UNIVERSITÀ DI PISA

MSc programme in physics

Federico Vincenzo Mastellone

Understanding oscillopathies in the Cortico-Basal Ganglia-Thalamocortical loop: an approach with three heterogeneous populations of Kuramoto oscillators

final project

Supervisor:
Prof. E. Cataldo

Co-Supervisor:
Prof. A. Mazzoni

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Introduction

Chapter 1

Background

1.1 The Basal Ganglia Complex

Among the various complex structures one can find in a mammal's brain the Basal Ganglia **(BG)** is one of those whose basic anatomy and connectivity hasn't ran into much change in half a billion years [1] [2].

It is located at the base of the forebrain and it consists of several nuclei; these nuclei form a highly *non linear network* so that each nucleus projects, somehow, to itself and the others. Some of these nuclei also project and receive projections from structures outside the BG — the *Striatum* and the *Globus Pallidus* are an example, being connected to the *Thalamus* and the *motor Cortex*.

One question rapidly arises: *why had this complex been preserved during evolution? What is its purpose?*

The BG are principally involved in the selection and implementation of purposeful actions in response to external and internal cues. This means that this structure is involved in those tasks in which a facilitation or a suppression of a movement is required. On top of that, it is involved in a series of fundamental non-motor behaviours such as: *emotions*, *language*, *procedural learning* and last but not least *decision making* [3]. It is worth adding that *Dopamine* — a *neurotransmitter* which is involved in the processing of reward after the completion of a task — is produced in the BG and plays a crucial role in controlling motor functions and in learning

new motor skills.

1.1.1   Anatomy

From a general point of view, the BG complex — such as any complex in the brain — consists of some input nuclei, some output nuclei and some internal nuclei whose role is that to process the signals incoming in the input nuclei.
Briefly, this is the list of nuclei composing the Basal Ganglia:

- The *Striatum* $\longleftrightarrow$ **(Str)**, which is formed by

  1. *Putamen*
  2. *Caudate nucleus*

- The *Globus Pallidus*, generally divided into

  1. the *internal* part $\longleftrightarrow$ **(GPi)**
  2. the *external* part $\longleftrightarrow$ **(GPe)**

- The *Substantia Nigra*, consisting of

  1. its *Pars Compacta* $\longleftrightarrow$ **(SNc)**
  2. its *Pars Reticulata* $\longleftrightarrow$ **(SNr)**

- The *Subthalamic Nucleus* $\longleftrightarrow$ **(STN)**

Input nuclei

The **Striatum** is the major input structure of the Basal Ganglia receiving projection from the Thalamus and pretty much every cortical area. These cortical areas can be grouped into regions each related to a different function: *sensorimotor*, *cognitive* and *affective*; each of these sends excitatory projections to subregions of the Striatum forming distinct channels. There is evidence pointing out that these channels are overlapping and this may serve an integrative function between cognitive, motor and limbic signals deriving from cortical areas.
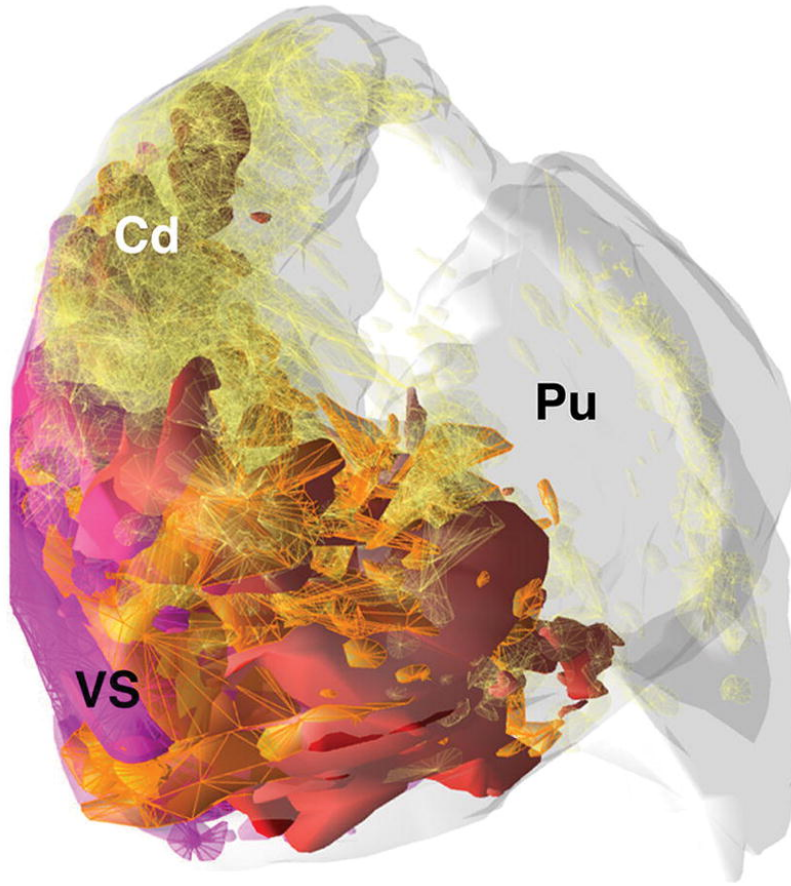
Figure 1.1: Three dimensional reconstruction of the Striatum including the *Caudate* **(CD)**, the *Putamen* **(PD)** and the *Ventral Striatum* **(VS)**. (Figure adapted from [4])

The Striatum also receives excitatory projections from the Thalamus which are topographically organized and overlapping in a similar fashion as the cortico-striatal projections. [2].

In addition to the inputs received from areas outside the Basal Ganglia, the Striatum also collects projections from the SNc and the *Ventral Tegmental Area* **(VTA)**; these afferent are extremely important since the main neurotransmitter released in the synaptic cleft is *dopamine*.

Among the total number of neurons in this structure, $N_{Str} = (2,791 \pm$
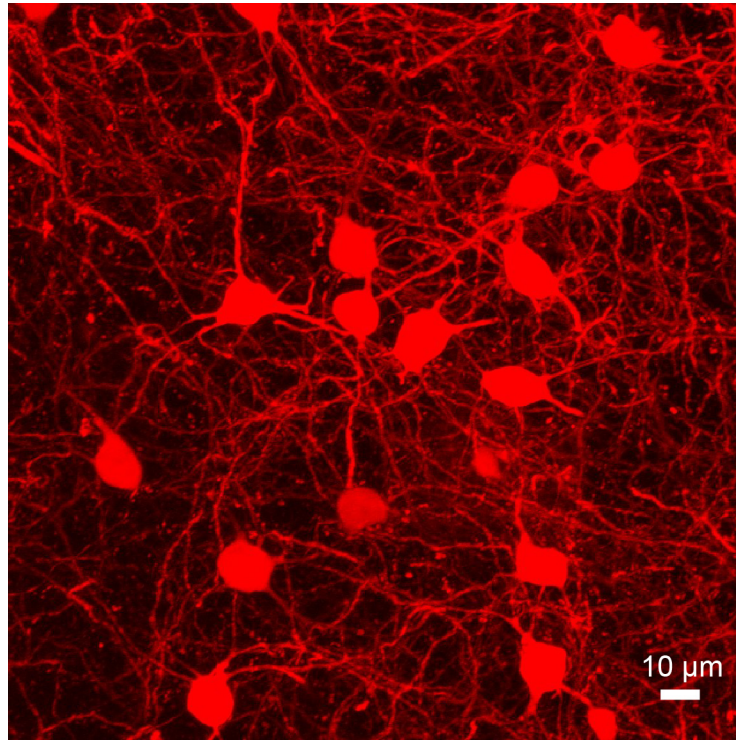
Figure 1.2: Confocal microscopy Z projection of medium spiny neurons (MSNs) in the mouse striatum.

$188) \cdot 10^3$ [5], 95% of them are *Medium Spiny Neurons* **(MSNs)** (Fig.1.2), a type of GABAergic inhibitory neuron, which can be divided in those having the D1-type dopamine receptors and those having the D2-type dopamine receptors; the difference consists in the chemical processes deriving from the *neurotransmitter-receptor* bound. D1 receptors initiates a second messenger-signaling cascade resulting in the depolarization of the post-synaptic MSN, while the same process results in the hyperpolarization of the post-synaptic MSN having the D2 receptor [6]. Hence, the role of D1 receptors is to enhance cortico-striatal influence and this is in contrast to the reduction mediated by D2 receptors.

Approximately half of the MSNs projects directly to the SNr or the GPi while the remaining half points to the GPe. Dopamine has thus a remarkable influence on the processing of the signals incoming from the Cortex

and travelling towards the other BG nuclei.

The other input nucleus in the BG is the **Subthalamic Nucleus** which, as the name suggests, is positioned just under the Thalamus and it's composed primarily of *glutamatergic neurons*, $N_{STN} = (13.56 \pm 1.41) \cdot 10^3$ [5]. As the Striatum the STN receives projections from the *Primary Motor Cortex*, the *Supplementary Motor Cortex* and the *Premotor Cortex* but in a smaller amount. Also, it has afferents coming from the GPe. The STN is the *only* nucleus in the *whole* Basal Ganglia complex to *send excitatory projections*, specifically to the GPi and to the SNr. Some studies' evidences also identify projections from the STN back to the GPe and the Striatum [2].

Intrinsic nuclei

As suggested in the aforementioned list, the *Globus Pallidus* can be divided into two parts, the interal one and the external one. The external part can be called an *intrinsic nucleus* given that it receives projections from nuclei belonging to the BG, such as the Striatum and the STN, and it sends projections to almost every BG nucleus [2]. It comprises $N_{GPe} = (45.96 \pm 5.12) \cdot 10^3$ GABAergic neurons [5]. Among the intrinsic nuclei in the BG one could also add the SNc and the VTA. These regions contain *dopaminergic neurons* projecting to the Striatum, this means that the main neurotransmitter released is *dopamine* although there's evidence that they can also release *Glutamate* and *GABA* [2]. The SNc comprises $N_{SNc} = (7.20 \pm 1.08) \cdot 10^3$ neurons [5].

Output nuclei

The internal part of the *Globus Pallidus*, as opposed to the external part, is considered an output nucleus of the BG due to its projections sent to

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Chapter 2

Methods and materials

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