier, 2019). Pharmacologically, acetylcholine can also modulate LTS activity via M1 muscarinic receptors (Melendez-Zaidi et al., 2019) and indirectly via nicotinic receptors (Elghaba, Vautrelle, & Bracci, 2016). Furthermore, DA excites LTS by activating D1-like receptors (Centonze et al., 2002). This accounts for the evidence that both striatal GABA (Harsing & Zigmond, 1997) and NO release (Morris et al., 1997) are increased by stimulating D1-like receptors. Moreover, LTS bursts can lead to release of NO which causes a slow and prolonged (>10 s) depolarization of ChINs (Elghaba et al., 2016), and, in addition, high-frequency stimulation (HFS) of frontal cortical areas can produce increased NO-levels in striatum (Ondracek et al., 2008; Park & West, 2009; Sammut, Park, & West, 2007) through an NMDA-dependent process. The LTS induce NO-dependent LTD at glutamatergic synapses (Calabresi, Gubellini, et al., 1999; Rafalovich et al., 2015) and regulate goal-directed learning (Holly et al., 2019). LTS target SPNs and because of their extended axonal arborizations they can influence the firing activity of SPNs over long distances. Additionally, ablation of LTS depolarizes the SPN resting membrane potential and the firing frequency as a function of the injected current, without significantly changing the cell capacitance, the rheobase or the I/V curve. Moreover in LTS-ablated mice, a reduction in the distal spine density on SPNs has been reported (Gazan, Rial, & Schifflmann, 2020).

FIGURE 1 The interaction between cholinergic interneuron (ChIN) and low-threshold spiking interneuron (LTS) and their extrinsic inputs. ChINs modulate LTS activity via muscarinic receptors (orange arrow) (here we focus on the M4R effect) while LTS modulate ChIN via nitric oxide (purple arrow). Input from cortex and thalamus is represented with dashed and filled lines depending on their strength, which represents the varying strength with which certain cortical areas, for example primary motor cortex (ipsilateral and contralateral), activate ChINs and LTS (Johansson & Silberberg, 2020).
The cortical and thalamic input is cell-type specific. ChINs receive a strong excitatory input from thalamus (Johansson & Silberberg, 2020). In contrast, LTS receive disynaptic inhibition (Assous & Tepper, 2019) and almost no excitation from thalamus (parafascicular nucleus) (Assous et al., 2017; Johansson & Silberberg, 2020). The strength of the cortical input to ChINs and LTS is dependent on the cortical area. In the primary motor cortex, LTS elicits stronger responses following optogenetic activation as compared to ChINs, and there is a lack of activation from contralateral primary motor cortex (Johansson & Silberberg, 2020). From other cortical areas, ChINs share similar input with LTS, anatomically (Choi, Holly, Davatolhagh, Beier, & Fuccillo, 2019; Guo et al., 2015; Klug et al., 2018). Here we simulate the effects exerted from primary motor cortex.

In this computational study, we focus on the slow modulatory effects of NO release from LTS and its effect on ChINs, and the reciprocal inhibitory muscarinic effect from ChINs to LTS (Figure 1). We consider cortical inputs from an area which has a prominent effect on LTS but a modest effect on ChINs, and a prominent thalamic excitatory effect on ChINs which is absent on LTS. We have not included the disynaptic inhibition that thalamus can exert on LTS (Assous et al., 2017; Assous & Tepper, 2019; Johansson & Silberberg, 2020), nor cortical areas which have similar input to both ChINs and LTS. Understanding the slow modulatory dynamics between ChINs and LTS and their dependence on the complementary extrinsic input would show how the levels of these neuromodulators could change on longer time scales. Ultimately, this would reveal how the intrinsic dynamics of this subcircuit could affect the activity of SPNs in the larger striatal microcircuit. The aim here is, however, to study the dynamic interaction between ChINs and LTS while the plasticity effects will be an objective of future studies.

2 MATERIALS AND METHODS

2.1 Morphology

The neurons were filled with neurobiotin (0.3%) (Vector Laboratories) during patch-clamp recordings. The slices were then transferred to 4% paraformaldehyde solution containing 14% picric acid in 0.01 M PBS for 12 hr at 4°C for fixation. The slices were thoroughly washed in PBS and incubated in 0.6% hydrogen peroxidase in methanol for 20 min, rinsed in PBS and transferred to the ABC solution (Vectastain EliteABC kit, Vector Laboratories) for 3 hr. After rinsing in PBS, the slices containing ChINs were incubated in diaminobenzidine (DAB, ImmPACT DAB, Vector Laboratories) for 3–5 min, rinsed and dehydrated in alcohol prior to mounting in Entellan (Merck). They were manually reconstructed using Neurolucida (MBF Bioscience) coupled to Zeiss Axio Imager A1. The slices containing LTS were transferred to 0.01 M PBS containing 0.3% triton-X100, 1% BSA and Cy5-conjugated streptavidin antibody (1:1:1000, Jackson ImmunoResearch Laboratories) for at least 6 hr. The slices were imaged using a Zeiss laser-scanning microscope (ZEISS LSM 800), and confocal z-stacks were retrieved. The z-stacks were used in a semi-manual reconstruction using Neutube (Feng, Zhao, & Kim, 2015) and custom code. The morphology of the LTS was previously published in Hjorth et al. (2020) (doi.org/10.25493/dvph-rde). The ChIN reconstruction in Figure S3 was previously published in Hjorth et al. (2020), and the reconstructions in Figures 2 and S4 can be found via doi.org/10.25493/3ev4-tdg

2.2 Optimization of multicompartmental models

The optimization process of the multicompartmental models consists of several steps as summarized in Figure S1. Firstly, the electrophysiological features were extracted from whole-cell patch-clamp recordings (ChINs: doi.org/10.25493/VW70-659; LTS: doi.org/10.25493/5GE0-6MF) using the Electrophys Feature Extraction Library, eFEL (github.com/BlueBrain/eFEL) a Python library. Secondly, using RNA sequencing data (Munoz-Manchado et al., 2018) ion channel expressions were determined and the respective ion channel models were implemented onto the morphological reconstructions based on availability. Thirdly, the multicompartmental models were simulated using NEURON (Hines & Carnevale, 2001) in Python 3 environment. Finally, the conductances of the ion channels models were optimized using BluePyOpt (Van Geit et al., 2016), a genetic algorithm. At the end of the optimization, the 10 best models were selected for validation. The validation score was calculated for these models using the protocols which were not included in the optimization (cf. Markram et al., 2015; Van Geit et al., 2016). The threshold for model acceptance was two standard deviations from the population average. Additionally, the models were tested for their intrinsic properties which include spontaneous activity, rebound and pause response (specifically for ChIN). To reproduce an intrinsically generated spontaneous activity, the reversal potential of the passive current was increased by a maximum of 5 mV for the ChIN models.

For the ChIN models, ion channel models were taken from a previous publication (Maurice et al., 2004) and included sodium, BK, SK, HCN, calcium (L-type and P-type), Kir, KCNQ, Kv2 and Kv4 ion channels. The LTS model included sodium, HCN, Kir, K-DR and calcium (M-type and T-type) channels. The LTS model and ChIN model (Figure S3) were previously published in Hjorth.
et al. (2020), while the ChIN models in Figures 2 and S4 are presented in this paper. In total, 20 ChIN models were constructed (i.e. 10 model parameter sets per morphological reconstruction, presented in Figures 2 and S4), which further adds to the ChIN models in the striatal microcircuit simulation (Hjorth et al., 2020).

### 2.3 Cortical and thalamic glutamatergic synaptic models

The cortical and thalamic input to ChIN and cortical input to LTS were previously modelled in Hjorth et al. (2020) using a Tsodyks-Markram glutamatergic model (Tsodyks, Uziel, & Markram, 2000).

Here, we focus on the cortical and thalamic inputs to LTS and ChINs, which were described in Johansson and Silberberg (2020), including primary motor cortex and parafascicular nucleus. The conductance of the glutamatergic synapse model was fixed, and the number of synapses was chosen to match the approximate excitatory postsynaptic potential (EPSP) amplitude and NMDA/AMPA ratios reported in Johansson and Silberberg (2020). The number of synapses used for the cortical and thalamic input was 55 and 140, respectively, for ChINs while the number of cortical synapses onto LTS was 66. The multicompartmental models were simulated with the...
glutamatergic synapse models and activated with 20 Hz stimulation (Figure 6) to reproduce the experimental stimulation protocols used in Johansson and Silberberg (2020).

2.4 | Muscarinic M4 model

The intracellular muscarinic model from Blackwell et al. (2019) was adapted by adding an ACh concentration mechanism which translates activation events into an ACh response. It was modelled using a two-state kinetic model. In particular, the model was stimulated with 2–3 Hz to match the spontaneous activity of ChINs and intermittent bursts of 20 Hz. The time constants and amplitudes were chosen to reproduce the same levels of simulated ACh concentration for 20 Hz as in Blackwell et al. (2019).

The muscarinic M4 model was included in the LTS model. The molecular species, ACh_M4, was recorded within the model, and the level of binding between ACh and M4 was translated in the modulation of Kir2 channel. Hence, changes in the levels of ACh_M4 due to spiking of the ChIN model would increase the conductance of the Kir2 channel. The ACh concentration mechanism was activated with 10 pulses at 20 Hz to reproduce the same protocol used in Figure 5 in Melendez-Zaidi et al. (2019) and constrained with the experimental data.

2.5 | Nitric oxide model

The NO model was based on data from Elghaba et al. (2016) and phenomenologically implemented using a modified integrate-and-fire process, as a detector of LTS spiking activity, which was linked to a synaptic model (both available in NEURON). It was reported that the NO activation was dependent on prolonged spiking activity (1–3 s) of the LTS. Thus, to capture the frequency dependence, the integrate-and-fire process was monitoring the spiking activity of the LTS and denoted the frequency checker. The parameters in the frequency checker were fitted so as to lead to an activation of the NO mechanism during periods of increased spiking activity in LTS. The NO mechanism was placed on the soma of the ChIN model, and the time constants of the mechanism were fitted to reproduce the depolarization and spiking increase in response to NO activation as reported in Elghaba et al. (2016). The interactions modelled between ChIN and LTS are summarized in Figure S2.

2.6 | Simulation of ChIN and LTS interactions

The simulations using the network included cortical, thalamic and cortical/thalamic activation. The background activity was generated as a Poisson process, using the homogeneous_poisson_process in the Elephant toolbox, Electrophysiology Analysis Toolkit (https://neuralensemble.org/elephant/). The synapses with background activity were randomly placed on the dendritic tree of the LTS and ChIN models with mean rate of 4 Hz for thalamic activity and 2 Hz for cortical activity. The burst activation of thalamic input was simulated using a 20 Hz pulse train stimulation during 700 ms. The cortical input was modelled as a 3 s increase in cortical activity using a Poisson process with a mean rate of 20 Hz. The simulation in Figure 8 included both a cortical input of 3 s as well as intermittent bursts of thalamic activity at 20 Hz with continuous background activity. In addition, high-frequency stimulation (100 Hz, 300 ms) was also performed to simulate high-frequency cortical bursting activity (Figure S5).

3 | RESULTS

Our goal here is to develop a model describing the reciprocal interaction between detailed multicompartmental models of cholinergic interneurons and low-threshold spiking interneurons, including their extrinsic input from cortex and thalamus as summarized in Figure 1. The ChIN-LTS interaction has been experimentally investigated in Elghaba et al. (2016) and Melendez-Zaidi et al. (2019), which have delineated the muscarinic modulation of LTS and the nitric oxide-dependent depolarization of ChINs.

The multicompartmental models of ChIN and LTS are presented in Figures 2 and 3, respectively. In Figure 2, we present a morphological reconstruction of a ChIN, which provides the basis for the multicompartmental models. The ChIN model presented in Figure 2 was constructed using ex vivo electrophysiological recordings from the cell in Figure 2h. The electrophysiological features from the I/V (Figure 2a) and suprathreshold protocols (Figure 2d) were used in the optimizations, which produced 10 models for this reconstruction. Figure 2b shows one of the 10 models stimulated with the same I/V protocols as in Figure 2a, and Figure 2e shows the response in the same model to suprathreshold stimulation protocol (Figure 2d). The models were evaluated using all protocols, and the extracted features were compared to the population average extracted from whole-cell patch-clamp recordings from ChINs (n = 22). The validation score was calculated for each model (Figure 2c, for subthreshold and Figure 2f, for suprathreshold) with an acceptance score of 2 standard deviations (red dotted line in Figure 2c,f). The ability of the model to produce a pause response following a current injection was also verified (Figure 2g). In total, 20 ChIN models were constructed and passed validation.

A reconstruction of an LTS is shown in Figure 3a with the dendritic arbour and the axonal ramifications. Left panels in Figure 3b,c show the response of the cell to hyperpolarizing and...
depolarizing current steps, respectively; while the right panels show the response of one of the 10 models. The performance of the model agrees closely with that of the biological counterpart. The optimized multicompartmental models are the basis for simulating the ChIN-LTS network presented below.

The ChIN-LTS reciprocal modulatory influence was modelled using a phenomenological nitric oxide model and a subcellular model of the muscarinic M4 receptor. In Elghaba et al. (2016), they showed that a prolonged optogenetic activation of LTS produced a slow depolarization of the ChIN mediated by NO. We have captured this NO effect via a slow synaptic current with two time constants corresponding to the data extracted from figure 9c in Elghaba et al. (2016). Additionally, we constructed a frequency checker mechanism.

**FIGURE 3** Reconstructed morphology and model of low-threshold spiking interneuron (LTS). (a) Reconstructed morphology with soma (in black), dendrites (in blue) and axon (in red). (b,c) Recorded response to somatic hyperpolarizing and depolarizing square-pulse current injection ex vivo (in red) and in one of the 10 corresponding models (in black). The models can be further improved by adding extra ion channel models to better capture some of the features, such as time to the first spike and spike amplitude. The LTS model has been previously used in Hjorth et al. (2020).

**FIGURE 4** (a) Modelling the nitric oxide effect of low-threshold spiking interneuron (LTS) on the cholinergic interneuron (ChIN). (b) Superposition of traces of three different multicompartmental models of ChIN (based on different morphologies) with an activation of the nitric oxide (NO) input which caused a prolonged depolarization. (c) The average response of the three models with NO activation compared to experimental data extracted from Figure 8 of Elghaba et al. (2016).
The LTS are directly modulated by ChINs primarily via M4R. The muscarinic effect on LTS (Figure 5a) was modelled using data extracted from Figure 5 of Melendez-Zaidi et al. (2019). Optogenetic activation of ChINs caused a large inhibition of LTS spiking, which is attributed to the muscarinic M4 receptor and its effects on the inward rectifier potassium channel (Kir). The muscarinic M4R receptor model was adapted from Blackwell et al. (2019). The modification of the model was due to the necessity of providing a dynamic function, which reproduces the changes in the acetylcholine concentration (Figure 5b). The receptor model was coupled to the Kir channel in the LTS model, which was then activated with the same frequency as in the experiment. The model response was compared to the normalized spike rate which replicated the pause seen in Figure 5c,d of Melendez-Zaidi et al. (2019).

The extrinsic cortical and thalamic inputs are then incorporated into the circuit. We focus here on the effects exerted from the primary motor cortex (Johansson & Silberberg, 2020), although we note that different effects have been obtained from other cortical areas (Melendez-Zaidi et al., 2019). The cortical (Figure 6a,d) and thalamic (Figure 6g) short-term synaptic dynamics were taken from Hjorth et al. (2020) in which they are modelled using the Tsodyks–Markram model of the glutamatergic synapse (Tsodyks et al., 2000). We placed the synaptic models on the reconstructed morphologies and stimulated them with
20 Hz pulse train (Figure 6b, e and h). The thalamic (parafascicular nucleus) input to ChINs is stronger than the cortical input (Johansson & Silberberg, 2020) as captured in Figure 6e,h. The LTS receive stronger input from cortex overall as compared to ChINs (Assous et al., 2018; Johansson & Silberberg, 2020). This difference is captured when comparing the simulations in Figure 6b,e of the primary motor cortex input. The effect of the synaptic input on the spiking of these spontaneously active interneurons showed that the LTS model increases its firing frequency during cortical activation. The ChIN model, on the other hand, responds to the weak cortical input with only a small change in spike time. The thalamic stimulation produces a burst followed by a pause in the discharge of the ChIN model although activation of D2 receptor is also known to be involved (Ding, Guzman, Peterson, Goldberg, & Surmeier, 2010). This is consistent with experiments in Johansson and Silberberg (2020) where parafascicular and primary motor cortex were activated and showed opposing effects on ChINs and LTS.

Finally, we examined how the thalamic activation of ChIN can be translated into a modulation of LTS (Figure 7a,a1), as well as how a cortical activation of LTS can affect ChIN (Figure 7b,b1). The repetitive thalamic activation of the ChIN model induces burst and pause responses (Figure 7a), which in turn leads to pauses in LTS via the muscarinic effect on the Kir channel (Figure 7a1). The prolonged cortical input to LTS increases its firing rate (Figure 7b1) and activates the NO on the ChIN model (asterisk in Figure 7b). The increased spiking activity of the ChIN leads to an accumulation of acetylcholine in the model and hence a muscarinic inhibition of LTS (Figure 7b1). An additional simulation showed that the model would predict nitric oxide production following HFS which is consistent with the experimental data (Figure S5).

Lastly, we investigated the effect of the simultaneous cortical and thalamic activation. The stimulation scheme used consisted of several thalamic activations (Figure 8a) during a prolonged cortical activation of LTS (Figure 8a1).
The cortical activation of LTS causes a depolarization of the ChIN model via the NO effect (Figure 8a,a1). The increased spiking of the ChIN model produces muscarinic inhibition of the LTS. The first thalamic activation (Figure 8a) further enhances the inhibition although the resulting pause in the ChIN model is reduced (compared to Figure 7a) due to the concurrent NO-mediated depolarization. The LTS model acquires a burst response pattern during the subsequent thalamic activations (Figure 8a1) due to decreased depolarization of the ChIN model. Additionally, the muscarinic inhibition of the LTS model is initially strong but is attenuated as the ChIN spiking frequency decreases. Hence, the appearance of the burst as well as the spiking frequency of the subsequent LTS bursts will be controlled by the length of the inhibition.

4 | DISCUSSION

We have simulated the muscarinic and nitric oxide-dependent interactions between ChIN and LTS in the striatum, to
investigate the resulting dynamics of this striatal subnet-
work and its response to cortical and/or thalamic activation.
Firstly, multicompartmental neuron models were optimized
using reconstructed morphologies and electrophysiological
ex vivo experimental data. Secondly, the neuromodulatory
effects of NO and ACh were modelled based on experimental
data (Blackwell et al., 2019; Elghaba et al., 2016; Melendez-
Zaidi et al., 2019). The muscarinic effect was modelled using
an ACh release mechanism coupled to the muscarinic (M4R)
postsynaptic receptor model on the LTS. The activation of
the receptor model increased the conductance of the Kir
channel and replicated the pause seen in experiments. The
depolarizing effect of NO, released from LTS following a
prolonged activation, was modelled in a phenomenological
way which incorporated the frequency dependence of the re-
sponse. Thirdly, the synaptic inputs from cortex and thalamus
were implemented in the models to reproduce the short-term
dynamics of the extrinsic connectivity. Finally, the network
was simulated with activation of cortical and thalamic input.
This showed that the timing of the respective inputs could
generate different patterns of activity in ChIN and LTS mod-
els with implications for the slow modulatory dynamics in
the striatum.

We simulate here the effects of the primary motor cortex
in which LTS and ChINs are activated with different strengths
(Johansson & Silberberg, 2020), although other cortical areas
can provide similar effects on these two types of neurons
(Johansson & Silberberg, 2020; Melendez-Zaidi et al., 2019).
The thalamic activation of ChIN would first yield a transient
burst followed by a pause. This causes an inhibitory response
in the LTS due to the muscarinic effects that co-occur with
the ChIN burst. Based on Assous et al. (2017) and Assous
and Tepper (2019), this effect could be further strengthened
through the disynaptic inhibitory effects of ThINs onto LTS.
Although LTS also express muscarinic M1 receptors, the
dominating effect following a burst of activity in ChINs is
primarily M4R-dependent (Melendez-Zaidi et al., 2019).
Furthermore, they also show that increased levels of ACh
could induce bursting in LTS and our model also produced
bursting but mediated by a repeated thalamic activation.
Although not included in the current model, bursting could
be a mechanism to release peptidergic neuromodulators like
somatostatin and possibly NO (Bartfai, Iverfeldt, Fisone, &
Serfozo, 1988; Dutton & Dyball, 1979; Goldberg, Lacefield,
& Yuste, 2004). D1-like receptors have also been shown to
excite LTS (Centonze et al., 2002) and provide an additional
mechanism for NO release (Morris et al., 1997).

Both ACh and NO can shape microcircuit activity in
many brain areas (Colangelo, Shichkova, Keller, Markram, &
Ramaswamy, 2019; Garthwaite, 2008; Haam & Yakel, 2017;
Picon-Pages, Garcia-Buendia, & Munoz, 2019), including in
the striatum (Abudukeyoumu et al., 2019). What could be the
implications of this with regard to the local striatal network?
The prolonged increase of the activity of the LTS population,
due to cortical activity, could cause a prolonged depolariza-
tion of the ChINs which in turn would lead to the activation
of M1R on both types of SPNs (Galarraga et al., 1999; Lv
et al., 2017; Shen, Hamilton, Nathanson, & Surmeier, 2005).
Additionally, the ChIN burst, due to thalamic activation, could
have the same effect. The ChIN pause following such a burst
might instead cause a transient hyperpolarization of SPNs,
similar to what is shown in experiments using subsecond optogenetic inhibition of ChINs (Zucca, Zucca, Nakano, Aoki, & Wickens, 2018). Additionally, ACh can cause presynaptic inhibition (Abudukeyoumu et al., 2019; Pakhotin & Bracci, 2007; Pancani et al., 2014) which could affect the processing of inputs. Moreover, the nicotinic receptors on dopaminergic terminals can further coordinate modulation of striatal microcircuits with transient dopamine released during synchronized activity of ChINs (Threlfell et al., 2012). The NO, released by LTS, has in itself a dual effect upon SPNs where it seems to cause depolarization as well as increase the responsiveness to glutamatergic input (West & Grace, 2004). NO also modulates short-term plasticity in conjunction with ACh (Blomeley, Cains, & Bracci, 2015). With regard to long-term plasticity, both NO and ACh are important (Centonze, Gubellini, Pisani, Bernardi, & Calabresi, 2003). NO is needed for the induction of LTD at corticostriatal synapses onto SPNs (Calabresi, Centonze, Gubellini, Marfia, & Bernardi, 1999; Calabresi, Gubellini, et al., 1999; Doreulee et al., 2003; Rafalovich et al., 2015; Sergeeva, Doreulee, Chepkova, Kazmierczak, & Haas, 2007). ACh, on the other hand, via M1R, promotes protein kinase C (PKC) production which is known to facilitate LTP induction (Calabresi, Centonze, Gubellini, Pisani, & Bernardi, 1998; Gubellini, Centonze, Tropepi, Bernardi, & Calabresi, 2004; Hawes, Gillani, Evans, Benkert, & Blackwell, 2013), and M1R signalling has also been shown to suppress endocannabinoid release (Narushima et al., 2007) involved in LTD in both types of SPNs (Lovingier, 2010). M1R activation might thus shift the overall balance towards LTP in at least the iSPNs, while in dSPNs postsynaptic M4 receptor activation might dominate to counteract LTP. This opens up the possibility that the control of the burst/pause dynamics in ChINs could be important, and a long enough pause might facilitate LTP in at least dSPNs (Bruce et al., 2019; Nair et al., 2015, 2019) and LTD in both types of SPNs (Augustin, Chancy, & Lovingier, 2018; Narushima et al., 2007; Wang et al., 2006).

During physiological conditions, it can be expected that thalamic and cortical activation occurs with different timings. Our simulations suggest that the emergent properties of the reciprocal interaction between ChIN and LTS can give rise to dynamic phenomena, which in turn provide modulatory effects on the surrounding network in which ChINs and LTS are embedded, as described above. The pauses in the LTS model following both cortical and thalamic activation could transiently decrease the GABAergic inhibition of distal SPN dendrites (Assous, 2020; Gazan et al., 2020). This could lead to an increased likelihood of NMDA plateaus (Du et al., 2017) which will likely facilitate plasticity at corticostriatal synapses.

The network implemented here includes several assumptions about the underlying mechanisms in the ChIN and LTS interaction. Firstly, the LTS is known to release somatostatin and neuropeptide Y in addition to NO (Kawaguchi et al., 1995); these neuromodulators are, however, reported to provide complementary effects to that of NO (Elghaba et al., 2016). Moreover, the inhibitory muscarinic effects on LTS due to thalamic activation were prominent (Melendez-Zaidi et al., 2019), although in Elghaba et al. (2016) the inhibitory effect was only present during spontaneous activity in the absence of GABA. Hence, the thalamic activation and spontaneous activity would respond differently to acetylcholine due to the additional input from GABAergic terminals and nicotinic receptor activation (Elghaba et al., 2016). The muscarinic effect on LTS was modelled using Kir2 ion channel, although the experimental data attributed the effect to Kir3 (Melendez-Zaidi et al., 2019). These two channels have, however, similar dynamics (Anumonwo & Lopatin, 2010), and at present, the ion channel model for Kir2 is used.

We assumed throughout our simulations that we could represent the behaviour of the local pool of LTS or ChINs with only one neuron each, and preliminary results show that similar effects are obtained with populations of ChIN and LTS models. This would imply that our predictions are relevant in those situations when the local population of ChINs and LTS are synchronously active/inactive. It is known that tonically active neurons (TANs/ChINs), in primates, are synchronously active to a varying degree both during control condition and in response to conditional cues (Raz, Feingold, Zelanskaya, Vaadia, & Bergman, 1996; Shimo & Hikosaka, 2001). However, it is less well known to what extent neighbouring LTS are coactivated from cortex. In these simulations, we have focused on the specific contribution of the ChIN and LTS interaction. In the future, we would like to investigate these interactions within the full-scale striatal microcircuit (Hjorth et al., 2020) including plasticity effects, with the two types of striatal projection neurons and fast-spiking interneurons with appropriate numbers and cellular density.

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**CONFLICT OF INTEREST**

The authors have declared that no competing interests exist.

**AUTHOR CONTRIBUTIONS**

JFN implemented the overall simulations; JFN and IC performed data curation and formal analysis (equal contribution).
SG and JHK supervised all aspects of the project (equal contribution). JFN, IC, SG and JHK were involved in conceptualization, writing, reviewing and editing.

DATA AVAILABILITY STATEMENT
ChIN morphological reconstructions (doi.org/10.25493/3ev4-tdg); ChIN electrophysiological data (doi.org/10.25493/VV70-659); LTS morphological reconstruction (doi.org/10.25493/dvph-rde); LTS electrophysiological data (doi.org/10.25493/SGE0-6MF). The code for the simulation is available on github: ChIN-LTS-Network-simulation: https://github.com/jofro/ChIN-LTS-Network-simulation.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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