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BARCELONATECH

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Study of Changes in Brain Connectivity Induced by Antipsychotics Drugs

MASTER THESIS

Candidate:

Sara Casagrande

Supervisor:

Prof. Alessandro Chiuso

Assistant Supervisor:

Prof. Mattia Zorzi

At Universitat Politécnica de Catalunya:

Prof. Joan Francesc Alonso López

Prof. Sergio Romero Lafuente

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"Faber est suae quisque fortunae"

Appio Claudio Cieco

Abstract

NOWADAYS, understanding how the brain is interconnected is still a wide and interesting research field. One of the approaches is to analyze the effect of psychopharmacological agents non-invasively via the human electroencephalogram (EEG). The aim of this work is to measure the changes in connectivity in the brain by processing the EEG data with three different analysis: **Spectral Power** (SP) in four distinguished bands (δ, ϑ, α, β), **Synchronization Likelihood** (SL), an undirected measure of connectivity that quantifies the amount of synchronization (time-symmetric) between signals, and **Transfer Entropy** (TE), a directional connectivity measure that evaluates the amount of direct (time-asymmetric) transfer of information between two processes. The SP, SL and TE measures are analyzed, using the Wilcoxon Signed Rank Test (WLCX), to understand which connectivity interconnections are more significant with respect to the others. SL and TE were further investigated via Graph Theory, evaluating the well-known parameters: Weighted Cluster Coefficient (C_W) and Weighted Path Length (L_W). The purpose of this thesis is to study the changes of connectivity, with the aforementioned methods, in EEGs data obtained from 20 volunteers who received single oral doses of haloperidol 3 mg, risperidone 1 mg, olanzapine 5 mg, and placebo in a randomized cross-over double-blind design. Recordings were performed until 12h after the intake, acquiring data each 1h. Results show, via SP analysis, that the data were acquired in a correct way because the expected changes are between $3 - 6$ hours after intake, more evident in olanzapine's recordings, and consistent with the literature. On the other hand, SL analysis showed mixed results: the main outcomes are decreases of all the three drugs, but in few recordings of haloperidol some increments in the early hours appear. Graph theory, evaluating SL, shows that C_W and L_W decreased (compared with placebo) but not in a statistically significant way. Using TE, the main alterations significant changes are obtained in the occipital region, with olanzapine. From the graphs obtained with TE the L_W coefficient cannot be evaluated because all the resulting graphs are disconnected. Moreover, mainly significant effects evaluating C_W are obtained with Haloperidol. In conclusion, the connectivity analyses show the changes induced by neuroleptic drugs, and although the changes indicated by graph theory are not significant, both the SL and TE show significant changes associated with the drug effects on the brain.

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1 Introduction

NOWADAYS, understanding how the brain is interconnected is still a wide and interesting research field. This project is focused on the study of changes of connectivity due to intake of different antipsychotics. Antipsychotics are thought to work by altering the effect of certain chemicals in the brain, called dopamine, serotonin, noradrenaline and acetylcholine. These chemicals have the effect of changing our behaviour, mood and emotions [Kapur et al. 2006].

Cognitive processing requires integration of information processed simultaneously in spatially distinct areas of the brain. The influence that two brain areas exert on each other's activity is usually described by an unknown function, which is likely nonlinear. As a consequence, the functional relationship between activities in different areas is described by nonlinear functions. It is not necessary to consider algorithms for detecting nonlinear dependencies for studying the changes of connectivity.

The main objective of this thesis is to assess the effects of antipsychotics on EEG activity and connectivity. Another important goal is to understand which areas of the brain are more affected. To do so, an experiment based on a drug intake on healthy subjects, in a double-blind randomized fashion, is carried out.

To accomplish the objectives, the analysis starts with one of the most recognized and classical methodology: the **Spectral Power** (SP) amplitude of EEG frequency bands. The second analysis is based on a quite new tool[1] the **Synchronization Likelihood** (SL), an undirected measure of connectivity that quantifies the amount of synchronization (time-symmetric) between signals. The third analysis is based on another new tool: the **Transfer Entropy** (TE), a directional connectivity measure that evaluates the amount of direct (time-asymmetric) transfer of information between two processes. A further evaluation based on the **Cluster Coefficient** and **Characteristic Path Length** is performed to try to assess the network characteristics of the SL and TE analyses. The following chapters explain the theoretical approach, the results obtained in each different analysis, and discussion along with some conclusion at the end.

[1] With the term *'new tool'* we mean that the latter has been used in the EEG analysis field quite recently.

2

Theoretical Approach

2.1 Data Description

The analyzed data in this study are taken from a study done in the *Hospital de la Santa Creu i Sant Pau* in Barcelona and also used in the work about Ocular Filtering of Romero et al. [2008]. This section is divided in two parts: the first part explains how the signal were acquired (Section 2.1.1), the second part describes how the data were preprocessed (Section 2.1.2).

2.1.1 Experimental Protocol

The experiment collects the data of 20 volunteers of either gender (10 males and 10 females) aged between 20 and 32 years (mean age: 23.75). Volunteers were in good physical health, confirmed by medical history, laboratory tests, ECG and urinalysis, and psychological health (Structured Clinical Interview for DSM-IV[1]). Volunteers were requested to abstain from any medications or illicit drug use in the 2 weeks prior to the experimental sessions and until the completion of the study. Volunteers also abstained from alcohol, tobacco and caffeinated drinks $24h$ prior to each experimental day. In a double-blind randomized

[1]The Structured Clinical Interview for DSM-IV is a diagnostic exam used to determine major mental disorders.[First et al. 1997]

fashion, each volunteer received either a single oral dose of placebo, olanzapine $5\,mg$, risperidone $1\,mg$ or haloperidol $3\,mg$ in four experimental sessions. Moreover, at least 1 week has been required between one experiment and the next one. Although these dosages were lower than clinical doses at low effective therapeutic range (olanzapine $10\,mg/day$, risperidone $2\,mg/day$ and haloperidol $5\,mg/day$), they can be considered of equal power from a pharmacodynamic point of view as they were administered to healthy volunteers.
In a medical point of view, the placebo is a substance with no active therapeutic effect, used in the study as control, the other three drugs are *antipsychotics* used to control Schizophrenia, bipolar disorder or other psychotic diseases, the haloperidol belongs to the family of *typical antipsychotics* and the other two to the family of *atypical antipsychotics*.
In each experimental day, drugs were orally administered in the morning ($8.00\ h$) under fasting conditions. Serial venous blood samples were taken at predefined times (from $0.5\,h$ to $10\,h$ in $1\,h$ intervals). Blood samples were heparinized and centrifuged. Plasma levels of haloperidol, risperidone and olanzapine were measured by a validated liquid chromatography tandem mass spectrometry method.
Simultaneously, the EEG signals were recorded. EEG recordings were assessed from 19 electrodes placed on the scalp according to the international $10/20$ system on the following locations: Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1 and O2, referenced to averaged mastoids, see figure 2.1.1. Additionally, vertical and horizontal EOG (VEOG and HEOG, respectively) signals were recorded. VEOG was obtained from mid-forehead ($2.5\,cm$ above the pupil) and from the average of one electrode below the left eye and another below the right eye ($2.5\,cm$ below the pupil). The HEOG signal was acquired from the outer canthi[2] as depicted in figure 2.1.2[3]. EEG and EOG signals were recorded using high-pass ($0.31\ Hz$) and low-pass filters ($45\,Hz$), with a sampling frequency of $100\,Hz$, by means of Neuroscan Synamps amplifiers.
Vigilance controlled EEG with eyes closed was recorded for $180\,s$; resulting into fourteen recordings taking into account each assumption and for each volunteer: two basal, one $30min$ before the intake, the other few minutes before the intake; then a recording for each hour until $12h$ after the intake. The experimental sessions were undertaken in a quiet room with the volunteers seated in a reclining chair. The experimenter remained outside the room during the vigilante controlled recordings, and attempted to keep the volunteers alert

[2]That means the lateral ends/angles of the palpebral fissure of the eye [Newman Dorland 1951].
[3]Image from Bartolo and Warbrick

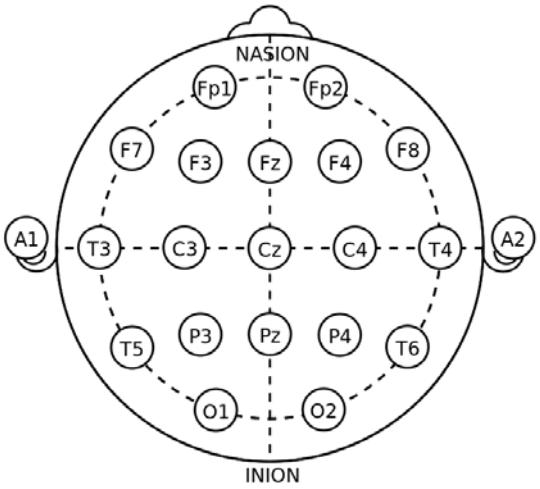


Figure 2.1.1 *Representation of the* $10/20$ *system for the EEG recordings.*

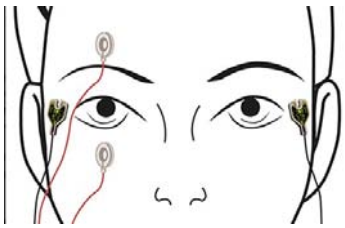


Figure 2.1.2 *Representation of the system for the EOG recordings.*

by acoustic stimulation as soon as drowsiness patterns appeared in EEG recordings.
Each data corresponding to a recording session is labeled as

$$V \star p \star re \star \tag{2.1}$$

where:

- $V\star$ define the number of the volunteer, from 1 to 20;
- $p\star$ define the day of the experiment, from 1 to 4;
- $re\star$ define the number of recording, from 1 to 14 where 1 and 2 are the basal and the others each hour recording.

To understand which drug was used in the different days it was created a correspondence Table 2.1.1 indicating which session correspond to each mediation.

During the processing of the data, we have noticed that three data recording where missing, one for haloperidol $V11p2re9$, one for risperidone $V4p2re14$ and the last one for olanzapine $V11p3re9$.

Volunteer	Placebo	Haloperidol	Risperidone	Olanzapine
1	3	2	1	4
2	2	1	4	3
3	1	4	3	2
4	4	3	2	1
5	4	2	1	3
6	3	1	4	2
7	1	3	2	4
8	2	4	3	1
9	2	3	1	4
10	4	1	3	2
11	1	2	4	3
12	3	4	2	1
13	3	4	1	2
14	4	1	2	3
15	1	2	3	4
16	2	3	4	1
17	2	4	1	3
18	3	1	2	4
19	1	3	4	2
20	4	2	3	1

Table 2.1.1 *Correspondence Table: day of intake and pills, for each volunteer.*

2.1.2 Signal Preprocessing

A two-step artifact processing procedure was applied (as in the study by Alonso et al. [2010]). The first stage consisted of an ocular artifact reduction process based on blind source separation (BSS). An automatic artifact (saturation, muscles and movement) rejection procedure was implemented in a second stage.

The BSS is a statistical signal processing technique whose goal is to express a set of signals as a linear combination of statistically independent signals. A possible way to formulate the BSS problem is to consider the following generative model for the data:

$$x = A \cdot s; \tag{2.2}$$

where x is a matrix composed of n row vectors (raw EOG and EEG signals recorded at different electrodes), s is a matrix composed of m row vectors (source signals), the columns of x and s correspond to the time points, and A is a $n \times m$ matrix. So x_i, the $i-th$ component of x, with $i \in (0,\, n]$, are mixtures composed of original sources s_j, the $j-th$ component of s, with $j \in (0,\, m]$. In this problem it is unknown the mixing process A or the sources s_j,

whose estimation is the objective of the BSS. Second-order statistics are usually sufficient to solve the linear BSS problem when temporal information is taken into account.
In this way, we obtain an estimate $\hat{s}$ of the source signal s. The aim of $\hat{s}$ is to identify the presence of ocular artifacts and cerebral activity.
The automatic identification of these ocular sources was based on frequency and scalp topography aspects of the source signals and was previously described in [Romero et al. 2008].
After ocular artifact reduction procedures, an automatic artifact identification algorithm based on temporal and spectral variables of EEG signals was applied. The procedure is done evaluating for each signals each $5s$ epoch. So an analyzed epoch was rejected due to artifacts if any of the following rules was broken:

- Maximum amplitude of EEG channels has to be lower than $\pm 150\,\mu V$ to avoid electrode-related artifacts or remaining ocular contamination.
- Absolute power in the $[35,\ 45]Hz$ band has to be lower than $25\mu V^2$ in each EEG channel to reject muscular artifacts. Frontopolar, frontal, and temporal derivations has a higher threshold set to $50\,\mu V^2$.
- Absolute power ratio in the intervals of α band $[7.5,\ 13]Hz$ and δ band $[1.3,\ 3.5]Hz$ bands has to be higher than a variable threshold, which depended on the EEG channel's amplitude and alpha activity present in the signal. This criterion was set to detect drowsiness patterns associated with a decrease in alpha activity and also to counterbalance a possible incorrect elimination of ocular artifacts, mainly indicated by an increase in delta activity.

As result of the analysis of each recording and each volunteer a vector composed of (Total Times)/(Epoch Times) $= 180s/5s =$ **36** slots was created, as shown in figure 2.1.3. These vectors contain in each slot a **0** or a **1**, if there is a 0 it means that the evaluated period of time is free of artifacts, otherwise there is a 1 that means the presence of an artifact.

Figure 2.1.3 *Example of the vector.*

At the end, over all the $5s$ slots of all the recordings and volunteers analyzed, the mean number of components recognized as artifacts is 9.35 ± 9 (mean $\pm$ standard deviation) slots.

After computing the two-step artifact processing procedure the signal has been cut in two different ways according to the analysis that has to be performed, as will be explained later on, using the information indicating the presence of artifacts in the $5s$ epochs.
Moreover, before cutting the signal and analyzing it, from each recording the values of the EOG were discarded, so in this work the total amount of channels analyzed for each recording is $\mathbf{n = 19}$.
To perform the Synchronization Likelihood analysis, explained in Section 2.2.2, the usual length of the signals is $8s$, as explained in [Rubinov and Sporns 2010]. For simplicity $10s$ segments were cropped out in order to exploit the previous epochs of $5s$. Each segment is created from two slots (epochs of $5s$) such that:

- the slots are consecutive and free of artifacts;
- the slots as close as more as possible to the center of the signal, that is $[86, 95]s$.

In the case that all the signal was artifacted, or there was not two consecutive slots free of artifacts, the signal has been cut manually, evaluating the behavior of the signal itself. The list with all the completely artifacted signals used (the ones in bold are the missing recordings) is shown below:

► Haloperidol

- V17 r10 (8h);
- V8 r14 (12h);
- **V11 r9 (7h)**;

► Risperidone

- V9 r3 (1h);
- V9 r9 (7h);
- V4 r10 (8h);
- **V4 r14 (12h)**;

► Olanzapine

- V8 r2 (basal2);
- V2 r3 (1h);
- V14 r5 (3h);
- V15 r5 (3h);
- V2 r6 (4h);
- V8 r6 (4h);
- V20 r6 (4h);
- V18 r7 (5h);
- V3 r8 (6h);
- V7 r8 (6h);
- V7 r9 (7h);
- V2 r10 (8h);
- **V11 r9 (7h)**.

Where the value in the parenthesis is the the time after intake.
To perform the Spectral Power Analysis and Transfer Entropy Analysis, explained then in Section 2.2.1 and Section 2.2.3 respectively, $60s$ of the signal was cropped out, as used in [Alonso et al. 2016]. The signal was cut in such a way that it is as artifact free as possible, so all the 24 different $12-$consecutive$-5s$ slots have been evaluated, and the cleanest one

chosen. As reported before, there was impossible to find completely artifacts-free data also for epoch of $10s$, so almost all the data segments are affected by artifacts to some degree.

Finally, each signal was filtered between 0.5 and 35 Hz, Lowest Frequency (LF) and Highest Frequency (HF) respectively, using a type-II Chebyshev filter of order 8 with sampling frequency $f_s = 100Hz$.

2.2 Data Analysis

Three different approaches has been used to evaluate the data acquired: the *Spectral Power* analysis, *Synchronization Likelihood* analysis and *Transfer Entropy* analysis. These three different methods allow the assessment of pharmacological effects on the brain from different perspectives. As we will see, Synchronization Likelihood and Transfer Entropy analysis are the starting point of *Graph Theory* analysis which evaluates the changes on the well-known Cluster Coefficient and Characteristic Path Length.

2.2.1 Spectral Power Analysis

The *Spectral Power* (SP) amplitude of EEG frequency bands is used to study the spontaneous electroencephalogram; this approach is one of the oldest and represents a substantiated way to analyze the spontaneous EEG.

Power spectral density (PSD) functions were calculated from the most artifact-free $60s$ epochs, as defined in Section 2.1.2 by Welch periodogram using a $5s$ Hanning window and 25% of overlapping.

The Welch periodogram [Welch 1967] comes as improvement on the standard periodogram, in such a way that it reduces the variability of the estimation. This tool is based on the idea of using periodogram spectrum estimates, which are the results of converting a signal from the domain of time to the domain of frequencies. Welch's periodogram also uses a windowing function that has the objective to reduce the spectral leakage without compromising spectral resolution. The method chosen in this thesis is the Hanning window which has the best features in this situation.

It is a well known fact that the EEG signals can be used to measure the vigilance state of the brain, which changes according to task performed by a person as seen also in Alonso et al. [2015]. These changes are mostly revealed by changes in a few different frequency bands

named as delta, theta, alpha, beta and gamma, whose ranges are defined below:

δ $[1.5,\ 3.5]$Hz; α $[7.5,\ 13]$Hz ;

ϑ $[3.5,\ 7.5]$Hz ; β $[13,\ 20]$Hz.

The mean average spectral powers in each band were quantified into 19 variables, one per EEG electrode, and then represented into Spectral Maps. These Spectral represent in an effective way if there are increasing or decreasing trends in the different electrode's area due to the effect of the drug and with respect to the control.

2.2.2 Synchronization Likelihood Analysis

The *Synchronization Likelihood* (SL) approach, which is based on the study of Stam and van Dijk [2002], wants to overcome some limitation due to the most used linear techniques, like the Coherency method. The latter produces a large knowledge on normal or pathological brain function, but has some drawbacks. In fact it is not suitable to characterize non stationary data with rapidly changing interdependencies. Moreover, a more important limitation is that it only captures linear relations between time series and thus it may fail to detect non-linear interdependencies.
The synchronization likelihood measure gives a straightforward normalized estimate of the dynamical interdependencies between two or more simultaneously recorded time series of a system. So the main idea is that SL divides each time series (signal) into a series of patterns and search for a recurrence of these patterns.
In order to describe this approach we need to introduce the following variables and parameters:

- $\mathbf{x_{k,i}}$ denotes the $k-th$ time series at time i;
- $\mathbf{k} \in [1, \cdots M]$ denotes the channel number (in this study $M = 19$);
- $\mathbf{i} \in [1, \cdots N]$ denotes the discrete time index;
- ℓ denotes the lag;
- $\mathbf{m}$ denotes the embedding dimension;

- $\mathbf{X_{k,i}}$ denotes the matrix with the embedded vectors

$$X_{k,i} = \left[x_{k,i}\, x_{k,i+\ell}\, x_{k,i+2\ell}\, \cdots x_{k,i+(m-1)\ell}\right], \tag{2.3}$$

  that is the representation of the state $k-th$ component of the of the system at time i;

- $\mathbf{w_1}$ denotes the window for the Theiler Correction[4] of autocorrelation effects;

- $\mathbf{w_2}$ is a window that sharpens the time resolution of the synchronization measure such that $w_1 \ll w_2 \ll N$;

- ε is referred to as critical distance.

For each time series k and each time i we define the probability $\mathbf{P^{\varepsilon}_{k,i}}$ that embedded vectors are closer to each other than ε:

$$P^{\varepsilon}_{k,i} = \frac{1}{2(w_2 - w_1)} \sum_{j \in \mathcal{C}_i}^{N} \mathbb{1}\left(\varepsilon - |X_{k,i} - X_{k,j}|\right); \tag{2.4}$$

where $\mathcal{C}_i = \{j = 1, ..., N,\ s.t.\, w_1 < |i-j| < w_2\}$; $|\cdot|$ is the *Euclidean distance* and $\mathbb{1}$ is the Heaviside step function:

$$\mathbb{1}(x) = \begin{cases} 0 & \text{if} \quad x \leq 0 \\ 1 & \text{if} \quad x > 0. \end{cases}$$

For each k and each i the critical distance $\varepsilon_{k,i}$ is determined in such a way that $P^{\varepsilon}_{k,i} = p_{ref}$ with $p_{ref} \ll 1$ (usually $p_{ref} \leq 0.05$). Now for each discrete time pair (i, j), that belongs to the window $(w_1 < |i-j| < w_2)$, it can be determined the number of channels $H_{i,j}$ through the formula:

$$H_{i,j} = \sum_{k=1}^{M} \mathbb{1}(\varepsilon_{k,i} - |X_{k,i} - X_{k,j}|); \tag{2.5}$$

the value of $H_{i,j} \in [0,\, M]$ and reflects how many of the embedded signals resemble each other.

The synchronization likelihood $S_{k,i,j}$ is defined for each channel k and each discrete time

[4]This correction defines the separation between values on the time series, to reconstruct embedded vectors. It is used because Autocorrelation may cause severe underestimation of the dimension. Theiler [1986] suggests to discard samples that are close to the reference point up to the correlation time (measured in samples). This procedure seems to work even though it does not exclude all correlations. So it may be useful when the time series is rather short and decimation is unacceptable.

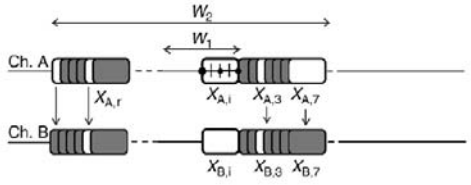
pair (i, j) as:

$$S_{k,i,j} = \begin{cases} \dfrac{H_{i,j} - 1}{M - 1} & \text{if} \quad |X_{k,i} - X_{k,j}| < \varepsilon_{k,i} \\ 0 & \text{if} \quad |X_{k,i} - X_{k,j}| \geq \varepsilon_{k,i}. \end{cases} \tag{2.6}$$

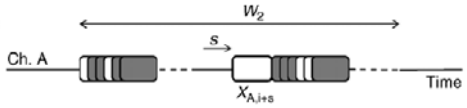
By averaging over all j we finally obtain $S_{k,i}$:

$$S_{k,i} = \frac{1}{2(w_2 - w_1)} \sum_{j \in \mathcal{C}_i}^{N} S_{k,i,j}. \tag{2.7}$$

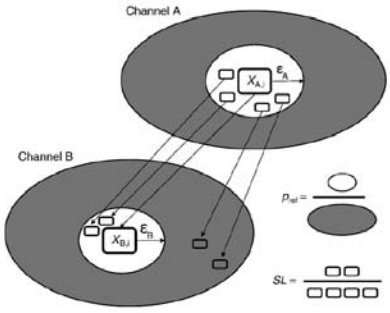
The synchronization likelihood $S_{k,i}$ is a measure which describes how strongly channel k at time i is synchronized to all the other $M - 1$ channels. It is worth to note that index (2.7) takes values in $[p_{ref},\ 1]$. $S_{k,i} = p_{ref}$ corresponds to the case where all M time series are uncorrelated and $S_{k,i} = 1$ corresponds with maximal synchronization of all M time series. The value of p_{ref} does not depend on the properties of the time series, nor is it influenced by the embedding parameters, indeed it is a parameter fixed by the user.
To have an overview and understand how the algorithm works, an example evaluating two different channels A and B is presented. Suppose to start the analysis at time i.



(A) *Description of parameters of SL.*



(B) *Description of SL time series.*



(C) *Description of evaluation of distance on SL.*

Figure 2.2.1 *Images taken from [Montez et al. 2006]*

.

In Figure 2.2.1A the reference vector of channel A is denoted $X_{A,i}$ (thick line square) here chosen to have embedding dimension $m = 3$ samples (small ticks) and lag $\ell = 2$ samples (dots). The reference vector is compared with the other embedded vectors (rectangles) $X_{A,j}$ $(j = \pm 1, 2 \ldots n)$ within a window of w_2. State vectors starting at times j in the time interval outside the window w_1 and within the window w_2 (windows centered at time i) are

compared with the reference vector. The time series is indicated with a solid horizontal line and the time intervals where the state vectors are constructed are indicated with a dashed line. The vectors $X_{A,j}$ closer to the reference vector $X_{A,i}$ than the critical distance, ε_A (see 2.2.1C) are represented in white, whereas the vectors that are not within the critical distance are represented in grey. The white squares are termed recurrences. Similarly for channel B, a reference vector $X_{B,i}$ is compared with all state vectors $X_{B,j}$ in the corresponding interval. If the vectors are closer to $X_{B,i}$ than ε_B they are represented in white, otherwise in grey. Synchronization likelihood is the number of simultaneous recurrences in channels A and B (in the example, we have two recurrences at $j = 3$ and $j = r$) divided by the total number of recurrences within channels (in the example $\frac{1}{2}$ for channel A and 1 for channel B).
Figure 2.2.1B explains how to obtain a SL time series: a new reference vector is constructed at time point $i + s$ (the arrow represents the s increment), and the procedure in panel a is repeated with respect to the new time point (the windows w_1 and w_2 are now centered at $i + s$).
Figure 2.2.1C shows a schematic representation of SL between the two channels in terms of state vectors and critical distances. $X_{A,i}$ and $X_{B,i}$ are the reference vectors of channels A and B, respectively. State vectors that are closer than the critical distance are shown inside white ellipses, whereas those that are not within the critical distance are represented inside grey ellipses. The lines connect pairs of state vectors at the same time point in both channels. There are two simultaneous recurrences out of four possible. SL of channel A and B at time i is the ratio between the number of simultaneous recurrences and the total number of recurrences within channels thus $\frac{1}{2}$ for channel A and 1 for channel B. In order words, SL is an index of the likelihood that a recurrence of a reference state in channel A is associated also with a recurrence of a reference state in channel B. Finally, p_{ref} is the ratio between the number of vectors closer than the critical distance and the total number of state vectors. Note that p_{ref} is the same for A and B, while the critical distance for A and B is usually different.

In this study, to attribute values to the SL parameters we have considered the reccomendations of the study by Montez et al. [2006], in which they analyze how precise and reliable is the SL algorithm using parameters adjusted to the time-frequency characteristics of the analyzed signal, with respect to the typical choice of parameters. Following the decision on the frequency range of interest, a time-delay embedding to form a state-space representation of

the system dynamics defined before in Section 2.1.2; the most delicate part of this approach is that the embedded vector $X_{k,i}$ must sample the signal at sufficiently short intervals to pick up the fastest oscillation and also to be long enough to sample the slowest oscillation. The parameters that have to be chosen accurately for the use of this algorithm are: m, ℓ, p_{ref}, n_{rec}, w_1 and w_2. The one that has to catch the fastest component is the lag ℓ, it has been chosen according to the Nyquist sampling theorem. The latter states that a dynamical process must be sampled at minimum twice the *Highest frequency* (HF) of its fluctuations in order for the discrete process to adequately represent the dynamics of the underlying process. The typical choice is:

$$\ell = \frac{f_S}{3 \cdot HF} \simeq 1; \tag{2.8}$$

so $\ell = 1$ has been chosen.

For catching the slowest component we need to design the parameter m. The latter has to designated evaluating the *Lowest Frequency* (LF) that has the longest period and thus determines the length of the state vector: $\ell(m-1) = \frac{f_S}{LF}$, so

$$m = \frac{3 \cdot HF}{LF} + 1 = 211. \tag{2.9}$$

Parameter p_{ref} denotes the percentage of vectors $X_{A,j}$ that are considered close enough to $X_{A,i}$ to represent the same state of the system. Once p_{ref}, then it also leads the critical Euclidean distance ε_A. Now p_{ref} is fixed as $p_{ref} = 0.05$ which means that 5% of the vectors $X_{A,j}$ will be considered recurrences of $X_{A,i}$. Then the same procedure has been done for the channel B. It is worth noting that p_{ref} is always the same for each channel, but the critical distance ε changes.

Remember that the SL method assumes that in a given period of time a pattern of activity will closely repeat itself a certain number of times. To prevent the inclusion of states that are similar, because states vary slowly relative to the sampling frequency, we define a window w_1 around time i, where state vectors are not compared for their possible similarity. The vectors starting inside the w_1 window are likely to not represent a recurrence of the reference state but the state itself. If w_1 is twice the length of the embedding vectors, the overlap between the first vector $X_{A,j}$ and the reference vector is only one sample, that is $\frac{w_1}{2}$ is larger than the period of the lowest frequency in the signal after the filtering. In view of

the consideration above, we choose:

$$w_1 = 2 \cdot \ell(m-1) = 420\ samples. \tag{2.10}$$

The window w_2 defines the time interval where the similarity of any given state vector is compared with the reference vector. Recall that w_1 has to be large enough to allocate a sufficient number of vectors for which it makes sense to take p_{ref} of them as recurrences. The relationship between w_1, w_2 , p_{ref} and the number of recurrences, denoted by n_{rec} is:

$$n_{rec} = (w_2 - w_1 - 1)p_{ref}. \tag{2.11}$$

Usually it is recommended that n_{rec} take values higher that 10. In this study we choose $n_{rec} = 16$, thus

$$w_2 = \frac{n_{rec}}{p_{ref}} + w_1 - 1 = 739; \tag{2.12}$$

so $w_2 = 740\ samples$ has been chosen.

These values differ from the commonly used standard choice: $m = \ell = 10$, $w_1 = 100$ and $w_2 = 10\%$ of the length of the data set. We did not adopt the standard choice because the latter implies a lower resolution, and less ability to adapt to the dynamics of the EEG signals.

Given the values $S_{i,k}$ returned by the algorithm, we construct the symmetric matrix M_{SL}, whose entries in position (i,k) and (k,i) is $S_{i,k}$. In our case this matrix has dimension 19. Thus, the total amount of connection among the channel is:

$$N_{SL} = \frac{N_{channel} \cdot (N_{channel} - 1)}{2} = 171 \quad . \tag{2.13}$$

2.2.3 Transfer Entropy Analysis

The *Transfer Entropy* (TE) has been introduced in the work of Schreiber [2000]. The latter aims to distinguish effectively driving and responding elements and to detect asymmetry in the interaction of subsystems. Calling X and Y the signals under study, the TE from process X to Y describes the amount of uncertainty reduced in future values of Y by knowing the past values of X given past values of Y.

In respect to the mutual information which neither contains dynamical nor directional information, TE aims to quantify, under minimal assumptions about the dynamics of the

system and the nature of their coupling, to measure the amount of predictive information between two systems separately for both directions and conditional to common input signals.

Before introduce the definition of TE, we define as Shannon Entropy of the discrete variable X following a probability distribution $p(x)$ the quantity:

$$H_X = -\sum_x p(x)\log(p(x)). \tag{2.14}$$

Up to a multiplicative factor (2.14) represents the average number of bits needed to optimally encode independent draws of X. In what follows similar interpretations will be meant up to a scaling factor.

The exceeding number of bits that will be coded if a different distribution $q(x)$ is used is given by the Kullback-Leibler divergence[5]:

$$K_X = \sum_x p(x)\log\left(\frac{p(x)}{q(x)}\right); \tag{2.15}$$

equivalently the formula for Y is K_Y. The Kullback-Leibler divergence for conditional probability is defined as follows:

$$K_{X|Y} = \sum_{x,y} p(x,y)\log\left(\frac{p(x,|y)}{q(x|y)}\right). \tag{2.16}$$

The mutual information (MI) of two processes X and Y with joint probability $p_{XY}(x,y)$ can be seen as the exceeding amount of code produced by erroneously assuming that the two systems are independent, i.e. $q_{XY}(x,y) = p_X(x)p_Y(y)$:

$$M_{XY} = \sum_{x,y} p(x,y)\log\left(\frac{p(x,\,y)}{p_X(x)p_Y(y))}\right). \tag{2.17}$$

This shows that mutual information is a useful way to quantify the deviation from independence of two processes. Note that $M_{XY} = M_{YX}$ this means that MI is symmetric that is it is not possible to understand the direction of the predictive information. Using the conditional entropy which is non-symmetric and adding a time lag in both the variables

[5] K_X is used to measure the deviance among probability densities. This distance measures the ability of the data to discriminate different values of X (i.e. how much X changes if we perturb x).

we obtain a directional MI:

$$M_{XY}(\tau) = \sum_{x,y} p\left(x_n,\, y_{n-\tau}\right) \log\left(\frac{p\left(x_n,\, y_{n-\tau}\right)}{p(x)p(y)}\right). \tag{2.18}$$

Consider now a system that may be approximated by a stationary Markov process of order k, then: $p(x_{n+1}|x_n \ldots x_{n-k+1}) = p(x_{n+1}|x_n \ldots x_{n-k+1},\, x_{n-k})$. The idea is to take as measure the deviation from the generalized Markov property,

$$p\left(x_{n+1}|x_n \ldots x_{n-k+1}\right) = p\left(x_{n+1}|x_n \ldots x_{n-k+1},\, y_n \ldots y_{n-l+1}\right); \tag{2.19}$$

with respect to only adding a slot delay as in (2.18).

In the absence of information flow from Y to X, the state of Y has no influence on the transition probabilities on system X. The incorrectness of this assumption can again be quantified by a Kullback-Leibler divergence (2.15) by which we define the TE:

$$\begin{aligned} TE_{Y\to X} &= \sum_{x_{n+1};\, x_n;\, y_n} p\left(x_{n+1},\, x_n,\, y_n\right) \log\left(\frac{p\left(x_{n+1}|\, x_n,\, y_n\right)}{p\left(x_{n+1}|\, x_n\right)}\right) \\ &= \sum_{x_{n+1};\, x_n;\, y_n} p\left(x_{n+1},\, x_n,\, y_n\right) \log\left(\frac{p\left(x_{n+1},\, x_n,\, y_n\right) p\left(x_n\right)}{p\left(x_n,\, y_n\right) p\left(x_{n+1},\, x_n\right)}\right); \end{aligned} \tag{2.20}$$

where, again, X and Y represent the signals under study, and n indicates the sample time; note that in Formula (2.19) $l = k = 1$ has been chosen.

Finally, we can define the matrix M_{TE} whose entry in position (i, k) is the $TE_{Y_i \to X_k}$. Moreover, note that in our case M_{TE} has dimension 19.

Since TE is an inherently non-symmetric measure (as opposed to SL), all the possible oriented connections are:

$$N_{TE} = N_{channel} \cdot (N_{channel} - 1) = 342 \quad . \tag{2.21}$$

TE was calculated in this work using a non-parametric methodology based on equiquantal binning, 3 bits were chosen, that is, estimating probability distributions using marginal equiquantization and histogram estimation over $2^3 = 8$ different levels. As written in the formula (2.20), the unitary delay was chosen.

2.3 Graph Theory Analysis

Brain connectivity refers to a pattern of anatomical links (called *anatomical connectivity*), of statistical dependencies (named *functional connectivity*) or of causal interactions (called *effective connectivity*) between distinct units within a nervous system. The units correspond to individual neurons, neuronal populations, or anatomically segregated brain regions. The connectivity pattern is formed by structural links such as synapses or fiber pathways, or it represents statistical or causal relationships measured as cross-correlations, coherence, or information flow. Neural activity, and by extension neural codes, are constrained by connectivity. Brain connectivity is thus crucial to elucidate how neurons and neural networks process information. It could be divided into different levels that are qualified differently in function of the scale: *microscale*, which considers individual synaptic connections linking individual neurons, *mesoscale*, which considers networks connecting neuronal populations, and *macroscale*, that consider brain region linked by fiber pathways. In this study the macroscale connectivity will be considered.

Brain connectivity may be studied and analyzed using a broad range of network analysis approaches. Graph theory is of special interest as it applies to structural, functional and effective brain connectivity at all levels.

Graphs are used to indicate the interrelation between couples of objects. More precisely, a graph is composed by vertices (corresponding in our case to the different 19 electrodes in this study) and edges (corresponding to statistical dependencies between neural elements). In their simplest form, graphs can be described by an adjacency matrix, say $\mathcal{A}$, with binary elements that represents the presence or absence of an edge between pairs of vertices.

Vertices can interact through direct connections, or indirectly via paths composed of multiple edges. The functional efficacy of these indirect interactions depends on the path length. Instead of $\mathcal{A}$, one could consider a weight matrix $\mathcal{W}$: in this case we have a weighted graph. Finally, it is worth noting that from the symmetric weight matrix M_{SL}, given by SL, we obtain a non-oriented graph, while with the weight matrix M_{TE}, given by TE, we obtain an oriented graph.

In what follows we will introduce the definition of **characteristic path length** and **cluster coefficient** [Goodrich and Tamassia 2010].

As we will see, these two quantities are linked to two different modes of brain connectivity: *segregation* and *integration*. Segregation refers to the existence of specialized neurons and

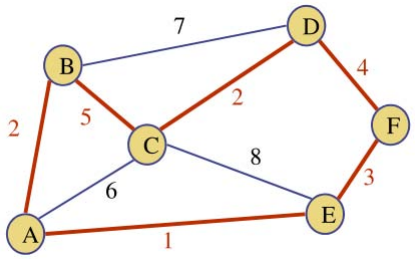
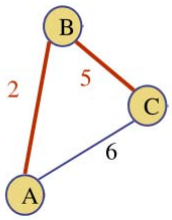
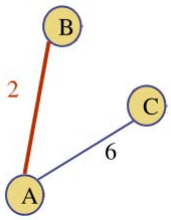


Figure 2.3.1 *Image representing a Weighted Graph with six nodes.*



(A) *Example of a triangle.*



(B) *Example of a disconnected triangle.*

Figure 2.3.2 *Portion of figure 2.3.1.*

brain areas, organized into distinct neuronal populations and grouped together to form segregated cortical areas. The complementary principle, integration, gives rise to the coordinated activation of distributed neuronal populations thus enabling the emergence of coherent cognitive and behavioral states. The interplay of segregation and integration in brain networks generates information that is simultaneously highly diversified and highly integrated, thus creating patterns of high complexity.
Now, we introduce the mathematical definition of the two coefficients above following Rubinov and Sporns [2010] and Costantini and Perugini [2014].

Consider the non-oriented graph of Figure 2.3.1 the minimum closed graph *A*-*B*-*C*, that is a triangle, see in Figure 2.3.2A. Notice that *A*-*B*-*C* is a graph of three nodes all connected to each other. We have a direct connection of a node A with a node B, given by $(A,\ B)$, plus an indirect connection that goes through another node, C, given by $(A,\ B,\ C)$. If the direct edge $(B,\ C)$ does not exist, the indirect path that travels through A is important because it conveys the unique information about the relationship between B and C. In this case, the missing direct edge between B and C is said to constitute a structural hole see Figure 2.3.2B. Conversely, if the direct edge $(B,\ C)$ is present, the importance of the indirect path is reduced and A can be considered redundant in establishing a connection between B and

C. This idea can be applied to the whole neighborhood of a node A. We define as local clustering coefficient for unweighted networks as the number of connections among the neighbors of a local node over the maximum possible number of such connections, that is (computed over general vertices i, j and q):

$$C_i = \frac{\sum_{j,q} a_{j,i}\, a_{i,q}\, a_{j,q}}{k_i(k_i-1)}; \tag{2.22}$$

where $a_{*,*}$ is the element $(*,*)$ of the adjacency matrix $\mathcal{A}$, and k_i the degree of the node i defined as

$$k_i = \sum_{j \in \mathsf{N}} a_{i,j}; \tag{2.23}$$

where N is the set of all the nodes in the considered graph. Averaging over all the N nodes, the cluster coefficient of the graph is obtained:

$$C = \frac{1}{N}\sum_{i=1}^{N} C_i. \tag{2.24}$$

To compute the weighted one there are some different studies, presented in Costantini and Perugini [2014], the one chosen in this work is Onnela et al. [2005]. We define 'intensity' as the geometric mean of its link weights and 'coherence' as the ratio of the geometric to the corresponding arithmetic mean. Using these measures, motif scores and clustering coefficient can be generalized to weighted networks; in other words it substitutes the number of triangles in the numerator with the sum of triangle's intensity. Mathematically it is defined as:

$$C_W = \frac{1}{n}\sum_{i \in \mathcal{N}} 2\frac{\sum_{j,q \in \mathcal{N}} (w_{j,i}\, w_{i,q}\, w_{j,q})^{\frac{1}{3}}}{k_i(k_i-1)}; \tag{2.25}$$

where $w_{*,*}$ is a element of the connection matrix W, $\mathcal{N}$ represents the neighborhood of the node i and n is the number of nodes in the graphs. This way takes into account weights of all edges in a triangle, but does not consider weights not participating in any triangle and is invariant to weight permutation for one triangle.

As last, it is necessary to define also the cluster coefficient for oriented graphs (or simply networks). This cluster coefficient is computed using the formula obtained in Fagiolo

[2007]:

$$C^{\rightarrow} = \frac{1}{n}\sum_{i\in\mathcal{N}}\frac{1}{2}\frac{\sum_{j,q\in\mathcal{N}}(a_{i,j}+a_{j,i})(a_{i,q}+a_{q,i})(a_{j,q}+a_{q,j})}{(k_i^{out}+k_i^{in})(k_i^{out}+k_i^{in}-1)-2\sum_{i\in\mathcal{N}}a_{i,j}a_{j,i}}; \tag{2.26}$$

where k_i^{in} is the directed *in-degree* of the node i:

$$k_i^{in} = \sum_{j\in\mathsf{N}} a_{i,j}; \tag{2.27}$$

and k_i^{out} is the directed *out-degree* of the node i:

$$k_i^{out} = \sum_{j\in\mathsf{N}} a_{j,i}. \tag{2.28}$$

Equivalently for the weighted and oriented graph the formula is based on (2.26) plus the Onnela modifications:

$$C_{W}^{\rightarrow} = \frac{1}{n}\sum_{i\in\mathcal{N}}2\frac{\sum_{j,\,q\in\mathcal{N}}\left(w_{j,\,i}\,w_{i,\,q}\,w_{j,\,q}\right)^{\frac{1}{3}}}{(k_i^{out}+k_i^{in})(k_i^{out}+k_i^{in}-1)-2\sum_{j\in\mathcal{N}}a_{i,\,j}a_{j,\,i}} \tag{2.29}$$

The cluster coefficient in summary, is a measure of local structure; nodes tend to create groups characterized by a relatively high density of ties. In conclusion, it is a measure of the segregation.

To define the path length coefficient consider the graph of Figure 2.3.2A. Analyzing the path from the node A:

- the distance of the direct interconnection from A to B and A to C is $d_{A,\star} = 1$;
- the distance of the indirect interconnection from A to B, crossing C, or equivalently from A to C passing throw B is $d_{A,\star,\star} = 2$.

So in this special case, i.e. all the nodes are interconnected to each other, the minimum path length is $L = 1$.

The characteristic path length is defined as:

$$L = \frac{1}{n}\sum_{i\subset\mathcal{N}}L_i = \frac{1}{n}\sum_{i\subset\mathcal{N}}\frac{\sum_{j\subset\mathcal{N},j\neq i}d_{ij}}{n-1}; \tag{2.30}$$

and d_{ij} is the shortest distance between the node i and node j.

Brain networks, if a threshold is not imposed, have $L = 1$ because usually they are mostly

fully connected.

More interesting is the case of the weighted path length, because it could result that indirect interconnections are 'cheaper' with respect to the direct ones. To define in the weighted path length it is necessary to consider the weighted distance d_{ij}^W which is defined as follows:

$$d_{ij}^W = \frac{1}{w_{ij}}. \tag{2.31}$$

The weighted characteristic path length is defined as:

$$L^W = \frac{1}{n} \sum_{i \in \mathcal{N}} \frac{\sum_{j \in \mathcal{N}, j \neq i} d_{ij}^W}{n-1}. \tag{2.32}$$

Finally, the characteristic path length for oriented graphs is defined as:

$$L^{\rightarrow} = \frac{1}{n} \sum_{i \in \mathcal{N}} \frac{\sum_{j \in \mathcal{N}, j \neq i} d_{ij}^{\rightarrow}}{n-1}; \tag{2.33}$$

where $d_{ij}^{\rightarrow}$ stays for the minimum directed distance between i and j. Then, the weighted and directed characteristic path length is:

$$L_W^{\rightarrow} = \frac{1}{n} \sum_{i \in \mathcal{N}} \frac{\sum_{j \in \mathcal{N}, j \neq i} d_{ij}^{W \rightarrow}}{n-1}; \tag{2.34}$$

where $d_{ij}^{W \rightarrow}$ is the weighted and directed distance.

Summing up, the shortest path length coefficient is used to understand how much the graph is interconnected, so it is a basis of the measure of integration.

2.4 Statistical Analysis with Wilcoxon Signed Rank Test

The *Wilcoxon Signed Rank Test* (WLCX) [Wilcoxon 1945] is a non-parametric statistical hypothesis test, which composes two related samples, matched samples or repeated measurements on a single sample. The aim of this test is to understand whether their population mean rank differ.

This method for comparing the means of two groups utilizes ranking methods, that is, methods in which scores $1, 2, 3, \ldots n$ are substituted for the actual numerical data, in order to obtain a rapid approximative idea of the significance of the differences in experiments of this kind information, moreover the magnitude of the differences as well as the signs is

used. To apply this method it is necessary to assume that:

- data are paired and are produced from the same population;
- every single pair is picked randomly and independently;
- data are measured on an ordinal scale[6].

The details of the calculation are as follows: let be n the number of pairs and $x_{1,i}$ and $x_{2,i}$ denote the measurements with $i = 1, \dots n$. Define H_0 as the difference between the pairs that follow a symmetric distribution around zero and H_1 as the difference between the pairs that do not follow a symmetric distribution around zero.
Iterating over i, from $i = 0$ to $i = n$, the absolute value of the measures $abs_i = |x_{2,i} - x_{1,i}|$ and their relative sign $sgn_i = sgn(x_{2,i} - x_{1,i})$ are computed. All the abs_i that have value equal to zero are discarded, obtaining now the reduced sample size with n_R samples.
The n_R remaining abs_i are reordered in ascending order (from the smallest to the biggest value) and ranked R_i, starting from 1 (given to the smallest). Ties receive a rank equal to the average of the ranks they span, i.e. if there are two abs_i that has the same values, and they have to be ranked from 6 to 7, their R_i will be $R_i = \frac{6+7}{2} = 6.5$.
An example is reported in the following image, Figure 2.4.1, where the abs values are already put in progressive order[7].

i	$x_{2,i}$	$x_{1,i}$	$x_{2,i} - x_{1,i}$			
			sgn	abs	R_i	sgn $\cdot R_i$
5	140	140		0		
3	130	125	1	5	1.5	1.5
9	140	135	1	5	1.5	1.5
2	115	122	−1	7	3	−3
6	115	124	−1	9	4	−4
10	135	145	−1	10	5	−5
8	125	137	−1	12	6	−6
1	125	110	1	15	7	7
7	140	123	1	17	8	8
4	140	120	1	20	9	9

Figure 2.4.1 *Example for the WLCX ordered by absolute value.*

[6]They cannot be boolean, otherwise they cannot be ranked.
[7]Image taken from Wikipedia.

The statistic test W is computed as

$$W = \sum_{i=1}^{n_R} sgn(x_{2,i} - x_{1,i}) \cdot R_i. \tag{2.35}$$

Under the null hypothesis, W follows a specific distribution with no simple expression. This distribution has an expected value of 0 and a variance of $\frac{n_R(n_R+1)(2n_R+1)}{6}$. In the case that n_R is large, W converges to a Normal distribution. To obtain the **p-value**, p, of the distribution is used the formula:

$$p = 2k \cdot \left(\frac{1}{2}\right)^n \tag{2.36}$$

using $\left(\frac{1}{2}\right)$ that is the probability to have a positive or negative rank sign and 2 that is the parameter for the two-sides WLCX, used in this work. Finally, k indicates the possibles arrangements of signs that give as result the same or lower rank differ. An example could be seen in the Figure[8] 2.4.2.

	ranks of observations								sum of positive ranks (SPR)
	3	3	3	3	3	6.5	6.5	8	
Signed of observed data	-	+	-	-	-	-	-	-	**3**
Other possible arrangements of signs in which SPR ≤ 3	-	-	-	-	-	-	-	-	**0**
	+	-	-	-	-	-	-	-	**3**
	-	-	+	-	-	-	-	-	**3**
	-	-	-	+	-	-	-	-	**3**
	-	-	-	-	+	-	-	-	**3**

Figure 2.4.2 *Example for the computation of the p-value. For this example* $p = 2 \cdot 6 \cdot \left(\frac{1}{2}\right)^8 = 0.0468$.

Once the statistical results are obtained, a correction of the higher chance of false positive results due the multiple comparison problem is needed. This effect occurs when a set of statistical inferences is considered simultaneously. It arises when a statistical analysis include a number of formal comparisons and the attention will be focused more on the strongest differences among all the comparison made. To correct this effect given from the fact that a lot of statistical comparisons, n, are performed, or in other words to interpret r significant results out of n tests, the *Cross and Chaffin binomial test* Cross and Chaffin [1982] has been used.

The binomial Theorem is applied to compute the probability that r or more Type I errors

[8] Image taken from courses.washington.edu

would occur when all n of the null hypothesis (H_{0i}) are true, then use this result as the level of overall significance s^*.

This study is the case of independent test situation, thus it is possible to set a limit r, based on some required level of significance s^*, for the rejection of the overall hypothesis. Following an upper limit is obtained for s^*, when r significant test results are dependent to an unknown event, so they reject a set of n hypothesis.

The formulation of this test is given starting from s as the probability of Type I error for each individual test (that is independent). Defining then s^*:

$$\begin{aligned} s^* &= \text{Prob(reject one or more of the } H_{0i} \mid \text{all } H_{0i} \text{ are true)} \\ &= 1 - \text{Prob(accept all } n \text{ of the } H_{0i} \mid \text{all } H_{0i} \text{ are true)} \\ &= 1 - C_{0_n}(s)^0(1-s)^n \\ &= 1 - (1-s)^n. \end{aligned}$$

In short s^* is the probability to commit at least one Type I error. If n is relatively large and s approximately small the relation between these two coefficient is:

$$s^* = n \cdot s.$$

Otherwise the formula that associates them is obtained using Bernoulli probability of success

$$s^* = \sum_{j=r}^{n} s^j (1-s)^{n-j}.$$

In this work three different thresholds are taken into account, depending on the considered approach (i.e. SP, SL or TE). In summary, if we perform n individual tests with significance set to 10%, a global map can be considered significant, with global significance set to 5%, if it has:

- 5 significant results for SP analysis (19 statistical tests);
- 25 'lines[9]', for the SL algorithm (171 statistical tests);
- 45 'lines', for the TE algorithm (342 statistical tests).

[9] Lines as significant interconnection changes between electrodes, due to pharmacological effect.

3

Spectral Power Approach

The SP analysis, as explained in Section 2.2.1, is one of the most common ways to study and evaluate the EEG data, even in clinical practice (not only in research).

The investigated data are $60s$ segments. First of all the data saved in the way in (2.1) are classified using the correspondence Table (2.1.1). To facilitate computer calculations, four multidimensional matrices are created: for placebo recording, for haloperidol, for risperidone and for olanzapine. Each matrix has three dimension: subject $\times$ recording $times$ samples, that means $20 \times 14 \times 6000$ elements.

Basal2 (B2) of each different drugs and placebo is subtracted, from each recording from $1h$ to $12h$ after the assumption, that the circadian fluctuations are taken out and only the main changes induced by the drugs will be seen.

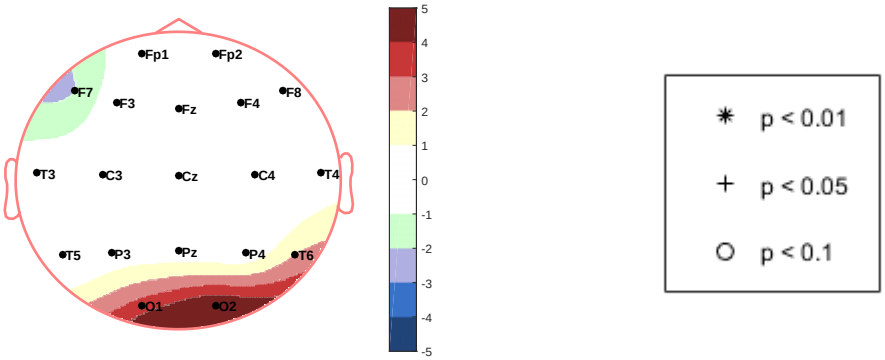
After the choice of the band of interest, the signal is processed using the Welch periodogram over the chosen band. To compute the values to depict in the final Spectral Maps the WLCX over the 20 volunteers is performed.

The WLCX test is computed using the spectral power for each electrode, subject and time (without the B2), comparing placebo and a drug. This allow to understand how much the antipsychotics intake changes the brain activity with respect the values obtained with the placebo assumption, that is the control.

The Statistical Parametric Maps (SPM) show the significant results of the 19 electrodes that

are been obtained via WLCX. Colors have been assigned using three different thresholds of significance based on the p-values $\mathbf{p}$ computed:

- for $\mathbf{p \leq 0.01}$ is assigned the value of 5 multiplied by the sign obtained from the statistical test[1]. The corresponding color is the darkest shade of red (if it is a significant increase) or blue (if it is a decrease);
- for $\mathbf{0.01 < p \leq 0.05}$ is assigned the value of 3.5 multiplied by the sign obtained from the statistical test. The intensity of the color is the intermediate;
- for $\mathbf{0.05 < p \leq 0.1}$ is assigned the value of 2 multiplied by the sign obtained from the statistical test. The lightest shades of red and blue are used;
- values of $\mathbf{p > 0.1}$ are considered not significant. White color is used to represent this values.



(A) *Legend of the SPM.*

(B) *Legend of the significant symbols in the Mean Plot.*

Figure 3.0.1 *Main Legends used in this Chapter.*

The colorbar is easy to understand looking at the Figure 3.0.1A.
As explained in Section 2.4, a map could be considered reliable, if it has at least 5 significant electrodes.
To analyze in a better way how the power is changing during the experiment, also a plot that presents the mean values of SP over the 19 electrodes and 20 volunteers has been

[1] $+1$ stays for increasing and -1 for decreasing.

obtained. The WLCX is applied to understand if the difference with respect to the placebo is significant[2], globally for the whole head, at each recording time.

3.1 Delta Band

A $\delta-$wave is a high amplitude brain wave with a frequency of oscillation between $[1.5\ 3.5]$Hz. Delta waves are usually associated with the deep stage NREM sleep and help in characterizing the depth of sleep. They are the slowest and highest amplitude classically described brainwaves. Their increase is a characteristic effect of antipsychotics [Romero et al. 2008].

In the following pages are represented the corresponding obtained Statistical Parametric

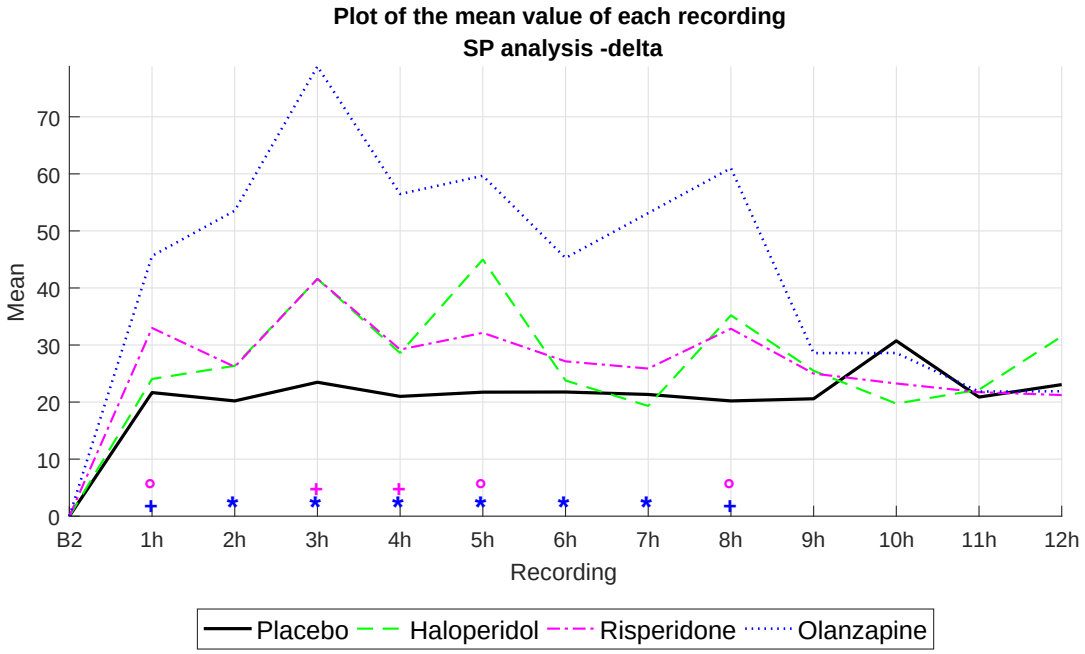
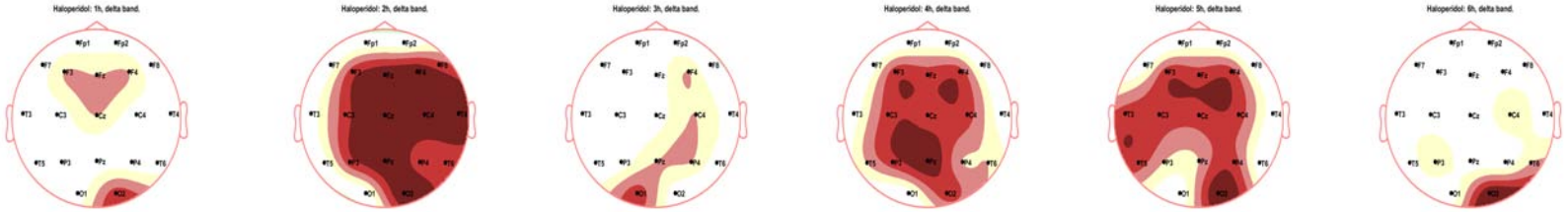


Figure 3.1.1 *Plot that represents the mean values of the power for δ band.*

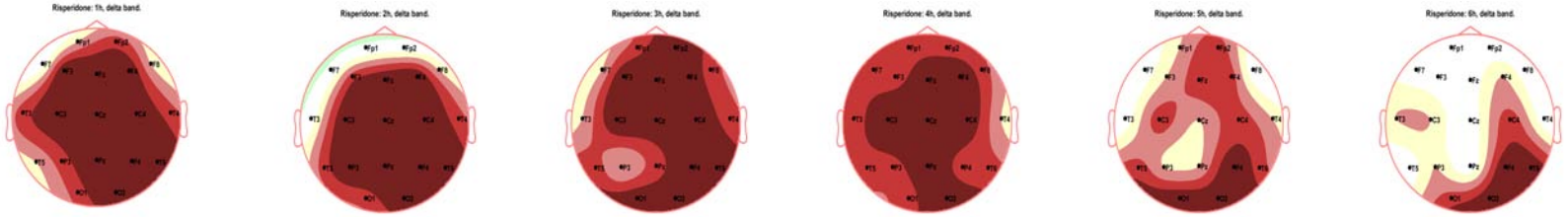
Maps (SPMs).

[2]In Figure 3.0.1B is reported the legend that describes the different symbols used to represent the different levels of significance.



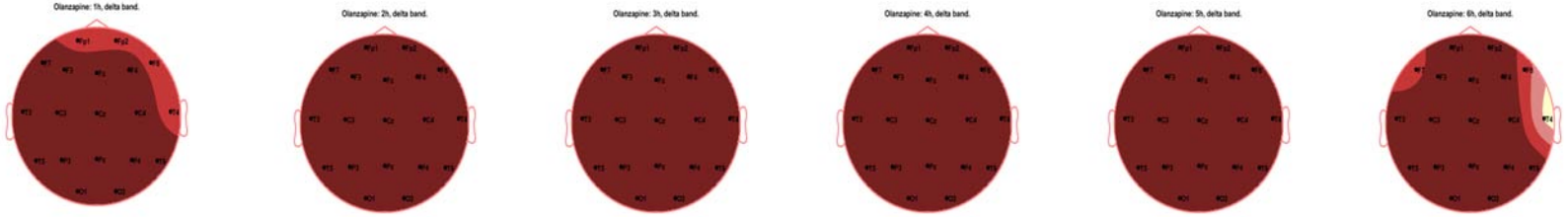
► 1h **► 2h** **► 3h** **► 4h** **► 5h** **► 6h**

△ HALOPERIDOL - SP



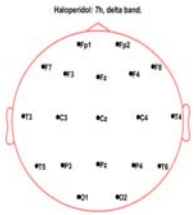
► 1h **► 2h** **► 3h** **► 4h** **► 5h** **► 6h**

△ RISPERIDONE - SP

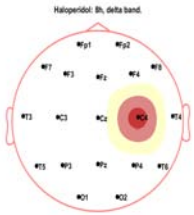


► 1h **► 2h** **► 3h** **► 4h** **► 5h** **► 6h**

△ OLANZAPINE - SP



► 7h



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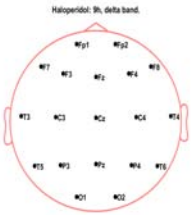
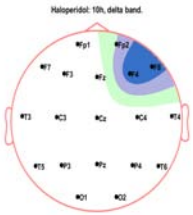
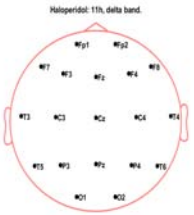


► 9h



► 10h



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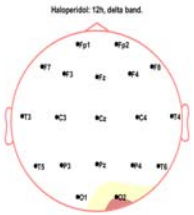
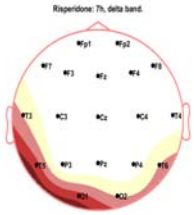


► 12h

△ HALOPERIDOL - SP



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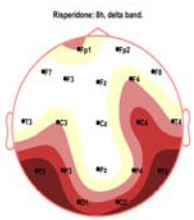

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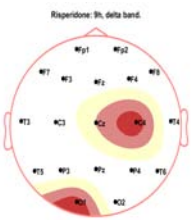

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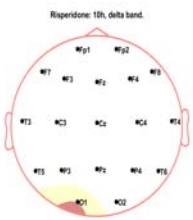

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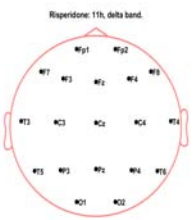

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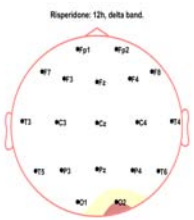
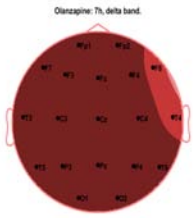
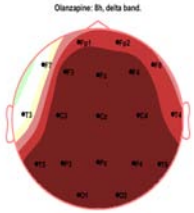


► 12h

△ RISPERIDONE - SP



► 7h



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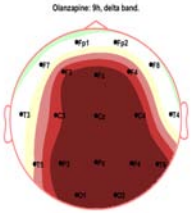

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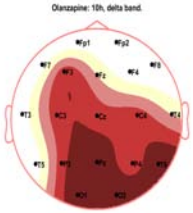

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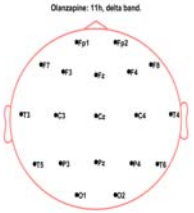
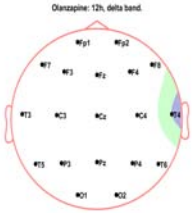


► 11h



► 12h

△ OLANZAPINE - SP

As conclusion of this analysis could be said that the highest average power is obtained under the olanzapine intake. It can be seen both in the SPM and in Figure 3.1.1, that olanzapine, reaches a peak three times bigger with respect to placebo's one, having highly significant differences ($p \leq 0.01$) in the more relevant hours ($3h - 6h$).
In risperidone too, some effects are present, but with lower significance.
In haloperidol, there are also some significant effects in the central zone in the early hours until $5h$, but smaller than the other two antipsychotics.
All the drugs generate increments of activity, as it can be seen in the SPM (mainly colored in red) and the average plot.
In Table (3.1.1) the relevance (i.e. the reliability) of the SPMs is reported, recall that a map is said relevant if the significant electrode are more then 5, according to the binomial criterion.

	Haloperidol	**Risperidone**	**Olanzapine**
1h	5	18	19
2h	13	15	19
3h	5	19	19
4h	12	19	19
5h	12	16	19
6h	4	9	19
7h	0	5	19
8h	1	11	17
9h	0	3	13
10h	3	1	12
11h	0	0	0
12h	1	1	1

Table 3.1.1 *Report of the number of electrodes that have a statistically significant effect.*

3.2 Theta Band

A $\vartheta-$wave is a brain wave with a frequency of oscillation between $[3.5\ 7.5]$Hz. This band is usually associated with drowsiness or meditation. These waves are more typical on children EEG and if they exceed in older ages it could be seen as abnormal activity.

In the following pages are represented the obtained SPMs.

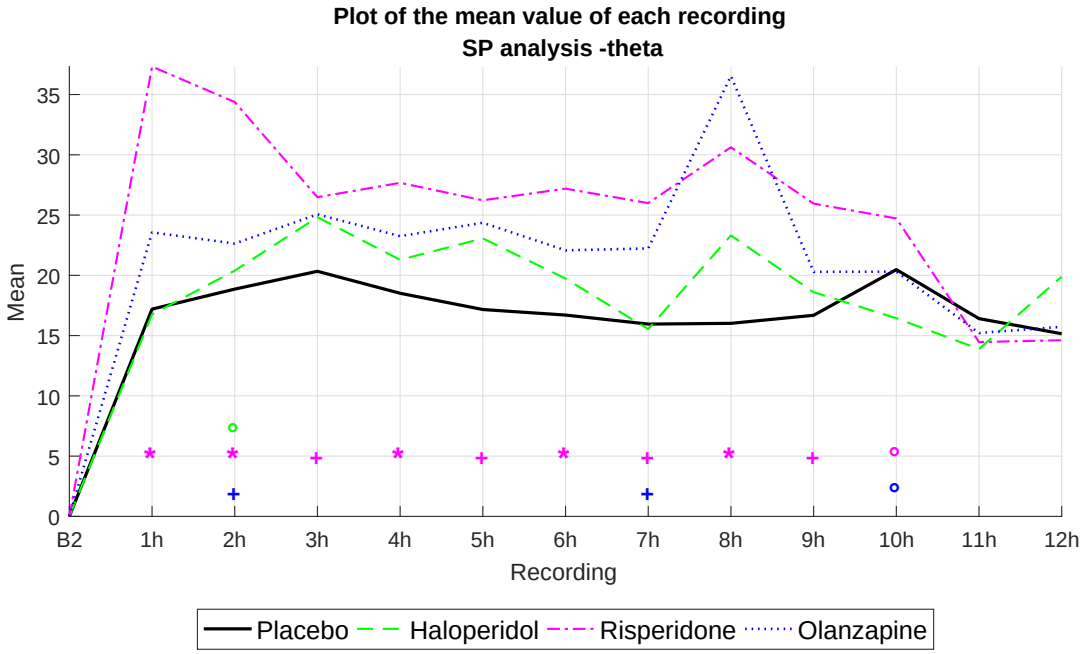
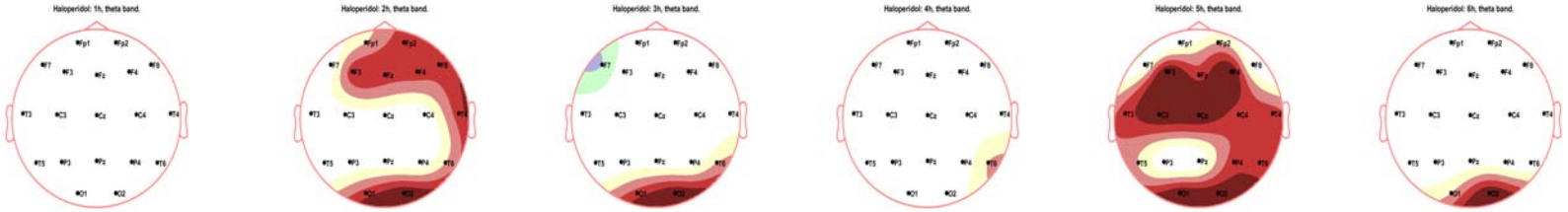
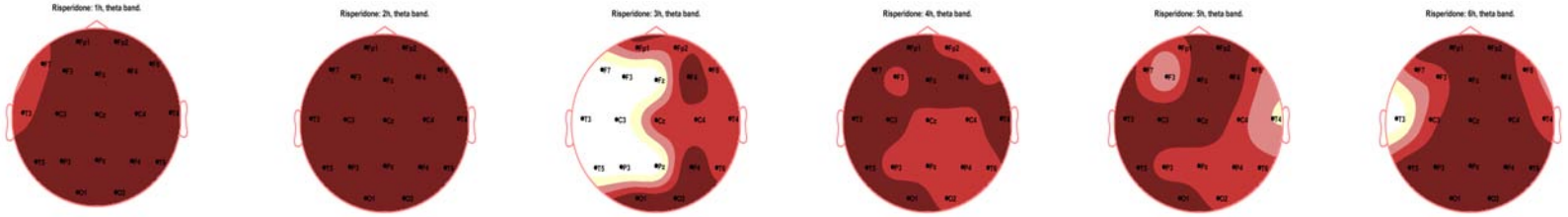


Figure 3.2.1 *Plot that represents the means values of the power for ϑ band.*



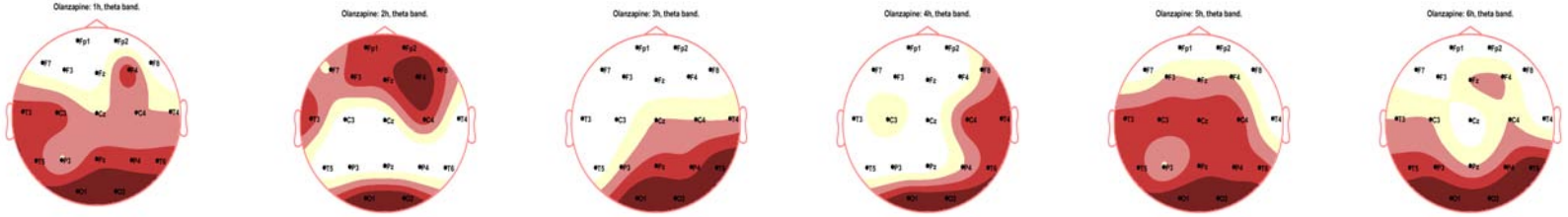
► 1h **► 2h** **► 3h** **► 4h** **► 5h** **► 6h**

△ HALOPERIDOL - SP



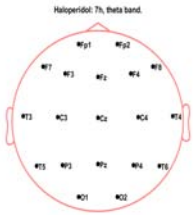
► 1h **► 2h** **► 3h** **► 4h** **► 5h** **► 6h**

△ RISPERIDONE - SP

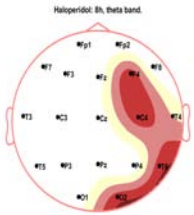


► 1h **► 2h** **► 3h** **► 4h** **► 5h** **► 6h**

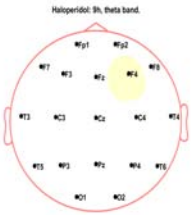
△ OLANZAPINE - SP



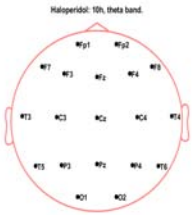
► 7h



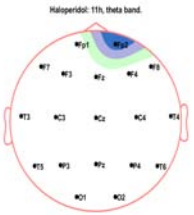
► 8h



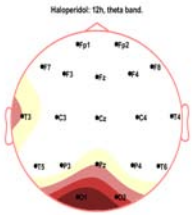
► 9h



► 10h

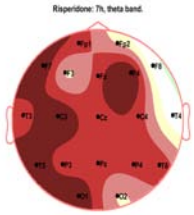


► 11h

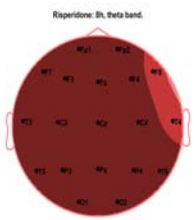


► 12h

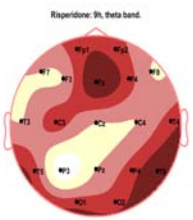
△ HALOPERIDOL - SP



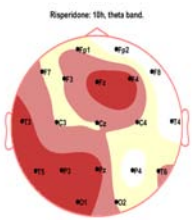
► 7h



► 8h



► 9h



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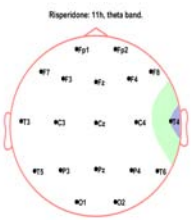
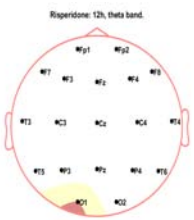
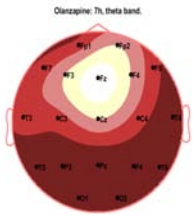


► 11h

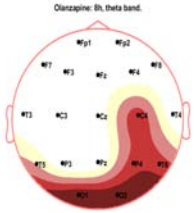


► 12h

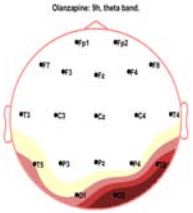
△ RISPERIDONE - SP



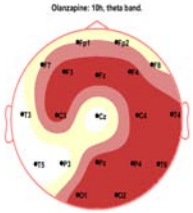
► 7h



► 8h



► 9h



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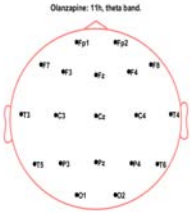
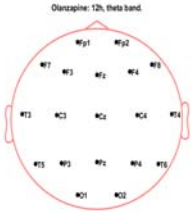


► 11h



► 12h

△ OLANZAPINE - SP

The results of the analysis in the ϑ band show from the intake of risperidone. In Figure 3.2.1 it can be seen that there are significant differences between risperidone and placebo, the drug reaches peaks that have values that doubled the control ones. This is also pointed out in the SPM.

Regarding to olanzapine not relevant mean changes are obtained and only two are quite significant. Moreover, evaluating the SPM it could be seen that the main activation are in the occipital zone.

Concerning the recordings of haloperidol intake there are not relevant results. Some changes in the central and occipital zone around five hour after the consumption.

In this band, like in the δ one, the changes are mainly increasing.

The relevance of the SPMs is in Table 3.2.1.

	Haloperidol	**Risperidone**	**Olanzapine**
1h	0	19	13
2h	10	19	11
3h	4	11	9
4h	1	19	8
5h	14	19	14
6h	2	18	12
7h	0	17	18
8h	5	19	6
9h	1	18	4
10h	0	15	15
11h	1	1	0
12h	4	1	0

Table 3.2.1 *Report of the number of electrodes that have a statistically significant effect.*

3.3 Alpha Band

A $\alpha-$wave is a brain wave with a frequency of oscillation between $[7.5,\ 13]$Hz. This band is also called the 'posterior basic rhythm'. These waves are high in amplitude, and reduced with open eyes, govern daydreams, fantasy, and denotes a state of consciousness detached and relaxed. People who have problems with this frequency will have difficulty in remembering [Qin et al. 2016].

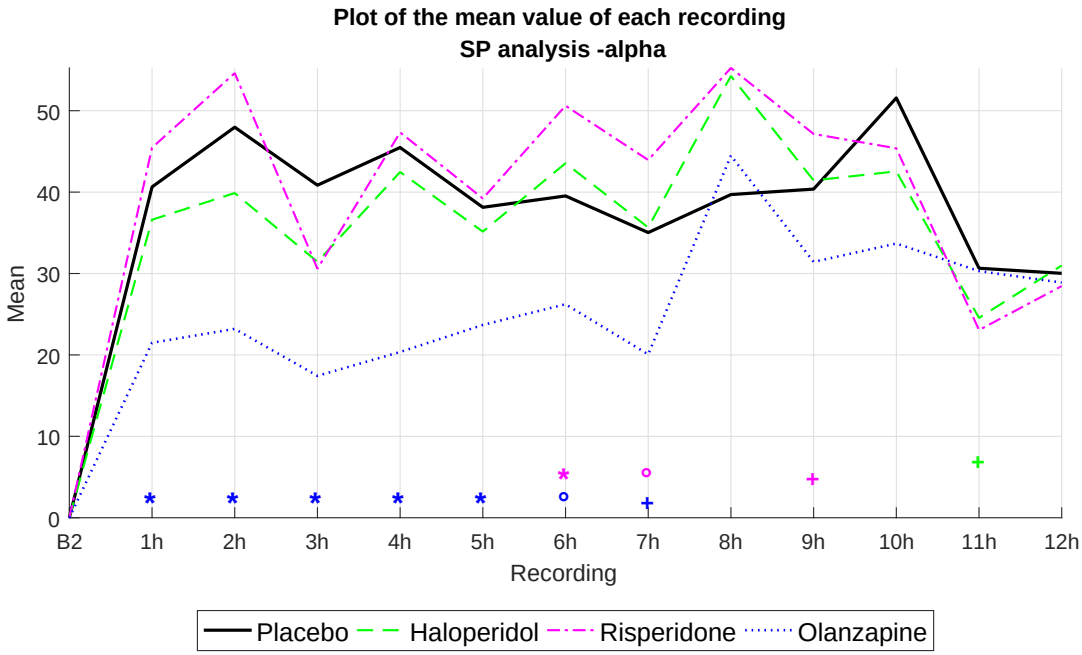
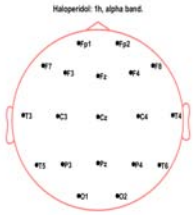
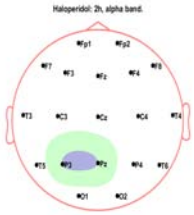


Figure 3.3.1 *Plot that represents the means values of the power for α band.*

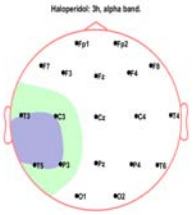
In the following pages are reported the obtained SPMs.



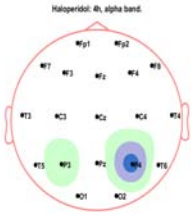
► 1h



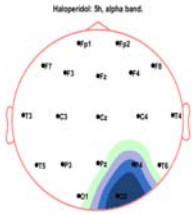
► 2h



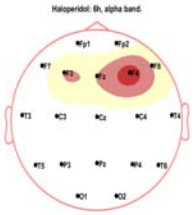
► 3h



► 4h

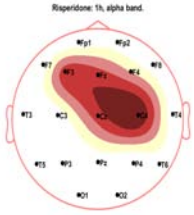


► 5h

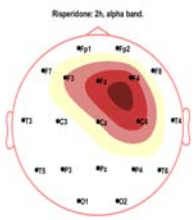


► 6h

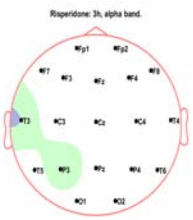
△ HALOPERIDOL - SP



► 1h



► 2h



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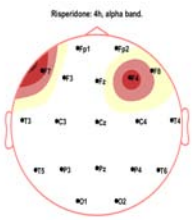
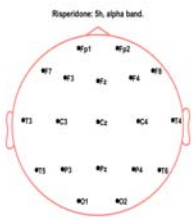


► 4h



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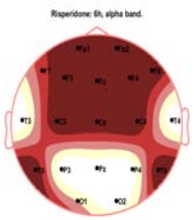
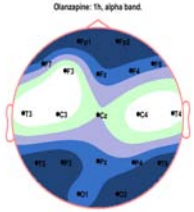


► 6h

△ RISPERIDONE - SP



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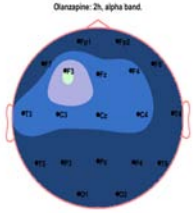

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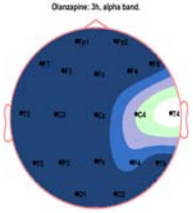

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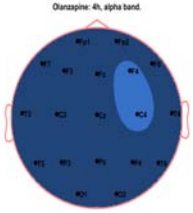

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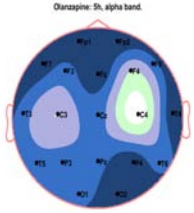

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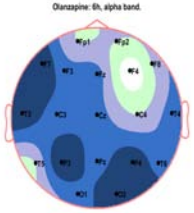
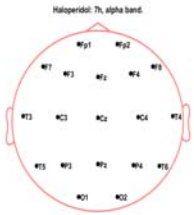


► 6h

△ OLANZAPINE - SP



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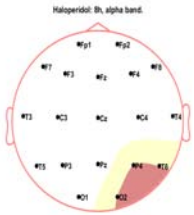

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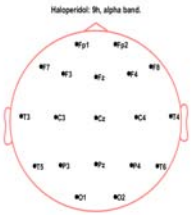

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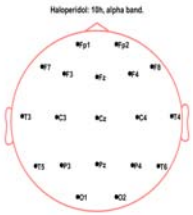
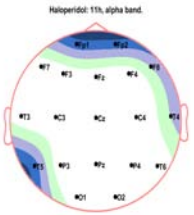
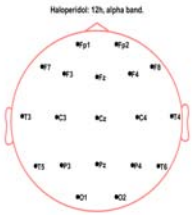


► 10h

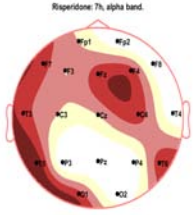


► 11h



► 12h

△ HALOPERIDOL - SP



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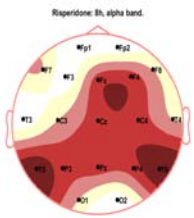

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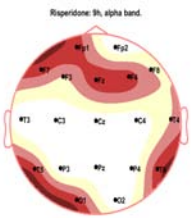

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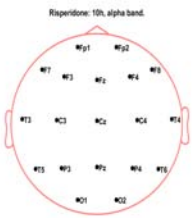

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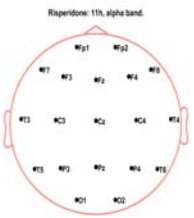

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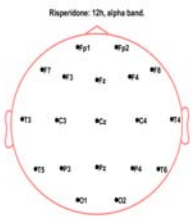
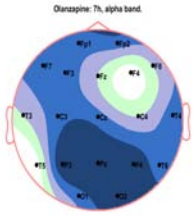


► 12h

△ RISPERIDONE - SP



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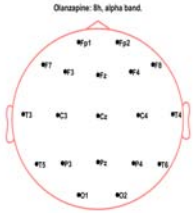

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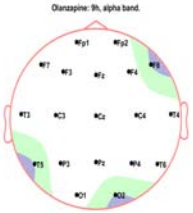

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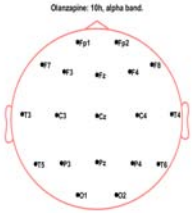

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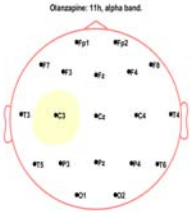

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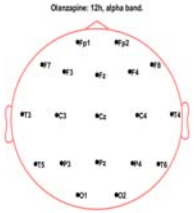


► 12h

△ OLANZAPINE - SP

In the α band the results are quite different for the drugs.

Regarding the plot of the means in Figure 3.3.1 it is easy to see that the changes in olanzapine are mainly decreasing (indeed the *blue* line is under the placebo line), in some recordings reaching half of the placebo's value, in risperidone are mostly increasing and haloperidol follows the placebo. Moreover, the decrements of olanzapine are all significant ($p \leq 0.01$) in the main hours $3h - 6h$.

What was detected in the mean plot is reflected in the SPM, but here is more evident that risperidone has a peak of changes around $6h - 8h$.

No significant results are obtained from haloperidol. Moreover, in Table 3.3.1 it can be seen that no more than 5 electrodes are affected of relevant changes.

	Haloperidol	**Risperidone**	**Olanzapine**
1h	0	5	14
2h	2	5	19
3h	4	2	18
4h	2	3	19
5h	2	0	18
6h	4	13	18
7h	0	12	17
8h	3	14	0
9h	0	10	3
10h	0	0	0
11h	5	0	1
12h	0	0	0

Table 3.3.1 *Report of the number of electrodes that have a statistically significant effect.*

3.4 Beta Band

A $\beta-$wave is a brain wave with a frequency of oscillation between $[13,\ 20]$Hz. Low amplitude of Beta with multiple and varying frequencies is often associated with anxious thinking or concentration. Rhythmic beta is associated with various pathologies and drug effects [Qin et al. 2016].

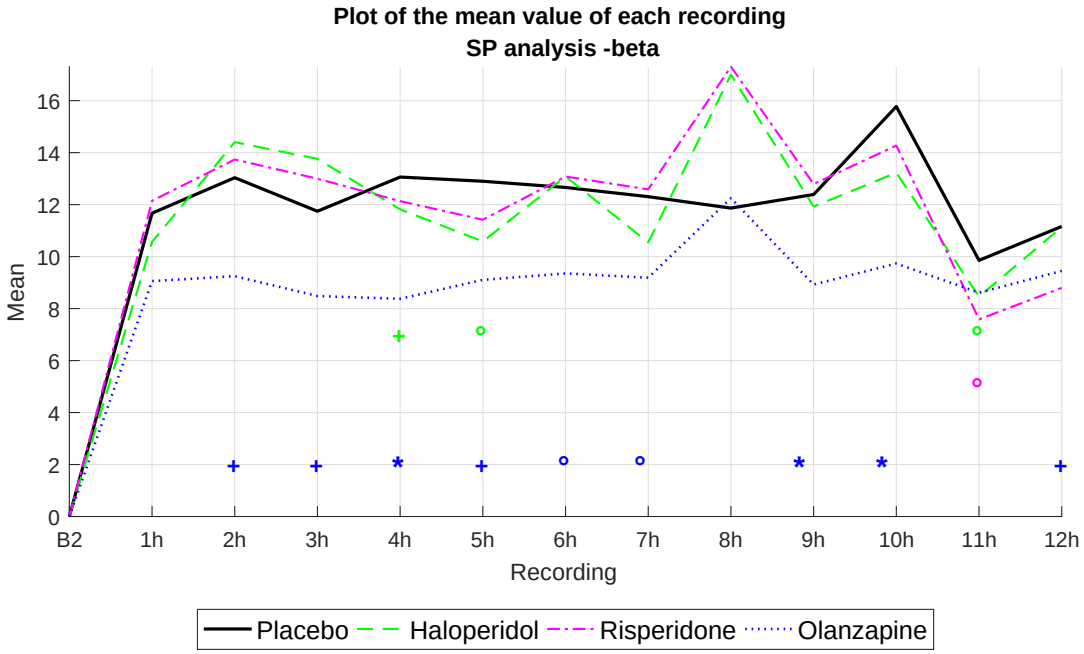
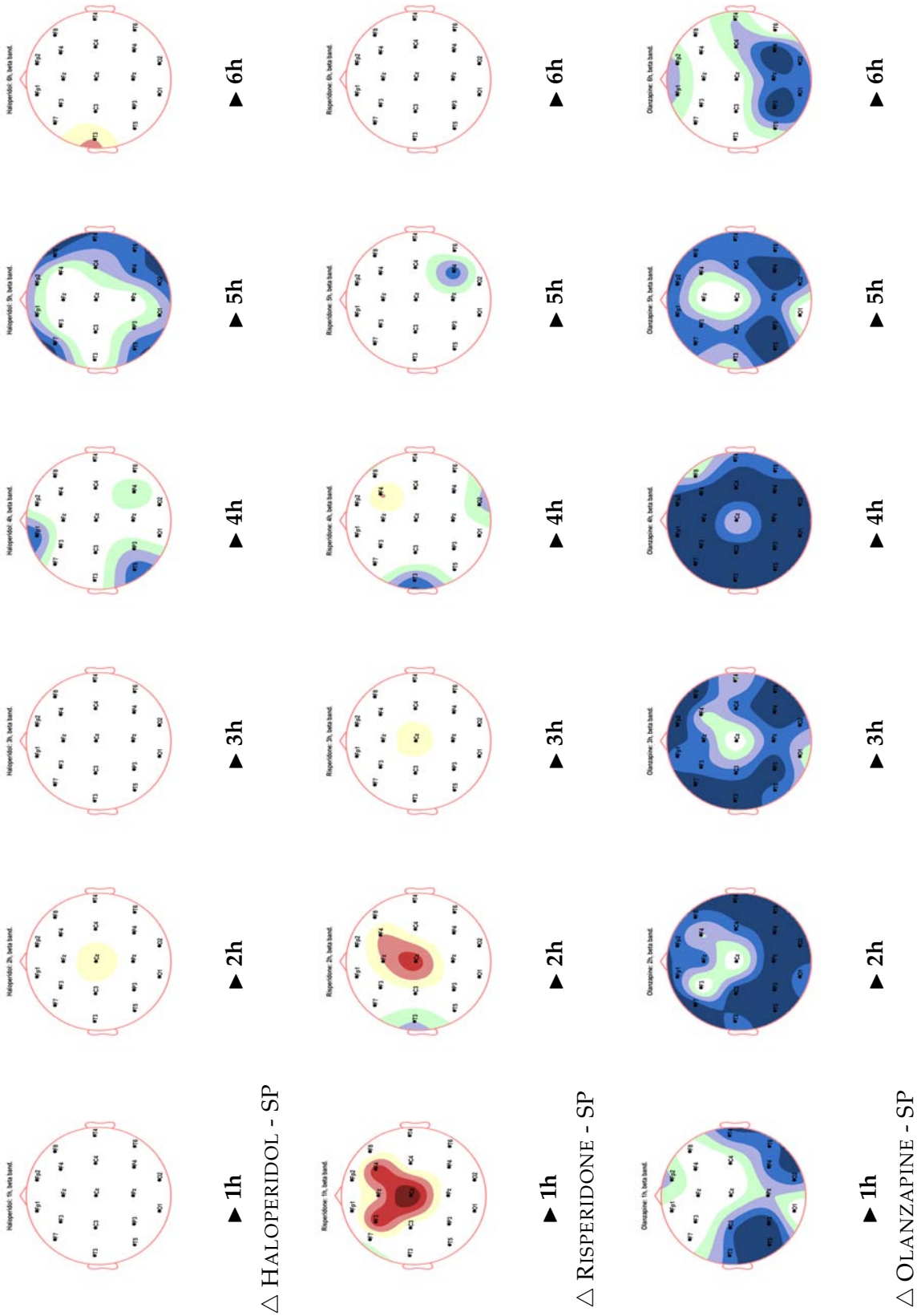
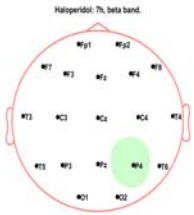


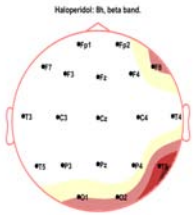
Figure 3.4.1 *Plot that represents the means values of the power for β band.*

In the following pages are represented the obtained SPMs.

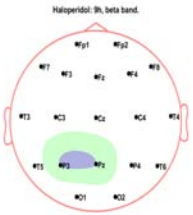

▲ 1h
▲ 2h
▲ 3h
▲ 4h
▲ 5h
▲ 6h
△ HALOPERIDOL - SP
△ RISPERIDONE - SP
△ OLANZAPINE - SP



► 7h



► 8h



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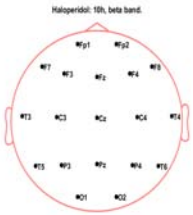
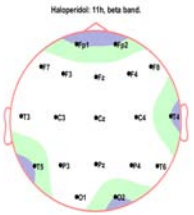
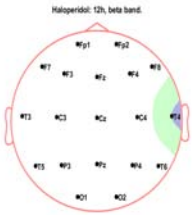


► 10h

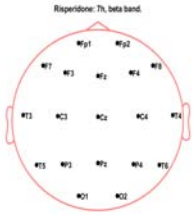


► 11h

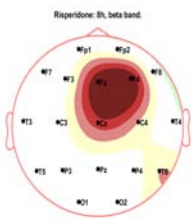


► 12h

△ HALOPERIDOL - SP



► 7h



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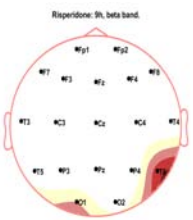

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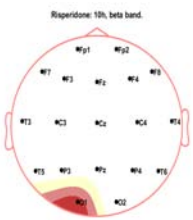
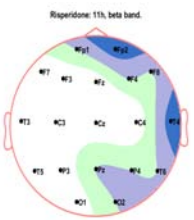


► 10h



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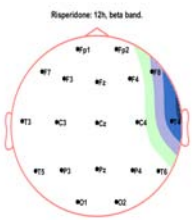
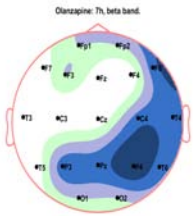


► 12h

△ RISPERIDONE - SP



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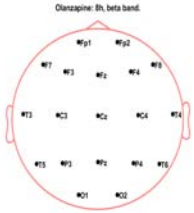

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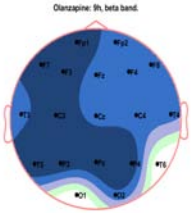

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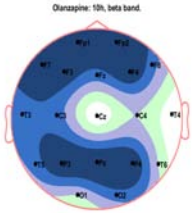
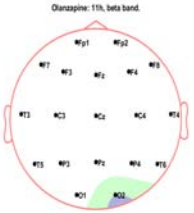


► 10h



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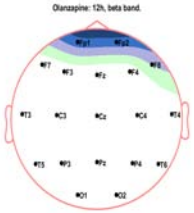


► 12h

△ OLANZAPINE - SP

Looking at the β band results, we see that they follow the ones obtained for the α band. As said in the previous analysis, section 3.3, the relevant changes are decreasing obtained with olanzapine, in the relevant time interval, moreover see Figure 3.4.1 it shows a significance of $p \leq 0.05$.

The other two drugs mimic the placebo's behavior; there is some relevance with haloperidol around $4/5h$, that can be better seen in the SPM.

The relevanceof the SPMs is reported in Table 3.4.1.

	Haloperidol	**Risperidone**	**Olanzapine**
1h	0	4	10
2h	1	4	17
3h	0	1	18
4h	4	3	19
5h	12	1	16
6h	1	0	10
7h	1	0	12
8h	4	5	0
9h	2	2	17
10h	0	1	17
11h	5	9	1
12h	1	2	3

Table 3.4.1 *Report of the number of electrodes that have a statistically significant effect.*

3.5 Conclusion

After evaluating the four band individually, it is useful to make a comparison between them.

As expected, the drug that has more effects is olanzapine. An interesting feature is that it can be seen that there is some similarity between the high frequency (α and β) the changes are decreasing and in the low frequency (δ and ϑ) there are increasing changes. These results were reported also in literature (like in Cerdán et al. [2005]), meaning that the results

obtained are coherent with the previous studies.
The risperidone shows some significant results, but in all the bands are mostly increasing changes. The affected zone is mainly the central part or the central-occipital.
Regarding the haloperidol, the only significant effects can be seen in the $\delta-$band in the central/central-occipital zone.

4

Synchronization Likelihood Approach

As explained in Section 2.2.2, this method divides each time series into a series of patterns, searching for a recurrence of these patterns. It is sensitive if one signal is repeating the pattern of another at the same time. It uses the observed time series as a representation of the underlying dynamical system in order to measure the degree of synchronization or coupling between each pair of channels.

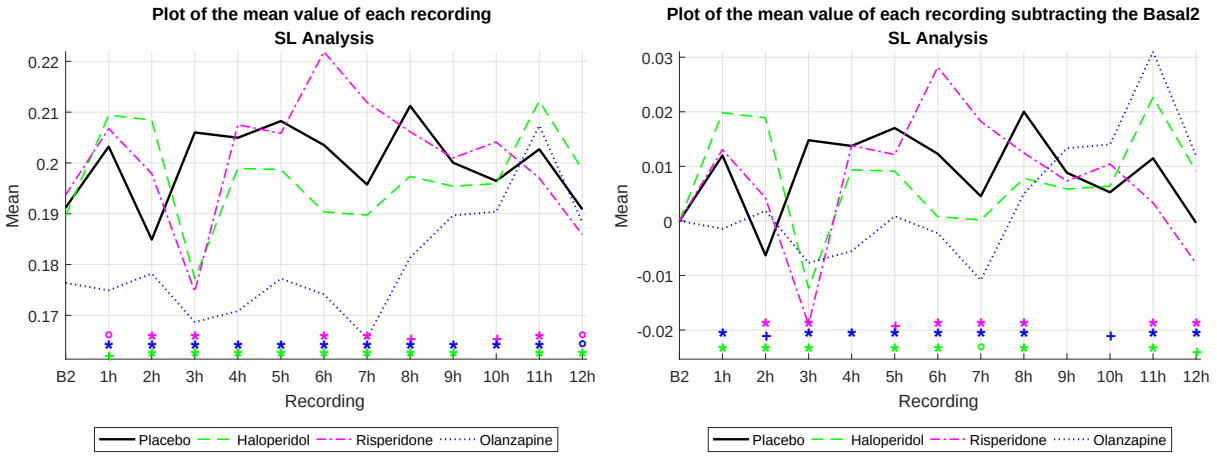
4.1 Evaluation of Synchronization Likelihood matrices via Statistical Analysis

The studied data are $10s$ segments. To begin, the SL algorithm is performed over all the data, obtaining for each recording, each volunteer and each day a 19×19 symmetric M_{SL} matrix. Furthermore the matrices were divided into the four different $4D-$vectors: placebo, haloperidol, risperidone and olanzapine.

To have a general overview of the behavior induced by the various drugs, two different average plots have been done. In Figure 4.1.1A the values obtained are shown, evaluating one recording per time, averaging the M_{SL} over the 20 volunteers, and finally after extracting the $N_{SL} = 171$ different results remember that the matrix is symmetric, the average was

computed. Moreover, in Figure 4.1.1B B2 was subtracted from each recording (from $1h$ to $12h$ after intake), and for the different drugs and placebo.

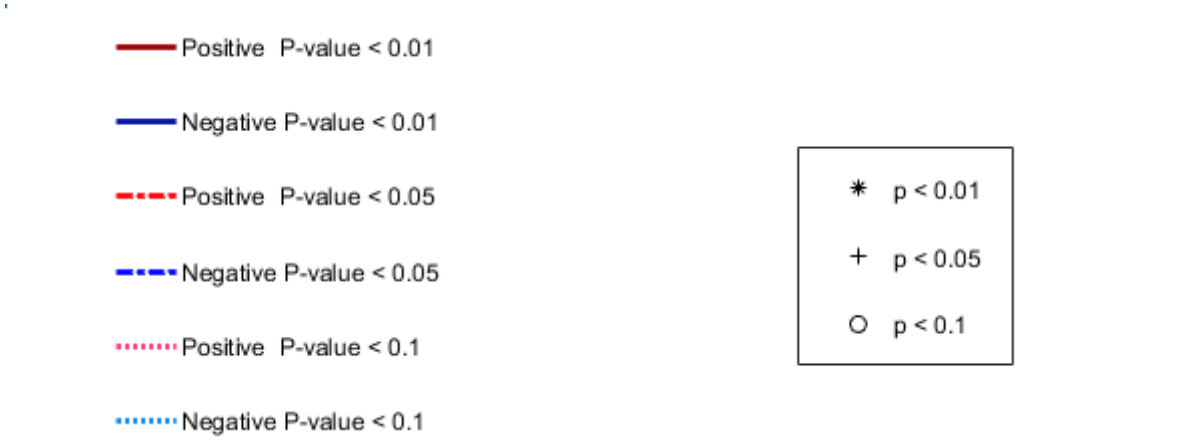
To give a more clear understanding of the plots, the WLCX has been computed over the



(A) *Plot of the mean values over the SL.* **(B)** *Plot of the mean values over the SL deleting the B2.*

Figure 4.1.1 *Plot of the mean behavior of the SL.*

vector of N_{SL} elements (for each recording), between the values of placebo and each drug. The value of significance is pointed out with different symbols, reported in the legend shown in Figure 4.1.2B.



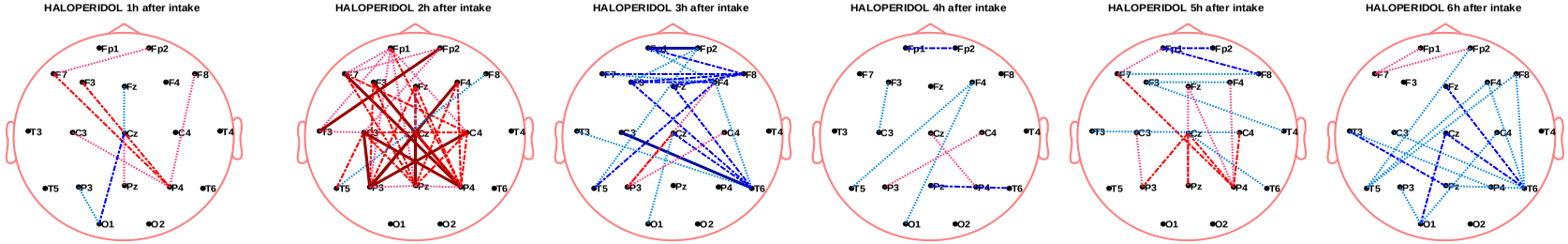
(A) *Legend for the significance on the Graph Connection Map* **(B)** *Legend of the significant symbols in the Mean Plot.*

Figure 4.1.2 *Main Legends used in this Chapter.*

Summing up, in Figure 4.1.1, the main changes and significant differences are obtained from olanzapine (blue line). In figure (4.1.1A), haloperidol and risperidone have a peak around $3h$; then haloperidol mainly follows the placebo behavior and risperidone has

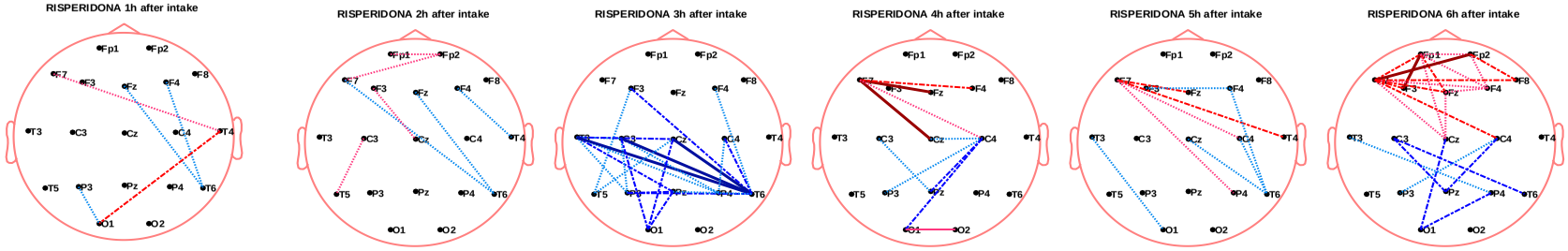
another peak around $6h$.
In Figure 4.1.1B, when subtracting the circadian effects (B2), the main thing that changes is that haloperidol and risperidone result less significant with respect to the previous evaluation.

To obtain the connectivity maps through WLCX, it is necessary to extract the N_{SL} values from the M_{SL} and save them in a vector. Since M_{SL} is symmetric, only the values over the upper diagonal were considered. The WLCX was computed between each drug and the placebo for each recording time, after subtracting the corresponding B2, in such a way that N_{SL} values of significance were obtained, one for each undirected connection between the 19 electrodes.
As explained in Section 2.4, every time that a multiple comparison test is applied, also the Cross and Chaffin Binomial Test has to be applied, obtaining that a SL Connectivity Map is considered reliable if it has at least $s^* = 25$ lines.
In the following pages the SL Connectivity Maps are shown considering the different significances explained in Figure 4.1.2A.
From the maps with more significant connections, it can be seen that persists the common peak in the significant hour $2 - 3h$, with increments or mainly increments for haloperidol and olanzapine, and risperidone shows more decrements. There could be seen also an additional peak around $8h$.
In general, haloperidol presents principally increments, risperidone shows decrements in the central-occipital part and has especially frontal increments after $6h$, and olanzapine mainly decrements. Moreover from the literature and the previous SP analysis, or simply from the figures (4.1.1) there were expected more significant results from olanzapine, but it is also true that olanzapine recordings showed more artifacts and in some cases this additional variability prevents the achivement of significant results in connectivity, which is much more sensitive to artifacts than spectral analysis.



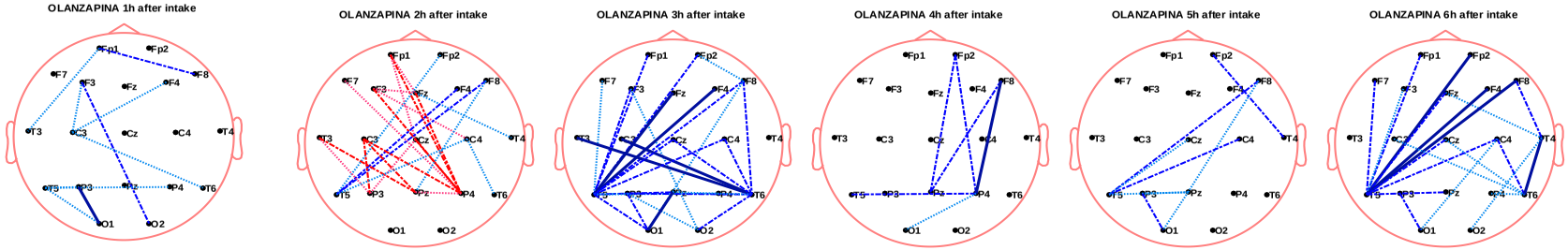
▶ 1h ▶ 2h ▶ 3h ▶ 4h ▶ 5h ▶ 6h

△ HALOPERIDOL - SL



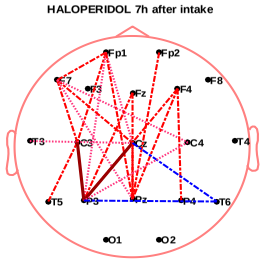
▶ 1h ▶ 2h ▶ 3h ▶ 4h ▶ 5h ▶ 6h

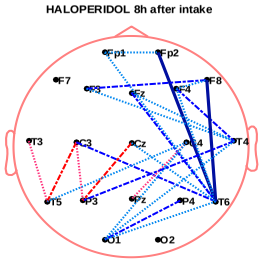
△ RISPERIDONE - SL

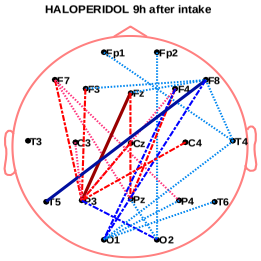


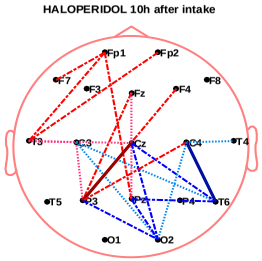
▶ 1h ▶ 2h ▶ 3h ▶ 4h ▶ 5h ▶ 6h

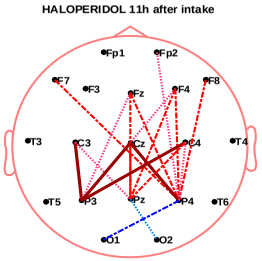
△ OLANZAPINE - SL

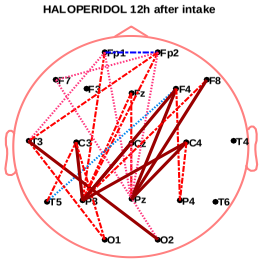






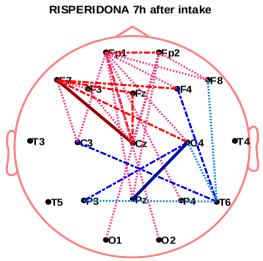


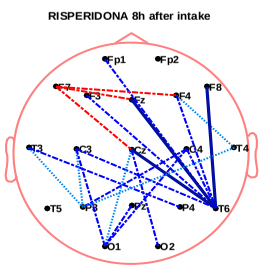


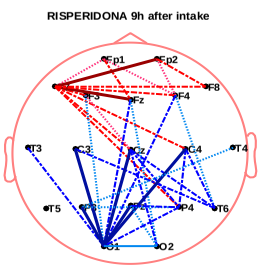


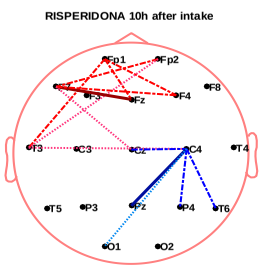
▶ 7h ▶ 8h ▶ 9h ▶ 10h ▶ 11h ▶ 12h

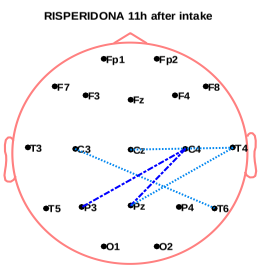
△ HALOPERIDOL - SL

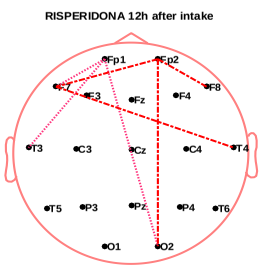






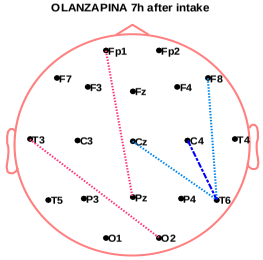


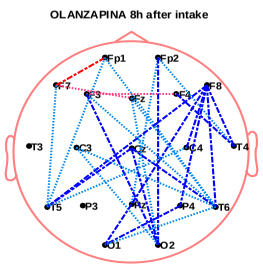


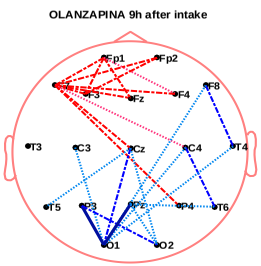


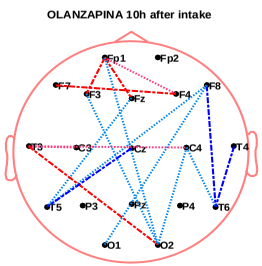
▶ 7h ▶ 8h ▶ 9h ▶ 10h ▶ 11h ▶ 12h

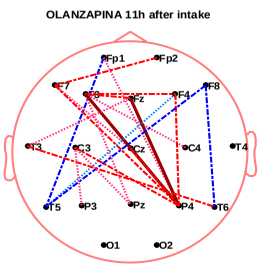
△ RISPERIDONE - SL

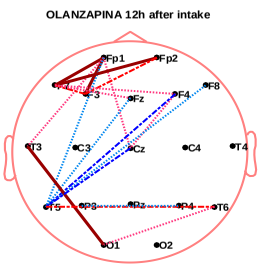












▶ 7h ▶ 8h ▶ 9h ▶ 10h ▶ 11h ▶ 12h

△ OLANZAPINE - SL

4.2 Synchronization Likelihood via non Statistical Analysis

One drawback of the maps built from statistically significant results is that they can mask or not show the underlying trends of the pharmacological effects (if they are subtle).
To understand if it is possible to obtain more informative results from the SL analysis, different approaches were used.

4.2.1 Analysis of the distribution

We analyze the connectivity maps by evaluating the mean value and the variance of the SL data, to see how many 'lines' are in the queues of the distribution. The procedure is as follows:

- convert the N_{SL} data from the matrix to a vector;
- subtract the Basal 2 from each recording ($\star h$) and intake (drug D and placebo P),

$$\tilde{D}_{\star h} = D_{\star h} - D_{B2};$$

- subtract from the obtained vector the vector of the placebo for the same time recording,

$$\bar{\tilde{D}}_{\star h} = \tilde{D}_{\star h} - P_{\star h};$$

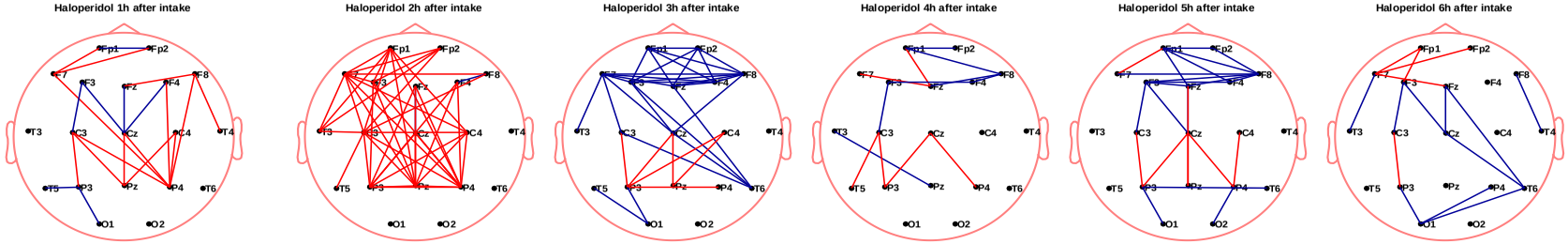
- compute the mean over the 20 volunteers for each recording,
- compute the mean value and the standard deviation $\mu_{D_{\star h}}$ and $\sigma_{D_{\star h}}$ of each $\bar{D}_{\star h}$;
- compute the mean value over the $\mu_{D_{\star h}}$ and $\sigma_{D_{\star h}}$, for each drug (haloperidol H, risperidone R and Olanzapine O),

$$\mu_D = \frac{1}{12}\sum_{\star=1}^{12} \mu_{D_{\star h}}; \qquad \sigma_D = \frac{1}{12}\sum_{\star=1}^{12} \sigma_{D_{\star h}}.$$

In this way all the graphs that regard the same antypsychotic plot the changes with respect to the same value of mean and standard deviation, so they are comparable.
In the following pages the maps are plotted according to the following rule. There is an interconnection (v) between two electrodes if:

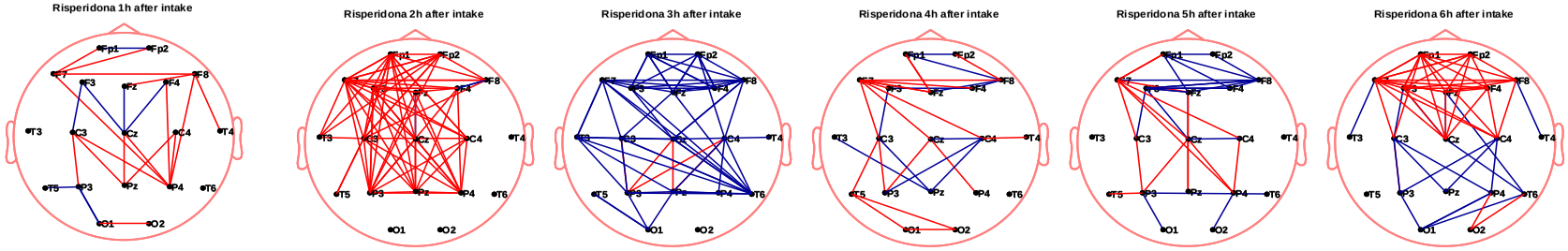
- $v \in [\mu_D + 1.5\sigma_D,\ \mu_D + 5\sigma_D]$ and the interconnection is depicted in red;
- $v \in [\mu_D - 5\sigma_D,\ \mu_D - 1.5\sigma_D]$ and the interconnection is depicted in blue.

The values $v > \mu_D + 5\sigma_D$ and $v < \mu_D - 5\sigma_D$ are discarded to reduce the outliers.



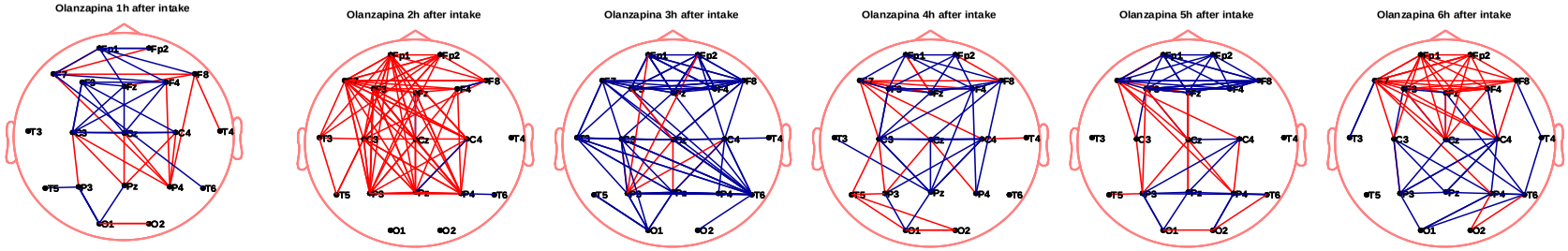
▶ 1h ▶ 2h ▶ 3h ▶ 4h ▶ 5h ▶ 6h

△ HALOPERIDOL - SL



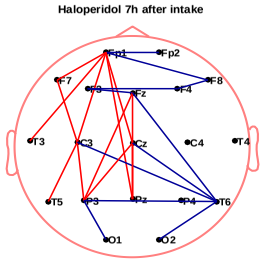
▶ 1h ▶ 2h ▶ 3h ▶ 4h ▶ 5h ▶ 6h

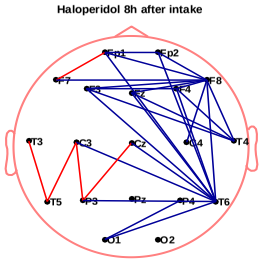
△ RISPERIDONE - SL

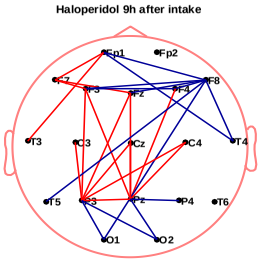


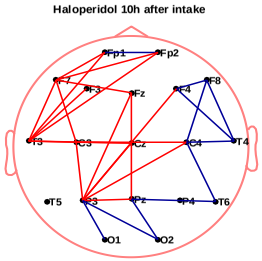
▶ 1h ▶ 2h ▶ 3h ▶ 4h ▶ 5h ▶ 6h

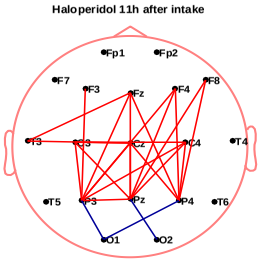
△ OLANZAPINE - SL

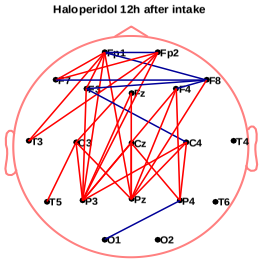






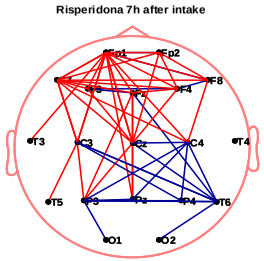


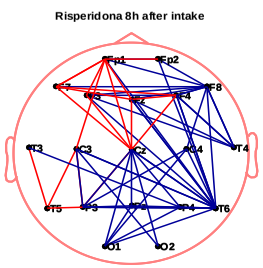


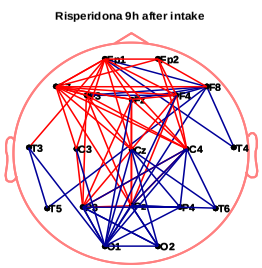


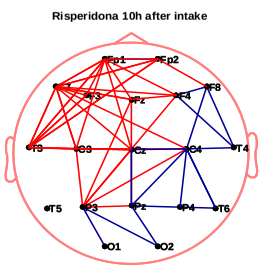
► 7h **► 8h** **► 9h** **► 10h** **► 11h** **► 12h**

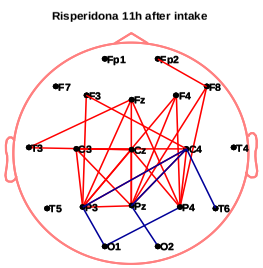
△ HALOPERIDOL - SL

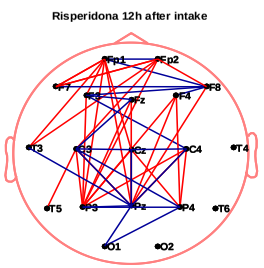






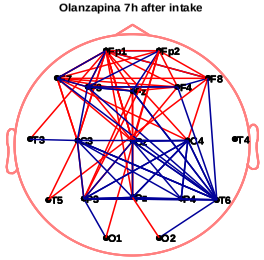


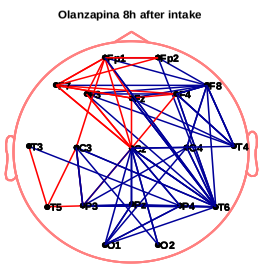


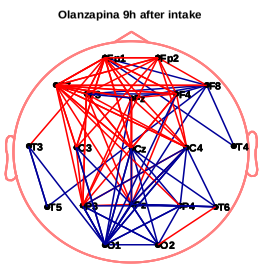


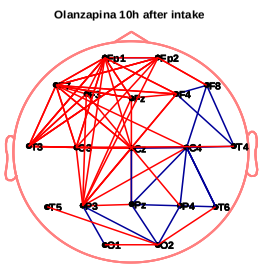
► 7h **► 8h** **► 9h** **► 10h** **► 11h** **► 12h**

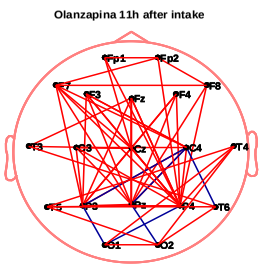
△ RISPERIDONE - SL

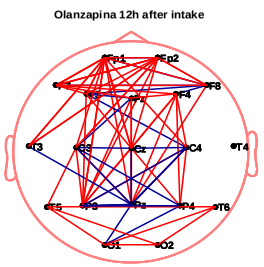












► 7h **► 8h** **► 9h** **► 10h** **► 11h** **► 12h**

△ OLANZAPINE - SL

In these graphs there is a little bit more about the fact that there is a peak of changes around $2-3h$, but here it can be seen that in $2h$ there is an increment of connectivity, over the value $\mu_D + 1.5\sigma_D$, and then a decrement below $\mu_D - 1.5\sigma_D$.
The maps with more lines are the ones regarding the olanzapine, as expected.
It can also be seen that more or less the hours with main effects are the same for all the antipsychotics, and also the zone more affected are similar, but with increasing number of line moving from haloperidol, to risperidone and then olanzapine.

4.2.2 Analysis of the means

In this case, we analyze the overall average connectivity of each of the 19 electrodes in order to plot heads similar to the ones created with the SP analysis.
The data (drug D and placebo P) are elaborated as follow:

- compute the mean over all the volunteers of the M_{SL}, obtaining $\tilde{D}$ and $\tilde{P}$;
- subtracte the mean of the B2 from each recording ($\star h$),

$$\bar{\tilde{D}}_{\star h} = \tilde{D}_{\star h} - \tilde{D}_{B2};$$

- subtract the mean value of placebo of the corresponding recording $\bar{\tilde{P}}_{\star h}$,

$$\bar{D}_{\star h} = \bar{\tilde{D}}_{\star h} - \bar{\tilde{P}}_{\star h};$$

- compute the mean over columns of $\bar{D}_{\star h}$ to obtain the average values of the 19 electrodes;
- compute the global maximum and minimum, to have the same way of comparison over the three drugs.

The discussion of the results, reported in the following pages (see the legend in Figure 4.2.1), can again start from the evidence of the peak around $3h$ after the intake, which is, for all the three antipsychotics, negative.
The maps of haloperidol show mostly decrements, only in $2h$ and after $10h$ some increments start to appear. Interesting results are obtained for risperidone, almost all positive (except

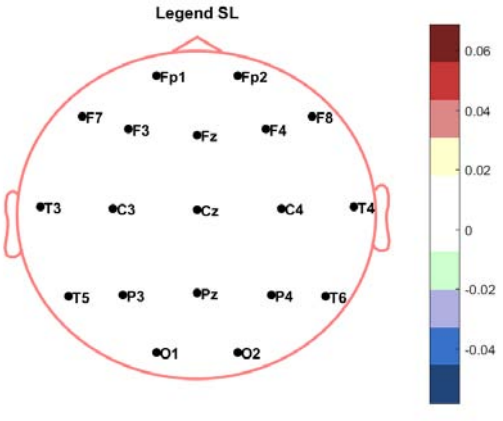
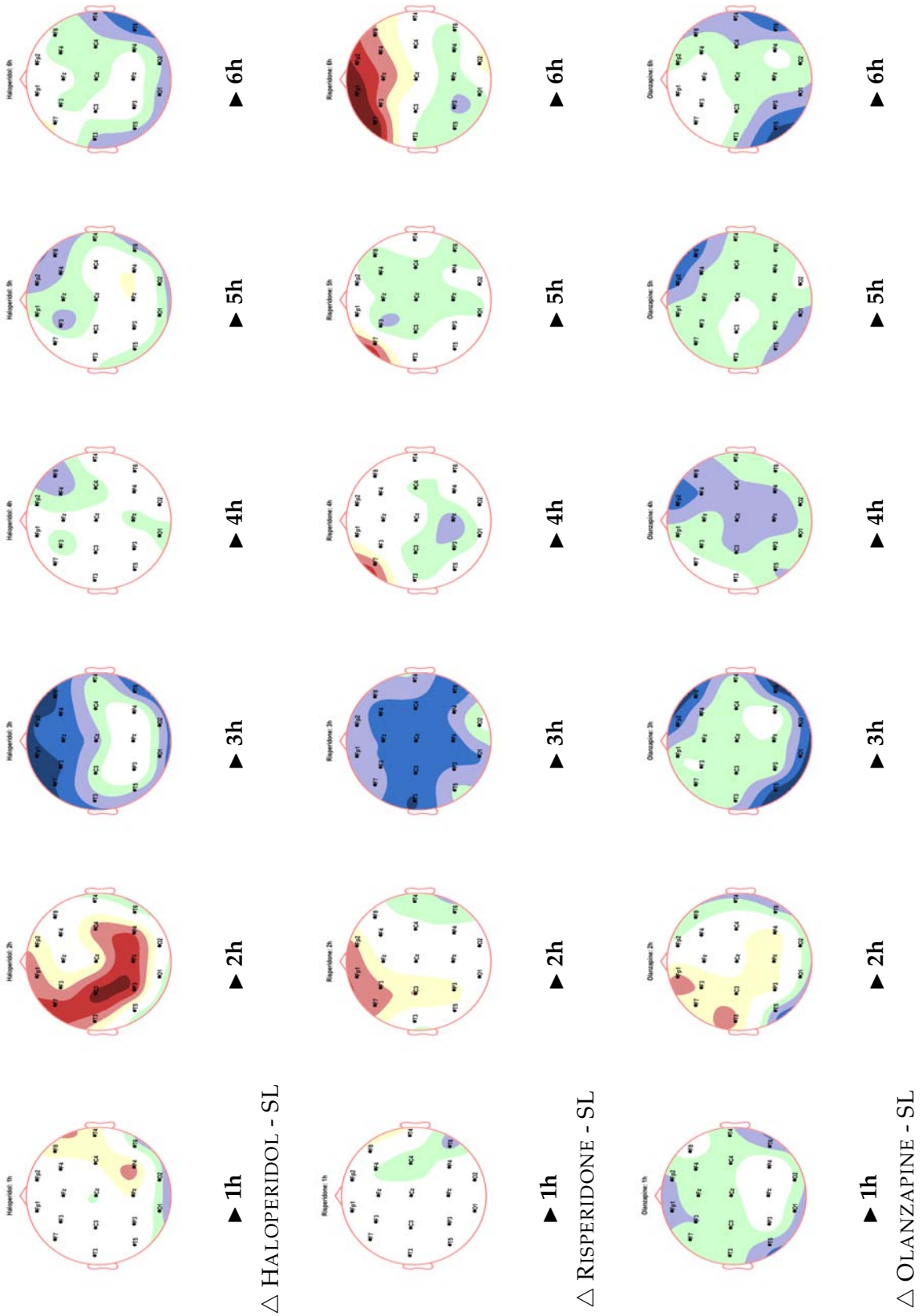
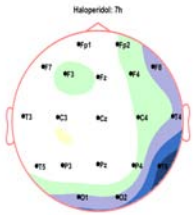


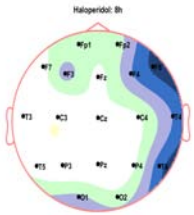
Figure 4.2.1 *Legend of the maps, the colorbar goes from the maximum possible value to the minimum.*

$3h$) and principally in the frontal zone. On the other hand, olanzapine shows decrements and mainly in the occipital zone.

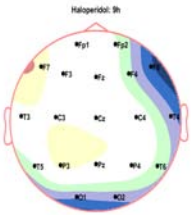

▲ 1h
▲ 2h
▲ 3h
▲ 4h
▲ 5h
▲ 6h
△ HALOPERIDOL - SL
△ RISPERIDONE - SL
△ OLANZAPINE - SL



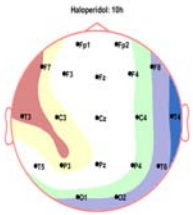
► 7h



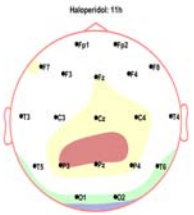
► 8h



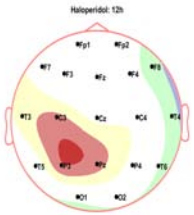
► 9h



► 10h

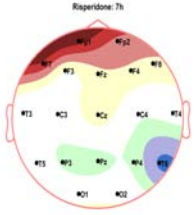


► 11h

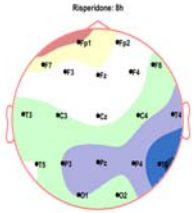


► 12h

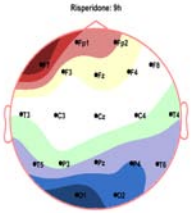
△ HALOPERIDOL - SL



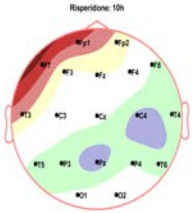
► 7h



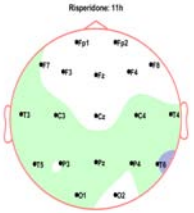
► 8h



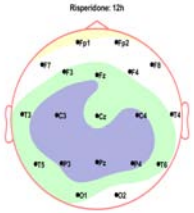
► 9h



► 10h

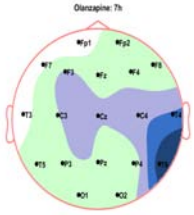


► 11h

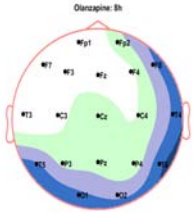


► 12h

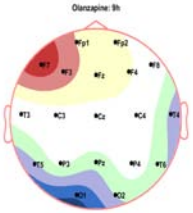
△ RISPERIDONE - SL



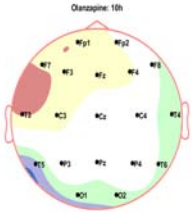
► 7h



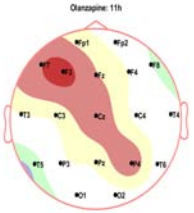
► 8h



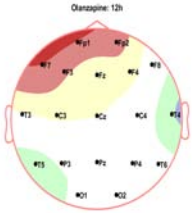
► 9h



► 10h



► 11h



► 12h

△ OLANZAPINE - SL

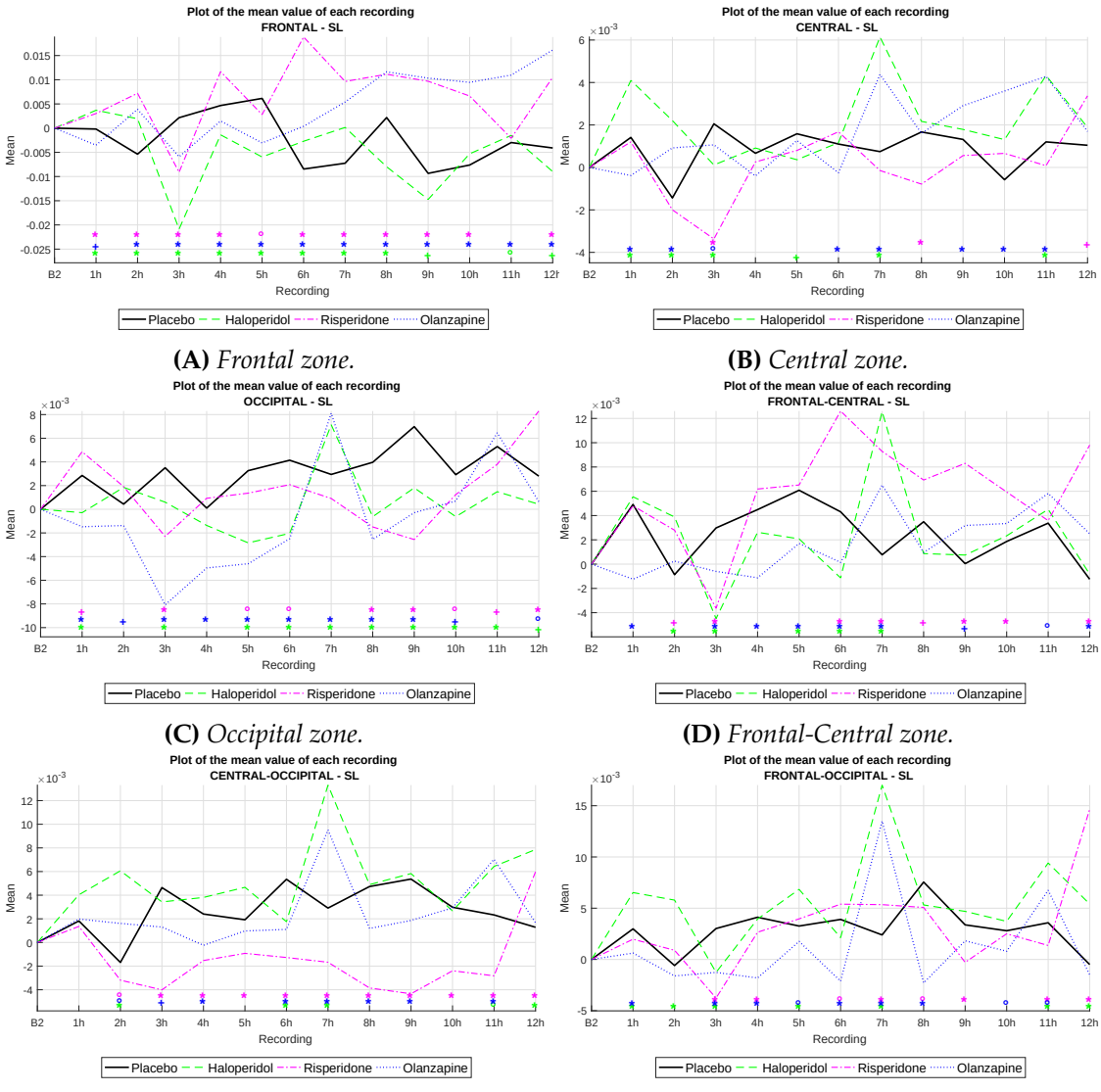
4.2.3 Topographic Analysis

From the previous analysis (Section 4.2.2) with the mean of electrodes, it can be seen that some effects are more evident and strong in specific zones. This is why, in what follows, it has been decided to plot also the mean values of connectivity divided by zones.
The considered areas are:

- **Frontal**, that considers the electrodes Fp1, Fp2, F7, F3, Fz, F4 and F8.
- **Central**, that considers the electrodes T3, C3, Cz, C4 and T4.
- **Occipital**, that considers the electrodes T5, P3, Pz, P4, T6, O1 and O2.
- **Frontal-Central**, that considers the electrodes interconnection between these two zones.
- **Central-Occipital**, that considers the electrodes interconnection between these two zones.
- **Frontal-Occipital**, that considers the electrodes interconnection between these two zones.

The data used in this analysis are the same used in figure 4.1.1B, also featuring the WLCX analysis to better understand the significance of each recording (the legend is reported in Figure 4.1.2B).
Figure 4.2.2, shows that the area with more significant results is the frontal. In the different plots haloperidol always presents a positive peak around $7h$ (except in the frontal), and after that it mainly follows the placebo behavior. In the analysis where the frontal area is involved, there is also a peak around $2 - 3h$ after intake. Both peaks have high significance ($p \leq 0.01$).
Regarding risperidone, a peak $3h$ after intake is always present with maximum significance ($p \leq 0.01$). In the frontal and in the frontal-central zones, the values are principally higher than placebo, on the other hand, in the central and occipital zones they are mostly lower. That explains why in the mixed zone there is a mixing of the effects: the central-occipital has prevalence of decreases, and in the frontal-central the drug is following the control effect.
Regarding the olanzapine intake, there is always the positive peak around $7h$ with the

maximum significance. In the frontal, central and in their combination it can be seen at the beginning a decrease in connectivity and, more or less around $6h$, an increase. In the occipital area there are mostly decreases, and they are dominant, so they can be seen also in the mixed zones.



(A) *Frontal zone.* **(B)** *Central zone.*

(C) *Occipital zone.* **(D)** *Frontal-Central zone.*

(E) *Central-Occipital zone.* **(F)** *Frontal-Occipital zone.*

Figure 4.2.2 *Plot of the mean considering separately the different zones.*

4.3 Conclusion

To close this chapter about the Synchronization Likelihood analysis, we have found that there is the constant to find the peak of connectivity changes around $2 - 3h$ after the intake, for all the different point of evaluation of the data. In some cases we have noticed another

peak at $7h$.

As discussed before, more significant results were initially expected for the olanzapine intake, but this lack of outcome could be justified by the fact that the olanzapine recordings are the ones more affected by artifacts with respect to haloperidol and risperidone.

5

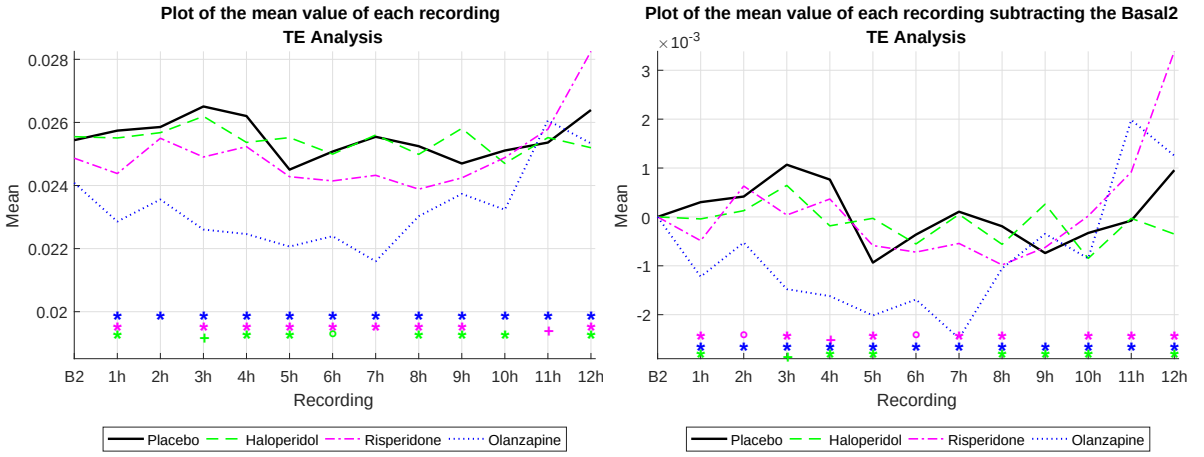
Transfer Entropy Approach

As explained in Section 2.2.3, the TE analysis is a technique that overcomes the mutual information.
This method computes the amount of uncertainty between two processes, knowing their past. Transfer Entropy is able to distinguish effectively driving and responding elements and to detect asymmetry in the interaction of subsystems.

5.1 Evaluation of Transfer Entropy matrices via Statistical Analysis

The data analyzed are $60s$ segments. The algorithm applied over all returns data the 19×19 non-symmetric matrices (M_{TE}) are obtained, and then saved in four $4D-$vectors, one for each drug and for placebo.
Before watching the results singularly, 'head by head', it is more interesting to have a global overview of the behavior of the different drugs with respect to placebo, in all the hours after the intake. This is reported in Figures 5.1.1. Specifically, in Figure 5.1.1A the mean without deleting the Basal2 recording (B2), and in Figure 5.1.1B withous B2.
The way to compute the values depicted is the same described in the section 4.1, with

the difference that the M_{TE} matrix is not symmetric, so the number of different values to evaluate are $N_{TE} = 342$. Also the Wilcoxon Signed Rank Test is computed over the vectors of N_{TE} elements, in such a way to give a significance to each recording. The outcome from WLCX is considered significant taking into account the same $p-$value ranges as in previous sections. Symbols used to indicate differences (see legend in (5.1.2B)) are also identic.



(A) *Plot of the mean values over the TE.* **(B)** *Plot of the mean values over the TE deleting the B2.*

Figure 5.1.1 *Plot of the mean behavior of the TE.*

To apply the WLCX to generate the Connectivity Maps it is necessary to extract the N_{TE} values from the M_{TE} and save them in a vector. Then, the WLCX was computed for each drug and the placebo recording, after subtracting the corresponding B2 (from 1h to 12h after intake different drug or placebo), in such a way that N_{TE} values of significance were obtained, one for each directed connection between the 19 electrodes.

As explained in the Section 2.4, every time that a multiple comparison test is used, also the Cross and Chaffin Binomial Test has to be applied, and in this case for TE, obtaining that a Connectivity Map is considered reliable if it has at least $s^* = 45$ lines. In the following pages the Maps plotted considering the same significance of before. The corresponding legend is shown in Figure 5.1.2A.

An interpretation of these results could be done comparing the graphs with the mean plots. In Figures 5.1.1 it is evident that the average connectivity of risperidone and haloperidol is fluctuating but its very similar to placebo. Olanzapine is the drug that points out the main results, almost always showing an average decrease of connectivity with respect to placebo. Moreover, deleting the B2 it can be seen that around $8h$ after intake, olanzapine is over the mean of the control. This increment of connectivity is also reported in the graphs maps of

(A) *Legend for the significance on the Graph Connection Map*

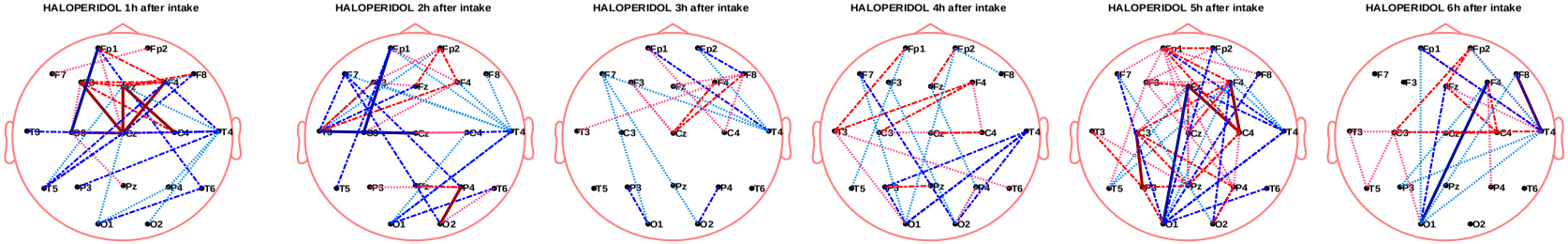
(B) *Legend of the significant symbols in the Mean Plot of the TE.*

Figure 5.1.2 *Main Legends used in this Chapter.*

connectivity.

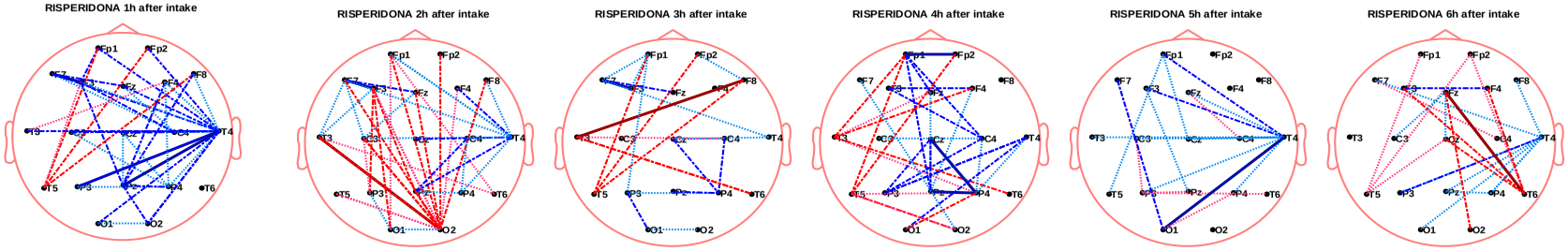
In the connectivity maps is present a peak around $2 - 3h$; in addition in olanzapine is appearing another decreasing one around $7h$, before the beginning of the increase. Haloperidol and risperidone in almost all the maps present increments of interconnection, that increase more after the $8h$.

In conclusion the better results, and more significant also, are obtained from olanzapine intake.



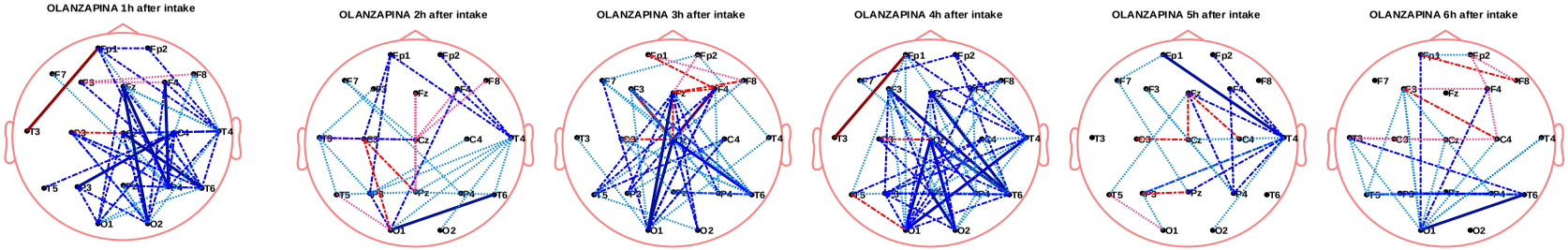
▶ 1h ▶ 2h ▶ 3h ▶ 4h ▶ 5h ▶ 6h

△ HALOPERIDOL - TE



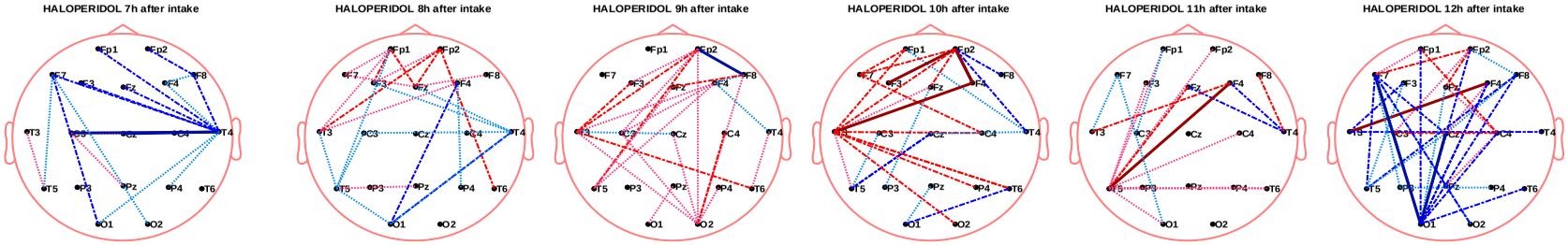
▶ 1h ▶ 2h ▶ 3h ▶ 4h ▶ 5h ▶ 6h

△ RISPERIDONE - TE



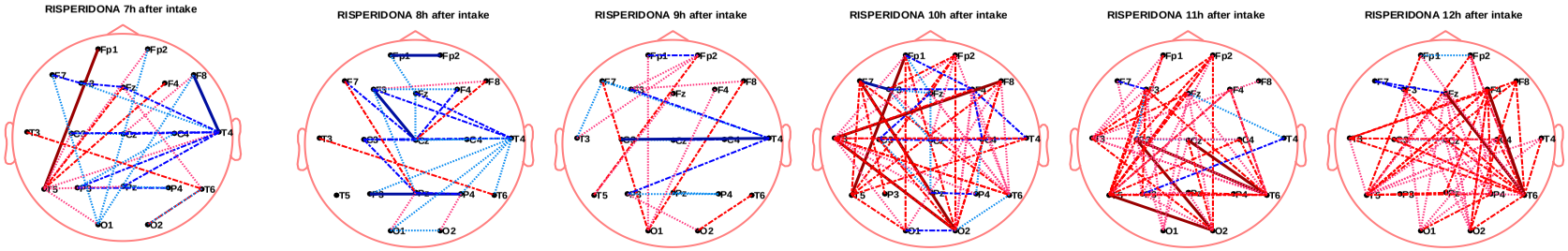
▶ 1h ▶ 2h ▶ 3h ▶ 4h ▶ 5h ▶ 6h

△ OLANZAPINE - TE



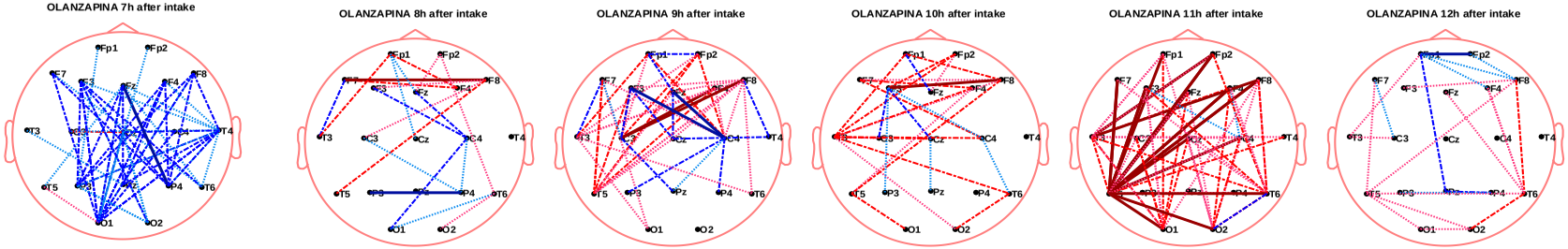
► 7h **► 8h** **► 9h** **► 10h** **► 11h** **► 12h**

△ HALOPERIDOL - TE



► 7h **► 8h** **► 9h** **► 10h** **► 11h** **► 12h**

△ RISPERIDONE - TE



► 7h **► 8h** **► 9h** **► 10h** **► 11h** **► 12h**

△ OLANZAPINE - TE

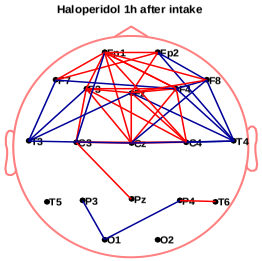
5.2 Transfer Entropy via non Statistical Analysis

One drawback of the maps built from statistically significant results is that they can mask or not show the underlying trends of the pharmacological effects (if they are subtle).
To understand if it is possible to obtain more informative results from the TE analysis, different approaches has been considered.

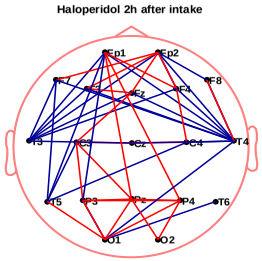
5.2.1 Analysis of the distribution

In this section the variation of connectivity as a distribution has been studied. For all the possible N_{TE} values, we applied an analysis analogous to that of Section 4.2.1.
In the same way and with the same threshold, all the values that are in the interval $[\mu_D + 1.5\sigma_D,\, \mu_D + 5\sigma_D]$ are seen as increment and the ones in $[\mu_D - 5\sigma_D,\, \mu_D - 1.5\sigma_D]$ are considered decrements.

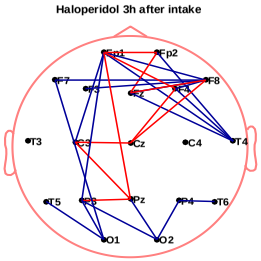
Evaluating the maps, the common element obtained is a maximum decrement of connectivity in the main hours $2 - 4h$, the increments start to be seen after $9h$. As in the SL analysis, the zones of the brain which are involved are similar, but for some drugs they are more evident because of the presence of a large number of lines.



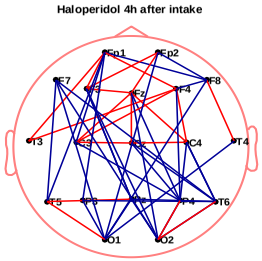
▶ 1h



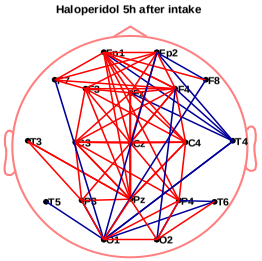
▶ 2h



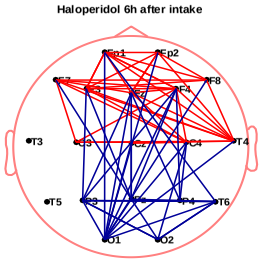
▶ 3h



▶ 4h

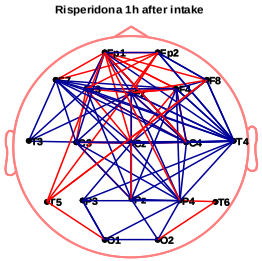


▶ 5h

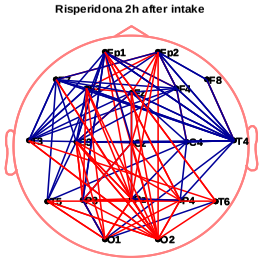


▶ 6h

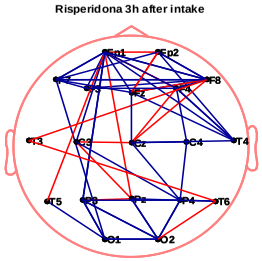
△ HALOPERIDOL - TE



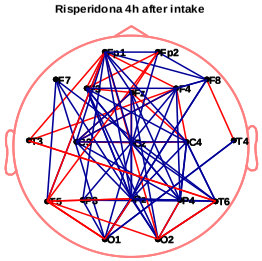
▶ 1h



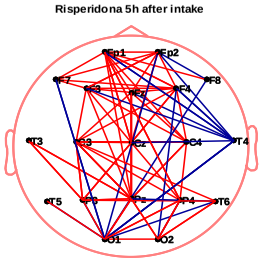
▶ 2h



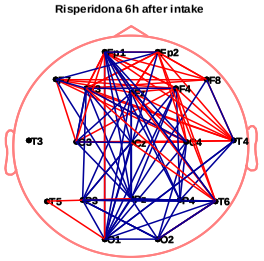
▶ 3h



▶ 4h

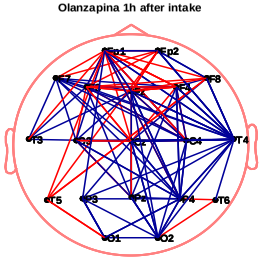


▶ 5h

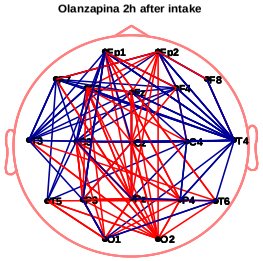


▶ 6h

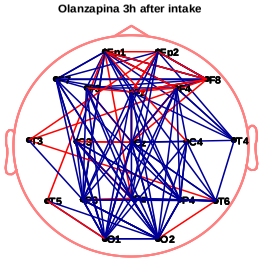
△ RISPERIDONE - TE



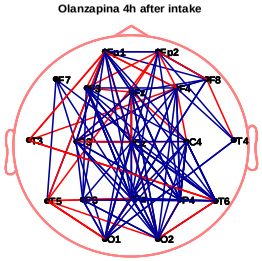
▶ 1h



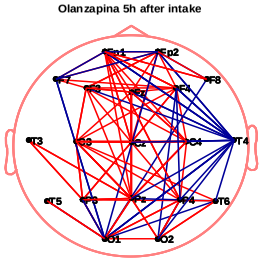
▶ 2h



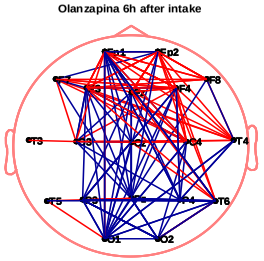
▶ 3h



▶ 4h

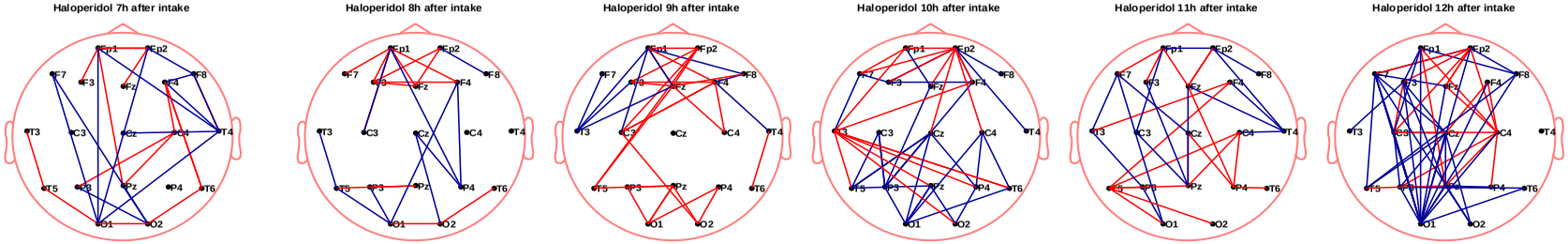


▶ 5h



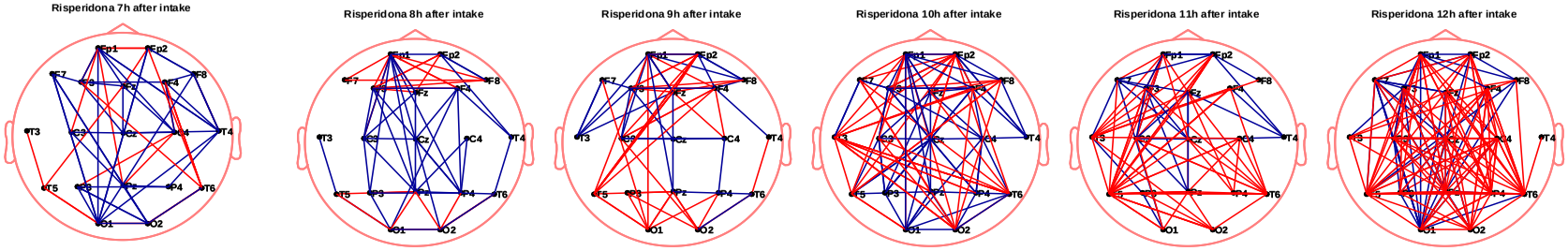
▶ 6h

△ OLANZAPINE - TE



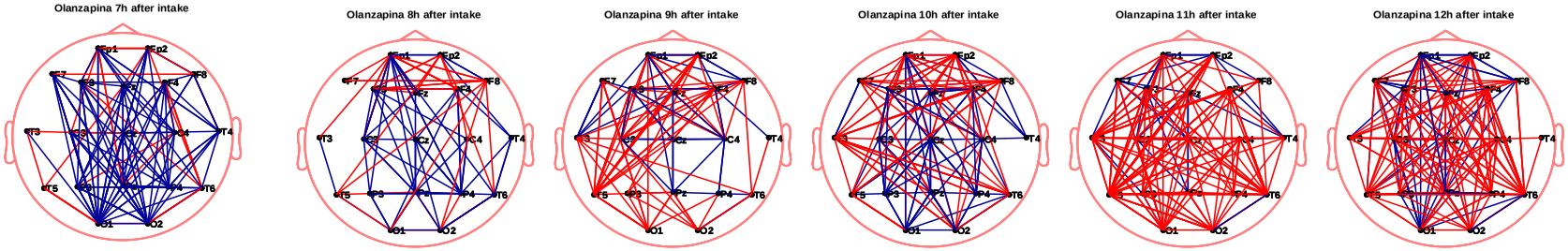
▶ 7h ▶ 8h ▶ 9h ▶ 10h ▶ 11h ▶ 12h

△ HALOPERIDOL - TE



▶ 7h ▶ 8h ▶ 9h ▶ 10h ▶ 11h ▶ 12h

△ RISPERIDONE - TE



▶ 7h ▶ 8h ▶ 9h ▶ 10h ▶ 11h ▶ 12h

△ OLANZAPINE - TE

5.2.2 Analysis of the means

To evaluate the overall average connectivity of the 19 electrodes, data were processed similarly to those obtained from SL, see Section 4.2.2.

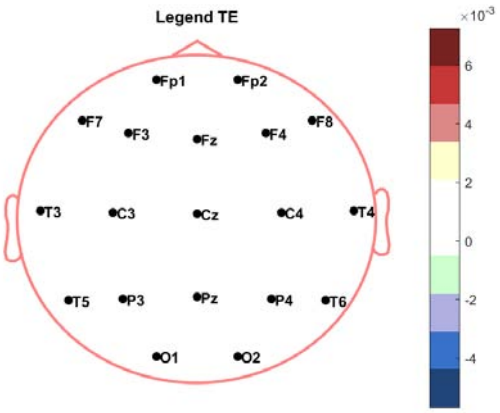
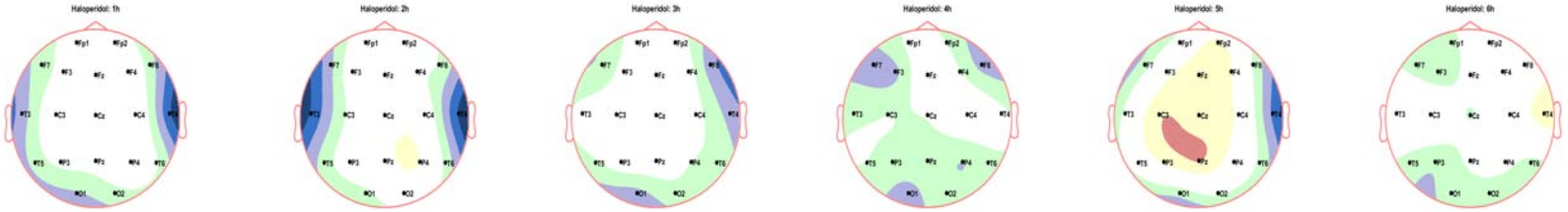


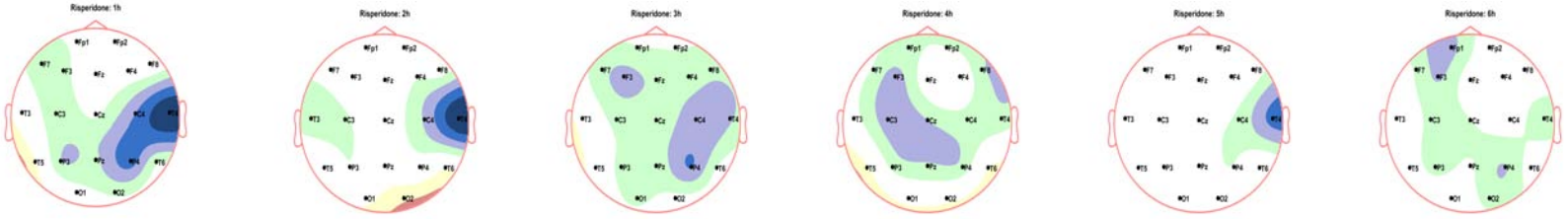
Figure 5.2.1 *Legend of the maps, the colorbar goes from the maximum possible value to the minimum.*

The results with this analysis confirm what was seen before: no big results for haloperidol, only a small negative significant change around $2h$ and $7h$, mainly in the frontal-lateral part of the brain; for risperidone, just small decrements around all the $12h$; and for olanzapine there is an evident decrease until $7h$ after intake.



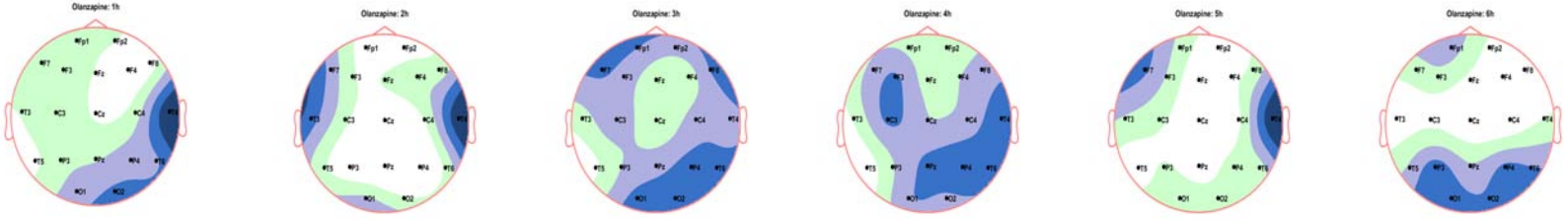
► 1h **► 2h** **► 3h** **► 4h** **► 5h** **► 6h**

△ HALOPERIDOL - TE



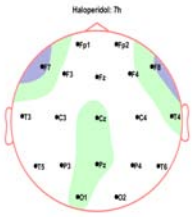
► 1h **► 2h** **► 3h** **► 4h** **► 5h** **► 6h**

△ RISPERIDONE - TE

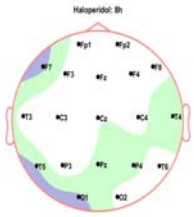


► 1h **► 2h** **► 3h** **► 4h** **► 5h** **► 6h**

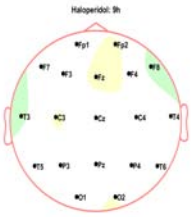
△ OLANZAPINE - TE



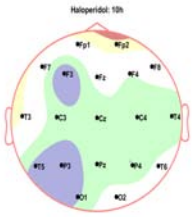
► 7h



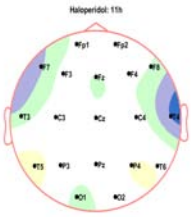
► 8h



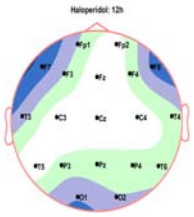
► 9h



► 10h

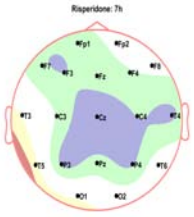


► 11h

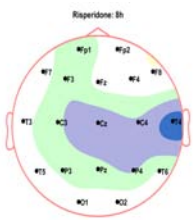


► 12h

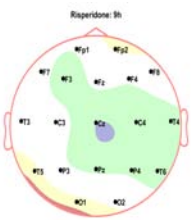
△ HALOPERIDOL - TE



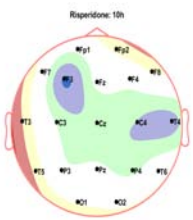
► 7h



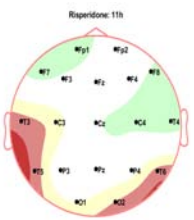
► 8h



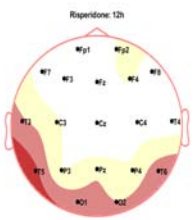
► 9h



► 10h

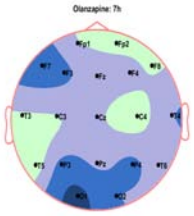


► 11h

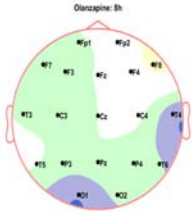


► 12h

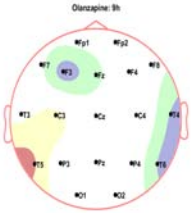
△ RISPERIDONE - TE



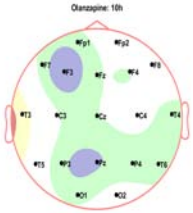
► 7h



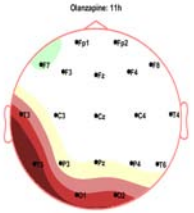
► 8h



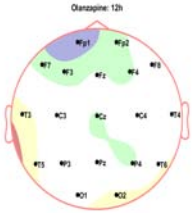
► 9h



► 10h



► 11h



► 12h

△ OLANZAPINE - TE

5.2.3 Topographic Analysis

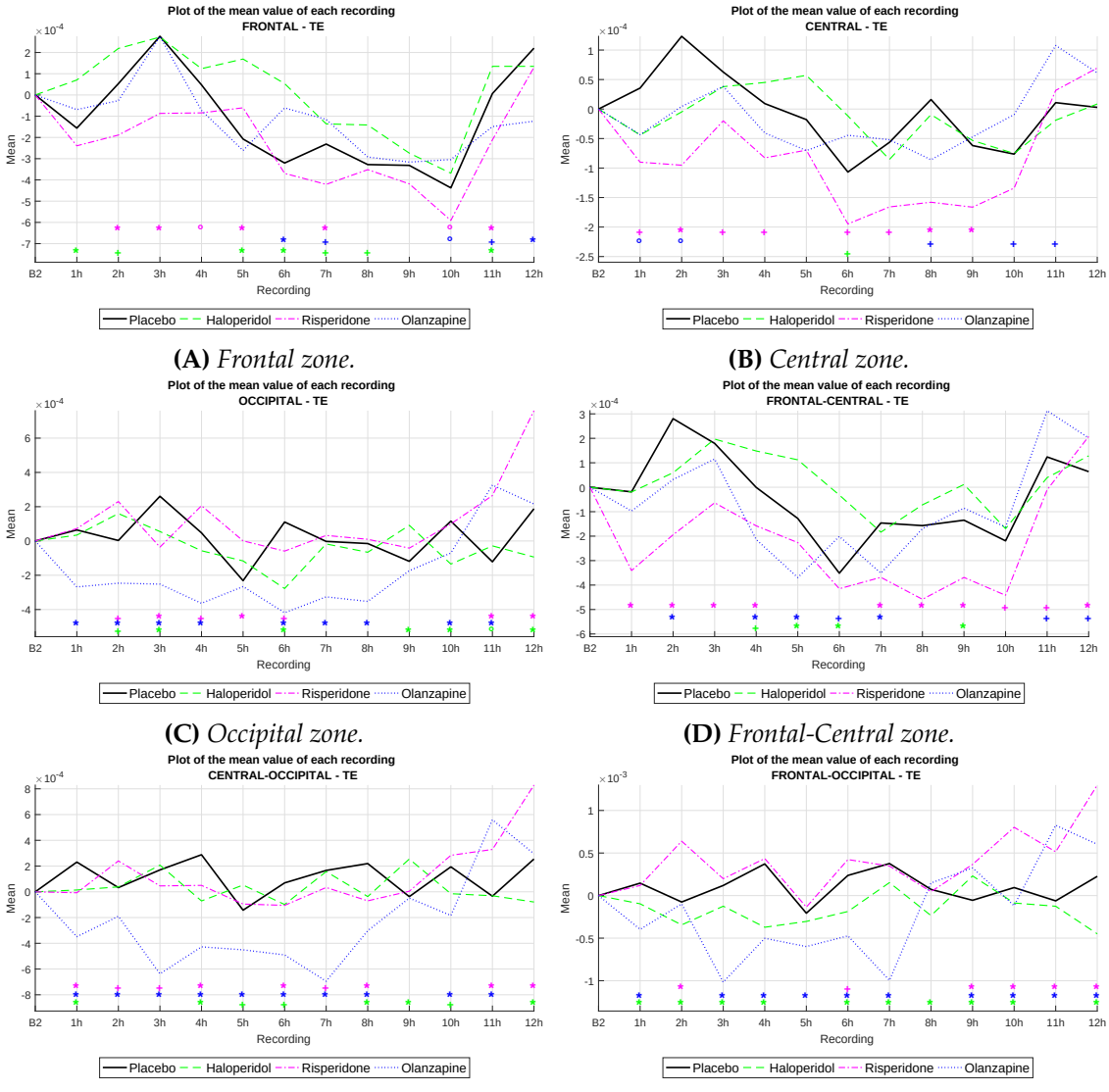
From the previous analysis of Section 5.2.2 with average connectivity per electrode it can be seen that some effects are more evident and strong in specific zones with respect to others. This is why in what follows we also consider the mean values of connectivity, divided by zones, which we report below:

- **Frontal**, that considers the electrodes Fp1, Fp2, F7, F3, Fz, F4 and F8.
- **Central**, that considers the electrodes T3, C3, Cz, C4 and T4.
- **Occipital**, that considers the electrodes T5, P3, Pz, P4, T6, O1 and O2.
- **Frontal-Central**, that considers the electrodes interconnection between these two zones.
- **Central-Occipital**, that considers the electrodes interconnection between these two zones.
- **Frontal-Occipital**, that considers the electrodes interconnection between these two zones.

These data have been processed analogously to those in the Section 4.2.3, and plotted with also the representation of significance, obtained from the WLCX.
In Figure 5.2.2, we see that there is not a single area more affected with respect to the others. Olanzapine changes are predominant in the occipital area, risperidone in the central area, and haloperidol does not have a clear one.
Globally, haloperidol is almost following the placebo behavior. In the frontal, central and occipital zone there are some significant differences (increases around $6h$ in the frontal zone and decreases around $3h$ in the occipital and frontal-central, $p \leq 0.01$). In the frontal-central there are mainly increases of connectivity around the hours $4 - 6$, but before and after mostly follows the placebo. The behavior of the central-occipital is strange, because it has peaks of increments and decrements alternatively, with $p \leq 0.01$ in the main hours.
For the risperidone, principally decrements can be seen, in the frontal, central and their combinations. There is a significant decrease of connectivity around the $2 - 5h$, with significance $p \leq 0.05$. As seen for the haloperidol, also for risperidone there is a fluctuating

behavior.

Finally, the olanzapine has mostly decrease, mainly in the occipital, central (with low significance), frontal-occipital and central-occipital. It has $p \leq 0.01$ in the central hours. Only in the frontal area it follows the behavior of the placebo, with a significant increase around $6h$.



(A) *Frontal zone.* **(B)** *Central zone.*

(C) *Occipital zone.* **(D)** *Frontal-Central zone.*

(E) *Central-Occipital zone.* **(F)** *Frontal-Occipital zone.*

Figure 5.2.2 *Plot of the mean considering separately the different zones.*

5.3 Conclusion

As conclusion of the Transfer Entropy analysis, the main results are found for olanzapine. In all the analysis it has the stronger outcomes, and all of them are decrements of connectivity with respect to the control; there is the presence of increments only after $7 - 8h$ intake.

6

Graph Theory Analysis

This chapter is based on the study of brain connectivity and interconnection evaluating directly the coefficients of the Graph Theory introduced in Section 2.3.

6.1 Graph Theory Analysis

The creation of the graphs given the matrix has been implemented using MATLAB, which has a toolbox to create oriented and non-oriented graph. In the implementation are omitted the 'self-loop', that means the interconnection between a node by itself.
This analysis is performed both for the matrices obtained with the SL and the TE approaches. We stress the fact that M_{SL} corresponds to a non-oriented graph, while M_{TE} corresponds to an oriented graph.
Calculations have been performed using the *Brain Connectivity Toolbox* on MATLAB based on the paper Rubinov and Sporns [2010], choosing the correct algorithm as a function of the matrix that is considered.
First the parameters C, C_W, L and L_W are computed for each graph, which means for each recording, volunteer and drug. The following step was to obtain the mean over the volunteer for each different recording and drug, to obtain the variance of the coefficients along time.
The best way to understand the changes along time is plotting them, subtracting the Basal2

values from each recording to cancel the circadian effects. Moreover also the Wilcoxon Signed Rank Test has been computed to understand if the variance of the coefficient of the drug is significant with respect to the control. As usual, the p-values used to indicate significance are (see the corresponding legend in Figure 6.1.1):

- $\mathbf{p \leq 0.01}$;
- $\mathbf{0.01 < p \leq 0.05}$;
- $\mathbf{0.05 < p \leq 0.1}$;

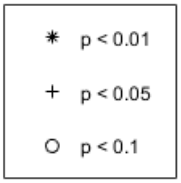


Figure 6.1.1 *Legend of the p-values.*

As said before, some interconnections in brain connectivity are really low when measured using SL or TE. Accordingly, it may happen that d^W takes large values, and as a consequence coefficient L_W lose significance, because it tends to infinity.

6.1.1 Synchronization Likelihood

Starting evaluating the results obtained from the synchronization likelihood matrices.

Cluster Coefficient

Table 6.1.1 shows the average coefficients (over all the subjects) that will be then represented in the plot of figure 6.1.2.

All coefficients are around the maximum value $C = 1$, there are only two significant values for olanzapine in $5h$ with significance of $p < 0.1$. There is also a peak in $7h$ for olanzapine and haloperidol, but it is not significant, neither the one at $12h$ for risperidone.

	Placebo	Haloperidol	Risperidone	Olanzapine
1h	1.000	1.000	0.999	0.999
2h	1.000	1.000	0.999	0.999
3h	1.000	0.999	1.000	0.999
4h	1.000	1.000	1.000	0.997
5h	0.999	0.998	1.000	0.995
6h	1.000	0.999	1.000	1.000
7h	1.000	0.950	1.000	0.949
8h	1.000	1.000	1.000	0.999
9h	1.000	0.999	1.000	0.999
10h	1.000	1.000	0.999	0.999
11h	0.999	0.999	0.999	1.000
12h	1.000	1.000	0.949	0.999

Table 6.1.1 *Table that reports the mean values of the **Cluster Coefficient** along the recordings.*

The average weighted cluster coefficient is reported in the Table 6.1.2 and plotted in Figure 6.1.3. It is clear for Figure 6.1.3, that the main changes are decreasing.

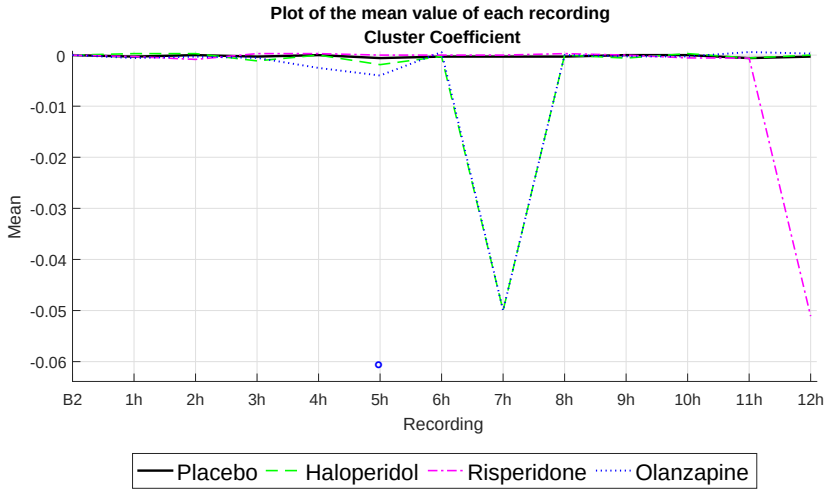


Figure 6.1.2 *Plot of the mean value of the **Cluster Coefficient** during the time.*

Significant differences are seen in the main hours, between $2-3h$, with results from WLCX of $p \leq 0.1$. All are decreases of the clustering coefficient, one in haloperidol and one in risperidone. That means a decreasing trend of segregation. On the other hand, decreases are also seen in olanzapine, but with no significance.

There is no presence of the non-significant peak at $7h$ showed in the previous figure, probably it was due to some rounding automatically done in computing the mean.

	Placebo	Haloperidol	Risperidone	Olanzapine
1h	0.209	0.214	0.211	0.179
2h	0.189	0.214	0.201	0.182
3h	0.212	0.179	0.177	0.171
4h	0.211	0.204	0.211	0.173
5h	0.213	0.204	0.213	0.180
6h	0.212	0.195	0.227	0.177
7h	0.201	0.194	0.218	0.169
8h	0.220	0.202	0.211	0.184
9h	0.207	0.202	0.203	0.194
10h	0.203	0.201	0.209	0.195
11h	0.208	0.218	0.202	0.215
12h	0.194	0.205	0.191	0.189

Table 6.1.2 *Table that reports the mean values of the **Weighted Cluster Coefficient** along the recordings.*

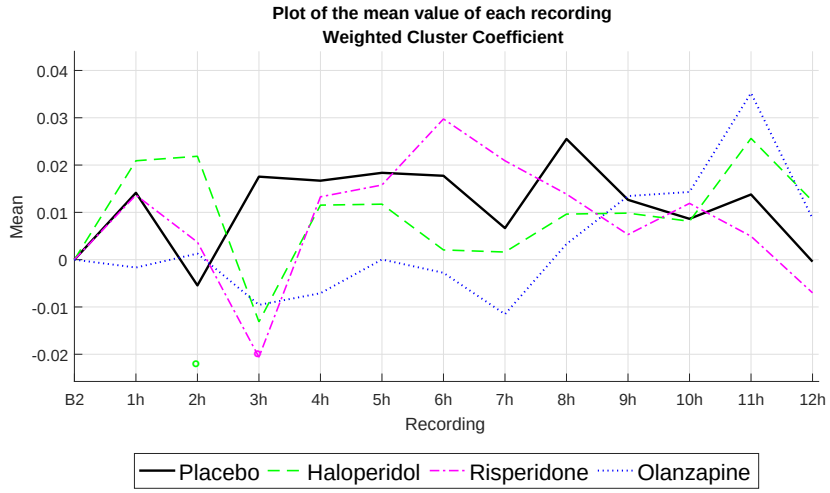


Figure 6.1.3 *Plot of the mean value of the **Weighted Cluster Coefficient** during the time.*

Characteristic Path Length

The results obtained for the other important parameter can also be seen in the Tables 6.1.3 and 6.1.4, and Figures 6.1.4 and 6.1.5.

The results of the plot in Figure 6.1.4 are in line with the ones found before; around $4-5h$ there is significant increments of L, that is in agreement with the decrements of C found at the same time.

As seen before, there are the significant peaks at $7h$ and $12h$, probably due to rounding effects.

	Placebo	Haloperidol	Risperidone	Olanzapine
1h	1.000	1.000	1.001	1.001
2h	1.000	1.000	1.001	1.001
3h	1.000	1.001	1.000	1.001
4h	1.000	1.000	1.000	1.004
5h	1.001	1.002	1.000	1.005
6h	1.000	1.001	1.000	1.000
7h	1.000	0.950	1.000	0.951
8h	1.000	1.000	1.000	1.001
9h	1.000	1.001	1.000	1.001
10h	1.000	1.000	1.001	1.001
11h	1.001	1.001	1.001	1.000
12h	1.000	1.000	0.951	1.001

Table 6.1.3 *Table that reports the mean values of the **Characteristic Path Length** along the recordings.*

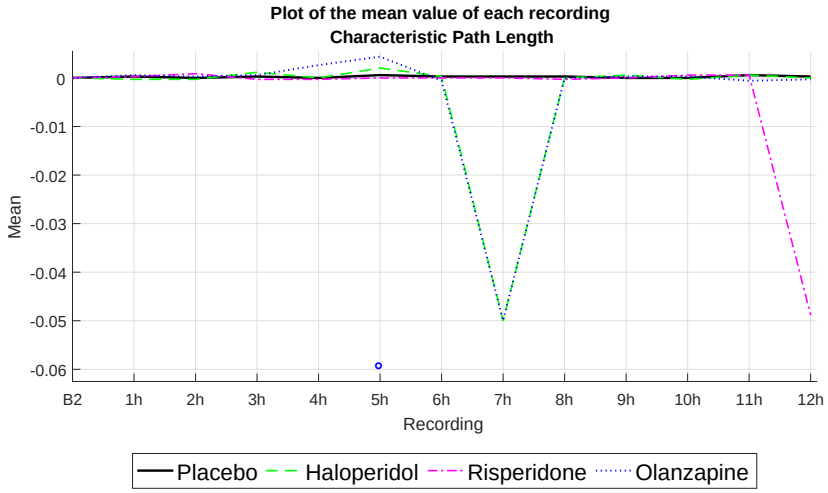


Figure 6.1.4 *Plot of the mean value of the **Characteristic Path Length** during the time.*

Regarding parameter L_W, almost all the values are ∞. To plot the result in Figure 6.1.5, a mean discarding the ∞ values has been performed. In this plot only the significance around the late hours $6 - 8$ has been found, mainly for haloperidol.

All the drugs shows decrements of L_W with respect to the control.

	Placebo	**Haloperidol**	**Risperidone**	**Olanzapine**
1h	Inf	0.086	Inf	Inf
2h	0.087	0.093	Inf	Inf
3h	Inf	Inf	0.072	Inf
4h	0.100	Inf	0.074	Inf
5h	Inf	Inf	Inf	Inf
6h	Inf	Inf	Inf	Inf
7h	Inf	Inf	Inf	Inf
8h	Inf	Inf	0.094	Inf
9h	0.098	Inf	Inf	Inf
10h	0.102	0.097	Inf	Inf
11h	Inf	Inf	Inf	Inf
12h	Inf	Inf	Inf	Inf

Table 6.1.4 *Table that reports the mean values of the **Weighted Characteristic Path Length** along the recordings.*

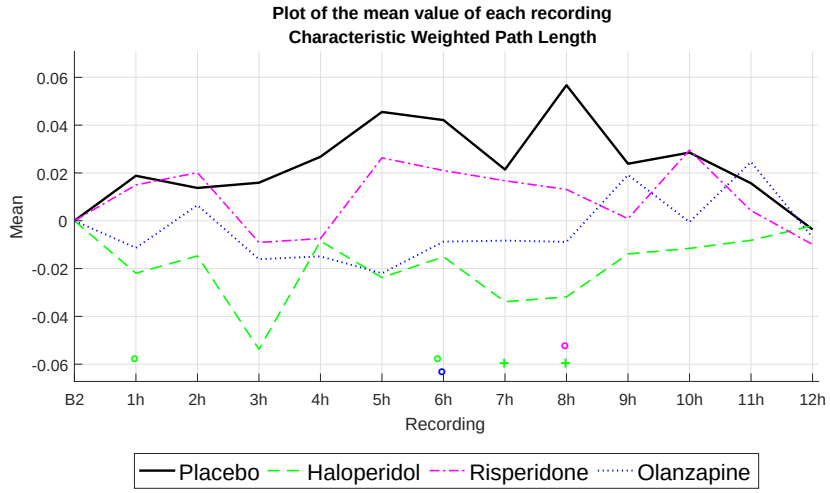


Figure 6.1.5 *Plot of the mean value of the **Weighted Characteristic Path Length** during the time.*

6.1.2 Transfer Entropy

The results obtained from the transfer entropy analysis, analogously to those of SL, are presented below.

Cluster Coefficient

Table 6.1.5 reports the mean cluster coefficients which are then represented in the plot of Figure 6.1.6.
In both Figure 6.1.6 and Table 6.1.5 there are no significant changes.

	Placebo	Haloperidol	Risperidone	Olanzapine
1h	1.000	1.000	1.000	1.000
2h	1.000	1.000	1.000	1.000
3h	1.000	1.000	1.000	1.000
4h	1.000	1.000	1.000	1.000
5h	1.000	1.000	1.000	1.000
6h	1.000	1.000	1.000	1.000
7h	1.000	0.950	1.000	0.950
8h	1.000	1.000	1.000	1.000
9h	1.000	1.000	1.000	1.000
10h	1.000	1.000	1.000	1.000
11h	1.000	1.000	1.000	1.000
12h	1.000	1.000	0.950	1.000

Table 6.1.5 *Table that reports the mean values of the **Clustering Coefficient** along the recordings.*

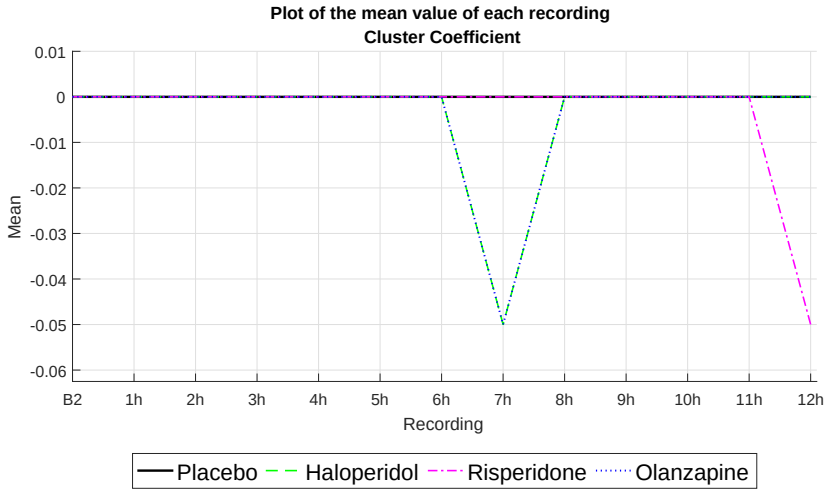


Figure 6.1.6 *Plot of the mean value of the **Clustering Coefficient** during the time.*

Significant results can be found only after $4h$ in risperidone, mostly with significance of $p \leq 0.05$, and all due to a decreasing with respect to placebo. Olanzapine mainly follows the control, there is significance only around $7h$. Haloperidol is going upstream with respect the other two antipsychotics, because is the only one in which it could be observed an increase of $C_W^{\rightarrow}$.

	Placebo	Haloperidol	Risperidone	Olanzapine
1h	0.356	0.354	0.357	0.354
2h	0.342	0.348	0.343	0.355
3h	0.328	0.376	0.381	0.316
4h	0.365	0.362	0.330	0.363
5h	0.358	0.360	0.348	0.353
6h	0.360	0.367	0.361	0.335
7h	0.367	0.333	0.353	0.322
8h	0.350	0.360	0.308	0.377
9h	0.361	0.354	0.334	0.372
10h	0.344	0.342	0.353	0.354
11h	0.357	0.399	0.342	0.349
12h	0.353	0.364	0.344	0.368

Table 6.1.6 *Table that reports the mean values of the **Weighted Clustering Coefficient** along the recordings.*

Characteristic Path Length

The values of the M_{TE} are usually in the order of 10^{-2} or 10^{-3}. As a consequence, the weighted characteristic path length takes very large values (i.e. in practice equal to infinity).

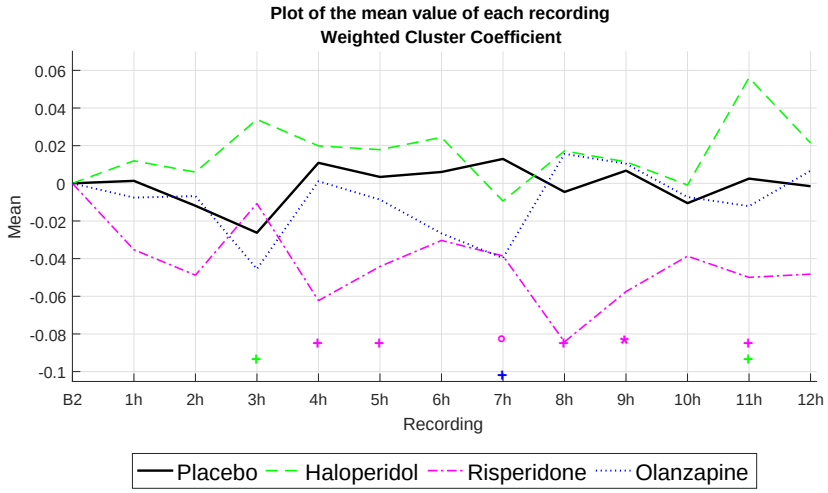


Figure 6.1.7 *Plot of the mean value of the **Weighted Clustering Coefficient** during the time.*

This can be seen from Table 6.1.8, where all the values are ∞; moreover the corresponding plot cannot be done, even discarding the ∞.

	Placebo	Haloperidol	Risperidone	Olanzapine
1h	1.000	1.000	1.000	1.000
2h	1.000	1.000	1.000	1.000
3h	1.000	1.000	1.000	1.000
4h	1.000	1.000	1.000	1.000
5h	1.000	1.000	1.000	1.000
6h	1.000	1.000	1.000	1.000
7h	1.000	0.950	1.000	0.950
8h	1.000	1.000	1.000	1.000
9h	1.000	1.000	1.000	1.000
10h	1.000	1.000	1.000	1.000
11h	1.000	1.000	1.000	1.000
12h	1.000	1.000	0.950	1.000

Table 6.1.7 *Table that reports the mean values of the **Characteristic Path Length** along the recordings.*

In Figure 6.1.8 the two peaks in $7h$ and $12h$ are always present, but they are not significant. So the characteristic path length, is constant, always standing at value $L^{\rightarrow} = 1$.

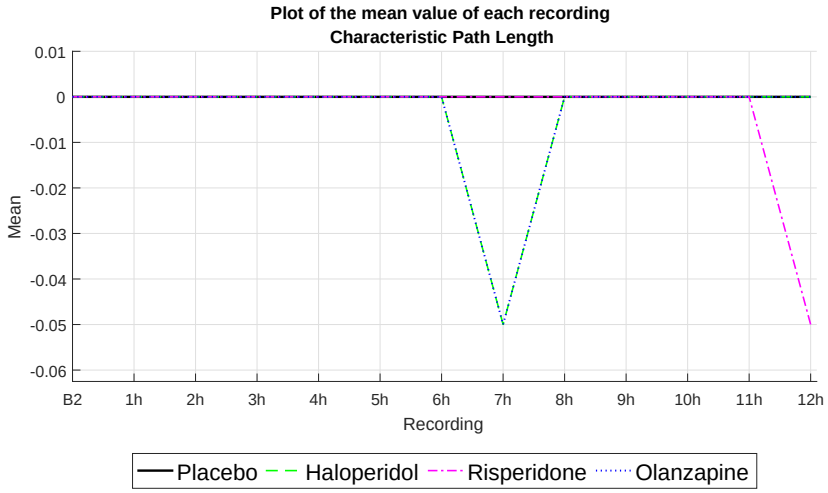


Figure 6.1.8 *Plot of the mean value of the **Characteristic Path Length** during the time.*

	Placebo	Haloperidol	Risperidone	Olanzapine
1h	Inf	Inf	Inf	Inf
2h	Inf	Inf	Inf	Inf
3h	Inf	Inf	Inf	Inf
4h	Inf	Inf	Inf	Inf
5h	Inf	Inf	Inf	Inf
6h	Inf	Inf	Inf	Inf
7h	Inf	Inf	Inf	Inf
8h	Inf	Inf	Inf	Inf
9h	Inf	Inf	Inf	Inf
10h	Inf	Inf	Inf	Inf
11h	Inf	Inf	Inf	Inf
12h	Inf	Inf	Inf	Inf

Table 6.1.8 *Table that reports the mean values of the **Weighted Characteristic Path Length** along the recordings.*

6.2 Conclusion

To conclude this analysis can be said that interesting results have been obtained evaluating the cluster coefficient, but not with the characteristic path length.

The strange peaks in $7h$ and $12h$ obtained in Figures 6.1.2, 6.1.4, 6.1.6 and 6.1.8 are probably due to the fact that there is exactly a data missed, see paragraph 2.1.1, creating this rounding effect.

The behavior of the drugs is in prevalence decreasing with respect to the control. Olanzapine is quite always decreasing, but never with significance or high significance, for both the

approaches, SL and TE, and all the parameters. Risperidone has few significance in all the study with the SL, and its behavior with respect to placebo is decreasing-increasing-decreasing in the parameter C_W, unlike is increasing-decreasing-increasing from the L_W point of view. On the other hand, regarding the TE analysis, this antipsychotic is the one with higher relevance in the $C_W^{\rightarrow}$ meaning that it causes less segregation in the brain connectivity. Finally the haloperidol is mostly decreasing in the SL analysis, with the higher significance with respect to the others drugs evaluating the L_W coefficient. A really upstream behavior is present in the $C_W^{\rightarrow}$, is the only antipsychotic that is always above the level of the placebo, but is significant only in $3h$.

7

Conclusions

This chapter presents a summary of the main results of this Thesis.

Starting by the drug that shows more powerful effects, as it is known from the literature, is the **olanzapine**. Spectral Power analysis has revealed that for the α and β bands there is a decrease, and in the δ and ϑ bands an increase of power. This is also confirmed by other studies, like Cerdán et al. [2005], as said in paragraph 3.5, or Yamada et al. [2004] in which it is also noticed that an increase of power in δ bands.

Regarding the Synchronization Likelihood, as remarked several times, it is more sensitive to artifacts, that is due to the fact that searching similar pattern between signals is more difficult, and less reliable if the data presents some alterations. The mainly results have been obtained between the $2-3h$ (increasing in $2h$), and then is coming out something also around the $8h$ (decreasing). In the Section 4.2.3, it is easy to see that the zone more affected is the occipital, and this result is also remarked in the work of Yoshimura et al. [2007], that assessed that the part of the brain most affected from changes due to olanzapine is the occipital, but with a different approach based on EEG micro-states.

Good results have been obtained with Transfer Entropy, because it uses the quantization over eight levels, so it is less sensitive to artifacts. The olanzapine mainly presents decreases, and only after $7-8h$ after intake some increments can be seen. The occipital effect is present, but not as evident as in the SL study.

Finally regarding the Graph Theory coefficients, no significant results are obtained, only the tendency of decreasing with respect to the control.

The second most powerful drug is the **risperidone**. In the SP analysis, this drug presents mainly decrements of power; it is confirmed reading the work of Yamada et al. [2004] where its effect as sedation is defined and that its effect is stronger with respect to the haloperidol's one.

Evaluating the SL approach, the results are mostly around $3h$ (decrements) and then some increments around $7h$. In the work of Yoshimura et al. [2007] and confirmed by the topographical analysis, it has been seen that the main effects are in the occipital area, but they are less evident with respect to the olanzapine ones. Using these data in the graph theory evaluation came out come significance (on the decreasing) of C_W and L_W parameters, which did not result for the olanzapine.

As for the olanzapine, also for risperidone the TE results are mainly decrements until the $7-8h$ after the intake, moreover from the topographic analysis it can be seen that the more affected area is, in this case, the central. Regarding the evaluation of the graph theory by TE pre-processed data, the risperidone is the one which gave more significant results in the $C_W^{\rightarrow}$, decreasing of segregation.

The third drug, **haloperidol**, shows some effects in SP only in δ band, and mainly in the central/central-occipital area. The fact that this antipsychotic has weak effect is also known in the literature [Yamada et al. 2004].

In both the SL and TE analysis the effects are not strong, and there is not a more affected area of the brain. Only in the average analysis in the Sections 4.2.2 and 5.2.2, it looks like that it affects partially the parietal parts.

From the graph theory point of view, there are some significance in the L_W coefficient, obtained with SL pre-processed data. Moreover, this is the unique drug for which and in the plot of $C_W^{\rightarrow}$ shows an increase with respect to placebo.

Finally, the effects of the three antipsychotics on the EEG were successfully studied through SP and connectivity analysis, demonstrating the need of assessing nonlinear interactions to better understand their action on the brain.

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