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Resting state networks characterization for individual subjects assessment

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Dedication

To Olga Lucia Guerra Melo and Jairo Aldemar Guaje Miranda, because without their support, I would not have had the chance to achieve these goals in my life or become the professional and person I have become. There are no words to describe how thankful I feel for all the sacrifices you have made for me and my brothers.

To Jairo Andres Guaje Guerra, Daniel Esteban Guaje Guerra and Diego Alejandro Guaje Guerra for being the best brothers I could ask for. Thanks for always believe in me and encourage me to be a someone who inspires and impact lives.

Abstract

Cumulative research in hemodynamic brain activity measured in resting state (RS) using functional magnetic resonance imaging (fMRI) suggests that healthy brain dynamics are distributed on large-scale spatial resting state networks (RSNs). These networks correspond to well-defined functional entities that have been associated to different low and high brain order functions. Characterization of several pathological and pharmacological conditions have been studied by measuring the changes introduced in the RSNs by these affections, resulting on powerful and descriptive biomarkers. Most of these studies have been performed using methods devised for group level analysis. Nevertheless, the use of these biomarkers in diagnostic/prognostic tasks may require single subject level assessment. In addition, some brain conditions are characterized by a high intra-subject variability, which violates the underlying assumptions of most of the group based methods. Recently, a multiple template matching (MTM) approach was proposed to automatically recognize RSNs in individuals subject's data. This method provides valuable information to assess subjects at individual level. In this work we propose a set of changes to the original MTM that improves the RSNs recognition task and also extends the functionality of the method. The key points of this improvement are: An standardization strategy and a modification of the method's constraints in order to add flexibility. Additionally, we also present a novel approach to quantify the degree of trustworthiness for each RSN obtained by using template matching. The main idea is to use a double validation process in the following way: First, RSNs are identified in a curated dataset which we'll call subjects of reference. Second, we propose to use these subjects of reference along with MTM to validate how much the template's assignations coincide. Finally, we integrate these solutions into an open source framework built on top of one of the most popular tools used by the community. Our results suggest that the method will provide complementary information for characterization of RSNs at individual level.

Keywords: Functional magnetic resonance imaging, resting state, spatial independent component analysis, resting state networks, template matching

Contents

1 Introduction

Some altered brain conditions constitute a real challenge for neuroscientists and also for clinical assessment. For instance, disorders of consciousness (DoC) which are commonly caused by traumatic/non-traumatic brain injuries and could lead to a coma state. In this condition, some patients may decline to cerebral death. Others, in contrast, may awake showing awake-sleep cycles but with absence of behavioral signs of consciousness. This condition is known as vegetative state or unresponsive wakefulness syndrome (VS/UWS) [45]. Some patients, in other hand, may progress to a minimally conscious state (MCS) showing non-reflexive and purposeful behaviors, but without the possibility of establishing functional communication [27].

Those patients are commonly diagnosed by using behavioral assessment tools, which aim to stimulate different sensory channels looking for conscious responses [28]. This approach has two important limitations: 1) it requires patient's collaboration, a difficult condition to achieve specially in fluctuating states of consciousness, 2) patients within these DoC conditions may exhibit subtle movements, which can be easily ignored during the assessment, limiting the diagnostic quality. These problems have resulted in high diagnostic error rates, between 37 - 43%, depending of the sensitivity of the instrument used for the evaluation [69]. This low diagnostic rate of patients is critical, because it may influence the quality of the rehabilitation treatment for the misclassified patients. Besides, it also affects the health system finances that will be charged with high economic cost associated to the care of patients incorrectly diagnosed. Wrong diagnosis may also result in high level of anxiety and stress for the patient itself and his/her family [48].

In order to reduce these levels of diagnostic uncertainty, in recent years the possibility of objectively evaluate these pathological conditions by using measures of brain structure and activity have been explored. Specifically, through the use of neuroimaging and electrophysiological measurements [46]. The construction of biomarkers of awareness has considerable potential as a supporting tool for the diagnosis of patients [46]. For instance, recent evidence suggests that it is possible to discriminate between brain states of preserved and altered conditions of consciousness (VS/UWS and MCS) [54, 72]. These strategies are based on measurements of the level of metabolic activity obtained by using Positron Emission Tomography (PET) [72]. Other approaches based on the quantification of the level of brain structural preservation or functional communication of different brain areas have also been explored [20, 30]. Recently, magnetic resonance imaging (MRI) has been explored as an alternative to build this kind of biomarkers [20]. This approach is minimally invasive

and may be used to characterize the neuronal substrates of brain activity.

1.1 Functional Magnetic Resonance Imaging (fMRI)

Brain dynamics have been studied using distinct methodologies. In particular, MRI is now one of the most popular technical approaches to carry out these studies. However, the universe of neuroimages that can be acquired using these techniques are large enough and involve different kinds of protocols: Structural MRI (sMRI), diffusion-weighted MRI (DW-MRI) [35, 60] and functional MRI (fMRI) [37, 49, 56], among others. Each protocol aims to capture or model a particular brain property or behavior.

For instance, fMRI captures and allows study isolated brain regions activity by measuring a relative oxygen metabolism of the cells in the brain [37]. This is mainly due to blood composition which has components that react to high magnetic fields produced by resonators, a reaction that depends of the oxygen atoms tied to hemoglobin molecules [58]. Oxygenated and deoxygenated hemoglobin molecules own different magnetic properties: oxygenated hemoglobin (oxyhemoglobin) has diamagnetic features and deoxygenated hemoglobin (carbonmonoxyhemoglobin) has paramagnetic features. The principle of fMRI is that punctual brain activity implies an increase in neuronal activity and to perform those tasks, neurons require nutrients, i.e., more oxygenated hemoglobin molecules are demanded as a consequence of neuronal activity [63]. The process of delivering those nutrients to neuronal tissue is formally known as the Hemodynamic Response (HR). In essence, fMRI does not measure neuronal brain activity, but the level of oxygen consumption associated to neuron's metabolism as a consequence of brain activity. This is, HR is recorded and registered in the so called Blood Oxygen Level Dependent (BOLD) signal [49].

In order to have dynamical information of the brain activity when fMRI studies are conducted more than one volume per subject is acquired, in other words, the relative level of oxygen of each brain region is captured in a well defined interval of time providing a temporal signal of each voxel. The inclusion of this temporal dimension allows clinicians and researchers to study behavior related conditions, i.e., find out elements that can affect brain behaviour without apparent alterations in the structure. Some conditions that can be studied following this approach are pathological instances like some cases of disorders of consciousness (DoC) [2, 23], schizophrenia [21], amnesia [53], among others.

1.2 Resting State (RS)

Functional protocols have been extensively used to study how specific tasks modulate brain activity. The underlying hypothesis behind this approach is that punctual brain areas are specialized in attending concrete cognitive processes [7, 8, 9]. In order to support this

hypothesis, classical neuroimaging studies aim to identify the brain's responses to specific stimulus. Nevertheless, new evidence suggests brain also exhibits a continuous level of spontaneous activity, i.e., activity which is present under no stimuli [7, 9]. This discovery became a new research field with high potential to study different brain conditions, as some pathological and pharmacological states [7]. The study of this spontaneous activity is now known as resting state (RS). In it, subjects lies under no stimuli condition for about 5 to 10 minutes, meanwhile, brain activity is recorded by using a technique capable of capture brain dynamic, for instance, fMRI or Electroencephalography (EEG) [7]. The main hypothesis behind RS is that brain behaves as an autonomous complex system, which study may provide insights about underlying brain organization [9, 8]. Then, the main challenge of RS analysis is to understand the sources of this spontaneous activity, considering the absence of any experimental stimulation.

Under the assumption that RS protocol provides valuable neuronal information, it would be expected to also be useful to study altered brain conditions. The hypothesis behind this statement is that some states may impact severely the underlying cerebral autonomous system measured through RS, changing its behavior [38]. For instance, it is possible to find severe pathologies in which resting state's brain dynamics are expected to be disturbed, such as, schizophrenia or depressive disorders [31]. Other brain altered conditions could also take advantage of the fact that RS does not require that patient be able to perform specific tasks, for example, in the assessment of the level of consciousness [2, 23]. Similarly, the dynamics exhibit during pharmacological states can also be studied following this approach, for instance, sedation under different kinds of anesthetics [2, 23, 68]. In all these examples the study of altered RS conditions have proved to be informative to construct biomarkers of many brain altered conditions [47] and it is still an active field.

1.2.1 Signal treatment and analysis

fMRI is a powerful tool to study brain dynamics in a high detailed spatial resolution. Nevertheless, keeping the balance between good spatial and temporal resolutions requires a very sensitive process which is prone to be affected by several noise sources. For that reason, data must be preprocessed to minimize the impact introduced by the artifacts in the acquisition. In this subsection, we describe some of the most commonly used corrections that are recommended to apply to fMRI data. Performing these preprocessing steps is mandatory to build robust analyses and get trustworthy and conclusive results. We also describe some common strategies to handle fMRI data. These steps and strategies are the following:

1. **Preprocessing**

   During acquisition phase some alterations can occur, producing noisy and low quality signals, which consequently could lead to inaccurate results and conclusions. Specifically, these alterations can be grouped in two categories: *subject related artifacts*,

such as movements or physiological noise introduced by non-neuronal activity and *resonator related alterations*, such as, synchronization between volumes acquisition or noise in the images itself [77]. In order to account for this noise source, it is necessary to ensure the quality of the captured signal by performing the following preprocessing steps: slice timing correction, realignment, co-registration, spatial normalization, transformation to the Montreal Neurological Institute (MNI) standard space, despiking and motion regression [77].

2. **Parcellation**

   Preprocessing stage mainly aims to fix the problems related to the acquisition, however it does not simplify the big amount of information contained in fMRI data. For that reason a common practice consists in to split data into smaller regions of interest (RoIs) which allows researchers focusing on study only key regions, which they consider relevant for their investigations. The process of splitting fMRI data in these anatomical/functional regions is formally known as parcellation. The three most popular modalities to perform this task are the following:

   - **Seed-Voxel Analysis:** In this approach scientists and clinicians define the RoIs by hand using their expert's criteria.
   - **Anatomical-Reference Segmentation:** In this case full brain is segmented using prior knowledge available in the literature related to well-defined anatomical atlas.
   - **Data-Driven Parcellation:** This approach consists of group fMRI signals in different voxels according to their similarity, resulting in RoIs for posterior analyses. The most popular approach in the area to perform this task is the so-called spatial Independent Component Analysis (sICA), which decomposes fMRI signal into statistically independent components, corresponding to spatial common structures and its associated behavior represented by a time course.

3. **Discarding sources of artifactual origin**

   A large amount of evidence [18, 19, 42] suggests that even though preprocessing is performed correctly, fMRI signal is highly contaminated by signals of non-neuronal origin. Mainly emerging from peripheral brain areas, cerebrospinal fluid (CSF) and in white matter [42]. Recent studies have characterized these signals, by using features like: high-frequency fluctuations (>0.1 Hz), prominent spikes in the time course, as well as, a saw-tooth pattern in the time course (sharply and regularly alternating up-and-down) and also presence of thresholded voxels in the superior sagittal sinus [42], among others.

These steps (preprocessing, parcellation and discarding of sources of artifactual origin) represent a fraction of a set of good practices to handle fMRI data and provide confidence to study some particular conditions, such as Resting State.

1.2.2 Resting State Networks (RSNs)

Literature suggests that fluctuations in the BOLD signal during RS reflect the fundamentals of neuronal activity of the brain, representing the natural state of the human mind in the absence of task-related neuronal action and external stimuli. Additionally, literature also suggests that these slow fluctuations correspond to well defined patterns of cognitive and behavioral relevance. These coherent fluctuations are grouped into separate anatomically and functionally networks, i.e., independent brain regions not necessarily adjacent which temporal dynamic is highly synchronized. At least ten of these entities have been consistently identified in control subjects and they involve sensory cortices, such as, visual and auditory processing, as well as, areas involved in higher cognitive functioning, such as, memory or executive processing, among others. These ten well defined entities are now called resting state networks (RSNs) [16] and include: default mode network (DMN, comprising attention and/or even consciousness), left and right executive control networks (ECN L and ECN R, respectively), auditory, salience, sensorimotor, three visual networks (lateral, medial and occipital) and cerebellum [16, 38, 44, 71], as observed in figure 1.1.

RSNs discovery reflects the underlying human brain system organization and confirms the idea that the baseline state of the brain is not an inactive process, but all the opposite, it seems to be very dynamic even at the level of stimuli-driven actions [7, 38]. Besides, the found spatial structures are consistent with previous studies which reported the existence of similar activation patterns in task-related fMRI experiments. Notwithstanding the apparent division, newer studies in RSNs analysis suggest that cerebral operation is not performed by isolated functional regions but results from a coordination phenomena among them.

1.2.3 Applications

From here, three different scenarios are of special interest: elucidate brain functioning in RS, clinical investigation and practice. The first one is usually performed by studying cohorts of healthy subjects, and from there construct biomarkers to characterize the "normal behavior" by solving the question of: **how can we make biomarkers of the normal state of the brain?**. In clinical investigations, an additional question should be overcomed: **how these biomarkers vary in altered brain conditions?**, and in clinical practice the main question is related to: **how these biomarkers may help to establish a diagnosis/prognosis for a specific individual?**.

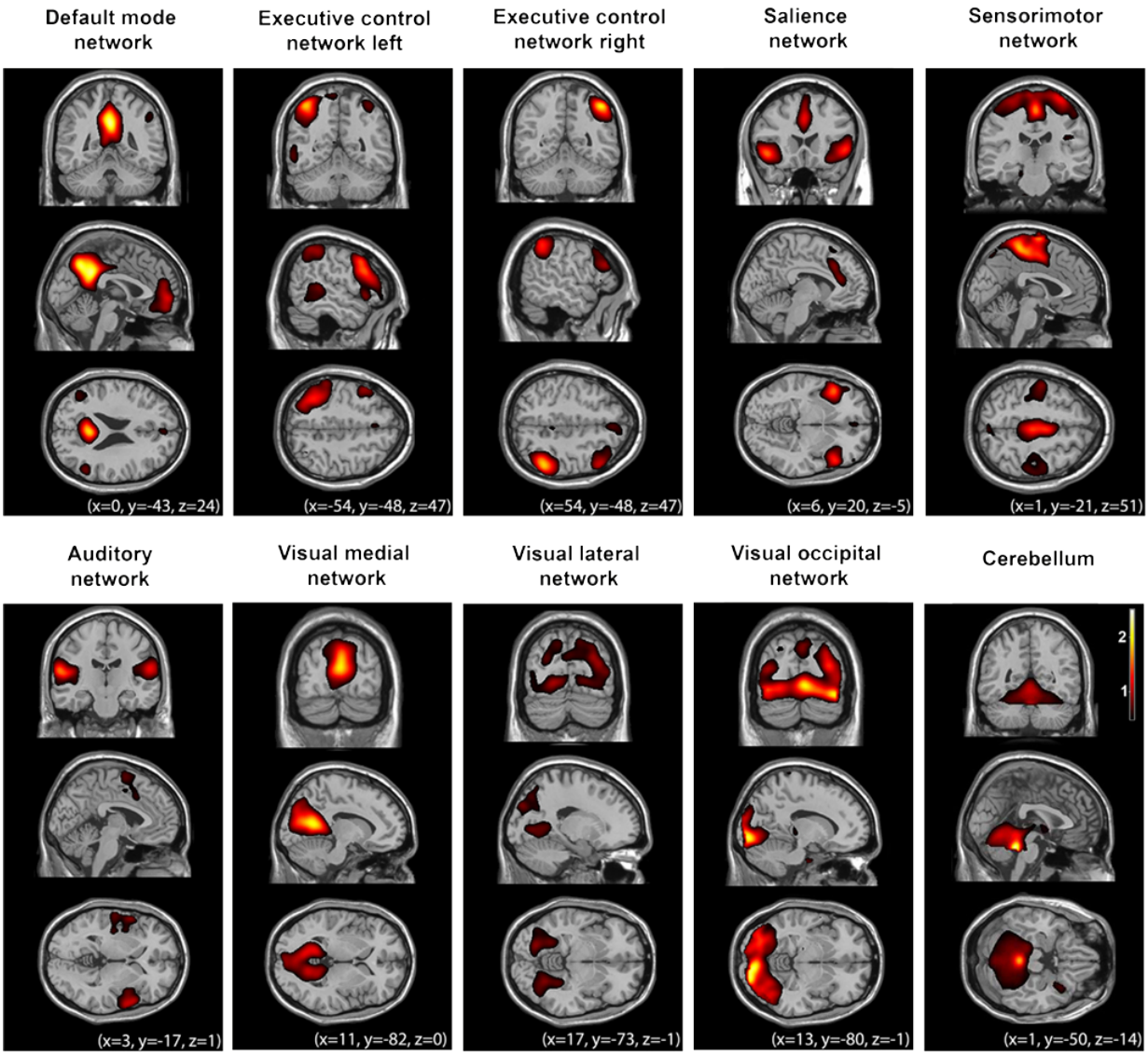


Figure 1.1. Resting State Networks in healthy subjects. Adapted from [38].

Several brain cognitive and behavioral processes have been investigated by using the RS approach. This work has resulted on powerful characterizations of these states. A relevant example was the discovery of the RSNs. A discovery that has been linked to the large subjacent system supporting sensory, cognitive and executive processing, among others. This finding has also offered a new approach to study altered brain conditions, specifically those in which subjects are unable to perform specific tasks.

RSNs have a high potential for clinical environments, several studies have been performed to characterize pathologies and highlight its differences at the group level, i.e., distinct populations are compared looking for differences in brain activity [20]. Some of

these approaches have proved to reveal meaningful patterns sensitive enough to be used for the task of discriminate between populations [19, 20, 54]. Pharmacological effects have also been studied using RSNs analysis and have provided a better understanding of how anesthetics impact in this underlying brain system. For these reasons RSNs analysis constitutes a highly active research area in neuroimaging [38, 47].

Summarizing, RS analysis has the potential to elucidate the neurophysiological process underlying pathological and pharmacological states. But it can also be used in more individualized tasks, particularly in diagnostic and prognostic tasks. This is mainly due to the hypothesis that RS could capture subtle inter and intra-subject variations which can improve diagnostics, prognostic and treatments by making them more accurate or even personalized.

1.3 Problem identification

Most of these RS and RSNs studies have been performed using methods devised for group level analysis [19, 20, 34]. Nevertheless, the use of these biomarkers in diagnostic/prognostic tasks may require single subject level analysis. In addition, some altered brain conditions are characterized by a high intra-subject variability, which violates the underlying assumptions of most of the group based methods, specially in devastating brain pathological states [19, 20, 34]. Therefore, characterization at individual level is important for clinical practice where the differentiation should be performed for each patient and not for a complete group. Up to now, some of the studies made in addressing single-patient categorization have been in the discrimination between MCS and VS/UWS focusing in non accessible or noisy approaches, such as, transcranial magnetic stimulation (TMS) in combination with EEG [14, 66] and combining different EEG measures [70]. By using fMRI, single patient classification has been performed by considering as discriminating feature the neuronal properties of various intrinsic connectivity networks [20].

However, in order to extend these approaches to clinical applications several additional conditions should be accomplished, for instance, we consider the following as the most relevant: *support characterization at individual level*, *high level of robustness to different clinical scenarios*, *trustworthiness scale to support the decision making process* and *high degree of reproducibility of the studies*. Support characterization at individual level refers to design methods that not only exhibit a potential to group level characterizations, but also be flexible enough to capture inter-subject, inter-sessions and intra-subject variabilities. This one particularly constitutes a major challenge because it has been shown that data obtained from patients often exhibits higher inter-trial as well as inter-individual variability than data obtained from controls [29, 43, 50]. High level of robustness to different clinical scenarios refers to the resilience of the methods for characterizing consisting patterns of the condition independently of the reasonable variations of the clinical settings [6]. Trustwor-

thiness scale to support the decision making process means that the methods results should be quantifiable under a standard and objective scale. In other words, a degree of confidence to the obtained results should be granted. Finally, high degree of reproducibility of the studies refers to the transparency in the performed studies, i.e., the credibility of scientific findings which is rooted to the evidence supporting them. This last point is critical since recent literature suggests that reproducibility is lower than is desirable [67, 51]. A recent study estimates that 85% of biomedical research efforts are wasted [51].

A common method used for characterization at individual level is to identify the RSNs by using spatial Independent Component Analysis (sICA) [41]. From this parcellation most studies search the RSNs manually by looking for the independent components (ICs) that better resembles specific well known spatial patterns associated to each RSN [5]. This process is time-consuming and requires high level of expertise, a factor that may greatly influence reproducibility [73]. Previous studies have approached the RSNs identification process by using template matching (TM) techniques [31]. A method to perform multiple templates matching (MTM) was proposed by Demertzi et. al. [20]. In this method a similarity measure is computed between representations of each RSN and each one of the subject's ICs. Then, an optimization problem pairs each template to the IC with highest visual similarity. This approach offers an automated and potentially reproducible method for the RSNs identification task [20, 55, 75]. This MTM method has a high potential to be used in clinical practice, because of its capacity to characterize individuals at the single level, in contrasts, to group based ICA analysis procedures [13]. Nevertheless, in order to offer a better clinical approximation, the previously described methods (high level of robustness to different clinical scenarios, trustworthiness scale to support the decision making process and high degree of reproducibility of the studies) should also be addressed.

1.4 Thesis aim

In this project, we propose to extend the RSNs analysis studies to account for individual subject assessment in clinical applications. Particularly, we propose a novel approach to support robust, trustworthy and reproducible RSNs characterization. To achieve that goal we studied the minimum requirements that the MTM method proposed by Demertzi et. al. [20] should accomplish to be used in future clinical environments. Specifically, we studied the problem of robustness by exploring the consistency of the RSNs identification for fMRI-RS data acquired in different centers. Additionally, we also faced the problem of design of trustworthiness scales by proposing a novel strategy to objectively measure the degree of reliability of the selected RSNs. Finally, we built and released a framework for automatic identification of RSNs considering and addressing the concept of reproducible and transparent science.

1.4.1 Objectives

In order to achieve the described aims the following objectives are proposed:

- **General Objective**
  Design and implement a computational framework to perform individual subject assessment from fMRI-RS data suitable to be used in clinical environments. The proposed framework should aim for reproducibility, tolerance and reliability issues.

- **Specific Objectives**
  - Reproduce and extend some methods found in the state of the art used for individual subject assessment of fMRI-RS data in clinical environments.
  - Design an objective measure to compute the degree of confidence of the previously described methods.
  - Implement the developed methods into an user-friendly and open source framework.

1.5 Justification

This work focuses in a research area with high impact in clinical and scientific environments. In the clinical field, the solutions herein proposed can be useful in diagnosis and prognosis tasks, through the improvement in the characterization of several pathological states. But, disease-oriented studies are not the only one clinical application, pharmacological conditions can also be studied. A direct consequence of clinical applications are the social repercussions, specifically their impact in public health systems. Which could take advantage of the developed methods to reduce misdiagnosis rates in patients. Patient's families may also be benefited, as diagnostic improvements can lead to more appropriate treatments and therefore, a better quality of life for the patient and his/her family.

From the scientific perspective, this work is in line with recent worldwide proposals involving scientific community of developed economies. In particular, the European Community's project "Human Brain Project", which started in 2013, the US government's initiative for brain study launched in 2013 and the Japanese Brain/Minds project, introduced in 2014. Initiatives that pursue a better understanding of how the brain works in several cognitives process and whose contributions could lead to the development of new diagnosis and prognosis tools. In countries like Colombia, there is a growing neuroscience community, proposals like this may help to strengthen the local scientific community.

1.6 Products and contributions

The following list, shows the disclosures derived of the development of this work:

- Guaje J., Rudas J., Demertzi A., Heine L., Phillips C., Tshibanda L., Noirhomme Q., Ramani R., Franco H., Laureys S., Soddu A. and Gómez F. (2014, April). *RestLib: A toolbox for single subject resting state analysis*. In Proc. 7th International Seminar in Biomedical Engineering. ISSN: 2322-7702. PP. 67-68.

- Rudas J., Guaje J., Demertzi A., Heine L., Tshibanda L., Soddu A., Laureys S. and Gómez F. (2014, August). *A method for functional network connectivity using distance correlation*. In Proc. Annual International Conference of the IEEE Engineering in Medicine and Biology Society. DOI: 10.1109/EMBC.2014.6944203. PP. 2793-2796.

- Guaje J., Rudas J., Demertzi A., Heine L., Tshibanda L., Soddu A., Laureys S. and Gómez F. (2014, September). *Trustworthiness for multiple template matching in resting state*. In 9th Computing Colombian Conference.

- Rudas J., Guaje J., Demertzi A., Heine L., Tshibanda L., Soddu A., Laureys S. and Gómez F. (2015, January). *Dynamic functional network connectivity using distance correlation*. In Proc. 10th International Symposium on Medical Information Processing and Analysis. DOI:10.1117/12.2073498. PP. 92870P-92870P.

- Guaje J., Molina J., Rudas J., Demertzi A., Heine L., Tshibanda L., Soddu A., Laureys S. and Gómez F. (2015, December). *Automatic identification of resting state networks: An extended version of multiple template-matching*. In Proc. 11th International Symposium on Medical Information Processing and Analysis. DOI:10.1117/12.2211530. PP. 96810V-96810V.

- Rudas, J., Martínez, D., Guaje, J., Demertzi, A., Heine, L., Tshibanda, L., Soddu A., Laureys S. and Gómez, F. (2015, December). *Reduction of resting state network segregation is linked to disorders of consciousness*. In Proc. 11th International Symposium on Medical Information Processing and Analysis. DOI:10.1117/12.2207971. PP. 96810U-96810U.

1.7 Document structure

This document is divided in 6 chapters as following: Chapter 2 presents our contribution to the multiple templates matching (MTM) method proposed by Demertzi et. al. [20]. Chapter 3 shows an approach that can be used to objectively quantify the degree of confidence of the MTM method. Chapter 4 discusses the open source framework RestLib and its potential uses for individual subject assessment in clinical applications. Finally, chapter 5 exposes a discussion around the contributions made in this work, its practical applications and pending or future work. Additionally, this chapter also includes an information sharing statement around the toolbox product of this dissertation thesis and the acknowledgments.

2 Automatic identification of resting state networks: An extended version of multiple templates matching

This chapter is based in the work titled "Automatic identification of resting state networks: An extended version of multiple template-matching". Presented in the 11th International Symposium on Medical Information Processing and Analysis.

2.1 Introduction

fMRI-RS constitutes a robust protocol to investigate several pathological conditions, such as Alzheimer's disease, Schizophrenia, disorders of consciousness (DoC), as well as, different pharmacological states, for instance, sedation under distinct kinds of anesthetics [2, 23]. Recent works suggest that the brain in RS is organized in well defined spatio-temporal functional entities. At least ten of them have been consistently identified in healthy subjects: the default mode network (DMN), the executive control left and right networks (ECL and ECR), the salience (Sal.), the sensorimotor (Sen.), the auditory (Aud.), the three visual networks (Medial, Lateral and Occipital) and the cerebellum (Cer.) [16, 38, 44, 71]. A common approach to study altered brain conditions in fMRI-RS is through the analysis of changes in the connectivity of these RSNs [25].

A common approach to characterize these RSNs is by using ICA [41]. A method in which fMRI-RS signal is decomposed into statistically independent components, corresponding to spatial common structures and its associated behavior represented by a time course. In most studies, RSNs are manually identified by looking for the independent component that better resembles specific well known spatial patterns associated to each RSN [5]. This process is time-consuming and requires high levels of expertise, a factor that may greatly influence reproducibility [73]. Previous studies have approached the RSNs identification process by using template matching techniques [31, 32]. Multiple templates matching (MTM) is one of those studies and consists on calculate a similarity measure between representations of each RSN and each one of the subject's ICs. Then, an optimization problem matches each RSN to the IC with highest visual similarity. This approach constitutes an automated and reproducible method for the RSNs identification task [20, 55, 75].

RSNs identification has been also complemented with IC artifact detection methods. In these approaches, an spatio-temporal characterization method is computed for each IC, and a machine learning algorithm is used to discriminate components of artifactual and non-artifactual origin [18, 20, 74]. The combination of template matching and artifact detection techniques has been used in the characterization of different pathological conditions (e.g. disorders of consciousness [20]) or pharmacological altered brain states (e.g. anesthesia induced by propofol [64]).

MTM and artifact detection have an important potential to be used in clinical environments, because their capacity to characterize individuals at the single level, in contrasts, to group based ICA analysis approaches [13]. Nevertheless, besides individual characterization, clinical applications require high level of robustness across different centers and a proper understanding of the method's parameters. In this work, we studied some of the minimum requirements that MTM methods [20] should accomplish in order to be used in future clinical environments. In particular, we study the consistency of the RSNs identification for fMRI-RS data acquired in different centers. For that, we propose a spatial and intensity normalization that enhances the method's robustness. Later, we explore the effect of different visual similarity measures between ICs and RSN templates, a critical parameter in the MTM algorithm, which may considerably affect its performance. Finally, we evaluate the sensibility of our method to changes in the similarity measure. Our results show that these extensions result in an approach that may have a good potential to be used in the identification of RSNs at individual level in clinical environments.

2.2 Materials and methods

2.2.1 Participants and data acquisitions

Data from 27 healthy controls (14 women, mean age 47 $\pm$ 16 years) were used for this study. Previous written consent to participate in the study was obtained from all subjects. Each subject were instructed to close their eyes, relax without falling asleep and avoid any structured thinking (e.g., counting, singing, etc.). Then, fMRI-RS data were acquired in a 3T scanner in Erlangen, Germany. Three hundred fMRI volumes multislice $T2^*$-weighted functional images were captured (32 slices; repetition time = $2000ms$). The three initial volumes were discarded to avoid T1 saturation effects. Additionally a high resolution structural T1-weighted image was also acquired for anatomical reference.

Additionally, data from 1000 Functional Connectomes Project was also used. FConn 1000 project (http://fcon_1000.projects.nitrc.org) captures and manages collections of fMRI-RS data acquired in more than 30 independent studies from around the world. These heterogeneous samples of data offer the opportunity to study the robustness and reliability of the RS oriented analysis. In order to measure the overall performance of our

proposed approach we have tested our methods in Baltimore's dataset. Data is composed by 23 subjects (15 women, mean age 29 $\pm$ 5 years). fMRI-RS data were acquired under opened eyes condition in a 3T scanner in Baltimore, MD, USA. One hundred and twenty three fMRI volumes multislice $T2^*$-weighted functional images were captured (47 slices; repetition time = 2500ms). The first five timepoints of each timeseries were discarded. For anatomical reference two high resolution structural images were also acquired.

2.2.2 Templates selection

RSNs templates were selected by an expert via visual inspection from a set of spatially ICs. These components were taken from 12 independently assessed controls (4 women, mean age 21 $\pm$ 3 years) scanned on a 3T scanner (32 slices; repetition time = 2460ms). The templates were then checked by another expert for accuracy of structural labeling.

2.2.3 Preprocessing

Data was mostly preprocessed using Statistical Parametric Mapping version 8 (SPM8; http:www.fil.ion.ucl.ac.uk/spm). Preprocessing steps performed were: spatial realignment, co-registration of functional onto structural data, segmentation of structural data, normalization into MNI space and spatial smoothing with a Gaussian kernel of 8 mm. Large head motions [61], noise spikes and spontaneous deep breaths were further corrected using ArtRepair (http://cibsr.stanford.edu/tools/ArtRepair/ArtRepair.htm).

2.2.4 Spatial Independent Component Analysis

MTM algorithm requires comparable entities to be performed. Given that each RSN template is a set of well defined brain regions, subject's fMRI volumes must be summarized in similar spatial maps. Although, there are many ways to accomplish that [65, 76], we have opted for a data oriented approach extensively used in the literature called Independent Component Analysis (ICA). This technique decompose fMRI signal into a set of independent components of brain activity. Due to fMRI's spatial dimension is higher than the temporal one, we used spatial ICA (sICA), a variant which decompose the signal into maximally independent spatial maps [52]. For this task, we have selected the Infomax algorithm as implemented in GroupICA for fMRI toolbox (GIFT; http://icatb.sourceforge.net/). Between the parameters required by this algorithm we set the number of ICs as 30. Then, the component images (spatial maps) were calibrated to the raw data so the intensity values were in units of Percent Signal Change (PSC) from the mean [12].

2.2.5 Extended Multiple Template Matching method

Components Normalization

Inter and intra-subject variability can be hard conditions to face, especially when protocols are changed. Clinical applications of RS (i.e. pathological and pharmacological studies), by its particular conditions, can be more prone to certain configurations. In order to offer a method that cover as much as possible this susceptibilities, our first contribution to the original MTM method is a normalization strategy.

Scanner related configurations, such as the number of slices are reflected in ICs. Therefore, the size of the spatial maps to be compared must be the same. PSC also induces inter and intra-variabilities that can alter Goodness of Fit (GOF) computation and consequently template matching results. To diminish the effects of PCS related variability and in order to make the ICs comparable versus the RSNs templates, we have normalized the intensities of each image between 0 and 1 using the following equation:

$$C_N = \frac{C + abs(min(C))}{max(C) + abs(min(C))} \tag{2.1}$$

where C is the 3D volume corresponding to each one of the subject's ICs.

Identification of RSNs at individual level

Over the original MTM [20], some changes have been proposed. First, the original method has been extended to allow compare not only ICs and templates, but compare two sets of spatial maps. Therefore, to overcome potentially concurrent assignations between images, the two original restrictions must be changed to:

(i) The set with fewer items must assign each one of its spatial maps to one of the other set.

(ii) Each one of the spatial maps of the set with more items can be assigned or not.

(iii) In case both sets have the same size, each one of the spatial maps must be assigned to a component of the other set.

Considering these constraints, we have that the TM optimization problem may be formulated as follows:

$$\underset{x}{\text{maximize}} \sum_{i=1}^{M}\sum_{j=1}^{N} x_{i,j} g_{i,j}$$

subject to

$$\sum_{i=1}^{M} x_{i,j} \begin{cases} = 1, & N \leq M \\ \leq 1, & \text{otherwise} \end{cases} ; \ \forall j \in \mathbb{Z} \mid 1 \leq j \leq N \tag{2.2}$$

$$\sum_{j=1}^{N} x_{i,j} \begin{cases} = 1, & M \leq N \\ \leq 1, & \text{otherwise} \end{cases} ; \ \forall i \in \mathbb{Z} \mid 1 \leq i \leq M$$

where M and N are the respective sizes of each set, $g_{i,j}$ is a GOF measure that quantifies the level of visual similarity between two spatial maps and $x_{i,j} \in \{0, 1\}$ is an assignation binary variable indicating the match between the map i and the map j. The proposed optimization problem was solved by using binary linear programming [33] as implemented in MATLAB Mixed-integer linear programming (MILP; intlinprog; http://www.mathworks.com/help/optim/ug/intlinprog.html). For our experimentation, we considered as similarity measure ($g_{i,j}$) a subtle variation over the GOF proposed by Greicius et. al. [31, 32]. This variation omits the z-score normalization in favor of the one given by the PSC and then quantifies the average of the voxels falling in one of the maps and then subtracts the average of the voxels outside this map. The original method is complemented by relaxing the chosen GOF measure, this is, the extended method treats the similarity measure as a parameter. Reported results also include the Pearson correlation coefficient as a GOF measure.

By solving this problem we get a coupling between the binary RSNs templates and the ICs with highest global GOF (taking into account all templates simultaneously). Given that usually the number of ICs (30) [1] is larger or equal than the number of the templates, the first constraint ensured that all binary RSNs templates will be assigned. The second restriction forced a unique identification of each IC, overcoming potentially concurrent component assignations.

2.2.6 Components classification

Each one of the assigned ICs were classified by its nature as "neuronal" or artifactual using a supervised machine learning algorithm. Specifically a binary classifier strategy using a Support Vector Machine (SVM) with a Radial Basis Function (RBF) kernel. The chosen implementation is the one made by the University of Waikato in Weka 3: Data Mining Software in Java [36] (http://www.cs.waikato.ac.nz/~ml/weka/), which works with LIBSVM - A Library for Support Vector Machines (https://www.csie.ntu.edu.tw/~cjlin/libsvm/). For the features vector we chose a novel approach called IC-fingerprint, which characterizes ICs as a multidimensional space of 11 descriptive measures [18], 4

spatial based (degree of clustering, skewness, kurtosis, spatial entropy) and 7 temporal based (one-lag autocorrelation, temporal entropy, power of five frequency bands: 0-0.008 Hz, 0.008-0.02 Hz, 0.02-0.05 Hz, 0.05-0.1 Hz, and 0.1-0.25 Hz).

2.2.7 Thresholding procedure

Previously described optimization problem ensures a mutual matching between an IC and a template, but does not provide any information about the level of certainty for the existence/absence of each RSN. This aspect is quite relevant on pathological subjects, where RSNs may be affected by the altered condition, resulting on ICs with different spatial patterns to the ones originally assumed by the RSN templates.

In order to estimate the sensibility of the proposed method, we conducted a simple experiment. A thresholding strategy which assumes that the highest GOF per template is in fact a RSN. In contrast, the lowest GOF is taken as a mismatch in the assignation. Given these 2 assumptions, a threshold can be placed and its impact in RSNs detection can be measured.

2.3 Results

Figure 2.1 shows the results of the original MTM and the improvements achieved by extending the method and different sets of configurations. Mainly, by changing the visual similarity measure, but also by testing with different datasets. As observed in columns 1 and 5 of each RSN, the extended method shows a significant improvement in the detection for the first 5 networks (from 85%, 89%, 78%, 56% and 33% respectively to 100%). Auditory network also experiences a better detection (85% vs 81%). In the case of visual medial network, although shows a lower detection (59% vs 70%), it still has a good detection percentage. Visual lateral, visual occipital and cerebellum networks however, resulted in the lowest detected networks (33%, 15% and 7% respectively), even lower than original method (44%, 52% and 26% respectively). It is worth to say that one of the improvements is in the detection of the DMN (from 85% to 100%), a very used network to study pathologies such as Alzheimer's Disease (AD) [32], Disorders of Consciousness (DOC) [24, 75], Schizophrenia [57], among others.

Columns 2 and 3 of each RSN show the behavior of Pearson correlation coefficient in contrast with Greicius inspired GOF [31, 32] for Baltimore's data. Columns 4 and 5 exhibit a similar experiment for Liege's dataset. In both studies we found a good detection of RSNs, at least in the first 6 enumerated networks (greater than 70%). Regarding to similarity measures, Greicius inspired GOF [31, 32] exhibits a slightly better performance. Finally, columns 3 and 5 summarize the best performance achieved for each dataset. In both cases, Greicius inspired GOF [31, 32] reports better detections. Common behavior between both

datasets includes a high detection of DMN, ECL and ECR (100%). Followed by Salience and Sensorimotor networks (between 80% and 100%), auditory network (between 70% and 85%) and lastly visual medial network (between 56% and 59%). Visual lateral, visual occipital and cerebellum networks were poorly detected (between 0% and 33%).

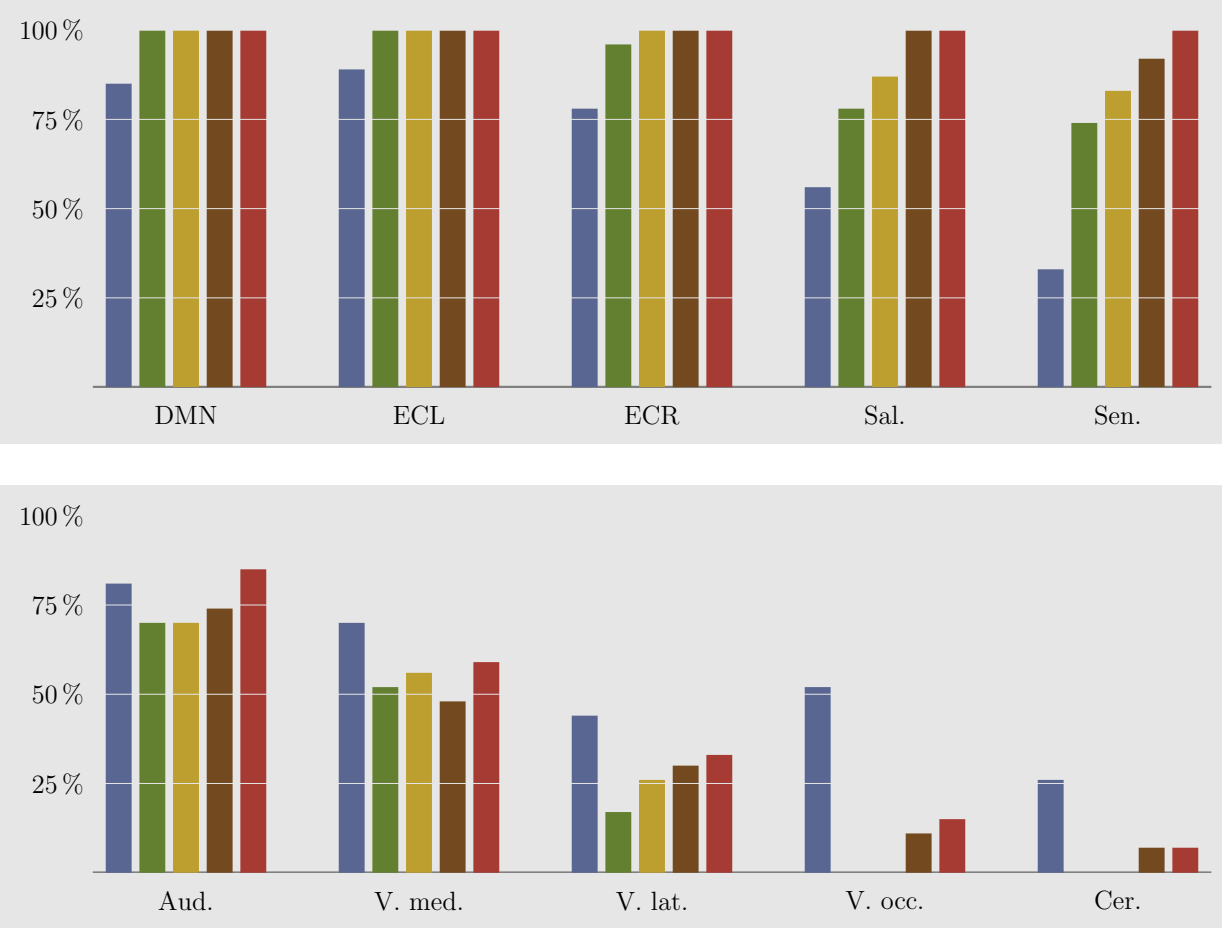
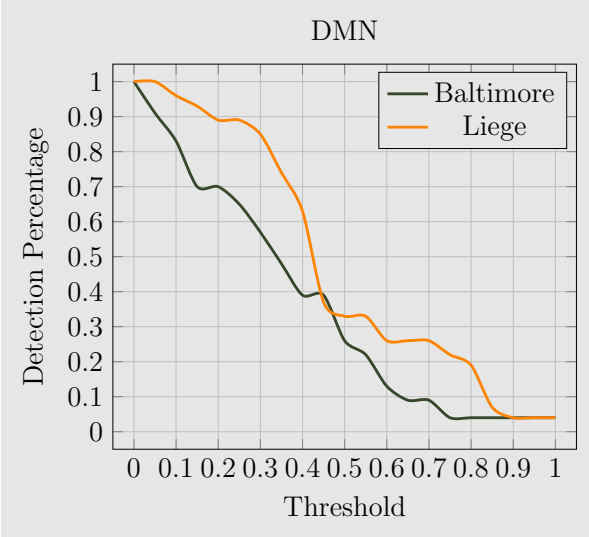
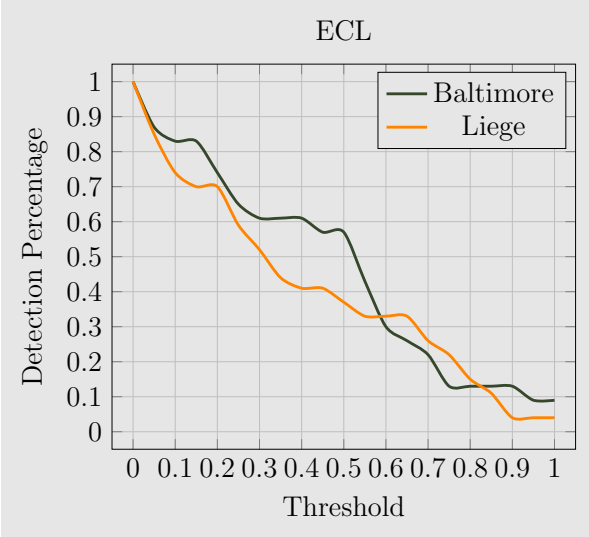
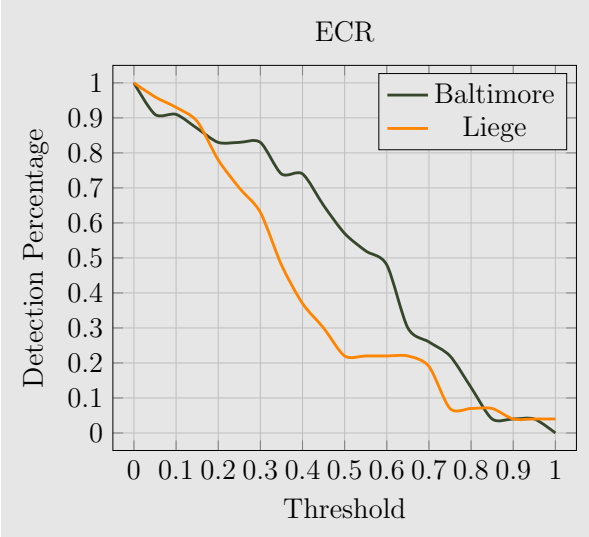


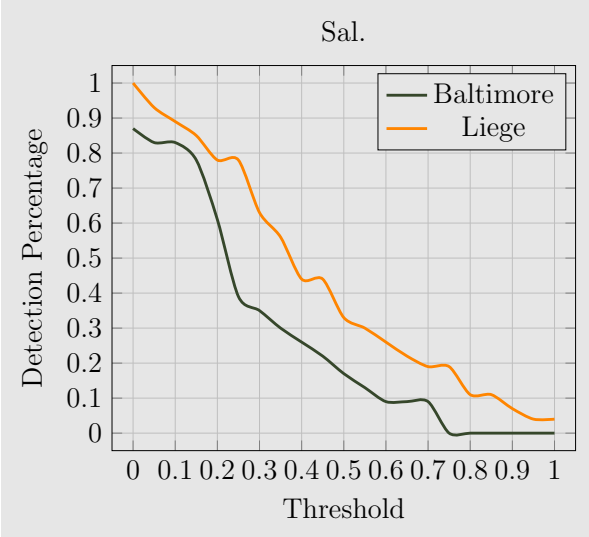
Figure 2.1. For each RSN, from left to right. First, results reported by Demertzi, Gómez, Laureys, Soddu, et. al. [20] (Blue). Followed by the results for Baltimore's dataset, Pearson correlation coefficient in contrast with Greicius inspired GOF [31, 32] (Green and Yellow). Finally, fourth and fifth values were obtained for Liege's dataset, Pearson correlation coefficient versus Greicius inspired GOF [31, 32] (Brown and Red). In all cases, the applied procedure was: normalization, GOF computation, RSNs detection and Artifacts identification.

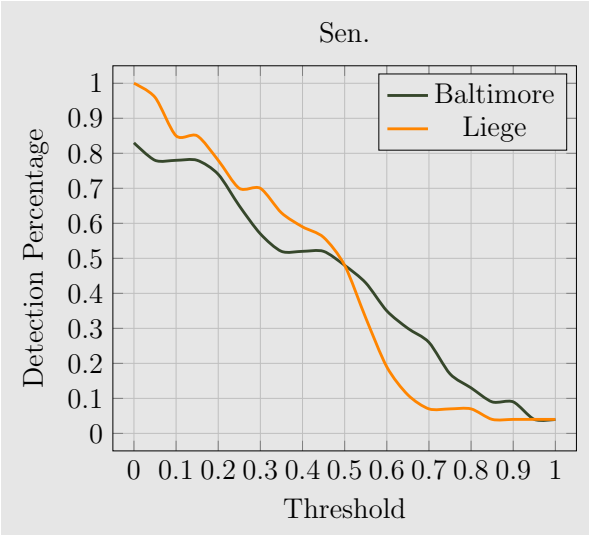
Figure 2.2 shows the effects of applying a set of thresholds over a normalized GOFs. From previously described results, we choose Greicius inspired GOF [31, 32] as the visual similarity measure.

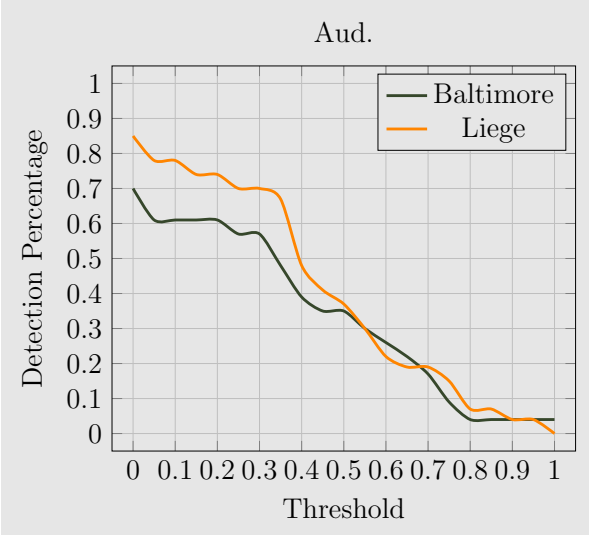

DMN
Baltimore
Liege
Detection Percentage
Threshold
0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1


ECL
Baltimore
Liege
Detection Percentage
Threshold
0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1


ECR
Baltimore
Liege
Detection Percentage
Threshold
0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1


Sal.
Baltimore
Liege
Detection Percentage
Threshold
0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1


Sen.
Baltimore
Liege
Detection Percentage
Threshold
0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1


Aud.
Baltimore
Liege
Detection Percentage
Threshold
0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1

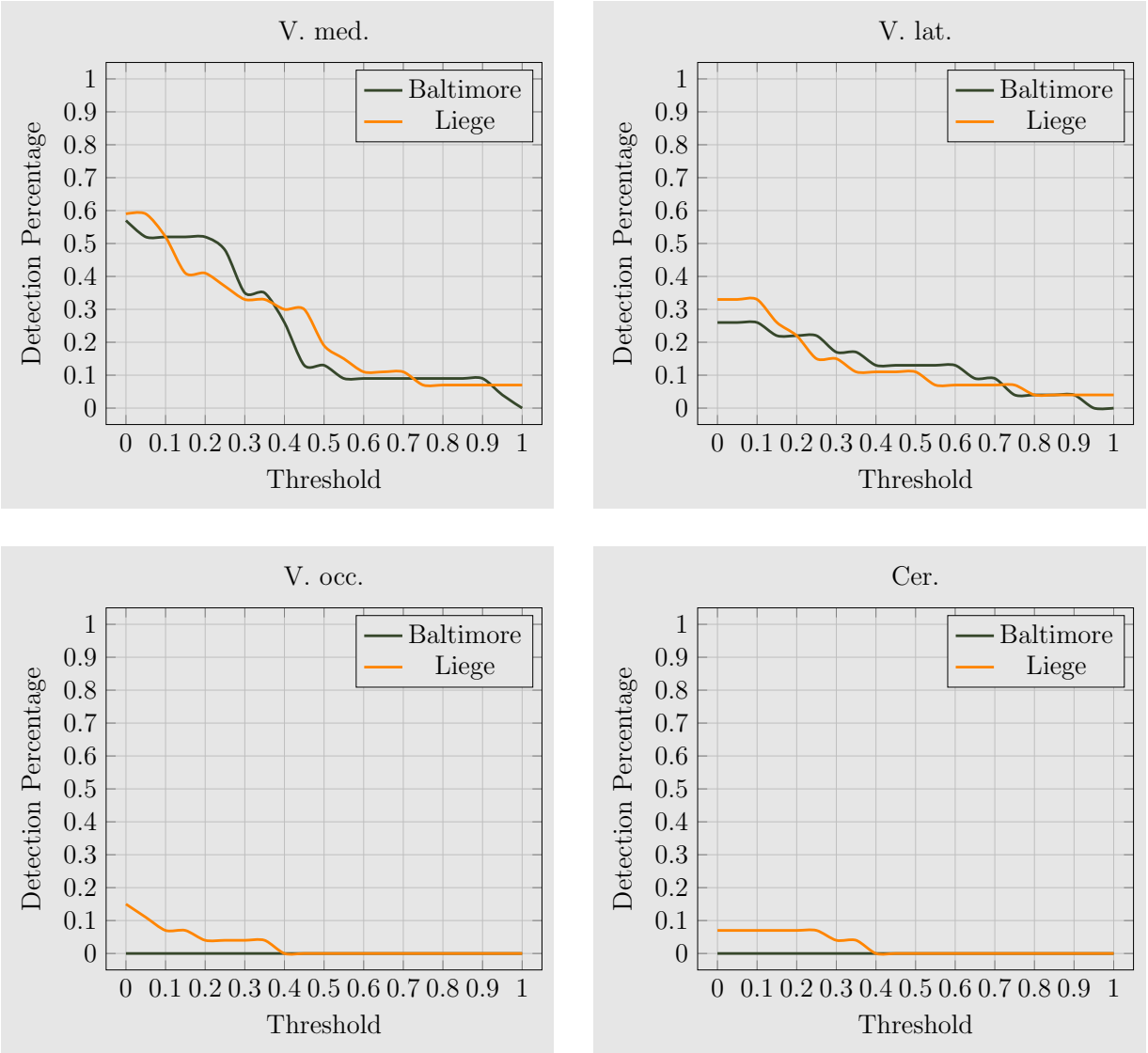


Figure 2.2. Effects of thresholding procedure (Subsection 2.2.7) in each RSN. Abscissa axis represents a set of normalized thresholds and ordinate axis shows the impact of these thresholds in the detection percentage. These results were obtained using Greicius inspired GOF [31, 32] as the visual similarity measure.

2.4 Conclusions

In this work we have proposed a set of novelties to extend the MTM method. Results suggest that this approach can detect RSNs independent of the study's variability. In the case of Liege's study we have achieved an overall improvement over the original results [20],

same detection patterns were observed in Baltimore's dataset. From that, we can conclude that normalization process improves the reproducibility of the method and is ready to be applied in clinical environments (pathological and pharmacological populations) where visual identification is problematic. Additionally, we found that Greicius inspired GOF [31, 32] reports better results than Pearson correlation coefficient. Future work includes the implementation of different similarity measures and as we suggested, evaluation of the method in patients.

3 Trustworthiness for multiple template matching in resting state

This chapter is based in the work titled "Trustworthiness for multiple template matching in resting state". Presented in the 9th Computing Colombian Conference.

3.1 Introduction

fMRI-RS provides a robust protocol to investigate several pathological conditions, such as Alzheimer's disease (AD), Schizophrenia, disorders of consciousness (DOC), as well as, different pharmacological states, for instance, sedation under distinct kinds of anesthetics [23, 2]. Recent work suggests that brain at resting state (RS) is organized in well defined spatio-temporal functional entities. At least ten of them have been consistently identified in healthy subjects: the default mode network (DMN), the executive control left and right networks (ECL and ECR), the salience, the sensorimotor, the auditory, the three visual networks (Medial, Lateral and Occipital) and the cerebellum [38].

One common approach to study altered brain conditions in fMRI-RS is through the analysis of changes on these networks [25]. RSNs are usually characterized by using ICA [41]. In this method, fMRI-RS signal is decomposed into statistically independent components, which correspond to sources of brain activity. Each source consists of a spatial map and its respective time course. Following, these sources are labeled as "neuronal" or artifactual and the corresponding RSNs are identified. Previous studies have approached the RSN recognition task manually or by using template matching approaches. Manual detection is time expensive and requires high levels of expertise, a factor that may influence reproducibility [73]. Multiple templates matching (MTM) is a recent approach that consists on pairing a set of RSN templates to the set of ICs with highest visual similarity [75, 55, 20], it provides an automated and reproducible approach.

The MTM approach provides valuable information about the existence/absence of different RSNs at individual level. For instance, using this method is possible to show that in healthy controls a set of well defined ICs that match to DMN, ECL, ECR and auditory networks can be found consistently at individual level [20]. It is also possible to show that the number of ICs of "neuronal" nature obtained by using this method can be used to characterize subjects in pathological conditions, such as, disorders of consciousness [20]

or in pharmacologically altered brain states, such as, anesthesia induced by propofol [64]. However, despite of the MTM utility, this method has an important limitation, it does not provide any information about the level of certainty for the existence/absence of each RSN. This aspect is very important in pathological subjects, where RSNs may be affected by the altered brain condition, resulting on ICs with different spatial patterns to the ones originally assumed by the RSN templates. For instance, figure 3.1 illustrates how the MTM may result in low visual similarity values for the Cerebellum network. In this case, the interpretation of this IC as the RSN Cerebellum may be incorrect. This limitation may be especially important for severe altered brain conditions, such as, unconsciousness where it is expected a complete reorganization of brain activity [40]. Therefore, it would be desirable to quantitatively assess how trustworthy is the assignation in order to improve the MTM sensibility to select reliable RSNs.

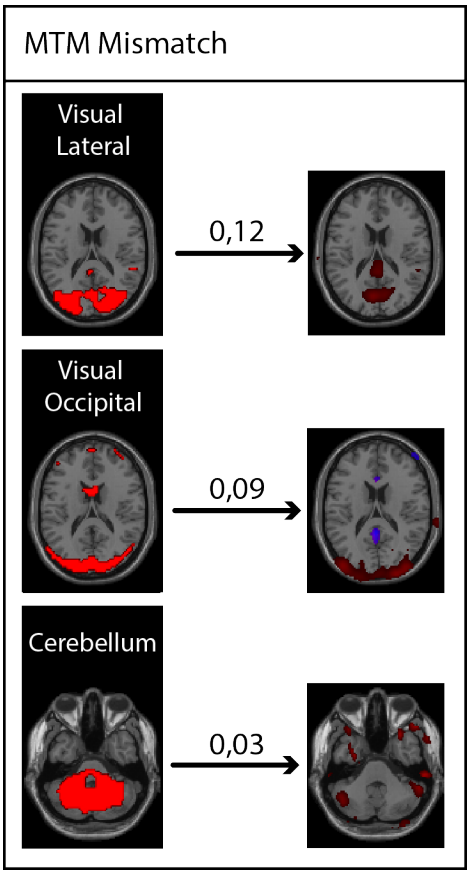


Figure 3.1. Multiple templates matching example. In this case Cerebellum network resulted in a very low visual similarity value. Therefore, even if this network was selected by the MTM approach, this assignment should not be taken into account for further analysis.

In this paper, we propose an approach to objectively assess the quality of the RSNs

assignations obtained by using MTM. In particular, we introduce a novel index for each RSN matched in a subject, which quantifies how much trustworthy is this assignation. The main idea is to use a catalog of subjects as reference to validate how much the assignations template-IC, provided by the MTM, coincides with the pairings obtained when comparing the subject of interest with a set of subjects of reference in which the RSNs were previously identified. We show that the method provides valuable complementary information for characterization of RSNs at individual level.

3.2 Materials and methods

3.2.1 Participants and data acquisitions

Data from 27 healthy controls (14 women, mean age 47 $\pm$ 16 years) were used for this study. Previous written consent to participate in the study was obtained from all subjects. For each subject, fMRI-RS data were acquired in a 3T scanner (Siemens medical Solution in Erlangen, Germany). Three hundred fMRI volumes multislice $T2^*$-weighted functional images were captured (32 slices; voxel size: $3 \times 3 \times 3\ mm^3$; matrix size 64; repetition time $= 2000ms$; echo time $= 30ms$; flip angle $= 78°$; field of view $= 192\ mm^2$). A structural T1 image was also acquired for anatomical reference.

3.2.2 Preprocessing

Data was processed using SPM8 (http:www.fil.ion.ucl.ac.uk/spm). Preprocessing included: spatial realignment, co-registration of functional onto structural data, segmentation of structural data, normalization into MNI space and spatial smoothing with a Gaussian kernel of $8\,mm$. Large head motions [61] were further corrected using ArtRepair (http://cibsr.stanford.edu/tools/ArtRepair/ArtRepair.htm).

3.2.3 Spatial Independent Component Analysis

In order to perform the MTM algorithm the fMRI signal was decomposed into sources of "neuronal"/physiological origin. For this task, we used ICA, which aims to decompose the signal into a set of ICs of brain activity. Because in the fMRI data the spatial dimension is much greater than the temporal one, we used spatial ICA (sICA), which decompose the signal into maximally independent spatial maps [52]. For the ICA decomposition we used 30 components and the infomax algorithm as implemented in GroupICA toolbox (http://icatb.sourceforge.net/).

3.2.4 Independent Components classification

After the ICA decomposition, a machine learning based labeling method was applied to discriminate between ICs of "neuronal" or "artifactual" origin. For this, a binary classification

method based on a support vector machines and an spatio-temporal feature vectors, used for description of each IC, was used [20, 34]. The spatio-temporal feature vector contained both spatial (i.e. degree of clustering, skewness, kurtosis, spatial entropy) and temporal information (i.e. one-lag autocorrelation, temporal entropy, power of five frequency bands: 0-.008 Hz, .008-.02 Hz, .02-.05 Hz, .05-.1 Hz, and .1-.25 Hz).

In order to reduce computations we selected only subjects with at least 10 components, one for each considered RSN. All of them labeled as "neuronal" for subsequent analyses steps. A total of 18 out of the 27 controls met this condition.

3.2.5 Multiple template matching trustworthiness method

The proposed approach consists in determine the degree of consistency of each IC labeled as RSN. For this, we propose to compare the IC assigned by the matching with the set of templates, with the IC assigned by a matching between subjects. In this last assignment, we aim to compute a pairing between the set of components of the subject of interest and the set of ICs of a subject of reference. Importantly, we assumed that RSNs were previously labeled on the reference subject. We said that an IC is consistent when the same subject IC is assigned twice to the same RSN, one using the template matching with the templates, and another one using a pairing between subjects.

The proposed concept is illustrated for the ICs of a prototype subject (column S1) and the ICs of a reference subject (column S2) in figure 3.2. In this case, T corresponds to the set of binary RSN templates. To determine consistent/inconsistent ICs three matching processes were performed: one between S1 and the binary RSN templates T (P1), one between S2 and the templates T (P2) and one inter-subjects between S1 and S2 ICs (P3). In this case, the consistent assignations (black arrows between S1 and S2) were obtained when the IC for a particular RSN agrees with the IC for the same RSN in the reference subject. Inconsistent assignations (red arrows) resulted from disagreements in the results of the between subjects matching (P3) and each individual labeling (P1 and P2). Therefore, in order to compute consistencies on paired components two pairing methods should be considered: 1) a method for matching of RSNs and ICs and 2) an approach for pairing between ICs subjects.

Identification of RSNs at individual level

For MTM, single subject sICA was computed. Following, the set of ICs that maximize the similarity with a set of binary RSNs templates were selected [20]. This matching works as follows. First, in order to overcome potentially concurrent IC assignations to the same template, two physiologic constraints are introduced: (i) a template had to be assigned to one of the subject's ICs and (ii) an IC could be labeled as a RSN or not.

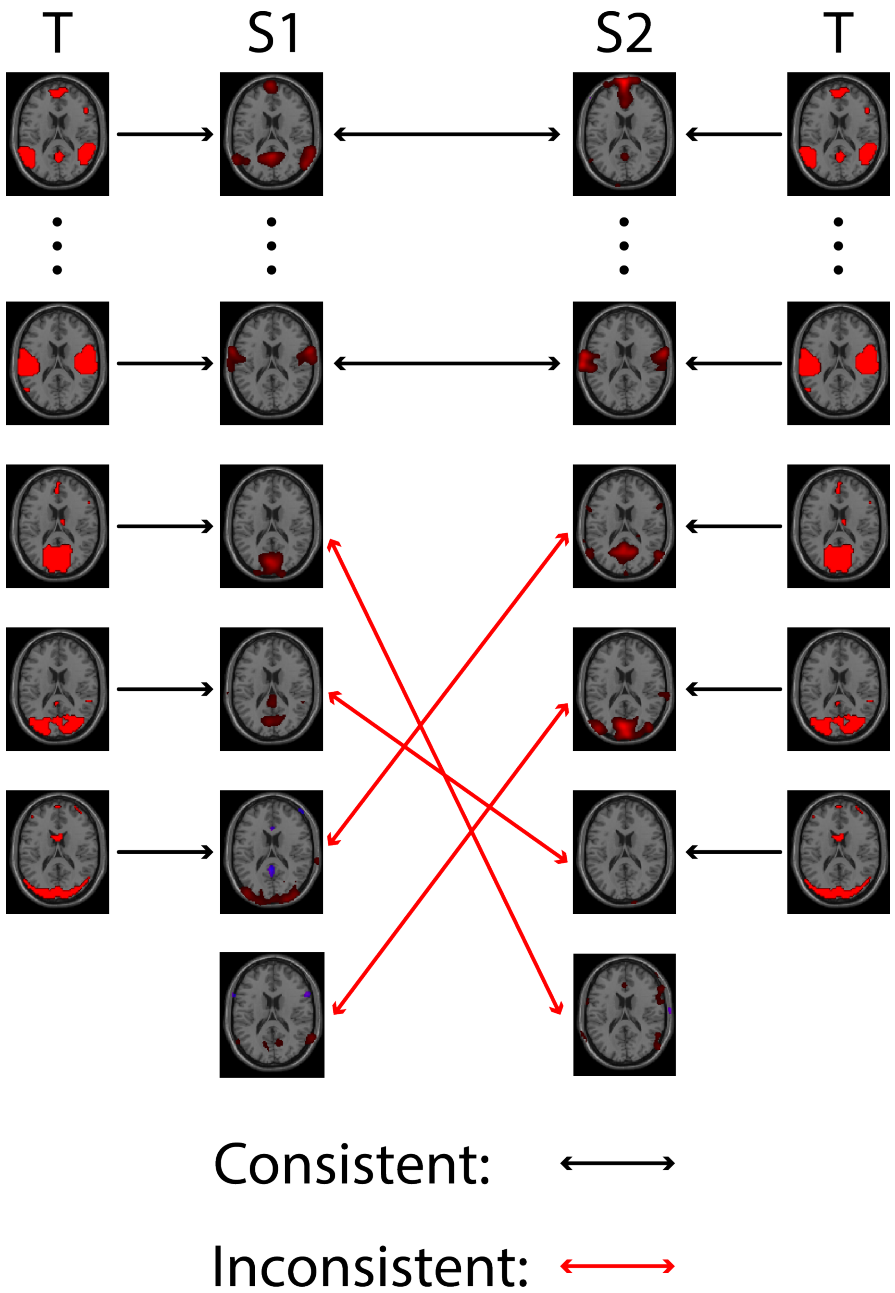


Figure 3.2. Consistent and inconsistent pairings. Three different sets of spatial components were considered: T the binary RSN templates, S1 the ICs of the subject to be characterized and S2 the components of the subject used as reference. To determine consistent/inconsistent ICs three matching processes are performed: one between S1 and the RSN templates T (P1), one between S2 and the binary RSN templates T (P2) and one inter-subjects between S1 and S2 ICs (P3). A pairing is consistent when there is an agreement in the assignation of the IC for P1 and P3. The pairing is inconsistent, otherway.

Given that the number of ICs is usually larger or equal than the amount of the templates, the first constraint ensured that all binary RSNs templates would be assigned.

The second restriction forced a unique identification of each IC, this overcame the potentially concurrent component assignations [20]. When considering these two restrictions the MTM optimization problem may formulated, as follows:

$$\begin{aligned} \underset{x}{\text{maximize}} \quad & \sum_{i=1}^{N}\sum_{j=1}^{M} x_{i,j} g_{i,j} \\ \text{subject to} \quad & \\ & \sum_{i=1}^{n} x_{i,j} = 1,\ 1 \leq j \leq M \\ & \sum_{j=1}^{M} x_{i,j} \leq 1,\ 1 \leq j \leq N \end{aligned} \tag{3.1}$$

where M is the number of different templates, N the quantity of ICs, $g_{i,j}$ is a goodness of fit measurement that quantifies the level of visual similarity between the template and the IC and $x_{i,j} \in \{0, 1\}$ is an assignation binary variable indicating the match between the template j and the IC i. By solving this problem a coupling between the binary RSNs templates and ICs with the highest global goodness of fit (taking into account all templates simultaneously) is eventually selected. The proposed optimization problem was solved by using binary integer programming [33]. For our experimentation, we considered as similarity measurement $g_{i,j}$ the Pearson correlation coefficient between the corresponding spatial components. Figure 3.3 illustrates the multiple templates matching approach.

Independent components matching

In order to compute the pairing between subject's ICs, a modification of the original MTM was proposed. As can be inferred from equation 3.1, the MTM method was originally designed to work with the set of binary templates. Therefore, the number of RSNs is always lower than the amount of ICs and an exact match is forced to pair all the RSNs. However, when two subjects should be paired it would be possible to have different number of ICs for each subject. In order to overcome this limitation MTM was modified to ensure that the subject with fewer ICs has all its components assigned, i.e., the binary RSN template role was assumed by the subject with fewer ICs.

Consistency method

For the consistency computations, first a matrix was constructed (figure 3.4). In this matrix, a row i correspond to one IC matched by MTM method (optimization problem 3.1),

and column k is related to one subject in the reference population. The entries $C_{i,j}$ in the consistency matrix were defined as follows:

$$C_{i,j} = \begin{cases} 1 & \text{if the assignation was consistent} \\ 0 & \text{Otherwise} \end{cases} \tag{3.2}$$

It is worthy to recall that according to our definition an assignation is consistent if there is an agreement between the IC matched using MTM and the IC selected when the subject of interest is matched with the subject of reference j.

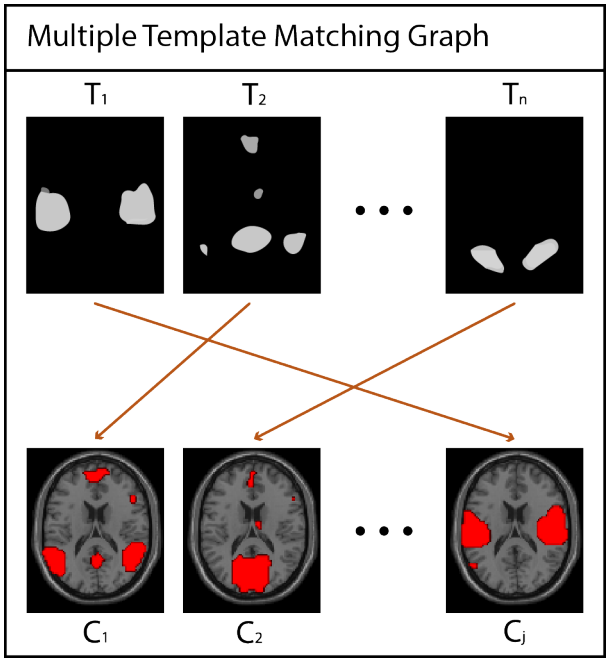


Figure 3.3. Multiple templates matching illustration. Binary templates are matched to the corresponding ICs using a visual similarity measurement.

Degree of consistency in a set of reference subjects

So far we have described how to compute consistent/inconsistent assignations between the subject of interest and one subject of reference. In this section, we describe how to use this information to compute the complete index. For this, the main idea is to count the number of consistent assignations in a set of subjects of reference, as illustrate figure 3.5. Therefore, we define the degree of consistency d_i for IC each matched as a RSN, as follows:

$$d_i = \frac{1}{J} \sum_{j=1}^{J} C_{ij} \tag{3.3}$$

with J the number of subjects on the reference population. d_i corresponds to the percentage of subjects for which the matched IC i was consistently found by the subjects in the reference population.

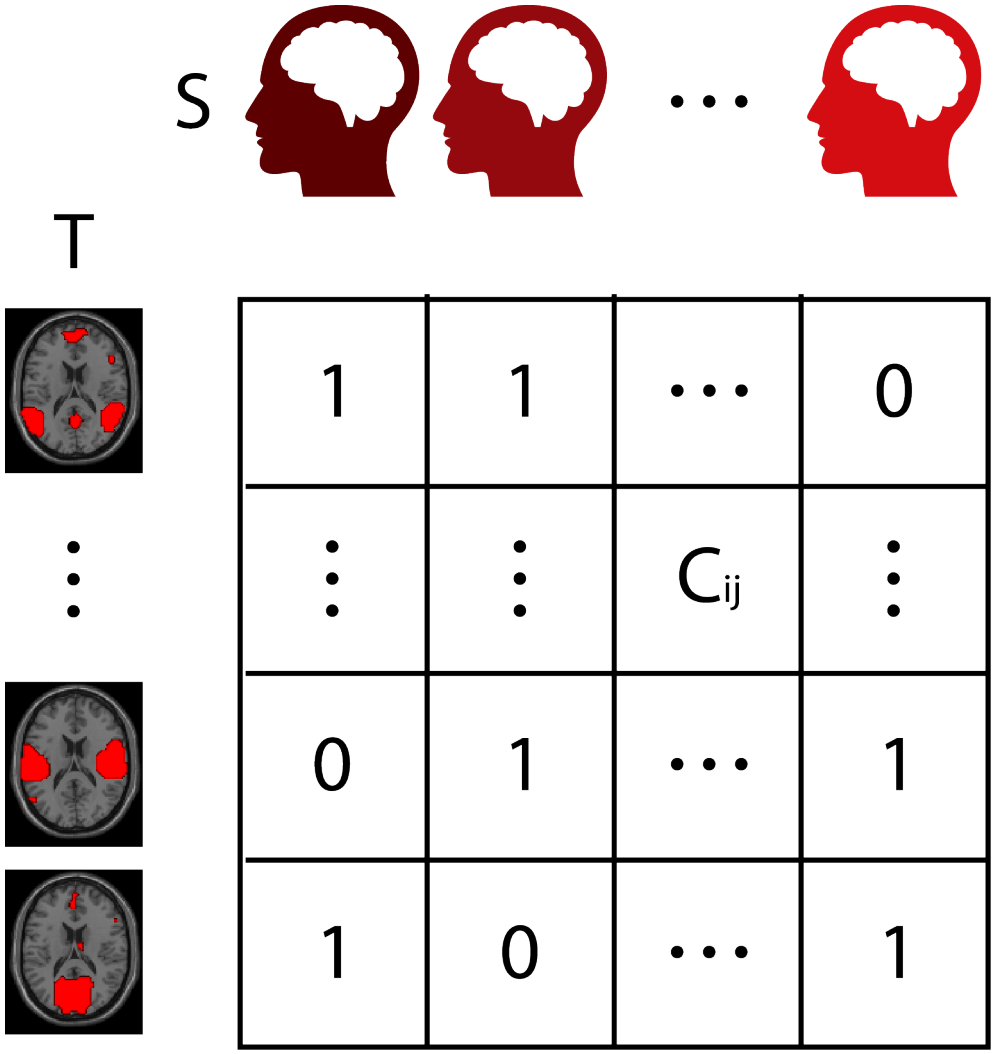


Figure 3.4. Consistency matrix for trustworthiness method. Rows corresponds to matched ICs using MTM. Columns correspond to subjects in a reference population. Entries are 1 when there is consistent assignation (figure 3.2), 0 otherwise.

3.3 Results

Figure 3.6 shows the degrees of trustworthiness for the 10 RSN over the 18 subjects. These results were obtained by considering the ICs matched for each subject and the other 17 subjects as reference population. As observed, the method is able to provide a quantitative

measurement for the degree of trustworthiness for each network. In this case, ECL resulted in the most reliable network followed by auditory. The method is also able to characterize low degrees of trustworthy, for instance, for ECR in subjects 6 and 16. In this case, these ICs probably should not be considered for further analyses. In general, Cerebellum and the three visual networks resulted in the lowest degrees of trustworthy for all the subjects.

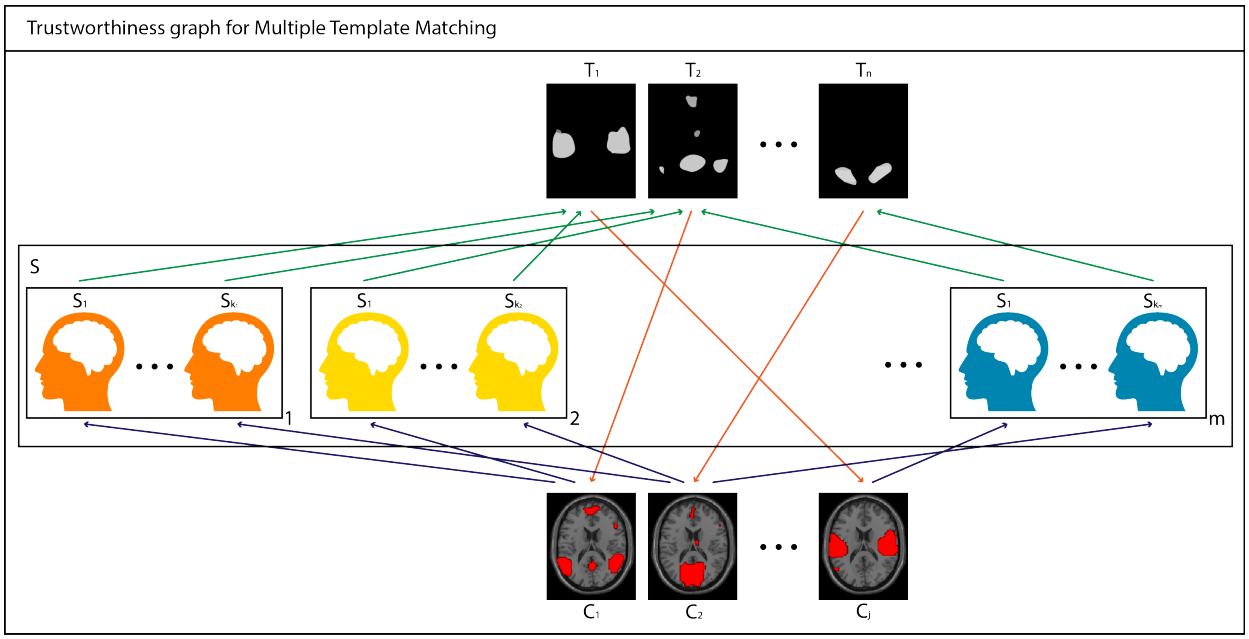


Figure 3.5. Matching between the subject's ICs, the subjects of reference and the templates. Degree of consistency is estimated using the number of consistent assignations computed on the set of reference subjects.

3.4 Conclusions

In this work we proposed a novel method to quantify the level of trustworthiness for the assignation obtained by using MTM. Results suggest that the approach will provide complementary information to support the existence of RSNs at individual level. Our results support the reliability observed in previous studies for four the selection of RSNs, namely, ECL, ECR, DMN and auditory [20]. Future work includes the evaluation of level of trustworthy for pathological populations in which the visual selection is problematic, such as, patients with disorders of consciousness.

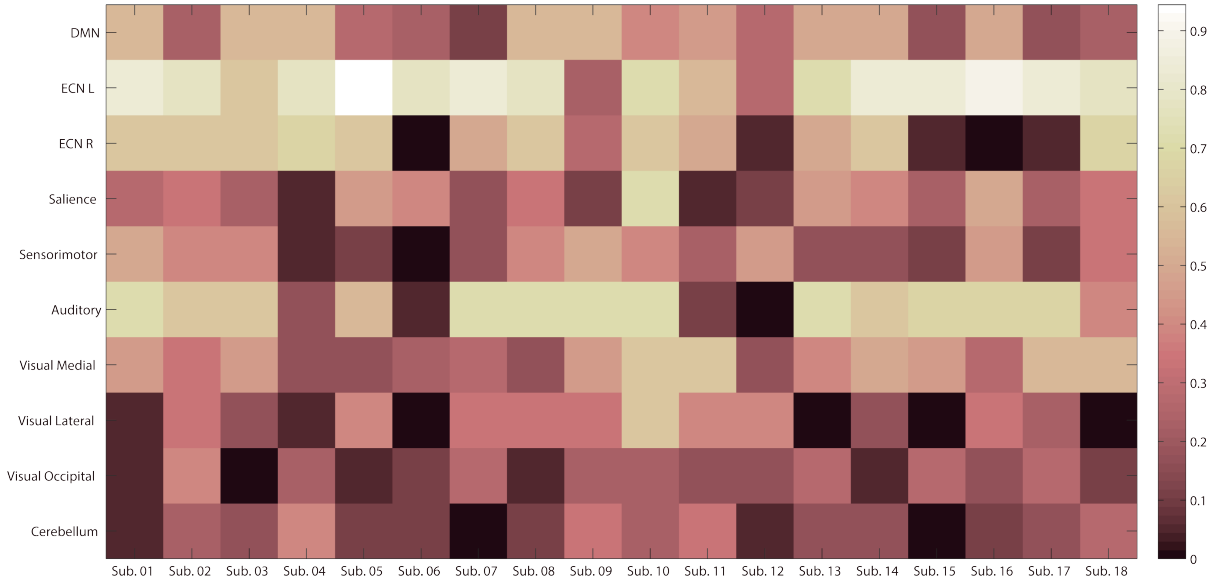


Figure 3.6. Consistency of each RSN for all the subjects in the experiment. Darker colors correspond to low consistency in the detection of the RSNs. Lighter colors correspond to highly detected RSNs across the population of reference.

4 RestLib: An open source tool for RSNs assessment

This chapter is based in the work titled "RestLib: A toolbox for single subject resting state analysis". Presented in the 7th International Seminar in Biomedical Engineering.

4.1 Introduction

Scientific reproducibility is one of the most important requirements of modern science. Recent evidence suggests that a considerable percentage of the scientific studies published today are poorly reproduced. For instance, Begley and Ellis report that 89% percent of the cancer related studies cannot be reproduced, even with the collaboration of the original authors [4, 6]. Baker reports that a small percentage (39%) of psychological studies can be reproduced [3]. In neuroimaging analysis recent work showed that even small software fails, for instance in statistical assessment, may result in overestimation of results, affecting a considerable numbers of studies using that software. Nowadays, there is a growing interest from the scientific community in improve several aspects of studies reproducibility. Contextualizing, scientific reproducibility or transparency, refers to the fact that any researcher may reproduce with minimal effort the results reported by others researchers. This can be guaranteed by using several strategies, including, *clearness and openness in the formulation of methodological protocols*, *data sharing practices*, *robust statistical analysis*, and *reproducibility related to software tools*, among others. Clearness and openness in the formulation of methodological protocol refers to a complete specification of the experimental procedure before the experimentation is performed. Data sharing refers to the publication of the data related to study in order to allow external validation. Robust statistical analysis is related to the need of having a well planned statistical protocol, which considers the population size, possible sources of noise and confound, and the results analysis, among others. Finally, reproducibility related to software tools is about the fact that methods used for data analysis should be available for the scientific community. Because of the computational focus of this thesis, in this chapter, we focused on reproducibility related to software tools issues of the methods herein reported.

Research in neuroimaging is a growing and diversified field, in general, several skills are required to successfully approach these studies, including, MRI physics, experimental protocol design, legal and ethical considerations, clinical expertise, data handling, and sta-

tistical analysis, among others. To overcome these challenges commonly multidisciplinary teams are joined to contribute from their different perspectives to the construction of the study. Ideally, each skill should be covered by a field expert, however, because of economical restrictions in most of the cases many of these tasks are covered by a small research team. In the case of data analysis it is usually performed by personnel with minimal technical training, or with a lack of specialized knowledge about particular issues of neuroimaging. In this context, the main idea of this work is provide a user friendly and open source toolbox that could make resting state analysis available to every neuroscience related researcher with a minimal knowledge of the underlying technical details of the approaches. More specifically, we propose RestLib an open source framework which comprises a helpful set of functionalities to perform resting state analyses for individual assessment, providing in this way access to the methods described in the previous chapters, among others. The toolbox was developed following the next guidelines:

1. The experiments supporting this tool were conducted assuming a high level of variance between research centers, resonator settings and other variables. Therefore, the resulting product aims to cover as many as possible these variabilities. This topic was treated in detail in chapter 2 of this document.

2. We consider that science should be as transparent as possible, in the context of neuroimaging studies this means, among other requisites to release all the elements required to reproduce the obtained results. Hence, the framework developed in this work is released using an open source license. Details around this requirement are treated in following sections of this chapter.

3. Clinical applications require objective measure scales that allow sense a degree of trustworthiness and support in a better way the decision making process. For that reason all the methods included in the framework are paired with an analysis to measure in an objective way its reliability. The proposed sensing strategy is explained and discussed in chapter 3 of this dissertation.

4. fMRI analysis is commonly performed using well designed projects like Statistical Parametric Mapping (SMP) or FMRIB Software Library (FSL). The idea of this requirement is to build our tool to be compatible with one of these popular projects, but also to be flexible enough to extend its functionalities with a minimum effort. This requirement is going to be better explained in this chapter.

5. We also take into account that the set of expected users not only involves professionals with high level of programming skills, but also professions with a lack or even a small level of these abilities. Having said that, this last requirement aims to design an easy to use tool and for that purpose the framework includes a graphical user interface (GUI). This topic is discussed in this chapter.

This chapter is structured as follows: first, we describe some methodological aspects related to software tools in resting state analysis, then we present in detail the architecture of the herein proposed framework and how this structure suits the necessities of the resting state community. Following, we introduce the contributions made in RestLib by presenting examples of possible research questions that can be addressed using the resting state analysis framework implemented. This section particularly shows the tool in action via the analysis of data acquired in RS, describe the functionalities and related limitations, and discusses the obtained results. We hope that by solving those punctual issues the interest of the neuroscientific community might increase.

4.2 Methods

Two of the most fundamental questions in the neuroimage processing field are how the information captured is related to the different brain processes, and how this information evolves with time. In that line, methods used to analyze single subject fMRI-RS data are mainly focused on characterize the relationship between a mental state and each image voxel time series. Apply these kind of strategies usually require a high level of knowledge affecting in that way the reproducibility of the methods. A possible way to minimize this effect is to use software solutions devised to encapsulate part of that expertise and also to automatize exhaustively tasks. Nevertheless, many existing implementations in software tools consist of small and isolated code snippets, or sets of packages, and lack of a dedicated single, integrated and flexible software framework. Additionally, the most common interaction with this solutions is through the command line, this is, they do not provide a user friendly graphical interface, neither for displaying results. As a consequence, to access to this kind of software is also required to have a high level of programming skills. We consider that a proposed solution in this matter should aim to be able to integrate directly via a user interface with well known software tools used by the neuroscience community. This section is oriented to explain how we addressed this issues in our proposed framework.

4.2.1 Framework architecture

The "Resting-State Analysis Library" (RestLib) was developed as an open source and cross platform framework implemented using the MATLAB programming language. The main tool used to build RestLib is the Matlab-batch system, a projects that aims to solve the problem of development of data analysis tools in a generic way. This software is used as the main source of interaction by well known software packages, such as SPM. Therefore, our proposed solution is compatible with SPM routines and its choice is perfectly suitable for both cognitive and clinical neuroscience research. The selection and use of the Matlab-batch system also facilitates the inclusion of novel contributions from others developers.

Matlab-batch system programming allows build well defined interchangeable modules.

To accomplish that, the framework provides a structured language to define inputs and outputs as MATLAB objects. Programmers can also add constraints and consistency checks to these elements. To ensure certain degree of safety, the system only runs procedures which meet all the consistency criteria. Therefore, in that way the algorithms are freed from checks for input completeness or consistency. Additionally, the framework also provides a shape to create templates for recurring processing tasks. These templates can be declared either by using the GUI or the MATLAB command line syntax and can be reused to perform analyses over large datasets in a consistent way. All settings and parameters in those templates are documented for future reference. With all these advantages and the compatibility with SPM we consider that the Matlab-batch system constitutes the best alternative available to perform full flexible resting state analyses and also offer a tool which advanced users can easily access technical details and expand the toolbox with their own developed methods.

Having said that, RestLib was built around three main modules: Preprocessing module, Spatial Decomposition module and RSNs Analysis module. The first one, named preprocessing includes wrappers for state of the art tools, specifically for ArtRepair and Artifact Detection Tools (ART), for the tasks of motion corrections and signal despiking. This module particularly integrates transparently and smoothly with SPM and its fMRI preprocessing routines (slice timing correction, realignment, co-registration, spatial normalization and transformation to the MNI standard space). The Spatial Decomposition module allows to interact with the tool GroupICA GIFT using the Matlab-batch system. It maps all possible combinations of parameters listed in GIFT for the task of decompose fMRI signal into spatial independent components using the ICA method. Finally, the RSNs Analysis module accomplish which we consider our two main contributions. The first one is classification module which determines the source of each one of the ICs as artifactual and non-artifactual. The second one is the identification module which selects the subset of ICs with the highest visual similarity to a set of RSNs templates.

4.3 Results

In this section we exemplify how the use of RestLib can address common neuroimaging research questions, particularly, we treat these two questions: **1) Given a set of independent components obtained by using ICA, which of them have a non-artifactual nature?**, and **2) How well known functional maps, such as the RSNs, can be automatically identified in a set of independent components?**. These two questions are of particular interest in clinical applications and practice. Additionally is worthy to mention that RestLib's functionalities can be accessed in two different ways: By using the Matlab-batch system embedded along with the SPM framework, or by scripting the functions in the toolbox. Therefore, both questions can be solved in a very flexible shape. We hope that by investigating theses questions, it provides a basic knowledge about

the RestLib framework and inspires neuroscientists to further explore their data using the herein proposed framework.

4.3.1 Question 1: Given a set of independent components obtained by using ICA, which of them have a non-artifactual nature?

As discussed before fMRI-RS protocol captures both, "neuronal" and artifactual signals [18, 19, 20, 42]. Nevertheless, most of the analysis performed over that protocol focus in non-artifactual signals [19, 20]. Therefore, a mandatory preprocessing step consists in determine the nature of the signal to focus just on the "neuronal" ones. Initial work to perform this discrimination focused on the energy of low frequency subbands to characterize non-artifactual sources [11, 13]. More recently, machine learning approaches have been proposed to discriminate between both categories by using a more sophisticated spatio-temporal characterization [18]. These approaches have provided high levels of discrimination between both categories [18].

Machine learning approaches aim to learn patterns of neuronality out of labeled examples of ICA sources [18]. These labels are provided by experts trained in the recognition of these patterns. Unfortunately, majority of research labs does not have access to the specialized knowledge required to construct the training datasets, or even to build the machine learning algorithm. In order to overcome this limitation, we provide a pretrained model to perform the discrimination task between sources of "neuronal" and artifactual origin. By using this approach we overcome the need of having trained personnel to perform this discrimination task. In addition, we accelerate the analysis process by automatizing it.

Materials and methods

For the neuronal component selection, a group of 19 healthy controls (10 women, mean age = 23 $\pm$ 3 years) were initially used for a supervised learning machine classification between "neuronal" versus artifactual components. ICs samples were obtained from the ICA decomposition (30 components) of this control group. Data were acquired on a Siemens Magneton 3T MR scanner with a gradient echo-planar sequence using axial slice orientation: 32 slices, TE = $40ms$, flip angle = 90°, voxel-size = $3.4\times3.4\times3.0\ mm^3$,TR = $2460ms$. We combined expert knowledge and machine learning to build an automatic classification model. The classifier was based on the IC-fingerprint, a low level representation of the spatio-temporal information of each independent component. This feature vector aims to characterize the high energy contributions of low frequency ranges (0.01 - 0.1 Hz) of the time course and the high sparsity of the spatial map, both properties typically attributed to neuronal sources in resting state [15, 17, 62]. A total of 570 ICs were labeled after visual inspection by the expert using one of the three possible categories: "neuronal" (n=224), artifactual (n=248) and "undefined" (n=98). Only samples labeled as "neuronal" and artifactual were used during the training process.

For the support vector machine (SVM), two different kernels were considered: a linear kernel and a radial basis function kernel (RBF). In the case of the RBF kernel, the γ parameter was varied from 0.1 to 1 using steps of 0.1. For the regularization parameter of both kernels we considered $log_{10}C \in \{-1, 0, \ldots, 8\}$ [39]. Additionally, a nested leave-one-out cross-validation (LOO-CV) strategy was used to select the best SVM parameter set. This procedure also provided an unbiased estimate of classifier generalization ability. We performed LOO-CV in the following way: For each fold, the data of a single control subject were excluded for the test set, and then the remaining data are repeatedly repartitioned, i.e. the data of the 18 remaining participants are split into a validation (1 control) and training set (17 controls). The optimal parameters for the SVM were selected on the validation set before applying it to the test set. The area under the Receiver Operational Curve (ROC) was used as performance measurement for the parameter selection [10]. The SVM-RBF classifier gave a performance on the training dataset of $0.940 \pm 0.003\%$ which was significantly higher than the SVM with linear kernel performance of $0.927 \pm 0.005\%$ ($p < 0.01$). The SVM-RBF also provided the best classification accuracy (94%) compared to visual selection in overall for neuronal components. Based on these results, we selected the SVM-RBF classifier for the task of neuronal IC labeling.

Results

Figure 4.1 shows the automatic classification results for two ICs computed at individual level. As observed "neuronal" components are characterized by low frequency information and a high overlapping with cortical regions. In contrasts, artifactual components are related to highly spiking signals with a major contribution of high frequencies in the temporal domain, as well as, an evident saw-tooth pattern in the time course.

4.3.2 Question 2: How well known functional maps, such as the RSNs, can be automatically identified in a set of independent components?

RSNs provide information about different subsystems (for instance, sensorial or cognitive). A common approach in fMRI-RS analysis is to focus on particular subsystems by focusing in specific RSNs. For instance, consciousness related studies have focused on DMN [55, 75] or experimentation about visual impairment has been studied using the visual networks [26]. In this kind of studies the aim is to compare the same RSN for different populations. Therefore, for each subject the corresponding RSN should be identified. RSNs exhibit highly characteristic spatial patterns which overlap well known brain regions. Therefore, in principle the identification in a set of ICs consists in identifying the components that better resemble the expected spatial pattern. However, in severely altered brain conditions, cerebral activity may be highly affected resulting in a reconfiguration of the RSN. In these

cases identification of specific RSN may be challenging. This problem is amplified when multiple networks should be studied simultaneously [20].

Commonly the labeling of RSNs should be performed by trained personal, a task that is prone to error and time-consuming. Specially, when multiple RSNs should be characterized. In RestLib we address this limitation by providing a multiple templates matching algorithm that automatically solves the problem of identification of the expected patterns of RSNs in a set of ICA components. This approach is based on a set of previously constructed templates of the RSN and runs without any intervention of the user.

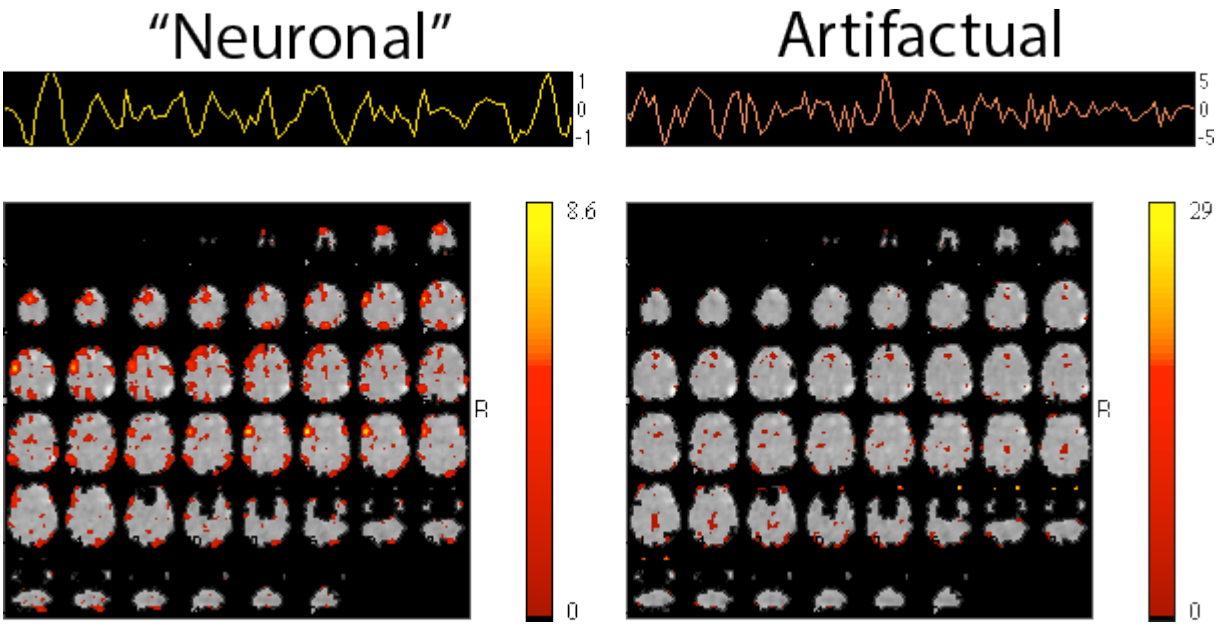


Figure 4.1. Classified components of the same subject. Upper part shows the temporal signal associated to the spatial component in the lower part.

Materials and methods

RSNs templates were selected by an expert via visual inspection from a set of spatially independent components. These components were taken from 12 independently assessed controls (4 women, mean age 21 $\pm$ 3 years) scanned on a 3T scanner (32 slices; repetition time = 2460ms). The templates were then checked by another expert for accuracy of structural labeling.

Results

Figure 4.2 illustrates the set of ICA components (top) that better resemble a set previously defined of RSNs templates (bottom) for a healthy control subject. Colors in the components corresponds to the templates assignation. This matching was performed automatically by

using the previously described method. As observed, the proposed approach is able to automatically find the complete set of RSNs templates among the 30 ICs. When the expert perform this task manually commonly he/she should look for each RSN one at a time.

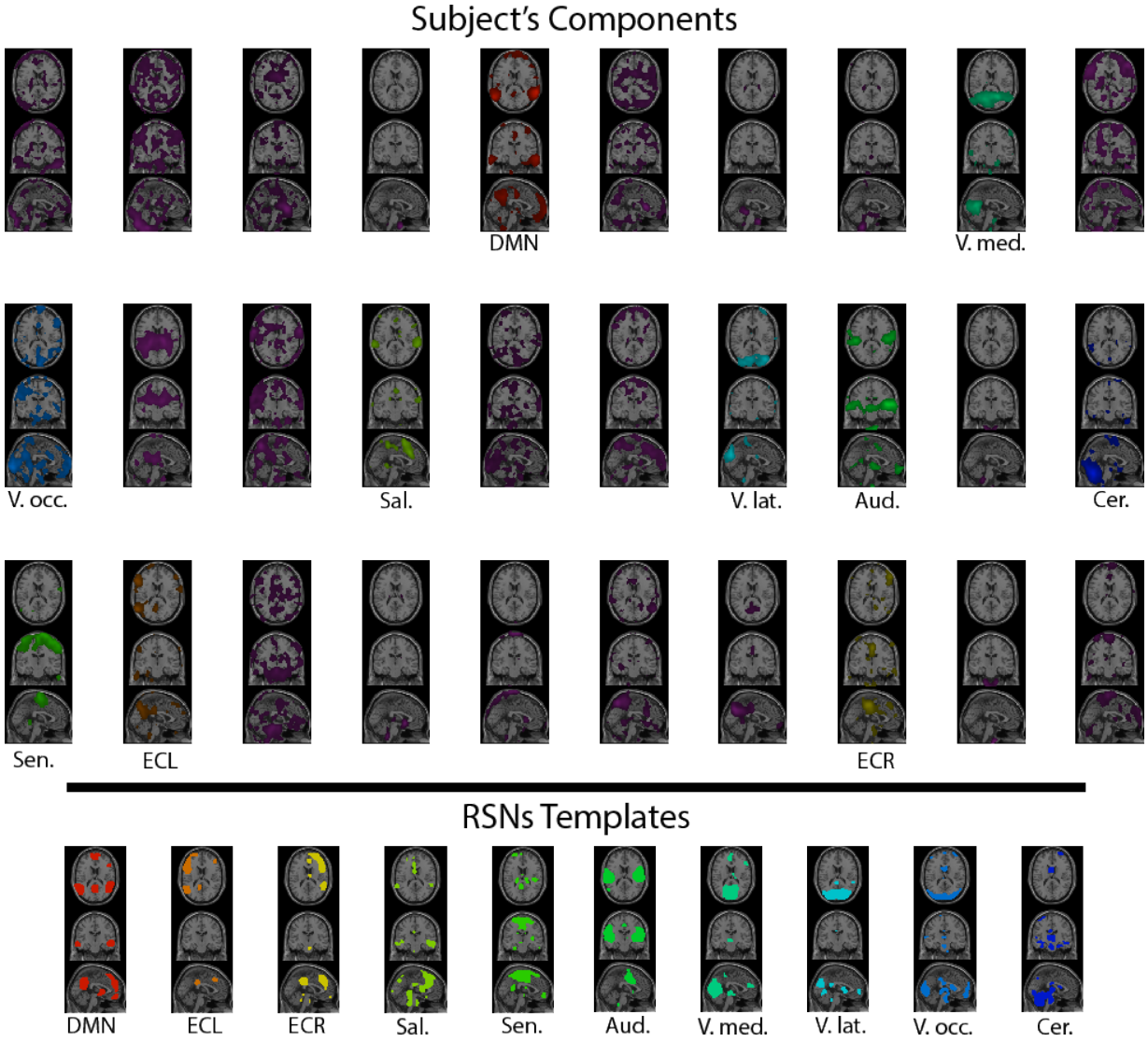


Figure 4.2. Automatically labeled components of the same subject. Axial, coronal and sagittal exhibited cuts correspond to the middle slice of each direction.

This methodology may bias the ICs selection by privileging some RSNs over others, for instance, DMN over the rest of the RSNs [32, 31]. In the proposed approach the visual similarity for the 10 RSNs is evaluated in parallel resulting in a more objective strategy. By using this approach, a large number of networks can be labeled without any human intervention, resulting also in a time saving approach.

4.4 Conclusions

ICA constitutes an excellent tool to parcellate the fMRI signal using a data-driven approach. However, this method does not identify spatial structures of interest, as well as, does not provide any information about the origin of the source, if "neuronal" or artifactual. Evidence reveals that removal of the artifactual contribution to the BOLD signal represents a critical step for any resting state based analysis [18, 42].

The used characterization, i.e., building the multidimensional fingerprint, was carefully selected to be independent of the spatial pattern of the components. This aspect makes this approach quite suitable in patients with severely affected brains where the spatial pattern can be highly disrupted.

Additionally, we would like to remark that we built RestLib to be compatible with SPM. Hence, users will have no difficulty in using the graphical interfaces. Thanks to its modular design, RestLib can easily be extended via the addition of new functionalities, therefore aiming to improve the interaction between the neuroimaging and clinic communities.

5 Discussion

In this thesis, we propose a novel framework to perform fMRI resting state analysis. This tool is able to characterize brain dynamics at single subject level for clinical environments. In addition, it considers several real requirements for clinics including, robustness to variations in acquisition protocols, measurements of the degree of reliability in results and high levels of reproducibility. The framework is based in a multiple templates matching approach to automatically identify the RSNs and it also considers a strategy to discriminate between artifactual and "neuronal" components. The proposed framework was tested in different clinical problems resulting in high levels of automation in the characterization.

Previous works in fMRI-RS characterization have focused on group studies, i.e., looking for differences in brain activity between populations [54]. These approaches are suitable to characterize general features of pathological/pharmacological brain conditions. Nevertheless, the use of fMRI to support patient characterization in clinics requires a single subject level assessment, for instance, for diagnostic or prognostic tasks [20]. In this work, we propose a novel method which is suitable to characterize fMRI dynamics at single subject level. The method aims to automatically identify the so called RSNs of "neuronal" origin. These functional entities have been linked to several pathological/pharmacological altered brain states, resulting in a highly valuable source of information to perform diagnostic/prognostic tasks. This characterization allows to study intra-subject patterns that may carry out valuable information about the patient condition. This requirement is specially important in severely affected brain states, such as, DoCs, among others. In addition, features extracted at individual level can be used to construct automatic diagnostic/prognostic tools based on machine learning approaches [54, 65].

The proposed framework also provides robustness to variations in acquisition protocols. Most of the studies in neuroimaging focus on very controlled capture settings. Nevertheless, acquisition protocols in clinical environments are widely heterogeneous. For instance, MRI facilities may highly vary across centers, including, several MRI vendors, different MRI magnetic field capabilities and distinct parameters in the capture settings. Clinical solutions must account for this variability or at least it should aim to support as many configurations as possible. The proposed framework was tested under different experimental conditions, including: spatial resolutions, lengths of the acquisition, repetition times and differences in the experimental conditions of acquisition, among others. Our results suggest that the proposed framework is robust enough to identify the RSNs. In particular, a large percentage of RSNs can be properly identified under different experimental conditions at

individual level.

Features extracted by automated characterization approaches provides important information to support decision making processes [73]. Nevertheless, these features should be supported by objective scales to measure the level of trustworthiness of the feature itself. This level refers to a degree of reliability about the existence of the feature. For instance, an automated method may identify an specific RSN. However, the identification alone is not enough to claim the existence of that RSN. It is necessary additional information to measure in an objective way the certainty of the label assignment. Our framework provides a first approach to tackle this limitation. In particular, we devised an strategy to measure the level of similarity with previously labeled RSN in other subjects. Therefore, we can build an index with low values for low detection percentage, i.e., labeling with low levels of trustworthiness, and high values for high levels of certainty about the label assignation.

Finally, in the last chapter we overcome the critical issue of reproducibility. To face that problem we propose RestLib, a MATLAB toolbox for accessible and flexible resting state analysis of fMRI data. Although MATLAB is not freely available software, it provides high level language, as well as its widespread use in the neuroscientific community makes it a favorable environment to analyze neuroimaging data. Furthermore, many MATLAB based toolboxes already exist to import, preprocess and analyze brain data. RestLib is therefore fully compatible with the most widely used of them, SPM [59]. And also allows an easy integration with motion correction methods and our proposed ICA related algorithms into the currently used pipelines, especially via the Matlab-batch system. Thanks to its graphical interfaces, RestLib requires no programming ability whilst allowing fully flexible resting state analysis. In addition, developers can easily add new algorithms, with very little prior knowledge of the toolboxs functionalities. In this work, we presented our software framework by exploring the type of questions that can be addressed using this methodology and that cannot be properly answered using group level analysis approach. With the development of RestLib, we hope not only to provide a working tool for neuroscientists but also a platform to motivate the development of the techniques and contribute to the resolution of some of its current limitations.

5.1 Future Work

As previously discussed we focused our efforts on support the characterization of several clinical states at single subject level. The expected consequence is that by using our framework the community can improve the characterization of several clinical states at individual level, which can lead to an enhancement in the characterization of those populations. Since each group of subjects is likely to have a specific pattern of fMRI-RS connectivity, different classifiers can be trained to distinguish between those populations, helping in that way to clinicians with the persistent challenge of how to implement the fMRI-RS paradigm on

an individualized basis for discrimination between hard to distinguish pathological states, such as MCS and VS/UWS [22].

Although MATLAB is extensively used by the science community in general. Mainly due to its complete modules to analyze different sources of data, as well as, its high level programming language. It still is a proprietary software and this fact may also influence the reproducibility of the studies. Therefore a future version of RestLib will be released as RestPy which will offer all the advantages of RestLib in an complete python based framework. The challenge of this task is to offer robust preprocessing routines commonly performed with tools like SPM or FSL. ICA implementations and different parcellation routines must also be included in the new framework in order to offer to neuroscientists and clinicians more tools to improve their jobs.

5.2 Information Sharing Statement

RestLib and all its documentation are available to download from: https://github.com/guaje/restlib. The toolbox code is distributed for free, but as copyright software under the terms of the GNU General Public License as published by the Free Software Foundation. RestLib is written for MATLAB 8.0 (R2012b) and onwards, and needs an installed version of SPM8 to work. For further information on how to use the software, please consult RestLib's manual, available here: https://github.com/guaje/restlib. Some of the datasets used in this paper are freely available to the general public, specifically the data from the 1000 Functional Connectomes Project (http://fcon_1000.projects.nitrc.org) which provides a website where data can be downloaded.

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