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Dottorato di Ricerca in Bioingegneria

Motor control system in Parkinson's disease: a modeling approach

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Keywords

- Parkinson’s disease
- Basal Ganglia
- Dinamic posture
- Postural strategy
- Sesory Organizaton Test
- Levodopa
- Neurocomputational model
- Synaptic plasticity
- Hebbian learning
- Reinforcement learning
- Dopamine
- Cholinergic interneurons

Thesis Abstract

Parkinson's disease is a neurodegenerative disorder due to the death of the dopaminergic neurons of the substantia nigra of the basal ganglia.

The process that leads to these neural alterations is still unknown.

Parkinson's disease affects most of all the motor sphere, with a wide array of impairment such as bradykinesia, akinesia, tremor, postural instability and singular phenomena such as freezing of gait.

Moreover, in the last few years the fact that the degeneration in the basal ganglia circuitry induces not only motor but also cognitive alterations, not necessarily implicating dementia, and that dopamine loss induces also further implications due to dopamine-driven synaptic plasticity got more attention.

At the present moment, no neuroprotective treatment is available, and even if dopamine-replacement therapies as well as electrical deep brain stimulation are able to improve the life conditions of the patients, they often present side effects on the long term, and cannot recover the neural loss, which instead continues to advance.

In the present thesis both motor and cognitive aspects of Parkinson's disease and basal ganglia circuitry were investigated, at first focusing on Parkinson's disease sensory and balance issues by means of a new instrumented method based on inertial sensor to provide further information about postural control and postural strategies used to attain balance, then applying this newly developed approach to assess balance control in mild and severe patients, both ON and OFF levodopa replacement. Given the inability of levodopa to recover balance issues and the new

physiological findings than underline the importance in Parkinson's disease of non-dopaminergic neurotransmitters, it was therefore developed an original computational model focusing on acetylcholine, the most promising neurotransmitter according to physiology, and its role in synaptic plasticity.

The rationale of this thesis is that a multidisciplinary approach could gain insight into Parkinson's disease features still unresolved.

Contents

General introduction

Parkinson's disease is a neurodegenerative disorder caused by the death of dopaminergic neurons of the substatia nigra, a structure of the basal ganglia located in the midbrain. The origin of this neurodegeneration is still unknown.

Parkinson's disease is mainly characterized by motor issues that include:

- bradykinesia (slowness of movements);
- akinesia (absence of movement);
- stiffness (muscle rigidity);
- postural control impairment;
- tremor.

Along all these problems there are many others, such as freezing of gait, that could appear or not. More in general, all these problems, once the disease has appeared, are only going to worsen.

Moreover, in the latest years research has pointed out how the neurodegeneration not only alters motor performances, but also cognition: patients with Parkinson's disease experience also an array of cognitive problems that can be assessed with traditional cognitive tests.

Currently no treatment is available to recover from the neurodegeneration, nor neuroprotection is available to avoid the disease: dopamine replacement therapies with Levodopa and deep brain stimulation can only help patients to temporarily recover, and often have side effects, losing also their effectiveness in time.

The aim of the present thesis is to investigate both motor issues and basal ganglia circuitry, adopting an engineering approach and therefore using tools such as data analysis and modeling.

The ultimate goal is to gain more insight into the neural processes of the disease, causing both cognitive and motor impairment, from a multidisciplinary approach.

In the first part of the thesis I will focus on postural control issues: I will provide a tool to assess postural strategies and I will apply it to Parkinson's disease patients of different severities, both ON and OFF Levodopa treatment.

In the second part of the thesis I will focus on basal ganglia circuitry: I will elaborate a new computational model of basal ganglia role in action selection, including the newest physiological findings and formulating also original laws to reproduce synaptic plasticity.

Chapter 1

Postural control and Parkinson's disease

Postural control is defined as the control of the body's position in space in order to obtain stability and orientation [1]. One of the functional goal of postural control is to maintain, achieve or restore balance by means of the coordination of movement strategies to stabilize the center of body mass during both self-initiated and externally triggered disturbances of stability [2].

Despite the appearances, balance is a complex skill based on the interaction of dynamic sensorimotor processes.

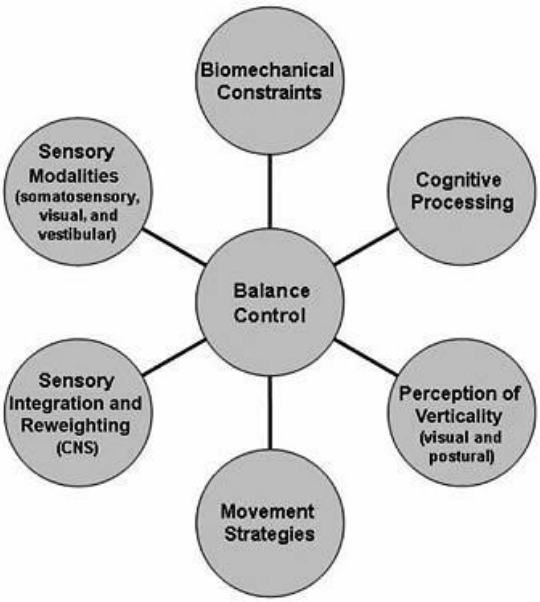

Figure 1.1: resources required for balance control. CNS stands for central nervous system (adapted from *Barros de Oliveira et al., 2008*)

Effective control of posture and equilibrium, as shown in the figure above, involves several types of control mechanisms. Some aspects are centrally (i.e. by the brain) determined, while others are driven by peripheral sensory input. Peripherally triggered postural responses react to external displacement of body posture, centrally initiated postural adjustments anticipate and participate in voluntary movements involving motion of the body's center of mass, and background muscle tone provides the stiffness through which both peripherally and centrally initiated postural activity must act [3].

Therefore posture, even if apparently a simple motor task, can instead provide great information, even on central processes controlled by the brain.

This aspect of postural analysis is appealing mainly for those neurodegenerative disorders, such as Parkinson's disease, that are primarily characterized by motor impairment but are known to be triggered by alterations in the neural circuitry of specific parts of the brain: while motor impairment is easy to be objectively assessed and therefore can be studied with instrumented tests, brain processes carried by specific circuits cannot be investigated in such an easy way.

The assessment of motor and balance performances of patients, compared with healthy subjects, performed with different techniques, helps to infer on the deficits reported by the patients in the different components of postural control, also on those linked to brain processes. The ultimate goal is to provide insight into the neural alterations causing motor and balance issues in these pathologies.

Postural instability is acknowledged to be one of the most disabling feature of Parkinson's disease [4][5]. Balance problems in Parkinson's disease have been related to reduced limits of stability [6] as well as impaired production of anticipatory

motor strategies and abnormal calibration thereof [7]. Moreover, problems in the initiation and smooth execution of complex motor behaviors have also been suggested to be at the bases of the instability of Parkinson's disease patients [8].

All these elements are also responsible for one of the most critical collateral issue for Parkinson's disease patients, that is the high risk for falls: epidemiological studies confirmed that falling is very common in Parkinson's disease patients, and up to 90% of patients would fall at some stage or the other [4].

Given both the need to provide insight into the altered neural circuitry at the basis of the pathology and the need to prevent the risk of falling, balance assessment seems to be a quite simple but relevant and informative task.

The most common type of balance assessment is provided by platform posturography [9], that records the sway of the mean point of floor reaction (center of foot pressure), which is generally assimilated to the projection of the body center of mass on the floor, even if this is really true only in pure static conditions. This kind of posturography has been widely used to study motor control in various physiological and pathological conditions.

Recently, with the diffusion of miniaturized body-worn inertial sensors, posturography has been performed also in different and more feasible ways: postural sway can be revealed by means of IMUs (Inertial Measurement Units) indeed [10].

Sway measurements have always been acknowledged to be fundamental in balance and motor assessment, both in static and dynamic conditions, and therefore widely investigated.

Multisegmental posturography has not gained so much success across the years, even if it could provide additional insights on different components of postural control.

Multisegmental posturography allows the direct investigation of the kinematics of the segmental movements controlling stance [9].

In particular, the segmental movements performed to attain balance have been classified in stereotypical movement patterns: the ankle, the hip and, sometimes, the stepping strategy [11].

Postural strategy use hence could contribute to further characterize postural control, and could help to gain more insight into movement disorders.

Several methods have been used and proposed [9][12][13], but none has spread gaining popularity, therefore multisegmental posturography is still rarely performed.

In the next chapter a new method with easy to use, body-worn inertial sensors to quantify postural strategy use is proposed, with clinical validation on controls and patients, namely Parkinson's disease and Progressive Supranuclear Palsy patients. Chapter 3 presents an additional application of the method that shows how postural control studies can help understand the neural circuitry impaired in Parkinson's disease.

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Chapter 2

Postural strategies assessed with inertial sensors in healthy and parkinsonian subjects

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A preliminary version of a part of this work has been exposed to the XII SIAMOC Congress, Bellaria, October 2012 as

Baston C, Mancini M, Schoneburg B, Horak FB, Rocchi L. Covariance analysis of accelerometer signals reveals altered postural strategies during the Sensory Organization Test in patients with Parkinson's disease

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2.1 Introduction

Idiopathic Parkinson's disease (PD) and Progressive Supranuclear Palsy (PSP) are both types of Parkinsonism that lead to a progressive decline in postural control. Although PSP can start with balance and gait disorders and is characterized by a faster deterioration than idiopathic PD, early symptoms may be so similar that PSP is often misdiagnosed as PD [1][2]. Both PD and PSP patients are at high risk for falls related to abnormal use of sensory information and abnormal motor coordination for postural control [3][4]. PD patients can have normal postural sway area in stance, even under altered sensory conditions, although they may show increased muscle co-contraction and falls in response to external perturbations [5]. PSP patients experience similar issues [1]. However, pathophysiology of postural instability in PSP is not completely understood, although vestibular, as well as visual contributions to stance and posture, have been explored [6].

Postural motor coordination to maintain body equilibrium during stance is organized into two distinct movement patterns: the ankle strategy and the hip strategy [7]. For the actual task stepping strategy is not required.

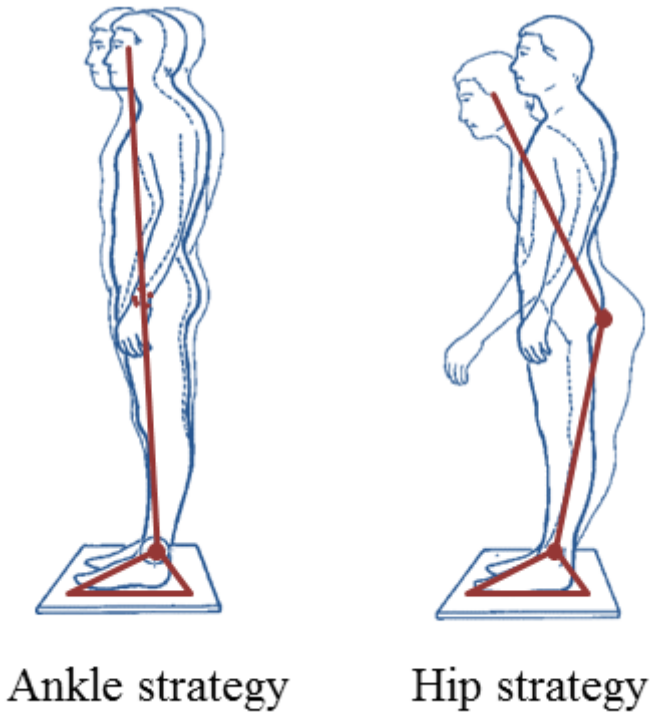

Figure 2.1.1: ankle and hip strategy

In the ankle strategy, the subject rotates the body about the ankle joints, whereas the hip strategy involves corrective movements primarily about the hip joints [8][9].

Subjects can also use a combination of ankle and hip strategies during transitions from one strategy to the other [7], or in response to different sensory conditions, modulating the two co-existing modes [10]. Larger, faster body sway is accompanied by more use of a hip strategy in healthy subjects [9][11].

A quantification of postural movement strategies used by the subjects while keeping their balance in challenging conditions may introduce important insights about their ability to use and integrate sensory information in controlling body equilibrium and in cases of subjects with movement disorders as PD and PSP subjects [5]. Direct measurements of body segment motions could quantify postural strategies [9] and

wearable sensors can be good candidates to this aim. Recently developed synchronized, wireless, inertial sensor systems for movement analysis are now available and able to measure acceleration and angular velocity of the body segments [12].

A strategy score based on horizontal ground reaction force has been proposed to characterize hip or ankle strategy [13], but this approach has also been shown to be inaccurate and unreliable since it is based on an indirect method to deduce the relative motion around the ankle and hip [14].

The aim of the present study is to introduce an instrumented easy-to-use method to measure postural strategy. The method is based on body-worn inertial sensors and it is applied on a cohort of 19 subjects, including subjects with PD, subjects with PSP and age-matched control subjects, to evaluate its feasibility and its potentials in clinical practice. In our approach, ankle strategy and hip strategy contributions are quantified both separately and combined using a novel postural strategy index, meant to provide a composite score suitable for clinical practice. The postural strategy index is also integrated with established measures of postural sway (namely the root mean square, RMS), considered as adjunctive information to characterize balance. Possible differences among the 3 kinds of subjects included in the study are explored and compared with results from clinical literature, to confirm the appropriateness of the method. To perturb balance for studying postural strategies, the Sensory Organization Test (SOT) of Neurocom's Equitest is used. It consists of a form of dynamic posturography comprising systematic alterations of somatosensory and/or visual information [9][13].

2.2 Methods

2.2.1 Subjects and experimental set-up

The present study includes 19 subjects recruited at the Oregon Health and Science University (Portland, OR). Five patients with PD (4 males, 1 female) and 7 patients with PSP (4 males, 3 females) able to stand and walk independently were recruited from the Movement Disorders Clinic and examined by a neurologist specialized in movement disorders. PD patients were tested off medication (after a washout of at least 12 hours), for homogeneity with PSP patients, who do not take levodopa-based medication [15]. The clinical characteristics of the patients were assessed by the Motor subsection of the UPDRS and resulted in a range of 13-53 (mean ± sd: 34±14) for PD subjects and in a range of 22-53 (mean ± sd: 35±11) for PSP subjects. In addition, 7 healthy subjects (3 males, 4 females) were recruited. The 3 populations were age matched (PD: 62±6 years, PSP: 68±5 years, control subjects: 68±7 years). Cognitive evaluation was performed in the parkinsonian patients using the Montreal Cognitive Assessment (MoCA) [16] resulting in mild cognitive impairment in PSP patients (MoCA >21) and normal values in PD (MoCA>26).

Participants were asked to stand quietly on a moveable plate (Neurocom Balance Master, Neurocom, Clackamas, OR), secured in a safety harness during the SOT. All participants were assessed during 6 sensory conditions in 3 consecutive trials of 20 seconds each: condition 1 (eyes open), condition 2 (eyes closed), condition 3 (sway referenced visual surround) with a stable base and condition 4 (eyes open), condition 5 (eyes closed), condition 6 (sway-referenced visual surround) with a moveable base

(sway referenced) [9][13]. Their feet were carefully aligned over a defined axis on the force plate.

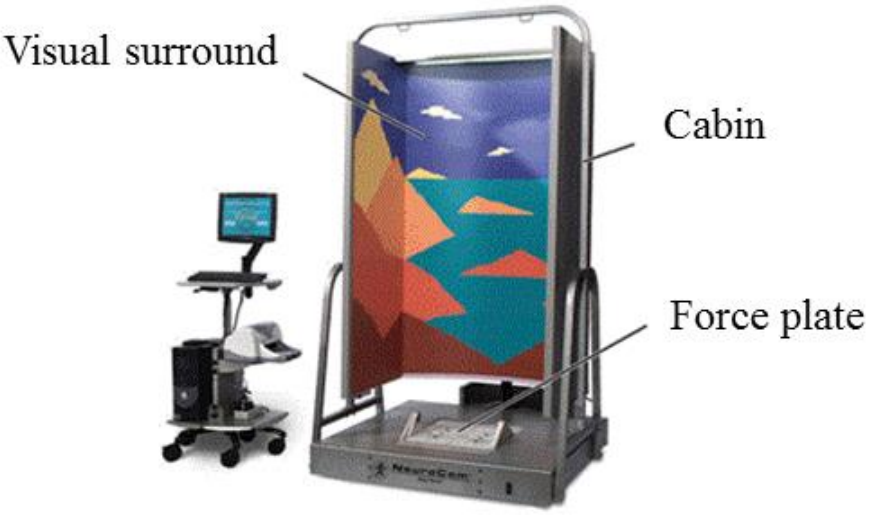

Figure 2.2.1.1: Neurocom Balance Master (Neurocom, Clackamas, OR)

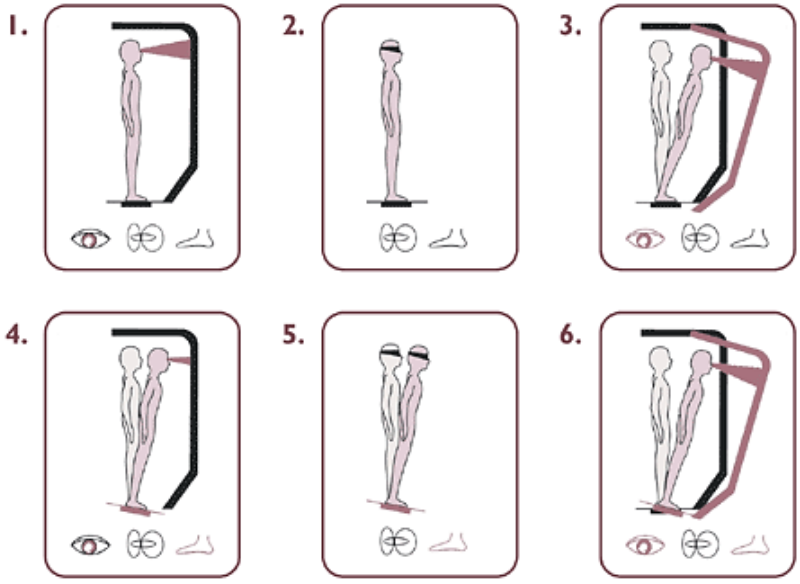

Figure 2.2.1.2: the 6 sensory conditions of the SOT

Figure 2.2.1.3: subject undergoing the protocol

During the SOT test, tri-axial accelerations were collected with two Opal inertial sensors (ADPM Inc, Portland, OR) placed on the trunk at L5 level and on the right shank with Velcro straps. The knee joint was not included in the model of postural control, in accordance with previous studies [7][9][10].

Data were collected at a sampling frequency of 128 Hz.

2.2.2 Signal processing and covariance analysis

To estimate the orientation of the body segment on which the sensor was mounted, after alignment of axes with respect to gravity, an anthropometric low-pass filter with a cut-off frequency of 0.5 Hz was applied on the antero-posterior (AP) component of the acceleration signal [17]. This approach allowed to obtain an estimation of the AP acceleration that mainly included the gravitational component, thus attaining an information proportional to the body segment orientation in the sagittal plane (with respect to the vertical axis). Figure 2.2.2.1.A shows a representative example of the trunk and shank estimated orientations during condition 2 of the SOT, represented by the 0.5 Hz filtered acceleration from the trunk (upper body) a_{05_TRUNK}, and by the filtered acceleration from the shank a_{05_SHANK}.

Afterwards, the coordination between the upper and lower segments of the body was quantified by a covariance index between the trunk and shank (CI_n), defined as the covariance of the signals a_{05_TRUNK} and a_{05_SHANK} normalized by the standard deviations of the two signals. A positive CI_n value close to 1 indicates that the two signals are in-phase, while a CI_n toward -1 indicates that the two signals are in counter-phase. Since the two a_{05} signals estimate segments orientation in the sagittal plane, in-phase pattern can be associated to a postural ankle strategy and counter-phase pattern to a hip strategy.

To be able to detect changes of CI_n in time during the 20 seconds trial length, CI_n was computed using a sliding-window algorithm (window width: 2 seconds, taking into account the frequency components of the signals; time-shift between consecutive windows: 0.1 seconds, mainly for the sake of smoothness of the output signal).

An example of CI_n calculated on a sliding window base is represented in Figure 2.2.2.1.B.

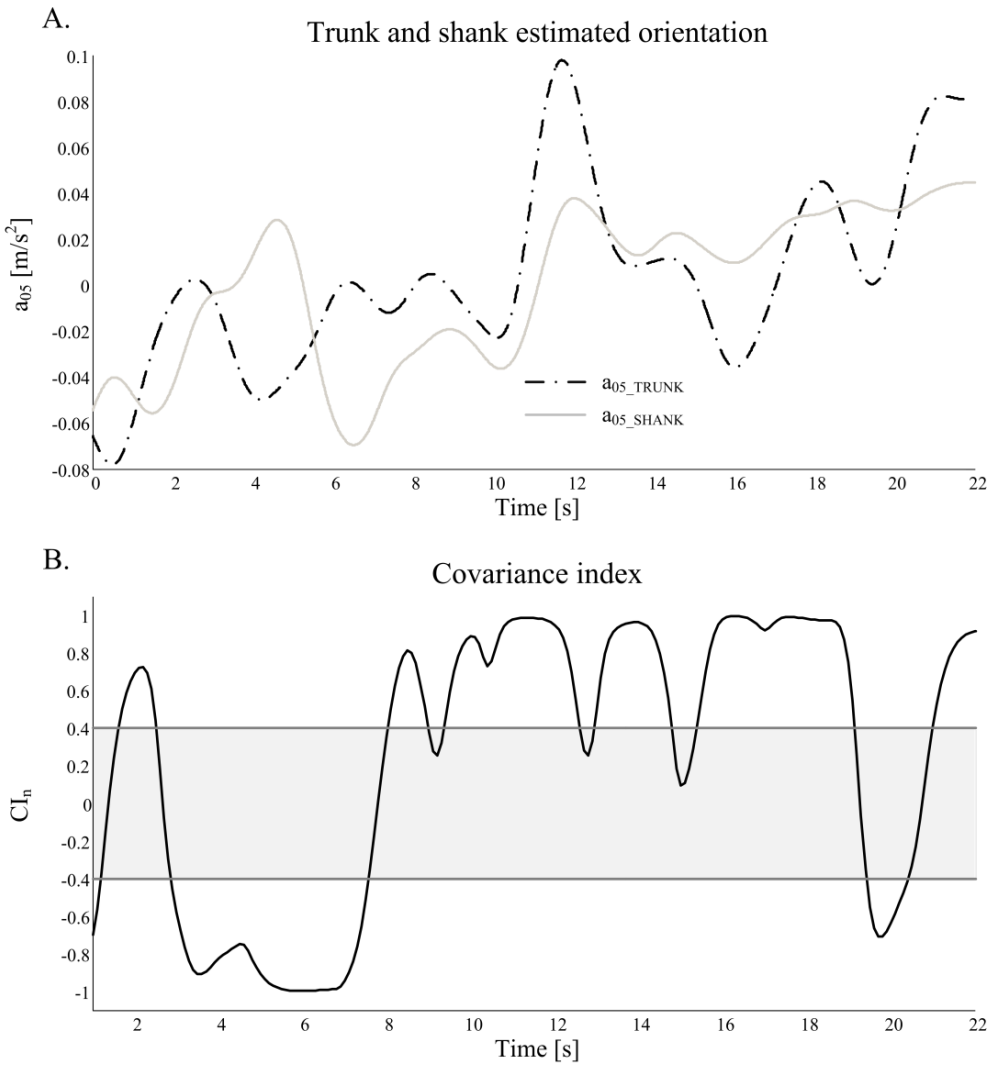

Figure 2.2.2.1: (A) Accelerometer signals, filtered at 0.5 Hz, of a control subject in condition 1 of the SOT. (B) Normalized covariance index, CI_n, computed by the sliding window algorithm. CI_n thresholds are represented (gray line, ±0.4). Both in-phase and counter-phase local patterns of the signals are present in the same trial.

During the time-frames for which CI_n was higher than a specific threshold, the postural behavior corresponded to in-phase pattern, while when CI_n was lower than a specific threshold, the postural behavior corresponded to counter-phase pattern. This specific thresholds used to distinguish between in-phase or counter-phase patterns were identified as +0.4 and -0.4 respectively, representing a medium correlation between the two variables (or signals), with significant interaction but no complete overlapping of the information in the variables [18]. The percentages of time, with respect to trial duration, corresponding to in-phase or counter-phase patterns (respectively T_{IP} and T_{CP}) were also considered. CI_n values in between ($-0.4 < CI_n < +0.4$) were not considered for analysis since they represent an undefined, transitional behavior.

2.2.3 Postural Strategy Index

An overall summary Strategy Index (SI) is also proposed in this study. Based on the calculation of a symmetry index [19], SI was defined as a function of strategy time rates to provide a more synthetic description of each trial.

Being T_{IP} the percentage of time spent in in-phase pattern and T_{CP} the percentage of time spent in counter-phase pattern, the SI is expressed as follows:

$$SI = \frac{T_{IP} - T_{CP}}{T_{IP} + T_{CP}} \cdot W$$

where W is a weight factor to balance the value of SI depending on the percentage of time during which a clearly identified pattern is present: $W = (T_{IP} + T_{CP})/100$ (with 100 representing the total trial duration).

The SI ranges from -1 to 1, reaching the value of 1 when pure in-phase pattern (ankle strategy) is predominant during the trial, and the value of -1 when pure counter-phase pattern (hip strategy) is predominant during the trial duration. Values close to 0 indicate that none of the strategies is the leading or that the rate of classified points is not enough to provide a clear description of the trial.

2.2.4 Postural measures characterizing sway

The present study also measured postural stability from accelerometric signals, based on recently published approaches [17][20]. Specifically, signals from the raw accelerations on the trunk , after correction of possible misalignment with respect to vertical axis, were used. Raw signals were filtered at 3.5 Hz (zero-phase, low-pass Butterworth filter), to exclude possible influence of tremor as suggested in [20]. The root mean square of the signal (RMS) was computed as measure describing the amount of sway [20]. This measure was calculated only from the AP component to allow more immediate comparison with the SI, computed from the AP signals as well. Only the AP direction was used since the surface rotational perturbations during the SOT were in the sagittal plane.

All the analyses mentioned in the previous sections were performed using Matlab R2012b.

To evaluate the differences between conditions and populations a repeated measure ANOVA followed by Tukey Kramer test for multiple comparison was performed (NCSS software).

2.3 Results

Representative a_{05_TRUNK} and a_{05_SHANK} traces are illustrated for a control subject (Figure 2.3.1.A) and for a PD subject (Figure 2.3.1.B) during condition 4 of SOT. While the trunk and shank signals of the control subject are mainly counter-phase, (CI_n <-0.4 for 80% of trial), suggesting a prevalent hip strategy to attain balance, the PD subject shows trunk and shank sway that are mainly in-phase (CI_n>0.4) during the entire trial, suggesting predominant adoption by the subject of ankle strategy.

Overall, the percentage of time spent in in-phase pattern is larger than the percentage of time spent in counter-phase pattern. Mean and standard deviation values of T_{IP} and T_{CP} are reported in Table 2.3.1. Table 2.3.1 also shows that the undefined/transitional area, in which subjects do not show a predominant pattern, is quite limited in all the subjects.

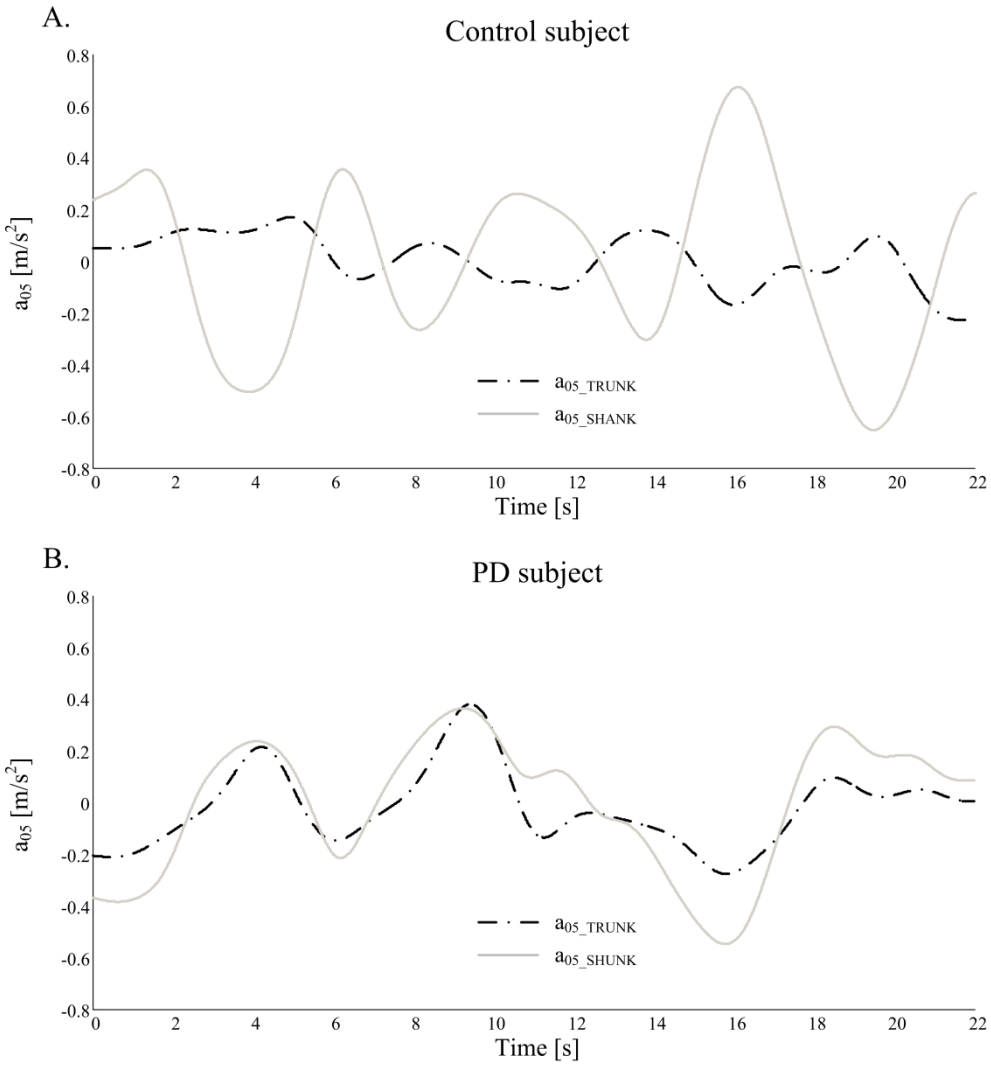

Figure 2.3.1: (A) Filtered accelerometer signals, a_{05}, of a control subject (condition 4 of the SOT) showing a predominant counter-phase pattern (T_{CP} = 80.0%) suggesting the principal use of hip strategy during the trial to attain balance. (B) Filtered accelerometer signals, a_{05}, of a PD subject (same condition) showing a predominant in-phase pattern (T_{IP} = 90.5%) suggesting that the subject preferred to use ankle strategy.

Out of the 7 PSP subjects included in this study, only 3 were able to complete all 6 SOT conditions, and some trials in conditions 4-6 were shortened by falls (all the PSP subjects experienced at least 1 fall in the last 2 conditions).

In contrast, all the PD and control subjects were able to perform all 6 conditions.

Table 2.3.1: Mean values and standard deviations of percentages of time, with respect to trials duration, characterized by counter-phase (T_{CP}) and in-phase pattern (T_{IP}) for the control, PD and PSP subjects in the different SOT conditions. The remaining percentage of time corresponds to undefined behavior.

	SOT Conditions					
	Cond. 1	**Cond. 2**	**Cond. 3**	**Cond. 4**	**Cond. 5**	**Cond. 6**
In-phase behavior (T_{IP}) [% of time w.r.t trial duration]						
CTR	62(21)%	83(17)%	67(16) %	49(21) %	71(16) %	75(12) %
PD	80(10) %	89(8) %	88(6) %	85(13) %	86(9)%	85(12)%
PSP	75(25) %	80(22) %	83(17) %	77(15) %	83(12) %	81(11) %
Counter-phase behavior (T_{CP}) [% of time w.r.t trial duration]						
CTR	19(13) %	8(10) %	15(9) %	32(20) %	15(14) %	11(7) %
PD	7(6) %	3(3) %	4(3) %	7(8) %	5(4) %	6(7) %
PSP	14(20) %	9(14) %	8(12) %	11(10) %	8(7) %	9(6) %
Undefined behavior [% of time w.r.t trial duration]						
CTR	19(9) %	9(8) %	17(9) %	19(6) %	13(5) %	13(6) %
PD	13(6) %	8(5) %	8(4) %	8(6) %	9(6) %	9(7) %
PSP	11(9) %	11(8) %	9(7) %	12(8) %	8(6) %	10(6) %

CTR: control subjects; PD: subjects with Parkinson's Disease, PSP: subjects with Progressive Supranuclear Palsy

The values of the postural strategy index, SI, are reported in Figure 2.3.2, with boxplots. The control subjects changed their strategy index across conditions, with more variability in conditions 1 and 4 than in other conditions. In addition, the eyes open sway-referenced surface condition (condition 4) was characterized by high inter-subject variability and the SI resulted significantly lower compared to all the other SOT conditions ($p<0.05$). In contrast, the PD group didn't show a marked

change in the use of postural strategies across conditions, with a SI close to 1 in all the SOT conditions. The PSP group revealed a trend similar to the PD group, except for a larger variability. Group differences in terms of SI were significant in condition 4, where both PSP and PD subjects showed a SI value higher than control subjects ($p<0.05$).

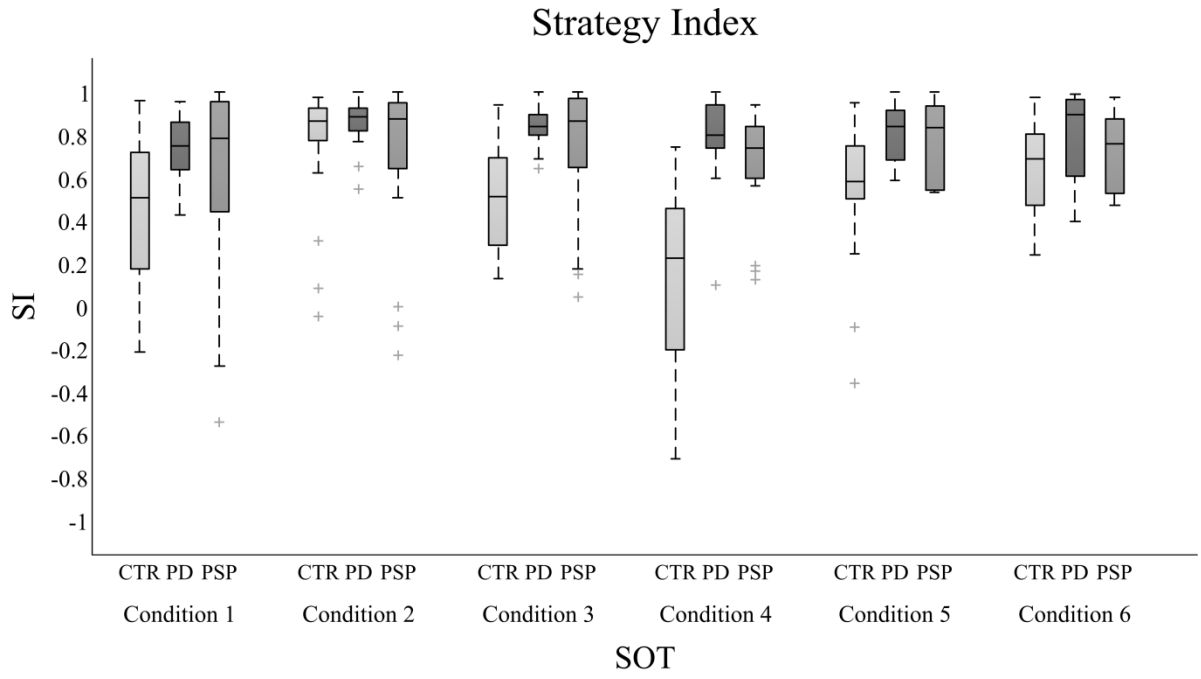

Figure 2.3.2: Postural strategy index (SI) values for control, PD and PSP subjects in each SOT condition, represented using boxplots (central line is the median values, the box includes from the 25th to 75th percentiles and the whiskers extend to the most extreme data-points, with outliers plotted individually). In control subjects, in condition 4 the SI resulted significantly lower compared to all the other SOT conditions ($p < 0.05$). Group differences in terms of SI were significant in condition 4, where both PSP and PD subjects showed a SI value higher than control subjects ($p < 0.05$)

AP RMS values are represented in Figure 2.3.3. This measure, which quantifies the amount of postural oscillation, is influenced both by conditions and kind of populations. AP RMS increased with the difficulty of the conditions, reaching the

highest values in conditions 5-6 (movable support base) compared to conditions 1-3 (fix support base) in all the groups ($p<0.05$). AP RMS values were similar between PD and control subjects in all the SOT conditions. In contrast, the PSP subjects who were able to perform all the SOT conditions showed a much larger AP RMS compared to control and PD subjects in conditions 4 and 5 of SOT ($p<0.05$). Condition 6 did not present any significant difference, probably because of the frequent falls in the PSP group and subsequent reduced number of data (only 4 PSP subjects performed at least one trial in condition 6).

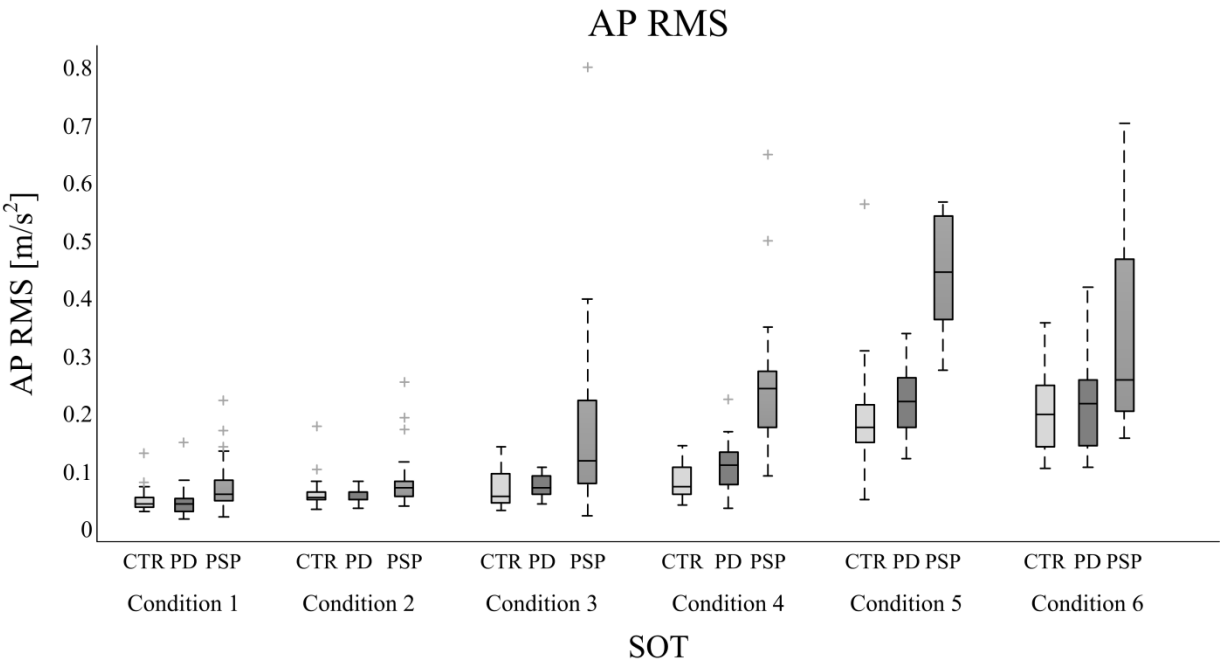

Figure 2.3.3: The values of the AP RMS measure for control, PD and PSP subjects are represented in each SOT condition with boxplots (central line is the median values, the box includes from the 25th to 75th percentiles and the whiskers extend to the most extreme data-points, with outliers plotted individually). RMS reached the highest values in conditions 5–6 (movable support base) compared to conditions 1–3 (fix support base) in all the groups ($p < 0.05$). The PSP subjects showed a much larger AP RMS compared to control and PD subjects in conditions 4–5 ($p < 0.05$). PSP subjects fell

frequently: all the PSP subjects experienced at least 1 fall in the conditions 5–6. In contrast, all the PD and control subjects were able to perform all 6 conditions

2.4 Discussion

This study introduces, for the first time, a method to characterize postural movement strategies with easy-to-use, body-worn, inertial sensors. Our results are consistent with previous studies about postural strategy in the kind of subjects included in the present study, and this confirms the feasibility of the approach and its potentials in studies about postural strategies. In fact, postural strategy quantification showed that control subjects modified their postural strategies with changes in sensory conditions. Specifically, control subjects primarily used an ankle strategy, rather than a hip strategy, in all 6 sensory conditions. However, when proprioception was altered by sway-referencing the support surface, the use of hip strategy increased, especially when vision was not disrupted (condition 4 for which significant statistical difference was shown with respect to the other conditions). This behavior is consistent with previous findings, which show that hip strategy in healthy subjects may occur when somatosensory information from the surface is impaired [21]. The adaptability of postural responses to external perturbation or sensory altered conditions is interpretable as an effective method to maintain balance [5][22][23]. PSP and PD subjects persisted in use of an ankle strategy even when proprioception was altered, although with a large variability across subjects within each group. The lack of use of a hip strategy by patients with PD is consistent with previous studies suggesting that PD patients have small postural responses [24], stiff postural coordination [9][24] and impaired proprioception [25][26]. Postural strategies have not previously been

described in patients with PSP, but the lack of a hip strategy may have contributed to the high frequency of falls in challenging sensory conditions, consistent with the clinical literature describing falls in PSP [4][15][27].

The same experimental approach that allowed to quantitatively characterize postural strategies, also allowed the assessment of the postural sway from the accelerometer on the trunk [17][20][28]. The postural sway, measured with RMS, was smaller than normal in PD, tested in the OFF state, in agreement with previous studies [19][24]. PSP subjects experienced several falls in the last SOT conditions, whereas PD patients did not, although the two groups had similar severity of symptoms. PSP subjects who did not fall showed larger postural sway than PD and control subjects, confirming severe balance impairment in PSP subjects [1][2]. This difference between parkinsonian groups is emphasized in condition 4, in which both PD and PSP subjects showed a predominant ankle strategy, unlike the control group. This may suggest that PD patients were able to overcome this specific sensory challenge just using an ankle strategy, probably by allowing very little sway as compensation, whereas PSP patients were not able to switch to hip strategy nor to compensate by reducing sway area, resulting in falls.

Further evaluation about PSP and PD populations are a desirable development of the present study, and our SI may be an interesting tool for such investigation. In addition, other symptoms of parkinsonsims may be evaluated with the present approach, such as tremor [29] or anomalous posture.

Our results suggest that a postural strategy index based on covariance of estimated inclination of upper and lower body segments in challenging sensory conditions during stance could add important insights into balance control in patients with

movement disorders. In addition, the simple and accessible experimental set-up can easily be performed even in a clinical setting and it also allows the computation of adjunctive measures describing balance maintenance [17][20][30].

2.4.1 Comparison with other methods

As previously said in chapter 1, different methods were proposed before this to assess postural strategy. Someone simply used stereophotogrammetric device to detect body segment oscillations [31], but this would mean having an expensive and dedicated stereophotogrammetric system, and this choice would be more suitable to research than clinical practice. Other authors used sway bars sensed with potentiometers to detect kinematic of hip and shoulder motion, measured in the sagittal plane [9], but also this method does not seem to be suitable to clinical practice. The indexes proposed by Neurocom have already been criticized, as it was previously said, but even nowadays they are still used since they easily come as an output of the Neurocom Balance Master, when performing the SOT.

A similar approach to the one described in this paper was presented in a previous paper [32], however the sensors, the set-up and the pre and post-processing were completely different. The authors also tried to summarize their information in a synthetic index, completely different from ours, but it was not effective enough, therefore it did not spread.

By contrast our method uses body-worn inertial sensors, common nowadays both in research and also in clinics. In this way our postural strategy analysis could be easily included even in clinical routines as an additional postural control assessment, with very little loss of time.

Moreover, our symmetric index is very simple to understand and can be used also by non-experts.

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Chapter 3

Effects of Levodopa on Postural Strategies in Parkinson's disease

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3.1 Introduction

Altered postural control and balance are major disabling issues of Parkinson's disease (PD), and multiple factors leading to postural instability have been identified, such as abnormal use of sensory information [1], reduced limits of stability [2] or abnormal scaling of postural responses [3]. Static and dynamic posturography have helped to provide insight into the different features of PD's postural deficits, both in dynamic perturbed conditions and in simple quiet upright stance [4][5][6].

Postural coordination to maintain body equilibrium is organized into two distinct movement patterns: the ankle strategy and the hip strategy [6]**.** Quiet unperturbed stance has long been associated only to ankle strategy, and the body modeled as a single-link inverted pendulum [7]. However, more recent evidences suggest that both patterns are observable during quiet stance [8][9].

A stiffer postural coordination [7][10] and impairments in proprioception [11] have been associated with the lack of use of a hip strategy in Parkinson's disease. Although postural control is known to deteriorate with disease severity, it is not known if severity of PD plays a role in postural coordination, or what is the effect of antiparkinson (levodopa specifically) medication in postural coordination. In addition, to date, both research and clinical practice use traditional measures of posturography to characterize standing posture control, probably due do the fact that simple, objective measure of postural coordination are lacking.

In the previous chapter a novel method to quantify postural strategies via a Strategy Index (SI) [12] calculated from acceleration signals across body segments allows easy, low cost and ubiquitous evaluation of postural strategies in PD patients.

The aim of the present study is to investigate the effects of disease severity and levodopa on postural strategies during quiet stance in PD. We hypothesized that patients with PD would show more ankle strategy and less hip strategy than age-matched control subjects and this stiffer postural strategy would progress with disease progression and severity of clinical rigidity.

3.2 Methods

3.2.1 Subjects and experimental set-up

This study included 70 participants with a diagnosis of idiopathic Parkinson's disease (PD) and a group of 21 healthy control subjects of similar age. All subjects with PD were treated with levodopa and all the participants were free of musculoskeletal and other neurological impairments that could affect gait and balance. The protocol was approved by the OHSU Institutional Review Board. All participants gave their informed consent according to the Declaration of Helsinki.

Information about age and gender of participants, as well as relevant clinical data of PD subjects, are provided in Table 3.2.1.1.

Table 3.2.1.1: mean values and standard deviations of clinical characteristics of PD patients and information about age, number and gender of the participants.

		Age	Participants	M/F	UPDRS		UPDRS rigidity subset		PIGD		Postural stability		ABC
CTR		67(6)	21	9/12	-		-		-		-		94(6)
PD	HY 1-2	67(5)	33	24/9	OFF	35(8)	OFF	3(1)	OFF	8(4)	OFF	0(0)	86(12)
					ON	29(8)	ON	2(1)	ON	7(4)	ON	0(0)	
	HY 3-4	67(7)	37	20/17	OFF	42(11)	OFF	5(2)	OFF	10(4)	OFF	1(1)	78(12)
					ON	35(10)	ON	4(2)	ON	9(4)	ON	1(1)	

PD subjects are divided into 2 groups of disease severity, according to the Hoehn & Yahr scale (33 subjects with H&Y 1–2 versus 37 subjects with H&Y 3–4), and furthermore assessed OFF and ON medication. Clinical data, such as the UPDRS Motor Part III, Rigidity (sum of the rigidity items of the motor UPDRS, i.e. rigidity of the neck, arms and legs), PIGD subscore (sum of the UPDRS items: rising from chair, posture, gait and postural stability), and Activities of Balance Confidence (ABC) characterize the PD groups.

PD subjects were tested in the morning, in their practical OFF state (at least 12h after their last levodopa dose) and in the ON state (1h after a levodopa dose that was 1·25 fold of their regular dose). All participants performed 3 repetitions of quiet standing (30s each) with their arms at their sides looking straight ahead. A template was used to achieve consistent foot placement [13]. Subjects were tested in a quiet hallway of the Oregon Clinical & Translational Research Center at OHSU.

Figure 3.2.1.1: subject being tested in quiet stance

For each trial, we used tri-axial accelerations collected from two inertial sensors (MTX, Xsens Technologies, Enschede, Netherlands) placed posteriorly on the trunk at L5 level and on the right tibia with Velcro straps. Data were collected at a sampling frequency of 50 Hz.

3.2.2 Postural analysis

The Strategy Index (SI) was computed as described in the previous chapter, from the antero-posterior accelerations detected at the lumbar and shank level, to assess the overall postural strategy use.

Postural sway dispersion was computed by means of the root mean square of the trunk acceleration signal (RMS) in the antero-posterior direction [14][12].

The median of SI and RMS was calculated across the 3 trial repetitions in the OFF and ON state.

Data were not normally distributed using the Kolgorov-Smirnov test, therefore we used a square root transformation and re-checked data distribution. A 2-way repeated measures ANOVA (severity x medication) was used to investigate the effects of disease severity and levodopa replacement on SI and RMS. When a significant difference was found, a post-hoc analysis was performed using Bonferroni adjustment to test which groups differed from each other. Student t-test was employed to investigate differences between PD and healthy control subjects. Pearson correlation was used to assess the relationship between sway metrics and clinical scores.

All the computations were performed using Matlab R2012b and NCSS software for statistical analysis.

3.3 Results

3.3.1 Strategy Index

PD and control groups had similar mean values of SI. This suggests that although some variability in postural strategies use occurs, the ankle strategy (SI=1) is generally preferred to hip strategy in quiet stance both by PD subjects (mild and severe, OFF and ON medications), and by control subjects. SI, RMS mean and standard errors for the PD and healthy subjects are represented in Figure 3.3.1.1.

However, the SI values in PD groups moved lower with more hip strategy, away from control subjects, when they were in the ON, compared to the OFF, dopa state. Statistical analysis showed significant differences in SI with medication ($F=18.9$, $p<0.0001$), but not with stage of disease.

Specifically, SI was significantly lower, i.e. more hip strategy represented, ($p=0.01$) in the ON, than in the OFF, state in the severe PD group, as shown in Figure 3.3.1.1.A. Surprisingly, SI decreased with disease severity both in the OFF and ON state, indicating more hip strategy in severe PD, but this observation did not reach statistical significance.

Mild PD subjects showed a nonsignificant trend toward larger SI values than control subjects and similar to severe PD subjects in the OFF medication condition. Only severe PD subjects in the ON state showed SI values significantly lower than control subjects ($T=2.2$, $p=0.02$).

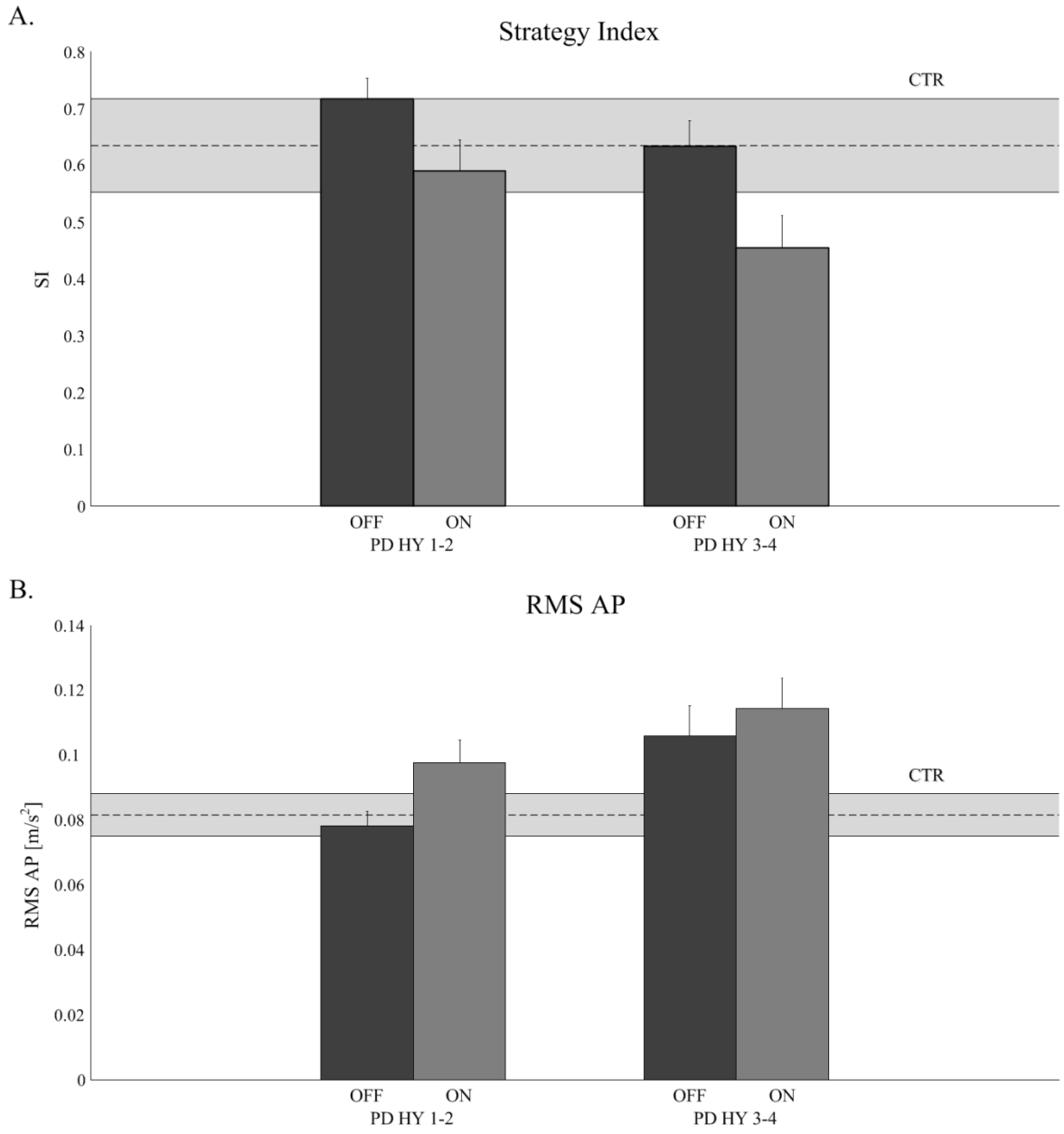

Figure 3.3.1.1. (A) Mean values and standard errors of Strategy Index (SI) for PD H&Y 1-2 (first group), OFF (0.72±0.04) and ON (0.59±0.05). SI for PD H&Y 3-4 (second group), OFF (0.63±0.04) and ON (0.45±0.06). SI for controls represented in the stripe behind (0.63±0.08). (B) Mean values and standard errors of the root mean square of distance, antero-posterior direction (RMS AP) for PD H&Y 1-2 (first group), OFF (0.078±0.005) and ON (0.098±0.007). RMS AP for PD H&Y 3-4 (first group), OFF (0.106±0.009) and ON (0.114±0.009). RMS AP for controls is represented in the stripe behind (0.081±0.007).

While SI values provide a general overall postural strategy use, Table 3.3.1.1 provides separate, specific information about each strategy adopted (T_{IP}: ankle strategy, and T_{CP}: hip strategy) reported with mean values and standard deviations.

Table 3.3.1.1: mean values and standard deviations of percentages of time, with respect to trial duration, characterized by hip strategy (T_{CP}) and ankle strategy (T_{IP}) for the controls and PD subjects. PD subjects are divided into H&Y 1–2 and H&Y 3–4, and further assessed OFF and ON Levodopa. T_{GREY} represents the percentage of time spent in undefined strategy.

			T_{IP}	T_{CP}	T_{GREY}
CTR			76(5)%	12(4)%	11(1)%
PD	HY 1-2	OFF	80(2)%	8(1)%	12(1)%
		ON	72(3)%	13(2)%	14(1)%
	HY 3-4	OFF	75(3)%	12(2)%	13(1)%
		ON	65(3)%	19(3)%	15(1)%

The percent of time in which the SI algorithm was not able to detect a clear postural strategy (T_{GREY}) was similar and limited for all the groups (11-15%), suggesting that the SI provides a reliable measure.

3.3.2 Postural sway dispersion

Mild PD ON and severe PD both in OFF and ON state showed trends toward larger RMS values than control subjects with statistical significance only for severe PD ON medication (T=-2.7, p=0.008). Statistical analysis showed significant differences in RMS sway both across the stage of the disease (F=5.7, p=0.02) and ON versus OFF levodopa (F=10.26, p=0.002). Specifically, RMS values were significantly larger (p=0.02) in the ON, than in the OFF, state for the mild PD subjects, as shown in the

first group of Figure 3.3.1.1.B, whereas RMS values increased with disease severity, both for the OFF and ON state.

RMS values of postural sway showed a trend opposite to SI differences across the PD groups, with mild PD in the OFF state showing the lowest RMS AP values, while the severe PD in the ON state showed the highest (see Figure 3.3.1.1.B).

3.3.3 Correlation of Postural Strategy with Clinical Scores

SI was not related to disease severity, as measured by the Motor Part of the UPDRS (UPDRS III), nor to UPDRS rigidity or PIGD subsets in the ON or OFF state except for a relationship between SI and PIGD in the OFF state ($r=-0.28$, $p=0.02$).

Postural sway RMS was related to UPDRS III ($r=0.33$, $p=0.005$), UPDRS PIGD subset ($r=0.24$, $p=0.04$) and postural stability (0.25, $p=0.04$) in PD subjects in the OFF state, but not the ON state.

SI and RMS showed negative association (i.e. the higher amount of sway, the more hip strategy used) only among PD subjects, both OFF ($r=-0.51$, $p<0.0001$) and ON medications ($r=-0.5$, $p<0.0001$), but not in control subjects.

Patient perception of balance (ABC) was associated to SI and to RMS both in PD subjects OFF (SI: $r=0.3$, $p = 0.01$, RMS: $r=-0.43$, $p = 0.0002$), and nearly in PD subjects ON medications (SI: $r=0.38$, $p = 0.001$, RMS: $r=-0.22$, $p = 0.08$), but not in control subjects.

3.4 Discussion

This study quantifies for the first time postural strategy as well as sway dispersion during quiet stance in subjects with PD across a range of severity in both the ON and OFF levodopa state. Our study demonstrated that:

1) use of primarily an ankle strategy was adopted to control quiet stance in both mild and severe PD as well as control subjects, although PD started to use more hip strategy in the ON dopa state;
2) both disease severity and levodopa-replacement were associated with increased sway dispersion in PD;
3) patients perception of balance, measured by the ABC, is associated with objective measures of postural sway.

Generally, PD subjects OFF medication showed a similar ankle strategy postural coordination, like healthy subjects, in maintaining balance in quiet standing with eyes open. However, levodopa replacement significantly reduced the strategy index in PD, implying more use of a mixed (hip with ankle) strategy in PD ON, compared to more ankle strategy in PD OFF. This could be due to the fact that levodopa replacement is effective in decreasing rigidity in PD, and decreased rigidity is associated with larger postural sway oscillations that require the use of a hip strategy. This finding is in keeping with previous results, as mentioned in the previous chapter, showing that larger body sway is accompanied by more use of hip strategy because it moves the body CoM more quickly than ankle strategy [7].

The switch to using more hip strategy when postural sway is larger is consistent with intact detection of postural sway and implementation of strategy change as needed. Postural sway is large in patients with somatosensory loss and patients with PD are known to have reduced central kinesthesia, especially in the ON levodopa state [15].

In contrast to the effect of levodopa state, disease severity (mild versus severe) did not affect the strategy index, although it is associated with larger sway dispersion.

Interestingly, postural sway dispersion was significantly related to both disease severity and medication. Larger sway dispersion was associated with more severe disease (both in the ANOVA and correlation analysis). As larger postural sway is associated with worse balance control in patients with more severe PD, we can speculate that this might be due to the alteration induced by other neurotransmitters in addition to dopamine, such as acetylcholine [16][17][18].

In addition, levodopa replacement increased sway dispersion in the mild, but not in the severe group. This might be due to the fact that early in the disease levodopa replacement is more effective in reducing rigidity compared to later in the disease. An increase of postural sway dispersion with levodopa may also represent worsening of balance control with levodopa, consistent with previous studies showing worse postural responses in the ON versus OFF states [3]. In fact, postural sway dispersion was strongly related to clinical measures of postural responses and gait, but only in the OFF levodopa state.

Surprisingly, rigidity and PIGD were not related to the SI, suggesting that whole body coordination of postural sway in stance is not dependent on the amount of rigidity or postural responses or gait. However, the rigidity score from the motor UPDRS is

dominated by limb, rather than axial, rigidity, which may be related to postural strategy if more precisely measured.

SI measure of postural coordination was significantly associated with the patients' perception of their own balance. The more use of hip strategy, the worse patients perceived their own balance. This relationship is of particular interest as the ABC can readily be used in clinical practice.

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Chapter 4

From movement and postural strategies to cognition and computational modeling

The activity of the basal ganglia was first assessed in movement. In order to obtain reliable results, several methods have been used to measure the activity of their different components, including single unit recording [1], 2-deoxyglucose (2-DG) autoradiography, and positron emission tomography (PET) [2].

Among all the techniques previously mentioned, single unit recording offers several advantages: it is the only direct way to measure neuronal activity during behavior, and allows the neuronal activity to be correlated with behavior with a temporal resolution of milliseconds [1].

As a proof, single unit recording helped assessing for the first time the correlation of the neural activity in the basal ganglia with movement [3].

After that, it became evident also the relationship between basal ganglia degeneration and diseases characterized by motor impairment, such as Parkinson's disease.

The basal ganglia are the largest subcortical structures in the human forebrain. They send outputs to brainstem nuclei involved in motor control. But their role implies more, and the position of the basal ganglia in the circuitry of the brain gives a clue to their function: the basal ganglia receive inputs from the cortex and then project

massively to thalamic nuclei, which in turn project back to the frontal cortex. This anatomy means the basal ganglia are in a prime position to influence the executive functions of the forebrain, such as planning for movement and even cognitive behaviors [4]. This tight linkage with the frontal cortex led to investigate the role of basal ganglia also in cognition.

The main contribution of basal ganglia to cognition is considered to be dealing with decision making and action selection [5], while before this role was acknowledged only in the choice of motor responses [1]. Allowing for context-appropriate selection, basal ganglia have moreover been assumed to establish and maintain associations between stimulus representations and response representations [6], and they seem to be more involved in learning of stimulus-response associations than in execution of habitual stimulus-response behavior [7]. In addition, basal ganglia have been assumed to establish associations not only between stimuli and responses, but between stimuli, responses and outcomes [8].

To better prove that basal ganglia functions are present simultaneously in the motor and cognitive domains, literature reports that patients with Parkinson's disease are also impaired cognition, and in particular in response selection [9].

Basal ganglia have also been hypothesized to establish and execute sequences of processes (both motor and non-motor) by linking each single response of a sequence to its respective predecessor, in a way that each response serves as an input to the subsequent one [10].

Other functions imply response initiation and termination [11], and, given the smaller dimensions of basal ganglia with respect to the cortex, dimensionality reduction of cortical information [12].

One relevant contribution to cognition deals with working memory gating and maintenance, i.e. if a determined stimulus will be maintained or not (gating) [13] and keeping the information by means of cortico-basal ganglia-thalamic loops (maintenance) [14].

Finally, an important contribution to cognition from basal ganglia deals with reinforcement learning [15][13]. Basal ganglia adapt behavior in such a way that reinforcements are maximized, i.e. the basal ganglia circuitry is able to adapt and create new association stimulus-response in order to maximize reward and minimize punishment depending on the specific stimulus presented in input. As a consequence, the previously rewarded actions and cognitive processes will tend to be repeated, while the punished ones will be avoided. Currently, from an anatomical viewpoint this function finds its anatomical substrate on the findings that phasic dopamine signals in basal ganglia encode reward and punishment signals [16].

After this synthetic overview on cognitive functions of basal ganglia, it is worth underline that all these functions are not necessarily in contrast with one another.

At present, cognitive testing is spreading in research and is becoming routine such as and together with motor assessment. A lot of diseases that previously were subject only to motor testing, such as Parkinson's disease, are now routinely scrutinized with classical cognitive tests such as Stroop and Go – No-Go task, or even double tasking, in order to gather information that, if interpreted together with motor assessment results, could give more insight into the neural processes impaired in the disease. This new approach led to new positive outcomes [17], but still cannot assess in detail the specific neural circuits alterations.

Computational model, on the contrary, model explicitly neural networks and can infer more in detail on the specific circuitry involved.

Computational models led an important role in the investigation of basal ganglia mainly dealing with cognition. Testing several hypothesis by implementing them they helped basal ganglia knowledge to improve at least in the last 20 years, with often positive results [15]. They can still provide a useful contribution to investigate further basal ganglia functions and alterations, as the major part of the circuitry still remains unknown.

Both clinical research and computational modeling always focused on the investigation of dopamine, and dopamine replacement (levodopa) therapies for Parkinson's disease are nowadays the gold standard for the treatment of the disease; however as the results reported in the previous chapter, it is clear that dopamine replacement cannot make Parkinson's disease patients recover and return to control values neither for postural sway nor for postural strategy use. This leads to the suspect that non-dopaminergic contributions could be involved in postural control. Recently, a growing body of literature focused on acetylcholine and acetylcholine alterations in Parkinson's disease, that positively correlated with movement impairment even better than dopamine [18][19][20][21]. The topic is a strong novelty in the research on Parkinson's disease and therefore still highly debated in the clinical world, also because the mechanism by which acetylcholine works is still not well understood. On the cognitive side even less is known.

Computational models are the mathematical models more suitable to investigate complex dynamic systems such as basal ganglia circuitry, and could give their contribution in understanding such difficult question.

In particular, biologically constrained computational models provide a useful framework both to interpret results coming from the implementation of different theories and to generate novel hypotheses, sometimes even non-intuitive ones, which can be further considered and tested with other methods [6].

Computational models use simplified neuronal units and neural dynamics to help understand how interactions among multiple parts of the circuit, and modulatory actions by different neurotransmitters, can support cognition and behavior.

In chapter 5 an overview on the present basal ganglia anatomy knowledge will be presented, while chapter 6 will describe a newly developed computational model that explicitly includes for the first time striatal cholinergic interneurons and their partially proven and partially hypothesized function and network. The model refers to decision making and action selection, being the main cognitive role of basal ganglia.

However, given the strong linkage between basal ganglia functions in movement and cognition, the insights provided by this model could be useful also to formulate hypothesis and to investigate the motor impairment in Parkinson's disease, which at the moment cannot be fully explained by the unique dopaminergic neurotransmitter term.

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Chapter 5

Basal Ganglia

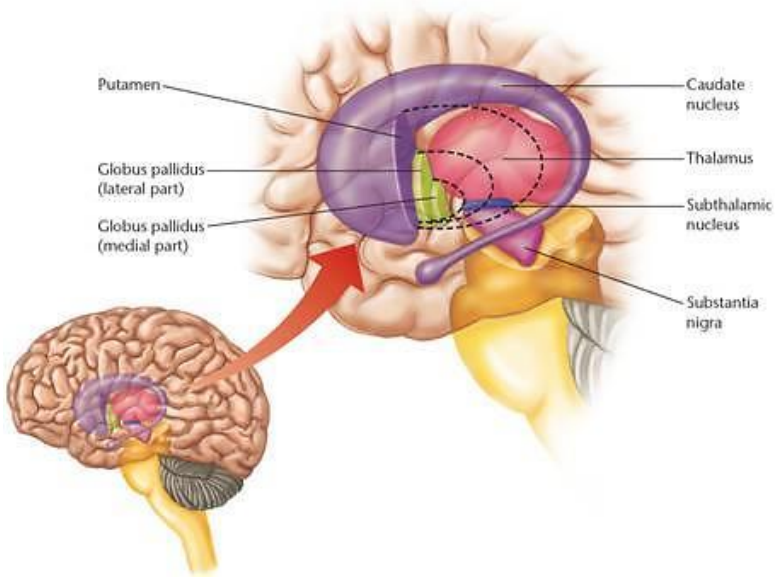

Figure 5.1: image of the basal ganglia structures in the human brain

5.1 Anatomy

The basal ganglia are a set of dynamically interacting subcortical nuclei located in the midbrain. The input nuclei of the basal ganglia are the striatum [1] and the subthalamic nucleus (STN) [2], being the first the main entry point and also the largest and most composite nucleus of the circuit. Nearly all the cortex projects to the striatum, which therefore provides substrate for the integration of information from different cerebral areas [3]. These projections are organized topologically [4]. Other

projections come from the STN [5], from the ventral tegmental area (VTA) and from the substantia nigra pars compacta (SNc) [6].

The STN receives excitatory cortical afferences that seem to be topologically organized too [7], even if there seems to be consistent convergence of input from different cortical areas onto individual neurons at the same time [8].

The globus pallidus pars interna (Gpi) and the substantia nigra pars reticulata (SNr) are classified as the output nuclei, and they both project GABAergic inhibition [9] to the thalamus [10] which in turn projects back to the cortex in a topologically organized way [11]. Output nuclei also project to the superior colliculus and the peduncolopontine nucleus [12]. All the output projections are inhibitory (GABA) [10]: the output nuclei are tonically active [13], therefore in resting condition they inhibit, while under stimulus they modulate the degree of inhibition they provide.

The globus pallidus pars externa (Gpe) and the substantia nigra pars compacta (SNc) are the intrinsic nuclei of the basal gaglia, i.e. the do not receive afferences from nor send efferences to external brain structures. Both Gpe and Gpi as well as SNr receive inhibitory GABAergic projections from the striatum, but as will be further specified in the next subsection, the striatum is highly heterogeneous, therefore striatal cells expressing different receptors for Dopamine preferentially target either Gpe or Gpi and SNr. In particular, striatal cells expressing D1 receptor project to Gpi and SNr and those expressing D2 receptor to Gpe [1]. The STN projects to both Gpe and Gpi, SNr, sending excitatory output [14]. Comparing striatal and STN projections to the Gpi and SNr, the STN projections appear to be highly divergent such that each neuron of the STN projects to many Gpi/SNr neurons, while the striatum provides more focused inhibition [15]. Gpe is also tonically active, even if less than the output

nuclei [13], providing GABAergic inhibitory efferent connections to all the basal ganglia's output nuclei and STN [16].

The SNc is made of large dopaminergic cells and receives GABAergic inhibitory input from the striatum [17], and also projecting back [18]. It is the dopaminergic cells in this structure that are the most vulnerable in Parkinson's disease.

5.1.1 The striatum

The striatum is the largest nucleus of the basal ganglia. For the 95% is composed by GABAergic medium spiny neurons (MSNs) [19]. These are the neurons that projects outside the striatum, towards the Gpe and Gpi. MSNs are in general tonically silent and do not respond to low stimuli coming from the cortex. These cells are bistable, i.e. they have 2 different levels of resting state, *up* and *down* [19]. Cortical signals are able to drive them into the up state, a condition in which the MSN can be easily become active by either an additional increase of excitation or a drop in inhibition [19].

The remaining 5% is made of striatal interneurons, that can be classified in GABAergic interneurons and cholinergic interneurons.

Cholinergic interneurons are large aspiny striatal neurons that use acetylcholine as a neurotransmitter, they are tonically active neurons (TANs) [20] and are the most interesting interneurons since their function even nowadays is not fully understood, even if they seem to play an important role combined with dopamine.

GABAergic interneurons target mainly MSNs [21], while cholinergic interneurons have a weak excitatory effect on the GABAergic interneurons and a strong effect on MSNs [19].

5.2 Pathways

The main theory that started gaining insight into basal ganglia functions were presented in [1] and [22]. Here they stated that basal ganglia could control the activity of the cortex by means of 2 pathways, the *direct* pathway (cortex → striatum → Gpi/SNr), to facilitate the activity, and the *indirect* pathway (cortex → striatum → Gpe → STN → Gpi/SNr) to provide inhibition instead. These authors also associated diseases such as Parkinson's disease to the overactivity of the indirect pathway. An additional shorter indirect pathway (cortex → striatum → Gpe → Gpi/SNr), named *short* in contrast with the previous *long* was then discovered [23]. The last pathway to be discovered was the *hyperdirect* pathway (cortex → STN → Gpi/SNr) [24].

The overall function of these pathways is to propagate the information from the cortex to the Gpi and SNr.

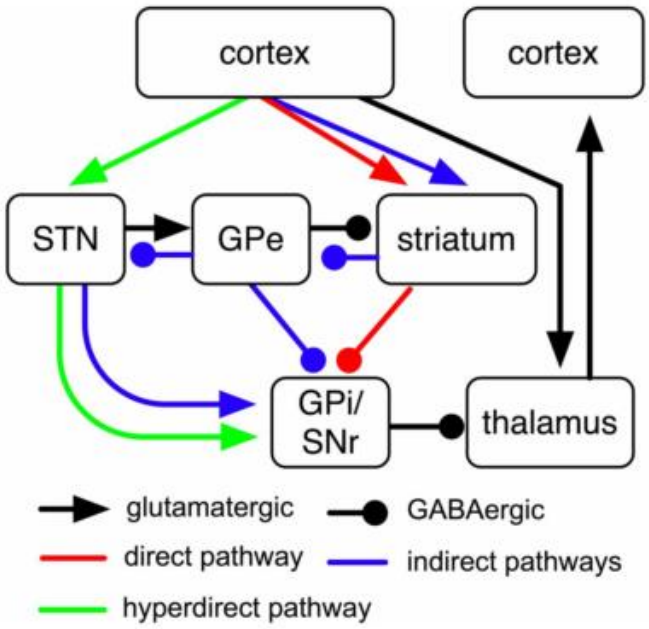

Figure 5.2.1: representative diagram of the basal ganglia pathways (from *Schroll et al., 2013*)

The pathways transmit information in a feed-forward manner, but also stabilizing feedback projections are present.

Striatal neurons arborize with a high degree of specificity, while STN excite large number of pallidal cells [25][26]. Based on these evidences, the direct and the short indirect pathway are assumed to have a focused effect, while the hyperdirect pathway and the long indirect pathway likely exert global effects [19].

The interpretation of basal ganglia functions provided by the 3 main pathways rely on the assumption of segregation of the dopaminergic receptors in the striatum, i.e. distinct striatal cells, expressing different dopaminergic receptors, project either to the Gpi/SNr, being part of the direct pathway, or to the Gpe, being part of the indirect pathway [27]. This approach has been challenged several times in the past, and co-localization of D1 and D2 dopamine receptors has been debated [28]. The 3 pathways have been questioned even nowadays [29], however, the they still seem to be the most simple and diffuse interpretation of basal ganglia functions.

5.3 Plasticity

The basal ganglia show plasticity phenomena. A large body of work assesses the role of the dopaminergic system in mechanisms of reward and punishment [30][19].

In particular, the activity of nigrostriatal dopamine neurons correlates with reward or with anticipation of reward [30], i.e., the firing will start even before the reward if the stimulus before was associated to a previous reward. On the contrary, a dopamine dip will occur if an expected reward will not be received.

The concept of plasticity in the basal ganglia has been linked, until nowadays, to dopamine, and it is due to the opposing effects that it exerts from MSNs expressing

either D1 or D2 dopamine receptors: indeed if dopamine binds to a D1 receptor, the neuron carrying the receptor gets excited, while if on the contrary dopamine binds to a D2 receptor, the neurons receives inhibition. In this sense dopamine is modulatory and its action depends on the type of dopamine receptor involved [19].

Dopamine can be present both in tonic and in phasic form: given its role on D1 and D2 receptors, and the functional organization in pathways of basal ganglia, tonic dopamine drives the overall propensity of basal ganglia to enhance either the direct (high tonic levels) or the indirect pathway (low tonic levels). Rewards and punishments, as said before, lead the nigrostriatal dopamine neurons to fire more or less than usual for a time window: this variation in firing activity induces a quick fluctuation with respect to the baseline, i.e. a dopamine peak (if dopaminergic neurons fire more) or a dopamine dip (if dopaminergic neurons fire less). This has consequences on the activity of the basal ganglia pathways, always because of their differential expression of dopaminergic receptors. Therefore during a peak, dopamine level is higher and the consequence is the further excitation of the MSNs expressing D1 and further inhibition of those expressing D2. On the contrary during a dip, less dopamine is present, therefore also less excitation for MSNs with D1 receptors and less inhibition for MSN with D2 receptors, with respect to normal.

These are neural basis for plasticity (both Long Term Potentiation and Long Term Depression) in the striatum: it is activity driven, modulated by the dopaminergic input, and ruled similarly to hebbian learning [31].

Cholinergic interneurons seem to have a role in learning too: cholinergic interneurons have both D1 and D2 receptors and stop firing when dopamine level is higher [32].

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Chapter 6

A biologically-inspired computational model of Basal Ganglia in action selection

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6.1 Introduction

While the role of the basal ganglia has historically been restricted to motor function, more recent researches focused on their involvement in cognition. Indeed, nowadays the implication of basal ganglia in a variety of cognitive functions has gained more and more consideration, as suggested by behavioral, clinical and biochemical experiments in human and especially non-human beings [1][2][3][4][5]. These results are further supported by anatomical findings, demonstrating that he basal ganglia are connected with many other structures of the brain that are implied in different cognitive tasks [1].

Notably, cognitive experiments on humans were performed both in healthy controls and in patients suffering from basal ganglia disorders, primarily Parkinson's disease [6][7][8][9].

Given the rise of attention of research not only to motor but also to cognitive aspects, the last 20 years have seen a growing body of literature investigating basal ganglia functions and behavior by means of computational modeling techniques [10][11].

The goal of these models is to investigate the mechanisms governing the basal ganglia functions in rigorous quantitative terms; to this aim, models incorporate biological knowledge on the different neural pathways implicated, and physiological knowledge on synaptic plasticity rules, into a coherent structure, in order to understand cognitive behavior and/or motor functions, as well as pathological conditions. Specifically, models allow disparate knowledge from different fields to be summarized and integrated into a single theoretical framework, resulting in emerging properties and peculiar features that stand-alone field of sciences cannot explain yet.

This chapter introduces a novel biologically-inspired neurocomputational model of basal ganglia in action selection. This model provides a summary of the up-to-date biological knowledge on basal ganglia circuitry, as well as novel hypotheses, including also new physiological findings linked to cholinergic interneurons, a kind of striatal interneurons exerting a crucial effect on synaptic plasticity, but never seriously investigated in a model before. The model exploits the basal ganglia network in depth, relating neuronal activity and behavioral outcomes, as well as plasticity phenomena, by means of a brand new Hebb rule, able to account both for dopaminergic and cholinergic influences on striatal neurons.

The aim is to demonstrate that the mathematical description that we propose, together with the introduction of the new elements just mentioned, allow the main basal ganglia functions to be faithfully mimicked, introducing plausible interpretations on how some structures could contribute to human cognitive and also motor functions, in healthy as well as in pathological condition.

6.1.1 Action Selection

The present model focuses on the analysis of basal ganglia role in behavioral action selection.

As previously mentioned in Chapter 3, action (or better response) selection is a central process in decision making and one of the main functions of basal ganglia. In the context of motor control, the details on how this function is actually performed have been widely debated [13]: while some authors supported an active role of the basal ganglia, assuming that they specifically encode detailed aspects of stimulus-response mapping [14], others promoted a subtly different and passive modulatory

role, in which the basal ganglia either facilitate or suppress stimulus response associations that are already represented in the cortex [15][16][17]. The last theory gained more general consensus among the scientific community, therefore we also acknowledge in our model that the role of the basal ganglia is to selectively facilitate the execution of a single command, while suppressing all the others.

The similarity between the circuitry previously observed in the motor domain and the circuits linking basal ganglia to more specific cognitive areas of the cortex [18] led to the theory that basal ganglia participate in cognitive decision making in a similar way they do for motor control.

In this sense basal ganglia contribute in both motor and cognitive domains to the general problem of action selection, defined as the task demanding to suppress the majority of choice possibilities while allowing only the evaluation of a limited number, in order to gate the appropriate behavior [19].

6.2 Methods

In the next sections the model will be described both in its functional aspects and in its mathematical implementation.

From a clinical viewpoint, the present model reproduces, although in a necessary simplified manner, biological information, both at the anatomical level, in terms of structures and connectivity, and at the physiological level, in terms of excitatory or inhibitory projections. From a functional viewpoint, the activity of biologically-inspired neurons is able to simulate basal ganglia behavioral response to different stimuli.

6.2.1 Task

As in the classical response selection, the network is presented with a stimulus and has to choose a response according to a specific rule.

In this work the stimulus *S* in input to the network is a 4-elements vector, in which each element is a normalized component assuming continuous values in the range [0,1], therefore indicating different strength in each element.

Each possible response is coded by a specific neuron in the cortex, which triggers the response when it becomes fully active (i.e. its activity is above a given threshold). The possible responses are 4 as well.

The choice of a stimulus made by a 4-element vector and of 4 possible responses, even if completely arbitrary, allows the functional role of the different pathways of the basal ganglia to be thoroughly analyzed: indeed 4 neurons are sufficient to investigate the complexity of the relationships occurring when multiple possible choices are competing together.

Given a stimulus S, in the default case (i.e. untrained network), the response gated by the network is associated to the highest element of the stimulus S.

Conversely, after training, the network can learn a different rule and therefore choose a different response, based on previous reward and punishment experiences.

6.2.2 General model structure

6.2.2.1 Neural model

Each computational unit, or neuron, of the model represents the overall activity of a population of biological neuronal cells, and its output y_i can be interpreted as its normalized firing rate.

y_i is described as a variable assuming continuous values in the range $[0,1]$: y_i assumes value 0 when the neuron is silent, while values close to 1 indicate that the neuron is firing at its maximal frequency.

Hereafter, we will identify as i a post-synaptic neuron, receiving synapses from pre-synaptic neuron j, whose activity is y_j: a neuron can receive synapses from multiple pre-synaptic neurons, and each pre-synaptic activities can contribute either to excite or to inhibit the postsynaptic neuron depending on the neurotransmitter they use, and sometimes on the post-synaptic receptor they bind. Also the strength of the excitation or inhibition can differ. These aspect are modeled within the synaptic weights w_{ij}, specific for every synapse (in this case for the synapse from the pre-synaptic neuron j to the post-synaptic neuron i): the sign of the weight represent the excitatory ($w_{ij} > 0$) or the inhibitory ($w_{ij} < 0$) nature of the synapse, while synaptic efficacy (i.e. strength) is reflected by the absolute value $|w_{ij}|$, which expresses the extent to which a pre-synaptic neuron j influences the activity of the post-synaptic neuron i. Although the absolute value of synaptic weights can change according to learning rules, as will be explained afterwards, the weights cannot change sign: indeed learning cannot transform an excitatory synapse in an inhibitory one nor vice-versa, in accordance

with physiological knowledge stating that neurons use always the same neurotransmitters.

A neuron can eventually also have additional inputs coming from external sources not directly represented in the model: non-synaptic external inputs to the neuron i are summarized in a single term I_i.

Synaptic and non-synaptic inputs to the post-synaptic neuron i are summarized in a synthetic variable x_i. Let there be N pre-synaptic neurons projecting to the post-synaptic i, we can write:

$$x_i = \sum_{j=1}^{N} w_{ij} y_j + I_i$$

In brief, x_i represents the overall input to the post-synaptic neuron i.

In order to mimic the cell membrane integrative process, the input x_i is transformed in a post-synaptic variable u_i, using a first order differential equation with time constant τ.

$$\tau \frac{du_i}{dt} = -u_i + x_i$$

In the last step, a sigmoidal function ς computes the activity of the neuron i, y_i, from the output of the previous differential equation u_i.

$$y_i = \varsigma(u_i)$$

In the present model, the sigmoidal function ς was implemented as

$$y_i = \frac{1}{1 + e^{-a(u_i - u_0)}}$$

where a and u_0 are parameters of the sigmoidal function ς suitable to describe the mapping between overall neural input and subsequent neural output in the context of our network.

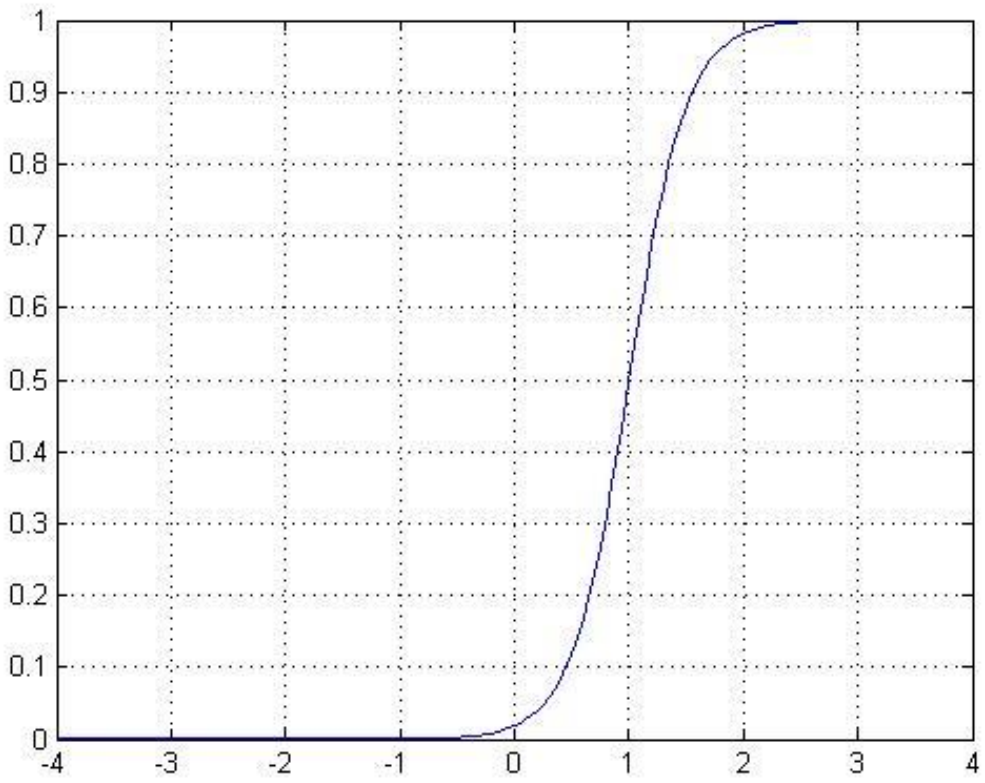

Figure 6.2.2.1.1: graphical representation of the sigmoidal function ς of the model

6.2.2.2 Network model

As previously specified, the structure of the network is inspired by the state-of-the-art biological knowledge, and represents the main components of the basal ganglia.

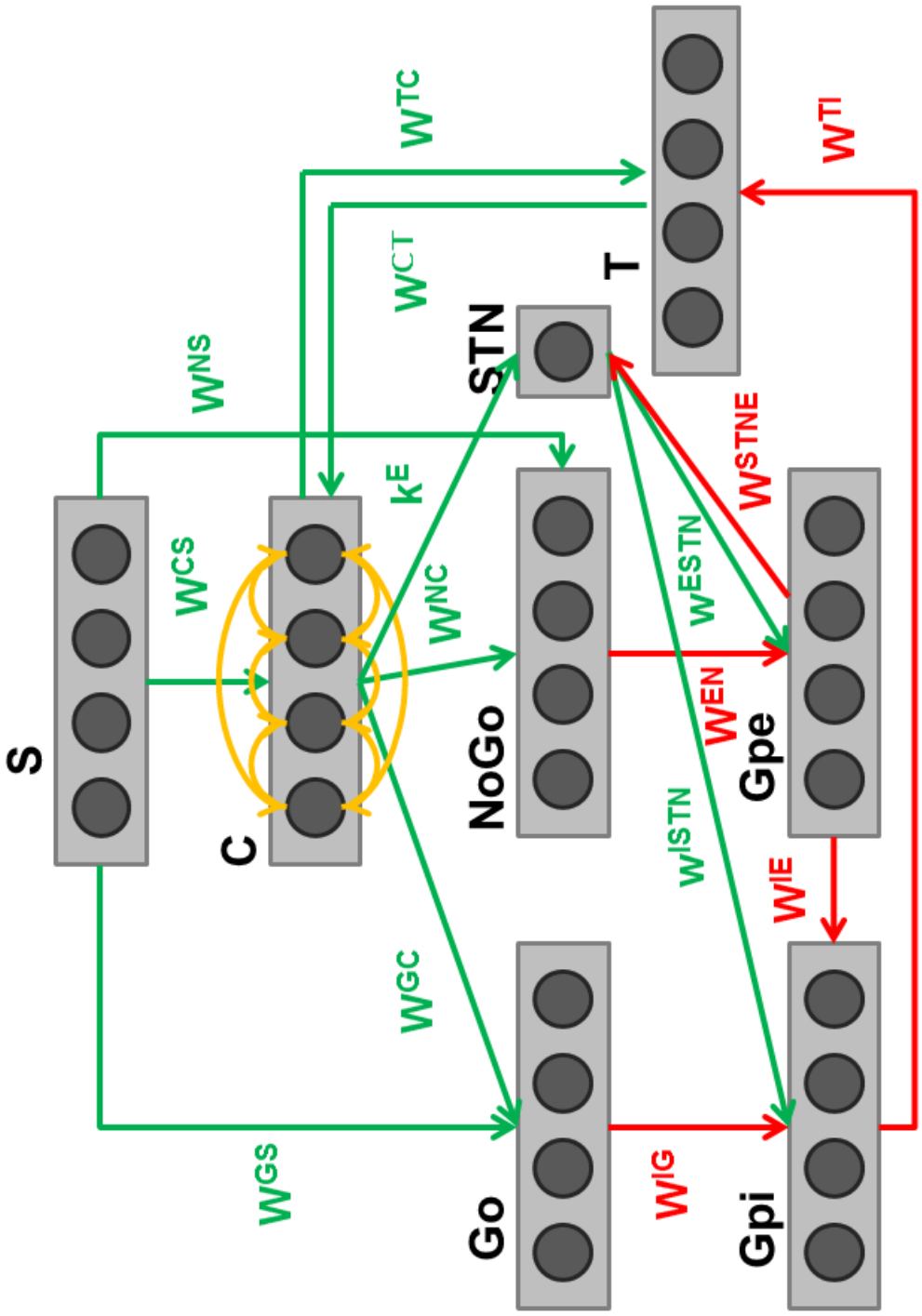

Figure 6.2.2.2.1: graphical representation of the overall basal ganglia model. Rectangle represent different structures, circles neurons, arrows projections: **green** excitatory, **red** inhibitory, **orange** lateral inhibition

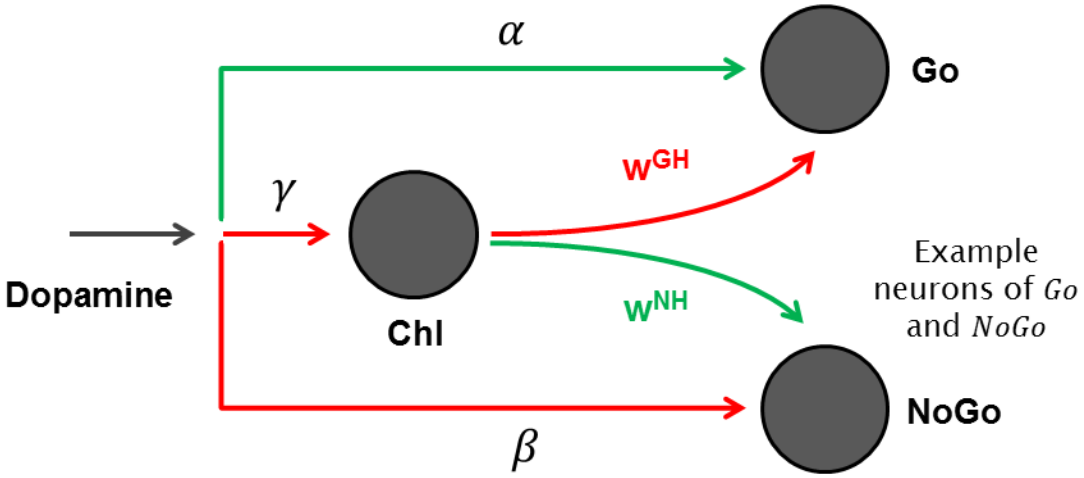

Figure 6.2.2.2.2: focus on the effect of dopamine and cholinergic interneuron on example Go and NoGo cells in the model. Arrows projections: **green** excitatory, **red** inhibitory

The model includes: the striatum, functionally divided according to dopamine receptor expression (D1: Go, D2: $NoGo$), subthalamic nucleus (STN), globus pallidus pars externa (Gpe) and globus pallidus pars externa (Gpi). A peculiarity of the present model, compared to the majority of previous ones, consists in an explicit representation of cholinergic interneurons (ChI) and of its specific network.

While all the other structures are modeled as 4-neurons layers, STN and ChI are modeled as single neurons since their activity represents a global property of the overall network, i.e. they do not act specifically but exert their action globally.

A first simplification with respect to biology was the use a single output region for the basal ganglia, thus neglecting the substantia nigra pars reticulata (SNr), which was described in the previous chapter.

A further simplification consisted in the use of dopamine (DA) directly as a modulating input factor, without explicitly representing the substantia nigra pars

compacta (SNc) dopaminergic neurons, which, as exposed in the previous chapters, are responsible for the release of the dopaminergic neurotransmitter. This again represents a peculiar modeling choice, that allows a simpler simulation both of normal and pathological conditions, in which dopamine levels can be artificially altered by the disease or by external intervention.

Other structures not belonging to the basal ganglia also represented in the model are the cortex (C) and the thalamus (T). Analyzing connections between basal ganglia and specific cortical areas is beyond the scope of the present work, therefore we do not refer to specific parts of the cortex itself.

6.2.2.2.1 Functional pathways

The present model acknowledges the classical view of basal ganglia [20], representing all the 3 main pathways (direct, indirect and hyperdirect). The loop between the STN and the Gpe here is meant to be a control loop to avoid STN overactivity and undesired oscillations [21], rather than a part of the long indirect pathway, whose function is already carried out by the short indirect one, here the only indirect pathway explicitly represented.

As in the predominant “brake accelerator” view previously mentioned [22], the basal ganglia are only able to provide feedback to the choices already selected by the cortex: in other words, the 3 pathways are only able to modulate the inhibition provided from the Gpi to the thalamus, and subsequently either support or block the response coded by the neuron of the cortex which is exciting its corresponding thalamic neuron.

The input of the model is the vector S, which can be interpreted as a cortical representation of an external stimulus. S is connected both to the portion of the cortex C devoted to response representation and to the striatum (both Go and $NoGo$) in order to let the basal ganglia contextualize the response selection to the specific stimulus.

When a stimulus S is presented in input to the network, a process of lateral inhibition among the neurons of the cortex selects a subset of possible responses, coded by the corresponding neurons in the cortex: the basal ganglia will only provide feedback to these candidate actions.

It is fundamental to underline that the basal ganglia are only able to provide feedback to the responses coded by the neurons previously selected by the cortex itself, as the thalamus receives only inhibitory projections from the basal ganglia output nuclei, while the excitation is provided only by the selected neurons of the cortex C.

The neuron of the cortex being among the chosen ones (i.e. a candidate response) and receiving also positive feedback by the basal ganglia becomes fully active, and thus its activity gets above the threshold. This allows the gating of its coded response, that is therefore chosen to be the output of the whole process.

If there is no stimulus in input (i.e. the network is in its steady state), the thalamus is globally inhibited since, without any excitation by the cortex, it receives only tonic inhibition by the Gpi [23]. On the contrary, an adequate stimulus can disinhibit the thalamus. In this sense, the model implements a winner-takes-all (WTA) mechanism, so that only the stronger response can be triggered. The WTA mechanism is attained through lateral inhibitions among neurons in the cortex, and a positive self-loop. The latter is realized by means of feedback connections between each neuron in the

cortex and its corresponding representation in the thalamus. The achievement of a sufficient activity by the winner requires that this self-loop is active, hence that the corresponding representation in the thalamus is previously disinhibited by the basal ganglia.

In order to regulate the thalamus inhibition/dishinibition, each neuron of the cortex is connected to its own Go (direct) and No-Go (indirect) pathway, being responsible for the focused facilitation of the response or its focused suppression.

In the Go pathway, the neuron of the cortex is connected to its corresponding neuron in the Go part of the striatum by means of an excitatory projection, and this neuron subsequently inhibits the corresponding neuron of the Gpi: the more the neuron of the Go is excited, the more the neuron of the Gpi is inhibited, decreasing his tonic activity. Therefore, if the thalamus is stimulated by the cortex, by means of this process the basal ganglia try to facilitate the gating of this specific response.

Similarly, in the No-Go pathway, the neuron of the cortex is connected to its corresponding neuron in the $NoGo$ part of the striatum still by means of an excitatory projection, which in turn inhibits the corresponding neuron of the Gpe, decreasing his tonic activity. This results in less inhibition provided to the Gpi, which thus becomes more active. By means of this complementary process, the basal ganglia try to stop the candidate action.

However, it is only the overall activity, i.e. the imbalance between the 2 pathways, due to different values of the synapses, that ultimately modulates the activity of the Gpi: if the Go pathway prevails, the Gpi provides less inhibition to the corresponding neuron of the thalamus (i.e. the basal ganglia feedback “let go” the response); on the

contrary if the No-Go pathway is more active, the Gpi provides more inhibition to the thalamus (i.e. the basal ganglia feedback “stops” the response).

Each of the Go and No-Go pathways runs in parallel for each neuron of the cortex [15].

This is how the network of the basal ganglia usually approaches the task of response selection, and the process appears to be quite straightforward. However, in particular situations, and with particular stimuli, the choice of which response to gate is a fairly demanding task. The choice for the cortex is particularly difficult when the pool of candidate responses contains multiple strong ones: in this case, the basal ganglia could provide fast but contradictory feedback to all of these, since conflicting responses could be all winning. The basal ganglia manage these challenging situations by means of the hyperdirect pathway: the role of the hyperdirect pathway, carried out by the STN, is indeed to provide an overall stop signal to all the units of the Gpi in order to prevent the basal ganglia to provide fast feedback to all the strong candidate responses, and to let more time to the cortex to solve the conflict and evaluate a reduced subset of candidate responses. More in detail, if there are multiple candidate responses, even if not all right, the subsequent conflict within the cortex induces the STN to excite all the neurons of the Gpi, providing an overall inhibition to all the neurons of the thalamus, and thus blocking any decision, until the cortex selects a suitable set of candidate actions. At that point the STN becomes progressively less active, allowing respectively the Gpi to be less inhibited and therefore the basal ganglia to provide feedback again.

6.2.2.2.2 Dopamine and acetylcholine

Evidences [2] have shown that basal ganglia are able to change their synaptic weights, in particular those between the cortex and the Go (W^{GC}) and the $NoGo$ (W^{NC}) part of the striatum, and similarly those between the stimulus representation S and the Go (W^{GS}) and the $NoGo$ (W^{GN}) part of the striatum.

As exposed in the previous chapter, dopamine (DA) is not uniquely excitatory or inhibitory, but can exert different effects depending on the receptor it binds: if it binds D1 receptor, it generally provides excitation, while if it binds D2 receptor it provides inhibition [15].

Therefore the effect of dopamine is different within the striatum, being primarily excitatory for the Go part and inhibitory for the $NoGo$ part.

In the model, dopamine is presented both in its tonic and in its phasic form. Phasic dopamine is released after the network has gated a response and a subsequent error feedback has occurred: if an unexpected reward occurred, further dopamine is released, producing the typical dopamine peak, while if the response received either a punishment or an unexpected absence of reward dopamine reports a dip, i.e. it falls below the tonic level during a delimited lapse of time. This produces a transient change in activity in the neurons of the striatum, with the Go neurons generally receiving further excitation in case of reward, meanwhile the $NoGo$ neurons result more inhibited. On the contrary, in case of punishment, the Go neurons are inhibited, while the $Nogo$ neurons are excited.

A further specification needs to be done in the peculiar case of reward and Go neurons: a contrast enhancement phenomenon has been reported [24], according to which the corresponding winning neuron in the Go actually receives excitation, while

the losing neurons in the same part of the striatum receive inhibition. This effects depends on the activity level of the neurons themselves, i.e. the more a Go neuron has higher activity, the more it gets excited by dopamine; on the contrary, if it is poorly active, it will be further inhibited.

No similar effects have been reported so far for the $NoGo$ neurons, and this particular effect on Go neurons seems to be restricted only to the reward case as well.

One of the strong novelties introduced by the present model is the explicit and detailed introduction of the network of striatal cholinergic interneurons, here represented by a single unit (ChI) that provides either inhibition to all the neurons of the Go or excitation to all the neurons of the $NoGo$, assuming an opposing role to dopamine. Even if it is still a strongly debated topic, the model adheres to an interpretation of cholinergic interneurons role which is in part supported by new research findings, but has never been assessed in previous neurocomputational models.

The dependence of cholinergic interneurons on dopamine seems well-established in physiological literature: cholinergic interneurons express both D1 and D2 receptor [25][26], therefore, just like the other striatal neurons, they can sense dopamine phasic changes.

In particular, data in medical literature report a decrease in cholinergic activity following an increase in dopamine concentration, suggesting an inhibitory effect of dopamine on cholinergic interneurons [27]. Conversely, a fall in dopamine should excite cholinergic neurons above their basal activity.

Indeed, the previous data suggest an additional modulatory role exerted by cholinergic interneurons on striatal neurons in case of dopamine depletion,

contributing to the dip observed in Go neurons phasic activity. A fall in dopamine should excite cholinergic interneurons which, in turn, exert a further inhibition to the Go pathway. The basic idea is that the dip of Go neurons during punishment could not be explained entirely by a direct dopamine inhibition effect, but also reflects a further inhibition exerted by cholinergic neurons. Recent findings showed that this mechanism could be explained by a Ca^{2+} and muscarinic M1 effect linked to cholinergic interneurons activity [26].

Finally, the model hypothesizes that a similar mechanism could be assumed, in a symmetrical form, also for $NoGo$ neurons, i.e., activation of cholinergic neurons during punishment should contribute to an excitation of the No-Go pathway.

The phasic activity of dopamine and cholinergic interneurons has its main effect on synaptic plasticity. Transient changes in striatal activity due to dopamine and acetylcholine lead to activity driven plasticity, which is able to change network behavior and create new stimulus-response associations with experience, as rewards and punishment go on in time. More in detail, synaptic plasticity induces a modification of the association between a specific stimulus S and the consequent response: previously rewarded outcomes will be more likely selected in the future, while punished ones will be actively avoided.

Synaptic plasticity is implemented by means of a peculiar Hebbian rule, specifically designed to reproduce this particular kind of neuromodulated activity driven plasticity. This will be exposed in the next section.

6.2.3 Mathematical description

In the following section, neurons referring to specific structures of the model will be denoted with superscripts, as specified in the Table 6.2.3.1: the cortex, the thalamus and each basal ganglia layer will be assigned a specific acronym, shorter than the one used in the basal ganglia model representation (Figures 6.2.2.2.1 and 6.2.2.2.2), to help an easier comprehension of the equations.

Table 6.2.3.1: table of the naming correspondences.

Structure in the model	Acronym for mathematical description
Cortex (C)	C
Striatum, Go	G
Striatum, NoGo	N
Subthalamic nucleus (STN)	STN
Globus pallidus pars interna (Gpi)	I
Globus pallidus pars externa (Gpe)	E
Thalamus (T)	T
Cholinergic inrerneuron (ChI)	H

The stimulus is simply indicated as S, as in the Figure 6.2.2.2.1.

The spatial position of individual neurons will be described by the subscripts i, $i = 1, \dots, N$, with $N = 4$ for the majority of the layers (C, Go, $NoGo$, Gpe, Gpi), as well as the stimulus S. STN and the cholinergic interneuron ChI, being both represented in the model as single units, do not need subscripts.

6.2.3.1 Mathematical description of the neural activity in structures

The equations are reported both in matrix and scalar form, to help the reader focus either on the correspondence with the Figures 6.2.2.2.1 and 6.2.2.2.2, or on the nature of the matrices, and therefore of the relationship within pre and post-synaptic neurons between the layers.

In the equations superscripts will identify the projection, as in the corresponding graphical representation of the model given by Figures 6.2.2.2.1 and 6.2.2.2.2: for instance W^{IJ} will identify the matrix of the synaptic weights from the structure J to the structure I of the model. Single elements of the matrix will be further identified by a double or single subscripts, as previously explained for structures and layers (for instance, while w_{ij}^{IJ} identifies a single element in a rectangular matrix, w_i^{IJ} does the same in a vector).

Referring to Figures 6.2.2.2.1 and 6.2.2.2.2, the nature of the synapses is represented by the specific color of the projections: excitatory projections are represented in green, while inhibitory ones are represented in red. Lateral inhibition is represented by orange arrows.

Among all the synaptic matrices and synaptic weights, we underline that a different denomination is used for k^E, since this projection does not connect single neurons, but informs the STN about the conflict within the cortex C, expressed by means of an energy function E.

Let $U^L = [u_1^L \ \dots \ u_i^L \ \dots \ u_N^L]^T$

Let $Y^C = [y_1^C \ \dots \ y_i^C \ \dots \ y_N^C]^T$

and $U^C = [u_1^C \ \dots \ u_i^C \ \dots \ u_N^C]^T$

- Matrix form

$$\tau_L \frac{dU^L}{dt} = -U^L + LY^C \quad (1.a)$$

$$\tau \frac{dU^C}{dt} = -U^C + W^{CS}S + U^L + W^{CT}Y^T \quad (2.a)$$

$$Y^C = \varsigma(U^C) \quad (3.a)$$

- Scalar form

$$\tau_L \frac{du_i^L}{dt} = -u_i^L + \sum_{\substack{j=1 \\ i \neq j}}^{N} l_{ij} y_j^C \quad (1.b)$$

$$\tau \frac{du_i^C}{dt} = -u_i^C + \sum_{j=1}^{N} w_{ij}^{CS} s_j + u_i^L + w_{ii}^{CT} y_i^T \quad (2.b)$$

$$y_i^C = \varsigma(u_i^C) \quad (3.b)$$

The first set of equations describe how the activity of the neurons in the cortex C is computed.

The introduction of an additional variable U^L is necessary to introduce the lateral inhibition L, by means of which a first pool of available response is selected.

Every neuron of the cortex C receives excitatory input from the whole stimulus S and an excitatory projection from the corresponding neuron in the thalamus. Moreover, it also receives and additional input U^L reflecting lateral inhibition from the other neurons in the cortex. The latter is characterized by a different time constant τ_L. If the neuron of the thalamus is active, the neuron of the cortex receives the positive feedback necessary to win the WTA selection.

Let $Y^G = [y_1^G \ \dots \ y_i^G \ \dots \ y_N^G]^T$

and $U^G = [u_1^G \ \dots \ u_i^G \ \dots \ u_N^G]^T$

- Matrix form

$$\tau \frac{dU^G}{dt} = -U^G + W^{GS}S + W^{GC}Y^C + \alpha \cdot DA \cdot (Y^G - \vartheta_G) + w^{GH}y^H \quad (4.a)$$

$$Y^G = \varsigma(U^G) \quad (5.a)$$

- Scalar form

$$\tau \frac{du_i^G}{dt} = -u_i^G + \sum_{j=1}^{N} w_{ij}^{GS}s_j + w_{ii}^{GC}y_i^C + \alpha \cdot DA \cdot \left(y_i^G - \vartheta_G\right) + w^{GH}y^H \quad (4.b)$$

$$y_i^G = \varsigma(u_i^G) \quad (5.b)$$

The second set of equations describe the activity of the neurons in the Go.

As for the cortex C, every neuron of the Go receives excitatory input from the whole stimulus S and excitatory projection from the corresponding neuron of the cortex C, starting here the direct pathway. In particular, it is worth noting that the array W^{GC} is diagonal, reflecting the separation among the different paths.

Dopamine (DA) and cholinergic interneuron (y^H) modulate the activity of each Go neuron.

Dopamine is excitatory ($\alpha > 0$) if the Go activity is above a certain threshold (ϑ_G), inhibitory on the contrary case: this mechanism realizes the contrast enhancement effect [24].

The cholinergic interneurons are always inhibitory ($w^{GH} < 0$) to the Go instead.

Both dopamine and acetylcholine exert tonic and phasic effects on Go activity, depending on their phasic activity (y^H) or phasic release after error feedback (DA).

Let $Y^N = [y_1^N \ \dots \ y_i^N \ \dots \ y_N^N]^T$

and $U^N = [u_1^N \ \dots \ u_i^N \ \dots \ u_N^N]^T$

- Matrix form

$$\tau \frac{dU^N}{dt} = -U^N + W^{NS}S + W^{NC}Y^C + \beta \cdot DA + w^{GH}y^H \quad (6.a)$$

$$Y^N = \varsigma(U^N) \quad (7.a)$$

- Scalar form

$$\tau \frac{du_i^N}{dt} = -u_i^N + \sum_{j=1}^{N} w_{ij}^{NS}s_j + w_{ii}^{NC}y_i^C + \beta \cdot DA + w^{NH}y^H \quad (6.b)$$

$$y_i^N = \varsigma(u_i^N) \quad (7.b)$$

The third set of equations describes the activity of the neurons in the $NoGo$.

Just like the Go, also every neuron of the $NoGo$ receives excitatory input from the whole stimulus S and excitatory projection from the corresponding neuron in the cortex C, starting here the indirect pathway instead (hence, the matrix W^{NC} is diagonal).

Dopamine (DA) and cholinergic interneuron (y^H) modulate the activity of each $NoGo$ neuron as well, but in a different way.

Dopamine is always inhibitory ($\beta < 0$) to all the $NoGo$ neurons, while the cholinergic interneurons provides excitation ($w^{NH} > 0$) to the $NoGo$.

Both dopamine and acetylcholine exert tonic and phasic effects on $NoGo$ activity, in a specular way than in the previous Go case.

Let $Y^E = [y_1^E \ \dots \ y_i^E \ \dots \ y_N^E]^T$

and $U^E = [u_1^E \ \dots \ u_i^E \ \dots \ u_N^E]^T$

- Matrix form

$$\tau \frac{dU^E}{dt} = -U^E + W^{EN}Y^N + W^{ESTN}Y^{STN} + I^E \quad (8.a)$$

$$Y^E = \varsigma(U^E) \quad (9.a)$$

- Scalar form

$$\tau \frac{du_i^E}{dt} = -u_i^N + w_{ii}^{EN}y_i^N + w^{ESTN}y^{STN} + I^E \quad (8.b)$$

$$y_i^E = \varsigma(u_i^E) \quad (9.b)$$

The fourth set of equations describe the activity of the neurons of the Gpe.

Every neuron of the Gpe receives an excitatory projection from the corresponding neuron of the cortex C, continuing the direct pathway, while the excitation (w^{ESTN}) from the STN is part of a feedback loop to control STN activity, as previously mentioned.

Every neuron is tonically active at rest, thanks to the external input (I^E).

Let $Y^I = [y_1^I \ \dots \ y_i^I \ \dots \ y_N^I]^T$

and $U^I = [u_1^I \ \dots \ u_i^I \ \dots \ u_N^I]^T$

- Matrix form

$$\tau \frac{dU^I}{dt} = -U^I + W^{IG}Y^G + W^{IE}Y^E + w^{ISTN}y^{STN} + I^I \quad (10.a)$$

$$Y^I = \varsigma(U^I) \quad (11.a)$$

- Scalar form

$$\tau \frac{du_i^I}{dt} = -u_i^I + w_{ii}^{IG}y_i^G + w_{ii}^{IE}y_i^E + w^{ISTN}y^{STN} + I^I \quad (10.b)$$

$$y_i^I = \varsigma(u_i^I) \quad (11.b)$$

The fifth set of equations describe the activity of the neurons in the Gpi.

Every neuron of the Gpi receives an excitatory projection from the corresponding neuron of the cortex C, continuing the indirect pathway, while the excitation (w^{ISTN}) from the STN is part of the hyperdirect way. Indeed, the STN excites all neurons in the Gpi, which in turns inhibit the corresponding neurons in the thalamus, thus braking any action selection.

Every neuron is tonically active at rest. In fact, the external input (I^I) overcomes the inhibitory input coming from the Gpe: that is the reason why, even receiving inhibitory projection by the corresponding neuron of the Gpe, the Gpi is active in the tonic state and inhibits the thalamus.

Let y^{STN} be a scalar, being the only neuron of the structure

and u^{STN} be a scalar for the same reason

- Matrix form

$$\tau \frac{du^{STN}}{dt} = -u^{STN} + k^E E + W^{STNE} Y^E \quad (12.a)$$

- Scalar form

$$\tau \frac{du^{STN}}{dt} = -u^{STN} + k^E E + \sum_{j=1}^{N} w_j^{STNE} y_j^E \quad (12.b)$$

$$\text{with } E = \sum_{\substack{i=1 \\ i \neq j}}^{N} y_i^C y_j^C \quad (13.b)$$

- Matrix and scalar form

$$y^{STN} = \varsigma(u^{STN}) \quad (14.a)(14.b)$$

The sixth set of equations describe the activity of the STN.

The STN is connected to the cortex C, but its activity does not depend on a single neuron, but on the overall activity of C, sensed by means of an energy function E. The latter reflects the conflict occurring in the cortex, i.e., it signals the presence of two or more cortical neurons simultaneously highly active. The higher E, the higher the excitation of the STN. This is how the hyperdirect pathway starts.

The projection from the Gpe is part of the feedback loop to control STN activity, as previously said.

Let $Y^T = [y_1^T \ \dots \ y_i^T \ \dots \ y_N^T]^T$

and $U^T = [u_1^T \ \dots \ U_i^T \ \dots \ U_N^T]^T$

- Matrix form

$$\tau \frac{dU^T}{dt} = -U^T + W^{TI}Y^I + W^{TC}Y^C \quad (15.a)$$

$$Y^T = \varsigma(U^T) \quad (16.a)$$

- Scalar form

$$\tau \frac{du_i^T}{dt} = -u_i^T + w_{ii}^{TI} y_i^I + w_{ii}^{TC} y_i^C \quad (15.b)$$

$$y_i^T = \varsigma(u_i^T) \quad (16.b)$$

The seventh set of equations describes the activity of the neurons in the thalamus T. Every neuron of the thalamus receives an excitatory projection from the corresponding neuron of the cortex C, and an inhibitory projection from the corresponding neuron of the Gpi: the imbalance between the 2 determines whether the corresponding action is gated or not. It is worth noting that the excitation from the cortex to the thalamus realizes, together with the backward excitation from the thalamus to the cortex, a positive feedback loop, which is an essential part of the WTA cortical mechanism.

Every neuron is tonically silent at rest, as a consequence of the tonic activity at rest of the Gpi

Let y^H be a scalar, being the only neuron of the structure

and u^H be a scalar for the same reason

- Matrix and scalar form

$$\tau \frac{du^H}{dt} = -u^H + I^H + \gamma \cdot DA \quad (17.a)(17.b)$$

$$y^H = \varsigma(u^H) \qquad \text{(18.a)(18.b)}$$

The last set of equations describe the activity of the cholinergic interneuron ChI.

The cholinergic interneuron is inhibited ($\gamma < 0$) by dopamine (DA), hence is influenced both tonically and phasically.

The ChI is tonically active at rest (I^H).

6.2.3.2 Hebbian rule

In this section we present the mathematical details of the hebbian rule specifically designed to reproduce synaptic plasticity as it occurs in the basal ganglia.

As it was previously mentioned, dopamine acts differentially on the striatum, being primarily excitatory for the Go part and inhibitory for the $NoGo$ part. In the present model this is expressed by means of 2 different parameters, $\alpha > 0$ and $\beta < 0$ (Figure 6.2.2.2.2), that modulate the dopaminergic term. Neural plasticity depends also on the activity of cholinergic interneurons, since these interneurons show a phasic pattern opposite to dopamine, suggesting an inhibition ratio between the 2 populations. In the model the inhibition exerted by dopamine on the cholinergic interneuron ChI is mediated by the parameter γ, as can be seen in Figure 6.2.2.2.2.

Thanks to the implemented Hebb rule, the synapses between the cortex C and Go (W^{GC}), C and $NoGo$ (W^{NC}), and between the stimulus S and Go (W^{GS}), and S and $NoGo$ (W^{NS}) change their value according to dopaminergic and cholinergic phasic effects. In fact, the latter modulate phasic activity in striatal Go and $NoGo$ neurons, which is then reflected in the post-synaptic activity of the Hebb rule.

The Hebb rule we designed differs from most similar rules used in previous model, since it reproduces this peculiar synaptic plasticity in a simple and straightforward way, without the need of any “eligibility trace” to work; i.e., it just exploits the direct effect of dopamine and acetylcholine on striatal neurons.

Let Δw_{ij} be the variation of the synapse between the pre-synaptic neuron j and the post-synaptic neuron i, the rule is expressed as follows:

$$\Delta w_{ij} = \sigma\left(y_j - \vartheta_{PRE}\right)^{+}(y_i - \vartheta_{POST})$$

where the real change in synaptic weight w_{ij} is not due to stand-alone neural activities, but to pre and post-synaptic terms instead, in which synaptic activities are compared to specific thresholds.

The introduction of pre and post-synaptic thresholds is a key element in the ability of this rule to reproduce plasticity due to the modulatory role of dopaminergic and cholinergic neurotransmitters: the post-synaptic term considers whether the post-synaptic activity y_i (in our case in the striatal neuron) is above or below a certain threshold ϑ_{POST}, which is set close to the tonic activity level. The difference therefore reveals the phasic activity of striatal neurons. In our model, the latency and the duration of phasic activities of striatal neurons have been set according to [2].

The pre-synaptic term instead, with the use of the function “positive part” ([]+), is more suitable to detect the availability of learning: only excited neurons of the cortex C or salient stimuli in S, above the threshold ϑ_{PRE}, will be allowed to change their synaptic weights. In particular, this means that only the chosen action (high value in *C*) and the present context (high values in *S*) are subjected to learning.

The Hebb rule here introduced, based on the contribution of both the pre and the post-synaptic terms, modulated by the scalar σ, is therefore able to reproduce synaptic potentiation or depression: when a stimulus S is presented to the network, if the correct response is gated, reward occurs, and corresponding striatal Go activity phasically increases, while corresponding $NoGo$ activity phasically decreases. According to the actual Hebb rule, the post-synaptic term, positive in the first case and negative in the second, induces potentiation in the corresponding direct pathway and depression in the corresponding indirect pathway of the winning neuron. Similarly, when the response gated is wrong, punishment occurs, inducing depression in the corresponding direct pathway and potentiation in the corresponding indirect pathway. Time after time, trial by trial, the overall effect of learning is to facilitate previously rewarded responses in the given context, and to suppress punished ones.

Despite what was just stated, even if synaptic weights can change their value, plasticity cannot change the nature of the projections, as previously mentioned, since the coherent use of the same neurotransmitter in the same projection represents a biological constraint. This was taken into account into the model by means of higher and lower saturation values: for excitatory synapses, $w_{ij}^{EXC} \geq 0$, for every i and j, while for inhibitory ones $w_{ij}^{IN} \leq 0$, for every i and j. An additional superior saturation was required for excitatory synapses, to avoid their “explosion” during training: the complete expression for excitatory synapses with both upper and lower bounds is therefore $0 \leq w_{ij}^{EXC} \leq 1.2$.

6.2.3.3 Parameters assignment

Since the model is extremely complex and contains many parameters, no automatic identification process was performed. Furthermore, most parameters describe average long-range connections among populations, for which neurophysiological data are not directly available. Hence, we used an heuristic approach to tune the parameters .

In particular, parameters were tuned to respect a certain number of constraints, related first to the normal working point in the absence of external stimuli, then to the response to external stimuli, and finally to the effect of rewards and punishments.

i) Individual neurons: the sigmoidal characteristics of individual neurons were given so that, in the absence of any input, the activity could be quite negligible (close to zero); the slope of the sigmoid allows a progressive increase from zero to the upper saturation, thus consenting a fine modulation of neuron activity. The time constant is the range normally adopted for rate neurons, and agrees with the temporal dynamics resulting from more sophisticated integrate and fire models.

ii) Basal working point: in basal conditions the cortex, the thalamus and the striatum must be inhibited; conversely the Gpi and Gpe exhibit a certain basal activity. We assumed that the basal activity of the Gpe is at about half the maximal; conversely, the basal activity of the Gpi is higher, close to the upper saturation. This high activity of the Gpi agrees with physiological data and is necessary to maintain the thalamus in the inhibited state. The previous constraints were realized by assigning values to the external inputs to the Gpi and Gpe, and to the connectivity from Gpi to Gpe, and from Gpe to the thalamus.

iii) Cortex and thalamus: the lateral connections within the cortex, and the connections from the cortex to the thalamus and back from the thalamus to the cortex were assigned to realize quite a strong winner takes all mechanism. In particular, the cortico-thalamic loop represents a self-excitation, necessary to lead the winner neuron close to the upper saturation. The lateral inhibition is strong enough so that the winner neuron (close to saturation) can almost completely inhibit all other cortical neurons. The synapses from the stimulus to the cortex have a moderate value so that, in the absence of thalamic excitation, a neuron in the cortex cannot reach a high activity level (hence the corresponding action is not triggered).

iv) Striatum: the synapses from the stimulus and from the cortex to the striatal (Go and $NoGo$) neurons were given moderate values before training, so that the striatal neurons in the active pathway could have an intermediate activity between inhibition and upper saturation (approximately 0.5). This activity is close to the threshold of the Hebb rule. As a consequence, the corresponding synapses are reinforced or weakened only in response to reward or punishment feedbacks, which significantly alter the neuron activity level. In the absence of feedback, the synapse changes are negligible.

v) Globus pallidus: the synapses from the striatum to the Gpe and Gpi were given so that even a moderate activation of a striatal neuron (as a consequence of the cortical winner neuron and sensory inputs) can induce almost complete inhibition of the downstream neurons (in Gpi and Gpe). The synapses from Gpi to the thalamus ensure that, when Gpi is active, the thalamus is completely inhibited. Hence, Gpi dishinibition corresponds to the desired gating mechanism.

vi) Sub-thalamic nucleus. The connectivity form the cortex to the STN has been chosen so that even a moderate conflict (i.e., two cortical neurons simultaneously quite active) can excite the STN. The connection from STN to the Gpi ensures strong excitation of Gpi even at moderate activity of the STN, thus blocking any gating by the basal ganglia. Finally, the feedback connections between the STN and Gpe were chosen to permit a rapid deactivation of the STN when conflict is resolved.

vii) Dopamine and acetylcholine: parameters which set the dopamine action on striatal neurons were assigned so that a dopamine increase, during reward, can activate the winner Go neuron in the striatum close to its upper saturation, and almost completely inhibit all $NoGo$ neurons. Similarly, a dip in dopamine must be able to strongly inhibit all Go neurons (also via activation of the cholinergic path) and excite the winner $NoGo$ neuron. These constraints were satisfied by setting appropriate gains from dopamine to striatum, and from dopamine to cholinergic to striatum. As a consequence, the Hebb rule can work as requested, favoring the Go pathway during reward and the No-Go pathway during punishment.

Starting from an initial cluster of values for the parameters, able to satisfy the constraints i) and ii), the technique was to assess the behavior of the network in order to have the desired behavioral output by progressively including subsequent constraints, fixing the previous parameters and determining the new ones .

Some parameters were obtained also including or knocking out specific structures, such as the STN.

This whole tuning procedure was iterated several times, considering cyclically the previous set of parameters, and finally evaluating the entire neural network in order to verify if the whole behavior could satisfy all biological requirements.

I. Table of parameters

Table 6.2.3.3.1: table of the parameters of the model

Name	Value
τ / τ_L	10 [ms] / 50 [ms]
a	4
u_0	1
ϑ_G	0.3
I^E	1
I^I	3
I^H	1.25
σ	0.1
ϑ_{PRE}	0.5
ϑ_{POST}	0.5
α	1
β	-1
γ	-1

II. Table of synapses

Table 6.2.3.3.2: table of the default synapses of the model (before training)

Name	Projection	Type	Value
$\boldsymbol{L}$	inhibition	extradiagonal matrix	$\begin{bmatrix} 0 & -1.2 & -1.2 & -1.2 \\ -1.2 & 0 & -1.2 & -1.2 \\ -1.2 & -1.2 & 0 & -1.2 \\ -1.2 & -1.2 & -1.2 & 0 \end{bmatrix}$
$\boldsymbol{W^{CS}}$	excitation	full matrix	$\begin{bmatrix} 1.1 & 0.2 & 0.2 & 0.2 \\ 0.2 & 1.1 & 0.2 & 0.2 \\ 0.2 & 0.2 & 1.1 & 0.2 \\ 0.2 & 0.2 & 0.2 & 1.1 \end{bmatrix}$
$\boldsymbol{W^{CT}}$	excitation	diagonal matrix	$\begin{bmatrix} 4 & 0 & 0 & 0 \\ 0 & 4 & 0 & 0 \\ 0 & 0 & 4 & 0 \\ 0 & 0 & 0 & 4 \end{bmatrix}$
$\boldsymbol{W^{GC}}$	excitation	diagonal matrix	$\begin{bmatrix} 0.48 & 0 & 0 & 0 \\ 0 & 0.48 & 0 & 0 \\ 0 & 0 & 0.48 & 0 \\ 0 & 0 & 0 & 0.48 \end{bmatrix}$
$\boldsymbol{W^{GS}}$	excitation	full matrix	$\begin{bmatrix} 0.9 & 0 & 0 & 0 \\ 0 & 0.9 & 0 & 0 \\ 0 & 0 & 0.9 & 0 \\ 0 & 0 & 0 & 0.9 \end{bmatrix}$
$\boldsymbol{W^{NC}}$	excitation	diagonal matrix	$\begin{bmatrix} 1.08 & 0 & 0 & 0 \\ 0 & 1.08 & 0 & 0 \\ 0 & 0 & 1.08 & 0 \\ 0 & 0 & 0 & 1.08 \end{bmatrix}$

W^{NS}	excitation	full matrix	$\begin{bmatrix} 0.1 & 0 & 0 & 0 \\ 0 & 0.1 & 0 & 0 \\ 0 & 0 & 0.1 & 0 \\ 0 & 0 & 0 & 0.1 \end{bmatrix}$
W^{EN}	inhibition	diagonal matrix	$\begin{bmatrix} -2.2 & 0 & 0 & 0 \\ 0 & -2.2 & 0 & 0 \\ 0 & 0 & -2.2 & 0 \\ 0 & 0 & 0 & -2.2 \end{bmatrix}$
W^{IE}	inhibition	diagonal matrix	$\begin{bmatrix} -3 & 0 & 0 & 0 \\ 0 & -3 & 0 & 0 \\ 0 & 0 & -3 & 0 \\ 0 & 0 & 0 & -3 \end{bmatrix}$
W^{IG}	inhibition	diagonal matrix	$\begin{bmatrix} -12 & 0 & 0 & 0 \\ 0 & -12 & 0 & 0 \\ 0 & 0 & -12 & 0 \\ 0 & 0 & 0 & -12 \end{bmatrix}$
W^{TC}	excitation	diagonal matrix	$\begin{bmatrix} 3 & 0 & 0 & 0 \\ 0 & 3 & 0 & 0 \\ 0 & 0 & 3 & 0 \\ 0 & 0 & 0 & 3 \end{bmatrix}$
W^{TI}	inhibition	diagonal matrix	$\begin{bmatrix} -3 & 0 & 0 & 0 \\ 0 & -3 & 0 & 0 \\ 0 & 0 & -3 & 0 \\ 0 & 0 & 0 & -3 \end{bmatrix}$
w^{ESTN}	excitation	scalar	1
w^{ISTN}	excitation	scalar	14
k^{E}	excitation	scalar	7
W^{STNE}	inhibition	raw vector	$\begin{bmatrix} -1 & -1 & -1 & -1 \end{bmatrix}$
w^{GH}	inhibition	scalar	-1
w^{NH}	excitation	scalar	1

6.3 Results

Here are presented some simulations that show how the present model is able to give a suitable representation of real basal ganglia behavior.

The majority of the following simulations are run with a tonic dopamine value (0.45).corresponding, in our set of parameters, to healthy tonic levels

6.3.1 Default behavior

As mentioned at the beginning of the chapter, in a response selection task the network, when presented with a stimulus, has to choose a response according to a specific rule. In the default case, the response gated by the network is associated to the highest element of the stimulus S.

In the following simulation the stimulus $S = [0.3\ 0.8\ 0.3\ 0.2]^T$ is presented in input to the network in its default, steady state.

The network responds correctly according to the default rule and gates the response coded by the neuron of the cortex associated to the highest element of the stimulus S, i.e. the second one.

Go and $NoGo$ signals show that both direct and indirect pathway are activated for the winning neuron. However, the correct response is gated because their imbalance resulted in a low activity of the corresponding neuron of the Gpi, therefore projecting less inhibition to the corresponding neuron of the thalamus. Hence, the corresponding winning neuron of the cortex was able to get the positive feedback and reach the gating threshold.

The STN signal shows that the network does not perceive any challenging situation in the cortex.

Furthermore, the cholinergic interneuron signal is stable at his tonic activity level during the whole simulation, since no error feedback was released.

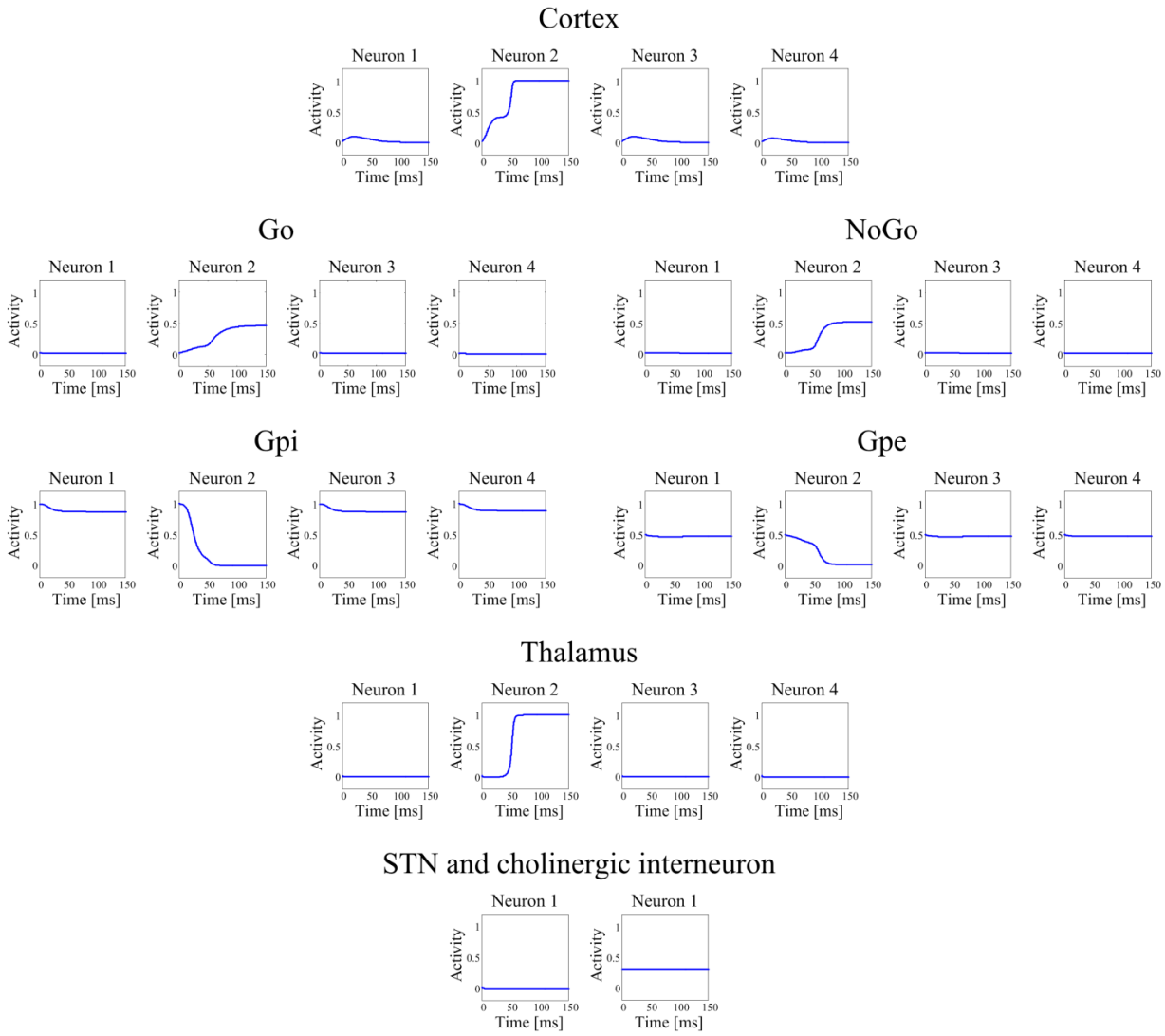

Figure 6.3.1.1: activity within time of the neurons in each structure of the whole network in a default case

6.3.2 Conflict resolution

In particular situations when the choice for the cortex is particularly difficult, the hyperdirect pathway, carried out by the STN, works to prevent any gating by the basal ganglia. To this aim, the STN provides an overall stop signal to the network, maintaining Gpi at high level of activity and subsequently the thalamus at low levels of activity. The overall result is to block basal ganglia feedback to all the neurons of the cortex, in order to let more time to the cortex to solve the conflict and evaluate the correct subset of candidate responses.

In the following simulation a conflicting stimulus $S = [0.85\ 0.9\ 0.85\ 0.1]^T$ is presented in input to the network in its default, steady state. S is able to induce a great conflict within the cortex, in particular among the first 3 neurons, since for the network they all represent strong candidate responses, suitable to be gated. However, the default preferred response is coded by the second neuron of the cortex C.

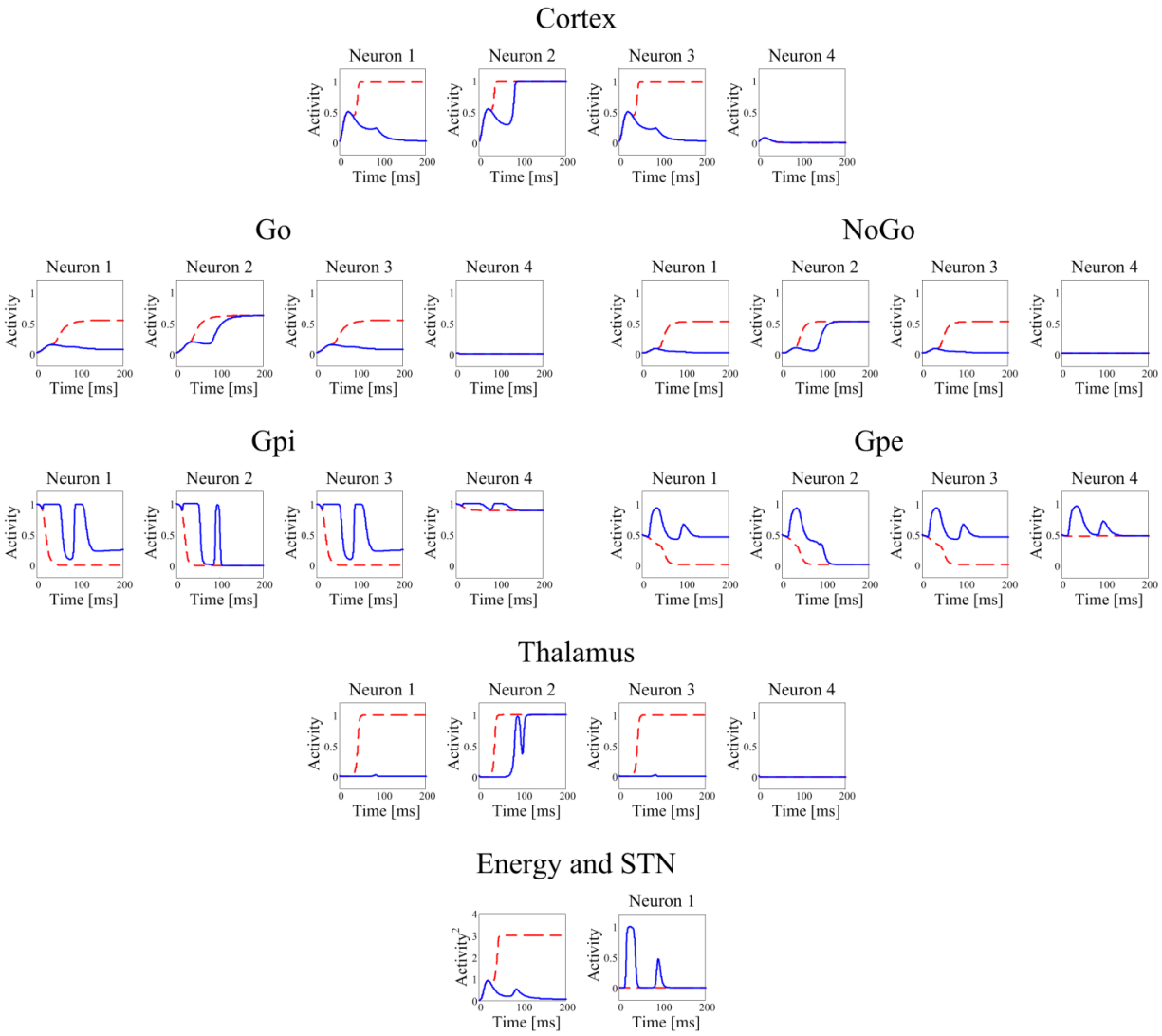

Figure 6.3.2.1: activity within time of the neurons in each structure of the whole network in a situation of conflict resolution, **red** with no $\boldsymbol{STN}$, **blue** with $\boldsymbol{STN}$

The red dotted signals represent a simulation run by artificially knocking out the STN and the hyperdirect pathway (as can be clearly seen in the corresponding panel, the signal of the STN activity is 0 throughout the simulation). Here, a non-physiological situation occurs, and all the strong candidate neurons rapidly achieve the activity threshold to be gated.

Both Go and No-Go signals for all the 3 strong candidate responses rise.

Finally, as confirmed by thalamic signals, without the STN the basal ganglia provide quick but contradicting feedback to every strong neuron, leading to a malfunctioning of basal ganglia (i.e., all three strong but contradictory responses are simultaneously gated). Furthermore, the energy signal value, representing a measure of the conflict within the cortex C, remains high during the whole simulation, underling that the situation remains unusual and unresolved. The blue signals represent the simulation performed assuming an intact STN: also in this situation an initial state of conflict is clearly evident both from the cortical signals in C and from the energy function. At first, the activity of the STN is high, in order to temporarily stop basal ganglia feedback until the conflict within the cortex is solved: this can be noticed also from a delay in the Gpi and in the thalamic signals, compared with the previous case.

The final results is that the cortex has more time and is now able to solve its conflict; as a consequence the basal ganglia can provide correct feedback, even if slower. The output response this time is the correct one, i.e. the one coded by the second neuron of C. More important, the model can select just one final response, avoiding conflicting experiences, despite the presence of multiple strong inputs.

Once the role of STN is accomplished, its activity is less necessary and essentially the neuron becomes silent.

6.3.3 Reward and punishment

In one of the previous subsections we mentioned that both dopamine and cholinergic interneurons are responsible for synaptic plasticity in the basal ganglia. Here we present how error feedback (i.e. reward and punishment) are able to alter striatal activity, which is at the basis of the activity driven synaptic plasticity described by our hebbian rule.

In the following simulation the stimulus $S = [0.4\ 0.8\ 0.6\ 0.5]^T$ is presented in input to the network in its default, steady state. The gated response is therefore the one coded by the second neuron of C.

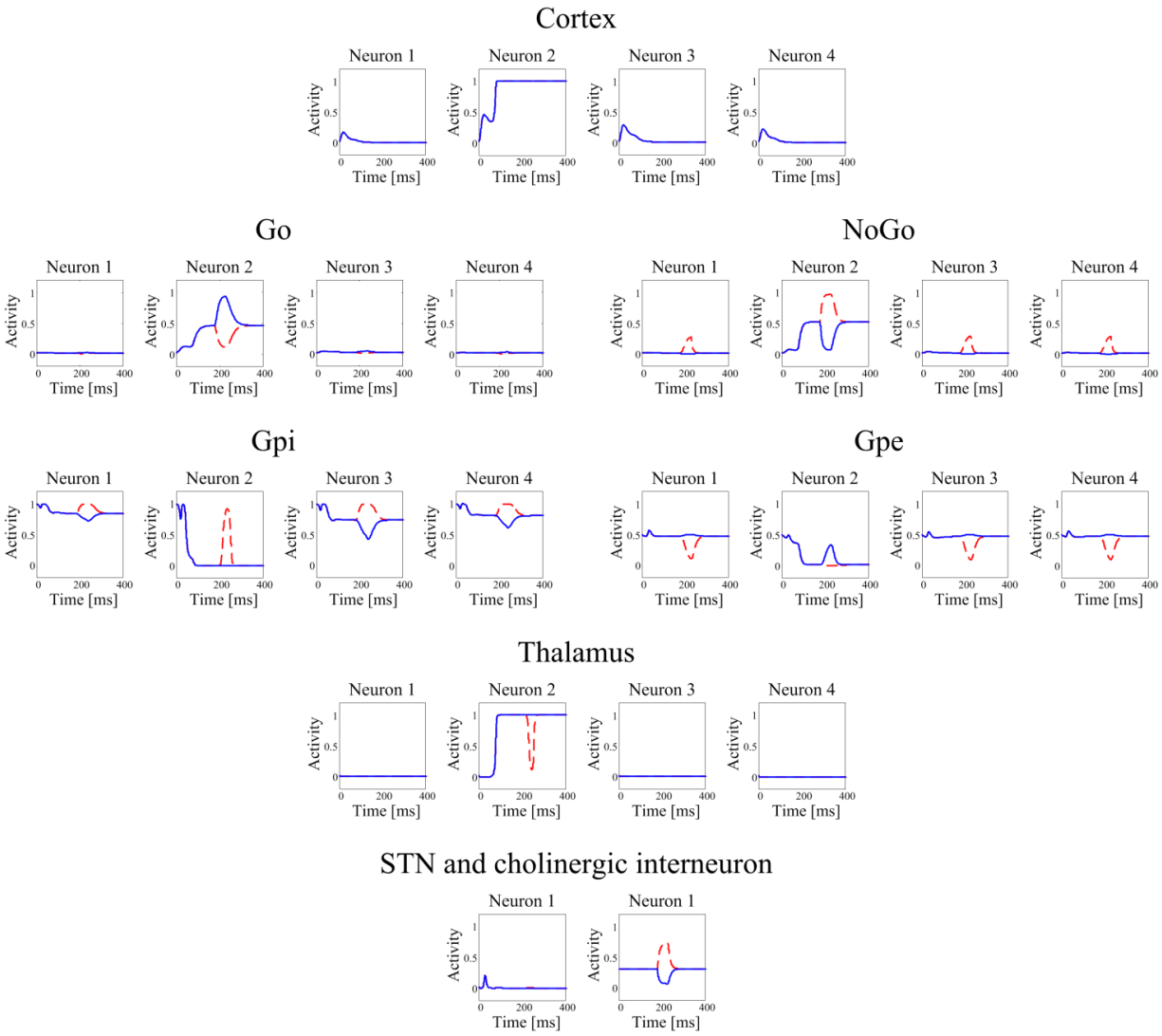

Figure 6.3.3.1: activity within time of the neurons in each structure of the whole network during error feedback, **red** punishment, **blue** reward

In the first simulation (red dotted signals) the response coded by the winning neuron of the cortex is assumed to be wrong, therefore a punishment occurs. In the second (blue signals) the same winning response is assumed to be right: as it can be easily seen, reward and punishment nearly cannot modify cortical activity at this stage.

The effect of reward and punishment is clearly noticeable in the activity of striatal neurons. In the second case, if the winning neuron encodes the wrong response (punishment), a transient dip in the corresponding Go unit occurs. This dip should be noticeable also in the corresponding Go unit of the losing neurons, but their activity is too low to be manifest. On the other hand, the $NoGo$ units clearly show a peak, particularly pronounced in the unit of the winning neuron.

In case of punishment, and therefore of phasic dopamine dip, we can notice that the model clearly show a transient peak in the cholinergic interneuron activity signal, underlying the inhibition role of dopamine on cholinergic interneurons.

In the second case, if the winning neuron encodes the right response, a transient peak in the corresponding Go unit occurs. Unfortunately in this part of the simulation the other Go signals do not allow to appreciate the contrast enhancement phenomenon that has been explicitly modeled in the network. The $NoGo$ neurons reports all a transient dip in their activity, particularly remarkable for the corresponding losing unit.

In the cholinergic interneuron signal this time we can assess a transient trend opposite than the previous case: this time the reward led to dopamine phasic release, therefore ChI activity this time records a transient dip.

As a consequence of the previous changes, the phasic activity in the striatum during error feedback, both in case of reward and punishment, leads the neurons well above (or well below) threshold thus driving a significant hebbian learning.

6.3.4 Contribution of ChI to reward and punishment

One of the main novelties introduced by the present model is to explicitly introduce striatal cholinergic interneurons and their role in synaptic plasticity, asserting that the phasic changes in their activity, due to dopamine variations, affect phasic striatal activity during error feedback, both in reward and in punishment.

In order to analyze the function of this specific mechanisms, in the following simulation we represent exactly the previous case, with the same stimulus S, this time assuming that ChI is not affected by dopamine phasic changes, and therefore keeps its tonic value.

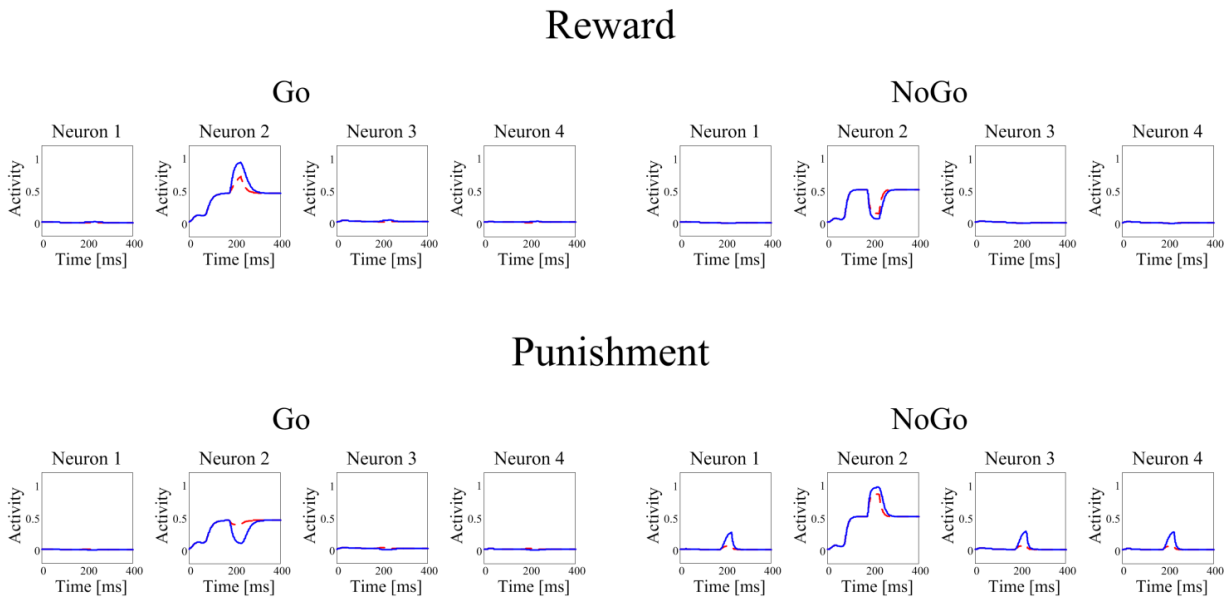

Figure 6.3.4.1: activity within time of the neurons in $\boldsymbol{Go}$ and $\boldsymbol{NoGo}$ structures during reward and punishment, **red** with no phasic activity of $\boldsymbol{ChI}$, **blue** with phasic activity of $\boldsymbol{ChI}$

We will will focus on the difference between red and blue dotted signals.

The red dotted signals have lower peaks and higher dips: this means that the contribution of ChI is essential for synaptic plasticity, in particular causing greater increases or decreases of phasic peaks or dips in striatal activities, compared to an established threshold ϑ_{POST}; this allows greater changes in synaptic weights according to our specific Hebb rule.

In particular, it can be noticed in this case that the contribution of ChI is particularly essential to the Go neurons, both in rewards and in punishment, otherwise their post-synaptic term in the Hebb rule would be close to 0, preventing any plasticity along the direct pathway.

6.3.5 Single example of Hebb rule during reward and punishment

In the following simulation we will provide an example of the first step of the application of our brand new Hebb rule, underlying how the different matrices chance according to the pre-synaptic term, represented either by the cortex C or by the stimulus S, and to the post-synaptic term of the rule.

According to the different error feedback, reward and punishment can induce differential effects in the synapses that can exert plasticity effects.

In the first case, we present the case in which the response gated is correct, therefore a reward occurs, while in the second case we consider a mistake and a punishment episode.

In both simulations a stimulus $S = [0.4\ 0.8\ 0.6\ 0.5]^T$ is presented in input to the network. The winning or losing response is always coded by the second neuron.

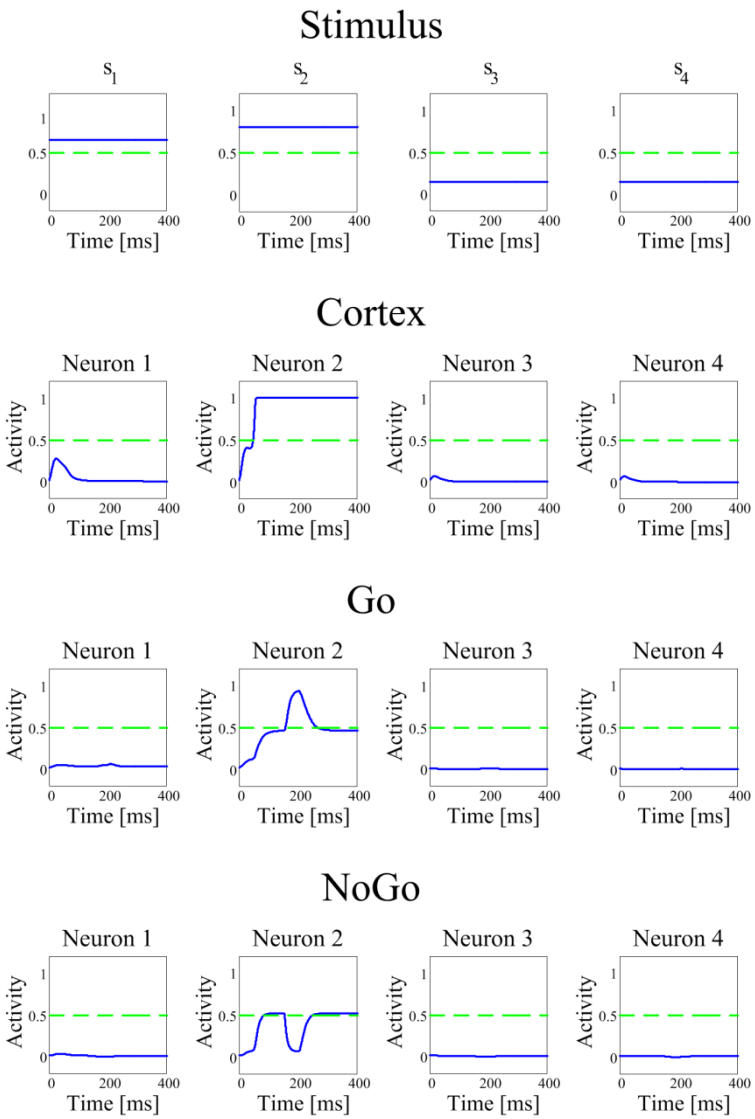

Figure 6.3.5.1: stimulus $\boldsymbol{S}$ and activity within time of the neurons in $\boldsymbol{C}$, $\boldsymbol{Go}$ and $\boldsymbol{NoGo}$ structures during reward in **blue**, pre and post-synaptic thresholds of the Hebb rule in **green**

In this first case, we analyse how synaptic values change

$$\Delta W^{GC} = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 0.0177 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

In this case the only neuron whose activity is above threshold is the second, as well as the second neuron of the Go: the second term of this diagonal matrix increases, as the Go pathway of the winning neuron.

$$\Delta W^{NC} = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & -0.0176 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

In this case the only neuron whose activity is above threshold is the second, therefore only the second neuron of the $NoGo$ is relevant to plasticity: the second term of this diagonal matrix decreases, as the No-Go pathway of the winning neuron.

$$\Delta W^{GS} = \begin{bmatrix} -0.0070 & -0.0141 & 0 & 0 \\ 0.0065 & 0.0131 & 0 & 0 \\ -0.0074 & -0.0149 & 0 & 0 \\ -0.0074 & -0.0149 & 0 & 0 \end{bmatrix}$$

This matrix is a full matrix, and represent context training: there is no variation for the stimuli below threshold, while all the stimuli above threshold increase the Go pathway of the winning neuron. The Hebb rule in the case of the stimulus trains also synapses related to neurons not rewarded neither punished, as their Go pathway decrease: this will facilitate again the neuron that has just won.

$$\Delta W^{NS} = \begin{bmatrix} -0.0075 & -0.0150 & 0 & 0 \\ -0.0065 & -0.0130 & 0 & 0 \\ -0.0075 & -0.0150 & 0 & 0 \\ -0.0075 & -0.0150 & 0 & 0 \end{bmatrix}$$

This matrix, again is a full matrix, and also represent context training: as in the previous case, there is no variation for the stimuli below threshold, while all the

stimuli above threshold decrease the No-Go pathway of the winning neuron. The Hebb rule also in this case trains synapses related to neurons not rewarded neither punished, as this time their No-Go pathway decrease.

Similar evaluations can be done for the punishment event.

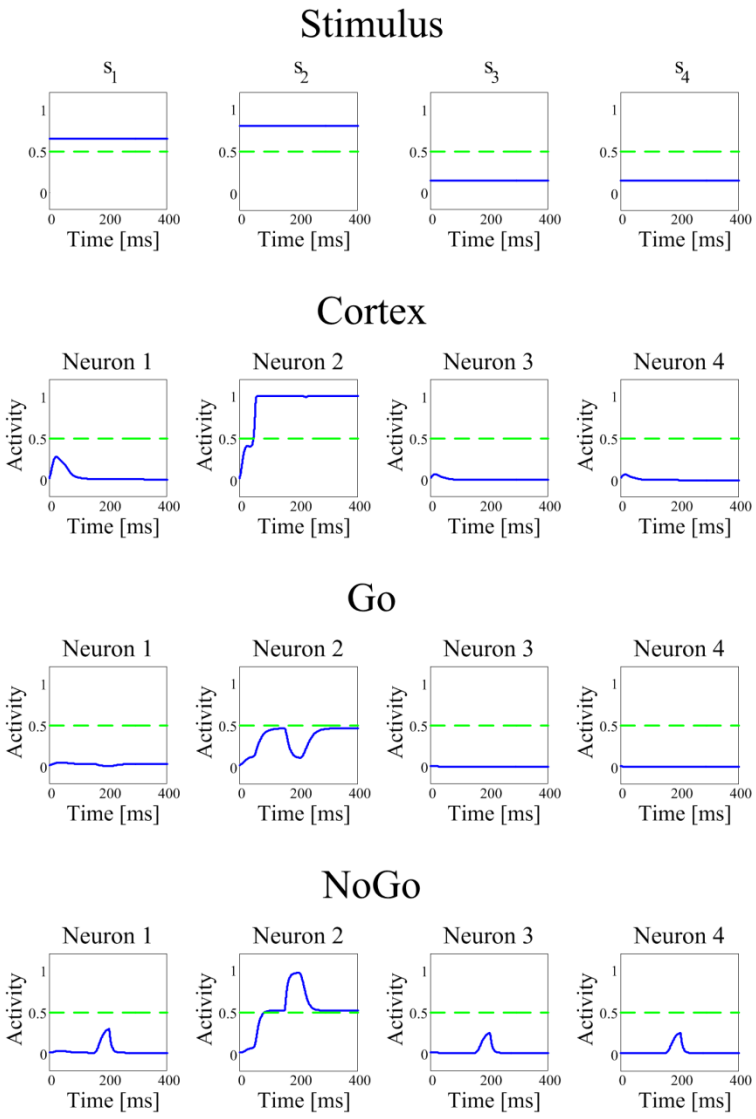

Figure 6.3.5.2: stimulus $\boldsymbol{S}$ and activity within time of the neurons in $\boldsymbol{C}$, $\boldsymbol{Go}$ and $\boldsymbol{NoGo}$ structures during punishment in **blue**, pre and post-synaptic thresholds of the Hebb rule in **green**

6.3.6 Training

Basal ganglia can change their behavior and their stimulus-response associations by means of synaptic plasticity. As previously said, we a priori established that, in the default case, the response gated by the network is associated to the highest element of the stimulus S. However, by means of synaptic plasticity and training, the network is able to establish new rules to have different outcomes in correspondence to the same stimulus.

Given a stimulus S, the aim of training is to shift the chosen response from the default, prepotent one (i.e. the one associated to the strongest element of S) to the one coded by the neuron associated to the second higher element of S.

The following simulation was produced with a stimulus $S = [0.15\ 0.15\ 0.9\ 0.7]^T$.

In this case, the aim is to progressively suppress the response coded by the third neuron of the cortex, and to train the network to gate the response coded by the fourth neuron, when this stimulus S is presented in input to the network.

In these simulations noise was added to the original stimulus S (normal distribution with mean value 0 and standard deviation 0.25) in order to generate the gating of alternative actions, and so various situations of reward and punishment during the different epochs. To avoid situation of non-normalized elements of the stimulus S, after the addition of the random values each element of the final S was compelled by upper and lower bounds to be in the range $[0,1]$.

The training consisted of 100 epochs.

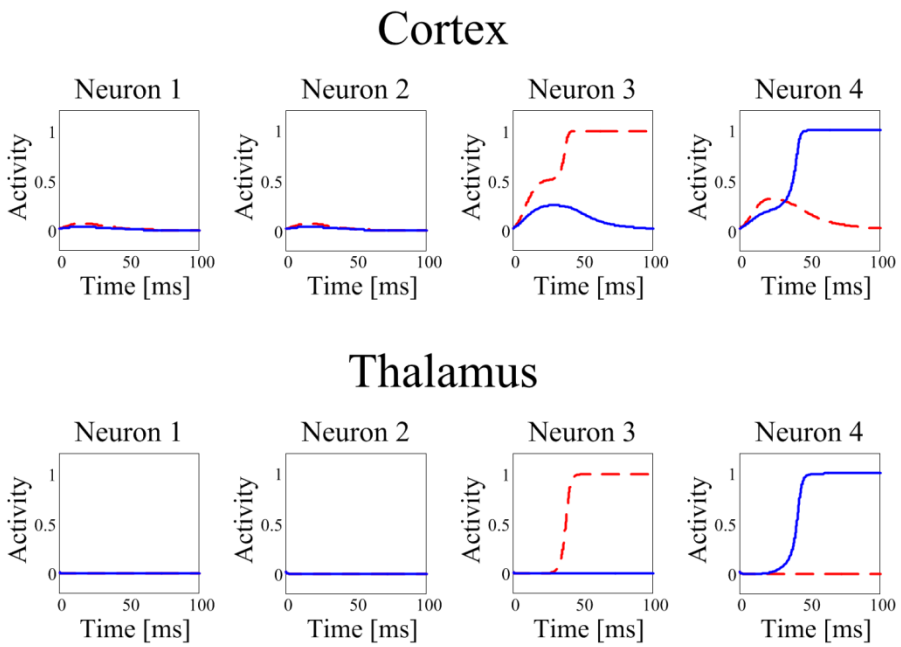

Figure 6.3.6.1: activity within time of the neurons in the cortex and in the thalamus: **red** before training, **blue** after training

This figure shows the temporal response of the network to the stimulus $S = [0.15\ 0.15\ 0.9\ 0.7]^T$, given without noise, first in the initial stage (red dotted signals) and the final stage (blue signals) of the training.

At the beginning, the the prepotent response is gated, as shown by the final activity both in the cortex and the thalamus. The first weak sign of training is shown by a little dip in the activity of the third neuron of the thalamus, showing that the training is starting punishing the prepotent response, as expected.

After 100 epochs of training, the network is presented the same stimulus S but now the basal ganglia gate the desired response, i.e. the one coded by the fourth neuron, showing that the training process was successful.

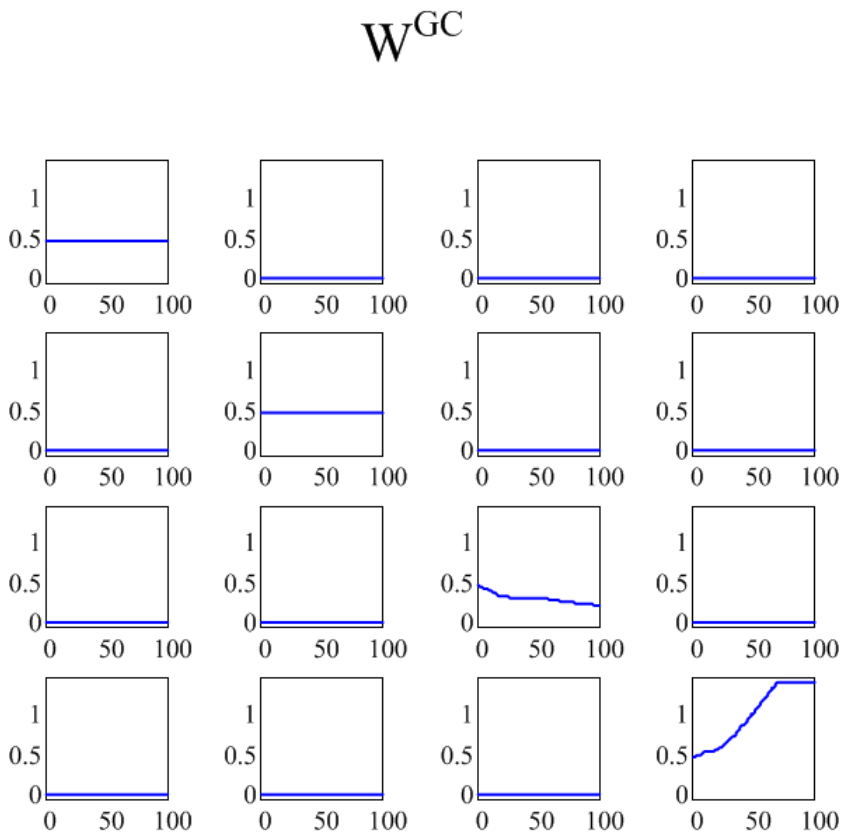

Figure 6.3.6.2: W^{GC} synapses update during the 100 epochs. Row i is post-synapctic neuron i, while column j is pre-synaptic neuron j

In order to better understand how learning works, the previous figure shows the changes in synapses W^{GC} during the 100 epochs of training.

It must be considered that this matrix is diagonal, as was specified in the table above, therefore only the elements on the diagonal are significant.

Recalling that W^{GC} is implied in the direct pathway, the decrease of the element in the position (3,3) attempts dis-facilitate the prepotent response.

On the contrary, the increase of the element in the position (4,4) corresponds to an increase in the facilitation of the desired response, with the corresponding synapse increased to its upper saturation.

W^{GS}

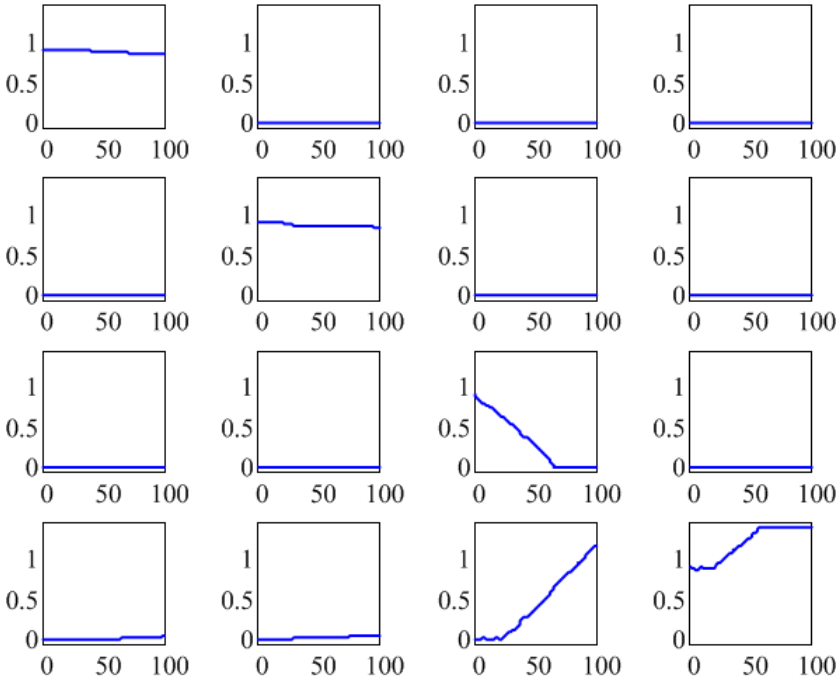

Figure 6.3.6.3: W^{GS} synapses update during the 100 epochs. Row i is post-synapctic neuron i, while column j is pre-synaptic neuron j

Figure 6.3.6.3 shows how the synapses W^{GS} change during the 100 epochs of training.

It must be considered that this matrix is a full matrix, as was specified in the table above.

The elements of interest for the present analysis are those in the positions (3,3), (3,4), (4,3), (4,4).

Recalling that also W^{GS} is implied in the direct pathway, the decrease of the element in the position (3,3) and the lack of increase of the element in the position (3,4) are consistent with the attempt to provide less facilitation to the prepotent response.

Similarly to W^{GC}, this time 2 synapses, (4,3) and (4,4), rise to provide more facilitation to the desired response.

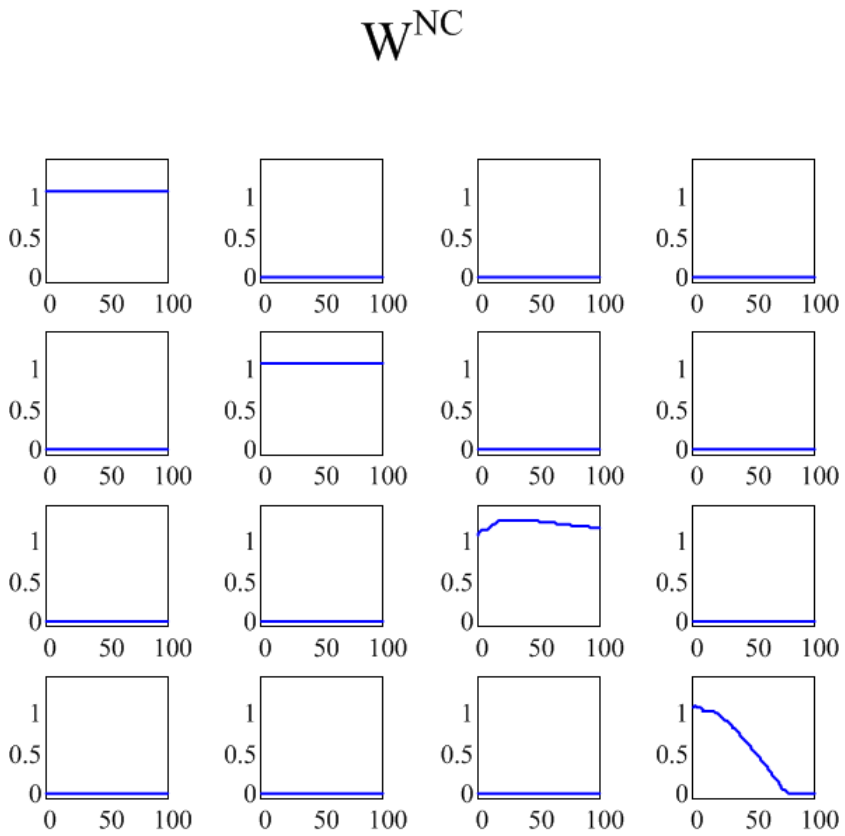

Figure 6.3.6.4: W^{NC} synapses update during the 100 epochs. Row i is post-synapctic neuron i, while column j is pre-synaptic neuron j

This figure shows how the synapses of W^{NC} change during the 100 epochs of training.

As W^{GC}, also this matrix is diagonal, and once again only the elements on the diagonal have to be considered.

Recalling that W^{NC} is implied in the indirect pathway, the slightly increase of the element in the position (3,3) corresponds to the attempt to suppress the prepotent response.

On the contrary, the decrease of the element in the position (4,4) corresponds to the attempt to provide less inhibition to the neuron coding the desired response; in this case the corresponding synapses is decreased to zero (lower saturation)

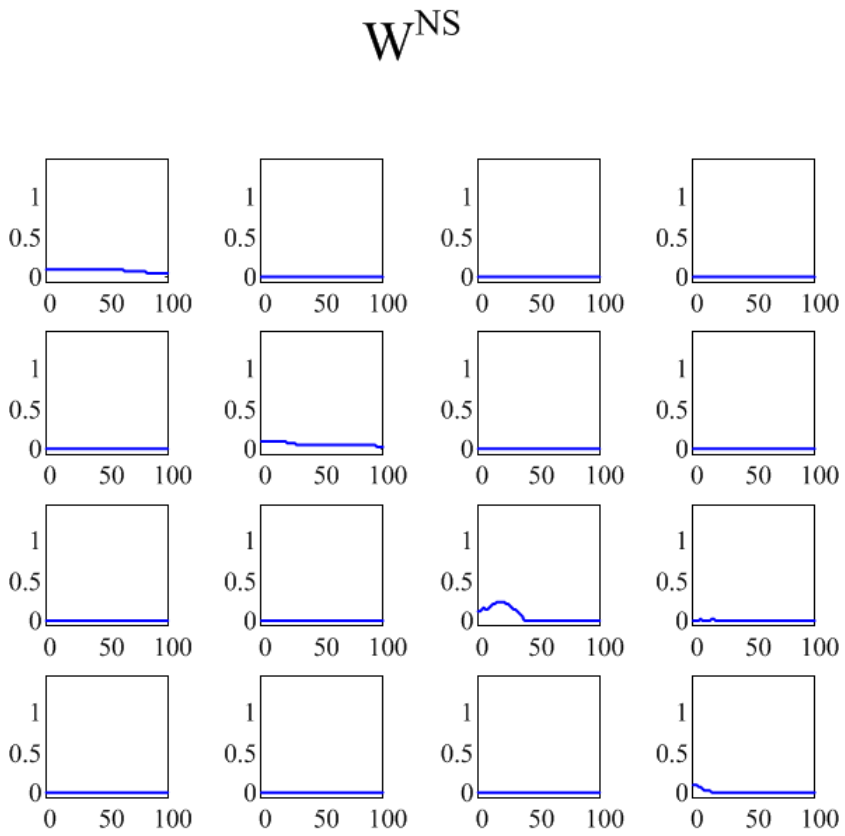

Figure 6.3.6.5: W^{NS} synapses update during the 100 epochs. Row i is post-synapctic neuron i, while column j is pre-synaptic neuron j

This figure shows how the synapses of W^{NS} change during the 100 epochs of training.

Similarly to W^{GS}, this matrix is a full matrix, and again the elements of interest for the present analysis are the ones in the positions (3,3), (3,4), (4,3), (4,4).

W^{NS} is implied in the indirect pathway, and its changes are less immediate to understand.

Indeed, this matrix exhibits only mild changes as a consequence of training. Some changes (suppression of the third action by an increase in the element (3,3)) are evident only during the first epochs. The reason is that, during the last epochs, punishment occurs only rarely, while the input stimuli S are still high. Hence, as a consequence of the Hebb rule, all synapses from S to the $NoGo$ are progressively suppressed.

However, despite this incongruence, the comparison between the cortical activity at the beginning and at the end of the training, in response to the same stimulus S, shows that the overall training of the synapses was successful and that the network after the training was able to adapt the stimulus-response coded as desired.

6.3.7 Network with low, normal and high tonic dopamine levels

In our model of the basal ganglia dopamine is present both in its tonic and in its phasic form.

The implication of phasic dopamine in synaptic plasticity has been widely discussed before. Now we wish to focus on how the model is able to reproduce behavioral changes due to different level of tonic dopamine, and how tonic dopamine impacts the basal ganglia behavior in our model.

In the following simulation the stimulus $S = [0.3\ 0.3\ 0.85\ 0.3]^T$ is presented in input to the network in steady state, assuming three different conditions each characterized by a different value of tonic dopamine: the normal value (0.45, blue line), a high value (0.55, black dashed line) and a low value (0.35, red dotted line).

As can be easily seen, the tonic level of dopamine has effects on each structure of the network.

In the cortex C, the higher the tonic dopamine level, the faster the response, just like that caused by a feedback by the thalamus.

One of the most interesting results is about striatal activity: our model straightforwardly translates the physiological knowledge that tonic dopamine level is associated to an overall imbalance in the direct-indirect pathway.

Indeed, a higher tonic dopamine level, compared to that used in all previous simulation, promotes the direct pathway with respect to the indirect pathway: this is particularly noticeable in the activity of the Go and $NoGo$ winning neurons, being activity in the first higher and in the second lower than normal. This could be interpreted as a possible simulation of traditional medicated Parkinson's disease, as it is generally characterized by higher tonic dopamine.

Low tonic dopamine level exerts the opposite effects instead, promoting the indirect with respect to the direct pathway: again, the clearest examples are the activities in the Go and $NoGo$ of the winning neurons, which are lower and higher than normal, respectively. This condition could also have a clinical interpretation, as it is widely known that one of the main feature of Parkinson's disease is tonic dopamine levels lower than normal.

Moreover, different levels of tonic dopamine exerts differential effect also on the tonic activity of ChI, as a lower dopamine level and therefore lower inhibition allows ChI to be more active, whereas higher dopamine levels tend to inhibit ChI activity.

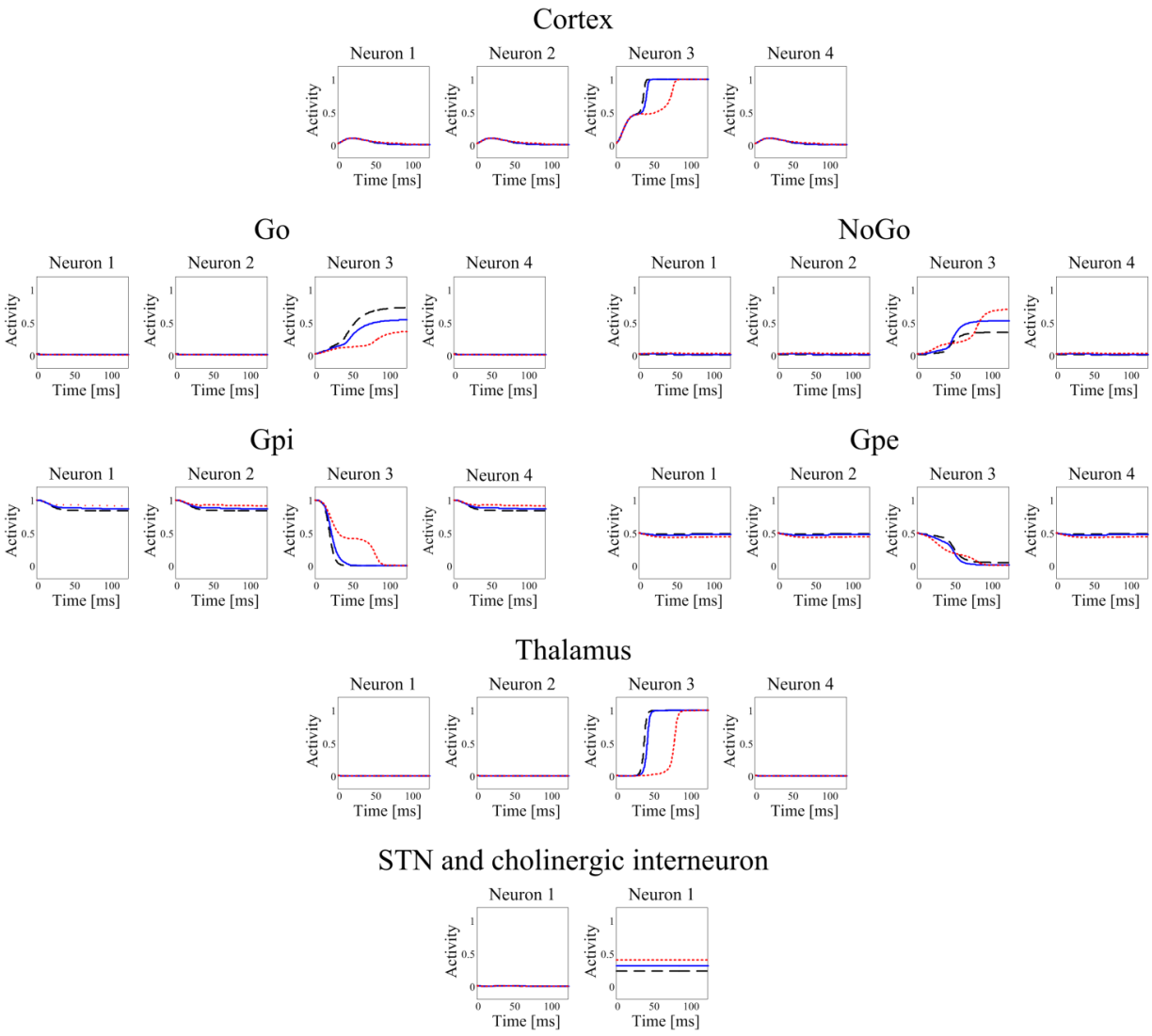

Figure 6.3.7.1: activity within time of the neurons in each structure of the whole network with different tonic dopamine levels, **red** low level, **blue** normal level and **black** high level

6.3.8 Sensitivity to the magnitude of stimulus with different levels of tonic dopamine

In this simulation we investigate the relationship between different levels of tonic dopamine and the response, using stimuli with a different magnitude; the aim is to assess whether there is a relationship between the tonic dopamine, the subjective sensitivity to the stimuli and the temporal delay of the gated response.

In the present simulation the network is presented with a stimulus $S = [0.3\ 0.3\ a\ 0.3]^T$, with $a \in [0.31,1]$.

Lowest tonic dopamine is assumed to be 0.35 (red dotted curve), low tonic dopamine 0.4 (green dot and dashed line) physiologic tonic dopamine 0.45 (blue line), as in the previous simulations, and high tonic dopamine 0.55 (black dashed line).

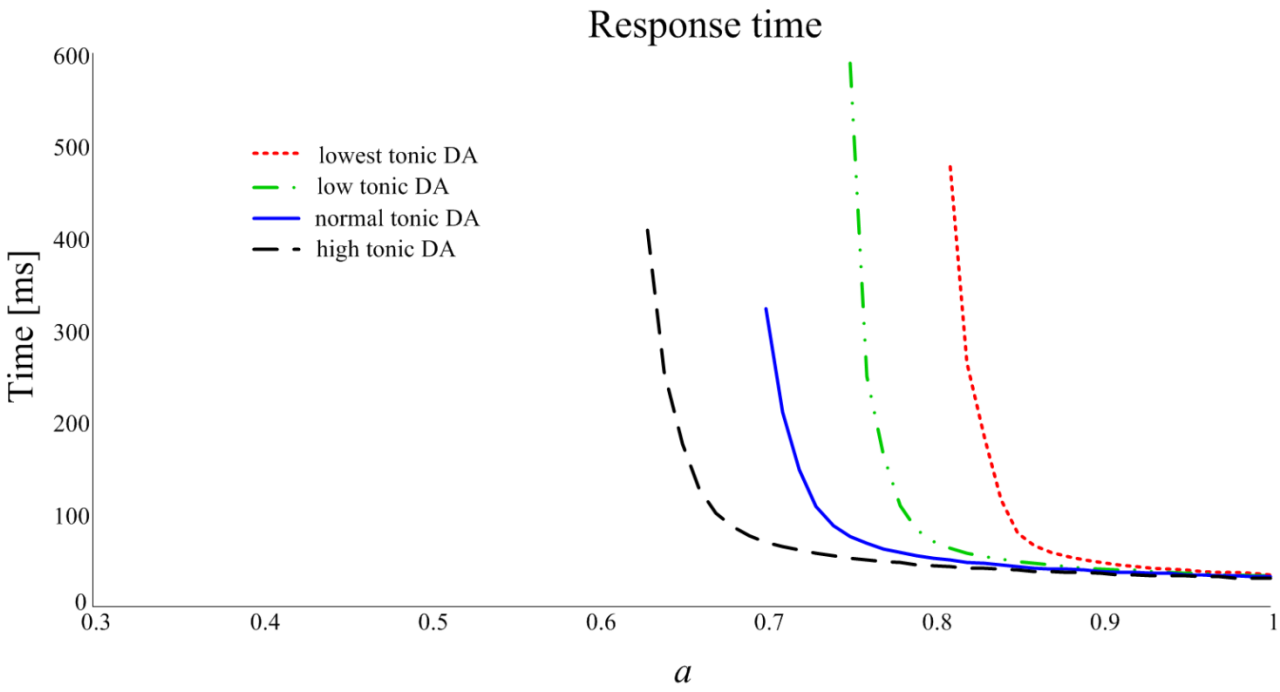

Figure 6.3.8.1: time responses to stimuli $\boldsymbol{S}$ of different magnitude, with **lowest**, **low**, **normal** and **high** tonic dopamine

The simulations show that, in case of low stimuli, the time required to achieve a valid response crucially depends on the dopamine level: high levels of dopamine result in faster responses compared with lower levels. Conversely, when the stimulus is high, the temporal response becomes scarcely affected by the dopamine level.

Furthermore, in case of low dopamine, the network is able to gate only strong stimuli, but it neglects the stimuli of low amplitude. Moreover, the lower the dopamine levels, the higher the magnitude of a stimulus necessary for activating the corresponding response.

This again could account for particular behavior in Parkinson's disease, which is characterized by either low tonic dopamine levels or, after overmedication, by tonic dopamine values higher than normal. In the first case, the model predicts that the subject can neglect important responses if the stimuli are not high enough. In the second, an hypersensitivity to the stimuli may occur.

6.4 Discussion

The results show that the model is able to provide insight into basal ganglia functions, to reproduce known physiological behavior, and provides a quantitative interpretation for pathological conditions.

Behavioral effects of direct, indirect and hyperdirect pathways are efficiently reproduced, and the model is able to explore also pathway alterations and network outcomes in case of malfunctioning of specific structures. Tonic and phasic dopamine role are also well incorporated. In particular, the original Hebb rule adopted in the training of the model is able to simulate dopamine induced plasticity in action

selection, shifting stimulus-response associations in time as a consequence of reward and punishment. This has been implemented in a straightforward way, without introducing any additional term that could be difficult to explain and cannot have a direct physiological counterpart. In particular, most previous models used a “three factors Hebbian rule”, which not only includes the pre-synaptic and post-synaptic terms, but also makes use of an “eligibility trace”, related with phasic dopamine, which allows synaptic plasticity only during the feedback (punishment or reward). Conversely, the present model exploits only the classical factors in the Hebb rule, assuming that dopamine acts directly on the activity of striatal neurons, according to physiological knowledge, without the need of any additional “ad hoc” term.

Furthermore, we provide a complete and accurate description of the mathematical implementation, including all parameter values and all equations, so that anyone can simulate the model on its own, testing the results and exploiting the model to investigate additional aspects.

The improvement with respect to other models, which will be discussed more deeply in the next section, consists not only in the formulation of a self-consistent Hebb rule which only exploits the effect of dopamine and acetylcholine on striatal neurons, without the use of additional hypotheses, but also on the explicit introduction of cholinergic interneurons in the network. The latter aspect reinforces the clinical relevance of the model and its practical role, since cholinergic medication is acquiring growing attention with respect to traditional gold-standard levodopa medication in the most recent clinical research.

6.4.1 Comparison with other models

Comparing different computational models is difficult on many levels, as all have their peculiarities.

We can distinguish computational models according to the approach they adopt.

A first class of models is based on the actor-critic formalism, that finds large application in basal ganglia modeling because of the strong resemblance between the temporal-difference (TD) error and the dopaminergic phasic signal, and between dopamine-dependent long-term synaptic plasticity in the striatum and learning guided by a prediction error signal [28][29]. These kind of models typically take their inspiration from the pioneering work by Shutlz [2][30]. They focus on temporal aspects of dopamine neurons firing, and their simple structure often allows the application of traditional identification rules for parameters estimation. However their results sometimes appear quite difficult to be interpreted from a biological viewpoint, as the representation of basal ganglia physiological circuitry is often too poor [29]. In the present study, for the sake of simplicity, we did not use a temporal rule, but just used the final values of all quantities at the end of the simulation to determine reward and punishment, and provided a phasic dopamine peak (reward) or dip (punishment) as an external input. Hence, our model just implements the “actor” part of the problem; inclusion of a “critic”, which decide whether reward or punishment should be given on the basis of previous experience, may be the subject of future refinement.

On the opposite side there are biological highly-detailed models, such as models with spiking neurons, often trying to reproduce even the effect of single conductances and ions channels in a rigorous approach: the aim of these models is to faithfully reproduce physiological neural properties [31]. In this case, however, the

mathematical formalism is often too cumbersome to reproduce the whole basal ganglia circuitry, therefore these models have to focus on specific circuitry subnetworks. Furthermore, information about specific conductances are difficult to retrieve or to justify: in other words, this approach, if not correctly bounded, could add additional degrees of freedom whose value assignment could introduce further identification issues.

Our model is placed between these two approaches: indeed, we provide an abstract representation of the neuronal elements, in order to reproduce plausible physiological properties of the overall circuitry, without the introduction of unnecessary degrees of freedom. In other words, we followed a parsimonious approach, that may be extremely useful in modeling complex systems, given the challenging parameters assignment process previously described. In this way we could focus on the overall basal ganglia circuitry and reproduce all its specific structures, performing simulations able to infer both the main mechanisms operating in the basal ganglia and their reciprocal interactions, as well as their role in the final behavior, both in healthy and in altered conditions.

Furthermore, comparing specific models is complicated not only for the kind of approach they use, but also since they simulate different phenomena: models dealing with action selection could be different from models dealing with working memory update, for instance; this difference, however, may not be based on actual differences in the quality of the model, but may reflect necessary different modeling assumptions. Therefore, the most appropriate way to compare our model with the computational literature should be to restrict this comparison only to models aimed at mimicking response selection among all the functions performed by the basal

ganglia. Nevertheless, sometimes we can find similar elements also in models reproducing different functions (for instance in the learning rule, if synaptic plasticity is present).

The main functional similarities between our model and others, dealing with response selection, are those with Frank's work [13][32][33], especially the latest works, in which he manages to introduce all the 3 main pathways, even though using a different mathematical framework (i.e. the LEABRA network [32]).

Other models that could be comparable in some points to ours are the one by Chersi et al. [34], and Stocco et al. [35]: both searched for a balance between mathematical representation and functional behavior, although with some evident differences.

However, none of the models previously mentioned, nor the general computational literature, account for the role of cholinergic interneurons as the present model. Only Stocco et al. [35] briefly allude to some role of interneurons, and particularly cholinergic ones, but only roughly. Conversely, the function of cholinergic interneurons in our model has been investigated and quantitatively assessed, reproducing their role in learning and plasticity, and proving a specific interpretation by means of both physiological findings and ad-hoc simulations.

A recent model by Ashby and Crossley [31] focuses on the role of cholinergic interneurons, but with fundamental differences. First the mathematical approach they used belongs to the second class of computational models here exposed (i.e. detailed mathematical description with conductance values); second, the interpretation that the authors give to the role of cholinergic interneurons is different from ours, since they assume these interneurons work only as a "switch", to allow the basal ganglia to recognize when learning should occur and when not. Hence, their

description resembles the “eligibility trace” modeling adopted by other models previously discussed.

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General conclusions

The work presented in this thesis provides insights into Parkinson's disease and basal ganglia circuitry both from a motor and from a cognitive viewpoint.

It presents original results that can open to future developments.

Here explained more in detail possible future outcomes.

1) The method to characterize postural strategies here proposed is simple and portable, both because of its computations and its use of inertial sensors, a kind of sensors that are more and more used not only in research contexts but also in clinics. Our Strategy Index (SI) can be easily interpreted also by non-experts and more in general by clinical staff not provided with an engineering background. The set-up of the method is extremely simple and this could be a good reason to insert also postural strategy assessment in clinical tests and routines, allowing to quickly obtain additional information about postural control, mainly in patients suffering from motor and balance impairments.
2) The neurocomputational model allows, as it just did, to investigate new hypotheses. Furthermore, it could be easily adapted to interpret cognitive tests, that nowadays are usually performed together with motor assessment in Parkinson's disease patients. This could allow to investigate in depth what nowadays is assessed only by means of statistical analysis, looking instead at how the neural circuitry behaves in contexts known to cause cognitive issues in patients.

3) Motor and cognitive performances could be correlated, helping to assess also motor issues in an indirect way.

This in general could lead to a better understanding of basal ganglia circuitry alterations, helping to focus on the relevant aspects related diseases, in particular Parkinson’s disease.

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