Dopamine synergistic effects on lateral inhibition and neuronal excitability promote the formation of striatal ensembles - implications for action selection

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Abstract

The striatum is the main input structure to the basal ganglia, and it plays an important role in action selection during motivated behaviors. This role is thought to involve the information processing of cortical and limbic input and be highly influenced by dopamine. Within the striatum, spiny projection neurons (SPNs) are functionally organized in neuronal ensembles that coordinate the selection of behaviors by promoting some and suppressing others. However, it is still unclear how neuronal ensembles are generated and how dopamine (DA) aids in this process. In this work, we use a computational model to study the orchestrated activity of the two main subclasses of SPNs: dSPNs and iSPNs. We assessed the role of the lateral inhibitory network on the ensemble activity and the selection of a chosen ensemble and determined the impact of DA at the cellular and synaptic levels. Our results revealed a critical interplay between a realistic connectivity pattern of lateral inhibition and the intrinsic excitability of SPNs. The model shows that DA's modulation of neuronal excitability and $GABA_A$ transmission synergize to promote ensemble formation, possibly accounting for DA function in action selection.

Keywords: striatum; SPNs; lateral inhibition; dopamine; network architecture; connectivity.

Model description

Spiny Projection Neurons (SPN) constitute more than 90% of the striatal neurons. They are GABAergic and express receptors for dopamine (DA), a neuromodulator critical for striatal function (L. M. Yager & Ferguson, 2015). SPNs can be divided into two main subtypes, dSPN and iSPNs, shown to promote and suppress behavior, respectively (A. V. Kravitz & Kreitzer, 2010). However, other experiments also showed that dSPNs and iSPNs are simultaneously active during behavior (G. Cui & Costa, 2013). Thus, striatal ensembles, defined here as groups of cells firing together and driving specific behaviors, involve the coactivation of subsets of dSPNs and iSPNs (Klaus et al., 2017). This implies that each given behavior involves activation of a specific ensemble and inactivation of others.

Network architecture: We assumed an organization into functional units (FUs; Fig.1) each controlling a specific behavior or motor pattern, as proposed before (D. A. Burke & Alvarez, 2017) and based on empirical evidence about striatal neuron activity during behavior (J. E. Markowitz & Datta, 2018). FUs consist of recurrently inhibited dSPNs and iSPNs, which promote and suppress, respectively, the associated behavior. We use the activity of dSPNs and iSPNs as proxies for the occurrence and suppression of the corresponding behaviors. Each cell in the network receives cortical input assumed to be constant (DC) in the first pass. FUs are connected by lateral inhibition consisting of recurrent inhibition between pairs of cells belonging, in principle, to the same or different SPN subtype.

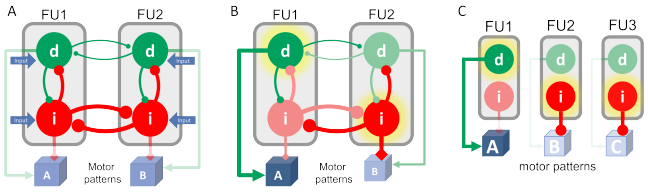

Figure 1: (A) **Hypothetical organization of the striatal local circuitry based on functional units (FUs) shows two exemplary FUs controlling motor patterns A and B via ensemble formation.** (B) Network state when motor pattern A is selected. dSPN of FU1 fires to produce behavior A, forming an ensemble with iSPN of FU2, which fires to suppress motor pattern B and ultimately promote motor pattern A. (C) Extension of the ensemble network to the case of 3 FUs. The connectivity patterns are as of (A) but not shown for simplicity. The dSPN corresponding to the chosen motor pattern fires together with the iSPNs of competing FUs.

Cellular model. Each cell was modeled by combining the Hodgkin-Huxley formalism (Hodkin & Huxley, 1952) and a reset voltage after a spike has occurred. These models have been systematically reduced as described in (U. Chialva & Rotstein, 2023) from higher dimensional (M. M. McCarthy & Kopell, 2011)(A. J. Gruber & Houk, 2003)(R. C. Evans & Blackwell, 2012).

Connectivity. Experimental results in the absence of DA show a natural asymmetry in the connectivity (synaptic strength between different subtypes of SPNs) (S. Taverna & Surmeier, 2008). The number of synapses arriving from iSPNs was significantly greater than the ones arriving from dSPNs. This implies that the striatal local network is not random, and it is organized in a way that, in the absence of DA, the iSPNs exert more inhibition than the dSPNs. This suggests that the striatum might have an active duty in shaping behavior downstream from the cortex.

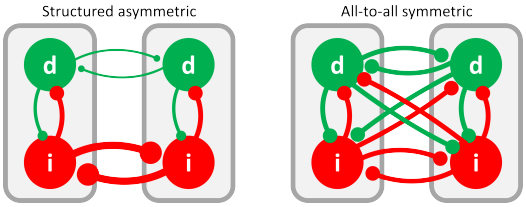

Figure 2: **Schematic network architecture for two FUs (shaded) consisting of recurrently inhibited dSPNs (d, green) and iSPNs (i, red).** The relative connectivity (inhibition) strengths are represented by the connector widths.

Dopamine (DA). DA has an asymmetric effect both at the synaptic and cellular levels. Experimental results (Burke & Alvarez, 2022) showed that DA has a differential effect on the inhibitory postsynaptic current amplitude (IPSC), depending on the presynaptic SPN subtype. To model this, at the time of DA onset, we multiply the original synaptic weights by experimentally observed factors measured in (Burke & Alvarez, 2022). At the cellular level, DA changes the excitability of the SPNs. In the absence of DA, iSPNs tend to be more excitable than dSPNs (Gerfen & Surmeier, 2011). DA again reduces this imbalance by increasing dSPNs excitability and decreasing iSPNs excitability (Gerfen & Surmeier, 2011). To model this DA effect, we modified the DC input of each cell to achieve a predetermined firing frequency according to previous data (H. Planert & Silberberg, 2013).

Results

1 FU. We start the systematic analysis from the simplest non-trivial case: one FU (one dSPN and one iSPN connected through lateral inhibition). For a certain range of inhibition, we see an alternation in dominance between iSPN and dSPN. As expected, the greater inhibition exerted from iSPN to dSPN, the lower the firing rate of dSNP. The bigger this difference is, the longer the periods of dominance of iSPNs. The mechanism controlling the switch of dominance is the timescale of the M-current, which acts as a slow negative feedback, leading to a switch in dominance. It transitions from a mix of escape and release in the basal state to an escape mechanism under the presence of DA (Wang & Rinzel, 1992).

2 FU. For two connected FUs, more complex patterns emerge as the result of the interplay of the cells' intrinsic properties and connectivity. Networks with structured architecture (both symmetric and asymmetric, Fig.2) form the hypothesized ensembles. In the symmetric case, the mean fire rate of iSPNs and dSPNs is the same, while in the asymmetric case, iSPNs tend to fire more, as expected. Networks with all-to-all architecture do not produce the hypothesized ensembles: in the asymmetric regime, the network does not produce any co-activation of cells, and in the symmetric regime, the network forms patterns showing excessive synchronization between iSPNs across different FUs. This excessive synchronization has been identified as a signature of striatal diseases, such as Huntington's and Parkinson's (A. Ponzi & Kozloski, 2020).

3 FU. More interesting and unique network patterns emerge for three (or more) connected FUs. For certain values of total inhibition and only when DA affected both excitability and lateral inhibition, the network adopted a spiking pattern where only one dPSN fired together with iSPNs from competing FUs (an ensemble). However, these ensembles are not produced when DA affects only excitability or synaptic transmission, for the same values of total inhibition. Thus, there exists a synergistic effect between DA changes in synaptic transmission and excitability that aids the network in reaching the hypothesized ensemble state. Moreover, the time of DA onset determines the ensemble selected in the following way: the last dSPN that was firing before DA came in is the one that stays firing, as seen in Fig.3.

Conclusion

Action selection has been previously modeled as coming directly from the cortex (J. Lindsey & Litwin-Kumar, 2024). Our simulations show how DA and the striatal microcircuit can aid in the task of action selection. First, the time of DA onset determines the ensemble selected. This time dependency could allow the network to choose different ensembles by modulating the timing of DA signals. Second, there exists a synergism between DA effects on excitability and lateral inhibition.

Our systematic analysis shows that an asymmetry in the connectivity and excitability of the states is essential to have a higher iSPN firing rate, but no clear ensembles are formed. DA disrupts the asymmetry and allows the system to lock in a chosen ensemble, based on the onset of DA elevation. We emphasize that, although this was the hypothesized behavior, it was not built in the network architecture, which was only designed to allow the co-activation of different cells.

Co-activation of cells is possibly due to the intrinsic currents in the SPNs. In our models, the M-current proved to be the most relevant conductance in terms of ensemble formation. Simpler models lacking intrinsic currents were not able to give any behaviorally relevant spiking patterns. In the presence of DA, simulations seem to indicate that network archi-

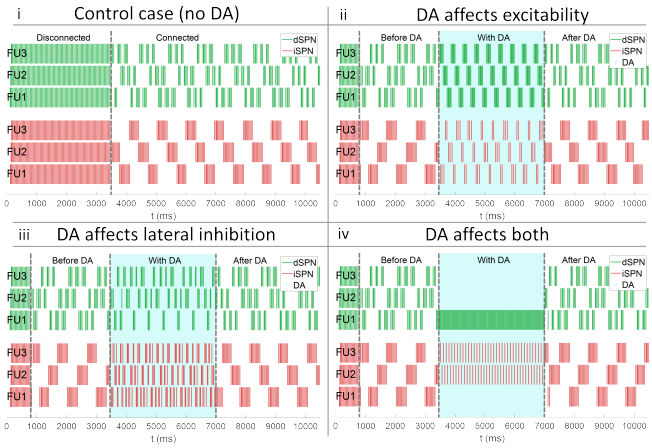

Figure 3: **Representative raster plots for structured asymmetric network activity for three functional units.** Vertical dashed-gray lines indicate the connectivity time (first), the DA onset (second) and the DA wash-off. Green ticks represent dSNP firing and red ticks iSPN firing. The activity of the disconnected cells is the same in all panels. (i) Control case: no DA is introduced. (ii) Case of DA affecting only neuronal excitability, we see an increase in the duration of dSPN bursts. (iii) Case of DA affecting only synaptic transmission. We see dSPNs become less inhibited and therefore exert a stronger effect on iSPNs. The iSPNs firing is less structured. (iv) Case of DA affecting both excitability and synaptic transmission. We see that combined DA effects work synergistically to produce the functional ensemble hypothesized in Fig.1C.

tecture plays a more prominent role in the spiking than relative connectivity weights. In a structured network architecture with symmetric connectivity, we still see ensemble formation as proposed in Fig.1C. However, for all-to-all architecture and asymmetric connectivity that spiking pattern is no longer achievable. Asymmetric connectivity seems to play a role in promoting asynchronous firing in the basal state (A. Ponzi & Kozloski, 2020).

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