From the Department of Neuroscience
Karolinska Institutet, Stockholm Sweden

The role of dopaminergic and cholinergic modulation on the striatal network - a computational investigation

Robert Lindroos

Karolinska Institutet

Stockholm April 3, 2020

coverart: “Brain freeze” by Doris Lindroos

Published by Karolinska Institutet

Printed by Eprint AB 2020

IBAN 978-91-7831-807-0

The role of dopaminergic and cholinergic modulation on the striatal network–a computational investigation

THESIS FOR DOCTORAL DEGREE (Ph.D)

By

Robert Lindroos

Principal Supervisor:
Jeanette Hellgren Kotaleski
Professor
Royal Institute of Technology
School of Computer Science
and Communication
&
Karolinska Institutet
Department of Neuroscience

Co-supervisors:
Sten Grillner
Professor
Karolinska Institutet
Department of Neuroscience

Konstantinos Meletis
Associate Professor
Karolinska Institutet
Department of Neuroscience

Opponent:
Panayiota Poirazi
Research director
Foundation for Research and
Technology Hellas
Institute of Molecular Biology
and Biotechnology

Examination Board
Karima Chergui
Associate Professor
Karolinska Institutet
Department of Pharmacology

Jonas Olofsson
Associate Professor
Stockholm University
Department of Psychology

Johan Hoffman
Professor
Royal Institute of Technology
School of Electrical Engineering
and Computer Science

ABSTRACT

The famous words from the French philosopher René Descartes (1596-1650), "I think therefore I am", proclaims that since we are thinking we must also exist.

At the time when this was stated, very little was known about the main organ involved in thinking, the nervous system. Today we know that the nervous system consists of interconnected cells, so called *neurons* that communicate with each other through electro-chemical signals. This has been known for little over a century and during this time we have gathered an impressive amount of detailed data on neurons and the circuits they make up. Despite this, we still don't have a detailed description of the overall computing mechanism of the central nervous system, the brain, or even single nuclei within the brain. One reason for this is the transient nature of the brain, continuously going in and out of operational modes, or so called brain states. The state of the brain is heavily influenced by neuromodulators–molecules changing the properties of neurons and the connections between them. One area strongly affected by neuromodulators is the striatum, the main input structure of the basal ganglia.

The basal ganglia are an evolutionary conserved set of interconnected nuclei tightly connected to the cerebral cortex and thalamus, with which they form a loop. From pathological states like Parkinson's disease we know that the basal ganglia are involved in motor control. More specifically they have been proposed to drive formation and control of automatic motor response sequences (including habits), but like in the rest of the brain, the *modus operandi* of the basal ganglia is not known. To bridge the gap between data and function we therefore need models and testable theories.

In this thesis I have studied the role of neuromodulation in the striatal microcircuit, with the aim of understanding how subcellular changes affect cellular behavior. The technique used is biophysically detailed computational modelling. The essence of these models tries to mimic the electro-chemical signals within and between neurons using as detailed a description of individual neurons as possible. From this standpoint a good model minimizes the number of assumptions used in construction, by restricting the model to experimentally measured entities.

Simulations of the striatal projection neurons in such models show that *complex spikes*–a particular type of neuronal signal associated with learning in other brain regions–may be triggered following manipulation of certain conductances in the cell membrane. In our simulations, the complex spikes were associated with large calcium signals in the dendrites, indicating a more robust form of crosstalk in the soma-to-dendrites direction than following regular action potentials. Together these simulations extend the theory of striatal function and learning.

LIST OF SCIENTIFIC PAPERS

1. Du, K., Wu, Y., **Lindroos, R.**, et al. (2017). Cell-type–specific inhibition of the dendritic plateau potential in striatal spiny projection neurons. Proc. Natl. Acad. Sci. U.S.A. 114, E7612–E7621. doi: 10.1073/pnas.1704893114

2. **R. Lindroos**, Dorst, M., Du, K., Filipović, M., Keller, D., Ketzef, M., Kozlov, A., Kumar, A., Lindahl, M., Nair, A., Pérez-Fernández, J., Grillner, S., Silberberg, G., and Hellgren Kotaleski, J.(2018). Basal ganglia neuromodulation over multiple temporal and structural scales—simulations of direct pathway MSNs investigate the fast onset of dopaminergic effects and predict the role of Kv4.2. Frontiers in Neural Circuits, 12:3. DOI: 10.3389/fncir.2018.00003.

3. J. Hjorth, A. Kozlov, I. Carannante, J. Frost Nylén, **R. Lindroos**, et al. (2020). The microcircuits of striatum *in silico*. Proc. Natl. Acad. Sci. U.S.A. (in press).

4. **R. Lindroos** and J. Hellgren Kotaleski. Predicting complex spikes in striatal projection neurons following neuromodulation by acetylcholine and dopamine. (manuscript)

Contents

List of Figures

List of abbreviations

ACh: acetylcholine
ChIN: cholinergic interneuron
Crtx: cortex
dopa: dopamine
dSPN: direct pathway spiny projection neuron
FS: fast spiking interneuron
GABA: gamma-aminobutyric acid
glut: glutamate
GPe: globus pallidus externa
GPi: globus pallidus interna
iSPN: indirect pathway spiny projection neuron
K^+: potassium
LTS: low threshold spiking interneuron
MSN: medium spiny neuron (other name for SPN)
NMDA: N-metyl-D-aspartate
Na^+: sodium
nAChR: nicotinic receptor
NO: nitric oxide
PV: cortical fast spiking interneuron
SN: substantia nigra
SNc: substantia nigra pars compacta
SNr: substantia nigra pars reticulata
SOM: somatostatin positive (cortical) interneuron
SPN: striatal/spiny projection neuron
STN: subthalamic nucleus
Str: striatum
Thal: thalamus
TH^+: tyrosine hydroxylase expressing interneuron
VIP: vasoactive intestinal polypeptide positive interneuron
VTA: ventral tegmental area

Acknowledgements

The journey towards completing this thesis has been long and hard and it is only with the support and guidance of a long list of people that I have managed to get through. To them I owe everything.

To my two girls, Rebecca and Doris, without you I would surely have been hopelessly shipwrecked ♡.

To my supervisor Prof. Jeanette Hällgren Kotaleski for taking me in as a PhD student and for always being there, calm and steady, with a phenomenal ability to always find a way to steer clear of obstacles.

To Johannes Hjorth and Matthijs Dorst[1] for providing me with much appreciated friendship on my sometimes lonely journey. Johannes, not officially a supervisor or mentor but in many aspects acting as both. A specific thanks for paying attention to details. Matthijs for introducing me to experimental neuroscience.

To my co-supervisors Prof. Sten Grillner and Prof. Konstantinos Meletis for general guidance in the academic world and inspiring leadership in shared projects.

To past and current members of the extended Hellgren Kotaleski lab. To Kai Du and Alexander Kozlov, for introducing me to computational neuroscience and for sharing their models. A special thanks to Kai for being a friend both on and off work. To Marko Filipovic for challenging me with a never ending stream of questions regarding models as well as biology. To Prof. Arvind Kumar for his straight forward manners, full of knowledge and never afraid of speaking his mind. To Andrei Kramer and Ilaria Carannante, for pushing me higher. To Johanna Frost Nylén for being clear-sighted and clever, always with good ideas on how to improve models and workflows. To Kadri Pajo for being a good roommate and "desk neighbour", always close to laughter. The rest of the Scilifelab crew, Anu Nair, Daniel Trpevski, Parul Tewatia, Olivia Eriksson, João Pedro Santos, Zahra Khodadadi and Jan Pieczkowski for inspiring discussions and insightful ideas.

To the Silberberg and Grillner labs, Maya Ketzef, Yvonne Johansson, Roberto de la Torre Martinez, Anna Tokarska, Zhi Chia, Shreyas Mysore Suryanarayana, Juan Perez Fernandez, Andreas Kardamakis, Brita Robertson, Peter Wallén, Abd Aljabbar Seek,

[1] plus better half, Josje van Lunteren

Elham Jalalvand and Daichi Suzuki. For sheltering me, a computational neuroscientist, among your quarters. For guidance in experimental techniques and general discussion and company. A special thanks to Prof. Gilad Silberberg in this context for being a generally stand up guy and for inspiring me in many aspects including starting to exercise.

To all members of the El Manira, Kiehn and Deliagina labs, specifically for coffee break company and Thursday *fika*. A special thanks to Manideep Gupta Vemula in this context for friendship including sailing companionship.

To my old friend Martin Cederlöf for guidance and insight into the academical world and for offering support in the writing of this thesis.

Finally I would also like to place a special thanks to my brother, sister, mother and father for believing in me. I love you all.

> "You can't imagine how much detail we know about brains. There were 28,000 people who went to the neuroscience conference this year, and every one of them is doing research in brains. A lot of data. But there's no theory. There's a little, wimpy box on top there"
>
> *Jeff Hawkins*

1 Introduction

The human brain is arguably one of the most complex systems known to man (or largely unknown to be precise). Over the last hundred years or so we have gathered an impressive amount of detailed data about what makes up a brain, such as characteristics of cell types and connections within and between brain areas. Despite this we are still lacking a detailed knowledge about the function of single brain areas, not to talk about the overall computing mechanisms of the brain.

At the very superficial level a brain is a network of networks that learns, builds policies and controls how we act in a given situation. Brain areas, brain cells (specifically neurons) and even proteins inside a cell, are all part of networks at different levels. Due to the complexity of the system and technological limitations, it is typically only possible to consider one or two levels at the same time.

At the cellular level neurons are excitable brain cells that communicate with each other through electro-chemical signals sent and received by a specialized apparatus. In general neurons consist of three parts, a dendritic tree, a cell body (soma), and an axon. The dendrites can be seen as antennas that receive the signals from other neurons (and other brain cells, glial cells). The soma integrates the signals from the dendrites and is also where the DNA is stored and where the transcription takes place (the initial step of protein production). The axon can be seen as a cable for sending signals, that enables specialized targeting of message delivery.

The connections between neurons are called synapses and come in two types, electrical and chemical. A chemical synapse consists of a release site on the sending, *presynaptic* side where neurotransmitters are released, and receptors in the receiving, *postsynaptic* side. The two sides are held in close proximity to each other by specialized anchoring proteins. The small gap between neurons (tens of nanometers), early on led leading neuroscientist[2] to believe that the nervous system consisted of a continuous network[3] (Valenstein, 2006). The short distance enables rapid diffusion of neurotransmitters from the presynaptic side to the postsynaptic side. The binding of neurotransmitters on the postsynaptic side can either excite or depress the receiving neuron (increase or decrease the membrane potential, respectively), but some neurons instead release signals that change the internal state of the receiving neuron. This phenomenon is called neuromodulation.

In this PhD project I have studied how the dendrites integrate signals in a specific part of the brain called the striatum. Since the striatum is densely innervated by neuromodulators, such as dopamine and acetylcholine, a specific focus has been on the role of neuromodulation in dendritic integration. In the following sections I will introduce the relevant brain structures and cell types, their role in learning and policy making, and how neuromodulation influences these policies.

1.1 General overview

One of the most well studied parts of the central nervous system is the outer layer of the brain, the cerebral cortex (from here on referred to as *the cortex*). The cortex is a sheet of neural tissue, evolutionary enlarged, that is particularly prominent in mammals. In humans it is extensively folded due to the largely increased area. The cortex is further divided into functionally segregated areas. For example, there is one part involved in integrating sensory signals (the somatosensory cortex), and another part involved in motor functions (the motor cortex). The motor cortex is topographically organized in such a way that nearby regions map to

[2]The leading protagonist of this theory was the Nobel laureate Camillo Golgi (1843-1926)

[3]The *reticular theory* was disproved by Sir Charles Scott Sherrington (1857-1952) for which he received the 1932 Nobel prize

nearby body parts. Electrical stimulation of short duration in a specific region causes twitching in the corresponding limb. However, longer duration stimulation of these regions gives rise to complex sequences of movements, for example moving the hand to the mouth or defensive movements (Graziano et al., 2002).

The cortex is populated by neurons during embryonic development and after a certain stage no new cells are added, there is no *neurogenesis* in the cortex (reviewed in e.g. Rakic, 1985, 2002). This is however not true for all brain regions. One region where new cells are born throughout life is the *hippocampus* (Gould et al., 1997, 1999b,a; Spalding et al., 2013). The hippocampus is a region involved in consolidation of short term memory into long term memory (Scoville and Milner, 1957) and formation of spatial maps (reviewed in, Moser et al., 2008). Another region that is both evolutionarily enlarged and neurogenic throughout life is the *striatum* (Ernst et al., 2014; Ernst and Frisen, 2015).

> "It is likely that the activity of striatal and other basal ganglia neurons encodes information in a complex manner and that the interaction of the nuclei of the basal ganglia with each other is similarly complex"
>
> *Roger L. Albin*
> *Anne B. Young*
> *John B. Penney*
> *-The functional anatomy of basal ganglia disorders*

1.2 Basal ganglia

The striatum is the largest nucleus in a subcortical brain structure called the basal ganglia, largely evolutionary conserved for over 560 million years (Stephenson-Jones et al., 2011). The basal ganglia are involved in motor selection, sequence learning and habit formation (for reviews see, Graybiel, 1998, 2008; Robertson et al., 2014), but have also been assigned the more general role of a centralized selection mechanism (Redgrave et al., 1999), or pattern

detector (Beiser and Houk, 1998). For an overview of the basal ganglia nuclei, see fig. 1.

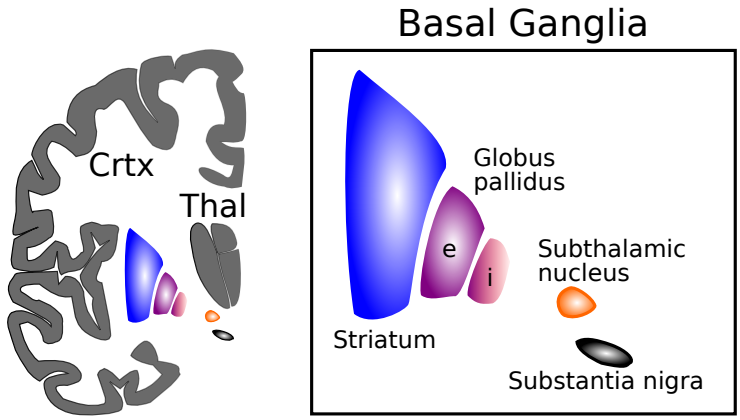

Figure 1: Overview of the basal ganglia *in relation to the cortex (Crtx) and thalamus (Thal) in one hemisphere of a human brain slice (in coronal/frontal view). The internal and external segments of the globus pallidus are marked with i and e, respectively. The caudate nucleus, part of the striatum is left out for simplicity, i.e. only the putamen is shown.*

Habit formation. Habit formation in this context is defined as a stimuli triggered behavior that is continuously being carried out regardless of action outcome, specifically after reward devaluation. Habit formation allows fast, parallel, and effortless decision making, which is often advantageous but may also be the reason why idiosyncrasies, such as addictions[4] are so hard to break (Schneider and Chein, 2003). Such subconscious and automated action selection that habits represent, could also be the reason why we sometimes seem to make irrational choices (McHaffie et al., 2005).

The direct and indirect pathways. The basal ganglia are classically divided into two parallel pathways; the *direct* and *indirect*

[4]defined as: "a treatable, chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual's life experiences" according to the American Society of Addiction Medicine

pathways. The names of these pathways come from their respective projection characteristics. In the direct pathway, the striatal projection neuron (SPN)[5], project directly to the basal ganglia output nuclei, the internal part of the globus pallidus (GPi) and substantia nigra pars reticulata (SNr). The indirect pathway on the other hand, projects to the external segment of the globus pallidus (GPe), which in turn projects to the output nuclei, both directly, and indirectly via the subthalamic nucleus (STN). For a graphical illustration of the two pathways, see fig. 2.

More recently it has been recognized that the STN also receives glutamatergic input directly from the cortex, and a *hyperdirect* pathway has been coined (Nambu et al., 2002).

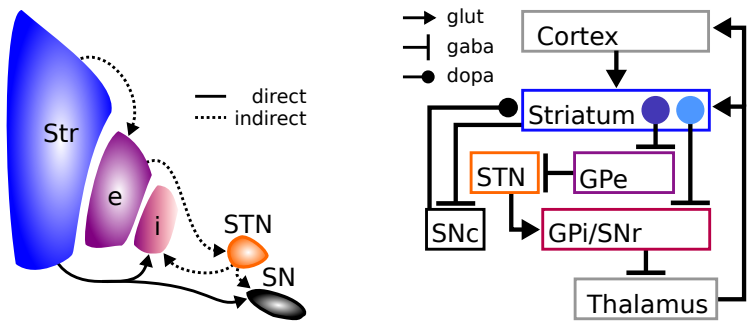

Figure 2: Direct and indirect pathways of the basal ganglia *illustrated as connectivity in the left panel and the classical box and arrow model in the right panel (remake based on Albin et al., 1989). As in fig. 1, the caudate nucleus of the striatum is not shown.*

The direct and indirect pathways are classically thought to start and inhibit actions, respectively, and are therefore sometimes also referred to as the GO and NO-GO pathways. This is also how the basal ganglia have often been described in classical *box and arrow* models. However, already the authors of one of the first of these models, acknowledged that describing the basal ganglia solely by the action of the direct and indirect pathways is an oversimplification (Albin et al., 1989, also see the quote at the beginning of this section). In recent years the antagonistic roles of the two pathways

[5]Also known as spiny projection neuron and medium spiny neuron (MSN).

have been further challenged in papers showing that both pathways need to be active for action initiation to occur (Cui et al., 2013; Tecuapetla et al., 2016).

Input to the basal ganglia. The basal ganglia are tightly connected with the cortex and thalamus, from where they receive glutamatergic (excitatory) input, but are also reciprocally connected to the dopaminergic system in the midbrain. Both glutamatergic and dopaminergic input converge in the main input structure of the basal ganglia–the striatum.

1.3 The striatum

The striatum is often referred to as a sensory-motor hub as it receives bilateral and multisensory input from a large part of cortex (Reig and Silberberg, 2014) and attentional related input from thalamus (Minamimoto and Kimura, 2002). The input is further topographically subdivided and shows response heterogeneity based on subregion (Tziortzi et al., 2014; Hunnicutt et al., 2016). With this in mind it is perhaps not surprising that there are functionally specialized regions also in the striatum. The ventral part of striatum[6] is involved in reward processing and motivation while the dorsal part is more motor related. In particular the lateral part of the dorsal striatum[7] is involved in habit formation while the medial part[8] is involved in goal directed action selection (Yin et al., 2004, 2005). Both circuits have been proposed to converge onto the same downstream targets (Redgrave et al., 2010). The size of the dorso-medial striatum is also reduced in obsessive compulsive disorder, indicating a larger influence of the automated circuits in dorso-lateral striatum on the output of the basal ganglia (Robinson et al., 1995). The striatum is also strongly innervated by dopaminergic fibers (Matsuda et al., 2009).

[6] Also known as the nucleus accumbens
[7] Also known as the putamen
[8] Also known as the caudate

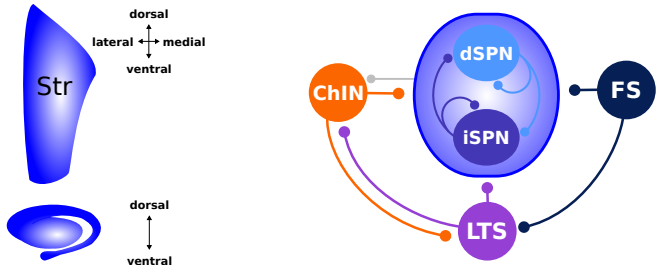

Figure 3: Illustration of the striatal microcircuit. *The left panel shows the striatal subpart putamen in frontal view (coronal slice, top) and the full striatum, caudate and putamen in side view (sagittal slice, bottom). The top and bottom panels are not in scale. The dorsoventral and mediolateral axes are also indicated with arrows. The right panel illustrates the connections between neurons in striatum. The striatal projection neuron (SPN) is shown in the middle and the input from fast spiking (FS), low threshold spiking (LTS) and cholinergic interneuron (ChIN) are placed in the outer part of the illustration (premake of figure 1 in* ***Paper 3****).*

1.4 The striatal microcircuit

About 90-95 percent of the striatal population consists of SPNs. The SPN population can be divided into two subpopulations based on genetic expression and projection target. One of these subtypes expresses the dopamine receptor type 1 and substance P (dSPN) and the other the dopamine type 2 receptor (D2R) and enkephalin (iSPN). It is the projection of these neurons that form the direct and indirect pathways (introduced above). Apart from projecting out of the striatum the SPNs also form inhibitory connections with neighboring SPNs[9] of both subtypes (Tunstall et al., 2002; Planert et al., 2010), targeting primarily distal dendrites (Koos et al., 2004). It seems like this connection is not reciprocal, i.e. two SPNs might not directly inhibit each other (more data is needed to decide, Tunstall et al., 2002; Planert et al., 2010).

[9]So called, lateral inhibition

1.4.1 Interneurons

Apart from the projection neurons responsible for connecting the brain area with its downstream targets, there are also so-called *interneurons*, neurons with local projections *within* a brain structure. In striatum there are at least three major types of interneurons as based on molecular profile, morphological characterization and electrical profile. For a simplified illustration of the striatal microcircuit, see fig. 3. For a more extensive review se Tepper et al. (2018).

Fast spiking interneurons The parvalbumin positive, fast spiking interneuron (FS), is characterized by a high frequency burst firing. It receives excitatory input from the cortex and forms an inhibitory connection[10] with primarily, but not exclusively (Kubota and Kawaguchi, 2000), the perisomatic region of the SPN (Kawaguchi, 1993; Bennett and Bolam, 1994; Straub et al., 2016).

Cholinergic interneurons A second class of interneuron is the large aspiny cholinergic interneuron (ChIN). The ChIN is tonically active and the major source of the neuromodulatory substance acetylcholine (ACh) in striatum (Kawaguchi, 1993; Wilson et al., 1990). The released ACh binds to fast ionotropic nicotinic receptors[11] (nAChR) as well as slower metabotropic receptors[12] in the cell membrane of other cells in the striatum, and incoming axonal terminals (reviewed in Oldenburg and Ding, 2011; Picciotto, 2013). It receives glutamatergic input mainly from thalamus (Ding et al., 2010) which can trigger a burst of activity followed by a pause, thought to be involved in associative learning (Aosaki et al., 1994; Ding et al., 2010). The ChIN population is also involved in network synchrony and motor gating (Howe et al., 2019).

Low threshold spiking interneurons The third group of interneurons is the tonically active *low threshold spiking* interneuron (LTS). The LTS is a heterogenous group of interneurons that can be subdivided based on gene expression. Somatostatin, neuropeptide

[10] So called, feedforward inhibition

[11] in direct control of ion channels

[12] triggering conformational changes on the opposite side of the membrane

Y and nitric oxide (NO) are expressed in various subpopulations of the LTS (Kawaguchi, 1993; Kawaguchi et al., 1995). The LTS has a sparse dendritic tree and forms long range axonal connections with SPN (Kawaguchi, 1993; Straub et al., 2016).

1.4.2 Connections

In the cortex, somatostatin positive interneurons (SOM) form inhibitory connections with distal dendrites of cortical projection neurons (the *pyramidal neuron*) and parvalbumin positive, fast spiking interneurons (PV) with the perisomatic region (reviewed in Tremblay et al., 2016). This functional organisation is also found in the striatum, with LTS primarily contacting the distal dendrites of SPNs and FS the perisomatic region (illustrated in fig. 4, Straub et al., 2016).

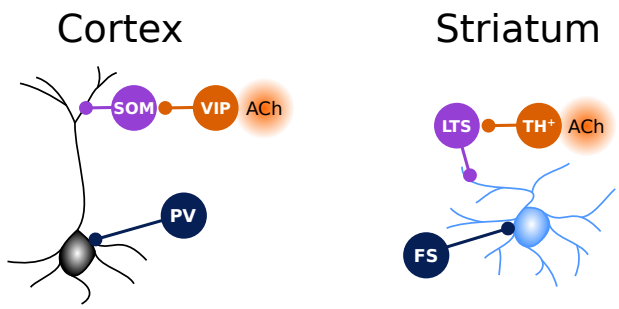

Figure 4: The same inhibitory motifs onto projection neurons are found in both striatum and the cortex. *The fast spiking interneurons (FS and PV, respectively) forms connections with primarily the perisomatic region of projection neurons while the distal dendrites are inhibited by somatostatin positive interneurons (LTS in striatum and SOM in the cortex). In both regions the distal inhibition can be disinhibited by interneurons activated by acetylcholine (VIP in the cortex and Th^+ in striatum).*

In the cortex there is also a third type of interneuron referred to as VIP (vasoactive intestinal polypeptide positive interneuron) that inhibits the SOMs and expresses nAChR. Pyramidal neurons can through this circuit be disinhibited via ACh release in the

cortex (Lee et al., 2013; Pi et al., 2013; Pfeffer et al., 2013; Muñoz et al., 2017). The striatal LTS are also under inhibitory control of a newly characterized striatal interneuron, the tyrosine hydroxylase expressing interneuron (TH^+, Ibáñez-Sandoval et al., 2010), also activated by nAChR agonists (Ibáñez-Sandoval et al., 2015; Luo et al., 2013).

The LTS also forms GABAergic (Straub et al., 2016) as well as neuromodulatory connections (mediated by NO) with ChINs, that in turn modulate LTS through both muscarinic and nicotinic receptors (Luo et al., 2013; Elghaba et al., 2016). The muscarinic effect is of modulatory nature.

1.5 Neuromodulation

Neuromodulators are substances that change the integrative properties of neurons. They come in a rich variety, where some have local effect while others diffuse broadly or are carried by the bloodstream[13] (Marder, 2012). Neuromodulators are well studied in the crustacean stomatogastric ganglion, where they dramatically change the circuit behavior (Marder and Weimann, 1992). They influence intrinsic properties of cells, e.g. ion channels but also the connections *between* cells (Thirumalai et al., 2006; Marder, 2012). Many different neuromulators can influence the same ion current, while being activated by different receptors in the membrane (Swensen and Marder, 2000).

1.5.1 Dopamine

One of the most well studied neuromodulators in the brain is dopamine. Dopamine has classically been associated with the reward prediction error of reinforcement learning (Schultz et al., 1997; Schultz, 2002) but is also critical for normal motor behavior, most obviously manifested in Parkinson's disease. In Parkinson's disease the dopaminergic neurons projecting to the striatum are dying[14], resulting in tremor, rigidity and a general difficulty to initiate movement. Recent studies have shown that the dopaminergic system is also involved in movement initiation in the healthy brain (Howe and Dombeck, 2016; da Silva et al., 2018; Howe et al., 2019).

[13] known as hormones

[14] primarily in substantia nigra pars compacta

Origin of dopaminergic input The dopaminergic neurons projecting to striatum are located in two adjacent nuclei, *substantia nigra pars compacta* (SNc) and the *ventral tegmental area* (VTA). The ones from SNc are projecting densely to dorsal striatum and are more involved in motor control while the ones from VTA send sparse projections to dorsal striatum that are more reward related (Howe and Dombeck, 2016).

The dopaminergic signal; local or global? Both the receptor density and axonal ramification is high in the striatum (Moss and Bolam, 2008; Matsuda et al., 2009). The axons primarily form connections with synapses and dendritic shafts (Pickel et al., 1981; Freund et al., 1984)), often close to cortical (Smith et al., 1994) and/or thalamic afferents (Moss and Bolam, 2008). Dopaminergic neurons further tend to fire in synchrony in dorsal striatum (Howe and Dombeck, 2016). This hence indicates that the dopaminergic signal is global, that is, in support of so-called *volume transmission* (see e.g. Moss and Bolam, 2008; Schultz, 2007). However, dopamine release can also be triggered directly from dopaminergic axons, without firing in the cell-bodies. Either directly by coordinated activation of ChINs (Threlfell et al., 2012) or indirectly by activation of thalamostriatal neurons (Cover et al., 2019).

The dense, synchronous dopaminergic signal transmitted by the neurons in SNc (Howe and Dombeck, 2016) and the local release triggered by ChINs and thalamic afferents, could hence represent two different modes of dopaminergic signaling (Costa, 2011).

Co-release and neuronal profile Dopaminergic neurons have been shown to co-release both GABA and glutamate in striatum (Chuhma et al., 2004; Tecuapetla et al., 2010; Tritsch et al., 2012; Chuhma et al., 2018). Recent studies also suggest that dopaminergic neurons in hypothalamus can switch identity, i.e. go from expressing one neurotransmitter to another. For example can a changed day-night cycle cause dopaminergic neurons in hypothalamus to instead release somatostatin (Dulcis et al., 2013). This change also correlates with behavior and is matched by a post-synaptic change of receptors (Dulcis et al., 2013)[15]. However, it

[15]For more on this subject, see review by Spitzer (2017)

should be noticed that no evidence of such a phenomenon has been found in the striatum to date.

Summary All together, the studies described above exemplify the complexity of the dopaminergic system on a superficial level. It is clear that more studies are needed to elucidate the multiplex nature of this system.

1.5.2 Acetylcholine

Acetylcholine (ACh, together with norepinephrine) is the primary neurotransmitter in the peripheral nervous system. It was the first substance shown to be endogenously released by nerve endings and therefore the first neurotransmitter identified. The discovery also elucidated the chemical, rather than electrical nature of the synapse[16] (Valenstein, 2006). In the central nervous system it is instead primarily acting as a neuromodulator, affecting how the cells and circuits operate.

The primary source of ACh in the striatum is local release by ChINs, but there is also an external source, originating in the pedunculopontine nucleus.

1.6 Dendritic computation

Dendrites have classically been seen as passive structures with the primary purpose to increase the surface area of the cell. New experimental techniques and technologies, developed over the last couple of decades, have demonstrated beyond doubt, that this is not the case. The dendrites are capable of shaping signals transmitted to the soma via active ion channels in the membrane, enabling dendrites with the ability to trigger dendritic spikes. Such dendritic spikes can be triggered by three major sources; sodium, calcium and N-methyl-D-aspartate (NMDA) channels.

Striatal SPNs can trigger the NMDA dependent type of dendritic spikes, also referred to as plateau potentials (Du et al., 2017; Plotkin et al., 2011). In **Paper 1** we showed that these plateau potentials can depolarize a large part of the dendritic tree, tens to hundreds of milliseconds, and thereby open an "integration window" where the cell is susceptible to excitation (Du et al., 2017).

[16] Otto Loewi (1873-1961), received the Nobel prize for this discovery in 1936

These plateau potentials are triggered when spatially clustered spines are co-activated, causing a depolarization of the local membrane, accompanied by a release of the magnesium block of the NMDA channels (Plotkin et al., 2011; Du et al., 2017). These dendritic spikes are hence dependent on functional clustering of spines. Functional clustering is not well studied in striatum, likely due to the relatively thin dendrites of SPNs and the non accessible location of the basal ganglia, embedded under the cortical sheet.

Pyramidal neurons In the cortex on the other hand, many recent studies have shown experimental evidence of such organization (e.g. Xu et al., 2009; Fu et al., 2012; Takahashi et al., 2012; Xu et al., 2012; Chen et al., 2015; Cichon and Gan, 2015).

During learning, spines in the distal dendrites re-organize in such a way that synapses on active spines strengthen while non-active spines are weakened (Cichon and Gan, 2015). The reorganization is further controlled by the local inhibitory microcircuit. Specifically the dendritically targeting SOMs (similar to the striatal LTS) seems to play an important role. If the activity of these cells are manipulated the normal spine turnover is impaired, leading to disrupted learning (Chen et al., 2015). Similarly, blocking inhibition disrupts specificity of spine potentiation and learning (Cichon and Gan, 2015).

In the process of learning, the total number of spines seems to be constant. As new spines are added others are removed (Xu et al., 2009). However, the number of spines originating from different *sources* can be dynamically updated. For example, the number of inhibitory contacts formed by SOMs onto pyramidal neurons are decreased, while the more proximally targeting PVs are increased (Chen et al., 2015). Likely permitting plasticity in the dendrites while keeping the overall excitability of the cell in check.

Spines that are clustered are also more likely to persist during learning (Fu et al., 2012).

"I am never content until I have constructed a mechanical model of the subject I am studying. If I succeed in making one, I understand; otherwise I do not."

Lord Kelvin

2 Methodological considerations

As stated in the quote above by sir William Thomson (Lord Kelvin, 1824-1927), a model can be used to test how well we understand a phenomenon, by reducing it to a few key components and see how well they explain the behaviour. A model can further be used to interpret data and make predictions where data are missing.

One of the first brain inspired models was the famous model by Mcculloch and Pitts (1943). Their model relies on the all-or-none principle of neurons to theoretically compute logical statements. The all-or-none principle states that if a neuron is stimulated strongly enough, an action potential[17] with a *fixed amplitude*, is triggered. This behavior of neurons had earlier been demonstrated by the Nobel laureate, Edgar Adrian (1889-1977) after he, for the first time, was able to experimentally record single action potentials (Adrian and Zotterman, 1926).

The McCulloch and Pitts-model was a so-called point neuron model, a phenomenological model that did not take dendrites into consideration. Many of the early network models used in computational neuroscience did use point neuron models, restricted by the computational powers of their time. These days, when computation is relatively cheap, many large-scale network models use compartmentalized models, including multiple ion channels and realistic morphologies (e.g. Markram et al., 2015). These are also the type of models used in this thesis.

[17] nerve impulse, also known as *spike*

2.1 Compartmentalized models

Compartmentalized models build on the seminal work of Wilfrid Rall (1922-2018). Rall first used cable theory to calculate the analytic solution to idealized passive trees (Rall, 1959) and then introduced compartmental modelling to *numerically* compute the current spread in biophysically realistic dendritic trees (Rall, 1964; Segev, 1995)[18].

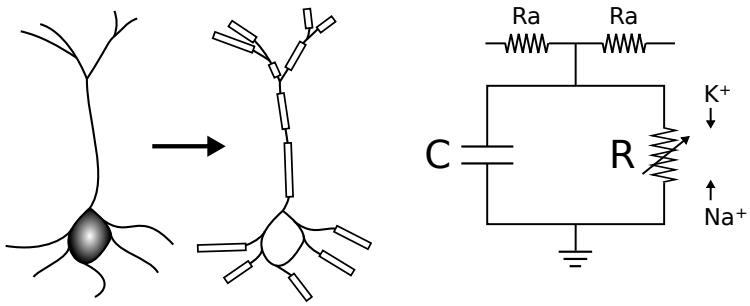

Figure 5: Compartmentalization of a neural morphology. *Illustration of how a morphology is split into axially connected compartments, each modelled as an RC-circuit (exemplified in the right panel). The main directions of ions during action potentials are indicated by arrows (sodium, Na^+ and potassium, K^+; in and out of the cell, respectively) .*

In compartmentalized modelling the electrical properties of the cell are calculated in discrete locations, so called compartments, where each compartment is modelled as an electrical circuit (illustrated in fig. 5). The compartments are connected in series, where voltage differences between connected compartments give rise to equalizing *axial* currents. The magnitude of this equalizing current is proportional to the voltage difference and scaled by a resistive element, the axial resistance (R_a). Besides this axial current there is typically also an ion exchange with the outside of the

[18]The importance of this work was not immediately recognized by the scientific community as the function of dendrites was not yet established, resulting in a conflict over the influence of dendritically located synapses with his former PhD supervisor, the Nobel laureate John Eccles (1903-1997, Jack and Redman, 1995)

cell, over the cell membrane. Mathematically the change in voltage at a compartment can be calculated as:

$$C_m \frac{dV_m}{dt} = I_{membrane} + I_{axial}. \tag{1}$$

Where C_m is the membrane capacitance and $I_{membrane}$ is the currents over the membrane from ion channels and injected currents etc ($I_{membrane} = I_{channels} + I_{injected}$). The channel currents can be calculated as:

$$I_{channels} = \sum_i (E_i - V_m) \cdot g_i \tag{2}$$

Where E_i and g_i are the reversal potential and the conductance of channel i. Axial currents can be calculated as:

$$I_{axial} = \sum_j (V^j_{neighbour} - V_m)/R^j_a \tag{3}$$

Where and $V^j_{neighbour}$ and R^i_a are the membrane potential and axial resistance of neighbour j (adapted from Bower and Beeman, 1998). Since the membrane is made from lipids and not directly permeable to ions, all exchange with the outside is regulated by transporters and ion channels.

2.2 Ion channels

Ion channels are typically modelled based on the formalism established by the Nobel laureates Alan Hogkin (1914-1998) and Andrew Huxley (1917-2012). Hogkin and Huxley described the mechanisms behind the all-or-none behavior of action potentials, by using the recently developed voltage clamp technique[19] applied to the membrane of the squid giant axon. This led them to the discovery that the action potential consisted of two separate currents, one fast and depolarizing and the other hyperpolarizing with slower kinetics. The ions responsible for the individual currents could further be identified as sodium and potassium, respectively (Hodgkin and Huxley, 1952). Using the voltage clamp technique they went on to characterize the flow of the two major ions as a function of voltage

[19] stabilizing the voltage at a fixed value by dynamically injecting a current, counteracting the membrane currents, using a feedback system

and time. The potassium channel was found to not inactivate with prolonged stimulation and the measured current following voltage steps of different magnitude could be well fitted with equation:

$$g_K = g_K^{max} \cdot n^4 \tag{4}$$

where n is the open probability of the channel activation gate. From this they postulated that the change of the activation gate followed the first order differential equation:

$$\frac{dn}{dt} = \alpha \cdot (1 - n) - \beta \cdot n \tag{5}$$

where α and β are the voltage dependent rate constants of inactivation and activation. The only thing left was to determine the rate constants over voltage.

The sodium channel was characterized using the same formalism, with the exception that the sodium channel also inactivated with prolonged activation. This resulted in the formula:

$$g_{Na} = g_{Na}^{max} \cdot m^3 \cdot h \tag{6}$$

where m and h are the open probability of the activation and inactivation gates, respectively. Both gates could also be characterized using the same type of voltage dependent differential equation as for the potassium channel n gate.

Unlike the potassium channel in the squid giant axon, many potassium channels in vertebrates, as well as in our models, also inactivate. Ion channels can further be dependent on the concentration of a certain ion or the extracellular pH-value, and not only the membrane potential.

2.3 Optimization and variability

The models used in this thesis were fit to experimental data by hand tuning (**Paper 1** and **2**) and computational techniques (**Paper 3** and **4**). Hand tuning gives a deep understanding of the role of individual ion channels in model behavior, but is very time consuming–which limits the number of solutions that can be explored using this technique. This is important to keep in mind since many different combinations of ion channel conductances can

give the same model behaviour (Prinz et al., 2004). Computational techniques on the other hand, provide many solutions but poor understanding of the role of individual ion channels. On a related note, it has been proposed that neurons themselves are also "optimized" to a specific network behaviour, rather than to have a fixed set of ion channels in the membrane (Prinz et al., 2004; Marder and Goaillard, 2006). This proposed strategy could perhaps also explain the large variability in gene expression seen in single cell types (Gokce et al., 2016).

2.4 Morphology and numerical accuracy

How you model the morphology of the cell is another important aspect of compartmentalized models. Commonly you use either *stylized* representations of the morphology, based on the general characteristics of the studied cell, or *reconstructions* of real cells. In this thesis reconstructions were used since they provide a natural source of variability and thereby give a more general result. The larger variability however, comes with a cost in the form of a less straightforward interpretation of the results. If the morphology is reconstructed after electrophysiological recordings are done, one can build a model of that particular cell. This technique was used for some of the models in **Paper 3**.

Further, the *accuracy* of the results are dependent on the number of compartments used in the model. Each model compartment should be small enough so that the spatially varying membrane current is well approximated by the value at the compartment center (Carnevale and Hines, 2003; Segev, 1998). Similarly as the spatial discretisation, the time step of the numerical integration should also be much smaller than the time scale of the fastest events in the simulation. Typically the action potential is the fastest event in electrophysiological models (Bower and Beeman, 1998), but subcellular processes may also operate on a fast time scale.

2.5 Neuromodulation and subcellular cascades

In **Paper 2**, a subcellular cascade was incorporated into the electrophysiological model to investigate how fast the effect of dopamine on single ion channels could lead to spiking in striatal projection neurons. The cascade was modeled using *mass action kinetics*

solved by differential equations similar to the ones used by Hodgkin and Huxley to model the ion flux through the membrane. For example, if species A and B react to form C:

$$A + B \rightarrow C, \tag{7}$$

then the change in concentration of C can be calculated as

$$\frac{d[C]}{dt} = k \cdot [A] \cdot [B], \tag{8}$$

where k is a rate constant. That is, the concentration of C will increase with a rate proportional to the product of the concentrations of A and B. The change in concentration of A and B are calculated in the same way, except that the sign in front of the rate constant is negative.

Such kinetic flows can be built using graphical tools, for example the *simbiology toolbox* in Matlab (MATLAB, 2012) and from there exported into standardized xml format (*System Biology Markup Language*, SBML). SBML is not directly supported by the softwares used for simulating compartmentalized models[20], but has to be transformed. There are tools available for this transformation (e.g. NeuroML; Cannon et al., 2014), but in my experience they are not reliable and user friendly yet. In **Paper 2** a combination of tools and custom made scripts were used in the conversion. To streamline the production and simulation of multiscale models I also implemented a script for direct conversion of SBML cascades utilizing the *python* library *libSBML* (not directly applied in this thesis, but used in other non published neuromodulation studies in the lab)[21]. **Paper 3** and **4** also included neuromodulation, but here the delay of the effect was implicitly taken in consideration rather than modelled using a subcellular cascade. Instead levels of modulation was *played* into affected channels using *step*, *sigmoidal* or *alpha* functions.

[20] In this thesis we used GENESIS (Bower et al., 1998) for Paper 1 and Neuron for Papers 2-4 (Hines and Carnevale, 1997)

[21] Neuron models are also runnable in python

3 Aims

The aim of this thesis was to study how neuromodulation, primarily in the form of dopamine, affects the integrative properties of neurons and microcircuits in the striatum. The aim of each constituent paper is given below.

Study 1

- To investigate the balance between excitation and inhibition in the context of dendritic integration.

Study 2

- To establish a dopaminergic response profile of striatal projection neurons.

Study 3

- To establish a framework for *in silico* studies of the striatal microcircuit, including neuromodulation of individual cell types.

Study 4

- To study the function of dopaminergic and cholinergic modulation in the context of dendritic integration in striatal projection neurons.

4 Results and discussion

In this thesis I have investigated the effect of neuromodulation on the striatal circuit with a focus on signal integration in the dendrites of the SPN. This has resulted in an extension of the theoretical framework of striatal function and in a set of testable predictions.

4.1 Paper 1: Excitation and inhibition in the dendrites of spiny projection neurons

In the first study we collaborated with an experimental lab at Stanford University (Du et al., 2017). Biophysically detailed simulations were used to predict cellular behavior and aid in experimental design. Advanced experiments, including uncaging of glutamate[22] in specific dendritic branches and cell type specific activation using optogenetics[23], were then carried out to test the predictions of the simulations.

This study was the second to show that SPNs can produce dendritic NMDA-spikes by direct glutamate uncaging. It also investigated the role of inhibition in general and sub-type specific inhibition in particular. The result showed that "on site" dendritic inhibition is the most efficient in silencing a cell during an ongoing NMDA-spike. In this way it extends the theoretical framework on the balance of excitation and inhibition.

4.2 Paper 2: Dopamine modulation of the striatal projection neuron

The second study investigated how the neuromodulator dopamine acts on the dSPN (Lindroos et al., 2018). Specifically, the question of how modulation of single channels are integrated into shaping the cellular behavior, was investigated. The aim of the study was to predict which of the many effects of dopamine that contributed the most in making the cell more excitable. The method used was

[22] the process involves unbinding of glutamate, covered by a shielding molecule, using precise photon beams

[23] photo-sensitive channels in the membrane of genetically targeted cell types– inserted using virus and activated using light

modelling, where an intracellular cascade was inserted into a biophysically detailed model of a single cell. The resulting multi-scale model was then used to predict the magnitude and time course of the dopaminergic effect on cellular behavior. The results showed that if the fast potassium current (carried primarily by the Kv4.2 channel) was modulated, combined with no modulation of the axon initial segment, the model was reliably more excitable. If only one of these conditions was met, the probability of a more excitable cell was low (this protocol was also re-validated in **Paper 4**).

Kinetics of dopamine modulation The time course of the dopaminergic effect on cellular behavior was also investigated. This showed that the cascade classically described as responsible for the modulation, was too slow to explain the fast effect observed following stimulation of dopaminergic terminals in the striatum (Howe and Dombeck, 2016). This hence suggests another form of dopaminergic action, e.g. co-release (Chuhma et al., 2018). However it is also possible that the restricted volume of dendritic branches and membrane bound forms of the protein structures involved, would allow a faster modulation than what we saw in our simulations.

4.3 Paper 3: Dopamine modulation of the striatal microcircuit

In **Paper 3**, we created a detailed large scale network of the striatal microcircuit, including the five best characterized cell types. The dopamine modulation was here extended to involve all cells in the circuit.

The framework developed in **Paper 2**, where modulation factors were randomly drawn from reported ranges, was used here as well. The overall behavior of the cell-models were then validated against electrophysiological experimental studies. The resulting modulation of projection neurons, gave on average an increased excitability of dSPN while iSPN decreased their excitability. Modulation of interneurons are less well studied in the striatum, but here FS increased their action potential discharge, LTS spiked from a depolarized state and ChINs responded with an increased burst-pause response.

Preliminary simulations of the network show that FS inhibition onto dSPN is relatively stronger than that from other SPNs while the opposite is true for iSPN, see fig. 6.

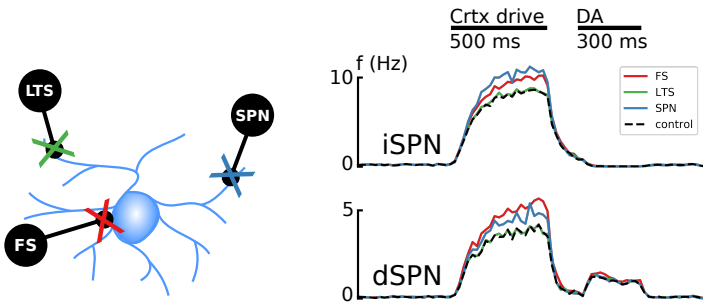

Figure 6: Selective inhibition in the striatal network; Preliminary results. *The right panels show the average spike frequency in striatal projection neurons of the direct and indirect pathway (dSPN and iSPN, respectively) following selective ablation of inhibition from: other SPNs (blue trace), fast spiking interneurons (FS, red trace) and low threshold spiking interneurons (LTS, green trace). The control condition, with all inhibition intact, is shown in black (dotted line).*

4.4 Paper 4: Predicting complex spikes in striatum following concurrent dopaminergic and cholinergic modulation

Paper 4 investigates the effect of neuromodulation on active dendritic properties in dSPN. The frameworks developed in **Paper 1** and **2** were here combined, and extended with additional cholinergic modulation. The results showed that concurrent dopaminergic and cholinergic modulation gave rise to learning related *complex spikes*. The complex spikes were triggered following dendritic NMDA-spikes. In some cases multiple nmda-spikes were triggered sequentially in the dendrites, prolonging the duration of the complex spike.

The somatic response to dendritic activation In **Paper 1** we showed that distal, but not proximal dendritic locations were favorable to trigger NMDA-spikes (Du et al., 2017). Here we generalized this notion by measuring the somatic response to activation in all parts of the dendritic tree. The results of this simulation showed that both morphological features, primarily distance to soma, and ion channel distribution along the dendrites influence the somatic response to a given input. This poses the question how a cell can produce a stable response given ongoing structural reorganisation of its morphology.

Memory formation in the dendrites The NMDA-spikes were further associated with robust calcium signals. Such signals would likely lead to plasticity. As mentioned above, NMDA-spikes are primarily triggered in the distal dendrites. Distally located spines are also more unstable than proximal ones and more prone to change following learning in cortical pyramidal neurons (Chen et al., 2015).

Does this mean that memories are formed in distal dendrites and "migrated" to the more stable proximal dendrites as they mature? Or, are early memories stored in proximal spines and newer ones "stacked" on top of these–stored progressively further out in the dendrites as the "memory slots" fill up? Either way, perhaps this is also why it is so hard to change someone's core values. It would be informative to investigate if the same type of organization can also be found in SPNs.

Neuromodulation *in vivo* The complex spikes in our simulations were also correlated with a decreased sodium current in the axo-somatic region. Here we contributed these changes to dopaminergic modulation, but also other neuromodulators could have the same effect since multiple intracellular pathways can reduce the sodium current (Chen et al., 2006).

It should be recognized that the uncertainty in our modulation paradigm is high as well as in the underlying experimental studies. The experimental data are recorded *ex vivo*, and often in unphysiologically high concentrations of neuromodulators. However, given the dramatic circuit changes observed in crustaceans following neuromodulation (Marder, 2012), it is not impossible that the network effect can also be large in the central nervous system of

vertebrates. To know for sure we need to develop techniques to measure these modulatory changes in the intact brain. Potentially, such techniques would also be useful in explaining the fast movement induction observed following stimulation of the dopaminergic and cholinergic systems (Howe and Dombeck, 2016; Howe et al., 2019).

The interplay between soma and dendrites Traditionally signal transduction in neurons is thought to occur from dendrites to soma. However during complex spikes there was also a somatic component that participated in elevating the membrane potential. The elevated potential in the somatic region was transmitted to the dendrites in the form of a robustly elevated calcium concentration. The calcium activation was detectable in a large part of the dendritic tree, in contrast to the more transient signal following a backpropagating action potential (Day et al., 2008). It is hence possible that signals can also be sent in the non-conventional direction, soma-to-dendrite, more reliably than previously thought.

"When you are face to face with a difficulty, you are up against a discovery"

Lord Kelvin

5 Conclusions and future perspective

In this thesis I have attempted to integrate data on different levels into a coherent picture of neuromodulation in the striatum, focusing on cause and effect. It has led to a set of predictions, of which the primary is that complex spikes may be triggered in the striatal projection neuron (SPN). This prediction can be validated or falsified through experiments.

In the hippocampus, complex spikes are triggered in the intact animal, involved in exploration of the physical environment. Since striatal cells are multisensory in nature (Reig and Silberberg, 2014; Graziano and Gross, 1993), perhaps the same setup can also be used to test for complex spikes in SPNs. However, it is not clear what SPNs would compute in such context and the yield would likely be low (Reig and Silberberg, 2014). On the other hand, it is not straightforward to come up with another behavioral paradigm where this could be tested, given that the representation of the input to striatal neurons are not as well characterized as the input to the hippocampus.

The underlying mechanisms observed in our simulations should also be explored in models of hippocampal pyramidal neurons. If found to produce complex spikes also in the area where they were first characterized (Bittner et al., 2015, 2017), this would strengthen our claim and increase the impact of our predictions.

Regarding the overall understanding of the computation of the central nervous system, we are starting to map out circuits involved in various aspects of behavior, but we still have a long way to go. The large number of cell types, the heterogeneity within populations, and the intricate connections *between* cells in the brain–as well as the number of receptors, neuromodulators and intracellular cascades *within* single cells–makes the mapping a daunting task. Like in the painting on the cover of this thesis (fig. 7), the picture of the neural circuits emerging are often rather abstract and hard to interpret.

Despite the complexity of the question at hand I think we should look ahead with optimism as both experimental and computational techniques developed over the last decade hold great promise for future breakthroughs.

Figure 7: The cover figure "Brain freeze". *Abstractly painted by my daughter Doris Lindroos.*

References

Adrian, E. D. and Zotterman, Y. (1926). The impulses produced by sensory nerve endings. *The Journal of Physiology*, 61(4):465–483.

Albin, R. L., Young, A. B., and Penney, J. B. (1989). The functional anatomy of basal ganglia disorders. *Trends Neurosci.*, 12(10):366–375.

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

Beiser, D. G. and Houk, J. C. (1998). Model of cortical-basal ganglionic processing: encoding the serial order of sensory events. *J. Neurophysiol.*, 79(6):3168–3188.

Bennett, B. and Bolam, J. (1994). Synaptic input and output of parvalbumin-immunoreactive neurons in the neostriatum of the rat. *Neuroscience*, 62(3):707 – 719.

Bittner, K. C., Grienberger, C., Vaidya, S. P., Milstein, A. D., Macklin, J. J., Suh, J., Tonegawa, S., and Magee, J. C. (2015). Conjunctive input processing drives feature selectivity in hippocampal CA1 neurons. *Nature Neuroscience*, 18(8):1133–1142.

Bittner, K. C., Milstein, A. D., Grienberger, C., Romani, S., and Magee, J. C. (2017). Behavioral time scale synaptic plasticity underlies CA1 place fields. *Science*, 357(6355):1033–1036.

Bower, J. M. and Beeman, D. (1998). Compartmental modeling. In Bower, J. M., Beeman, D., Nelson, M., Rinzel, J., Segev, I., Crook, S., Cohen, A., Protopapas, A., Bhalla, U. S., Wilson, M. A., Vanier, M., Schutter, E. D., Goddard, N. H., and Hood, G., editors, *The Book of GENESIS: Exploring Realistic Neural Models with the GEneral NEural SImulation System*, chapter 2. Springer-Verlag, second edition.

Bower, J. M., Beeman, D., Nelson, M., Rinzel, J., Segev, I., Crook, S., Cohen, A., Protopapas, A., Bhalla, U. S., Wilson, M. A., Vanier, M., Schutter, E. D., Goddard, N. H., and Hood, G. (1998). *The Book of GENESIS: Exploring Realistic Neural*

Models with the GEneral NEural SImulation System. Springer-Verlag, second edition.

Cannon, R. C., Gleeson, P., Crook, S., Ganapathy, G., Marin, B., Piasini, E., and Silver, R. A. (2014). Lems: a language for expressing complex biological models in concise and hierarchical form and its use in underpinning neuroml 2. *Frontiers in Neuroinformatics*, 8:79.

Carnevale, N. T. and Hines, M. L. (2003). Expressing conceptual models in mathematical terms. In Carnevale, N. T. and Hines, M. L., editors, *"The NEURON Book"*, chapter 3. CAMBRIDGE UNIVERSITY PRESS, first edition.

Chen, S. X., Kim, A. N., Peters, A. J., and Komiyama, T. (2015). Subtype-specific plasticity of inhibitory circuits in motor cortex during motor learning. *Nat. Neurosci.*, 18(8):1109–1115.

Chen, Y., Yu, F. H., Surmeier, D. J., Scheuer, T., and Catterall, W. A. (2006). Neuromodulation of Na+ channel slow inactivation via cAMP-dependent protein kinase and protein kinase C. *Neuron*, 49(3):409–420.

Chuhma, N., Mingote, S., Yetnikoff, L., Kalmbach, A., Ma, T., Ztaou, S., Sienna, A.-C., Tepler, S., Poulin, J.-F., Ansorge, M., Awatramani, R., Kang, U. J., and Rayport, S. (2018). Dopamine neuron glutamate cotransmission evokes a delayed excitation in lateral dorsal striatal cholinergic interneurons. *eLife*, 7:e39786.

Chuhma, N., Zhang, H., Masson, J., Zhuang, X., Sulzer, D., Hen, R., and Rayport, S. (2004). Dopamine neurons mediate a fast excitatory signal via their glutamatergic synapses. *J. Neurosci.*, 24(4):972–981.

Cichon, J. and Gan, W. B. (2015). Branch-specific dendritic Ca2+ spikes cause persistent synaptic plasticity. *Nature*, 520(7546):180–185.

Costa, R. M. (2011). A selectionist account of de novo action learning. *Curr. Opin. Neurobiol.*, 21(4):579–586.

Cover, K. K., Gyawali, U., Kerkhoff, W. G., Patton, M. H., Mu, C., White, M. G., Marquardt, A. E., Roberts, B. M., Cheer, J. F.,

and Mathur, B. N. (2019). Activation of the Rostral Intralaminar Thalamus Drives Reinforcement through Striatal Dopamine Release. *Cell Reports*, 26(6):1389–1398.e3.

Cui, G., Jun, S. B., Jin, X., Pham, M. D., Vogel, S. S., Lovinger, D. M., and Costa, R. M. (2013). Concurrent activation of striatal direct and indirect pathways during action initiation. *Nature*, 494(7436):238–242.

da Silva, J., Tecuapetla, F., Paixão, V., and Costa, R. M. (2018). Dopamine neuron activity before action initiation gates and invigorates future movements. *Nature Publishing Group*, 554(7691):244–248.

Day, M., Wokosin, D., Plotkin, J. L., Tian, X., and Surmeier, D. J. (2008). Differential excitability and modulation of striatal medium spiny neuron dendrites. *J. Neurosci.*, 28(45):11603–11614.

Ding, J. B., Guzman, J. N., Peterson, J. D., Goldberg, J. A., and Surmeier, D. J. (2010). Thalamic gating of corticostriatal signaling by cholinergic interneurons. *Neuron*, 67(2):294–307.

Du, K., Wu, Y. W., Lindroos, R., Liu, Y., Rozsa, B., Katona, G., Ding, J. B., and Kotaleski, J. H. (2017). Cell-type-specific inhibition of the dendritic plateau potential in striatal spiny projection neurons. *Proc. Natl. Acad. Sci. U.S.A.*, 114(36):E7612–E7621.

Dulcis, D., Jamshidi, P., Leutgeb, S., and Spitzer, N. C. (2013). Neurotransmitter switching in the adult brain regulates behavior. *Science*, 340(6131):449–453.

Elghaba, R., Vautrelle, N., and Bracci, E. (2016). Mutual control of cholinergic and low-threshold spike interneurons in the striatum. *Frontiers in Cellular Neuroscience*, 10:111.

Ernst, A., Alkass, K., Bernard, S., Salehpour, M., Perl, S., Tisdale, J., Possnert, G., Druid, H., and Frisen, J. (2014). Neurogenesis in the striatum of the adult human brain. *Cell*, 156(5):1072–1083.

Ernst, A. and Frisen, J. (2015). Adult neurogenesis in humans- common and unique traits in mammals. *PLoS Biol.*, 13(1):e1002045.

Freund, T. F., Powell, J. F., and Smith, A. D. (1984). Tyrosine hydroxylase-immunoreactive boutons in synaptic contact with identified striatonigral neurons, with particular reference to dendritic spines. *Neuroscience*, 13(4):1189–1215.

Fu, M., Yu, X., Lu, J., and Zuo, Y. (2012). Repetitive motor learning induces coordinated formation of clustered dendritic spines in vivo. *Nature*, 483(7387):92.

Gokce, O., Stanley, G. M., Treutlein, B., Neff, N. F., Camp, J. G., Malenka, R. C., Rothwell, P. E., Fuccillo, M. V., Sudhof, T. C., and Quake, S. R. (2016). Cellular Taxonomy of the Mouse Striatum as Revealed by Single-Cell RNA-Seq. *Cell Rep*, 16(4):1126–1137.

Gould, E., Beylin, A., Tanapat, P., Reeves, A., and Shors, T. J. (1999a). Learning enhances adult neurogenesis in the hippocampal formation. *Nat. Neurosci.*, 2(3):260–265.

Gould, E., McEwen, B. S., Tanapat, P., Galea, L. A., and Fuchs, E. (1997). Neurogenesis in the dentate gyrus of the adult tree shrew is regulated by psychosocial stress and NMDA receptor activation. *J. Neurosci.*, 17(7):2492–2498.

Gould, E., Reeves, A. J., Fallah, M., Tanapat, P., Gross, C. G., and Fuchs, E. (1999b). Hippocampal neurogenesis in adult Old World primates. *Proc. Natl. Acad. Sci. U.S.A.*, 96(9):5263–5267.

Graybiel, A. M. (1998). The basal ganglia and chunking of action repertoires. *Neurobiol Learn Mem*, 70(1-2):119–136.

Graybiel, A. M. (2008). Habits, rituals, and the evaluative brain. *Annu. Rev. Neurosci.*, 31:359–387.

Graziano, M. S. and Gross, C. G. (1993). A bimodal map of space: somatosensory receptive fields in the macaque putamen with corresponding visual receptive fields. *Experimental Brain Research*, 97(1):96–109.

Graziano, M. S., Taylor, C. S., and Moore, T. (2002). Complex movements evoked by microstimulation of precentral cortex. *Neuron*, 34(5):841–851.

Hines, M. L. and Carnevale, N. T. (1997). The neuron simulation environment. *Neural Computation*, 9(6):1179–1209.

Hodgkin, A. L. and Huxley, A. F. (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve. *The Journal of Physiology*, 117(4):500–544.

Howe, M., Ridouh, I., Allegra Mascaro, A. L., Larios, A., Azcorra, M., and Dombeck, D. A. (2019). Coordination of rapid cholinergic and dopaminergic signaling in striatum during spontaneous movement. *eLife*, 8:e44903.

Howe, M. W. and Dombeck, D. A. (2016). Rapid signalling in distinct dopaminergic axons during locomotion and reward. *Nature*, 535(7613):505–510.

Hunnicutt, B. J., Jongbloets, B. C., Birdsong, W. T., Gertz, K. J., Zhong, H., and Mao, T. (2016). A comprehensive excitatory input map of the striatum reveals novel functional organization. *Elife*, 5.

Ibáñez-Sandoval, O., Tecuapetla, F., Unal, B., Shah, F., Koós, T., and Tepper, J. M. (2010). Electrophysiological and morphological characteristics and synaptic connectivity of tyrosine hydroxylase-expressing neurons in adult mouse striatum. *Journal of Neuroscience*, 30(20):6999–7016.

Ibáñez-Sandoval, O., Xenias, H. S., Tepper, J. M., and Koós, T. (2015). Dopaminergic and cholinergic modulation of striatal tyrosine hydroxylase interneurons. *Neuropharmacology*, 95:468 – 476.

Jack, J. and Redman, S. (1995). Introduction. In Segev, I., Rinzel, J., and Shepherd, G. M., editors, *"The Theoretical Foundation of Dendritic Function"*, chapter 2. MIT Press, first edition.

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

Kawaguchi, Y., Wilson, C. J., Augood, S. J., and Emson, P. C. (1995). Striatal interneurones: chemical, physiological and morphological characterization. *Trends Neurosci.*, 18(12):527–535.

Koos, T., Tepper, J. M., and Wilson, C. J. (2004). Comparison of ipscs evoked by spiny and fast-spiking neurons in the neostriatum. *Journal of Neuroscience*, 24(36):7916–7922.

Kubota, Y. and Kawaguchi, Y. (2000). Dependence of gabaergic synaptic areas on the interneuron type and target size. *Journal of Neuroscience*, 20(1):375–386.

Lee, S., Kruglikov, I., Huang, Z. J., Fishell, G., and Rudy, B. (2013). A disinhibitory circuit mediates motor integration in the somatosensory cortex. *Nature Neuroscience*, 16(11):1662–1670.

Lindroos, R., Dorst, M., Du, K., Filipović, M., Keller, D., Ketzef, M., Kozlov, A., Kumar, A., Lindahl, M., Nair, A., Pérez-Fernández, J., Grillner, S., Silberberg, G., and Kotaleski, J. (2018). Basal ganglia neuromodulation over multiple temporal and structural scales—simulations of direct pathway MSNs investigate the fast onset of dopaminergic effects and predict the role of Kv4.2. *Frontiers in Neural Circuits*, 12.

Luo, R., Janssen, M. J., Partridge, J. G., and Vicini, S. (2013). Direct and GABA-mediated indirect effects of nicotinic ACh receptor agonists on striatal neurones. *Journal of Physiology*, 591(1):203–217.

Marder, E. (2012). Neuromodulation of neuronal circuits: Back to the future. *Neuron*, 76(1):1 – 11.

Marder, E. and Goaillard, J. M. (2006). Variability, compensation and homeostasis in neuron and network function. *Nat. Rev. Neurosci.*, 7(7):563–574.

Marder, E. and Weimann, J. M. (1992). 1 - modulatory control of multiple task processing in the stomatogastric nervous system. In Kien, J., McCrohan, C. R., and Winlow, W., editors, *Neurobiology of Motor Programme Selection*, Pergamon Studies in Neuroscience, pages 3 – 19. Pergamon, Amsterdam.

Markram, H., Muller, E., Ramaswamy, S., Reimann, M., Abdellah, M., Sanchez, C., Ailamaki, A., Alonso-Nanclares, L., Antille, N., Arsever, S., Kahou, G., Berger, T. K., Bilgili, A., Buncic, N., Chalimourda, A., Chindemi, G., Courcol, J.-D., Delalondre, F.,

Delattre, V., Druckmann, S., Dumusc, R., Dynes, J., Eilemann, S., Gal, E., Gevaert, M., Ghobril, J.-P., Gidon, A., Graham, J., Gupta, A., Haenel, V., Hay, E., Heinis, T., Hernando, J., Hines, M. L., Kanari, L., Keller, D., Kenyon, J., Khazen, G., Kim, Y., King, J., Kisvarday, Z., Kumbhar, P., Lasserre, S., Le Bé, J.-V., Magalhães, B., Merchán-Pérez, A., Meystre, J., Morrice, B., Muller, J., Muñoz-Céspedes, A., Muralidhar, S., Muthurasa, K., Nachbaur, D., Newton, T., Nolte, M., Ovcharenko, A., Palacios, J., Pastor, L., Perin, R., Ranjan, R., Riachi, I., Rodríguez, J.-R., Riquelme, J., Rössert, C., Sfyrakis, K., Shi, Y., Shillcock, J., Silberberg, G., Silva, R., Tauheed, F., Telefont, M., Toledo-Rodriguez, M., Tränkler, T., Van Geit, W., Díaz, J., Walker, R., Wang, Y., Zaninetta, S., DeFelipe, J., Hill, S., Segev, I., and Schurmann, F. (2015). Reconstruction and Simulation of Neocortical Microcircuitry. *Cell*, 163(2):456–492.

MATLAB (2012). *version 7.14.0.739 (R2012a)*. The MathWorks Inc., Natick, Massachusetts.

Matsuda, W., Furuta, T., Nakamura, K. C., Hioki, H., Fujiyama, F., Arai, R., and Kaneko, T. (2009). Single nigrostriatal dopaminergic neurons form widely spread and highly dense axonal arborizations in the neostriatum. *J. Neurosci.*, 29(2):444–453.

Mcculloch, W. S. and Pitts, W. (1943). A logical calculus nervous activity. *A logical calculus of the ideas immanent in nervous activity*, 52(l):99–115.

McHaffie, J. G., Stanford, T. R., Stein, B. E., Coizet, V., and Redgrave, P. (2005). Subcortical loops through the basal ganglia. *Trends Neurosci.*, 28(8):401–407.

Minamimoto, T. and Kimura, M. (2002). Participation of the thalamic CM-Pf complex in attentional orienting. *J. Neurophysiol.*, 87(6):3090–3101.

Moser, E. I., Kropff, E., and Moser, M.-B. (2008). Place cells, grid cells, and the brain's spatial representation system. *Annual review of neuroscience*, 31:69–89.

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

Muñoz, W., Tremblay, R., Levenstein, D., and Rudy, B. (2017). Layer-specific modulation of neocortical dendritic inhibition during active wakefulness. *Science*, 355(6328):954–959.

Nambu, A., Tokuno, H., and Takada, M. (2002). Functional significance of the cortico-subthalamo-pallidal 'hyperdirect' pathway. *Neurosci. Res.*, 43(2):111–117.

Oldenburg, I. A. and Ding, J. (2011). Cholinergic modulation of synaptic integration and dendritic excitability in the striatum. *Current opinion in neurobiology*, 21(3):425–32.

Pfeffer, C. K., Xue, M., He, M., Huang, Z. J., and Scanziani, M. (2013). Inhibition of inhibition in visual cortex: the logic of connections between molecularly distinct interneurons. *Nature Neuroscience*, 16(8):1068–1076.

Pi, H.-J., Hangya, B., Kvitsiani, D., Sanders, J. I., Huang, Z. J., and Kepecs, A. (2013). Cortical interneurons that specialize in disinhibitory control. *Nature*, 503(7477):521–524.

Picciotto, M. R. (2013). Acetylcholine as a neuromodulator. *Neuron*, 76(1):116–129.

Pickel, V. M., Beckley, S. C., Joh, T. H., and Reis, D. J. (1981). Ultrastructural immunocytochemical localization of tyrosine hydroxylase in the neostriatum. *Brain Res.*, 225(2):373–385.

Planert, H., Szydlowski, S. N., Hjorth, J. J. J., Grillner, S., and Silberberg, G. (2010). Dynamics of synaptic transmission between fast-spiking interneurons and striatal projection neurons of the direct and indirect pathways. *Journal of Neuroscience*, 30(9):3499–3507.

Plotkin, J. L., Day, M., and Surmeier, D. J. (2011). Synaptically driven state transitions in distal dendrites of striatal spiny neurons. *Nat. Neurosci.*, 14(7):881–888.

Prinz, A. A., Bucher, D., and Marder, E. (2004). Similar network activity from disparate circuit parameters. *Nat. Neurosci.*, 7(12):1345–1352.

Rakic, P. (1985). Limits of neurogenesis in primates. *Science*, 227(4690):1054–1056.

Rakic, P. (2002). Neurogenesis in adult primate neocortex: an evaluation of the evidence. *Nat. Rev. Neurosci.*, 3(1):65–71.

Rall, W. (1959). Branching dendritic trees and motoneuron membrane resistivity. *Experimental Neurology*, 1(5):491–527.

Rall, W. (1964). Theoretical significance of dendritic trees for neuronal input-output relations. *Neural Theory and Modeling*, pages 73–97. ed. R Reiss. Stanford, CA: Stanford Univ. Press.

Redgrave, P., Prescott, T. J., and Gurney, K. (1999). The basal ganglia: a vertebrate solution to the selection problem? *Neuroscience*, 89(4):1009–1023.

Redgrave, P., Rodriguez, M., Smith, Y., Rodriguez-Oroz, M. C., Lehericy, S., Bergman, H., Agid, Y., DeLong, M. R., and Obeso, J. A. (2010). Goal-directed and habitual control in the basal ganglia: implications for Parkinson's disease. *Nat. Rev. Neurosci.*, 11(11):760–772.

Reig, R. and Silberberg, G. (2014). Multisensory integration in the mouse striatum. *Neuron*, 83(5):1200–1212.

Robertson, B., Kardamakis, A., Capantini, L., Perez-Fernandez, J., Suryanarayana, S. M., Wallen, P., Stephenson-Jones, M., and Grillner, S. (2014). The lamprey blueprint of the mammalian nervous system. *Prog. Brain Res.*, 212:337–349.

Robinson, D., Wu, H., Munne, R. A., Ashtari, M., Alvir, J. M., Lerner, G., Koreen, A., Cole, K., and Bogerts, B. (1995). Reduced caudate nucleus volume in obsessive-compulsive disorder. *Arch. Gen. Psychiatry*, 52(5):393–398.

Schneider, W. and Chein, J. (2003). Controlled and automatic processing: Behavior, theory, and biological mechanisms. *Cognitive Science*, 27(3):525–559. cited By 257.

Schultz, W. (2002). Getting formal with dopamine and reward. *Neuron*, 36(2):241–263.

Schultz, W. (2007). Multiple dopamine functions at different time courses. *Annu. Rev. Neurosci.*, 30:259–288.

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

Scoville, W. B. and Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery & Psychiatry*, 20(1):11–21.

Segev, I. (1995). Introduction. In Segev, I., Rinzel, J., and Shepherd, G. M., editors, *"The Theoretical Foundation of Dendritic Function"*, chapter 4. MIT Press, first edition.

Segev, I. (1998). Cable and compartmental models of dendritic trees. In Bower, J. M., Beeman, D., Nelson, M., Rinzel, J., Segev, I., Crook, S., Cohen, A., Protopapas, A., Bhalla, U. S., Wilson, M. A., Vanier, M., Schutter, E. D., Goddard, N. H., and Hood, G., editors, *"The Book of GENESIS: Exploring Realistic Neural Models with the GEneral NEural SImulation System"*, chapter 5. Springer-Verlag, second edition.

Smith, Y., Bennett, B. D., Bolam, J. P., Parent, A., and Sadikot, A. F. (1994). Synaptic relationships between dopaminergic afferents and cortical or thalamic input in the sensorimotor territory of the striatum in monkey. *J. Comp. Neurol.*, 344(1):1–19.

Spalding, K. L., Bergmann, O., Alkass, K., Bernard, S., Salehpour, M., Huttner, H. B., Bostrom, E., Westerlund, I., Vial, C., Buchholz, B. A., Possnert, G., Mash, D. C., Druid, H., and Frisen, J. (2013). Dynamics of hippocampal neurogenesis in adult humans. *Cell*, 153(6):1219–1227.

Spitzer, N. C. (2017). Neurotransmitter Switching in the Developing and Adult Brain. *Annu. Rev. Neurosci.*, 40:1–19.

Stephenson-Jones, M., Samuelsson, E., Ericsson, J., Robertson, B., and Grillner, S. (2011). Evolutionary conservation of the basal

ganglia as a common vertebrate mechanism for action selection. *Curr. Biol.*, 21(13):1081–1091.

Straub, C., Saulnier, J. L., Begue, A., Feng, D. D., Huang, K. W., and Sabatini, B. L. (2016). Principles of Synaptic Organization of GABAergic Interneurons in the Striatum. *Neuron*, 92(1):84–92.

Swensen, A. M. and Marder, E. (2000). Multiple peptides converge to activate the same voltage-dependent current in a central pattern-generating circuit. *Journal of Neuroscience*, 20(18):6752–6759.

Takahashi, N., Kitamura, K., Matsuo, N., Mayford, M., Kano, M., Matsuki, N., and Ikegaya, Y. (2012). Locally synchronized synaptic inputs. *Science*, 335(6066):353–356.

Tecuapetla, F., Jin, X., Lima, S. Q., and Costa, R. M. (2016). Complementary Contributions of Striatal Projection Pathways to Action Initiation and Execution. *Cell*, 166(3):703–715.

Tecuapetla, F., Patel, J. C., Xenias, H., English, D., Tadros, I., Shah, F., Berlin, J., Deisseroth, K., Rice, M. E., Tepper, J. M., and Koos, T. (2010). Glutamatergic signaling by mesolimbic dopamine neurons in the nucleus accumbens. *J. Neurosci.*, 30(20):7105–7110.

Tepper, J. M., Koós, T., Ibanez-Sandoval, O., Tecuapetla, F., Faust, T. W., and Assous, M. (2018). Heterogeneity and diversity of striatal gabaergic interneurons: Update 2018. *Frontiers in Neuroanatomy*, 12:91.

Thirumalai, V., Prinz, A. A., Johnson, C. D., and Marder, E. (2006). Red pigment concentrating hormone strongly enhances the strength of the feedback to the pyloric rhythm oscillator but has little effect on pyloric rhythm period. *Journal of Neurophysiology*, 95(3):1762–1770. PMID: 16319213.

Threlfell, S., Lalic, T., Platt, N. J., Jennings, K. A., Deisseroth, K., and Cragg, S. J. (2012). Striatal dopamine release is triggered by synchronized activity in cholinergic interneurons. *Neuron*, 75(1):58–64.

Tremblay, R., Lee, S., and Rudy, B. (2016). GABAergic Interneurons in the Neocortex: From Cellular Properties to Circuits. *Neuron*, 91(2):260–292.

Tritsch, N. X., Ding, J. B., and Sabatini, B. L. (2012). Dopaminergic neurons inhibit striatal output through non-canonical release of GABA. *Nature*, 490(7419):262–266.

Tunstall, M. J., Oorschot, D. E., Kean, A., and Wickens, J. R. (2002). Inhibitory interactions between spiny projection neurons in the rat striatum. *Journal of Neurophysiology*, 88(3):1263–1269. PMID: 12205147.

Tziortzi, A. C., Haber, S. N., Searle, G. E., Tsoumpas, C., Long, C. J., Shotbolt, P., Douaud, G., Jbabdi, S., Behrens, T. E., Rabiner, E. A., Jenkinson, M., and Gunn, R. N. (2014). Connectivity-based functional analysis of dopamine release in the striatum using diffusion-weighted MRI and positron emission tomography. *Cereb. Cortex*, 24(5):1165–1177.

Valenstein, E. S. (2006). *The War of the Soups and the Sparks: The Discovery of Neurotransmitters and the Dispute Over How Nerves Communicate*. Columbia University Press, New York Chichester.

Wilson, C., Chang, H., and Kitai, S. (1990). Firing patterns and synaptic potentials of identified giant aspiny interneurons in the rat neostriatum. *Journal of Neuroscience*, 10(2):508–519.

Xu, N.-l., Harnett, M. T., Williams, S. R., Huber, D., O'Connor, D. H., Svoboda, K., and Magee, J. C. (2012). Nonlinear dendritic integration of sensory and motor input during an active sensing task. *Nature*, 492(7428):247–51.

Xu, T., Yu, X., Perlik, A. J., Tobin, W. F., Zweig, J. A., Tennant, K., Jones, T., and Zuo, Y. (2009). Rapid formation and selective stabilization of synapses for enduring motor memories. *Nature*, 462(7275):915–919.

Yin, H. H., Knowlton, B. J., and Balleine, B. W. (2004). Lesions of dorsolateral striatum preserve outcome expectancy but disrupt habit formation in instrumental learning. *Eur. J. Neurosci.*, 19(1):181–189.

Yin, H. H., Ostlund, S. B., Knowlton, B. J., and Balleine, B. W. (2005). The role of the dorsomedial striatum in instrumental conditioning. *Eur. J. Neurosci.*, 22(2):513–523.