From Department of Neuroscience
Karolinska Institutet, Stockholm, Sweden

ON THE FUNCTIONAL ORGANISATION OF BASAL GANGLIA INPUTS

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Stockholm, 2020

Published by Karolinska Institutet
Printed by Eprint AB 2020

ISBN 978-91-7831-775-2

On the cover: An adaptation of Andreas Vesalius drawings depicting the anatomy of the brain (prima & secunda septimi libri figura in 'De Humani Corporis Fabrica', published in 1543, Oporini, Basel)

On the Functional Organisation of Basal Ganglia Inputs

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To Laurence, my parents & my sister.

ABSTRACT

The basal ganglia allow organisms to adjust their behaviour according to changes in their internal state or their environment. One essential prerequisite for the selection and execution of appropriate movements is the convergence of inputs from various sources, conveying sensory information, motor commands, reward value, and more. These diverse inputs are integrated in the striatum, the input structure of the basal ganglia. In the last decades, numerous striatal cell types have been identified, their molecular profiles have been extracted and their local connectivity has been revealed. However, relatively little is known about the functional organisation of striatal inputs innervating these different neuron populations.

The aim of this thesis is to examine how striatal inputs are integrated by the main cell types of this microcircuit. In **Paper I**, we uncover the mechanisms underlying sensory deficits in a mouse model of Parkinson's disease. We show that one type of striatal projection neurons encodes the laterality of somatosensory inputs better than the other output neuron in healthy mice and that this encoding is lost in the dopamine-depleted state. In **Paper II**, we map the excitatory synaptic pathways of five striatal input structures (ipsi- and contralateral somatosensory and motor cortex, and the parafascicular nucleus) onto five different classes of striatal neurons. The study characterises the synaptic strength, receptor composition, and short-term plasticity of each pathway with an unprecedented level of detail and comparability, thereby contributing to the understanding of the role of different striatal cell types. In **Paper III**, we create an *in silico* model of the striatum that integrates data from the subcellular to the microcircuit level. This model will be publicly available for testing new hypotheses and continuously updated with novel findings.

In summary, the work presented in this thesis provides a further step in untangling the heterogeneous excitatory inputs that drive the activity of the primarily inhibitory microcircuit of the striatum and thus basal ganglia. We show that each striatal input targets a different set of striatal neurons and that the intricate organisation of these afferents is a function of both the presynaptic region and the postsynaptic cell type. Ultimately, knowledge of the functional connectivity of cortico- and thalamostriatal pathways as well as their synaptic properties will be essential for understanding and modelling the cortico- and thalamo-basal ganglia network in health and disease.

LIST OF SCIENTIFIC PAPERS

I. Ketzef M, Spigolon G, **Johansson Y**, Bonito-Oliva A, Fisone G, Silberberg G. Dopamine Depletion Impairs Bilateral Sensory Processing in the Striatum in a Pathway-Dependent Manner. *Neuron*, 2017, 94: 855 – 865.

II. **Johansson Y** & Silberberg G.
The Functional Organisation of Cortical and Thalamic Inputs onto Five Different Types of Striatal Neurons is Determined by Source and Target Cell Identities. *Cell Reports*, 2020

III. Hjorth J, Kozlov AK, Carannante I, Frost Nylén J, Lindroos R, **Johansson Y**, Tokarska A, Dorst MC, Suryanarayana SM, Silberberg G, Hellgren Kotaleski J, Grillner S.
The microcircuits of striatum *in silico*. *PNAS*, 2020, *manuscript*

Publications not included in this thesis:

I. Pollak Dorocic I, Fürth D, Xuan Y, **Johansson Y**, Pozzi L, Silberberg G, Carlén M, Meletis K.
A Whole-Brain Atlas of Inputs to Serotonergic Neurons of the Dorsal and Median Raphe Nuclei. *Neuron*, 2014, 83: 663 - 678.

II. Lazaridis I, Tzortzi O, Weglage M, Märtin A, Xuan Y, Parent M, **Johansson Y**, Fuzik J, Fürth D, Fenno LE, Ramakrishnan C, Silberberg G, Deisseroth K, Carlén M, Meletis K.
A Hypothalamus-Habenula Circuit Controls Aversion. *Molecular Psychiatry*, 2019, 24(9): 1351-1368.

CONTENTS

LIST OF ABBREVIATIONS

AAV	Adeno-associated virus
ACh	Acetylcholine
AHP	Afterhyperpolarisation
APP	Avian pancreatic polypeptide
BG	Basal ganglia
CA	Catecholamine
ChAT	Acetylcholine transferase
ChIN	Cholinergic interneuron
ChR2	Channelrhodopsin-2
CL	Centrolateral nucleus of the thalamus
CM	Centromedian nucleus of the thalamus
CNS	Central nervous system
CR	Calretinin-expressing interneuron
DA	Dopamine
DAB	Dopamine blockers
dMSN	Direct pathway medium spiny neuron
EM	Electronmicroscopy
eYFP	Enhanced yellow fluorescent protein
FSI	Fast-spiking interneuron
GABA	Gamma-aminobutyric acid
GAD	Glutamic acid decarboxylase
GBZ	Gabazine
GFP	Green fluorescent protein
GPe	Globus pallidus, external segment
GPi	Globus pallidus, internal segment
HD	Huntington's disease
HR	Halorhodopsin
iMSN	Indirect pathway medium spiny neuron

IR-DIC	Infrared differential interference contrast
L-DOPA	Levodopa (dopamine precursor)
Lhx6	LIM homeobox protein 6
LTSI	Low-threshold spiking interneuron
NOS	Nitric oxide synthetase
NPY	Neuropeptide Y
PD	Parkinson's disease
PF	Parafascicular nucleus of the thalamus
PPN	Pedunculopontine nucleus
PV	Parvalbumin
SNc	Substantia nigra, pars compacta
SNr	Substantia nigra, pars reticulata
SOM	Somatostatin
STN	Subthalamic nucleus
TAN	Tonically active neurons
TH	Tyrosine hydroxylase
THIN	Tyrosine hydroxylase-expressing interneurons
TRN	Reticular nucleus of the thalamus
6-OHDA	6-hydroxydopamine

1 INTRODUCTION

A fundamental goal in neuroscience is to understand the neural substrates underlying movements. The search for the neural basis of movement is as diverse as movements themselves, which range from monosynaptic reflex circuits in the spinal cord to complex finger movements requiring numerous brain areas such as the cortex, the basal ganglia (BG), and the cerebellum to work in concert. For centuries, researchers have tried to identify these structures, their specific functions, and the pathways linking them together, that ultimately allow them to act as an integrated system governing movement. The work in this thesis will focus on the BG, with a particular emphasis on the functional organisation of BG inputs, which target primarily the striatum.

To provide the context for this thesis, the following introduction is composed largely as a historical account of research on the BG; from early anatomical findings, to the major milestones as neuroscience techniques became more advanced, and finishing with our current detailed understanding of this structure. The history of BG research inherently does not neatly follow the structured chapters of a textbook, but rather constitutes a winding road of correct and faulty discoveries, which through dispute and replication, have ultimately revealed the pathways and functions of this structure.

1.1 THE DISCOVERY OF THE BASAL GANGLIA

The first drawing of the BG was published by the Flemish anatomist Andreas Vesalius in his 7th book, 'De Humani Corporis Fabrica', in 1543 (Fig. 1). Vesalius illustrated several nuclei of the BG such as the caudate, putamen, and the globus pallidus in great detail. However, he was mostly interested in the anatomical outlines of grey and white matter and did neither name these structures, nor speculate on their function. This changed with the English physician and anatomist Thomas Willis, who is perhaps most famous for coining the term 'neurology'. Willis's broad body of work considerably advanced our understanding

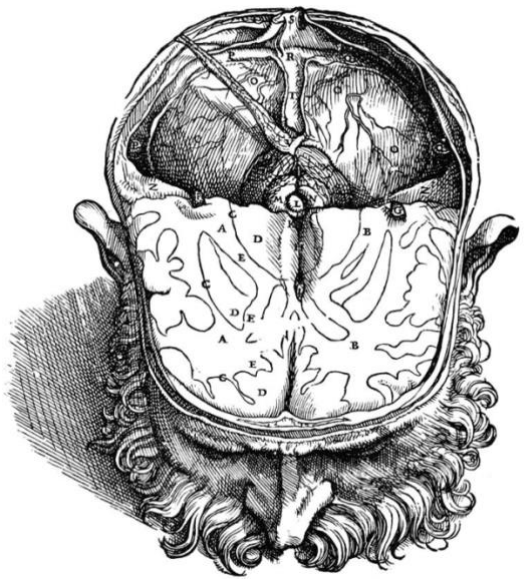

Fig. 1) Andreas Vesalius illustration of the basal ganglia in 'De Humani Corporis Fabrica' (Figure 7), Oporini, Basel.

of the central nervous system (CNS) in general because he '[…] shifted the seat of the anima from the chambers of the brain to the actual substance of the brain itself […]' according to Sherrington (Sherrington, 1940).

In the BG field, Willis was the first to use the term 'corpus striatum' for the large, striated structure already depicted by Vesalius and, most notably, he linked anatomy to function: while studying the brain of deceased patients who had suffered from paralysis, Willis repeatedly discovered signs of degeneration in the striatum and went on to describe the significance of the striatum for motor function in his book '*Cerebri Anatome*' (Willis, 1664). He understood the striatum as '*sensorium commune*', a sensorimotor integration centre, responsible for sensation and execution of voluntary movements ('the animal spirits concerned with the execution of willed action are directed into the appropriate nerves'). Subsequent research showed that this description overestimated the role of the striatum, and that Willis likely unknowingly also traced some thalamic fibres carrying sensory information. As a result, some of Willis attempts to localise nervous functions have been criticized and partly been described as unsubstantiated speculations. However, considering the techniques available in the 17th century, Willis final conclusions regarding the striatum were remarkably correct and constitute a significant milestone in basal ganglia research.

Raymond Vieussens was one of the first ones to refer to the basal ganglia as the 'great cerebral ganglion' in his 'Neurographia universalis' (1684). However, there was no consensus which nuclei form part of the BG and the structures included varied considerably over time. A major step in defining the BG was taken by Félix Vicq d'Azyr, who characterised the substantia nigra ('locus niger crurum cerebri') and separated the thalamus from the 'striated body'. With the help of new fixation methods, this French anatomist complemented the pioneering studies of Willis. In 1786, Vicq d'Azur published his work in the '*Traité d'anatomie et de physiologie'*, which contained 35 coloured figures of the human brain that exceeded all previous illustrations in terms of quality and accuracy. However, similar to Vesalius, Vicq d'Azur focused primarily on illustrating the components of the BG without naming each individual nucleus. Most of the BG terminology is based on the subsequent work of the German physician and anatomist Karl Friedrich Burdach. The detailed anatomical descriptions that Burdach presented in his book '*Vom Baue und Leben des Gehirns*' (published between 1819-1826) were widely adapted by neuroscientists and numerous structures of the CNS were named by him. In the BG, he identified for example the pale structure ('blasser Klumpen') as 'globus pallidus' (GP), differentiated clearly the caudate from the 'lens-shaped nucleus' that he called 'putamen', and delineated the internal and external capsules that separate major BG nuclei. Although the

overall structure of the BG was by then almost completely described, the understanding of BG function substantially lagged behind the anatomical progress. Burdach himself, a classic *Naturphilosoph* of his time, was highly committed to study form in order to understand function, but his ideas about striatal physiology were largely speculative. He considered the striatum as the site of 'volition', without presenting any evidence supporting his idea. Yet, Burdach's anatomical description of the individual components of the BG remains largely valid today and only a few additions and changes have been made. The only component of the BG that had escaped Burdach's detailed characterisation is the subthalamic nucleus (STN), which was discovered in 1865 by the psychiatrist Jules Bernard Luys (Parent, 2002). Later, the Vogts (Oskar and Cécile Vogt), a married couple devoted to studying the cytoarchitecture of the brain, further adjusted the ground plan of the different structures of the BG when they realized that the putamen is, contrary to prevailing views, not associated with the GP but rather with the caudate nucleus (Vogt and Vogt, 1920). Moreover, they recognised that the caudate and putamen are linked via the nucleus accumbens and therefore started to use the term 'striatum' to refer to these three structures together.

1.2 THE ROLE OF BG IN MOVEMENT CONTROL

Since the first association of the BG with movement by Willis in 1664, our understanding of the function of the BG has increased tremendously. However, scientific progress was strongly shaped by historical events, the development of novel methods, prevailing views, and often focused on those neural structures that were *in vogue*.

At the beginning of the 19th century, the soul was still thought to be a metaphysical agent acting via the nervous system, and cortex was mostly considered an unexcitable shell whose primary function it is to protect the brain beneath. Disproving these concepts took several decades and the novel ideas proposed by various neuroscientists often left the scientific community deeply divided. Franz Josef Gall associated cortical areas with different mental functions, but introduced the pseudoscience of phrenology, which suggested that these areas can be assessed by studying the external shape of the skull (Temkin, 1947). Gall's concept that cortical functions can be localised and studied individually was strongly rejected by the prominent French physiologist Marie Jean Pierre Flourens (Flourens, 1824; Pearce, 2009). Flourens instead successfully propagated the premise that cortex is an omnipotent structure that in its whole entity represents the soul. However, in a case study published in 1861, Paul Broca demonstrated that local lesions of a particular cortical area, later named 'Broca's area', severely impaired language capacity. These findings supported Gall's concept of the localisation of

cognitive functions, but remained antagonised by Flourens. Although Gall and Flourens strongly dismissed several aspects of each other's ideas, they both recognised the importance of cortex for higher functions and as seat of our consciousness and will (York and Steinberg, 2011). One year after Broca's paper, the work of Herbert Spencer on evolutionary neurophysiology further supported the revolutionizing transition that elevated cortex from a 'protective shell' to an essential neural structure (Spencer, 1862). Spencer suggested that cortex is a more evolved structure and thus has a 'higher' status than older neural structures from a phylogenetic point of view.

These novel ideas and disputes provided the fundament for several important breakthroughs that substantially advanced our understanding of movement control. Inspired by Spencer's publication, John Hughling Jackson, a practising neurologist, considered cortex as the highest evolutionary level of the nervous system, which controls lower levels (York and Steinberg, 2011). Hughling Jackson strongly rejected the idea of metaphysical actions in the brain and advocated physicians to focus on 'disease of the tissue, damage of organs, and disorder of function' (Hughlings-Jackson, 1864). While applying this mechanistic approach to patients suffering from epilepsy, Hughling Jackson noticed that partial seizures often begin locally in one hand and then 'march' systematically up the body towards the face. He reported these findings in a landmark paper called 'A study of convulsions' in which he hypothesised that the spasms are caused by an uncontrolled discharge in a cortical area with explicit motor function and that the explosive discharge is conveyed via 'lower' motor centres to the muscles (Hughlings-Jackson, 1870; York and Steinberg, 2011). This publication set the foundation for the idea of a specialized, high-level motor area in cortex that sends movement commands via other structures such as the BG to the muscles. Moreover, he concluded that the body is represented in the brain and that 'the march' of spasms is a recapitulation of these neural representations. He also suggested that the somatotopic representation of the body exists in cortex, striatum, and thalamus and that unstable activity in the striatum causes chorea (Hughlings-Jackson, 1868). In the same year, the German physicians Gustav Theodor Fritsch and Eduard Hitzig provided experimental evidence for the existence of a higher motor cortex by showing that electrical stimulation of the cortical motor area of dogs elicits contractions of the muscles on the contralateral side of the body ('Über die elektrische Erregbarkeit des Grosshirns'; Fritsch and Hitzig, 1870). They also noticed that stimulation of different locations evoked movements in different muscle groups, proving the existence of somatotopic cortical maps. Overall, their study confirmed the existence of a specialized local motor cortex, proved the electrically excitable nature of cortex beyond doubt and showed that individual cortical functions can indeed be studied separately. Subsequently, the Scottish neurophysiologist David

Ferrier extended their work to numerous other species including primates and outlined the modern concept of the motor cortex for voluntary movements (Ferrier, 1874).

Once cortex had received the first recognition as a functionally important neural structure in the early 19th century, the scientific zeitgeist shifted increasingly to cortical research addressing its anatomy, function, and diseases in detail. As a result, little attention was paid to the BG and the few existing reports - that had already associated the striatum with motor control – receded in prominence. Instead, the prevailing idea became that the symptoms observed in Parkinson's disease (PD), chorea and other, similar movement disorders are primarily caused by lesions of the cortical vascular system, arteriosclerosis or dementia (Dowse, 1878; Alzheimer, 1894, 1898; Campbell, 1894; Strumpell, 1908; Auer and McCough, 1916). Additionally, there was no established classification system for the wide spectrum of movement disorders, whose names and defining symptoms varied across the literature, and there was no consensus which structures are critically involved in these pathologies, with suggestions ranging from cortex to spinal cord (Durand-Fardel, 1854; Redlich, 1894). Numerous scientists even doubted whether these 'functional diseases' involve any detectable anatomical alterations at all.

Those widespread believes were fundamentally challenged by the Vogts, who - besides their anatomical contributions - significantly advanced the physiological understanding of the BG: the couple compared the brains of healthy controls to those of patients who suffered from different movement disorders and other comorbidities. They used relatively novel staining techniques including the Nissl staining for cell bodies and Weigert's staining for fibres and showed that the functional impairments were, in fact, accompanied by structural changes (Nissl, 1894; Weigert, 1898; Schoenberg and Schoenberg, 1979). During their studies, striatal lesions emerged as the pivotal factor and the Vogts established, once again, a causal link between the function of the BG and motor control (Vogt, 1911; Vogt and Vogt, 1920). Based on their detailed pathophysiological studies they hypothesised that the striatum constitutes a 'regulating organ' that provides coordinated inhibition to the GP. They further concluded that the GP acts as the output organ of the BG by inhibiting other brain areas, which in turn contact motor neurons. Striatal lesions release the GP from its 'control centre' and therefore result in involuntary, primitive movements as observed in Huntington's disease (HD). The idea that the GP is initiating 'primitive movements' also explained the characteristic movements of babies: myelination of axons arising in the GP is completed earlier in development than the myelination of corticostriatal and striatopallidal nerve fibres and therefore the uncoordinated motions of new-borns were understood to reflect the motor output of an unrestrained GP. In their publication, the Vogts suggested that the BG govern the suppression and release of movements

and that diseases of this structure therefore result in excess (HD, chorea) or absent (PD) movements. The development of this concept was a major breakthrough and it remains largely valid to this day.

Overall, the period between the late 19th and the early 20th centuries laid the foundation for our modern understanding of motor control by identifying the primary motor cortex (M1) necessary for the execution of voluntary movements that sends its information to downstream targets including the BG, which modulate the release and suppression of movements. These concepts have subsequently been refined and extended but can still be recognised in our current scheme of the BG circuit. Yet, the Vogts and other scientists of that period were unable to explain why the BG, and in particular the striatum, are so susceptible to degeneration while other parts of the brain are spared.

1.3 THE ROLE OF DOPAMINE

One person who made a major contribution to our understanding of neurotransmitters and unknowingly paved the way to a better understanding of the BG was one of the daughters of the Vogts, Marthe Vogt. In 1954, she published a ground-breaking paper on the role of two catecholamines (CA) in the brain (Vogt, 1954). Both CAs, epinephrine (E) and norepinephrine (NE), had already been identified and were known to play a role in the vasomotor system (Von Euler, 1946; Holtz, 1950). Marthe Vogt investigated whether these two compounds, which she referred to together as 'sympathin', play a role in the function of the CNS itself. To this end, she mapped the localisation of sympathin in the brain both under physiological conditions and after the administration of various drugs (Vogt, 1954). Her studies showed that sympathin was an important neurotransmitter involved in the communication between cells and her findings formed the basis for the pharmacological treatments of various mental disorders.

A few years later, dopamine (DA), the third CA, was identified by Kathleen Montagu, who however did not speculate on the physiological role of this compound (Montagu, 1957). At the time, the prevailing view was that DA was an intermediate product used in the synthesis of sympathin, i.e. E and NE (Blaschko, Hagen and Welch, 1955; Demis, Blaschko and Welch, 1956). In the same year, the Swede Arvind Carlsson reported that administration of a precursor of all three CAs, now known as 'L-DOPA', can restore motor behaviour in mice that had been depleted of all their CAs and were therefore lethargic (Carlsson, Lindqvist and Magnusson, 1957). Yet, Carlsson did not investigate which of the three CAs had caused the behavioural effect. These two publications sparked a whole series of important discoveries that shed some initial light on the mechanisms by which the BG exert their role in motor function. Carlsson

himself went on to show that the levels of DA and NE are about the same in the brain, indicating that DA might have a function in its own right, and showed that application of L-DOPA primarily causes an increase in DA, but not NE (Carlsson, Lindqvist and Magnusson, 1957; Carlsson and Waldeck, 1958). Hornykiewicz was the first one to show that DA has a vasodepressor function, which cannot be attributed to E or NE, providing the first evidence that DA itself qualifies as a biologically active substance (Hornykiewicz, 1958). Inspired by Marthe Vogt's study on E and NE, the Swedes Bertler and Rosengren assessed the localisation of DA in the brain and found that DA, in contrast to NE, is predominantly localised in the striatum (Bertler and Rosengren, 1959). Together, these findings showed that DA has a physiological function beyond serving as a precursor for other CAs, and that DA plays a central role in striatal physiology and therefore potentially also in motor behaviour.

The first insights into the specific function of striatal DA came from a study performed by Ehringer and Hornykiewicz. These two researchers, also guided by the preceding studies of Marthe Vogt, assessed the DA and NE levels in the post-mortem brains of humans who had suffered from PD and HD, and compared these findings to those of healthy controls (Ehringer and Hornykiewicz, 1960). They found a drastic reduction in striatal DA levels in all samples obtained from PD patients, and pathological changes in the substantia nigra pars compacta (SNc) in some of them. In contrast, the brains of HD patients all showed normal physiological levels of DA. Their finding on the cell loss in the SNc was in accordance with an early publication from 1938, in which the highly localised cell death in the SNc was reported as a hallmark feature of PD patients (Hassler, 1938). The knowledge of the lack of DA in PD patients was soon combined with the preceding findings relating to L-DOPA, paving the way for the use of this DA precursor as the primary treatment for PD, which continues to be administered to this day with unsurpassed anti-akinetic effects (Barbeau, 1961, 1962; Birkmayer and Hornykiewicz, 1961, 1962).

The research in the 1950s revealed that akinetic pathologies such as PD are associated with a drastic reduction of DA in the striatum but these findings also raised several novel questions. First, it was unclear whether the lack of DA was a symptom of the disease or a causal factor. Second, the source of DA had not yet been localised and both striatal cells and afferent fibres innervating the striatum were suspected to release DA. In 1963, Hornykiewicz was able to show that DA levels were also reduced in the SNc in PD patients and speculated that striatal DA originates there (Hornykiewicz, 1963). This idea was confirmed independently by two groups that provided the first evidence of a dopaminergic nigrostriatal pathway in rats and primates, respectively (Andén *et al.*, 1964; Dahlström and Fuxe, 1964; Sourkes and Poirier,

1965; Nauta and Mehler, 1969). Ironically, Hassler, the first to notice cell loss in the SNc in PD, strongly rejected the idea of a nigrostriatal pathway and argued in favour of the striatum as the source of DA (Mettler, 1970). Numerous studies on DA show, however, that the dopaminergic neurons are in fact localised in the SNc and that their axons provide the dopaminergic input to the striatum.

1.4 THE MAIN PATHWAYS OF THE BG CIRCUIT

The anatomical and pathological findings described so far had already recognised the core structure of the BG as well as the direction of the flow of information within this circuitry (Fig. 2). The striatum attracted Vesalius's interest due to the great number of fibre tracts innervating it and the striatal body constitutes the principal entrance point to the BG. Long lasting speculations on cortical and thalamic inputs were ultimately confirmed in the 1940s, while the dopaminergic projection from the SNc to the striatum was only discovered in the 1960s. The large bulk of incoming information is processed locally in the striatum before being conveyed via the 'direct' or the 'indirect' pathway to the output nuclei. The 'direct' ('striatonigral') pathway runs from the striatum directly to the internal segment of the GP (GPi) and the substantia nigra pars reticulata (SNr), whereas the 'indirect' ('striatopallidal') pathway runs via the external segment of the GP (GPe) to the STN and finally also converges onto the GPi/SNr (Fig. 2). The GPi/SNr constitutes the output structure of the BG (as predicted by the Vogts) and they innervate the ventral anterior and ventral lateral nuclei of the dorsal thalamus. These thalamic nuclei project in turn to motor areas in cortex, thereby completing the processing loop

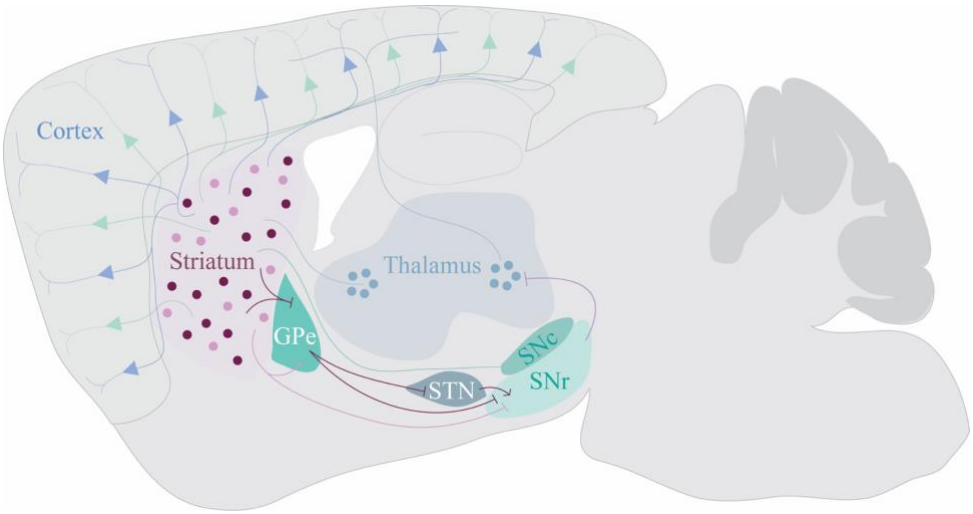

Fig. 2) The classic model of the BG circuit. The direct pathway is shown in magenta, the indirect pathway is indicated in dark red. Striatal inputs include glutamatergic projections arising in thalamus and cortex (green and blue) and dopaminergic afferents originating in the SNc (green). The output (violet) is sent via the SNr/GPi to thalamus.

that starts and ends in cortex and allows both the BG and the thalamus to modulate movement related information.

1.5 THE STRIATUM

The striatum is the input structure of the BG and although it has often been noted due to its particular striped pattern, little was known about the structure itself for a long time. This was largely because of the technical limitations that restricted neuroscientific research to the macroscopic level until the end of the 19th century. Yet, Marie Francois Xavier Bichat developed the 'theory of membranes' and Rudolf Virchow the concept of 'cellular pathology' (1858), which suggested that diseases are caused by alterations of tissues and cells, respectively (Bichat, 1816; Breathnach, 2002; Molenaar, 2003). In the 19th century, cells had been identified as the individual building blocks of organisms but the nervous tissue constituted an exception. The complex shapes of neurons rendered their visualisation particularly difficult and the identity of a 'unitary' neural component was unknown. Therefore, the theories of Bichat and Virchow were only confirmed later when novel staining methods, which were adapted from the textile dying industry, became available (Cook, 1997). Virchow's publication on 'Cellularpathologie' inspired Camillo Golgi to study the structure of the nervous system, which led to the ground-breaking development of the 'Golgi staining' in 1873. This was the first time that neurons could be revealed in their entirety and the Golgi staining became one of the most

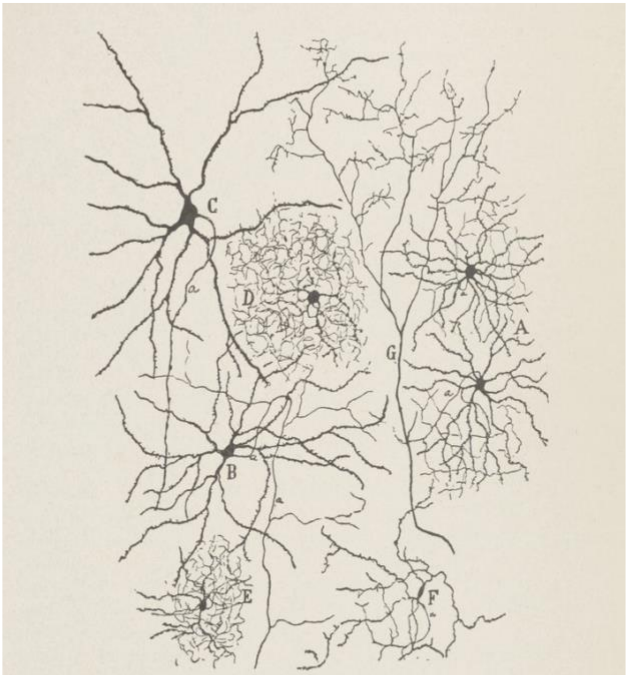

FIG. 325. — Quelques types cellulaires du noyau strié pris dans la région voisine du *claustrum;* cerveau d'enfant. Méthode de Golgi.

A, cellules de petite taille à cylindre-axe court ; — B, cellule à cylindre-axe long et descendant ; — C, cellule géante à cylindre-axe long ; — D, E, cellules naines à cylindre-axe court — G, fibre ascendante ramifiée ; — *a*, cylindre-axe.

Fig. 3) The neuronal cell types of the striatum in the brain of a child depicted by Ramón y Cajal with the Golgi staining method. Adapted from 'Histologie du système nerveux de l'homme & des vertébrés', volume II, 1911. (A, B) Putative medium spiny neurons (MSN), (C) putative cholinergic interneuron (ChIN), (D, E) putative fast-spiking interneuron (FSI), (F) putative low-threshold spiking interneuron (LTSI), (G) putative corticostriatal, ascending fibre innervating the striatum.

widely applied histological staining methods. Despite his own excellent method, Golgi thought that all nerve cells were connected to each other in one continuum and postulated his idea as the 'reticular theory'. This concept was later challenged and disproved by Santiago Ramón y Cajal, a Spanish neuropathologist, who modified Golgi's staining technique. Cajal concluded on the basis of his own extensive histologic studies that nerve cells are discrete entities that receive signals via their processes and send information via their axons. This idea became known as the 'neuron doctrine', and in 1906 the Nobel Prize was jointly awarded to the disagreeing Golgi and Cajal 'in recognition for their work on the structure of the nervous system'. Once it was established that neurons constitute their own entities, researchers started to wonder how they communicate with each other, and in 1903 Thomas R. Elliott suggested that the nerve endings of one cell might release a chemical messenger - a neurotransmitter - for that very purpose.

Cajal's publication 'Histologia del sistema nervioso del hombre y de los vertebrados' from 1910, comprises an entire chapter on the 'corpus striatum', which at that time still comprised the neostriatum, the putamen and the GP (Fig. 3) (Haycock and Bro, 1975). Looking back on these careful and intricate drawings today, it is clear that Cajal had distinguished several important striatal neuron populations based purely on their distinctive morphologies, despite the lack of any knowledge of their neurotransmitter identity, local connectivity, or indeed their function.

Medium spiny neurons

Cajal pointed out that the striatum consists of a high number of small neurons with a 'large number of spiny, moderately branched, radiating dendrites', which are now referred to as medium spiny neurons (MSNs, Fig. 3 'A' and 'B'). He and numerous other scientists mistook MSNs for local circuit neurons within the striatum, which was most likely due to the technical difficulty of tracing axons in general, and the complex branching into collaterals of the axons of MSNs specifically (Vogt and Vogt, 1920; Fox *et al.*, 1971; Kemp and Powell, 1971; Mensah and Deadwyler, 1974; Haycock and Bro, 1975; Bishop, Chang and Kitai, 1982). The fibre tracts arising from the striatum that give rise to the direct and indirect pathway had already been described anatomically but it was unknown from which cells these axons originate. It took several decades until the misconception about MSNs was corrected and they were recognised as the projection neurons of the striatum that convey striatal output via the direct and indirect pathway to downstream targets. The development of a novel histochemical method was key to this breakthrough: a new tracing method based on horseradish peroxidase provided the means to identify the origin of axons because it labelled the associated somata via retrograde axonal

transport (Kristensson, Olsson and Sjöstrand, 1971; LaVail and LaVail, 1972). In 1975, Grofová provided the first evidence for long-range projections derived from MSNs by showing that the axons in the SNr originate from medium-sized neurons located in the striatum (corresponding to the direct pathway) and in the GPe (corresponding to a section of the indirect pathway; Grofová, 1975).

The long-range projections of MSNs were further proven by revealing their neurotransmitter identities. In 1950, Eugene Roberts and Sam Frankel first discovered γ-Aminobutyric acid (GABA) as a major amine produced by the brain, and a few years later a Canadian research group revealed the functional significance of this amine by showing that GABA inhibits the firing of action potentials in neurons in crayfish (Roberts and Frankel, 1950; Bazemore, Elliott and Florey, 1957). Subsequently, staining for glutamic acid decarboxylase (GAD), the enzyme catalysing the α-decarboxylation of L-glutamate to form GABA, was used as an indirect evidence for the GABAergic nature of neurons and axon terminals (McLaughlin *et al.*, 1974) The GPi and the GPe were soon found to have exceptionally high levels of GABA, whereas striatal GABA levels were moderate (Fonnum *et al.*, 1974; Ribak *et al.*, 1976; Tappaz, Brownstein and Palkovits, 1976; Fonnum, Gottesfeld and Grofová, 1978; Nagy, Carter and Fibiger, 1978). If the biochemical levels of GAD or the number of symmetric (i.e. GABAergic) synapses detected by electron microscopy (EM) decreased in response to lesioning of afferent fibres, these fibres were considered to be GABAergic. By this method it was shown that neither striatal GAD levels, nor the number of symmetric synapses in the striatum, were affected by lesioning afferent fibres of the striatum, indicating that the majority of striatal input is not GABAergic and therefore striatal GABAergic axons must originate within the striatum itself from inhibitory neuron populations (McGeer and McGeer, 1975; Fahn, 1976; Hassler *et al.*, 1977; Ribak, Vaughn and Roberts, 1979). Additionally, these studies revealed that the GPe, the GPi and the SNr receive GABAergic input from the striatum (Fonnum, Gottesfeld and Grofová, 1978; Nagy, Carter and Fibiger, 1978). Moreover, the ultrastructural features of GAD-positive striatal neurons agreed with the EM description of medium-sized spiny neurons, supporting the idea that it is indeed MSNs that project to these three nuclei (Fox *et al.*, 1971; Kemp and Powell, 1971; Ribak, Vaughn and Roberts, 1979). Staining for another signalling molecule, 'substance P', further showed that this excitatory neuropeptide was expressed by a fraction of striatal MSNs (in addition to GABA) and that this subpopulation of MSNs projects primarily in the direct pathway to the GPi/SNr (Walker *et al.*, 1976; Brownstein *et al.*, 1977; Gale, Hong and Guidotti, 1977; Kanazawa, Emson and Cuello, 1977; Cuello and Kanazawa, 1978). These MSNs are therefore referred to as 'dMSNs', while MSNs projecting in the

indirect pathway are called ‘iMSNs’. Together, the detailed ultrastructural and biochemical studies on striatal MSN confirmed that MSNs are projection neurons and they indicated that this GABAergic neuron population might consist of different subpopulations (dMSNs vs iMSNs) that differ in their target structures (GPe vs GPi/SNr) as well as their expression of molecular markers (± substance P).

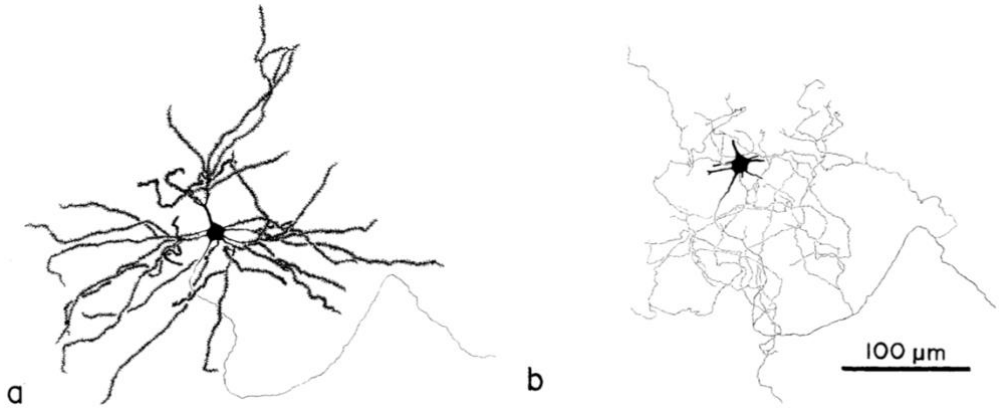

Fig. 4) Camera lucida drawings of the spiny dendritic tree (a) and axon (b) of an MSN, adapted from Wilson & Groves, 1980.

In the 1980s, these two GABAergic subpopulations of MSNs were characterised in more detail. MSNs of the direct pathway, targeting the GPi/SNr, were found to co-express not only substance P, but also dynorphin, whereas MSNs of the indirect pathway, that innervate the GPe, contained enkephalin (Hong, Yang and Costa, 1977; Finley, Maderdrut and Petrusz, 1981; S. Vincent *et al.*, 1982; Loopuijt and Van der Kooy, 1985; Gerfen and Scott Young, 1988). Subsequently, in a seminal publication by Gerfen and colleagues, the direct pathway MSNs and the indirect pathway MSNs were shown to express type 1 (D1) or type 2 (D2) DA receptors, respectively (Gerfen *et al.*, 1990). The G-protein coupled DA receptors had been identified as early as in 1972 and the first division into two subgroups followed in 1978 (Spano, Govoni and Trabucchi, 1978; Kebabian and Calne, 1979; Stoof and Kebabian, 1981). This classification is based on the different second messenger pathways that are activated via the respective receptor types, which result in a net excitation or hyperpolarisation in case of striatal dMSNs or iMSNs, respectively (Memo *et al.*, 1986; Surmeier and Kitai, 1993; Greif *et al.*, 1995). Therefore, release of DA in the striatum increases the activity in dMSNs projecting in the direct pathway, while decreasing the activity in iMSNs, which extend their axons in the indirect pathway. This results in a greater inhibition of the GPi/SNr and accordingly in the disinhibition of movement-promoting structures such as thalamus, that are downstream of the GPi/SNr. The opposing effect of DA on the excitability of dMSNs and iMSNs - and thus the

activity of the direct and indirect pathway - constitutes a fundamental principle of BG functioning.

Based on these findings, the two pathways were thought to act in an antagonistic fashion: the direct pathway promotes the initiation of movements, whereas the indirect pathway is crucial for the termination and inhibition of inappropriate movements. Together, they govern the selective activation of intended motor programs while competing motor sequences are suppressed (Wilson, 2007). The idea of two opposing pathways has subsequently been challenged by new findings that indicated that the direct and the indirect pathway receive similar inputs and that they are both involved in positive reinforcement (Kress *et al.*, 2013; Vicente *et al.*, 2016). Therefore, it was suggested that the segregation of information in the two pathways might be complementary and support, for example, the selection of different action strategies.

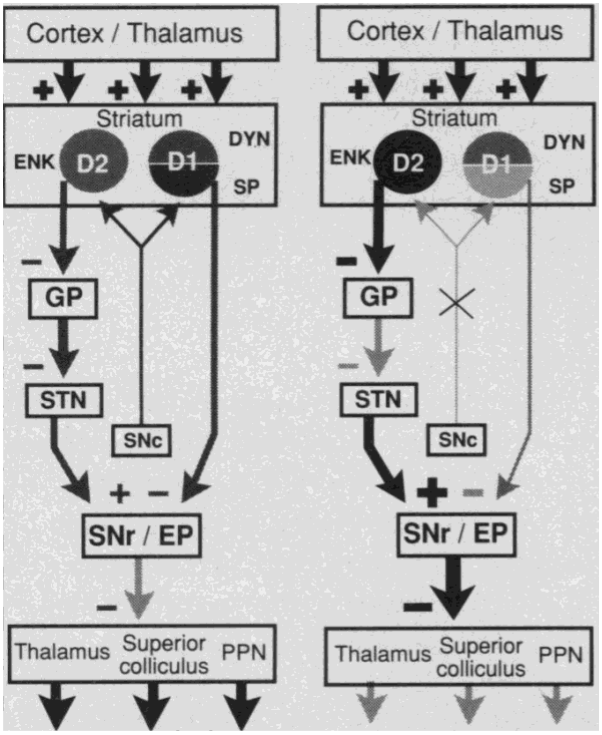

Fig. 5) The first diagram of the BG circuit distinguishing striatal D1- and D2-expressing MSNs projecting to their respective targets and showing their output in health and in a mouse model of PD. Adapted from Gerfen *et al.*, 1990.

The study of Gerfen revealed not only the pathway-specific expression of D1- and D2-receptors in MSNs, but it also addressed the role of DA in a mouse model of PD. In this model the DA input is lesioned by injecting the neurotoxin 6-OHDA. The resulting scheme explains the mechanisms underlying PD by showing that loss of DA selectively decreases the activity of dMSNs, while increasing the activity of iMSNs (Fig. 5). Because of their different projections, this results in an overall greater inhibitory signal sent from the GPi/SNr, which in turn results in the classic symptoms of PD: bradykinesia and akinesia. These findings of Gerfen provided a crucial piece of information explaining how DA levels relate to movement.

Overall, MSNs account for about 95% of the striatal neurons, which are approximately equally divided into the D1- or D2-receptor expressing subclasses (Kemp and Powell, 1971; Graveland and Difiglia, 1985; Gerfen *et al.*, 1990). Both types are distributed throughout the striatum and they are heavily intermingled. MSNs are characterised by a relatively hyperpolarised resting membrane potential (E_{MEM}) and fire only sparsely *in vivo* (DeLong, 1973; Wilson and Groves, 1981). MSNs were long suspected to be the major target of striatal afferents, which was confirmed with EM studies that showed that most striatal inputs form asymmetric axo-spinous synapses on medium-sized neurons (Kemp and Powell, 1971; Hattori *et al.*, 1973; Wilson and Groves, 1980). Subsequently, it was demonstrated that cortical afferents target the spines of MSNs, as do inputs from the centro-lateral nucleus (CL) of the thalamus. The parafascicular nucleus (PF) of the thalamus, in contrast, rather targets the dendritic shafts than the spines of MSNs (Deschênes, 1996; Deschênes, Bourassa and Parent, 1996; Lacey, Bolam and Magill, 2007). Anatomical studies have shown that each corticostriatal axon contacts a great number of MSNs while only forming one or very few synapses with each MSN (Zheng and Wilson, 2002). Around 5.000 – 10.000 cortical afferents are estimated to converge on every single MSN (Kincaid, Zheng and Wilson, 1998; Huerta-Ocampo, Mena-Segovia and Bolam, 2014). Overall, cortical synapses are slightly more numerous than thalamic synapses (Smith *et al.*, 2004). Moreover, cortico- and thalamostriatal fibres are intermingled at the spines of the distal dendritic trees of MSNs, thereby rendering them an ideal site for synaptic integration and coincidence detection (Somogyi, Bolam and Smith, 1981; Smith and Bolam, 1990). The distal location of most excitatory synapses implies, however, that these inputs are also subject to strong dendritic filtering (Rall, 1969). The almost complete absence of excitatory inputs targeting the somata or proximal dendrites of these spiny neurons, together with the high number of synapses formed on each MSN, provides the anatomical basis for one of the main functions of these neurons: the typically silent MSNs fire when related afferent areas become synchronously active (Wilson, Chang and Kitai, 1983; Kincaid, Zheng and Wilson, 1998; Wickens and Wilson, 1998). Inhibitory synapses were shown to primarily contact the somata, proximal dendrites and the axon shaft of MSNs, which explains why these inputs are extremely powerful (Park, Lighthall and Kitai, 1980; Wilson and Groves, 1980). These GABAergic inputs are either derived from adjacent MSNs, that provide lateral inhibition onto each other, from local interneurons or, less frequently, from inhibitory long-range projections originating in cortex and the midbrain (Koós and Tepper, 1999; Gittis *et al.*, 2010; Planert *et al.*, 2010; Brown *et al.*, 2012; Tritsch, Ding and Sabatini, 2012; Rock *et al.*, 2016; Melzer *et al.*, 2017).

Striatal interneurons

The striatum is composed of MSNs and local interneurons. Each interneuron class accounts for at most one percent of the striatal neurons. These rare populations show a large morphological variety and they are often characterised by thin axons, which has rendered their identification particularly difficult, resulting in numerous different classification systems of striatal cell types (Fox *et al.*, 1971; Kemp and Powell, 1971; Haycock and Bro, 1975; Difiglia, Pasik and Pasik, 1980; Dimova, Vuillet and Seite, 1980; Bolam, Wainer and Smith, 1984). The development of histochemical methods in the 1980s allowed researchers to label and hence study these neuron classes and has proven an extremely powerful tool. The main challenge was to find neuronal markers that would visualise a discrete group of neurons that shared the same morphological features. The histochemical approach provided the means for a better morphological characterisation of different types of neurons, which outperformed the widely applied random staining obtained with the Golgi method. At the same time, this technique did not shed much light onto the physiological function of the expressed proteins or the neurons that express them.

Fast-spiking interneurons

Fast-spiking interneurons (FSIs) are characterised by medium-sized somata and a heavily ramified dendritic field, which extends typically 200 – 300 μm around the somata (Kemp and Powell, 1971; Haycock and Bro, 1975). Morphologically, they can easily be distinguished from MSNs due to the absence of spines, yet little else was known about these neurons for a long time.

With the help of novel biochemical methods, the presence of a small striatal interneuron population of medium sized, aspiny neurons that express the calcium-binding protein parvalbumin (PV) was reported in 1985 (Gerfen, Baimbridge and Miller, 1985). Very little was known about PV at that time besides its abilities to bind calcium in the micromolar range and its highly discrete distribution in fast- but not slow-twitch muscle fibres (Pechère, Derancourt and Haiech, 1977; Celio and Heizmann, 1982). A few years later, it was shown that these PV-positive neurons are also GABAergic and EM studies showed that they are reciprocally connected via chemical and electrical synapses and that they form GABAergic synapses onto the somata and proximal dendrites of MSNs (Cowan *et al.*, 1990; Kita, Kosaka and Heizmann, 1990; Kita, 1993). Staining for PV revealed that FSIs constitute about 1% of the striatal neuron population and that they are not distributed homogeneously in the striatum. Rather, they are found along a gradient reaching the highest number in the rostral part of the dorsolateral striatum (Gerfen, Baimbridge and Miller, 1985; Kita, Kosaka and Heizmann, 1990).

These studies also revealed that FSIs are targeted massively by cortical afferents, whereas thalamic inputs are comparatively sparse (Kita, 1993). In contrast to the innervation of MSNs, a given cortical neuron can form multiple serial synapses onto one FSI (Ramanathan *et al.*, 2002). In accordance, patch clamp recordings of FSIs showed that these interneurons display a greater responsiveness to cortical activation than MSNs (Parthasarathy and Graybiel, 1997; Mallet *et al.*, 2005; Fino *et al.*, 2014). Furthermore, these recordings revealed that the intrinsic properties of FSIs also contribute to their high sensitivity to cortical input: FSIs are characterised by a higher input resistance than MSNs and require consequently less cortical stimulation for firing an action potential (Gittis *et al.*, 2010). Moreover, FSIs have a particularly short membrane time constant (tau_{mem}), action potential duration, and afterhyperpolarisation (AHP), which form the basis of their name and allow them to fire with great temporal precision in response to excitatory inputs (Kawaguchi, 1993).

As predicted by EM studies, electrophysiological recordings found that FSIs exert a powerful inhibitory control of MSNs. The GABA released from their highly branched and dense axonal arborization targets hundreds of surrounding dMSNs and iMSNs simultaneously (Kawaguchi, 1993; Bennett and Bolam, 1994; Koós and Tepper, 1999; Mallet *et al.*, 2005; Planert *et al.*, 2010). Feed-forward inhibition executed from this strategic position allows FSIs to delay or prevent action potentials in MSNs, and the symmetric synapses of 4 to 27 FSIs onto one MSN are estimated to be sufficient to counterbalance the excitatory input from approximately 10.000 corticostriatal synapses targeting the distal dendrites of MSNs (Koós and Tepper, 1999, 2002). Patch-clamp recordings also provided physiological evidence for the reciprocal chemical inhibition between striatal FSIs and for the gap junctions between them (Kawaguchi, 1993; Bennett and Bolam, 1994; Koós and Tepper, 1999; Mallet *et al.*, 2005; Russo *et al.*, 2013).

Together, the reliable occurrence of peri-somatic GABAergic synapses formed by FSIs onto MSNs allows this class of interneurons to exert a powerful control of MSNs and hence striatal output, despite their comparatively low abundance. Their efficient positioning within the striatal network demonstrates that FSIs play a crucial role in maintaining the balance between excitation and inhibition, in regulating network gain and in controlling the precise spike timing of MSNs. Moreover, inhibition of adjacent MSNs provides a mechanism for the selective suppression of specific subpopulations of MSNs that mediate unwanted movements (Kita, 1996; Parthasarathy and Graybiel, 1997; Gittis *et al.*, 2010; Planert *et al.*, 2010). More recent studies assessed the function of FSI mediated feed-forward inhibition on a behavioural level and found that it restricts plasticity in MSNs, which in turn facilitates sequence learning (Owen, Berke and Kreitzer, 2018).

Cholinergic interneurons

Cholinergic interneurons (ChINs) constitute only 1% of the striatal cells but they are the largest neurons and have therefore caught the attention of many scientists. The somata of these 'voluminous giant cells' can have diameters of up to 50 μm and their axons are more accessible to tracing than those of other neurons because they are relatively large and travel for considerable distances without becoming thinner (Fig. 6) (Kemp and Powell, 1971; Haycock and Bro, 1975). This led wrongly to the assumption that these 'long axon cells' constitute the projection neurons of the striatum and that ChINs innervate cortex as well as other BG nuclei (Kemp and Powell, 1971; Haycock and Bro, 1975; Parent, Boucher and O'Reilly-Fromentin, 1981). Again, the physiological role and the true projection targets unravelled when the neurotransmitter identity of this neuron class was revealed.

ChINs release acetylcholine (ACh), which was the very first neurotransmitter that was discovered. Otto Loewi, a German-American pharmacologist, demonstrated that stimulating the vagus nerve of a frog led to the release of a substance, which when transferred to a different preparation was sufficient to slow the heartbeat of this second frog. This compound, which he called 'Vagusstoff', was later identified by Henry Dale as ACh. The discovery of ACh and its effects provided evidence for Thomas R. Elliott's hypothesis that chemical transmission occurs via neurotransmitters and was therefore a milestone in the long-lasting controversy surrounding the issue of whether neural transmission is solely electrical or also chemical. As a result, Loewi and Dale earned the Nobel Prize in 1936. In the battle of 'soup versus spark', John Eccles was one of the main defenders of a purely electrical transmission in the 1940s and 1950s. Ironically, it was Eccles resistance to the idea of a chemical component in synaptic transmission that drove him to perform several crucial experiments that ultimately became key evidence for the chemical nature of synaptic transmission. Eccles focused on the role of ACh in the spinal cord and showed that this neurotransmitter is not only used in the peripheral nervous system, but also in the CNS (Eccles, Eccles and Fatt, 1956). Later, it was shown that, in the brain, the highest concentrations of ACh and its associated enzyme choline acetyltransferase (ChAT) are found in the striatum (Hebb, 1957; Hebb and Silver, 1961; Fahn and Côté, 1968; Cheney, LeFevre and Racagni, 1975). Yet, it was highly controversial where the ACh-producing neurons are located and to which areas they project. Some researchers thought there was a cholinergic striatonigral pathway, while opponents of this idea suggested a nigrostriatal projection that results in release of ACh in striatum (Shute and Lewis, 1963, 1967; Olivier *et al.*, 1970). This dispute was addressed by McGeer, who found that striatal levels of ACh remain stable after lesioning striatal afferents and efferents. He concluded therefore that the source of

ACh must be within the striatum and that the ACh-producing neurons do not project outside of this structure (McGeer *et al.*, 1971). Histochemical experiments performed by Henderson revealed that ACh is contained in a population of particularly large nerve cells that accounts for about 1% of all striatal neurons, matching previous EM descriptions of ChINs (Henderson, 1981). Moreover, Henderson's retrograde tracing studies using injections of horseradish peroxidase in the striatum and the SN, also confirmed that there are no cholinergic projections linking these two structures of the BG. His findings, and a large number of preceding reports, provided sufficient evidence to establish ChINs as local circuit neurons in the striatum (McGeer *et al.*, 1971; Butcher and Butcher, 1974; Bolam, Wainer and Smith, 1984). Moreover, it was shown that ChINs constitute the only non-GABAergic neuron population in the striatal network (Ribak, Vaughn and Roberts, 1979). These findings have been complemented by a recent study that provided evidence for an additional, smaller source of ACh in the striatum that arises in the brainstem pedunculopontine and laterodorsal tegmental nuclei (Dautan *et al.*, 2016).

The histochemical and morphological characterisation of striatal neuron classes was accompanied by the first electrophysiological recordings in the striatum. During these recordings two firing patterns were observed. The majority of neurons, which was subsequently identified as MSNs, showed very low firing rates, while another, much smaller population of neurons was tonically active (TANs; DeLong, 1973; Wilson and Groves, 1981; Kimura, Rajkowski and Evarts, 1984). In a motor learning task, putative MSNs increased their firing in a time-locked manner to the onset of the movement, whereas the TANs were found to respond primarily to the sensory cue that served as a signal for

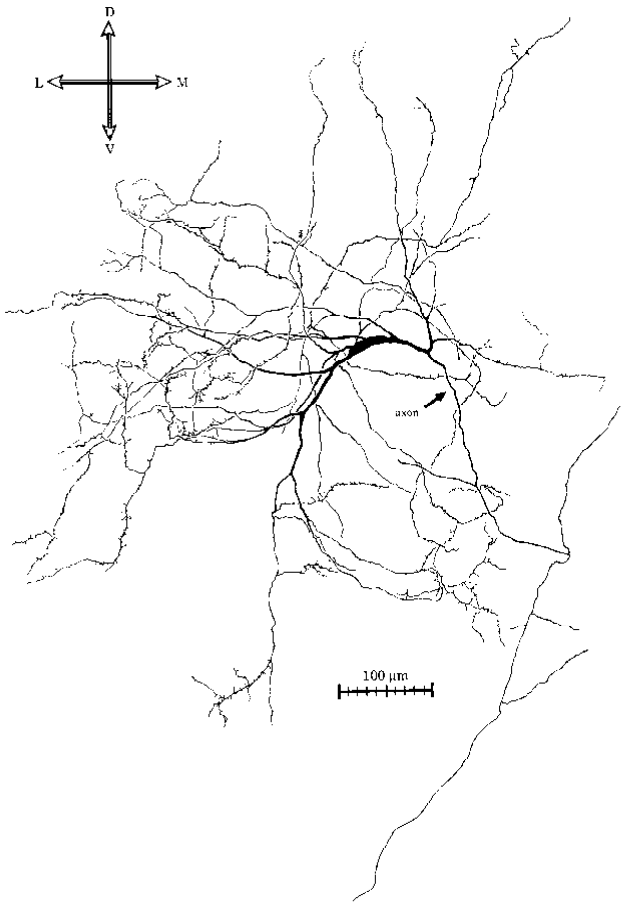

Fig. 6) The complete dendritic tree and a fraction of the axon of a ChIN, adapted from Wilson et al., 1990.

movement initiation (Kimura, 1986). These strikingly different activity patterns indicated that MSNs and TANs each receive their own set of inputs and that they exert different functions in the striatal microcircuit. It was however unknown which class of striatal interneurons corresponds to the TANs.

The first link between striatal ChINs and TANs was made in 1990 by Wilson and colleagues (Wilson, Chang and Kitai, 1990). They had acquired blind intracellular recordings in rats *in vivo* and over a period of 8 years, they managed to record a sufficiently high number of these rare TANs to claim that the spontaneously active neurons in the striatum are ChINs. The recorded cells had been filled intracellularly with dyes, which subsequently revealed the distinctive large somata of ChINs.

These recordings also showed that ChINs are characterised by a relatively depolarised resting membrane potential and a large membrane time constant compared to MSNs and FSIs and that they respond to cortical as well as thalamic inputs. Several studies revealed that ChINs are weakly innervated by cortical afferents, while being targeted heavily by thalamic projections (Wilson, Chang and Kitai, 1990; Lapper and Bolam, 1992; Dimova *et al.*, 1993; Reynolds and Wickens, 2004; Smith *et al.*, 2004). In line with these findings, it has been shown that ChINs respond strongly to thalamic inputs (Ding *et al.*, 2010). Anatomical studies show that ChINs receive inhibitory synapses with dense-cored vesicles on their soma and less densely packed ones on their proximal dendrites, suggesting that they are subject to perisomatic inhibition (Ribak, Vaughn and Roberts, 1979; Bolam, Wainer and Smith, 1984; Takagi, Somogyi and Smith, 1984). It has been further shown that they receive inhibitory inputs from other striatal interneuron classes that express for example somatostatin (SOM) or tyrosine hydroxylase (TH) as well as from inhibitory long-range inputs that innervate the striatum (Rock *et al.*, 2016; Straub *et al.*, 2016; Melzer *et al.*, 2017; Assous and Tepper, 2019).

The release of ACh by ChINs has widespread effects including a metabotropic excitation of dMSNs and iMSNs, as well as FSIs, that all express M_1 muscarinic receptors (Lin *et al.*, 2004; Perez-Rosello *et al.*, 2005). Besides these striatal neurons, corticostriatal axon terminals are also subject to cholinergic modulation (Barral, Galarraga and Bargas, 1999; Alcantara *et al.*, 2001). The presynaptic receptors belong mostly to the M_2 class ($M_{2/4}$ type) and their activation suppresses vesicle release from corticostriatal terminals (Calabresi *et al.*, 1998; Galarraga *et al.*, 1999; Pakhotin and Bracci, 2007). Together, this network provides a feed-forward circuit in which ChINs respond preferentially to thalamic input and their activation can in turn attenuate corticostriatal inputs. The thalamic activation typically evokes a burst of action potentials in ChINs that is followed by a prolonged pause in their spiking. This burst-pause

pattern is a hallmark of ChINs and it has been observed both *ex vivo* and *in vivo* (Aosaki *et al.*, 1994; Matsumoto *et al.*, 2001; Ding *et al.*, 2010). While the bursts generate a transient inhibition of corticostriatal input, the subsequent pause provides a time window during which MSNs display an increased responsiveness to cortical input. This feed-forward pathway gives ChINs a central role in the suppression of ongoing motor activity in response to salient stimuli that redirect attention. Moreover, this pattern of activity is also observed in response to sensory cues predictive of reward, as seen already in some of the earliest recordings of ChINs (Kimura, 1986; Kimura, Yamada and Matsumoto, 2003; Morris *et al.*, 2004; Apicella, 2007).

Low-threshold spiking interneurons

Low-threshold spiking interneurons (LTSIs) were first identified because of their expression of SOM and avian pancreatic polypeptide (APP; S. R. Vincent *et al.*, 1982). There were speculations that these peptides act as transmitters and that SOM might depress neuronal activity, but their functions were far from understood (Hökfelt, Elfvin and Elde, 1977). Additional histochemical experiments showed that the SOM-positive cells also have a particularly high activity of the enzyme NADPH-diaphorase and that this enzyme is not expressed in FSIs (Scherer-Singler *et al.*, 1983; Vincent *et al.*, 1983; Kita, Kosaka and Heizmann, 1990). Later it was revealed that NADPH diaphorase is identical to nitric oxide synthase (NOS), the enzyme generating nitric oxide (NO) (Dawson *et al.*, 1991). Interestingly, neurons expressing this oxidative enzyme had already been noted to survive the widespread cell death observed in HD (Dawbarn, De Quidt and Emson, 1985; Kiyama, Seto-Ohshima and Emson, 1990). The mechanisms underlying these protective effects were however unknown. Additionally, neuropeptide Y (NPY) was shown to co-localise largely with SOM in the mammalian striatum and raised questions whether earlier studies on APP had accidentally visualised NPY because of antibody cross-reactions (Smith and Parent, 1986). The expression of GABA by SOM-positive neurons was at first ambiguous because early reports did not find GAD expression in SOM-positive cells, but subsequent histochemical and electrophysiological studies provided evidence for the GABAergic nature of these neurons (Kita, Kosaka and Heizmann, 1990; Vuillet *et al.*, 1990; Kubota, Mikawa and Kawaguchi, 1993; Lenz *et al.*, 1994). Altogether, the histochemical staining methods resulted in a highly heterogeneous descriptive set of molecular markers that were associated to varying degrees with LTSIs. These somewhat inconclusive findings are noteworthy because they constitute the primary reason why this neuron population is comparatively poorly understood to this day.

One advantage of those novel markers was that they could be combined with other methods to gain more insight into the respective neuron class. For example, staining for SOM and NADPH

diaphorase was used for more detailed morphological studies including both light microscopy and EM. By this means, these neurons were found to be aspiny, medium-sized neurons with few, long, and smooth dendrites and relatively large axonal fields that frequently form synapses onto distal dendritic spines of putative MSNs. They receive only occasionally input onto their somata and two types of synapses targeting their proximal and distal dendrites were observed (DiFiglia and Aronin, 1982; Bennett and Bolam, 1993). The inputs onto their proximal dendrites were found to belong to cholinergic and dopaminergic afferents, whereas those targeting the distal dendrites derived from cortical afferents (Kubota *et al.*, 1988; Vuillet, Kerkerian, Kachidian, *et al.*, 1989; Vuillet, Kerkerian, Salin, *et al.*, 1989; Vuillet *et al.*, 1992). Depending on the molecular marker, stereological cell counts estimated that this neuron class accounts for 0.6 to 0.8% of the striatal neurons (Figueredo-Cardenas *et al.*, 1996; Rymar *et al.*, 2004). The application of immunohistochemistry together with retrograde tracing and lesioning of striatal afferent and efferent fibre tracts demonstrated that LTSIs constitute a local interneuron population (Smith and Parent, 1986; Bennett and Bolam, 1993).

In the 1990s, Kawaguchi combined patch-clamp recordings with subsequent staining for a variety of markers including NAPDH diaphorase. These recordings provided the first physiological characterisation of this neuron class and coined the name 'low-threshold spiking' interneuron. LTSIs show a depolarised resting membrane potential, the highest input resistance of all striatal neuron types and a long membrane time constant. Some LTSIs were found to have persistent depolarising spikes, which are now commonly referred to as plateau potentials ('PLTS') (Kubota, Mikawa and Kawaguchi, 1993; Kawaguchi *et al.*, 1995; Koós and Tepper, 1999). The depolarised resting membrane potential of LTSIs implied that these cells might have been confused with the other class of spontaneously active striatal neurons, the ChINs, in preceding blind *in vivo* recordings.

The novel insights into the properties of LTSIs resulted in several hypotheses on their function. The synaptic contacts of LTSIs onto the spines of MSNs indicated that they might be involved in regulating the activity of MSNs by feed-forward inhibition. This idea was supported by showing that activation of LTSIs inhibits MSN firing in a monosynaptic and GABA-dependent manner (Koós and Tepper, 1999). Unfortunately, the recorded LTSIs were not recovered for subsequent staining of their molecular markers in that study. Other studies were unable to replicate the strong inhibition of MSNs by LTSIs and observed only a sparse and weak inhibitory connection between them (Gittis *et al.*, 2010). This discrepancy might be due to regional differences within the striatum. Fino and colleagues reported that LTSIs exert a more

powerful inhibition of MSNs in the dorsomedial striatum than in the dorsolateral striatum (Fino *et al.*, 2018).

Alternatively, these contradictive findings might be explained by the presence of different subpopulations of LTSIs. In particular, the use of different mouse lines labelling LTSI subpopulations may contribute to the variability in their characterisation. Moreover, the physiological significance of the three neuropeptides expressed by LTSIs is still largely undescribed, which is due to the technical challenges associated with studies on neuromodulation. LTSIs might, however, use NO, NPY or SOM as their principal neuroactive substance and exert primarily slower neuromodulatory effects in the striatal circuit. For example, it has been shown that the release of NO by LTSIs regulates corticostriatal plasticity and that it increases the excitability of ChINs (Centonze *et al.*, 2001; Blomeley, Cains and Bracci, 2015). The release of SOM was found to reduce the presynaptic release of GABA at the lateral synapses between MSNs (Lopez-Huerta *et al.*, 2008). At the behavioural level, LTSIs have been shown to control the initial stages of goal-directed learning by decreasing their reward-associated activity (Holly *et al.*, 2019).

Other classes of striatal interneurons

The three classes of striatal interneurons described above were the first to be discovered but their characterisation was only the beginning of a long series of studies on further striatal neuron populations (Fig. 7). Together with FSIs, ChINs and LTSIs, another group of interneurons was found in the early 1990s. These neurons were characterised by the expression of the calcium-binding protein calretinin (CR) (Kawaguchi *et al.*, 1995). Calretinin-positive interneurons constitute the most abundant type of striatal interneurons in humans but due to the lack of transgenic mouse lines labelling this neuron, very little is known about these cells (Wu and Parent, 2000). Other interneuron types have been distinguished based on the expression of the enzyme TH, a serotonin receptor (5HT3A), and a nicotinic receptor (ChRNa2, Torkarska et al., *in preparation*; Ibáñez-Sandoval *et al.*, 2010; Muñoz-Manchado *et al.*, 2016). NPY-expressing neurons have been further subdivided into NPY-neurogliaform neurons and NPY-PLTS neurons and PV-expressing FSIs were suggested to be considered a subpopulation of a larger group of neurons that all express Pthlh (Ibáñez-Sandoval *et al.*, 2011; Muñoz-Manchado *et al.*, 2018).

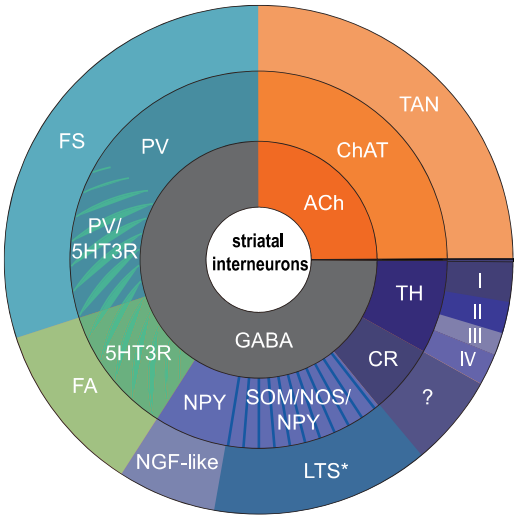

Fig. 7) The diversity and classification of striatal interneurons. The plot represents the proportions of different striatal interneuron types considering their neurotransmitter identity (inner circle), the expression of marker proteins (centre circle) and their firing patterns (outer circle). Fast-adapting (FA); neurogliaform (NGF). Adapted from Burke, Rotstein and Alvarez, 2017.

The classification of striatal cell types is still ongoing. Traditionally, neuron populations were distinguished based on their anatomy revealed by Golgi staining. The introduction of histochemical methods replaced anatomy with molecular markers and subsequent electrophysiological recordings offered yet another classification system, which is based on firing patterns. The most recent approach is based on sequencing, and incorporates not only a single marker but the entire genetic profile of the neurons (Muñoz-Manchado *et al.*, 2018). However, morphological features, the expression of marker proteins, and the intrinsic properties do not only occur in discrete groups but might change along gradients, rendering the neat division of striatal neurons into distinct cell types difficult. Nonetheless, it is helpful to divide the diverse striatal neuron populations into separate groups as long as the limitations of this classification are considered.

1.6 STRIATAL INPUTS

The characterisation of different classes of striatal neurons throughout the 1980s and 1990s and the identification of their neurotransmitters, highlighted an important fundamental fact: there are no excitatory glutamatergic neurons in the striatal circuit. In contrast, there is a large variety of GABAergic populations, several of which provide fast inhibitory input to MSNs, the neurons responsible for sending all output to downstream BG structures (Koós and Tepper, 1999; Tepper, Koós and Wilson, 2004; Ibáñez-Sandoval *et al.*, 2010). Of the two classes of spontaneously active neurons, ChINs and LTSIs, only ChINs can increase excitability by acting on specific subtypes of cholinergic receptors. Their effect on MSNs is, however, only weakly modulatory and is not sufficient to evoke spiking (Lin *et al.*, 2004). Moreover, striatal activity is not only constrained by local inhibitory networks but also by GABAergic long-range

projections originating in cortex and the GP that target striatal MSNs and interneurons (Bevan, 1998; Mallet *et al.*, 2012; Rock *et al.*, 2016; Saunders, Huang and Sabatini, 2016; Melzer *et al.*, 2017). Intracellular electrophysiological recordings further revealed that MSNs are characterised by an exceptionally negative E_{Mem}, which implies that they require a considerable amount of excitation to fire an action potential.

Based on these new insights into striatal physiology, one major concept of BG functioning started to emerge: the tight GABAergic control and the hyperpolarised E_{Mem} of MSNs have to be overcome in order to allow spiking of these neurons. This highlights the critical importance of excitatory inputs to the striatum, and revealing these excitatory inputs is now understood to be indispensable for understanding the activity of MSNs and their downstream targets. Since local interneurons are powerfully controlling MSNs, it is equally important to understand when and how they are activated. As a result, the focus of BG research shifted from striatal neuron populations to the excitatory long-range fibres targeting the striatum which are now recognised to provide the main driving force for striatal activity and thus BG operations.

The fibre bundles targeting the striatum are numerous and the striatum has always been the undisputed input nucleus of the BG. Vesalius provided the first image of the highly organized parallel fibre bundles that pass through the striatum. Numerous researchers, including Willis, speculated that they play a central role in the sensorimotor function of the striatum. In the 19th century the first indirect evidence was presented that suggested that the innervating fibres and, accordingly, also the striatum, are topographically organized (Hughlings-Jackson, 1868). The first detailed descriptions of these prominent axon bundles were provided by Cajal and Wilson, who both distinguished different types of ascending and descending fibre systems as well as branching patterns (Wilson, 1913; Haycock and Bro, 1975). They also characterised the trajectories of individual axons and noticed that they often branch off from the large axon bundles passing through the striatum. However, the available fibre staining techniques, the Weigert and the Marchi staining, visualised only degenerating or myelinated axons and prevented an unbiased description of the neural pathways in the brain (Nauta and Gygax, 1954). Therefore, even the existence of the prominent corticostriatal pathway was doubted for a long time (Wilson, 1913; Pollak, 1922; Verhaart and Kennard, 1940). This pathway was finally proven by Glees, who was able to visualise non-myelinated corticostriatal fibres (Glees, 1944). However, most of our understanding of striatal inputs was only acquired during the last decades, when the physiological significance of these tracts was evident, and novel techniques gave new insights into the organisation of these pathways.

Corticostriatal inputs

Virtually all cortical areas project to the striatum and provide a vast amount of information to the striatal microcircuit (Yeterian and Van Hoesen, 1978; Wall *et al.*, 2013; Guo *et al.*, 2015). Most of the cortical projections arise from pyramidal cells in layer 5 (L5), the main output neurons of cortex. These neurons can be subdivided into two types: pyramidal tract-type (PT-type) neurons extend projections ipsilaterally to the thalamus, STN, GPi, superior colliculus, and brainstem with collaterals in the striatum (Fig. 8) (Donoghue and Kitai, 1981; Cowan and Wilson, 1994; Rojas-Piloni *et al.*, 2017). As a result, their information is fed simultaneously to several nuclei of the BG network. In contrast, intratelencephalic (IT-type) neurons project to ipsi- and contralateral cortex and striatum (Wilson, 1987; Alloway *et al.*, 2006; Kress *et al.*, 2013). The bilateral IT-type projections show an anterior-posterior gradient with frontal areas having denser projections to the contralateral striatum than posterior primary sensory areas (Reig and Silberberg, 2016; Hooks *et al.*, 2018). Within cortex, PT- and IT-type pyramidal cells receive different inputs. IT-type neurons connect to each other and to PT-type neurons, while PT-type pyramidal cells do not synapse onto IT-type neurons (Morishima and Kawaguchi, 2006; Kiritani *et al.*, 2012). Moreover, IT-type neurons are preferentially localised in the upper layer 5, whereas PT-type neurons are more frequently found in the lower layer 5 of cortex (Rojas-Piloni *et al.*, 2017; Hooks *et al.*, 2018). The differences between PT- and IT-type neurons in their projection targets, layer-specific localisation, and local connectivity, indicate that they might serve different functions but their respective roles are not yet fully understood. Studies on sensory processing suggest that PT- and IT-type neurons process complementary sensory information but more studies are needed to characterise them (de Kock and Sakmann, 2009; Oberlaender *et al.*, 2011; Kim *et al.*, 2015).

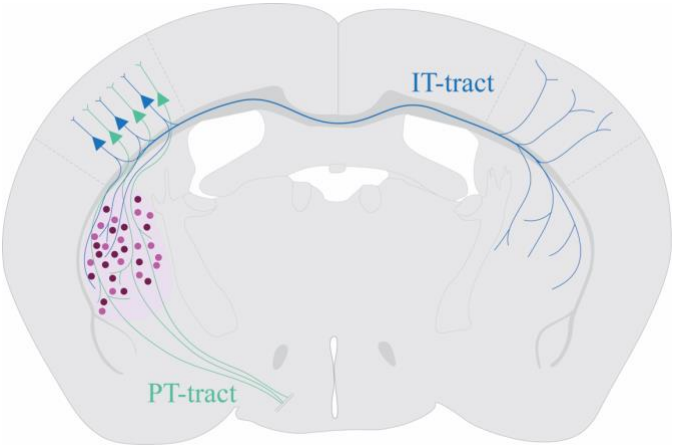

Fig. 8) The projections of the corticostriatal PT- and IT-tract. PT-type neurons (green) project ipsilaterally to the striatum and further downstream to other nuclei (not depicted). In contrast, IT-type neurons (blue) project to ipsi- and contralateral cortex and striatum.

Based on these findings, it was speculated that PT- and IT-type neurons also convey different aspects of information to the striatum and hence might express different preferences at their striatal targets for dMSNs and iMSNs. Anatomical studies suggested that dMSNs receive predominantly input from IT-type neurons, while iMSNs receive greater input from PT-type cells (Lei *et al.*, 2004). However, these findings have been disputed because electrophysiological studies found that dMSNs show greater responses to PT-type input than iMSNs (Kress et al., 2013). Moreover, activation of IT-type axons did not yield any differences in the responses of dMSNs and iMSNs in that study. Other research groups have suggested that the relative responses of dMSNs and iMSNs depend primarily on the cortical area that provides the input and less on the cell-type within that area (Wall *et al.*, 2013). These studies were gradually extended and assessed not only the responses of MSNs to cortical input but also those of striatal interneurons.

Overall, it was speculated that the corticostriatal pathway provides cell type- and region-specific input to the striatum. However, as exemplified by MSNs, there was no consensus on which properties critically shape the postsynaptic responses and whether there are organisational principles that apply generally to striatal inputs. The reasons for this uncertainty lie in the complexity of this particular projection: the corticostriatal pathway is linking diverse pre- and postsynaptic cell types and it arises in functionally distinct cortical areas. Therefore, numerous variables have to be considered when assessing the role of an individual input to different striatal neuron populations. This, however, is technically challenging. For example, anatomical findings characterising synaptic contacts do not linearly correlate with the physiological strength of an input because synaptic responses depend not only on synapse location and number, but also on dynamic pre- and postsynaptic properties such as release probability, receptor composition, short- and long-term plasticity and many more. Therefore, the EM studies on corticostriatal synapses have been followed up by electrophysiological studies that assessed these synaptic properties on a functional level. Originally, this was done by placing a stimulating electrode within the striatum that was used to activate striatal afferents while recording from different neuron populations (Kawaguchi, 1993). However, as the striatum is innervated by both cortical and thalamic afferents, more sophisticated slice preparations and more specific stimulation locations outside of the striatum soon took over (Fino, Glowinski and Venance, 2005; Smeal *et al.*, 2007; Ding, Peterson and Surmeier, 2008; Doig, Moss and Bolam, 2010; Ibáñez-Sandoval *et al.*, 2011; Sciamanna *et al.*, 2015; Arias-García *et al.*, 2018; Owen, Berke and Kreitzer, 2018). By placing the stimulation electrode in the corpus callosum, for example, a more specific activation of corticostriatal fibres can be achieved. Yet, there is always a risk that the pulse applied to the stimulation electrode might

spread to nearby structures or activate by-passing axons originating in other brain areas. Moreover, the cortical areas that give rise to the activated fibres remain unknown and one cannot study inputs from one distinct cortical area. Furthermore, both excitatory and inhibitory inputs are co-activated and, unless synaptic blockers are used, the contribution of each individual pathway cannot be extracted. With the introduction of the Cre/lox system and optogenetic methods in the 2000s, another major step was taken in the systematic dissection of striatal inputs. This approach enabled the selective activation of defined inputs such as, for example, L5 pyramidal cells in Thy1-cre or Emx1-cre mice, which are all excitatory. However, as long as these mice are crossbred with a ChR2 reporter, optogenetic stimulation of afferent fibres will still reflect activation of virtually all cortical afferents without spatial specificity. Alternatively, ChR2 can be expressed locally by injecting a cre-dependent or a promoter-driven virus into a single cortical area and this approach is becoming increasingly popular (Parker, Lalive and Kreitzer, 2016; Assous *et al.*, 2017). Based on these diverse methods, numerous studies have shed light onto the corticostriatal pathway and also investigated other striatal inputs.

Thalamostriatal inputs

Similar to the corticostriatal projection, the existence of the thalamostriatal pathway was disputed until it was unequivocally proven in the 1940s. The observation of Gerebtzoff, who reported a severe retrograde degeneration in the PF and centromedian (CM) thalamus after lesioning the striatum of rabbits, was central to this (Gerebtzoff, 1940). One year later, the Vogts showed that this also applies to the CM of humans and they argued that the CM, unlike many other thalamic nuclei, primarily interacts with the striatum and not cortex (Vogt and Vogt, 1941). By now it is well established that the CL, the CM and the PF give rise to thalamostriatal fibres (McLardy, 1948; Jones and Leavitt, 1974; Nauta, 1974). In rodents, no region has been defined as CM due to the lack of clear histological boundaries and therefore the CM and the PF are often considered together as the caudal complex (PF/CM). Similarly, the CL is often grouped together with the paracentral and the central medial nuclei as the rostral thalamic nuclei. These thalamic inputs are often studied as a whole and they are thought to provide attentional, ascending sensory and salience information (Kinomura *et al.*, 1996; Minamimoto and Kimura, 2002; Huerta-Ocampo, Mena-Segovia and Bolam, 2014). However, there are also several lines of evidence showing that inputs from the PF and the CL display a high degree of functional specificity. For example, neurons in the CL have bushy dendrites and low-threshold calcium spike bursts, whereas neurons of the PF show reticular-like dendritic arbours and discharge at lower frequencies (Deschênes, 1996; Deschênes, Bourassa and Parent,

1996; Smith *et al.*, 2004; Lacey, Bolam and Magill, 2007). Moreover, neurons in the CL target dendritic spines of MSNs, whereas fibres arising in the PF tend to form synapses onto the shafts as well as, to a lesser extent, onto the spines of MSNs (Smith et al., 2004; Lacey et al., 2007). Regarding striatal interneurons, only thalamostriatal fibres from the PF have been found to additionally target ChINs and FSIs (Lacey et al., 2007; Rudkin and Sadikot, 1999; Lapper & Bolam, 1992; Kachidian et al., 1996; Gou et al., 2015). Together, these findings indicate that these two pathways serve different functions, which still need to be elucidated in more detail in the future.

In terms of striatal activity, input from the PF was soon identified as a strong source of excitation for ChINs (Meredith and Wouterlood, 1990; Lapper and Bolam, 1992; Baldi *et al.*, 1995; Ding *et al.*, 2010; Threlfell *et al.*, 2012). Stimulation of PF evokes the classic burst-pause firing pattern and the bursts result in ACh release. This neurotransmitter, in turn, evokes the release of DA from axon fibres arising in the SNc and suppresses vesicle release from corticostriatal inputs (Ding *et al.*, 2010; Threlfell *et al.*, 2012). The powerful excitation of ChINs by PF has, since its first description, attracted a lot of attention and numerous studies focusing on this pathway have followed (Aceves Buendia *et al.*, 2019; Tanimura *et al.*, 2019). As a result, PF inputs are strongly associated with the activation of ChINs, while much less is known about the role of this input in exciting MSNs. This raises the question whether the strong responses of ChINs to PF input have a significant effect on MSNs and critically shape their responses to PF input or whether their impact on MSNs is nonetheless only modulatory. Similar to MSNs, the responses of other striatal cell types to PF inputs have been somewhat neglected. For FSIs anatomical data indicate that only 4% of the asymmetric synapses targeting them are of thalamic origin, suggesting that PF provides, compared to cortex, only a minor contribution to the excitation of FSIs (Kita, 1993; Rudkin and Sadikot, 1999). Yet, this has not been followed up by physiological studies. Thalamic synapses have not been found on LTSIs in rodents, while thalamostriatal synapses targeting LTSIs have been demonstrated in primates (Kachidian *et al.*, 1996; Sidibé and Smith, 1999). Altogether, the reports on the thalamostriatal pathway indicate that it might evoke cell type-specific responses in the striatal microcircuit - as observed for the corticostriatal pathway. Recent findings suggest moreover that striatal inputs from the PF comprise three different projections that arise from molecularly and physiologically distinct subpopulations of PF neurons (Mandelbaum *et al.*, 2019).

Studies on the thalamostriatal pathway are frequently limited by the same technical challenges as studies on the corticostriatal pathway. The drawbacks of electrical stimulation apply generally and in case of thalamostriatal inputs they obscure the identity of fibres originating in

the PF and in the CL, respectively. The reason for this is that the projections arising in the PF and the CL navigate together along the same tract to the striatum (Deschênes, 1996; Deschênes, Bourassa and Parent, 1996). Optogenetic approaches often take advantage of the selective expression of VGlut2 in the thalamus as opposed to the expression of VGlut1 in cortex, although both PF and CL express this marker (Lacey *et al.*, 2005; Raju *et al.*, 2006). Separating PF and CL inputs is additionally compounded by their nearby anatomical positions. As a result, very little is known about the physiological differences of these two thalamic inputs to the striatum.

Current and future studies on striatal inputs

There is a broad range of studies assessing the anatomical and physiological role of cortical and thalamic inputs synapsing onto different types of striatal neurons. They suggest strongly that these projections target the striatum in a cell type- and input-specific manner. Yet, the input-specificity is rarely addressed systematically. Instead, the sum of all cortical or all thalamic inputs is studied simultaneously despite robust evidence showing that both cortex and thalamus are composed of functionally distinct divisions. Moreover, the physiological responses of striatal neurons are often addressed individually in different studies under varying experimental conditions. These technical differences strongly hamper the comparability of the cell type-specific responses to a given input. The relative responses of different striatal cell types to a shared input are, however, essential because it has been shown that all inputs target more than one striatal neuron population. Thus, the impact of any input is not defined by its effect on a single cell class but by the excitation that it evokes simultaneously in several cell types that are all part of the same interconnected microcircuit. Consequently, the current understanding is that the relative responses of the diverse striatal neuron populations need to be characterised for all inputs targeting this structure. Such a systematic analysis reveals not only the individual components underlying striatal activity but also their functional significance. Moreover, a systematic analysis will demonstrate which cell types process what kind of information and in turn provide insights into the roles of the different striatal neuron classes. Studies comprising several striatal cell types and / or several inputs are also better suited for detecting the organisational rules that shape the synapses between different pre- and postsynaptic neurons. Once striatal activation patterns are characterised, this knowledge can additionally serve as a reference for diseases such as PD that interfere with striatal functioning. Furthermore, this data can be implemented in computational models of the striatum, and other studies, that focus on individual pathways, can use these models to estimate how their striatal input relates to the remaining striatal network.

Overall, all findings on the BG, the striatum, its cell types, and its inputs, have not only provided novel insights into the complexity and importance of these structures but they have also raised new questions that continue to guide ongoing research. Accordingly, recent findings on striatal inputs constitute the framework for the projects presented in this thesis.

2 AIMS

The general aim of this thesis is to explore the long-range excitatory inputs of the striatal microcircuit and to shed light on the synaptic properties that ultimately determine how these inputs shape striatal activity in health and disease.

The specific aims are:

1) To study the role of the corticostriatal pathway originating in the primary somatosensory cortex in sensory impairments in a mouse model of Parkinson's disease (**paper I**).

2) To map the functional connectivity of five excitatory striatal input structures onto five neuron populations (**paper II**).

3) To create an *in silico* model of the striatum that includes data ranging from the subcellular to the microcircuit level (**paper III**).

3 METHODS

Historically, the field of neuroscience primarily relied on lesion studies to learn about the function of different areas of the brain. However, understanding complex functions such as perception, learning, and behaviour requires more sophisticated techniques that can reveal the organisation of the underlying neural circuits and that can modify their activity systematically. Owing to a great number of technological advances in recent decades, several tools are now available that allow researchers to study neural circuits in a cell-type specific manner and to manipulate their activity with high spatiotemporal control. These techniques have been fundamental for gaining new insights into how different classes of neurons act together and process the information required for generating appropriate behavioural responses. Collectively, these methods have rapidly accelerated our understanding of the nervous system and brought us ever closer to 'cracking' the neural code.

3.1 TRANSGENIC MICE AND VIRUSES

Transgenic mice

Non-human mammals such as pigs and primates are often used as models for studying the nervous system owing to their close similarity to human physiology and pathophysiology. However, the laboratory mouse has become a primary model species as it is amenable to a broad range of genetic modifications. One of the most widely used techniques nowadays is based on site-specific recombinases (SSRs) such as the Cre/Lox system, that can cut and paste DNA fragments between two short recognition sites, thereby providing the means for defined genetic deletions, inversions and translocations (Sadowski, 1986; Metzger and Feil, 1999). A major advantage of the Cre/Lox system is that it allows tissue-specific (Gu *et al.*, 1994) and inducible (Kühn *et al.*, 1995) genetic modifications. The Cre (cyclization recombination) recombinase, an enzyme originally derived from bacteriophage P1, recombines two target sites on the P1 genome called LoxP (locus of crossing-over [X] of P1) (Hoess and Abremski, 1985). The LoxP sites are partially asymmetric, thereby defining the direction of the recombination process. When both LoxP sequences have bound to two Cre monomers each, a complex is formed and the DNA strand is cleaved, exchanged or ligated in the centre ('spacer region') of the LoxP sequences.

The expression of many proteins is restricted to subsets of neurons and this natural cell type-specificity can be exploited as a handle to drive the expression of Cre in a specific cell

population. Using knock-in strategies or bacterial artificial chromosomes (BAC), the gene encoding Cre is linked to the endogenous promoter of such proteins, resulting in the expression of Cre in defined neuronal populations. The expression of Cre in D1- and D2-Cre mice as well as the expression of eGFP in Lhx6 mice used in this thesis all rely on BAC engineering (Gong *et al.*, 2003, 2007). During the last two decades numerous additional Cre lines have been developed with the help of the knock-in strategy, allowing cell type-specific manipulations of rare neuron populations such as PV-, SOM-, or ChAT-expressing interneurons, respectively (PV-Cre, SOM-Cre, CHAT-Cre mice).

Once Cre is expressed in a cell type of interest, these cells can be manipulated either by crossing the mice with a reporter mouse line or by local virus injections. tdTomato mice ('Ai9') constitute a commonly used reporter mouse line carrying a LoxP-flanked STOP cassette followed by the gene encoding red fluorescent protein (RFP). The offspring of a tdTomato mouse crossed with a D1-Cre mouse expresses Cre in all D1-receptor expressing neurons which will in turn excise the STOP signal preceding the gene encoding RFP. As a result, only D1-receptor expressing cells will express RFP and can therefore be identified visually under a fluorescent microscope. Alternatively, a viral approach can be used to induce the expression of a gene of interest locally at the site of the virus injection.

Virus mediated gene delivery

There are numerous viruses that can be used as vectors for delivering selected genes into neurons. The advantages of virus mediated gene expression are that they are small (approx. 20 – 200 nm), they can be injected locally into any brain region, and they allow high expression levels of the transferred genes. Replication-deficient lentiviruses and adeno-associated viruses (AAV) are both frequently used to deliver functional tools needed in circuit studies as they induce persistent and non-toxic gene expression. Lentiviruses carry 8-9 kB of genetic material while AAV can only carry <5 kB. Despite their small packaging size, AAV constitute an attractive tool since their coat protein can be synthetically modified to manipulate the virus's tropism and thus its affinity for particular neuron populations or neuronal entrance points (i.e. somata vs. axon terminals). The single-stranded DNA transferred by AAV does not integrate into the genome but remains largely extra-chromosomal. Consequently, there is no risk of disrupting endogenous genes. Similar to Cre, the expression of the viral vectors can be restricted to selected cell types in wild type animals by using promotor elements of cell type-specific proteins. For example the AAV2-CaMKIIa::hChR2(H134R)-EYFP virus can be used to drive the expression of channelrhodopsin (ChR2) and enhanced yellow fluorescent protein (eYFP) selectively in Ca/calmodulin-dependent protein kinase II a (CaMKIIa)-expressing

principal neurons, while transduced GABAergic and glial cells remain unaffected (Liu and Jones, 1996; Aravanis *et al.*, 2007). Alternatively, cell-type specific expression of viral constructs can be achieved with a Cre-dependent vector: Cre-dependent viruses carry a double-floxed inverted open-reading-frame (DIO) and the gene of interest is placed between two incompatible Cre recombinase recognition sequences. In the presence of Cre, the open reading frame (ORF) is irreversibly inverted and allows the gene of interest to be expressed under the promotor used in the AAV. Viral transduction of cre-dependent constructs offers the cell type-specificity of the Cre/Lox system and the region-specificity achieved by local virus injections in selected brain areas. These features, as well as the high efficiency of AAV transduction, have rendered this approach an indispensable tool for revealing the function of distinct neural populations.

3.2 PATCH-CLAMP ELECTROPHYSIOLOGY

The main method used in this thesis is the patch-clamp technique, which was first developed by Erwin Neher and Bert Sakmann and earned them the Nobel Prize in Medicine or Physiology in 1991. Their work connects to a series of preceding studies that date back as far as the end of the 18th century when Luigi Galvani first discovered that a dead frog leg muscle twitches when an electric shock is applied to one of its nerves. Following Galvani's finding of 'animal electricity' numerous scientists contributed to our understanding of the electrical nature of nerve signals. Throughout time, scientific progress was tightly linked to the development of new technical instruments that were sensitive enough to detect small electrical signals and that allowed the application of controlled pulses. The first action potential was recorded in the 1860s by Julius Bernstein, a student of Bois-Reymond, who invented the 'current slicer' (Fig. 9) (Bernstein, 1868; Schuetze, 1983). Yet, it took almost another century to reveal what underlies the transient, regenerating voltage change that acts like a wave of electrical excitation passing along a membrane. In the 1950s, Hodgkin and Huxley postulated the existence of ion channels and revealed the role of sodium and potassium in mediating the action potential based on their work on the squid giant axon (Hodgkin and Huxley, 1952a, 1952c, 1952b). Their findings were merited with the Nobel Prize in Medicine or Physiology in 1963. The recordings of Hodgkin and Huxley were however all on the macroscopic level and the ultimate proof for the existence of ion channels was only achieved in 1976 when Neher and Sakmann developed the patch-clamp technique.

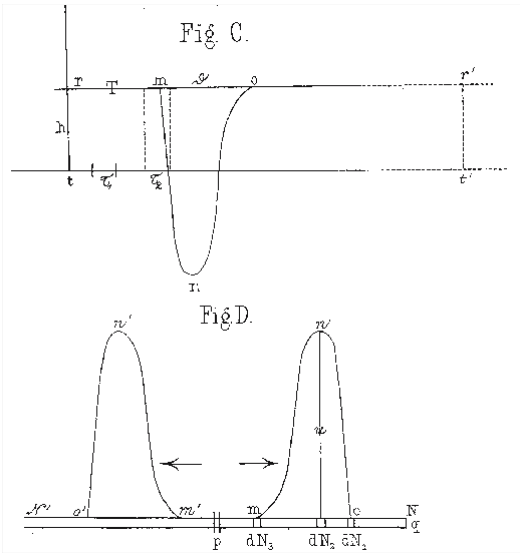

Fig. 9) The first depiction of a recording of an action potential. The negative variation corresponds to an action potential recorded with a differential rheotome by Julius Bernstein in a frog nerve. Both the time course ('Fig. C') and the spatial distribution ('Fig. D') are illustrated. Published in 1868. (Bernstein, 1868)

Patch-clamp electrophysiology is based on an exceptionally tight seal between a tiny patch of cell membrane and a micropipette, which reduces noise and ensures that all ions passing through the membrane flow directly into the recording pipette. This remarkable approach allowed Neher and Sakmann to record from individual ion channels and to finally verify the hypotheses of Hodgkin and Huxley. The development of the patch-clamp technique constituted a major breakthrough in biology because it provided a tool for studying the (dys-) function and gating of individual channels at high resolution and for manipulating currents that flow through single channels or those that flow across the whole membrane of a cell. As a result, the method sparked a wide range of studies in cellular physiology that advanced our understanding and pharmacological control of excitable as well as non-excitable cells in, for example, the nervous, the immune, and the endocrine system.

Since its development, the patch-clamp technique is widely applied in neuroscience and it remains the method of choice for measuring the activity of ion channels. Moreover, it still provides the highest fidelity read-out of neural activity: patch-clamp recordings cover the whole range of neuronal voltage changes from the sub- to the suprathreshold level and fast events such as the opening and closing of ion channels are detected with great temporal resolution. The method can be applied in different configurations of which two have been used in this thesis: in 'cell-attached' recordings a pipette is used to form a seal with a patch of membrane and currents flowing across this part of the membrane are recorded. Alternatively, the patch of membrane within the pipette can be disrupted by applying a small amount of suction resulting in the 'whole-cell' configuration. In this case, the cytoplasm is continuous with the pipette solution and currents across the whole cell membrane are recorded. The acquisition of simultaneous whole-cell recordings from two or more neurons allowed

researchers for the first time to study synaptic connections not only on an anatomical but also on a functional level. By this means, complex neural circuits can be dissected and the properties of individual pathways can be characterised in detail.

The major drawbacks of this technique are that usually only one or few cells can be recorded at a time and that it requires well trained experimenters. Moreover, when studying neuronal circuits, there are extensive long-range connections across the brain for which no paired recordings of the functional connection have been acquired yet due to the technical challenges of accessing cell bodies that are far apart while maintaining the axon between them.

3.3 OPTOGENETIC DISSECTION OF CIRCUITS

Since electrophysiological recordings are laborious and limited to few cells, the introduction of optogenetic tools, that allow manipulation of large neuron populations, revolutionized the field of neuroscience. Optogenetic techniques are based on the expression of light-activated proteins that in turn activate or inactivate neurons. These proteins are typically rhodopsins that contain a membrane bound opsin protein and a light-sensitive chromophore and they act as ion channels or pumps that transport ions across the membrane in response to light (Oesterhelt and Stoeckenius, 1971, 1973; Matsuno-Yagi and Mukohata, 1977). Microbial opsins are also called single-component systems because both operations, light sensing and ion conductance, are carried out by the same protein. In 1979, Francis Crick speculated about the enormous potential of using the natural light-transduction machinery to allow optical control of neural activity and about the importance of doing so in defined neural populations (Crick, 1979). However, it was widely assumed that microbial opsins are both too slow and too weak to control neural activity, that their expression might be poor and possibly toxic for mammalian cells, and that the chromophore, all-*trans* retinal, would have to be added to the tissue. Thus, little progress was made for several decades. This changed in the early 2000s, when ChR2, a rhodopsin that acts as a light-gated cation channel, was discovered in the unicellular green alga *Chlamydomonas reinhardtii* (Nagel *et al.*, 2002, 2003; Sineshchekov, Jung and Spudich, 2002; Suzuki *et al.*, 2003). Within a few years, scientists were able to create a plasmid encoding a ChR2-YFP fusion protein and to infect mammalian neurons with a lentivirus carrying the plasmid (Boyden *et al.*, 2005). The infection of cultured hippocampal neurons resulted in a stable and safe expression of ChR2 and light activation induced rapid depolarising currents that were sufficient to drive spiking. More specifically, upon illumination with ~470 nm blue light, the all-*trans* retinal isomerizes and triggers a conformational change, which results in opening of the channel pore. Interestingly, the light-transduction machinery worked although no all-*trans* retinal had

been added to the culture medium and it turned out that no exogenous cofactor is needed in vertebrate tissues (Douglass *et al.*, 2008). Overall, this approach disproved previous misconceptions and allowed researchers to perform Crick's 'ideal' experiment: it was now possible to genetically target a specific neuron population and to exert temporally precise control of its neural activity in a non-invasive way based on light while examining the effects of the perturbation.

Since the first use of ChR2, the optogenetic toolbox has been greatly expanded by further exploration of the natural diversity of rhodospins occurring in algae and by improving the expression levels, membrane localisation, photocurrents, photosensitivity, and channel kinetics of identified microbial opsins via molecular engineering strategies: for example, the expression levels of ChR2 were greatly increased by replacing algal codons with mammalian ones ('humanized ChR2', hChR2; Zhang *et al.*, 2006, 2007; Adamantidis *et al.*, 2007; Aravanis *et al.*, 2007). The introduction of the H134R mutation in hChR2 doubled its ionic currents, but this happened at the expense of the channel-closure kinetics and thus poorer temporal precision (Nagel *et al.*, 2005; Gradinaru *et al.*, 2007). The channel kinetics critically determine the frequency at which spike trains can be driven and, therefore, hChR2(H134R) is now widely used for low-frequency stimulation (typically < 40Hz). Many neuronal cell types, such as FSIs, show high-frequency spiking and bursts, but activation of hChR2(H134R) and numerous other opsins at frequencies above 40Hz results in spike doublets, omissions and plateau potentials. To faithfully replicate the physiological activity of these neurons, fast variants of ChR2 have been developed. These comprise for example 'ChETAs', a series of ChR2 variants with an amino acid modification that mediates fast channel closure and thus high signal fidelity (ChR E123T/A; Gunaydin *et al.*, 2010). In 2014, another fast ChR2 was discovered in *Stigeoclonium helveticum* and called 'Chronos' (Klapoetke *et al.*, 2014). Chronos is now a widely applied general-use ChR2 because it combines fast on- and off-kinetics with high light sensitivity.

Overall, there are many different subclasses of opsins and both excitatory and inhibitory effects can be elicited. All variants of ChR2 open a cation channel in response to light, which causes a depolarisation, but in other opsins the light sensing machinery is linked to anion channels or ion pumps. In fact, the discovery of photoinhibition preceded the discovery of photoexcitation. The first identified single-component opsin is a light-activated proton pump called bacteriorhodopsin that transports protons out of the cell (Oesterhelt and Stoeckenius, 1971; Racker and Stoeckenius, 1974). A few years later, halorhodopsin (HR) was discovered in archaebacteria (Matsuno-Yagi and Mukohata, 1977). HR constitutes a light-activated chloride pump that has a hyperpolarising effect due to the inwards transport of Cl^-. A major drawback

of HR is the desensitisation and it was soon replaced with a homologous version found in *Natronomonas pharaonic*, NpHR, which is characterised by a more stable outward current (Lanyi and Oesterhelt, 1982; Scharf and Engelhard, 1994; Zhang *et al.*, 2007). Proton pumps were first used as optogenetic tools in 2010 when archaerhodopsin-3 (Arch) was identified during a screening of microbial opsins (Chow *et al.*, 2010). Arch was an attractive tool because this proton pump generated larger photocurrents than HRs. Finally, the optical control of neural activity achieved with inhibitory opsins, as with excitatory ones, is continuously being developed and new generations of opsins allow even more precise and powerful perturbations of neural systems.

4 RESULTS & DISCUSSION

The main aim of this thesis was to gain new insights into the functional organisation of BG inputs in health and disease and to implement this knowledge in an *in silico* model of the striatum.

4.1 SOMATOSENSORY INPUTS TO STRIATAL DMSNS AND IMSNS IN HEALTH AND PD

In **paper I** we looked at the pathway linking one specific cortical area - the primary somatosensory cortex (S1) - to striatal dMSNs and iMSNs in control and in PD. In mice, the main function of S1 is to process incoming information from the whiskers. The near-vision of these rodents is very blurry and therefore they mainly use their whiskers to map out their immediate surroundings. The processed whisker information is subsequently sent to the striatum, where sensory inputs are combined with motor commands to guide the execution of movements. We were interested in studying the corticostriatal projection from S1 in control and in a mouse model of PD because it is known that PD patients suffer not only from motor deficits but also from sensory impairments (Artieda *et al.*, 1992; Sathian *et al.*, 1997; Zia, Cody and O'Boyle, 2003). The mechanisms underlying the loss of tactile discrimination were, however, not well understood. Additionally, this project also allowed us to gain new insights into the organisation of BG inputs by assessing the synaptic properties between a functionally defined cortical area and two of its postsynaptic neuron populations in striatum.

4.1.1 dMSNs distinguish between ipsi- and contralateral whisker information

We characterised the whisker responses of dMSNs and iMSNs in anaesthetised mice in control and in a mouse model of PD. The model is based on local injections of the neurotoxin 6-OHDA into the medial forebrain bundle, which causes loss of DA projections (Fig. 10). *In vivo* whole-cell recordings of MSNs revealed that dMSNs encode the side of the whisker stimulation, i.e. whether the stimulation occurred ipsi- or contralateral to the recorded neuron, better than

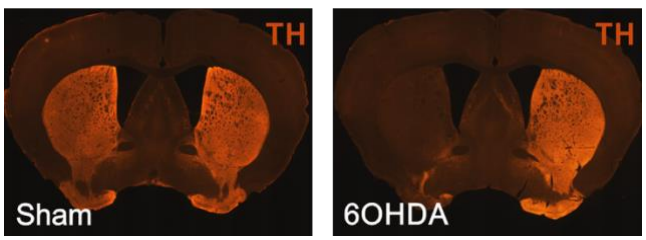

Fig. 10) Unilateral injections of 6-OHDA into the medial forebrain bundle result in the loss of over 90% of the dopaminergic fibres innervating the striatum, which can be visualised by staining for TH.

iMSNs. More specifically, dMSNs showed significantly larger responses and a shorter peak delay for contralateral whisker stimulation than for ipsilateral whisker stimulation (Fig. 11). This difference between ipsi- and contralateral stimulation was less pronounced in iMSNs, and therefore the responses of dMSNs reflect the origin of the sensory stimulation more accurately.

4.1.2 Sensory discrimination is lost in the 6-OHDA mouse model of PD

Our data also demonstrated that the sensory discrimination between ipsi- and contralateral whisker stimulation is lost in the mouse model of PD. In mice treated with 6-OHDA, neither dMSNs nor iMSNs distinguished between ipsi- and contralateral whisker stimulation and the peak delay, as well as the amplitude, of their responses were the same for both sides of stimulation.

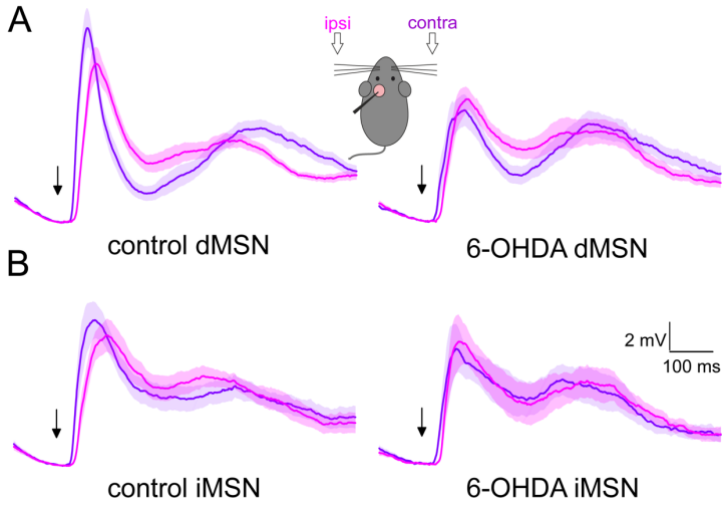

Fig. 11) *In vivo* whole-cell recordings of the responses of dMSNs (A) and iMSNs (B) to ipsi- and contralateral whisker stimulation in control and in the 6-OHDA mouse model of PD.

Additionally, our recordings revealed that the intrinsic properties of dMSNs were altered following the loss of DA. Under control conditions, dMSNs were characterised by a lower input resistance and a lower firing frequency compared to iMSNs. In the DA depleted striatum, the input resistance and the firing frequency of dMSNs increased to the respective levels of iMSNs, so that their intrinsic properties were no longer significantly different. This result is in line with previous studies that also observed an increase in the input resistance of dMSNs in PD, equalizing the properties of both types of MSNs (Fieblinger *et al.*, 2014). Thus, the lack of DA in the PD model affected mainly dMSNs; their intrinsic properties became more similar to those of iMSNs, and the encoding of the laterality of whisker stimulation was lost.

The observed changes could be caused by several mechanisms. For example, sensory discrimination of ipsi- and contralateral whisker stimulations could be affected at the level of S1 itself in PD. Control experiments showed, however, that cortical neurons were able to encode differences between ipsi- and contralateral stimulation both in control and in the DA

depleted state, suggesting that the loss of laterality encoding following 6-OHDA injection is not localised in the cortical network itself.

4.1.3 Mechanisms underlying the sensory deficits in DA depleted mice

We next focused on the neural circuits downstream of cortex including the synaptic properties of S1 terminals in striatum and the intrinsic properties of MSNs. These experiments were done *ex vivo* in order to localise pathological changes without interference from other neural networks. To this end we obtained simultaneous whole-cell recordings of striatal dMSNs and iMSNs in acute slices and confirmed that the excitability of dMSNs is increased following loss of DA (Fig. 12). Moreover, this finding suggested that the increase in input resistance in dMSNs is not due to a loss of inputs *in vivo* but rather caused by pathological alterations in these neurons themselves.

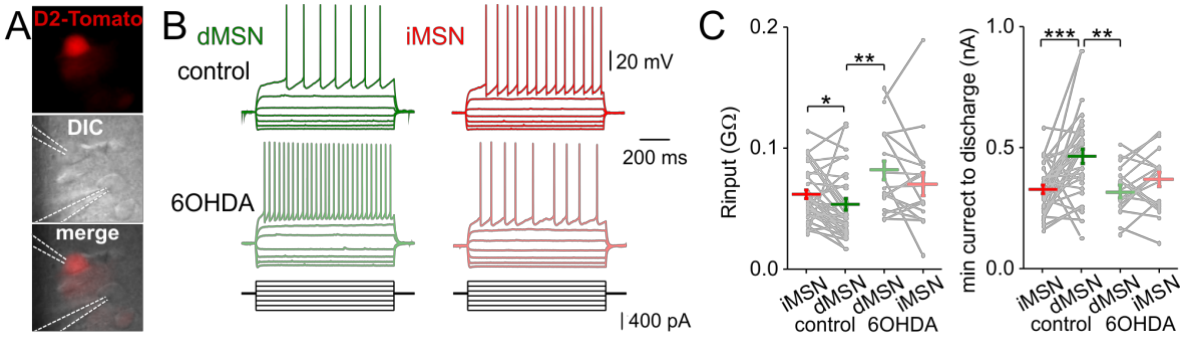

Fig. 12) The excitability of dMSNs, but not iMSNs, is increased in a mouse model of PD. (A) Simultaneous whole-cell recordings from dMSNs and iMSNs were obtained *ex vivo* in D2-tdTomato mice. (B) Representative example recordings illustrating how a series of hyper- and depolarising step currents was applied to dMSNs and iMSNs in order to extract the input resistance in control and in the 6-OHDA mouse model of PD. (C) Summary graphs of the input resistance and minimum current required to induce an action potential in MSNs in control and in PD.

We also addressed whether the loss of laterality encoding in DA depleted mice is caused by cell type-specific pathological processes affecting the projections from S1 to striatal dMSNs and iMSNs in terms of synaptic strength, receptor composition, or short-term plasticity. Local virus injections (AAV2-CamKIIa-ChR2-YFP) in S1 induced the expression of ChR2 in cortical projection neurons and enabled us to activate S1 terminals *ex vivo* while recording the responses of striatal MSNs (Fig. 13A). These experiments were all performed in the presence of gabazine to isolate the excitatory postsynaptic potentials and currents (EPSPs and EPSCs) elicited by the optogenetic stimulation of S1 axon terminals.

dMSNs and iMSNs were found to respond with equal amplitudes to S1 inputs in control, 6-OHDA, and following bath application of DA blockers (DAB, Fig. 13B). We characterised

these responses in more detail and revealed that in dMSNs, specifically, the receptors mediating the responses to S1 inputs were affected by the loss of DA. In control, dMSNs had a higher AMPA to NMDA ratio than adjacent iMSNs, whereas this difference was lost in the Parkinsonian state. Hence, similar to our previous findings, the loss of DA reduced the differences between dMSNs and iMSNs by rendering the receptor composition of dMSNs more similar to the AMPA to NMDA ratio of iMSNs. When studying the short-term plasticity of S1 corticostriatal synapses, we observed that the responses of both dMSNs and iMSNs to 20 Hz stimulation were less depressive following the 6-OHDA mediated loss of DA than in control. In contrast, acute blockade of DA by bath application of D1- and D2-receptor antagonists in slices of control mice rendered the responses of dMSNs and iMSNs more depressive. The opposing results of acute blockade of DA, compared to the chronic loss of DA in the mouse model of PD, point toward compensatory processes that might affect the cellular and the network level. Treating mice with L-DOPA increased the sensory responses in both dMSNs and iMSNs and partially restored the sensory discrimination.

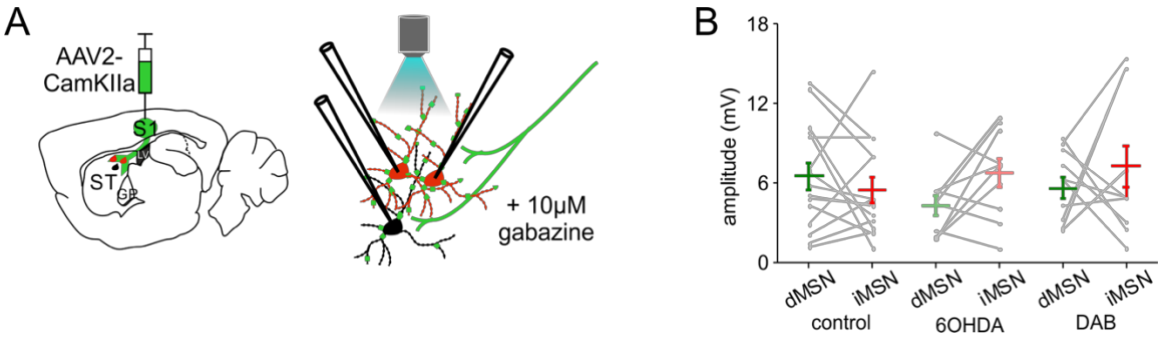

Fig. 13) ***Ex vivo*** **responses of MSNs to optogenetic stimulation of S1 inputs.** (A) Left: scheme of viral injection of AAV2-CamKIIa-YFP-ChR2 in S1 in D1- or D2-tdTomato mice. Right: simultaneous whole-cell recordings of identified dMSNs and iMSNs were acquired in the presence of gabazine in the striatum. S1 terminals were activated with blue LEDs by wide-field stimulation. (B) Amplitudes of corticostriatal EPSPs in simultaneously recorded dMSNs and iMSNs in control, 6-OHDA and after blockade of DA in control mice.

In summary, paper I provides novel insights into the mechanisms underlying the largely neglected sensory deficits in PD. This study shows that it is primarily dMSNs that encode the laterality of whisker information and that this sensory discrimination is lost in the DA depleted state. Pyramidal cells in S1 maintain their ability to distinguish between ipsi- and contralateral somatosensory inputs in 6-OHDA treated mice, which strengthens the hypothesis that the pathological changes associated with DA loss occur primarily at corticostriatal synapses and in striatal dMSNs. The effects on dMSNs include an increased excitability and changes in their glutamate receptor expression.

4.2 CELL TYPE- AND INPUT-SPECIFICITY OF CORTICO- AND THALAMO-STRIATAL SYNAPSES

Paper I, like numerous other publications on striatal inputs, solely focusses on MSNs without addressing striatal interneurons. Therefore, we were interested in exploring the responses of three types of interneurons to S1 inputs in **paper II**. Moreover, a second aim of this project was to include several structures projecting to the striatal microcircuit in order to create a map depicting the diverse excitatory inputs that drive striatal activity and to shed light on the properties of these synapses (Fig. 14).

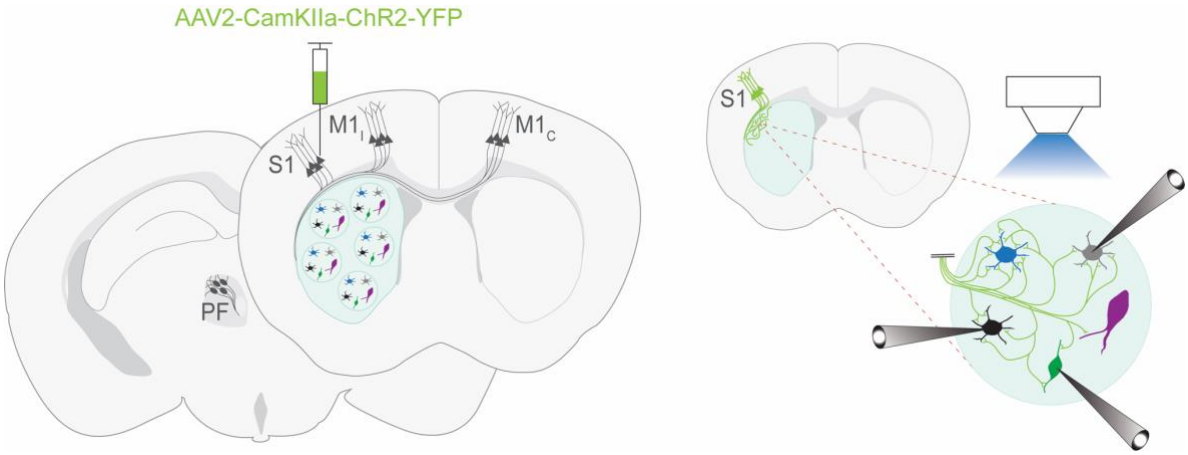

Fig. 14) The expression of ChR2 was induced by local virus injections in several brain structures that project to the striatum. Subsequently, simultaneous whole-cell recordings were obtained from different cell types while activating one of the inputs with optogenetics.

4.2.1 Corticostriatal inputs evoke cell type-specific responses in the striatum

First, we characterised the responses of striatal interneurons, as well as MSNs, to optogenetic activation of S1 afferents. We included three of the major interneuron classes - FSIs, LTSIs, and ChINs - which were targeted using the corresponding transgenic mouse lines that label these populations. All interneurons were recorded in parallel with adjacent, responding MSNs. Consequently, small responses (or a lack thereof) reflect true, cell type-specific differences that cannot be due to variability in virus injections, tissue preparation or other experimental conditions. We found that S1 input preferentially excites striatal MSNs and FSIs, whereas both LTISs and ChINs are targeted less frequently and with weaker synapses (Fig. 15).

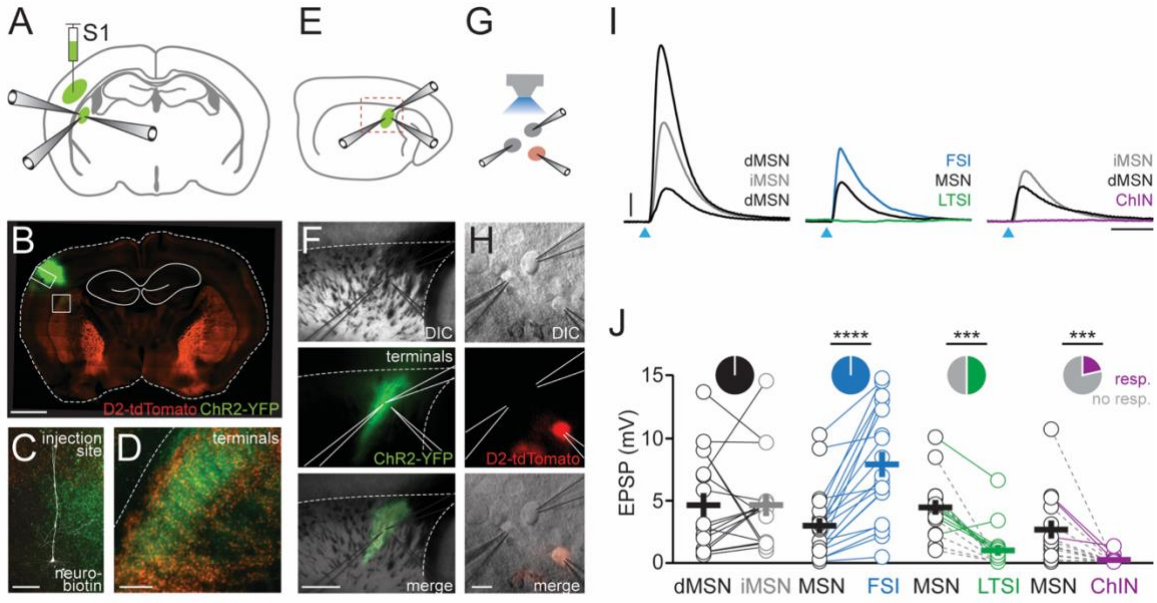

Fig. 15) S1 inputs preferentially excite striatal MSNs and FSIs. (A) Scheme and (B) confocal image of unilateral injections of AAV2-CamKIIa-ChR2-YFP in S1 in D2-tdTomato mice. (C) High magnification of cortex in (B) showing a neurobiotin-filled pyramidal cell (white) expressing ChR2-YFP in S1. (D) High magnification of the striatum in (B) showing the expression of ChR2-YFP (green) in the axon terminals derived from S1 and iMSNs (red). (E) Schematic of simultaneous whole-cell recordings in striatum within the area innervated by axons from S1 (green). (F) Triplet whole-cell recordings in striatum. Differential interference contrast (DIC, top), epifluorescent image of YFP-expressing S1 axon terminals (centre), and overlay (bottom) of a parasagittal slice with recording pipettes. Scale bar: 500 µm (G) Schematic of recordings: tdTomato-positive and tdTomato-negative neurons were recorded simultaneously, while S1 fibres were stimulated with blue light. (H) DIC and fluorescent images of simultaneous patch-clamp recordings from td-Tomato positive (iMSNs) and td-Tomato negative (putative dMSNs) neurons. Scale bar: 10 µm (I) Relative strength of EPSPs in striatal neurons evoked by activation of S1 inputs in the presence of gabazine. Simultaneously recorded responses are overlaid. Note: the DA receptor subtype of 'MSN' is unknown. (J) Summary graph of EPSP amplitudes obtained as shown in A-I. Solid lines indicate paired recordings in which both neurons responded, dashed lines indicate pairs in which only one neuron responded. The proportion of responding cells is shown in pie charts.

4.2.2 Corticostriatal pathways are input-specific

Next, we repeated this set of experiments for corticostriatal inputs originating in the primary motor cortex (M1), which is mainly involved in planning voluntary movements. M1 differs not only functionally from S1, but also in its brain-wide connectivity patterns. Mapping the responses of striatal neurons to two distinct cortical regions addressed the long-lasting debate surrounding whether all cortical areas target the striatum uniformly and therefore can be

pooled, or whether they need to be dissected individually as suggested by Wall (Wall *et al.*, 2013). In our hands, input from M1, in contrast to S1, evoked larger responses in dMSNs than in iMSNs and the short-term plasticity also varied depending on the activated input. These data confirm that the excitation provided by different cortical areas is not uniform but depends on the cortical origin (Fig. 15). Therefore, future studies on the corticostriatal pathway will benefit from a consideration of this cortical input specificity.

Wall also reported that neurons in M1 preferentially innervate iMSNs while those in S1 provide biased input to dMSNs (Wall *et al.*, 2013). However, this was not reflected in the synaptic strengths observed in our experiments. Together, these findings suggest that a great number of neurons in M1 provide less excitation to iMSNs than the relatively smaller number of M1 neurons that targets dMSNs.

4.2.2 Hierarchical input strength targeting interneurons

Interestingly, the response pattern of striatal interneurons to optogenetic activation of M1 were similar to those observed for S1. Both cortical structures excited FSIs more than MSNs, whereas LTSIs and ChINs received weaker and sparser inputs than MSNs (Fig. 16, 17). These data suggest a hierarchical organisation of input strength for M1 and S1 input: FSIs are at the top and receive the strongest excitation; LTSIs receive less excitation than FSIs; followed finally by ChINs, who receive the least excitation from a shared input structure. The amplitude of the excitation observed in projection neurons, MSNs, positions them in between FSIs and LTSIs. This cell type-specific order of input strength has also been observed *in vivo* when stimulating corticostriatal projections (Sharott *et al.*, 2009). Additionally, this pattern has not only been repetitively observed for corticostriatal pathways but also for thalamocortical ones (Gibson, Belerlein and Connors, 1999; Beierlein, Gibson and Connors, 2003; Cruikshank, Lewis and Connors, 2007). Altogether, these data raise the possibility that this emerging hierarchy of cell type-specific input strength from ipsilateral long-range projections constitutes a major organisational principle of the CNS.

4.2.3 Inputs from contralateral cortex (IT-tract) differ from ipsilateral input

Unlike S1, M1 projects robustly to both ipsi- and the contralateral striatal hemispheres. The axons innervating the contralateral striatum are, however, all derived from IT-tract neurons, whereas ipsilateral projections comprise both PT- and IT-type fibre terminals. Previous studies on the IT-tract resulted in a controversy relating to whether IT-tract inputs are biased towards

dMSNs or not (Lei *et al.*, 2004; Kress *et al.*, 2013). In our recordings, activation of contralateral M1 inputs evoked equally large responses in dMSNs and iMSNs, supporting the idea that this pathway does not favour either population of MSNs. Moreover, triplet recordings including interneurons showed that this input does not follow the same hierarchical pattern as reported for ipsilateral inputs. Compared to ipsilateral inputs, IT-tract neurons excite dMSNs and iMSNs, FSIs, and LTSIs more equally (Fig. 16). IT-tract inputs from M1 also emerged as the most powerful source of excitation for striatal LTSIs, indicating that this neuron population might be particularly important for integrating bilateral cortical motor commands. ChINs were selectively avoided by IT-tract inputs, demonstrating that striatal afferents form their synapses in a highly cell type-specific manner. The properties of ipsilaterally projecting IT-tract axons have neither been addressed in this study, nor in the one of Kress and remain an interesting subject for future studies (Kress et al., 2013).

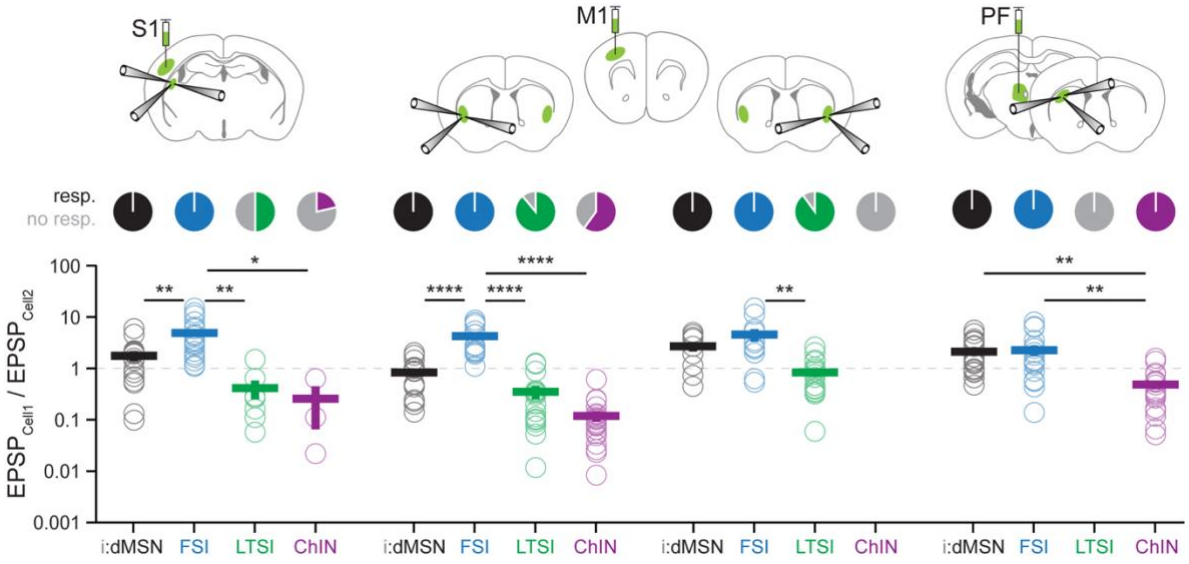

Fig. 16) The relative synaptic strength of four inputs to five striatal cell types. Top: schematic of the four inputs, including their injection sites in S1, M1, and PF and their corresponding recording sites in striatum. Centre: pie charts illustrating the proportion of responding neurons. Bottom: the relative strength of responses in iMSNs compared to dMSNs and FSIs, LTSIs, and ChINs compared to MSNs. Each circle represents the ratio of the EPSP amplitudes of two simultaneously recorded responding neurons.

4.2.4 Thalamocortical inputs vs corticostriatal inputs

Thalamic inputs originating in PF differed strongly from all cortical inputs as they excited iMSNs more than adjacent dMSNs; as predicted by anatomical studies, they did not target

striatal LTSIs; and they provided the most reliable and strongest input to ChINs of all input structures tested (Fig. 16, 17). Moreover, MSNs displayed a significantly larger NMDA component in their responses to PF inputs compared to cortical ones. NMDA receptors are blocked at negative voltages and often depend on coinciding inputs that evoke a local depolarisation by opening nearby AMPA receptors. Since the synapses of PF and cortex are intermingled at the distal dendrites of MSNs, synchronous inputs from these two structures might be necessary for releasing NMDA receptors from their blockade (Somogyi, Bolam and Smith, 1981; Smith and Bolam, 1990). Once NMDA receptors are activated though, they could amplify and prolong the excitation of MSNs substantially. Accordingly, inputs from PF might not only impact the firing of striatal ChINs, but also increase the activity of MSNs, and future studies on thalamic inputs might benefit from assessing ChINs and MSNs together. Besides the PF, the CL also contributes to the thalamostriatal projection, but this input has not been included in the present study.

4.2.5 From synaptic and cellular properties to the function of neuronal populations

Except for input resistance, dMSNs and iMSNs are characterised by highly similar electrophysiological properties and they are equally excited by inputs from S1, as shown in paper I. Here, we expand these findings by showing that they also share inputs from M1 and PF and that they display similar synaptic properties at cortico- and thalamostriatal synapses, respectively. The fact that both dMSNs and iMSNs responded reliably to all tested inputs supports the notion that the direct and indirect pathways are co-activated by striatal afferents and act together to guide the execution of movement (Tecuapetla *et al.*, 2016). In contrast, the proposed concept that movement initiation is associated with a selective increase in the activity of dMSNs (or in iMSNs during movement termination) is not supported by our findings (Kravitz *et al.*, 2010). According to our data, the selection of appropriate movements might rather be achieved by afferents that innervate both dMSNs and iMSNs but display a bias towards one of the two populations. The preferential excitation of dMSNs by M1 inputs might constitute the neural substrate of a bias that promotes movement initiation. Correspondingly, inputs from PF, that favour iMSNs over dMSNs, might enable the suppression of competing motor programs. It is important to note that, in our work, we focused on the direct monosynaptic excitation of dMSNs and iMSNs. There are, however, additional factors that are likely to influence the activation of MSNs such as the GABAergic connections between MSNs and striatal interneurons.

FSIs are defined by electrophysiological properties such as a short membrane time constant, narrow action potentials, and a fast AHP, that are all thought to increase the temporal precision of their firing. These features are crucial for mediating precisely timed feed-forward inhibition onto MSNs. The synaptic properties reported in this study include a lack of NMDA receptors and the expression of a particularly fast subtype of AMPA receptors, both of which further sharpen the spike timing of these neurons and support their time-locked functions. FSIs showed the largest responses to all inputs compared to the other striatal cell types, suggesting that all afferents recruit feed-forward inhibition, even though thalamic inputs are less efficient than cortical ones according to our data.

LTSIs and ChINs both have relatively depolarised membrane potentials, rendering them highly responsive to weak inputs. PF reliably activated ChINs, but did not provide input to LTSIs. In contrast, inputs from contralateral M1 constituted the strongest driving force for LTSIs, while specifically not innervating ChINs. These findings demonstrate that striatal inputs are highly cell-type specific. Moreover, they support the hypothesis that ChINs process primarily attention- and salience-related information, rather than direct motor commands, while the opposite is shown for LTSIs. Since the role of LTSIs is not yet fully understood, these results will guide future research related to their function.

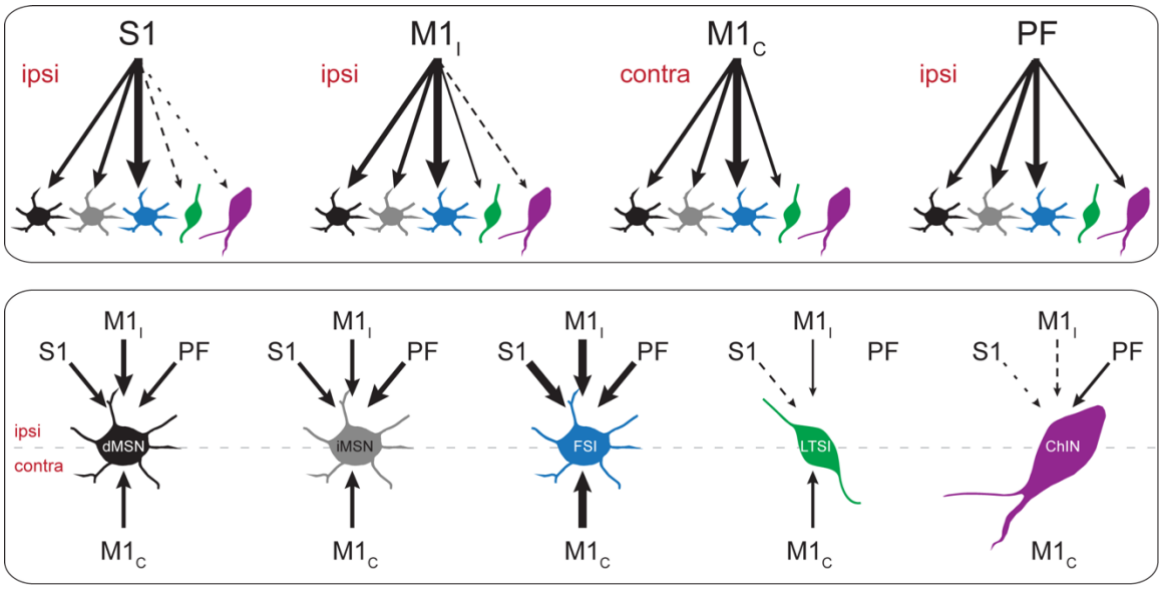

Fig. 17) Mapping the strength and connection probability of four inputs targeting five striatal neuron populations. Top: scheme illustrating which cell types are most robustly excited by each input. Bottom: scheme illustrating which input is most robustly exciting each striatal cell type. The thickness of the arrows reflects the synaptic strength, while dashed lines indicate connections that occur less frequently.

In summary, the data of paper II show that cortico- and thalamostriatal afferents target the striatal microcircuit in an input- and cell type-specific manner. Accordingly, each striatal neuron class receives a unique set of information that is integrated over a particular time scale. Understanding when and how striatal neurons are activated is crucial for revealing their roles within the striatal network.

4.3 CREATING THE STRIATAL MICROCIRCUIT *IN SILICO*

The aim of **paper III** was to construct a near full-scale model of the mouse striatal network to provide an open-source platform for testing new hypotheses on striatal function.

The striatum has been studied extensively, which has provided detailed information on its cell types, its microcircuit and afferent innervation, and its involvement in behaviour and disease. The data resulting from these highly diverse studies is, however, rarely combined. Therefore, in creating this *in silico* model of the striatum, we were particularly interested in including anatomical, morphological, and electrophysiological data of different striatal neuron classes and combining this with their intrastriatal and afferent connections.

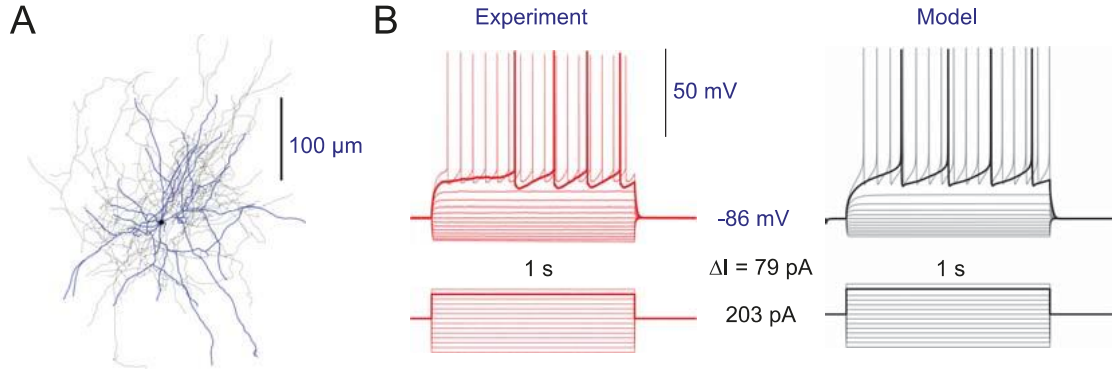

Fig. 18) Modelling dMSNs based on experimental data. (A) Reconstruction of the morphology of a dMSNs including dendrites (blue) and axon collaterals (grey). (B) Sub- and suprathreshold responses of a dMSNs obtained experimentally *ex vivo* (red) and in the model (black).

4.3.1 Modelling different striatal neuron populations

Five different striatal neuron populations were included in this model, comprising both striatal projection neurons (dMSNs and iMSNs) and the three types of striatal interneurons (FSIs, LTSIs, and ChINs) described in paper II. Together, these cell types account for >98% of all striatal cells. Each of these cell types was modelled based on detailed morphological reconstructions specifying, among other things, the location of synapses, the shape of the somata and dendritic arbour, and axonal ramifications. Electrophysiological recordings were used for extracting the electrical properties of the membranes of these neurons and for modelling their firing patterns. Moreover, information on ion channel subtypes was implemented. These single-cell models were all optimized and validated to closely reflect the properties of their natural counterparts (Fig. 18).

4.3.2 Building the striatal microcircuit

Subsequently, the models of these five populations were placed with appropriate densities within the simulated volume. Additionally, chemical and electrical synapses were introduced to reflect the connectivity pattern within the striatal network, as well as inputs from extra-striatal sources including cortex, thalamus, and the SNc (Fig. 19, Fig. 20). The synaptic properties of these connections were adjusted to mimic the natural failure rates and to follow the short-term plasticity observed *ex vivo*.

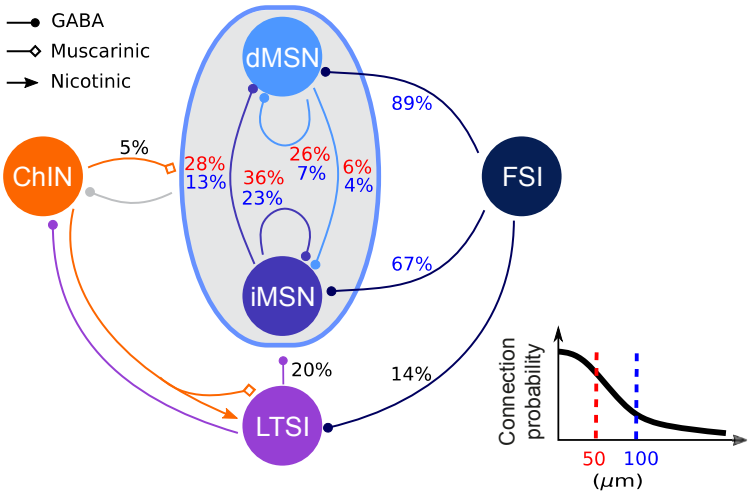

Fig. 19) The striatal microcircuit. The connections between five striatal cell types were modelled. Connection probabilities within and between neuronal subtypes are shown by respective arrows; red numbers correspond to the connection probabilities for somata 50 µm apart from each other, while blue numbers correspond to a distance of 100 µm. GABAergic, muscarinic and nicotinic synapses were incorporated into the model.

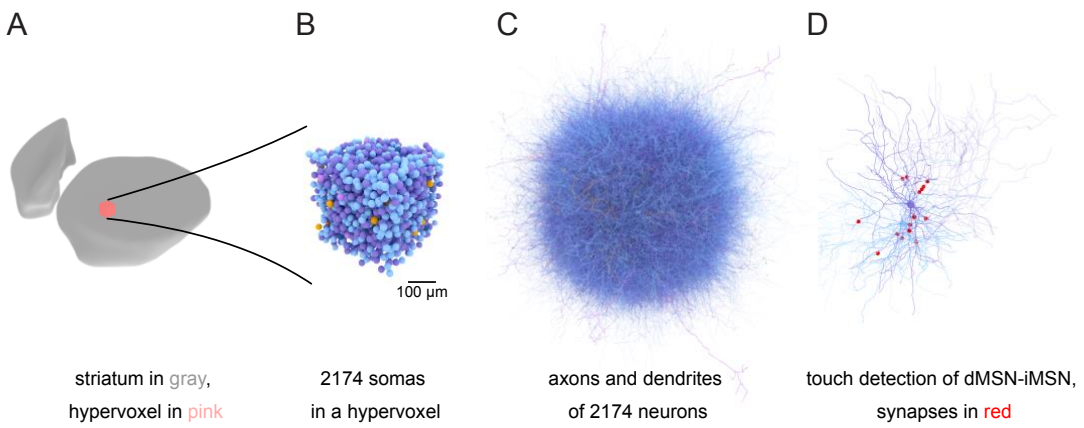

Fig. 20) The placement of synaptic contacts in the *in silico* model. (A) The striatum (grey) is divided into hypervoxels (pink) and synapses are placed with a touch detection algorithm that runs on all hypervoxels in parallel. (B) High resolution of a hypervoxel comprising the somata of approx. 2174 neurons. (C) The axons and dendrites of these neurons in relation to the hypervoxel comprising their somata. (D) Touch detection of two neurons. Synapses are indicated in red.

4.3.3 Simulation of the network

Overall, the simulation comprised 10,000 neurons, their local connectivity, and their glutamatergic and dopaminergic long-range inputs, which were all integrated into the microcircuit. The afferent inputs could be driven at physiological baseline levels during which MSNs fired sparsely, while spontaneously active neurons such as ChINs and LTSIs showed higher levels of activity (Fig. 21). The observed firing patterns matched *in vivo* recordings of the respective neuron types (Sharott *et al.*, 2009; Thorn and Graybiel, 2014; Sippy *et al.*, 2015). Moreover, all inputs could be modulated to mimic for example motor commands arising in M1 or dopaminergic inputs from the SNc. As observed *ex vivo* (in paper II) and *in vivo*, cortical inputs increased the firing of MSNs and FSIs without altering the firing of ChINs (Sippy *et al.*, 2015). In contrast, DA inputs selectively increased the firing of dMSNs, while decreasing the firing of iMSNs.

The model incorporates an unprecedented level of data on the properties of the striatal microcircuit in one platform. Yet, the model can be further improved and novel findings can be implemented. Future additions might incorporate the remaining striatal interneuron classes, such as TH- or 5HT$_{3A}$-expressing interneurons, according to the availability of detailed experimental data characterising their morphological, intrinsic and synaptic properties. Moreover, different striatal compartments can be implemented. The current platform mimics a

matrix component in the dorsal striatum but about 15% of the striatum comprise striosomes, and this fraction could be included in future versions. Additionally, Fino and colleagues have shown that FSIs and LTSIs exhibit region-specific differences between the dorsolateral and dorsomedial striatum, which need to be considered when expanding the current platform (Fino *et al.*, 2018). Finally, this platform can serve as a valuable tool for mimicking diseases such as PD and their underlying mechanisms and for testing novel hypotheses.

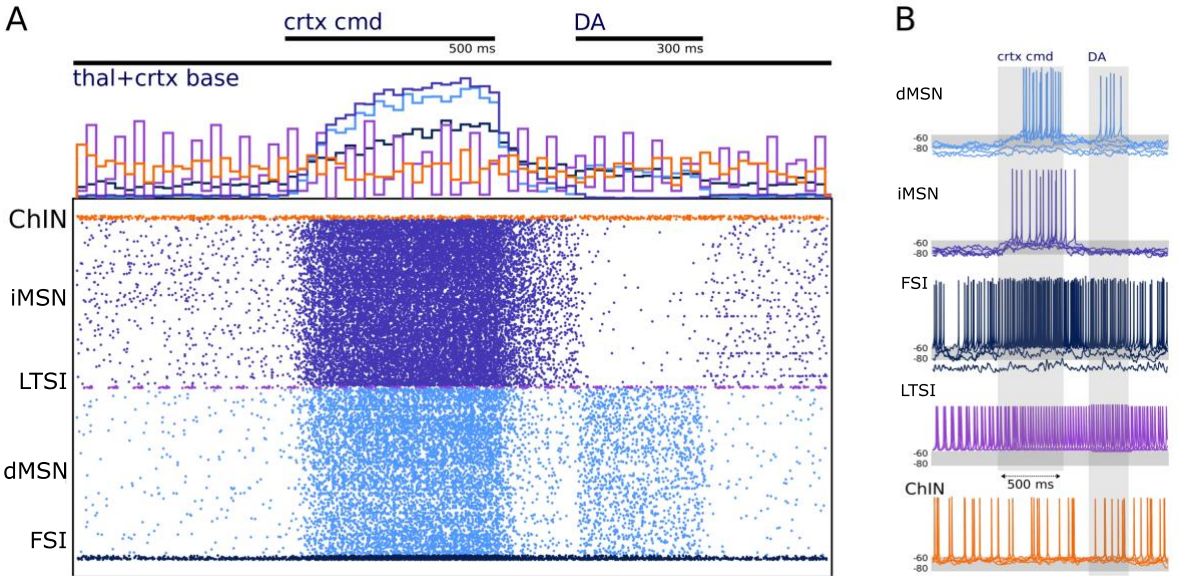

Fig. 21) Simulation of the striatal network. (A) The activity of different striatal neuron classes is shown in raster plots (bottom) and in overlaid spike histograms (centre), while the timing of glutamatergic and dopaminergic inputs is indicated with lines (top). (B) Example traces showing the responses of five simulated striatal cell types to glutamatergic baseline input, to a cortical command signal, and to stimulation of DA afferents.

In summary, this study provides a shared simulation platform of the striatal microcircuit, which integrates data from a wide range of biological levels. This model can be used to generate new hypotheses on striatal function and network phenomena. Moreover, this platform provides a tool to study questions that are difficult to address experimentally.

5 CONCLUSIONS & PERSPECTIVE

The basal ganglia are responsible for the appropriate execution of movements, which requires the integration of vast and diverse information about our intentions, internal state and our surroundings. This integration is performed by the striatum, the entrance nucleus to the basal ganglia. The aim of this thesis was to characterise the functional organisation of the pathways that provide these inputs to the striatum.

A major focus of the work in this thesis is the synaptic properties that shape the transmission between presynaptic axon terminals entering the striatum and their postsynaptic neuronal targets. We restricted our studies to excitatory inputs, which account for the vast majority of striatal inputs, and asked whether the incoming information is transmitted uniformly across these synapses. One essential prerequisite for answering this question was to interrogate a variety of presynaptic input structures and different postsynaptic cell types in the striatum. To this end, we chose both cortical (S1, M1) and subcortical (PF) input structures that are known to project to the striatum. At the striatal level, we studied both projection neurons (dMSNs and iMSNs) and local interneurons (FSIs, LTSIs, ChINs). We assessed the connectivity, synaptic strength, receptor composition, short-term plasticity, and susceptibility to PD of these pathways and provide a comprehensive map of the connectivity patterns of inputs to the striatum including a detailed characterisation of their synaptic properties.

One of the main findings of this thesis is that the connections between striatal afferents and their neuronal targets are not uniform but in fact highly diverse. We observed that striatal inputs target the striatal microcircuit in a highly cell type-specific manner and that one input might evoke large, fast, reliable responses in one population (PF → FSIs), and reliable, but slower responses in another population (PF → ChINs), while exclusively not contacting a third class of striatal neurons (PF → LTSIs). Moreover, we reported a high degree of input-specificity and show that the responses of one striatal neuron population can be characterised by strong AMPA component and short-term depression in response to one input (S1 → dMSNs), while the same cell type responds with a prominent NMDA component and facilitatory responses to another input (PF → dMSNs). Overall, we revealed a highly selective organisation of excitatory striatal afferents, which is determined by both the presynaptic input structure and the postsynaptic cell type.

Furthermore, we identified two general rules that govern the connections and the synaptic properties of inputs targeting striatal interneurons. First, the interneuron subtypes were each

found to display a distinct profile of glutamate receptor expression. For example, responses in FSIs were predominantly mediated by AMPA currents, regardless of the input, whereas all responses in ChINs were largely based on the opening of NMDA receptors. The expression of cell type-specific receptors might contribute to the function of these interneurons in the striatal microcircuit (Owen, Berke and Kreitzer, 2018). These cell type-specific receptor compositions have also been observed in other brain areas, which strengthens the notion that the expression of glutamate receptors in interneurons is defined by cell type, not input pathway (Jonas *et al.*, 1994; Matta *et al.*, 2013; Camiré *et al.*, 2018). The NMDA and AMPA currents of LTSIs were too small to be robustly extracted with our methods, but it will be interesting to assess if they too display a distinct receptor profile, regardless of input. In contrast to interneurons, the NMDA to AMPA ratio of MSNs was input-specific, suggesting that synaptic integration in projection neurons is more complex.

Second, we identified a hierarchy in the relative strengths of cortical inputs to striatal interneuron types, which was remarkably constant for afferents from ipsilateral S1 and M1. Overall, the responses of the three striatal interneuron populations followed a pattern whereby FSIs showed the largest and most reliable responses to both cortical inputs. In contrast, LTSIs consistently responded with smaller amplitudes than MSNs, and the cortical afferents did not target all LTSIs within the innervated area in the striatum. Finally, the responses of ChINs were the sparsest and the weakest for both inputs. The functional strength of these inputs correlated with the anatomical number of synapses that corticostriatal afferents form with each of these neuron populations (Wilson, Chang and Kitai, 1990; Lapper and Bolam, 1992; Kita, 1993; Doig *et al.*, 2014). More studies are needed to test whether this arrangement also applies to corticostriatal inputs originating in other cortical areas. Yet, the remarkable similarity of thalamocortical pathways, which were found to follow the same hierarchy in terms of input strength and connection probability, suggests that this pattern constitutes a widespread organisational principle of the CNS.

dMSNs and iMSNs shared almost all intrinsic properties and displayed the same receptor composition and short-term plasticity for most, if not all, inputs. On the other hand, they also critically differed from each other in terms of susceptibility to PD and input strength for a subset of the tested inputs. For example, dMSNs showed larger responses to M1 inputs than iMSNs. These differences were often pathway-specific and they have the potential to crucially impact striatal function by promoting the activity in the direct pathway, which in turn facilitates movement. Because of these occasional, but critical, differences, striatal inputs targeting MSNs cannot be pooled and inputs to both subpopulations of MSNs need to be addressed separately.

In recent years, novel striatal input structures have been identified. These inputs include the reticular nucleus of the thalamus (TRN), the pedunculopontine nucleus (PPN) in the brainstem, the GPe, and inhibitory neurons in cortex (Mallet *et al.*, 2012; Rock *et al.*, 2016; Melzer *et al.*, 2017; Klug *et al.*, 2018; Assous *et al.*, 2019). The PPN is the only structure of these inputs that provides excitatory input to the striatum and targets FSIs and ChINs, while inputs to MSNs have been shown to be sparse or absent (Klug *et al.*, 2018; Assous *et al.*, 2019). The glutamate receptors mediating striatal responses to this brainstem input have not been assessed yet. Therefore, inputs from the PPN constitute an excellent candidate to validate (or disprove) the hypothesis that the glutamate receptor composition is defined by the striatal interneuron type, but not by the input structure. The remaining input areas provide primarily long-range inhibition to the striatum. The TRN innervates specifically FSIs without forming contacts with MSNs (Klug *et al.*, 2018). Neurons in the GPe have been shown to contact striatal MSNs, FSIs and ChINs. Interestingly, activation of GPe terminals inhibited FSIs five times more than MSNs, while the inhibitory responses recorded in ChINs were significantly smaller than those in adjacent MSNs (Klug et al., 2018). The relative strength of this inhibitory input matches well the hierarchical pattern observed for excitatory corticostriatal and thalamocortical inputs. Inhibitory inputs from cortex have been found to target MSNs and ChINs and their connectivity was also input- and cell type-specific, as observed for the excitatory inputs described in this thesis (Melzer *et al.*, 2017). Yet, none of these studies addressed the synaptic properties of these connections, nor the responses of LTSIs to these inputs. Moreover, inputs from the CL have not been characterised functionally although this pathway was identified anatomically about a century ago. These aspects need to be addressed in the future to acquire a more complete understanding of the inputs controlling striatal activity. Additionally, it is currently only partially understood how striatal neurons respond to coinciding inputs from different neural structures. Anatomically, it is well established that numerous input structures converge onto striatal neurons (Kincaid, Zheng and Wilson, 1998; Ding, Peterson and Surmeier, 2008; Huerta-Ocampo, Mena-Segovia and Bolam, 2014). Synchronous activity in distinct afferent fibres frequently evokes sub- or supralinear summation and induces synaptic plasticity. In our *in silico* model this was addressed by implementing a baseline level of cortical and thalamic inputs. However, there are currently only a few studies which have investigated the neuronal computation performed by striatal neurons in response to coincident inputs (Mendes *et al.*, 2020). Therefore, more studies are needed to reveal how each striatal cell type integrates different combinations of converging inputs.

Besides these additional input structures, the striatum is also composed of more classes of interneurons than the three types included in this thesis. For some of the recently identified

interneuron classes, including the ChRNa2- and 5HT$_{3A}$-receptor expressing neurons, little is known about the inputs that activate or inhibit them. Other interneuron types, such as the THINs, the NPY-NGF, and the NPY-PLTS have been studied in more detail and striatal afferents were shown to evoke input- and cell type-specific responses in these neurons as well (Assous *et al.*, 2017). Interestingly, this study has also revealed that excitatory inputs are sufficient for activating feed-forward circuitry within the striatum, including a disynaptic inhibition of LTSIs as a result of thalamic inputs that excite THINs. Thus, despite the lack of PF inputs targeting LTSIs directly, the activity of these interneurons is still modulated by PF inputs. This finding highlights the importance of combining our understanding of striatal inputs with the local interactions between striatal neurons in future studies. In the meantime, the interplay between striatal inputs and local network interaction can already be studied in the *in silico* model.

In this context, the work presented here takes the first step in characterising the functional properties of BG inputs that target striatal neurons, and uncovers a highly selective organisation of these pathways. The resulting map can be used for identifying candidate pathways in future studies, that aim to reveal the circuits underlying behaviours involving the BG.

6 ACKNOWLEDGEMENTS

My PhD studies have been a wonderful experience - thanks to the many people, who have accompanied and supported me throughout this time.

First of all, I would like to thank you, **Gilli**, for offering a lot of freedom during my PhD but also reliable support whenever needed. From the first day I walked into your lab, you have always been solution-focused, taught what's needed and most pragmatically handled every situation to ensure the best for everyone in your lab - while also always being available for hummus and Franziskaner – Toda!

I would like to thank my co-supervisors, **Dinos Meletis** for all the fruitful collaborations and **Lennart Brodin** for helping us to renew the *'antique'* equipment for the patch clamp course.

Working alongside (and sometimes with) **Sten Grillner** and **Abdel El Manira** has been very inspiring and has provided an excellent environment for learning how to approach electrophysiological and scientific questions.

Big thanks to **Gilberto Fisone** for being very supportive whenever it was needed!

Thanks, **Udo Kraushaar**, for teaching me how to patch and for introducing me to Igor ;) I couldn't have been better prepared for this PhD.

Thank you, **Elin,** our good soul, for your reliable work, your relentless effort to create a good lab environment and your company throughout all the years.

A big thanks to all the past and present lab members. **Maya**, my lab mate in crime & whatsapp #1, so different and yet so close, I know I can always count on you; **Matthijs**, no one can beat your readiness to help others, thanks for being such an amazing team player. **Roberto**, it's destiny that we're crossing paths again, I'm curious where we meet next! **Anja & Zach,** it's been fun to have you in the lab, thanks for chats & coffees!

Giada, Ste, Eva & Carina, we never run out of topics & activities, thanks for endless laughs at work, Pino's, and on the walls and slopes of various countries!

Shreyas, thanks for all the rounds of coffee while teaching & I hope all your future plans will work out smoothly ;) **Mani**, thanks for all the fun throughout the years. **Ila**, where's the party? **Sal**, you hadn't met me yet, but you had already bought me opera tickets – thanks for the welcoming start you gave me, all the laughs, and the cookies! **Caitlin, Mike, Laura, Paul,**

Susanne, Pawel, Jessica, Andreas Kalckert, Lovisa, Ramon, Henrike, Carmelo, Roberto, Teresa, Haizea, Pierre, Irene, Leander, Moritz, Sofie, Iakovos, Cantin - inside & outside of work, it's been fun with you! A big thanks also to all the past and present **Fika-table** members for coffee, chats, cakes, and keeping this wonderful tradition alive.

And, of course, a huge thanks to the 'life outside', **VV & Erik**, thanks for non-stop Swedish-Bavarian fun - dahoam is koa ort, des is a g'fui! **Linda**, egal ob bergauf oder bergab, wir laufen gemeinsam durch's Leben; **Marianne**, Quatschen, Training, gutes Essen, was braucht man mehr? **Katrin, Julia**, **Marina & GizGiz,** round #2 for you guys, so fern und doch so nah, looking forward to all our next adventures! **Jana**, wo wäre ich bzw. was wüsste ich nur ohne dich?

Last, but not least, vielen lieben Dank an meine Eltern, **Mats und Sonja**, und meine kleine-große Schwester, **Julia**, für die ununterbrochene Unterstützung und das felsenfeste Zutrauen, tack ska ni ha! **Laurence**, I couldn't have wished for a better partner by my side. Thanks for everything and more!

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